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Orthogonal Blocking of Regular and Nonregular Strength-3 Designs

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Abstract

There is currently no general approach to orthogonally block two-level and multi-level orthogonal arrays and mixed-level orthogonal arrays. In this article, we present a mixed integer linear programming approach that seeks an optimal blocking arrangement for any type of regular and nonregular orthogonal array of strength 3. The strengths of the approach are that it is an exact optimization technique which guarantees an optimal solution, and that it can be applied to many problems where combinatorial methods for blocking orthogonal arrays cannot be used. By means of 54- and 64-run examples, we demonstrate that the mixed integer linear programming approach outperforms two benchmark techniques in terms of the number of estimable two-factor interaction contrasts. We demonstrate the generality of our approach by applying it to the most challenging instances in the catalog of all orthogonal arrays of strength 3 with up to 81 runs. Finally, we show that, for two-level fold-over designs involving many factors, the only way to arrange the runs in orthogonal blocks of size four is by grouping two pairs of fold-over pairs in each of the blocks.

KEY WORDS: Aliasing; Confounding; Mixed Integer Linear Programming, Mixed-Level Orthogonal Array, Multi-Level Orthogonal Array, Orthogonal Blocking, Pure-Level Orthogonal Array, Two-Level Orthogonal Array

1 Introduction

One of the oldest principles in design of experiments is the principle of blocking. This principle involves the grouping of experimental units into homogeneous groups called blocks.

The blocking has to be done so that the treatment comparisons of interest are not affected by the differences between the blocks.

Initially, much of the research on blocking considered a single categorical treatment factor at several levels. For this situation, randomized complete block designs, balanced incomplete block designs and many different arrangements with two crossed blocking factors have been developed. An extensive collection of such designs was given by Cochran and Cox (1957).

A separate strand of research was concerned with the blocking of complete or fractional factorial designs. Most of this work concentrates on regular designs, in which any factorial effect is either completely aliased with another factorial effect or orthogonal to it. For regular blocked factorial designs, each factorial effect is either completely confounded with the blocks or orthogonal to the blocks. Early work on blocking two-level factorial designs has been published by the National Bureau of Standards (1957), while the first work on blocking three-level designs was done by Connor and Zelen (1959). With the increasing interest in regular fractional factorial designs, blocking continued to be an important research theme (Wu and Hamada, 2009).

Recently, the focus in the research on fractional factorial designs has moved from regular to nonregular designs, in which interactions can be partially aliased with main effects or with other interactions. This feature is now recognized as being helpful to estimate many more different models than would be possible with regular designs (Hamada and Wu, 1992).

This paper deals with the blocking of orthogonal arrays (OAs) of strength 3 or resolution IV. Whenever such an OA is used as an experimental design, the main-effect estimators are independent, but the estimators of the two-factor interaction effects are aliased with each other (Hedayat et al., 1999). Despite the dependence of the estimators of the two-factor interaction effects, it is oftentimes possible to estimate several two-factor interaction effects. Because main-effect estimates are not influenced by two-factor interactions and because some of the two-factor interaction effects are estimable, an OA of strength 3 is a good design option in the presence of two-factor interaction effects. Strength-3 arrays often require a substantial number of runs, which makes it harder to conduct all the runs under homogeneous circumstances. This necessitates good methods for blocking strength-3 arrays.

The goal of this paper is to propose a practical strategy for finding blocking arrangements for strength-3 OAs, so that all the main effects are orthogonal to the block effects and that the confounding of two-factor interactions with the blocks is minimized. To this end, we applied mixed integer linear programming (MILP) techniques to an extensive catalog of strength-3 designs. We compare the results from the MILP approach with two benchmark strategies. The first benchmark approach is a D-optimal blocking approach. The second benchmark approach is an extension of the modular arithmetic commonly used to block regular designs (see, e.g., Wu and Hamada, 2009) to cope with nonregular OAs of strength 3.

We illustrate the importance of blocking arrays of strength 3 in the next section, by means of a calcium fortification study involving a strength-3 OA with one eight-level factor, one four-level factor and two two-level factors. In Section 3, we review earlier work on the blocking of OAs, with a special focus on nonregular arrays. In Section 4, we return to the calcium fortification study to lay out the existing techniques that can be used for blocking OAs of strength 3. We discuss the set of 64-run OAs considered for the calcium foritification study and apply the D-optimal benchmark approach to find blocking arrangements in eight blocks for each of the OAs. We also introduce an artificial example featuring a set of 54-run OAs with five three-level factors to illustrate the second benchmark approach, involving modular arithmetic, to block nonregular designs. Next, in Section 5, we describe our MILP approach in detail using the OAs from Section 4 as illustrations. In Section 6, we demonstrate the potential of the MILP approach via its application to a rich collection of strength-3 OAs with up to 81 runs. Finally, in Section 7, we summarize the advantages of our approach and discuss a few technicalities.

We end this section by introducing the notation we use. An orthogonal array (OA) with m factors, N runs and strength t is an $N \times m$ matrix of symbols. Each column corresponds to a categorical treatment factor and involves a certain number of symbols, and these symbols are arranged so that, for every set of t columns, each t-tuple of symbols occurs equally often (Rao, 1947). Every symbol in a given column represents a factor level. In this paper, we consider only orthogonal arrays of strength 3. We assume that the set of factors can be partitioned in γ subsets, where all m_i factors in a given subset i have the same number of levels, s_i. We denote by $\text{OA}(N; s_1^{m_1} \times s_2^{m_2} \times \ldots \times s_\gamma^{m_\gamma})$ the set of non-isomorphic strength-3 OAs involving N runs, m_1 factors acting at s_1 levels, m_2 factors acting at s_2 levels, etc. We drop the exponent m_i when it equals one, i.e. when there is exactly one factor with s_i levels. Finally, OAs with $\gamma = 1$ are pure-level arrays, while those with $\gamma > 1$ are mixed-level

Table 1: Experimental factors in the calcium fortification study.

Factor	Name	Number of levels
A	Calcium source	8
B	Food product	4
C	Calcium concentration	2
D	Stomach condition	2

arrays.

2 Motivating example

In the summer of 2007, researchers of FrieslandCampina, a dairy company in the Netherlands, wanted to compare different ways of calcium fortification in liquid food products. They were particularly interested in the presence of this compound after the food has been processed by the stomach. The study involved a laboratory simulation of the intestinal tract in a reaction vessel. The four experimental factors and their numbers of levels are given in Table 1.

The experimenters used eight different calcium sources in the study, as well as four different food products in which to dissolve the calcium. For each of the calcium sources, a high and a low concentration was used. The calcium solution was put into a reaction vessel, together with fluids mimicking those in the human stomach. Two different stomach conditions were studied: a fasted condition and a fed condition. After a fixed time period, new fluids were added to simulate conditions of the small but important part of the intestinal tract right after the stomach, called the duodenum. At the end of another fixed period, a first sample was taken to measure the calcium concentration, and new fluids were added to make the conditions similar to those in the next part of the intestinal tract, the ileum. At the end of each experimental run, a second sample was taken to measure the calcium concentration again.

A full factorial design for the calcium fortification study would have required $8 \times 4 \times 2^2 = 128$ runs. That design would have enabled the researchers to estimate a statistical model involving an intercept, four main effects, six two-factor interactions, four three-factor interactions, and one four-factor interaction. However, the researchers' interest was in the main effects, with possibly some two-factor interactions. In total, 12 contrasts have to be estimated to quantify all main effects, and 42 contrasts have to be estimated to quantify all two-factor interaction effects. A 64-run half fraction of the full factorial design, which would allow all main effects and many two-factor interaction contrasts to be estimated, was considered an appropriate design option. In total, there are four nonregular 64-run OAs of strength 3. The strength of 3 implies that all the main-effect estimators are orthogonal to each other and to the estimators of the two-factor interaction contrasts. The estimators of the two-factor interaction contrasts are not independent, but, nevertheless, the four available OAs allow estimation of 39 or 41 of the 42 existing two-factor interaction contrasts. Therefore, the strength-3 OAs were well suited for the calcium fortification study. Also, the OAs offer the advantage that they halve the number of runs compared to the full factorial design.

