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Construction of Order-of-Addition-Orthogonal Array Designs

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Abstract

Experiments that account for sequential order of components are order-of-addition (OofA) experiments and a full design of such experiments requires $m!$ runs for any m components. Current literature focuses on the construction of fractional designs that are optimal and efficient under the models available to date. This paper provides a systematic construction method of order-of-addition orthogonal arrays (OofA-OA) which were proved as optimal fractional OofA designs. The number of independent, synergistic and antagonistic pairs possible for any m components is also determined. An important balance property of OofA-OA is also explained.

Key words: Order-of-addition; Orthogonal array; Pair-wise order model; Optimality.

1. Introduction

The sequence by which ingredients or components are added into a system may have some definite effect on the response or final output. Experiments that deal with such sequential order of adding components are termed as order-of-addition (OofA) experiments. In early research, designs for cross over experiments constructed by Williams (1949) in which each experimental unit will be given a set of m treatments in a sequential order, were extensively used for OofA experiments. Order-of-addition experiments have been applied in agriculture (Wagner, 1995), food science (Jourdain *et al.*, 2009), cell biology (Black *et al.*, 2001), medical biology (Ding *et al.*, 2015) and many other fields in order to explore the optimal order of components added into the system. These experiments have shown that qualitative and/or quantitative outcome may vary depending on the sequence in which ingredients were added. The foremost reference to an OofA experiment; "the lady tasting tea" wherein only two ingredients, tea and milk, for which the taste of final product was determined by the order in which the ingredients were added (Fisher, 1971). Karim *et al.* (2000) performed an OofA experiment to study the effect of cocoa flavonoids on the vasodilatory capacity of rabbits. Also in engineering, Wilson (2018) proposed an approach to compute the expected utility

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when the number of tasks to perform is too large and the sequencing of these tasks has some importance on the expected utility.

An OofA experiment involving m components yield $m!$ orders among which an optimal order has to be screened out using appropriate designs. We hereby call the ingredients or materials in an OofA experiment as components. Each order can be viewed as a permutation of m components, $m \geq 2$. A full design with all the $m!$ orders may not be possible to accommodate while designing the experiment when m is too large. For example, $m = 9$ gives 362,880 orders which is impossible to be contained in a single experiment. This makes us to choose a fraction or subset of the full design so that it may be accommodated in an experiment. Randomly choosing the orders from all the possible orders is relatively inefficient (Zhao *et al.*, 2020). There are many models developed so far for the experimentation of OofA problems. See Peng *et al.* (2019), Mee (2020) and Yang *et al.* (2021) for the models and related optimality proofs therein. An early model, pair-wise ordering (PWO) of effects proposed by Van Nostrand (1995) assumes that sequential order of components affects the response through pair-wise order effects or pseudo factor effects. The readers are referred to Lin and Peng (2019), Voelkel and Gallagher (2019), Tsai (2022), Zhao *et al.* (2020), Winker *et al.* (2020) and Chen *et al.* (2020) for the construction of PWO designs which satisfy efficiency, optimality and relatively smaller run size criterion.

Many designs were constructed for the OofA experiments under the PWO model. Among them, an optimal fractional design, order-of-addition-orthogonal array (OofA-OA) was introduced by Voelkel (2019). The concept behind orthogonal arrays (OA) were used to generate OofA-OA as there is a need to keep the balance while framing a design for OofA experiments. Zhao *et al.* (2021) proposed a systematic construction method for OofA-OAs which is regarded as superior among all the fractional PWO designs. Furthermore, Zhao *et al.* (2022) investigated the existence of OofA-OA with strength 3 and stated that OofA-OAs with strength 3 excel more in terms of balance properties than OofA-OAs with strength 2. In this paper, we propose a systematic method of constructing OofA-OA for any value of m from an existing OofA-OA with $m - 1$ components.

2. Preliminaries

Even though many models including component-position model by Yang *et al.* (2021) have been developed for OofA experimentation, PWO model is the most promising and acceptable model as it is simple and easy to understand. We consider PWO model for the current research. Let us suppose that there are m components which results in $m!$ orders, each of which is a permutation of these m components and it is denoted by $\mathbf{a} = (a_1, ..., a_m)^T$. Let us write OA_f to denote the full OofA design with $m!$ rows and m columns. If we denote y_k as the response due to kth order,

$$y_k = \beta_0 + \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} \beta_{ij} z_{ij} + \epsilon_k \tag{1}$$

