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COMBINING TWO-LEVEL AND THREE-LEVEL ORTHOGONAL ARRAYS FOR FACTOR SCREENING AND RESPONSE SURFACE EXPLORATION

Hongquan Xu[1], Jessica Jaynes[1] and Xianting Ding[2]

University of California, Los Angeles[1] *and Shanghai Jiao Tong University*[2]

Abstract: Experimental design and analysis is an effective and commonly used tool in scientific investigations and industrial applications. Orthogonal arrays, such as factorial and fractional factorial designs, are popular experimental plans for identifying important factors. Motivated by an antiviral drug experiment, we introduce a new class of composite designs based on a two-level factorial design and a three-level orthogonal array. These designs have many desirable features and are effective for factor screening and response surface modeling. Some advantages are that they can use resolution IV designs in the screening stage, they can perform in-depth analyses, and they can be used in either a single or a sequential experiment. We study the construction method and compare the new composite designs with existing ones. We illustrate the methodology with data from an experiment that studies the effects of five antiviral drugs on the Herpes simplex virus type 1.

Key words and phrases: Composite design, drug combination, fractional factorial design, generalized minimum aberration, response surface methodology.

1. Introduction

In many experiments the researcher is faced with a number of factors that affect the response of interest. An appealing technique is the response surface methodology (Box and Wilson (1951)) that seeks to relate the response variable to several predictors through experimentation, modeling, data analysis, and optimization (Wu and Hamada (2009)). The initial stage of factor screening identifies important factors from a larger number of potential factors, typically using a two-level factorial or fractional factorial design, possibly with some center points. The second stage of sequential experimentation determines the optimum region, and the final stage fits a polynomial model in this region. The last stage often uses some second-order designs that allow the estimation of a second-order model. Many second-order designs have been proposed in the literature, the most popular are the central composite designs (CCD) introduced by Box and Wilson (1951) and variations such as the small composite designs of Draper and Lin (1990). Other second-order designs include those of Box and Behnken (1960),

augmented pairs designs (Morris (2000)), subset designs (Gilmour (2006)), and more. For a comprehensive account of response surface methodology, see Box and Draper (2007), Khuri and Cornell (1996), and Myers, Montgomery, and Anderson-Cook (2009).

Progress in science and technology often calls for innovation in methodological and theoretical development of experimental design. Since the successful demonstration of HIV treatment with drug combinations, combinatory drugs have been broadly applied to various aspects of disease treatment (De Clercq (2004)). The advantage of combinatory drugs is that they often have higher efficacy and lower drug dosages than individual drugs. However, it is challenging to identify potential drug combinations by trial and error because of the large number of possible combinations and the complexity of the underlying biological system. Researchers at UCLA Micro Systems Laboratories investigated a system with Herpes simplex virus type 1 (HSV-1) and six antiviral drugs: IFN-alpha (A), IFN-beta (B), IFN-gamma (C), Ribavirin (D), Acyclovir (E), and TNF-alpha (F). They chose seven dosage levels for each drug, which led to $7^6 = 117,649$ drug combinations. They used a feedback system control method to search for optimal drug combinations (Ding et al. (2012)). The search was stochastic and performed in iterations. Each iteration tested 32 drug combinations and took up to 4 days due to the preparation of cell culture and viral infection. Each virus and drug combination was performed in a test tube, the experimental unit. They conducted 21 iterations and found that the drug effects were nonlinear and non-additive and that there were complex drug interactions; however, they could not pinpoint drug interactions. One of the authors was consulted in order to understand the HSV-1 system and the interactions. Some standard designs such as fractional factorial designs and central composite designs were used for this purpose. After a few iterations, TNF-alpha (F) was found not effective in treating HSV-1 and dropped (Jaynes et al. (2013)). With consideration of experimental cost, time, and statistical efficiency, one of us constructed a composite design consisting of a 16-run factorial design with 2 levels and an 18-run orthogonal array with 3 levels. The resulting composite design had 3 levels and 34 runs so that the entire experiment could be conducted in one iteration. Two researchers conducted the experiment independently with different random orders, yielding two replicates. Table 1 shows the design and data of the experiment, where the run order was randomized. For each drug -1, 0, and 1 correspond to no drug, intermediate drug dosage, and high drug dosage, respectively. The observed data, readout, were the percentage of infected cells after the combination drug treatment. Ding et al. (2012, 2013) and Jaynes et al. (2013) gave details of the experimental procedure and other technical issues.

Table 1. Design and data of the antiviral drug experiment.

	Factor					Readout	
Run	A	B	C	D	E	Replicate 1	Replicate 2
1	1	−1	−1	−1	−1	69.8	72.0
2	−1	1	−1	−1	−1	66.4	67.4
3	−1	−1	1	−1	−1	83.0	68.6
4	−1	−1	−1	1	−1	16.2	23.4
5	−1	−1	−1	−1	1	46.1	33.6
6	1	1	1	−1	−1	68.6	65.5
7	1	1	−1	1	−1	6.8	7.2
8	1	1	−1	−1	1	15.6	19.1
9	1	−1	1	1	−1	11.1	7.0
10	1	−1	1	−1	1	19.8	20.3
11	1	−1	−1	1	1	3.7	4.7
12	−1	1	1	1	−1	5.8	3.9
13	−1	1	−1	1	1	2.6	4.0
14	−1	1	1	−1	1	42.2	23.2
15	−1	−1	1	1	1	1.8	5.2
16	1	1	1	1	1	3.1	3.4
17	−1	−1	−1	−1	−1	78.6	81.9
18	0	0	0	0	0	13.3	16.7
19	1	1	1	1	1	3.4	3.8
20	−1	−1	0	0	1	21.4	25.2
21	0	0	1	1	−1	8.6	4.4
22	1	1	−1	−1	0	18.0	27.3
23	−1	0	−1	1	0	7.3	2.4
24	0	1	0	−1	1	17.9	23.7
25	1	−1	1	0	−1	52.9	54.3
26	−1	1	1	0	0	13.2	8.8
27	0	−1	−1	1	1	2.1	4.5
28	1	0	0	−1	−1	73.4	73.9
29	−1	0	1	−1	1	19.6	14.6
30	0	1	−1	0	−1	59.1	41.7
31	1	−1	0	1	0	1.4	2.6
32	−1	1	0	1	−1	7.3	4.8
33	0	−1	1	−1	0	22.3	24.0
34	1	0	−1	0	1	14.1	18.3