At any time during the calcium fortification study, eight similar vessels were operating simultaneously. Small differences in operating conditions over time implied that treatment comparisons between simultaneously operating vessels were more precise than comparisons of treatments from different groups. Therefore, the problem was to block one of the nonregular 64-run strength-3 OAs in eight blocks of size eight, such that the main effects were orthogonal to the blocks and the two-factor interactions were confounded with blocks to the smallest possible extent.

For one of the 64-run designs with 41 estimable two-factor interaction contrasts, we obtained a blocking arrangement yielding independent estimates for the main effects by applying the D-optimal blocking algorithm of Cook and Nachtsheim (1989), as implemented in SAS version 9.1, assuming a main-effects model involving eight blocks of eight runs. Like the original OA, the blocked design still allows estimation of 41 two-factor interaction contrasts. The blocked design is given in Table 2. For the calcium fortification study, seeking a D-optimal blocking arrangement for a main-effects model yielded a desirable blocking arrangement of the 64-run OA, offering a maximum number of estimable two-factor interaction contrasts. This will not be the case in general because that approach does not take into account the confounding of two-factor interactions with blocks. Therefore, in this paper, we develop a general method for blocking strength-3 OAs that copes with this weakness.

Table 2: Design for the calcium fortification experiment involving eight blocks of eight runs.

Block	A	B	C	D	Block	A	B	C	D
1	0	1	0	0	5	0	3	0	1
1	1	1	1	0	5	1	0	0	1
1	2	2	1	1	5	2	3	0	0
1	3	0	1	0	5	3	2	0	0
1	4	2	1	1	5	4	0	1	0
1	5	0	0	0	5	5	2	1	0
1	6	3	0	1	5	6	1	1	1
1	7	3	0	1	5	7	1	1	1
2	0	0	1	1	6	0	3	1	0
2	1	2	1	1	6	1	2	0	0
2	2	0	0	1	6	2	3	1	1
2	3	1	0	1	6	3	2	1	1
2	4	3	1	0	6	4	1	0	0
2	5	3	0	0	6	5	1	0	1
2	6	1	0	0	6	6	0	0	0
2	7	2	1	0	6	7	0	1	1
3	0	1	1	1	7	0	2	0	1
3	1	0	1	0	7	1	3	0	0
3	2	1	0	1	7	2	0	1	0
3	3	0	0	1	7	3	1	1	0
3	4	2	0	0	7	4	3	0	1
3	5	2	0	1	7	5	1	1	0
3	6	3	1	0	7	6	0	1	1
3	7	3	1	0	7	7	2	0	1
4	0	0	0	0	8	0	2	1	0
4	1	1	0	1	8	1	3	1	1
4	2	2	0	0	8	2	1	1	0
4	3	3	1	1	8	3	3	0	0
4	4	1	1	1	8	4	0	0	1
4	5	3	1	1	8	5	0	1	1
4	6	2	1	0	8	6	2	0	1
4	7	0	0	0	8	7	1	0	0

3 Review

In this section, we review recent work on the blocking of nonregular orthogonal designs. Unlike regular orthogonal designs, nonregular designs have partially aliased effects. This was first recognized by Hamada and Wu (1992), who demonstrated that a 12-run Plackett-Burman design allowed the detection of an interaction effect that was partially aliased with main effects. The work of Hamada and Wu sparked interest in nonregular designs of strength 2. Deng and Tang (2002) studied small two-level designs obtained from Hadamard matrices. Sun et al. (2002) obtained two-level 20-run designs that cannot be obtained by projections from Hadamard matrices of order 20. Schoen et al. (2010) enumerated all pure- and mixed-level OAs of strength 2 with up to 28 runs, with the exception of two-level strength-2 arrays involving 28 runs and eight or more factors. In strength-2 orthogonal designs, the contrast vectors of the main effects are all orthogonal to each other, but they are not orthogonal to the contrast vectors of the two-factor interactions.

Blocking arrangements for nonregular two-level designs were first studied by Cheng et al. (2004). Their blocking method is suitable for experiments where the number of blocks is a power of two. Jacroux (2009) obtained blocking arrangements for nonregular two-level OAs with more flexible numbers of blocks by using foldover techniques and grouping the resulting blocks. Finally, Schoen et al. (2011) proposed a method for blocking general strength-2 OAs (i.e., OAs with factor that can have any numbers of levels) and provided extensive tables of optimally blocked designs with up to 27 runs, for any number of blocks that allows the main effects to be estimated independently from the block effects.

While the published work on the blocking of orthogonal arrays is mainly concerned with strength-2 OAs, there is an increasing interest in the application of strength-3 pure-level and mixed-level OAs. Schoen et al. (2010) enumerated most series of strength-3 arrays with up to 64 runs. The two-level strength-3 OAs with up to 24 factors and up to 48 runs were classified by Schoen and Mee (2012). Three-level strength-3 OAs with up to 10 factors and 81 runs were classified by Sartono et al. (2012). All other things being equal, strength-3 OAs generally require a larger number of runs than strength-2 OAs. As it is difficult to carry out large numbers of runs under homogeneous circumstances, it is of utmost importance to study blocking arrangements for OAs of strength 3.

The literature on blocking strength-2 OAs exploits the fact that the design for the treatment factors combined with the blocking factor also form a strength-2 array. Therefore, to obtain a blocking arrangement of an m-factor OA, one can start from a set of $(m+1)$-factor strength-2 OAs that include the future blocking factor and search for the best projection into m factors. This approach is not fruitful for strength-3 arrays, for the following reason. While the treatment design should be of strength 3, the strength of the combined design involving the treatment factors as well as the blocking factor can be 2, assuming that the blocking factor does not interact with the treatment factors. For the typical run sizes of strength-3 OAs, it is computationally infeasible to construct a catalog of all non-isomorphic

$(m+1)$-factor designs of strength 2, the treatment part of which is of strength 3. As a result, for designs with a strength of 3 or more, a new blocking strategy is needed that is computationally less demanding.

4 Two benchmark techniques

In this section, we first return to the calcium fortification example, introduced in Section 2 to illustrate the need for blocking methods for orthogonal arrays of strength 3 involving factors with different numbers of levels. We discuss the 64-run series of OAs that was considered for the treatment design, and then apply the D-optimal benchmark technique to find arrangements of the OAs in eight blocks. In the second part of this section, we study an example involving 54-run OAs with five three-level factors, and use that example to introduce the second benchmark approach based on the modular arithmetic originally developed for blocking regular designs.

4.1 Calcium fortification example

The primary goal of the calcium fortification experiment at FrieslandCampina was to estimate the main effects of the factors, but the experimenters expressed genuine interest in quantifying two-factor interactions as well. For three reasons, it was natural to use one of the four arrays of the type $\mathrm{OA}(64; 8 \times 4 \times 2^2)$ reported by Schoen et al. (2010) as the treatment design for that study. First, the run size of 64 is divisible by 8, which is the number of vessels that was available at any time. The OAs therefore make it possible to use an eight-level blocking factor. Second, as the arrays have strength 3, they allow an independent estimation of the main effects, which were of primary interest. Finally, the designs have a large number of runs, and therefore offered the prospect of being able to estimate many two-factor interaction contrasts. We now discuss the four treatment designs in detail.

4.1.1 Four different treatment designs

Table 3 shows the four non-isomorphic arrays of the type $\mathrm{OA}(64; 8 \times 4 \times 2^2)$ in schematic form. We assume that the factor level combinations are sequentially sorted according to the levels of the eight-level factor, the levels of the four-level factor, and the levels of the

Table 3: Schematic representation of the four strength-3 arrays of the type $\mathrm{OA}(64; 8\times 4\times 2^2)$ considered for the calcium fortification experiment.