where β_0 denotes the overall mean, β_{ij} is the PWO effects of ith and jth component, ϵ_k represents the error term with mean zero and constant variance. To better understand the PWO factors $z_{ij}(\mathbf{a})$ defined by Van Nostrand (1995), we suppose that $m = 3$ components and an order $1 \rightarrow 3 \rightarrow 2$, means 1st component followed by 3rd and 2nd components are added in succession, denoted as $\mathbf{a} = (1, 3, 2)$. Then, the PWO factors z_{ij} become $z_{12} = 1, z_{13} = 1, z_{23} = -1$. For denoting the PWO factors z_{ij}, two components are taken at a time from m components such that $1 \leq i < j \leq m$, yielding $\binom{m}{2}$ PWO factors. As there are $m(m-1)/2$ PWO factors and one general mean effect term in the model (1), $p = \binom{m}{2} + 1$ parameters have to be estimated from the model. Model (1) can be expressed in matrix form as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon} \tag{2}$$

A fractional OofA design d with run size n is said to be ϕ-optimal if its moment matrix $\mathbf{M} = \frac{1}{n}\mathbf{X}'\mathbf{X}$ (where $\mathbf{X}$ denotes the model matrix) is equal to the moment matrix of the full design. Interestingly, Peng *et al.* (2019) proved the optimality of full OofA design in terms of several popular optimality criteria. Additionally, Zhao *et al.* (2021) established that any ϕ-optimal fractional OofA design is certainly an OofA-OA.

We denote P_f as the full PWO design and P_d as the fractional PWO design where d denotes the fractional OofA design with run size n. Any pair of PWO factors (z_{ij}, z_{kl}) can be called as

Synergistic pair : if $i = k$ or $j = l$
Antagonistic pair : if $i = l$ or $j = k$
Independent pair : if $i \neq k, l$ or $j \neq k, l$ (no common component).

In a full PWO design, the frequencies of all t-tuples in any t column subarray for these different pairs are as follows. We denote n_{++} as the number of times $(+,+)$ happens in a pair of PWO factors (z_{ij}, z_{kl}). Similarly, n_{+-}, n_{--}, n_{-+} are also defined. For

Synergistic pair: $n_{++} = m!/3, n_{+-} = m!/6, n_{-+} = m!/6, n_{--} = m!/3$
Antagonistic pair: $n_{++} = m!/6, n_{+-} = m!/3, n_{-+} = m!/3, n_{--} = m!/6$
Independent pair: $n_{++} = m!/4, n_{+-} = m!/4, n_{-+} = m!/4, n_{--} = m!/4$

If the ratios among the frequencies of all t-tuples in any t column subarray of P_f equal to the ratios among the frequencies of all t-tuples in any t column subarray of P_d, then d is said to be the OofA-OA(N, m, t).

3. Construction of OofA-OA from an existing OofA-OA

In this section, a method of construction of OofA-OA with $m+1$ components from an OofA-OA with m components is described. As we know, the run size for an OofA-OA is a multiple of 12, the resulting design obtained will have a run size $12h(m+1)$ where $1 \leq h \leq (m!/12) - 1$. We denote the existing design d as OofA-OA$(12h, m, 2)$ and the resultant design d' as OofA-OA$(12h(m+1), m+1, 2)$.

Theorem 1: If there exists an OofA-OA for m components, an OofA-OA for $m+1$ components can be obtained from it by placing the $(m+1)$th component in every possible position of each run of the existing OofA-OA.

Table 1: An OofA-OA(12,5,2)

1	5	3	2	4
1	5	4	2	3
2	1	4	3	5
2	3	4	1	5
2	5	1	3	4
2	5	4	3	1
3	1	4	2	5
3	5	1	2	4
3	5	4	2	1
4	1	3	2	5
4	5	1	2	3
4	5	3	2	1

Proof: Adding $(m+1)$th component in $m+1$ positions of each run of the existing OofA-OA results in $m+1$ runs per existing run in the new design. Since we add $(m+1)$th component in every possible position of every run of the existing design, the ratio of frequencies among $n_{++}, n_{+-}, n_{--}, n_{-+}$ in any two columns of the new design d' will be,

$$\frac{n_{++}}{n_{--}} = 1$$

for any synergistic, antagonistic and independent pairs. Similarly, the ratio of

$$\frac{n_{++}}{n_{+-}} = \frac{n_{++}}{n_{-+}} = \frac{n_{--}}{n_{+-}} = \frac{n_{--}}{n_{-+}} = \begin{cases} 2, & \text{for any synergistic pair} \\ 1/2, & \text{for any antagonistic pair} \\ 1, & \text{for any independent pair} \end{cases}$$

These ratios are equal to that of full design P_f and hence are OofA-OA. This completes the proof. □

Example 1: Consider an OofA-OA(12,5,2) from which an OofA-OA for 6 components may be constructed. Table 1 displays the design of OofA-OA(12,5,2) and Table 2 shows the OofA-OA(72,6,2). Here $h = 1$ and the resulting design has run size 72. Here, the component 6 is added in every 6 positions of the OofA-OA(12,5,2) to generate OofA-OA(72,6,2).