Motivated by this, we introduce a new class of composite designs that combine a two-level factorial or fractional factorial design and a three-level orthogonal array, and refer to them as *orthogonal-array composite designs* (OACD). An orthogonal array of N runs, k columns, s levels, and strength t, denoted by $OA(N, s^k, t)$, is an $N \times k$ matrix in which all s^t level combinations appear equally often in every $N \times t$ submatrix. The strength t is often omitted when $t = 2$. Or-

thogonal arrays, including factorial or fractional factorial designs, are used in various applications. Hedayat, Sloane, and Stufken (1999) has a full account of the theory and application of orthogonal arrays. The current research is inspired by the recent developments in the study of nonregular fractional factorial designs; see Xu, Phoa, and Wong (2009) for a comprehensive review.

There are numerous applications using either 2-level factorial designs or 3-level orthogonal arrays; see Box, Hunter, and Hunter (2005), Dean and Voss (1999), Mee (2009), Montgomery (2009), and Wu and Hamada (2009) for examples. However, there are few published applications using both a 2-level factorial design and a 3-level orthogonal array in a single experiment. The goal here is to introduce the idea of combining two- and three-level designs and to provoke future research in the area. In Section 2 we formally introduce the concept of OACDs and explore their properties. Advantages include the ability of using resolution IV designs for factor screening, the ability of in-depth analyses, and the capability for sequential experimentation. In Section 3 we study the construction of OACDs and present a list of designs with 3 to 10 factors. In Section 4 we compare OACDs with other composite designs in terms of such statistical properties as estimation efficiency and projections. In Section 5 we consider blocking an OACD in a sequential experiment and give conditions when an OACD can be orthogonally blocked. In Section 6 we analyze the data from the antiviral drug experiment; we fit three models using different parts of the data and compare the results. Section 7 gives a summary.

2. Orthogonal-array Composite Designs

We first give a general definition of composite designs. For k factors, denoted by $x_1, \ldots, x_k$, a composite design consists of: (i) n_c cube points $(x_1, \ldots, x_k)$ with all $x_i = -1$ or 1; (ii) n_a additional points with all $x_i = -\alpha, 0$ or α; (iii) n_0 center points with all $x_i = 0$. Note that the cube points have 2 levels and the additional points have 3 levels. A composite design has a total of $n_c + n_a + n_0$ points and has three or five different levels depending on whether $\alpha = 1$ or not. Two-level factorial or fractional factorial designs are often used as the cube points and referred to as the factorial portion. Box and Wilson (1951) and Box and Hunter (1957) originally proposed to use a full factorial or a fractional factorial design of resolution V in a central composite design (CCD). This can lead to a large number of runs when $k > 5$. To reduce the run sizes, Draper and Lin (1990) proposed small composite designs (SCD) by using Plackett-Burman designs as the factorial portion. In both CCD and SCD, $n_a = 2k$ axial points (with one of $x_i = \alpha$ or $-\alpha$ and all other $x_i = 0$) are chosen as the additional points. Morris (2000) introduced the augmented pairs design (APD) by adding one point for each pair of the cube points. An APD has $n_a = n_c(n_c - 1)/2$ additional points.

We propose to use runs of a 3-level orthogonal array as the additional points and refer to the resulting design as an OACD: an OACD is a composite design such that its n_a additional points form a 3-level orthogonal array. The design in Table 1 is a 34-run OACD with $n_c = 16, n_a = 18, n_0 = 0$ and $\alpha = 1$. The factorial portion (the first 16 runs) is a 2-level fractional factorial design with resolution V defined by $I = ABCDE$; the 18 additional runs form a 3-level orthogonal array with a center point (run 18) and no extra center point. We can construct many OACDs with different run sizes by combining readily available 2-level factorial designs and 3-level orthogonal arrays.

Composite designs are often used to fit a second-order model. For k quantitative factors, the second-order model is

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i=1}^{k-1} \sum_{j=i+1}^{k} \beta_{ij} x_i x_j + \epsilon, \tag{2.1}$$

where $\beta_0, \beta_i, \beta_{ii}$ and β_{ij} are the intercept, linear, quadratic and bilinear (or interaction) terms, respectively, and $\epsilon \sim N(0, \sigma^2)$ is the error term. For the quadratic terms β_{ii} to be estimable, all factors must have at least 3 levels. A design is called a *second-order design* if it allows all parameters in (2.1) to be estimated. The 34-run OACD given in Table 1 is a second-order design: we can use the 2-level factorial portion to estimate the linear effects and two-factor interactions among the factors, and use the 3-level orthogonal array to estimate linear and quadratic effects.

The OACD differs from the CCD or SCD in the way they choose the additional points. The CCD or SCD employs a one-factor-at-a-time approach for the additional points because each axial point has only one nonzero component. As a consequence, the axial points provide no information on bilinear (or interaction) terms; resolution IV designs cannot be used as the two-level portion. For this reason, the SCD must use a resolution III design as the factorial portion even if a resolution IV design with the same size exists. In contrast, the additional points in the OACD study the effects in a factorial fashion and provide new information on bilinear terms as well as linear and quadratic terms. One immediate benefit is that the OACD can use resolution IV designs as the two-level portion, important in a sequential experiment because the OACD can use a better design than the SCD in the initial stage. Thus, to study 6 factors in 16 runs, the OACD approach can use a resolution IV design while the SCD approach has to start with an inferior resolution III design even though a resolution IV design with the same size exists. A resolution IV design enables all linear effects to be estimated apart from any bilinear effects, whereas in a resolution III design some linear effects are fully aliased with bilinear effects. Resolution IV designs are generally

preferred to resolution III designs of the same size in the initial screening stage. In Section 4 we further demonstrate that using resolution IV designs instead of resolution III designs as the factorial portion leads to more efficient estimation, particularly the estimation of the linear effects.