I	II	III	IV
$4\mathbf{a}$	$3\mathbf{a}$	$2\mathbf{a}$	$2\mathbf{a}$
$4(\mathbf{a}+\mathbf{1})$	$\mathbf{b}$	$2\mathbf{b}$	$\mathbf{b}$
	$\mathbf{b}+\mathbf{1}$	$2(\mathbf{b}+\mathbf{1})$	$\mathbf{c}$
	$3(\mathbf{a}+\mathbf{1})$	$2(\mathbf{a}+\mathbf{1})$	$\mathbf{c}+\mathbf{1}$
			$\mathbf{b}+\mathbf{1}$
			$2(\mathbf{a}+\mathbf{1})$

first two-level factor. All combinations of levels of these factors appear in the design exactly once. The four arrays only differ with respect to the second two-level factor.

The levels of this factor are shown in Table 3 for each of the four non-isomorphic OAs. In the table, the symbols **a**, **b**, and **c** represent the 8-dimensional vectors

$$\mathbf{a} = (0, 1, 0, 1, 1, 0, 1, 0)^T,$$

$$\mathbf{b} = (0, 1, 1, 0, 0, 1, 1, 0)^T,$$

and

$$\mathbf{c} = (0, 1, 1, 0, 1, 0, 0, 1)^T.$$

They are the building blocks for the four OAs' final two-level column, along with their mirror images which we represent by $\mathbf{a} + \mathbf{1}$, $\mathbf{b} + \mathbf{1}$ and $\mathbf{c} + \mathbf{1}$, respectively.

The final two-level column of array I involves four copies of the vector **a** and four copies of its mirror image $\mathbf{a} + \mathbf{1}$. Array II's final column involves three copies of **a**, one copy of **b**, three copies of $\mathbf{a} + \mathbf{1}$ and one copy of $\mathbf{b} + \mathbf{1}$. Array III has two copies of **a** as well as two copies of **b**, with their respective mirror images. Finally, array IV's final column contains two copies of **a**, one copy of **b**, one copy of **c**, and the corresponding mirror images.

None of the four OAs permits estimation of all 42 two-factor interaction contrasts. Array I allows 39 two-factor interaction contrasts to be estimated, while the other three arrays offer 41 estimable two-factor interaction contrasts. The average D-efficiency over all models with two, three or four two-factor interactions is slightly better for arrays III and IV than for arrays I and II. As a result, before considering the OAs' suitability for a blocked experiment, there was an a priori preference for the arrays III and IV.

4.1.2 D-optimal blocking

The run size of the four candidate designs is 64. The runs should be grouped in blocks of size 8, and the challenge is to define eight blocks such that the main effects are orthogonal to the blocks, while minimizing the number of two-factor interaction contrasts which are confounded with the blocks.

At the time the calcium fortification study was conducted, in May 2007, the four non-isomorphic treatment designs in Table 3 were available, but the literature did not offer any guidance concerning the blocking of an OA involving an eight-level factor, a four-level factor and two two-level factors. The solution adopted by the third author of this paper, who acted as a consultant for the study, was to feed the four designs to PROC OPTEX of SAS® version 9.1 to obtain D-optimal blocking arrangement for a model containing main effects only. The SAS procedure employs the blocking algorithm of Cook and Nachtsheim (1989). Whenever the procedure returns a blocking arrangement with a D-efficiency of 100%, the resulting design is an orthogonally blocked design for the main effects, implying that the main effects can be estimated independently.

When using 50 random starts of the blocking algorithm, the OPTEX procedure was able to produce blocking arrangements with a D-efficiency of 100% for arrays I and II, but not for arrays III and IV. The blocking arrangements of arrays I and II permitted estimation of 39 and 41 two-factor interaction contrasts, respectively. As a results, blocking these OAs did not lead to a loss of estimable two-factor interaction contrasts when compared with the unblocked OAs. Since array II offered a larger number of estimable interaction contrasts, it was that design which was used for the calcium fortification study. The D-optimal blocking pattern is shown in Table 2.

4.2 Artificial example

In this section, we consider a 54-run experiment with five three-level factors, the runs of which have to be arranged in nine blocks of six. The block size of six is a multiple of the number of levels of each factor, which suggests that it may be possible to find blocking arrangements of OAs that allow an independent estimation of the main effects. We assume that a precise estimation of the main effects is the primary goal, and that estimability of two-factor interaction contrasts is a secondary goal.

4.2.1 Four different treatment designs

Assuming a design involving b blocks, the model of interest in the articial example involves ten parameters for the five main effects, 40 parameters for the two-factor interaction contrasts and b parameters for the block effects and the intercept. To estimate that model, at least $50+b$ experimental runs are needed. The regular one-third fraction of the full factorial 3^5 design listed in Wu and Hamada (2009) has 81 runs and resolution V, or strength 4. Therefore, the design permits estimation of all the main effects and two-factor interactions independently. However, there are attractive strength-3 OAs with a run size of only 54 if we are primarily concerned with estimating main effects.

In particular, there are four different arrays of the type $\mathrm{OA}(54; 3^5)$, which were introduced in the literature by Hedayat et al. (1997). The statistical properties of these OAs were explored by Sartono et al. (2012). The four OAs differ in the number of estimable two-factor interaction contrasts. The numbers of estimable two-factor interaction contrasts equal 31, 35, 36, and 39, and, therefore, we refer to the OAs as the 31-2FI array, the 35-2FI array, the 36-2FI array and the 39-2FI array. It is clear that none of the OAs permits estimation of all two-factor interaction contrasts and that, if the experiment were not blocked, the 39-2FI array OA would be preferred.

4.2.2 Blocking using modular arithmetic

We now want to block the four arrays of the type $\mathrm{OA}(54; 3^5)$ in nine blocks of size six. Because all factors have three levels and the number of blocks is a power of three, we can apply the blocking methodology for regular three-level designs involving modular arithmetic (Wu and Hamada, 2009) to the four nonregular 54-run OAs. To this end, we calculate three-level blocking basic factors (BBFs) by decomposing the four degrees of freedom for each two-factor interaction and the eight degrees of freedom for each three-factor interaction into orthogonal components of two degrees of freedom each. For example, we calculated $F = X_1 + 2X_2 + X_3 \pmod 3$ as one of the BBFs, where X_i represents the level of the ith factor in the design.

As there are ten two-factor interactions each involving four degrees of freedom, a total of 20 BBFs can be constructed from the two-factor interactions. For every OA of strength 3, these BBFs are automatically orthogonal to the main effects. As there are ten three-factor interactions involving eight degrees of freedom each, 40 BBFs can be constructed from the three-factor interactions. However, there is no guarantee that these BBFs are orthogonal to the main effects. As our end goal is to obtain a blocking arrangement in which the main effects and the blocks are orthogonal, we only retain the BBFs that are orthogonal to the main effects.

To block a 54-run array into nine blocks of size six, we need to select two BBFs and associate each of the corresponding nine level combinations with a separate block. The BBFs of two degrees of freedom each, and their interaction involving four degrees of freedom, are then all confounded with the blocks. The final step then is to verify whether the resulting nine-level blocking factor is orthogonal to the main effects. Among all the arrangements that satisfy this orthogonality requirement, we select the arrangement that minimizes the confounding of the two-factor interactions with the nine blocks.

An exhaustive search over all BBFs revealed that, using the modular arithmetic approach, orthogonal nine-block arrangements cannot be obtained for the 31-2FI and 36-2FI arrays. The best arrangement for the 35-2FI array sacrifices the estimability of six two-factor interaction contrasts, leaving 29 estimable ones. The best arrangement for the 39-2FI array sacrifices eight estimable two-factor interaction contrasts, leaving 31 estimable ones. Therefore, in case nine blocks of size six are desired and modular arithmetic is used, our recommendation would be to use the 39-2FI array.