As we know, an OofA design with m components has $\binom{m}{2}$ PWO factors and these PWO factors in an OofA-OA can be classified as synergistic pairs, antagonistic pairs and independent pairs. Theorem 2 states the number of synergistic, antagonistic and independent pairs possible for an OofA-OA with m components.

Theorem 2: An OofA-OA with m components have $\binom{\binom{m}{2}}{2} - 3\binom{m}{3}$ independent pairs, $\binom{m}{3}$ antagonistic pairs and $2\binom{m}{3}$ synergistic pairs.

Proof: For an m component OofA design, there are $\binom{m}{2}$ PWO factors under the PWO model. Total number of possible pairs of PWO factors are $\binom{\binom{m}{2}}{2}$ which include all the independent, synergistic and antagonistic pairs. Now, we determine the number of antagonistic

Table 2: An OofA-OA(72,6,2)

6 1 5 3 2 4	6 2 1 4 3 5	6 2 5 1 3 4	6 3 1 4 2 5
1 6 5 3 2 4	2 6 1 4 3 5	2 6 5 1 3 4	3 6 1 4 2 5
1 5 6 3 2 4	2 1 6 4 3 5	2 5 6 1 3 4	3 1 6 4 2 5
1 5 3 6 2 4	2 1 4 6 3 5	2 5 1 6 3 4	3 1 4 6 2 5
1 5 3 2 6 4	2 1 4 3 6 5	2 5 1 3 6 4	3 1 4 2 6 5
1 5 3 2 4 6	2 1 4 3 5 6	2 5 1 3 4 6	3 1 4 2 5 6
6 1 5 4 2 3	6 2 3 4 1 5	6 2 5 4 3 1	6 3 5 1 2 4
1 6 5 4 2 3	2 6 3 4 1 5	2 6 5 4 3 1	3 6 5 1 2 4
1 5 6 4 2 3	2 3 6 4 1 5	2 5 6 4 3 1	3 5 6 1 2 4
1 5 4 6 2 3	2 3 4 6 1 5	2 5 4 6 3 1	3 5 1 6 2 4
1 5 4 2 6 3	2 3 4 1 6 5	2 5 4 3 6 1	3 5 1 2 6 4
1 5 4 2 3 6	2 3 4 1 5 6	2 5 4 3 1 6	3 5 1 2 4 6
6 3 5 4 2 1	6 4 1 3 2 5	6 4 5 1 2 3	6 4 5 3 2 1
3 6 5 4 2 1	4 6 1 3 2 5	4 6 5 1 2 3	4 6 5 3 2 1
3 5 6 4 2 1	4 1 6 3 2 5	4 5 6 1 2 3	4 5 6 3 2 1
3 5 4 6 2 1	4 1 3 6 2 5	4 5 1 6 2 3	4 5 3 6 2 1
3 5 4 2 6 1	4 1 3 2 6 5	4 5 1 2 6 3	4 5 3 2 6 1
3 5 4 2 1 6	4 1 3 2 5 6	4 5 1 2 3 6	4 5 3 2 1 6

pairs. Let $(z_{ij}\ z_{kl})$ be an antagonistic pair for which $i = l$ or $j = k$ is possible. We generally write $(z_{ij}\ z_{kl})$ such that $i < j$ and $k < l$. Thus, only three distinct components are needed for forming an antagonistic pair. Now, 3 distinct components can be taken from m components in $\binom{m}{3}$ ways. Hence, number antagonistic pairs is $\binom{m}{3}$. For synergistic pair, $(z_{ij}\ z_{kl})$, there are two options: (i) $i = k$. If so there are only three components, *i.e.* i, j, l. (ii) $j = l$. If so there are only three components, *i.e.* i, j, k. For both these options, $\binom{m}{3}$ pairs are possible. So, $2\binom{m}{3}$ synergistic pairs are possible for m component OofA-OA. Therefore, number of independent pairs is $\binom{\binom{m}{2}}{2} - 3\binom{m}{3}$. This completes the proof. □

4. Some results on OofA-OA

An OofA-OA of run size N have the following property as specified in Theorem 3.