Another reason for using an orthogonal array as the additional points is data analysis. The analysis of the initial screening stage can suggest some useful, but not conclusive, evidence on the significance of the effects. Even with the added runs the results may not be conclusive due to possible mistakes or errors in the experiment or variation of factors not used in the experiment. The OACD allows one to perform multiple analyses with different parts of the data for cross validation. One can perform separate analyses for the two-level factorial portion and the three-level orthogonal array (if both have at least 8 runs). For the two-level portion, one can use standard analysis techniques and fit a model with linear and bilinear terms. For the three-level orthogonal array, one can fit a model with linear and quadratic effects. One can further use all of the data and fit a second-order or other model to estimate linear, bilinear and quadratic terms. Then each of the linear effects is estimated three times and each of the bilinear and quadratic effects is estimated twice, and one can check the consistency of the estimations from the three models. If the data are reliable and the models are appropriate, we expect the estimates to be consistent across different models; a discrepancy indicates possible problems with the models or potential outliers. The OACD thus has the built-in ability to perform some cross validation on the data quality and analysis results. We illustrate this in Section 6 with the antiviral drug experiment.

Like the CCD, the OACD can be used in a single experiment or in a sequential experiment. An OACD can be used in two ways in a sequential experiment. We can use the 2-level factorial portion in the first stage for factor screening and add the 3-level orthogonal array in the last stage for response surface modeling. Alternatively, we can use the 3-level orthogonal array for screening linear and quadratic effects in the initial stage and add the two-level portion for exploring the bilinear effects in the last stage. This feature is particularly appealing in practice as many industrial and engineering experiments use 3-level orthogonal arrays under the name of the Taguchi method. For example, we can use the popular $OA(18, 3^7)$ to study 5 or 6 factors in the screening experiment and use a 8 or 16-run two-level factorial in a follow-up experiment. Cheng and Wu (2001) and Xu, Cheng, and Wu (2004) previously studied methods of using a single 3-level design for both factor screening and response surface exploration. Their designs are not intended for sequential experiments.

3. Construction of the OACD

To construct an OACD, we need to select a 2-level design and a 3-level orthogonal array. In many cases, several 2-level and 3-level designs are available and the choice of individual designs is important. A general guideline is that we use good or optimal 2-level and 3-level designs, then properly align their columns so that the resulting OACD has good or optimal properties with respect to some criterion of interest.

For the 2-level design, we can choose a 2^k full factorial (if $k \leq 4$) or a regular 2^{k-p} fractional factorial design. When choosing a regular fraction, we recommend a minimum aberration design (which always has maximum resolution). Wu and Hamada (2009) gave many minimum aberration designs, up to 128 runs. To have a smaller design, we can use Plackett-Burman designs as the factorial portion, see Draper and Lin (1990). We recommend the generalized minimum aberration criterion (Tang and Deng (1999); Xu and Wu (2001)) to choose columns among Plackett-Burman designs. The generalized minimum aberration criterion is an extension of the minimum aberration criterion and can screen out poor designs effectively. Generalized minimum aberration designs minimize the overall contamination of nonnegligible interactions on the estimation of main effects (Tang and Deng (1999); Xu and Wu (2001)) and tend to be model-robust under traditional model-dependent efficiency criteria (Cheng, Deng, and Tang (2002)).

For the 3-level portion, one can pick an orthogonal array that accommodates at least k 3-level factors and choose the minimum aberration or generalized minimum aberration subset. Once a 2-level and a 3-level design are chosen, they can be put together to form an OACD. For example, the 34-run OACD given in Table 1 is a simple combination of a minimum aberration 2_V^{5-1} design, $E = ABCD$, and a generalized minimum aberration five-column design that is a subdesign of the commonly used $OA(18, 3^7)$. The levels, $-1, 0$, and 1, in the 3-level orthogonal array can be rescaled to $-\alpha, 0$ and α if necessary.

The properties of the resulting design may depend on which 2-level column is aligned with which 3-level column. A naive approach that puts two designs together works well and resulting designs often have good properties when we combine optimal 2-level and 3-level designs. In some situations, one can improve the properties of resulting designs by carefully aligning 2-level and 3-level columns. Each OACD has a total $k!$ different column alignments. One approach, when k is small, is to search all $k!$ alignments and find an optimal column alignment with respect to some criterion. This exhaustive search can be time consuming and often unnecessary for large k, say $k > 10$. A second more practical approach is to try a number of random alignments and choose the best column alignment with respect to some criterion.

A 3-level orthogonal array may contain a center point already and the number of extra center points (n_0) can be as small as 0. When $\alpha = 1$, the 2-level design and the 3-level orthogonal array may have some common runs so that the resulting OACD has repeat runs; for example, runs 16 and 19 in Table 1 are the same. If desirable one can avoid any repeat runs by permuting the levels in some columns of the 2-level or 3-level design, but repeat runs are useful in estimating the pure error and therefore we recommend keeping them. Furthermore, keeping them allows separate analyses for the two-level and three-level data. In cases where the run size is critical, one can delete the repeat runs.

For comparison purposes in Section 4, we list two OACDs for $k = 3$ and three OACDs for $k = 4, \ldots, 10$ in Table 2. The first column in Table 2 corresponds to the number of factors, k. The next three columns correspond to the two-level factorial portion: the specific design used, the number of cube points (n_c), and the design generators or columns. Here a 2^k design is a full factorial and no generators or columns are given. A 2_r^{k-p} design is a regular fractional factorial design with k factors, each at two levels, consisting of 2^{k-p} runs, and of resolution r. The p generators are given in the fourth column. All the 2^{k-p} designs used in Table 2 have maximum resolution and minimum aberration. There are six cases where Plackett-Burman designs with 12 or 20 runs are used, and the fourth column shows the subset of the design. For convenience, the Plackett-Burman designs are given in the Appendix. The last two columns in Table 2 specify the 3-level orthogonal array: the specific design and the column choice. We use four commonly used orthogonal arrays of strength 2, namely $OA(9, 3^4)$, $OA(18, 3^7)$, $OA(27, 3^{13})$, and $OA(36, 3^{12})$; see the Appendix. The $OA(9, 3^4)$ and $OA(27, 3^{13})$ are regular fractional factorial designs. For convenience, we arrange $OA(27, 3^{13})$ according to Xu (2005) so that the first k columns form a minimum aberration design. All 3-level columns in Table 2, with the exception of $k = 6$, are chosen because they form a minimum aberration or generalized minimum aberration design. For $k = 6$, the generalized minimum aberration design from $OA(18, 3^7)$ consists of the column choice $(2 - 7)$; however, this choice does not lead to a second-order design when it is combined with the 12-run Plackett-Burman design. For this reason, we choose the first 6 columns.