5 Using mixed integer linear programming to find blocking arrangements

To obtain orthogonal blocking arrangements for given strength-3 OAs, we suggest a mixed integer linear programming approach. Linear programming (LP) is a common method to determine the values of a set of decision variables so as to maximize or minimize a particular linear objective function, while satisfying a set of linear constraints. When all the variables in the solution are required to be integer, the method is named integer linear programming

(ILP). It is called mixed integer linear programming (MILP) if only some of the variables are required to be integer. In this section, we show how MILP can be used to find good blocking arrangements for strength-3 OAs.

5.1 Description of methodology

Suppose that we have a strength-3 OA $\mathbf{Z}$ involving N runs and m factors, where each factor has s_i levels, $i = 1, 2, \ldots, m$. Our goal is to find an optimal orthogonal blocking arrangement for a given treatment design or OA of strength 3. Any arrangement in b blocks can be represented by means of an $N \times b$ indicator matrix $\mathbf{B} = [b_{ij}]$, where b_{ij} equals 1 if the ith run is assigned to the jth block and 0 otherwise. The elements of $\mathbf{B} = [b_{ij}]$ are binary decision variables in our linear programming approach.

We require the blocking factor to be orthogonal to the main effects. Therefore, each level of any treatment factor must appear equally often in each block. This requirement can be cast in a linear constraint. To this end, replace the ith column of $\mathbf{Z}$ by $(s_i - 1)$ orthogonal contrast columns, normalize these columns such that they have the same length, and denote the normalized columns by $\mathbf{z}_{i(1)}, \mathbf{z}_{i(2)}, \ldots, \mathbf{z}_{i(s_i-1)}$. The ith main effect is orthogonal to the blocking factor if and only if $\mathbf{z}_{i(q)}^T \mathbf{B} = \mathbf{0}_{1\times b}$ for all $q = 1, 2, \ldots, s_i - 1$. If we collect all $p_1 = \sum_{i=1}^{m} (s_i - 1)$ main-effect contrast columns in a single $N \times p_1$ matrix $\mathbf{X}$, then the orthogonal blocking requirement can be written as $\mathbf{X}^T\mathbf{B} = \mathbf{0}_{p_1\times b}$.

There may be more than one way to achieve orthogonality between the main effects and the blocks. In that case, we prefer a blocking arrangement that enables us to estimate as many two-factor interaction effects as possible. The way to find such a blocking arrangement is by minimizing the confounding between the two-factor interactions and the blocking factor. To quantify this type of confounding, we construct the $N \times p_2$ matrix $\mathbf{W}$ containing the $p_2 = \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} (s_i - 1)(s_j - 1)$ two-factor interaction contrast vectors. This is done by element-wise multiplication of all pairs of main-effect contrast vectors corresponding to different treatment factors. The elements of the matrix product $\mathbf{D} = \mathbf{W}^T\mathbf{B}$ then measure the extent to which each two-factor interaction contrast is confounded with each of the blocks. The LP model to search for an optimal blocking arrangement can then be formulated as "Find $\mathbf{B}$ such that $\mathbf{X}^T\mathbf{B} = \mathbf{0}_{p_1\times b}$ and the confounding of two-factor interactions with blocks, as measured by $\mathbf{D} = \mathbf{W}^T\mathbf{B}$, is minimal."

Ideally, $\mathbf{D} = \mathbf{W}^T\mathbf{B} = \mathbf{0}_{p_2 \times b}$, which would mean that the blocks are also orthogonal to all two-factor interaction effects. In many practical situations, this will be impossible to achieve due to the large number of two-factor interaction contrasts of interest. Therefore, in our MILP approach, we sequentially minimize the element of $\mathbf{D}$ that has the largest absolute value and the sum of all the absolute values of the elements of $\mathbf{D}$. If we denote by d_{ij} the elements of $\mathbf{D}$, by $\mathbf{w}_i$ the ith column of $\mathbf{W}$ and by $\mathbf{b}_j$ is the jth column of $\mathbf{B}$, so that $d_{ij} = \mathbf{w}_i^T\mathbf{b}_j$, then we first minimize

$$d = \max_{i,j} \{|d_{ij}|\},$$

followed by

$$S = \sum_{i=1}^{p_2}\sum_{j=1}^{b} |d_{ij}|.$$

By prioritizing the minimization of d, we ensure that none of the two-factor interaction contrasts is severely confounded with any of the blocks. Given that d is minimal, we can then focus on minimizing the remaining, less severe, counfounding.

The sequential minimization can be cast in a single objective function, using the big-M method (Winston, 2003). The objective function of our MILP approach then becomes

$$f(\mathbf{B}) = Md + S,$$

where $M >> 1$.

In brief, our MILP approach involves searching a binary matrix $\mathbf{B}$, which minimizes $f(\mathbf{B})$, subject to $\mathbf{X}^T\mathbf{B} = \mathbf{0}_{p_1 \times b}$. Its exact implementation, however, involves several additional constraints to determine the absolute values $|d_{ij}|$ as well as their maximum d. The detailed specification of our MILP model is as follows:

$$\text{Minimize } f(\mathbf{B}) = Md + \sum_{i=1}^{p_2}\sum_{j=1}^{b} d_{ij(A)} + \sum_{i=1}^{p_2}\sum_{j=1}^{b} d_{ij(B)} \quad \text{where } M >> 1 \tag{2}$$

Subject to

(1) $\mathbf{w}_i^T\mathbf{b}_j - d_{ij(A)} + d_{ij(B)} = 0,$ $\quad i = 1, \ldots, p_2,\ j = 1, \ldots, b$

(2) $0 \leq d_{ij(A)} \leq d,$ $\quad i = 1, \ldots, p_2,\ j = 1, \ldots, b$

(3) $0 \leq d_{ij(B)} \leq d,$ $\quad i = 1, \ldots, p_2,\ j = 1, \ldots, b$

(4) $\mathbf{X}^T\mathbf{B} = \mathbf{0}_{p_1 \times b},$

(5) $\mathbf{B}^T\mathbf{1}_N = (N/b)\mathbf{1}_b,$

(6) $\mathbf{B}\mathbf{1}_b = \mathbf{1}_N,$

(7) $b_{ij} \in \{0, 1\}.$

In the constraints as well as in the objective function, the absolute values $|d_{ij}|$ are all replaced with two non-negative linear variables $d_{ij(A)}$ and $d_{ij(B)}$. This is the standard way of linearizing the nonlinear absolute value operator. Constraint (1), along with the non-negativity constraint for $d_{ij(A)}$ and $d_{ij(B)}$ in (2) and (3), ensures that $d_{ij(A)} > 0$ and $d_{ij(B)} = 0$ when $d_{ij} > 0$, and that $d_{ij(A)} = 0$ and $d_{ij(B)} > 0$ when $d_{ij} < 0$. The constraints (2) and (3) define d as the upper bound of all $d_{ij(A)}$ and $d_{ij(B)}$. Constraint (4) specifies that the blocking factor must be orthogonal to the main effects. The additional constraints (5) and (6) specify the structure of the binary matrix $\mathbf{B}$: every column should contain exactly N/b ones, and every row should contain exactly one entry that is equal to 1. The number N/b is the block size. Finally, constraint (7) imposes that each element b_{ij} of $\mathbf{B}$ is a binary decision variable. The model is a MILP model, because it contains integer decision variables b_{ij} as well as real decision variables ($d_{ij(A)}$, $d_{ij(B)}$, and d).

If $b = N/s_1$, we can add additional constraints to the model to speed up the search for an optimal solution. Consider, for example the problem of blocking an array of the type $\text{OA}(64, 8 \times 4 \times 2^2)$ in eight blocks of size eight. If such an array is sorted in increasing order of the level of the eight-level factor, the resulting array has equal settings for this factor in the first eight runs. Since we desire an orthogonal blocking arrangement, these eight runs have to be assigned to different blocks. Therefore, we add the constraints $b_{ii} = 1$ to the MILP formulation, for $i = 1, 2, \ldots, 8$. This reduces the number of binary variables in $\mathbf{B}$ by one eighth, and leads to a faster solution of the MILP. Similar constraints can speed up the blocking of arrays of the type $\text{OA}(64, 4^b \times 2^a)$ in 16 blocks, and of arrays of the type

Table 4: Optimal assignment to blocks of the runs of the four arrays of the type $OA(64, 8 \times 4 \times 2^2)$ in Table 3 for the calcium fortification study.