We arrange the 3-level columns in Table 2 so that when the 2-level and 3-level designs are combined, the resulting OACD is optimal with respect to D-efficiency (defined in Section 4.2) under the second-order model. For example, consider the second design listed for $k = 5$ in Table 2. For the 2-level factorial portion we use a subset of a 12-run Plackett-Burman design with columns (1-5) and for the 3-level design we use an $OA(18, 3^7)$ with columns (2,5,3,4,6). The resulting OACD has maximum D-efficiency when columns (1,2,3,4,5) of the Plackett-Burman design are aligned with columns (2,5,3,4,6) of the $OA(18, 3^7)$, respectively.

Table 2. Some OACDs for $k = 3, \ldots, 10$.

	2-level factorial portion			3-level OA	
k	Design	n_c	Columns and generators	Design(n_a)	Columns
3	2^3	8	-	OA(9)	(1-3)
3	2^{3-1}_{III}	4	$C = AB$	OA(9)	(1-3)
4	2^4	16	-	OA(9)	(1-4)
4	PB(12)	12	(1-4)	OA(9)	(1,3,4,2)
4	2^{4-1}_{IV}	8	$D = ABC$	OA(9)	(1-4)
5	2^{5-1}_{V}	16	$E = ABCD$	OA(18)	(2-6)
5	PB(12)	12	(1-5)	OA(18)	(2,5,3,4,6)
5	2^{5-2}_{III}	8	$D = ABC, E = AB$	OA(18)	(2-4,6,5)
6	2^{6-1}_{VI}	32	$F = ABCDE$	OA(18)	(1-6)
6	PB(20)	20	(1-5,13)	OA(18)	(1,4,6,3,2,5)
6	PB(12)	12	(1-5,7)	OA(18)	(2,5,3,4,6,1)
7	2^{7-1}_{VII}	64	$G = ABCDEF$	OA(18)	(1-7)
7	2^{7-2}_{IV}	32	$F = ABCD, G = ABE$	OA(18)	(1,2,5,3,4,7,6)
7	PB(20)	20	(1-5,13,16)	OA(18)	(3,1,5,7,4,2,6)
8	2^{8-2}_{V}	64	$G = ABCDE, H = ABCF$	OA(27)	(1-8)
8	2^{8-3}_{IV}	32	$F = ABCD, G = ABE, H = ACE$	OA(27)	(1,3,4,5,2,7,8,6)
8	PB(20)	20	(1-5,13,16,15)	OA(27)	(6,3,8,4,2,1,7,5)
9	2^{9-2}_{V}	128	$H = ABCDE, J = ABCFG$	OA(27)	(1-9)
9	2^{9-3}_{IV}	64	$G = ABCDE, H = ABCF, J = ADF$	OA(27)	(1,3,8,2,6,7,5,4,9)
9	2^{9-4}_{IV}	32	$F = ABCD, G = ABE, H = ACE, J = ADE$	OA(27)	(5,6,1,7,2,4,9,3,8)
10	2^{10-3}_{V}	128	$H = ABCDE, J = ABCFG, K = ABDF$	OA(27)	(1-10)
10	2^{10-4}_{IV}	64	$G = ABCDE, H = ABCF, J = ADF, K = ABEF$	OA(27)	(5,6,8,2,3,4,10,7,9,1)
10	2^{10-5}_{IV}	32	$F = ABCD, G = ABE, H = ACE, J = ADE, K = BCDE$	OA(36)	(7,6,3,2,9,1,10,8,5,4)

We present two or three OACDs with different sizes in Table 2 for each k. We call them OACD X, OACD Y, and OACD Z, corresponding to the largest, the second largest, and the smallest run size, respectively. The three OACDs are chosen based on popular existing designs and run size consideration. In particular, for each k, the OACD X has a similar run size to the CCD and the OACD Z has a comparable run size to the SCD. It is possible to construct other OACDs with different sizes and properties, especially when $k \geq 6$, if we combine different 2-level or 3-level designs. In practice, one can choose or construct an OACD based on the consideration of the run size or design efficiency, which is to be discussed in the next session.

4. Comparisons with Existing Composite Designs

We compare the OACDs given in Table 2 with three classes of composite designs: the CCD, APD, and SCD. The factorial portion of the CCD is a minimal fractional factorial design (or full factorial plan) of resolution V in all k factors. In all cases, the CCD and OACD X have the same factorial portion. The factorial

Table 3. Comparison of the number of runs and degrees of freedom, with $n_0 = 5$.

	CCD		APD		SCD		OACD X		OACD Y		OACD Z	
k	N	df	N	df	N	df	N	df	N	df	N	df
3	19	4	15	4	15	4	22	7	18	4	-	-
4	29	4	41	8	21	4	30	6	26	7	22	5
5	31	4	41	6	27	4	39	6	35	6	31	6
6	49	4	41	4	33	4	55	5	43	5	35	5
7	83	4	41	4	43	4	87	4	55	4	43	5
8	85	4	83	4	57	4	96	4	64	4	52	5
9	151	4	83	4	63	4	160	5	96	4	64	4
10	153	4	83	4	73	4	160	4	96	4	73	4

portion used in the APD is the 8-run Plackett-Burman design for $k = 4, \ldots, 7$, and the 12-run Plackett-Burman design for $k = 8, \ldots, 10$; see Morris (2000). The factorial portion in the SCD is taken from a Plackett-Burman design according to Table 4 of Draper and Lin (1990). In the study performed by Morris (2000), the SCD for $k = 9$ was omitted due to singularity. We believe that the reason for the singularity is that Morris used a cyclical shift to the right when constructing Plackett-Burman designs, whereas Draper and Lin (1990) performed a cyclical shift to the left, which allows the SCD of 9 factors to be considered.

We need to specify the value of α and number of center points for comparison. Following Morris (2000), we choose $\alpha = 1$ so that all designs have 3 levels and are comparable, and five center points ($n_0 = 5$). Note that the number of center points is arbitrarily chosen, and can vary depending on the experimental requirements. As pointed out by Morris (2000), the choice of the number of center points can greatly influence the estimation efficiency of a design; however, the general relationship between designs remains roughly the same.

4.1. Number of runs and degrees of freedom

An important concern in the construction of experimental design is the trade-off between estimation efficiency and run size. Generally, a design with smaller number of runs is favorable due to cost; however, designs with a larger number of runs provide more efficiency. Table 3 compares the total number of runs, N, and the degrees of freedom, df, for replication for each design considered.

The CCD and OACD X have larger run sizes than other classes with the exception of $k = 4$ and 5, when the APDs have the largest run sizes. The SCD and OACD Z have smaller run sizes than others with the exception of $k = 3$ and 7.

All designs have at least 4 degrees of freedom for pure error estimation, corresponding to the original 5 center point replicates taken. Generally, the OACD X, Y, and Z have more degrees of freedom for error estimation than the other designs, hence have a larger number of runs.

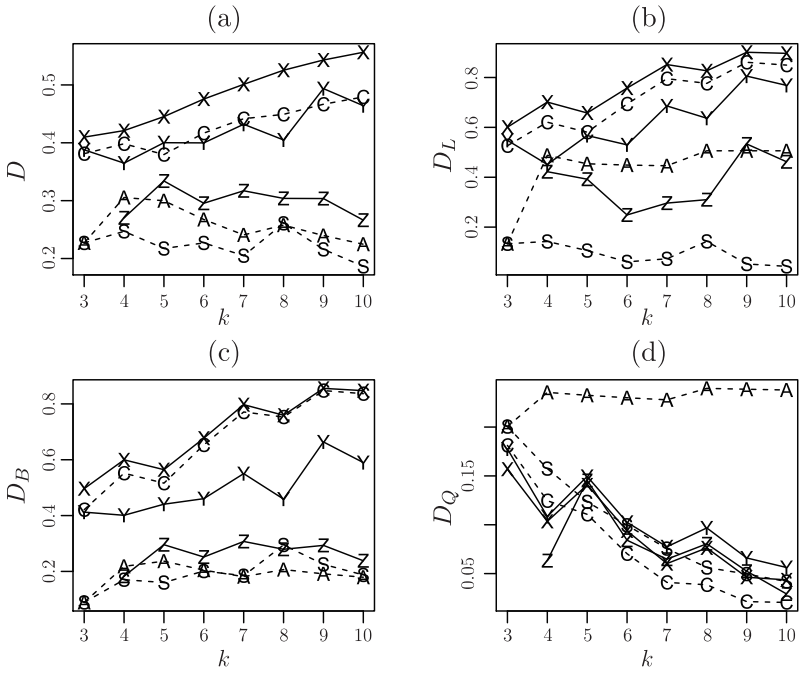

Figure 1. Efficiencies of composite designs with $n_0 = 5$: (a) D-efficiency; (b) D_L-efficiency; (c) D_B-efficiency; (d) D_Q-efficiency. Composite design (symbol): APD (A), CCD (C), SCD (S), OACD X (X), OACD Y (Y) and OACD Z (Z).

4.2. Model coefficient estimation

We compare design efficiencies in parameter estimation; D optimality is the popular choice in this. For an N-point design, if $\mathbf{X}$ is the model matrix of the second-order model (2.1) with $p = (k+1)(k+2)/2$ parameters, the (overall) D-efficiency is $D = N^{-1}|\mathbf{X}'\mathbf{X}|^{1/p}$, describing the information per run for the design. For s, a subset of factors, the D_s-efficiency is

$$D_s = N^{-1}|\mathbf{X}_s^T\mathbf{X}_s - \mathbf{X}_s^T\mathbf{X}_{(s)}(\mathbf{X}_{(s)}^T\mathbf{X}_{(s)})^{-1}\mathbf{X}_{(s)}^T\mathbf{X}_s|^{1/q},$$

where $\mathbf{X}_s$ and $\mathbf{X}_{(s)}$ are the submatrices of $\mathbf{X}$ corresponding to the parameters in s and not in s, respectively, and q is the number of parameters in s.

We divide the model parameters into three groups: the k linear parameters $(\beta_i, i = 1, \ldots, k)$, the $k(k-1)/2$ bilinear parameters $(\beta_{ij}, 1 \le i < j \le k)$, and the k pure quadratic parameters $(\beta_{ii}, i = 1, \ldots, k)$. For each subset of the model parameters we compute the D_s-efficiency, D_L, D_B, and D_Q, say.

Figure 1 shows a graphical representation of the D-efficiencies of the designs under consideration for $k = 3, \ldots, 10$. Figure 1(a) compares overall D-efficiency

for all designs. Generally, OACD X has the highest D-efficiency, followed by CCD and OACD Y. The overall D-efficiency for OACD Z is higher than the APD and SCD, except for $k = 4$. Figure 1(b) shows D_L-efficiency. The general pattern is similar to the overall D-efficiency considered in Figure 1(a): the OACD X has the highest efficiency followed by the CCD and then the OACD Y. Figure 1(c) shows D_B-efficiency. The OACD X has slightly higher D_B-efficiency than the CCD, followed by the OACD Y; the OACD Z, APD, and SCD are similar in their efficiencies. Figure 1(d) shows D_Q-efficiency. For all k, the APD has the highest efficiency, with the exception of $k = 3$, where the SCD performs just as well. The other designs are all comparable.

For the OACDs in Table 2, the 2-level and 3-level columns are aligned to maximize overall D-efficiency. For OACD X, the D-efficiency is invariant under the column alignment since $\mathbf{X}'\mathbf{X}$ does not depend on the 2-level design when it is a full factorial or has resolution V. For OACD Y and Z, the D-efficiency could be reduced, often slightly, with a random alignment; however, a few alignments could result in designs with D-efficiency of 0 for the OACD Y with $k \geq 8$ and the OACD Z with $k \geq 6$, due to small run sizes.

Among the three types of OACDs in Table 2, OACD X has the highest efficiency and largest run size, and OACD Z has the smallest run size and lowest efficiency. If the primary goal is precise estimation, OACD X is recommended; if the runs are expensive and a small design is desirable, OACD Z is recommended. The OACD Y compromises on run size and design efficiency and could be a better choice in other situations.