Array	Eight-Level Blocking Factor
I	1234567835721846586324178624715364178235438567217168354227514386
II	1234567887214365645278138637514213862475347512865741682325683741
III	1234567856127843472538616587413238167254478365218154236723761485
IV	1234567886217354386124577385264165471382256748137438156241528736

$OA(54, 6 \times 3^a)$ in 9 blocks. Note that, for orthogonality between main effects and blocks to be possible, the block size must be a common multiple of all factor levels. For example, in an array of the type $OA(72, 4 \times 3^2 \times 2)$, the block sizes can be 12, 24, or 36. As a result, the numbers of blocks can be 6, 3, or 2, respectively. We implemented our MILP approach using the OPTMODEL procedure embedded in the SAS/OR software.

5.2 Examples

We first used the MILP model to block the four designs of the type $OA(64; 8 \times 4 \times 2^2)$ given in Table 3 into eight blocks. Recall from Section 4.1 that, with 50 random starts, the OPTEX procedure was able to find orthogonal arrangements in eight blocks for the arrays I and II, but not for the arrays III and IV. Both Array I and II could be blocked such that no estimable two-factor interaction contrasts were lost due to the blocking.

The MILP approach succeeded in finding orthogonal arrangements in eight blocks for all four arrays, so that no estimable two-factor interaction contrasts are lost. Table 4 provides the optimal blocking factors resulting from the MILP solution. If the MILP approach had been available earlier, we would have chosen the blocked array III or IV for the calcium fortification study, because these OAs offer 41 estimable two-factor interaction contrasts and have average D-efficiencies that are 1% higher than that of array II over all models that include the main effects of the blocking factor and the treatment factors, and two to four two-factor interaction effects.

In Table 5, we compare the number of estimable two-factor interaction contrasts for the blocking arrangements of the four arrays of the type $OA(54; 3^5)$, involving nine blocks of six runs, obtained by the benchmark procedure based on modular arithmetic, and the MILP approach. The table's second and third column show the number of estimable contrasts obtained with the benchmark procedure and the MILP model, respectively, after accounting

Table 5: Number of estimable two-factor interaction contrasts from the four arrays of the type $OA(54; 3^5)$ arranged in nine blocks of size six using the benchmark approach involving modular arithmetic and the MILP approach.

Array	Benchmark	MILP
31-2FI	–	inf
35-2FI	29	34
36-2FI	–	34
39-2FI	31	35

for the blocks. Clearly, the best results are obtained for the 39-2FI array, which was arranged in nine blocks of size six by the MILP approach, so that 35 two-factor interaction contrasts are estimable. This number is the maximum possible, given that 54 degrees of freedom are available, that nine of these are used to estimate the intercept and the block effects, and that ten degrees of freedom are required to estimate the main effects of the treatment factors. In this case, four two-factor interaction effects that were estimable in the absence of blocking are no longer estimable after blocking the array in nine blocks of six runs.

An interesting result is that the MILP approach indicated that blocking the array 31-2FI orthogonally is infeasible. In other words, there exists no blocking arrangement for that OA for which the main effects are orthogonal to the blocks. The fact that the benchmark approach was unable to find an orthogonal arrangement for the array 31-2FI already suggested that this was at least a difficult problem, but that approach cannot provide a proof of the non-existence of an orthogonal blocking arrangement. For the array 36-2FI, the benchmark approach also did not result in a feasible solution. However, in this case, the MILP approach did return a solution with 34 estimable two-factor interaction contrasts (of the original 36). The array 35-2FI could be blocked orthogonally by both the benchmark procedure and the MILP approach. However, the latter approach is by far superior to the former, because 34 of the original 35 estimable two-factor interaction contrasts remain estimable, as opposed to 29 for the benchmark approach. For the 39-2FI array, the MILP approach resulted in a loss of four estimable contrasts, while the benchmark procedure resulted in a loss of eight such contrasts.

We conclude that the MILP approach gives blocking arrangements of arrays of the types $OA(64; 8 \times 4 \times 2^2)$ and $OA(54; 3^5)$ that are generally superior to the benchmark procedures.

6 Application to a catalogue of strength-3 designs

The MILP algorithm is also successful in blocking all known series of strength-3 OAs with run sizes ranging from 24 to 81. To substantiate this assertion, we report in this section the results of the MILP approach when applied to all the pure-level and mixed-level types of OAs listed in Table 6. We first discuss the sets of OAs we have used to test the MILP approach and then discuss the computational results.

6.1 The series

In total, we have studied 54 types of OAs. Each type is defined by its run size, the number of factors and the numbers of levels of each of the factors. These parameters are given in the first two columns of Table 6. In the column labeled '#NI', Table 6 also lists the number of non-isomorphic arrays of each type, and the distribution of the number of estimable two-factor interaction contrasts when the arrays are not blocked is given in the column labeled '# Estimable 2FI Contrasts'. The frequency of each number of estimable contrasts is given by means of a superscript. For example, there are 11 non-isomorphic arrays of the type OA$(32, 4 \times 2^6)$. One of these offers 21 estimable two-factor interaction contrasts, while eight other arrays offer only 20 such contrasts, and the last two arrays permit estimation of 19 two-factor interaction contrasts. This is denoted by $21^1, 20^8, 19^2$.

All the non-isomorphic designs referred to in Table 6 have been generated by the algorithm of Schoen et al. (2010). The numbers of non-isomorphic arrays for the 72- and 80-run cases are new to the literature.

Table 6: Results of the MILP approach for 54 different types of OAs with N runs, #NI isomorphism classes, b blocks, and r/r_b estimable two-factor interaction contrasts in absence/presence of blocking. Asterisks indicate cases where the number of estimable two-factor interaction contrasts is maximal. The superscript s indicates SOS treatment designs, while the superscript t indicates cases where OAs with a maximum r value cannot be blocked orthogonally.

N	Factors	#NI	# Estimable 2FI Contrasts	b	r	r_b
24	3×2^4	3	$14^2, 11^1$	4	14	14^*
	2^{12}	1	11^1	12	11^s	0^*
	2^{11}	1	11^1	12	11	0^*
27	3^4	1	18^1	9	18^s	10^*
32	$4^2 \times 2^4$	2	21^2	8	21^s	14^*

continued on next page

Table 6 (continued)