The original 34-run OACD used in the antiviral experiment was OACD X for $k = 5$. The comparison in Figure 1 confirms that the 34-run OACD is more effective than the CCD or other designs in estimating the parameters.

4.3. Projection properties

An OACD has a simple and appealing structure when it is projected onto any two factors. The two-level portion produces four corner points $(\pm 1, \pm 1)$, each replicated $n_c/4$ times. When $\alpha = 1$, the three-level orthogonal array generates four corner points, four mid-side points $(0, \pm 1)$ or $(\pm 1, 0)$, and one center point $(0, 0)$, each replicated $n_a/9$ times.

Figure 2 gives a graphical representation of the projection properties for the six designs for $k = 4$, with $n_0 = 0$: CCD, APD, SCD, OACD X, OACD Y, and OACD Z. Each plot shows the number of design points in each corner, mid-side, and center, in a two-dimensional projection. Roughly speaking, more design points located at the corners lead to higher D, D_L and D_B efficiency, while more design points located at the mid-sides and center increase quadratic efficiency. The OACDs have relatively more corner points and less center point replicates

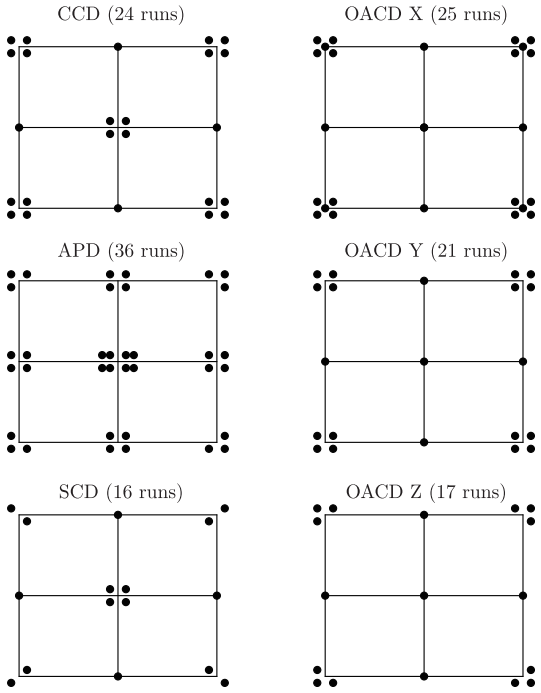

Figure 2. Projection properties of composite designs in four factors, with $n_0 = 0$.

than CCD, APD, and SCD. This is desirable for achieving high overall efficiency. The APD has more mid-side points than any of the other designs, which explains why the estimates for the quadratic effects are more efficient.

5. Blocking the OACD

When OACDs are used in a sequential experiment, it is important to know how blocking affects the design properties and efficiency. A second-order design is said to *block orthogonally* if it is divided into blocks in such a manner that block effects do not affect the usual estimates of the parameters of the second-order model.

Box and Hunter (1957) showed that, in general, for a second order composite design to block orthogonally with N number of points assigned to b blocks with n_w points in the wth block, two conditions must hold.

1. Each block is a first-order orthogonal design, so,

$$\sum_{u=1}^{n_w} x_{iu}x_{ju} = 0, \qquad i \neq j = 0, 1, \ldots, k, \qquad \text{for all } w,$$

where x_{iu} and x_{ju} are the levels of the ith and jth variables in the uth run of the wth block with $x_{0u} = 1$ for all u.

2. The fraction of the total sum of squares for each variable contributed by every block is equal to the fraction of the total observations that occur in the block, so,

$$\frac{\sum_{u=1}^{n_w} x_{iu}^2}{\sum_{u=1}^{N} x_{iu}^2} = \frac{n_w}{N}, \qquad i = 1, 2, \ldots, k, \qquad \text{for all } w.$$

These conditions can be used to orthogonally block an OACD. For simplicity, we consider arranging an OACD in two blocks. The first block consists of a two-level fractional factorial design (with n_c runs) plus n_{c0} center points, and the second block consists of a three-level orthogonal array (with n_a runs) plus n_{a0} center points. The first condition is always valid because the fractional factorial and additional points are orthogonal. The second condition is equivalent to

$$\alpha = \sqrt{\frac{3n_c(n_a + n_{a0})}{2n_a(n_c + n_{c0})}}. \tag{5.1}$$

We obtain orthogonal blocking if we choose α according to (5.1), and, in particular, when $n_{a0} = n_{c0} = 0$, the choice of $\alpha = \sqrt{3/2}$ yields an orthogonal blocking.

6. Analysis of the Antiviral Drug Experiment

Here we illustrate the analysis strategy for the OACD with the antiviral drug experiment in Table 1. Following Ding et al. (2013), in the analysis we use the square root of the readout as the response so that the usual assumptions on the error are reasonable. We include a blocking variable (*replicate*) in the model to assess possible effects from the two researchers. It is coded as -1 for replicate 1 and 1 for replicate 2.

We began the analysis by fitting a standard second-order model plus the blocking variable using all of the data to estimate the linear, bilinear, and quadratic effects. The model fit the data very well with $R^2 = 0.96$. To verify that this is a reasonable model, we broke the data into the first 16 and the last 18 runs. For the two-level 16-run design we fit a model containing all linear and bilinear effects. For the 18-run orthogonal array we fit a model with all linear and pure quadratic terms. To distinguish the three models, we use the run sizes and refer to them as 34-run, 16-run, 18-run models, respectively. Table 4 shows the estimates of the parameters for the three models. Each linear effect is estimated three times and each bilinear and quadratic effect is estimated

Table 4. Estimates of parameters for the HSV-1 data.

	34-Run	16-Run	18-Run
Intercept	3.99 ***	4.61***	3.62***
A	-0.13	-0.27**	0.18
B	-0.23**	-0.28 **	-0.42*
C	-0.20*	-0.14	-0.39*
D	-2.07***	-2.15***	-1.97***
E	-1.22***	-1.11***	-1.31***
AB	0.12	0.14	-
AC	0.26**	0.16	-
AD	0.08	0.18	-
AE	-0.13	-0.11	-
BC	0.14	0.27**	-
BD	-0.09	-0.07	-
BE	0.13	0.13	-
CD	-0.11	-0.13	-
CE	0.05	0.07	-
DE	0.54***	0.51***	-
A^2	0.26	-	0.38
B^2	0.09	-	0.22
C^2	-0.01	-	0.11
D^2	-1.17***	-	-1.07***
E^2	1.41***	-	1.47***
replicate	-0.03	-0.05	-0.01
$\hat{\sigma}$	0.55	0.48	0.78
R^2	0.96	0.98	0.92
df	46	15	24

NOTE: Significance levels are coded as 0 (***) 0.001 (**) 0.01 (*) 0.05.

twice. Among the three models, the 16-run model fits the 16-run data the best with $R^2 = 0.98$ while the 18-run model fits the worst with $R^2 = 0.92$. Figure 3 compares the absolute values of the t statistics for these three models, where the dashed and dotted lines correspond to a t value of 2 and 3, respectively.

Figure 3 clearly shows that the linear effects D and E, the bilinear effect DE, and the quadratic terms D^2 and E^2 are consistently the most significant (p value < 0.001) terms. With D, E, DE, D^2, and E^2 having estimates over the three models of approximately, -2, -1.2, 0.5, -1.1, and 1.4, respectively; see Table 4. The blocking variable (replicate) is not significant among all models, indicating that there was no significant difference between the two researchers.

We also observed some discrepancy among the estimates from different models. Among the bilinear effects, AC was significant (p value < 0.01) in the 34-run model only and BC was significant (p value < 0.01) in the 16-run model only. This was due to different data being used to fit different models with quite dis-

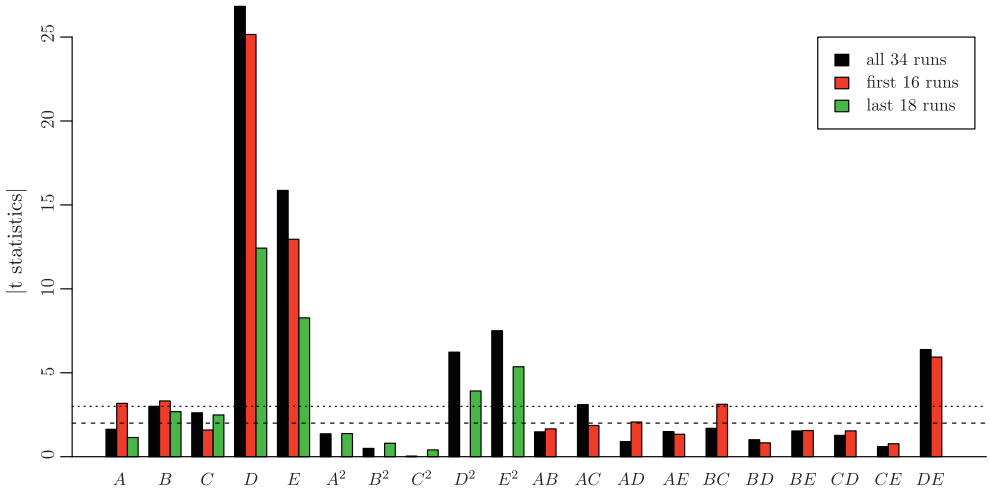

Figure 3. Analysis of the antiviral drug experiment.

tinct aliasing or correlation structure. Here AC and BC were highly correlated with the five extremely significant effects (D, E, DE, D^2, and E^2) in the full second-order model, whereas all estimates in the 16-run model were uncorrelated. Among the linear effects, A, B, and C were identified as significant at the 0.05 or 0.01 levels in one or more models. The estimates of A were negative in the 34-run and 16-run models, but the estimate was positive in the 18-run model. This discrepancy was caused by the significant bilinear terms not included in the 18-run model. When we fit a new model by adding the interaction DE in the 18-run model, the estimates of D and E remained unchanged and the estimates of A, B, and C were -0.01, -0.23 and -0.20, respectively, closer in value to the estimates in the 34-run and 16-run models. Further, the R^2 value in the 18-run design with DE included increased from 0.92 to 0.95 and the residual standard error ($\hat{\sigma}$) decreased from 0.78 to 0.60.

We performed residual analysis and found that replicate 1 of run 14 was an outlier. We refit the 34-run and 16-run models without it and found similar results with the addition that AB was significant in the 34-run model at the 0.05 level and AB and AC were significant in the 16-run model at the 0.05 level.

Overall, the data analysis identifies D and E as effective drugs, each having nonlinear (quadratic) effects on HSV-1. Drugs A, B, and C have some, but much smaller effects, than D and E. We further saw strong interaction between D and E, and some mild significant interactions among A, B and C. This can be explained by the fact that D and E are chemical drugs, while A, B, and C are Interferon protein drugs. The data suggest that the interactions within the Interferon and chemical drug groups are significant, which agrees with published

reports from clinical trials (Sainz and Halford (2002); Terzano, Petroianni, and Ricci (2004)). The data further suggest that the interactions between the two groups are small, implying possible distinct antiviral pathways between these two drug categories.

7. Summary

We propose a class of new composite designs, OACDs, and study the construction and properties. The OACDs provide a good trade-off between estimation efficiency and run size economy, and can be used as an alternative to the popular CCD and other existing composite designs.

We provide a general guideline in the construction of OACDs and present a collection of OACDs based on popular 2-level and 3-level designs. Our use of regular designs can be done with suitable nonregular designs. Nonregular designs are flexible in terms of run sizes and have many appealing properties (Xu, Phoa, and Wong (2009)), so we can construct a wide range of OACDs based on available nonregular designs. We will further explore the properties and use of these OACDs in the future.