N	Factors	#NI	# Estimable 2FI Contrasts	b	r	r_b
	$4^2 \times 2^3$	2	21^2	8	21	15*
	4×2^7	8	21^8	8	21^s	14*
	4×2^6	11	$21^1, 20^8, 19^2$	8	20^t	15*
	2^{16}	5	15^5	16	15	0*
	2^{15}	5	15^5	16	15	0*
36	$3^2 \times 2^2$	3	13^3	6	13	13*
40	5×2^6	1	29^1	4	29^s	26*
	5×2^5	1	29^1	4	29	27*
	2^{20}	3	19^3	20	19^s	0*
	2^{19}	3	19^3	20	19	0*
48	$6 \times 4 \times 2^2$	3	$31^2, 29^1$	4	31	31*
	6×2^7	45	35^{45}	8	35^s	28*
	6×2^5	30	$34^1, 33^4, \ldots, 27^1$	8	34	30*
	$4 \times 3 \times 2^4$	19	$32^{14}, 31^5$	4	32	32*
	4×2^{11}	560	33^{560}	12	33^s	22*
	4×2^{10}	2217	$33^3, 32^{2212}, 31^2$	12	33	22
	3×2^9	3	36^3	8	36^s	29*
	3×2^7	3056	$35^{209}, 34^{299}, \ldots, 21^8$	8	35	31*
	2^{24}	60	23^{60}	24	23	0*
	2^{23}	130	23^{130}	24	23	0*
54	6×3^3	2	$40^1, 36^1$	9	40	34*
	$3^5 \times 2$	4	41^4	9	41	34*
	3^5	4	$39^1, 36^1, 35^1, 31^1$	18	35^t	20*
56	7×2^5	7	$40^4, 39^3$	4	40	40*
64	$8 \times 4 \times 2^2$	4	$41^3, 39^1$	8	41	41*
	8×2^7	924	49^{924}	8	49^s	42*
	8×2^5	192	$45^{13}, 44^{35}, \ldots, 37^1$	8	45	44*
	4^6	1	45^1	16	45^s	30*
	4^5	1	45^1	16	45	30
	$4^5 \times 2^2$	1	46^1	16	46^s	31*
	$4^5 \times 2$	1	45^1	16	45	30
	$4^4 \times 2^6$	1	45^1	16	45^s	30*
	$4^4 \times 2^5$	1	45^1	16	45	30
	$4^3 \times 2^8$	2	46^2	16	46^s	31*
	$4^3 \times 2^2$	107	$46^{17}, 45^{11}, \ldots, 37^3$	16	46	37*
	$4^2 \times 2^{12}$	2159	45^{2159}	16	45^s	30*
	$4^2 \times 2^5$	104949	$49^{3177}, 48^{16490}, \ldots, 31^2$	16	49	36
72	9×2^6	498	$57^{106}, 56^{186}, \ldots, 53^6$	4	57^s	54*
	9×2^5	96	$50^{77}, 49^{19}$	4	50	50*
	$6^2 \times 2^2$	6	$45^5, 43^1$	12	45	45*
	$6 \times 3 \times 2^4$	293	$44^{285}, 43^8$	12	44	44*
	$4 \times 3^2 \times 2$	18	23^{18}	6	23	23*
	$3^2 \times 2^{12}$	27	$55^1, 51^8, \ldots, 37^3$	12	51^t	44*
80	$5 \times 4 \times 2^6$	4814	$66^{93}, 65^{59}, \ldots, 57^1$	4	66^s	63*
	$5 \times 4 \times 2^5$	217319	$57^{210268}, 56^{5967}, \ldots, 47^1$	4	57	57*
81	9×3^4	2	64^2	9	64^s	56*
	9×3^3	3	$60^1, 58^1, 54^1$	9	58^t	58*
	3^{10}	1	60^1	27	60^s	inf
				9	60^s	52*

continued on next page

Table 6 (continued)

N	Factors	#NI	# Estimable 2FI Contrasts	b	r	r_b
	3^9	1	60^1	27	60	36^*

Table 6 includes the most challenging types of strength-3 OAs, namely the OAs involving the largest possible numbers of factors for a given number of levels. For example, the arrays of the type OA$(40; 5 \times 2^6)$ are included because six is the maximum number of two-level factors in an array of the type OA$(40; 5 \times 2^a)$. Many of the arrays in the table belong to the class of second order saturated (SOS) designs, meaning that the rank of their model matrix corresponding to a model with an intercept, all main effects and all two-factor interactions equals the number of runs (Cheng et al., 2008). Arranging such arrays in b blocks which are orthogonal to the main effects automatically reduces the number of estimable two-factor interaction contrasts by $b - 1$, independent of what blocking arrangement is used. SOS designs are therefore not suitable for evaluating the ability of the MILP approach to maximize the number of estimable two-factor interaction contrasts. Of course, the MILP approach remains useful as a technique to search for a blocking arrangement of SOS designs that allows independent main-effect estimates, which is a challenge in itself.

In Table 6, we indicate the types of OAs solely consisting of SOS designs by means of the superscript s. Whenever we encountered such a type of OAs, we also studied OAs of a similar kind but with fewer factors. In those cases, Table 6 also includes results for the non-SOS designs with the largest number of factors. For example, all arrays of the type OA$(48, 3 \times 2^9)$ are SOS designs. We therefore studied arrays with fewer two-level factors until we obtained designs which do not possess the SOS property. It turns out that the maximum number of two-level factors for which non-SOS designs exist is seven, which is why we have also studied arrays of the type OA$(48, 3 \times 2^7)$. As a matter of fact, there are 209 arrays of that type offering 35 estimable two-factor interaction contrasts, while 38 degrees of freedom are available after estimating the main effects and the block effects. In that case, arranging the OAs in b blocks does not necessarily lead to a decrease of $b - 1$ in the number of estimable two-factor interaction contrasts.

6.2 Blocking

In this section, we discuss the results of the MILP approach for blocking OAs as presented in Table 6. For each type of array, we determined the maximum number of blocks for which an orthogonal blocking arrangement could exist. We studied these cases because they are often the most challenging ones: it is generally harder to find optimal orthogonal blocking patterns for larger numbers of blocks. Moreover, as soon as a blocking arrangement with a large number of small blocks has been found, it is easy to construct orthogonal blocking arrangements with fewer blocks simply by merging blocks. For example, we were able to identify orthogonal blocking arrangements of arrays of the type $\mathrm{OA}(48, 6\times 2^7)$ involving eight blocks of six runs. Because merging blocks preserves orthogonality, blocking arrangements in four blocks of size 12 and two blocks of size 24 are feasible as well. Merging blocks generally leads to a large number of estimable two-factor interaction contrasts.

The number of blocks b for which we report optimal blocking arrangements is shown in the fifth column of Table 6. The table's last two columns, labeled r and r_b, show the number of estimable two-factor interaction contrasts in the absence of blocking and in the presence of blocking, respectively. Whenever $r - r_b < b - 1$, fewer than $b - 1$ estimable two-factor interaction contrasts have to be sacrificed to obtain a good blocking arrangement.

Some of the sets of OAs we explored contain very large numbers of arrays. It would be computationally expensive to apply the MILP approach to all the arrays in such a set. In these cases, we first applied the MILP approach to all OAs with a maximum r value, i.e. with the largest number of estimable two-factor interaction contrasts in the absence of blocking. In case the MILP model was infeasible for all of these OAs (meaning that no blocking arrangement exists that leads to independent main-effect estimates), we applied the MILP blocking approach to OAs with the next best value of r. For example, the array of the type $\mathrm{OA}(54, 3^5)$ with an r value of 39 cannot be orthogonally blocked when 18 blocks of size three are desired. Therefore, we tried to block the array with an r value of 36 into 18 blocks. As this also failed, we continued with the array that has an r value of 35. For this array, the MILP approach did yield an orthogonal blocking arrangement in 18 blocks of size three, offering 20 estimable two-factor interaction contrasts. We also applied the MILP approach to arrays with the next best value of r when arrays with the maximum value for

r did not yield a blocking arrangement that reaches the following upper bound for r_b:

$$UB = \min \left\{ r, N - \left[b + \sum_{i=1}^{m} (s_i - 1) \right] \right\}, \tag{1}$$

where N is the number of runs, m is the number of factors, b is the number of blocks, and s_i is the number of levels of the i-th factor. For example, the optimal arrangement of the only array of the type $\text{OA}(32, 4 \times 2^6)$ with an r value of 21 in eight blocks of size four offers an r_b value of 14. The upper bound for r_b for this design is, however, 15. We therefore applied the MILP approach to an OA with an r value of 20 and this resulted in an 8-block design with r_b of 15. In Table 6, the superscript t indicates types of OAs where blocking the best OAs in terms of the r value did not lead to the best possible value for r_b.

Whenever, for a given OA, the MILP model turns out to be infeasible, this should not be interpreted as a failure of the MILP approach. It simply indicates that there exists no blocking arrangement for that OA for which the main effects are orthogonal to the blocks. This is because the MILP approach is an exact optimization method, unlike for instance the optimal design algorithm of Cook and Nachtsheim (1989) implemented in the SAS procedure OPTEX and used for the calcium fortification study. As an example, there is no way in which the single array of the type $\text{OA}(81, 3^{10})$ can be arranged into 27 blocks so that all main-effect estimates are independent. This explains the entry 'inf', short for infeasible, in Table 6 for that array. Note, however, that it is possible to block the array into nine blocks of nine runs. This demonstrates it is less challenging to find orthogonal blocking arrangements when there are fewer and larger blocks.