Acknowledgements

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Appendix

PB(12)

Run	1	2	3	4	5	6	7	8	9	10	11
1	+	+	−	+	+	+	−	−	−	+	−
2	−	+	+	−	+	+	+	−	−	−	+
3	+	−	+	+	−	+	+	+	−	−	−
4	−	+	−	+	+	−	+	+	+	−	−
5	−	−	+	−	+	+	−	+	+	+	−
6	−	−	−	+	−	+	+	−	+	+	+
7	+	−	−	−	+	−	+	+	−	+	+
8	+	+	−	−	−	+	−	+	+	−	+
9	+	+	+	−	−	−	+	−	+	+	−
10	−	+	+	+	−	−	−	+	−	+	+
11	+	−	+	+	+	−	−	−	+	−	+
12	−	−	−	−	−	−	−	−	−	−	−

PB(20)

Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−
2	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+
3	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+
4	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−
5	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−
6	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−
7	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−
8	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+
9	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−
10	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+
11	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−
12	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+
13	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+
14	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+
15	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+
16	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−
17	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−
18	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+
19	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+
20	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

OA(9)

Run	1	2	3	4
1	−	−	−	−
2	−	0	0	+
3	−	+	+	0
4	0	−	0	0
5	0	0	+	−
6	0	+	−	+
7	+	−	+	+
8	+	0	−	0
9	+	+	0	−

OA(18)

Run	1	2	3	4	5	6	7
1	−	−	−	−	−	−	−
2	−	0	0	0	0	0	0
3	−	+	+	+	+	+	+
4	0	−	−	0	0	+	+
5	0	0	0	+	+	−	−
6	0	+	+	−	−	0	0
7	+	−	0	−	+	0	+
8	+	0	+	0	−	+	−
9	+	+	−	+	0	−	0
10	−	−	+	+	0	0	−
11	−	0	−	−	+	+	0
12	−	+	0	0	−	−	+
13	0	−	0	+	−	+	0
14	0	0	+	−	0	−	+
15	0	+	−	0	+	0	−
16	+	−	+	0	+	−	0
17	+	0	−	+	−	0	+
18	+	+	0	−	0	+	−

OA(27)

Run	1	2	3	4	5	6	7	8	9	10	11	12	13
1	−	−	−	−	−	−	−	−	−	−	−	−	−
2	−	−	0	0	−	+	0	+	+	−	0	0	+
3	−	−	+	+	−	0	+	0	0	−	+	+	0
4	−	0	−	0	+	0	−	0	+	0	0	+	−
5	−	0	0	+	+	−	0	−	0	0	+	−	+
6	−	0	+	−	+	+	+	+	−	0	−	0	0
7	−	+	−	+	0	+	−	+	0	+	+	0	−
8	−	+	0	−	0	0	0	0	−	+	−	+	+
9	−	+	+	0	0	−	+	−	+	+	0	−	0
10	0	−	−	0	0	0	0	−	0	0	−	0	0
11	0	−	0	+	0	−	+	+	−	0	0	+	−
12	0	−	+	−	0	+	−	0	+	0	+	−	+
13	0	0	−	+	−	+	0	0	−	+	0	−	0
14	0	0	0	−	−	0	+	−	+	+	+	0	−
15	0	0	+	0	−	−	−	+	0	+	−	+	+
16	0	+	−	−	+	−	0	+	+	−	+	+	0
17	0	+	0	0	+	+	+	0	0	−	−	−	−
18	0	+	+	+	+	0	−	−	−	−	0	0	+
19	+	−	−	+	+	+	+	−	+	+	−	+	+
20	+	−	0	−	+	0	−	+	0	+	0	−	0
21	+	−	+	0	+	−	0	0	−	+	+	0	−
22	+	0	−	−	0	−	+	0	0	−	0	0	+
23	+	0	0	0	0	+	−	−	−	−	+	+	0
24	+	0	+	+	0	0	0	+	+	−	−	−	−
25	+	+	−	0	−	0	+	+	−	0	+	−	+
26	+	+	0	+	−	−	−	0	+	0	−	0	0
27	+	+	+	−	−	+	0	−	0	0	0	+	−

OA(36)

Run	1	2	3	4	5	6	7	8	9	10	11	12
1	−	−	−	0	0	−	−	0	−	+	+	−
2	−	−	−	−	+	−	+	−	+	−	−	0
3	−	−	0	−	−	+	0	+	−	−	0	−
4	−	−	+	+	−	0	−	−	0	0	−	−
5	−	0	+	+	−	−	0	0	+	−	+	+
6	−	0	+	0	+	0	+	+	+	+	0	−
7	−	0	−	−	+	+	−	+	0	0	+	+
8	−	0	0	+	0	+	+	−	−	+	−	+
9	−	+	0	+	0	−	−	+	+	0	0	0
10	−	+	0	−	−	0	+	0	0	+	+	0
11	−	+	+	0	+	+	0	0	−	0	−	0
12	−	+	−	0	0	0	0	−	0	−	0	+
13	0	0	0	+	+	0	0	+	0	−	−	0
14	0	0	0	0	−	0	−	0	−	0	0	+

Run	1	2	3	4	5	6	7	8	9	10	11	12
15	0	0	+	0	0	−	+	−	0	0	+	0
16	0	0	−	−	0	+	0	0	+	+	0	0
17	0	+	−	−	0	0	+	+	−	0	−	−
18	0	+	−	+	−	+	−	−	−	−	+	0
19	0	+	0	0	−	−	0	−	+	+	−	−
20	0	+	+	−	+	−	−	0	0	−	0	−
21	0	−	+	−	+	0	0	−	−	+	+	+
22	0	−	+	0	0	+	−	+	+	−	−	+
23	0	−	−	+	−	−	+	+	0	+	0	+
24	0	−	0	+	+	+	+	0	+	0	+	−
25	+	+	+	−	−	+	+	−	+	0	0	+
26	+	+	+	+	0	+	0	+	0	+	+	−
27	+	+	−	+	+	0	−	0	+	+	−	+
28	+	+	0	0	+	−	+	+	−	−	+	+
29	+	−	0	0	+	+	−	−	0	+	0	0
30	+	−	0	−	0	−	0	0	0	0	−	+
31	+	−	+	+	0	0	+	0	−	−	0	0
32	+	−	−	0	−	0	0	+	+	0	+	0
33	+	0	−	0	−	+	+	0	0	−	−	−
34	+	0	−	+	+	−	0	−	−	0	0	−
35	+	0	0	−	0	0	−	−	+	−	+	−
36	+	0	+	−	−	−	−	+	−	+	−	0

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Department of Statistics, University of California, Los Angeles, CA 90095, USA.

E-mail: hqxu@stat.ucla.edu

Department of Statistics, University of California, Los Angeles, CA 90095, USA.

E-mail: jljaynes@ucla.edu

School of Biomedical Engineering, Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, 200030, China.

E-mail: dingxianting@sjtu.edu.cn

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