Ideally, the number of estimable two-factor interaction contrasts in the presence of blocking equals the number of estimable contrasts in the absence of blocking, in which case $r = r_b$. However, this equality cannot be achieved for many of the arrays in the table. For example, in the absence of blocking, the best arrays of the type $\text{OA}(48, 3 \times 2^7)$ offer 35 estimable two-factor interaction contrasts, and leave three degrees of freedom for estimating the error variance. Arranging that design in eight blocks requires estimation of seven block effects. Therefore, the best blocking arrangement in terms of estimability of two-factor interaction contrasts sacrifices the three degrees of freedom for estimating the error variance and the estimability of four two-factor interaction contrasts. The upper bound for the number of estimable two-factor interaction contrasts in the case of eight blocks is therefore 31. As the entry for arrays of the type OA$(48, 3 \times 2^7)$ in Table 6 shows, the MILP approach produced a blocking arrangement that reaches the upper bound for this case. The same goes for many other OA types listed in the table. We have indicated all these cases using an asterisk. The fact that there are many such cases is an indication that the MILP approach is very powerful. Note that, for some of these cases, $r = r_b$, so that no estimable two-factor interaction contrasts are lost due to the blocking.

The optimal arrangement of an array of the type OA$(54; 3^5)$ with an r value of 35 in 18 blocks offers 20 estimable two-factor interaction contrasts only, and therefore leaves six degrees of freedom for error variance estimation. This suggests that the MILP approach was not capable of finding the best possible blocking arrangement in terms of the number of estimable two-factor interaction contrasts. However, using the MCS algorithm of Schoen et al. (2010), we were able to confirm that there is only one possible way to extend the three-level array with an 18-level blocking factor so that the resulting array has strength 2. In other words, there is only one way to block the three-level array in 18 blocks. Therefore, the reported r_b value of 20 is the maximum one possible.

As noted by Schoen and Mee (2012), the two-level strength-3 OAs with N runs and $N/2$ or $N/2-1$ factors are all fold-over designs. For these arrays, the only blocks of size two that result in independent main-effect estimates are formed by grouping the fold-over or mirror image pairs. All two-factor interaction contrasts are then completely confounded with the blocks, so that r_b always equals zero. This can be seen in Table 6, for arrays of the types OA$(24; 2^{12})$, OA$(24; 2^{11})$, OA$(32; 2^{16})$, OA$(32; 2^{15})$, OA$(40; 2^{20})$, OA$(40; 2^{19})$, OA$(48; 2^{24})$ and OA$(48; 2^{23})$. In the Appendix, we show that, for any two-level fold-over design with a number of factors greater than or equal to $3N/8 + 1$ and greater than or equal to $N/2 - 4$, the only way to obtain arrangements involving four runs per block is to merge the blocks of size two.

Only five blocking arrangements reported in Table 6 do not have the maximum attainable r_b value. This indicates that the MILP model performed well over a wide range of cases. Four of the cases where r_b did not reach its upper bound involve 64-run arrays, namely those of the types OA$(64; 4^5)$, OA$(64; 4^5 \times 2)$, OA$(64; 4^4 \times 2^5)$ and OA$(64; 4^2 \times 2^5)$. The fifth such case involves 48 runs, one four-level factor and ten two-level factors.

7 Discussion

The construction of orthogonal blocking arrangements of a given strength-3 orthogonal array by MILP is preferable to using conventional methods for at least two reasons. First, the method explicitly requires orthogonal blocking. This feature is not shared by the other approaches we discussed. Using the benchmark techniques for regular designs based on more than one combinatorial interaction component requires a checking procedure. Using the benchmark optimal design technique to optimize the D-efficiency of a given orthogonal array with an additional blocking factor does not guarantee that 100% D-efficiency will be reached. Therefore, in the optimal design approach, the blocking is not necessarily orthogonal to the main effects.

The second reason to prefer the MILP approach is the fact that it directly minimizes the confounding between the two-factor interactions and the blocks. As a consequence, the resulting blocking arrangement preserves a large number of estimable two-factor interaction contrasts. This is accomplished by first minimizing the worst kind of confounding between the two-factor interaction contrasts and the blocks, and subsequently minimizing the total confounding. Even if not all the confounding between interaction contrasts and blocks can be removed, the interaction contrasts often remain estimable. This can be seen from Table 6, where, in all but five cases, the MILP approach was able to reach the upper bound on the number of estimable two-factor interaction contrasts in the presence of blocking.

We end this paper with two practical notes concerning our implementation of the MILP approach in PROC OPTMODEL of SAS®. First, the required branch-and-bound procedure may take a long time to find the optimal solution to the MILP model. Therefore, it might be wise to limit the execution time by providing the software with a maximum number of nodes or iterations, or a maximum running time. In that case, one should then accept that the program may stop before it obtains an optimal solution. However, 2000 nodes sufficed to obtain an optimal solution in almost all cases we studied. This is because the branch-and-bound procedure seems capable of finding an optimal solution relatively fast, and the bulk of the computing time serves to confirm that that solution is indeed optimal. Finally, in most of the cases studied here, the two-factor interaction contrast matrix $\mathbf{W}$ is not of full rank. Removing columns so that a matrix of full rank, r, results or replacing the matrix $\mathbf{W}$ with the matrix of r principal components also did not not result in an improved performance.

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Appendix. Arranging Two-Level Fold-Over Designs in Blocks of Size Four

In this appendix, we consider orthogonal blocking of an N-run two-level fold-over design with m factors in blocks of size four. Fold-over designs exist for $m \leq N/2$. We can always obtain orthogonal blocks of size four by placing two fold-over or mirror image pairs in each block. We prove that this is the only way to obtain blocks of this size whenever the number of factors, m, satisfies

$$m \geq \max(\frac{N}{2} - 4, \frac{3N}{8} + 1). \tag{2}$$

Consider a strength-3 orthogonal array of the type $\text{OA}(N; 2^n)$ with $n = N/2$. Denote the design by $\mathbf{D}$ and assume that the factor levels are $+1$ or -1. Butler (2004) shows that $\mathbf{D}$ must be a fold-over design. Therefore, we can re-order the runs of $\mathbf{D}$ so that

$$\mathbf{D} = \begin{pmatrix} \mathbf{H} \\ -\mathbf{H} \end{pmatrix}, \tag{3}$$

where $\mathbf{H}$ is a Hadamard matrix of order n, normalized in such a way that the entries of its first column are all $+1$. Because $\mathbf{H}'\mathbf{H} = n\mathbf{I}_n$ for any Hadamard matrix, we also have that $\mathbf{H}\mathbf{H}' = n\mathbf{I}_n$. Hence, the rows of a Hadamard matrix are orthogonal, so that the Hamming distance between any two different rows of $\mathbf{H}$ is $n/2$. Therefore, the Hamming distance between any two rows of $\mathbf{D}$ is either $n/2$ or n. The distance is n if both rows are each other's mirror images. The distance is $n/2$ if the two rows are either both in $\mathbf{H}$ or both in $-\mathbf{H}$. The distance is also $n/2$ if one of the rows is in $\mathbf{H}$ and the other is in $-\mathbf{H}$, but the rows are not mirror images. This is because we can split $\mathbf{D}$ according to a column other than the first, for which the two rows have the same entry. In the newly split matrix, which also consists of a Hadamard matrix and its negative, the two rows are in the same half of the design. The Hamming distance between them is therefore $n/2$.

Now, consider a strength-3 orthogonal array $\mathbf{B}$ of the type $\text{OA}(N; 2^m)$ with $N/3 \leq m \leq N/2$. According to Butler (2004), the design $\mathbf{B}$ is also a fold-over design. Therefore, $\mathbf{B}$ can be written as

$$\mathbf{B} = \begin{pmatrix} \mathbf{A} \\ -\mathbf{A} \end{pmatrix}. \tag{4}$$

Vijayan (1976) and Bulutoglu and Kaziska (2009) show that, for $m \geq n-4$, $\mathbf{A}$ is a projection of some Hadamard matrix of order n. So $\mathbf{A}$ can be obtained by removing $(n-m)$ factors from a Hadamard matrix. If $\mathbf{a}$ and $\mathbf{b}$ are two different rows of $\mathbf{B}$ and $\mathbf{a} \neq -\mathbf{b}$, then

$$H_{ab} \in \{n/2, n/2-1, \ldots, m-n/2\}, \tag{5}$$

where H_{ab} is the Hamming distance between these rows. We call $m \geq n-4$ the Hadamard bound.

Because $\mathbf{B}$ is a fold-over design, orthogonal blocks of size two can only be obtained by using fold-over pairs as blocks. If blocks of size four are required, merging pairs of blocks of size two will satisfy the orthogonality requirement. We now establish a lower bound on m for which this is the only possible way to construct orthogonal blocks of size four.

Because of the level balance within each block required by orthogonal blocking, each block of size four must contain two rows from $\mathbf{A}$, say $\mathbf{w}$ and $\mathbf{x}$, and two rows of $-\mathbf{A}$, say $\mathbf{y}$ and $\mathbf{z}$. If $\mathbf{y}$ and $\mathbf{z}$ must be the mirror images of $\mathbf{w}$ and $\mathbf{x}$, then the orthogonal blocks can only be constructed by merging two blocks of size two, i.e. by grouping two fold-over pairs for each block of size four.

We represent the four rows and their pairwise sums as

$$\begin{array}{rlcllll} & \mathbf{w} & : & w_1 & w_2 & \cdots & w_m \\ + & \mathbf{x} & : & x_1 & x_2 & \cdots & x_m \\ \hline & \mathbf{w}+\mathbf{x} & : & p_1 & p_2 & \cdots & p_m \end{array}$$

and

$$\begin{array}{rlcllll} & \mathbf{y} & : & y_1 & y_2 & \cdots & y_m \\ + & \mathbf{z} & : & z_1 & z_2 & \cdots & z_m \\ \hline & \mathbf{y}+\mathbf{z} & : & s_1 & s_2 & \cdots & s_m \end{array}$$

By the requirement that the blocking factor must be orthogonal to the treatment factors, $p_i + s_i$ must be zero for all $i = 1, 2, \ldots, m$. Moreover, the values of p_i and s_i are necessarily either -2, 0, or $+2$. We consider each of these cases separately.

- If $p_i = -2$, $w_i = x_i = -1$. This implies that $s_i = +2$. Therefore, $y_i = z_i = +1$. Hence, $y_i = -w_i$ and $z_i = -x_i$.

- If $p_i = +2$, $w_i = x_i = +1$, $s_i = -2$, and $y_i = z_i = -1$. Hence, $y_i = -w_i$ and $z_i = -x_i$.

- If $p_i = 0$, $w_i = -x_i$. Therefore, $s_i = 0$ and $y_i = -z_i$.

Because of the last case, it does not necessarily follow that $\mathbf{y} = -\mathbf{w}$ and $\mathbf{z} = -\mathbf{x}$. However we now show that this is the only possibility for $m \geq \max(n-4, \frac{3N}{8}+1)$. Assume that $\mathbf{y}$ and $\mathbf{z}$ are not the mirror images of $\mathbf{w}$ and $\mathbf{x}$. Because $\mathbf{w}$ and $\mathbf{x}$ come from the same part of $\mathbf{B}$, we have that

$$H_{wx} \in \{n/2, n/2-1, \ldots, m-n/2\}\,. \tag{6}$$

Suppose that $H_{wx} = k$ and that we rearrange the columns of $\mathbf{B}$ such that $p_1 = \ldots = p_k = 0$ and $|p_{k+1}| = \ldots = |p_m| = 2$. This results in the following layout of the rows $\mathbf{w}, \mathbf{x}, \mathbf{y}$, and $\mathbf{z}$:

$$\begin{array}{llllllll}
\mathbf{w} & : & w_1 & \ldots & w_k & w_{k+1} & \ldots & w_m \\
\mathbf{x} & : & x_1 = -w_1 & \ldots & x_k = -w_k & x_{k+1} = w_{k+1} & \ldots & x_m = w_m \\
\mathbf{y} & : & y_1 & \ldots & y_k & y_{k+1} = -w_{k+1} & \ldots & y_m = -w_m \\
\mathbf{z} & : & z_1 = -y_1 & \ldots & z_k = -y_k & z_{k+1} = -w_{k+1} & \ldots & z_m = -w_m
\end{array}$$

Let $\mathbf{w}^* = (w_1, \ldots, w_k)$, and define $\mathbf{x}^*, \mathbf{y}^*$, and $\mathbf{z}^*$ similarly. We establish the following results:

- $H_{wx} = H_{w*x*} = k$.

- $H_{yz} = H_{y*z*} = k$.

- $y_i = -w_i$ for $i = k+1, \ldots, m$. Therefore, $H_{wy} = H_{w*y*} + m - k$. Further, because $\mathbf{y}$ is not the mirror image of $\mathbf{w}$, $H_{wy} < m$. This implies that $H_{w*y*} < k$ and $H_{w*z*} > 0$. Analogously, $H_{w*z*} < k$ and $H_{w*y*} > 0$. Therefore, $(m-k) < H_{wy} < m$ and $0 < H_{w*y*} < k$. In other words, $H_{w*y*} \in \{1, \ldots, k-1\}$.

- $H_{w*y*} = H_{wy} - m + k$. Combining this equality with Equation (5) results in $H_{w*y*} \in \{k - n/2, \ldots, n/2 - m + k\}$.

- $H_{xy} = H_{x*y*} + m - k = k - H_{w*y*} + m - k = m - H_{w*y*}$. Therefore, $H_{w*y*} = m - H_{xy}$. Combining this equality with Equation (5) results in $H_{w*y*} \in \{m - n/2, \ldots, n/2\}$.

Now, if we define S_1, S_2 and S_3 to be $\{1, \ldots, k-1\}$, $\{k - n/2, \ldots, n/2 - m + k\}$ and $\{m - n/2, \ldots, n/2\}$, respectively, the previous results can be summarized as

$$H_{w*y*} \in S_1 \cap S_2 \cap S_3. \tag{7}$$

In the following table, we show how the possible values for H_{w*y*} depend on the value of $k = H_{wx}$:

k	$S_1 \cap S_3$	$S_2 \cap S_3$
$n/2$	$\{1, \ldots, n-m\}$	$\{m - n/2, \ldots, n/2 - 1\}$
$n/2 - 1$	$\{1, \ldots, n - m - 1\}$	$\{m - n/2, \ldots, n/2 - 2\}$
$m - n/2 + 1$	$\{1\}$	$\{m - n/2\}$
$m - n/2$	$\emptyset$	$\emptyset$

The elements in both sets in each line of the table are ordered from small to large. When the two sets do not overlap, their intersection is an empty set. If each intersection results in an empty set, **y** and **z** cannot be mirror images of **w** or **z**. All the intersections are empty if $n - m < m - n/2$, or $m > 3n/4$. Therefore, $3n/4 + 1$ is a lower bound on the number of factors m for which orthogonal blocks of size four can only be constructed by merging fold-over pairs.

Combining this lower bound with the Hadamard bound, we obtain that

$$m \geq \max(n - 4, \frac{3n}{4} + 1), \tag{8}$$

or

$$m \geq \max(\frac{N}{2} - 4, \frac{3N}{8} + 1). \tag{9}$$

In the following table, we list values for the lower bound on the number of factors for several run sizes. If, for instance, a 40-run design is used, 16 or more factors are studied and blocks of size four are required, then the only possibility to obtained an orthogonally blocked design is by combining two fold-over pairs in each block.

Run Size	Number of Factors
24	10
32	13
40	16
48	20

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