Theorem 3: If a fractional OofA design with run size N is an OofA-OA$(N, m, 2)$, then,
$n_{++} = n_{--} = N/3, n_{+-} = n_{-+} = N/6$ for any synergistic pair
$n_{++} = n_{--} = N/6, n_{+-} = n_{-+} = N/3$ for any antagonistic pair and
$n_{++} = n_{--} = N/4, n_{+-} = n_{-+} = N/4$ for any independent pair.

Proof: As there are four two-tuples $(++, --, +-, -+)$ in an OofA-OA of strength 2, for any independent pairs of PWO factors, the frequencies of these two-tuples will be same to satisfy the equality of ratio of frequencies of these two-tuples in an OofA-OA with respect to the full OofA design. Effortlessly, we can write, $n_{++} = n_{--} = n_{+-} = n_{-+} = N/4$ for any independent pair. Obviously, the minimum run size required for an OofA-OA of strength 2 is 12. An OofA-OA$(N, m, 2)$ will always be a multiple of 12 which means N is a multiple of 12. To satisfy the ratio mentioned in the proof of Theorem 1, again we need, $n_{++} = n_{--} = N/3, n_{+-} = n_{-+} = N/6$ for any synergistic pair and $n_{++} = n_{--} = N/6, n_{+-} = n_{-+} = N/3$

for any antagonistic pair. This confirms Theorem 3. $\square$

Theorem 4: For any OofA-OA $(N, m, 2)$, consider any two synergistic pairs $(z_{im}\ z_{jm})$ containing the mth component, the corresponding z_{ij} has the following symbols with frequency as given below

Two-tuples $(z_{im}\ z_{jm})$	z_{ij}	Frequency
$++$	$+$	N/6
$++$	$-$	N/6
$+-$	$+$	N/6
$-+$	$-$	N/6
$--$	$+$	N/6
$--$	$-$	N/6

Proof: For an OofA-OA$(N, m, 2)$, for any synergistic pair, $n_{++} = n_{--} = N/3, n_{+-} = n_{-+} = N/6$ according to Theorem 3. We can see that n_{++} and n_{--} for the two-tuples $(z_{im}\ z_{jm})$ is $n_{++} = n_{--} = 2\frac{N}{6} = N/3$. Now, if z_{im} is $+1$ and z_{jm} is -1, z_{ij} will be $+1$ and vice versa. For example, if $1 \rightarrow 5$, $z_{15} = +1$; $5 \rightarrow 2$, $z_{25} = -1$, then, $z_{12} = +1$. This completes the proof. $\square$

Example 2: Consider an OofA-OA (12,5,2) given in Voelkel (2019). The array is given in transpose form.

$$\begin{pmatrix} 1 & 1 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 4 & 4 & 4 \\ 5 & 5 & 1 & 3 & 5 & 5 & 1 & 5 & 5 & 1 & 5 & 5 \\ 3 & 4 & 4 & 4 & 1 & 4 & 4 & 1 & 4 & 3 & 1 & 3 \\ 2 & 2 & 3 & 1 & 3 & 3 & 2 & 2 & 2 & 2 & 2 & 2 \\ 4 & 3 & 5 & 5 & 4 & 1 & 5 & 4 & 1 & 5 & 3 & 1 \end{pmatrix}'.$$

The corresponding PWO matrix is given as

$$\mathbf{P} = \begin{array}{c} \begin{array}{cccccccccc} z_{12} & z_{13} & z_{14} & z_{15} & z_{23} & z_{24} & z_{25} & z_{34} & z_{35} & z_{45} \end{array} \\ \begin{pmatrix} + & + & + & + & - & + & - & + & - & - \\ + & + & + & + & + & - & - & - & - & - \\ - & + & + & + & + & + & + & - & + & + \\ - & - & - & + & + & + & + & + & + & + \\ - & + & + & - & + & + & + & + & - & - \\ - & - & - & - & + & + & + & - & - & - \\ + & - & + & + & - & - & + & + & + & + \\ + & - & + & - & - & + & - & + & + & - \\ - & - & - & - & - & - & - & + & + & - \\ + & + & - & + & - & - & + & - & + & + \\ + & + & - & - & + & - & - & - & - & + \\ - & - & - & - & - & - & - & - & - & + \end{pmatrix} \end{array}$$

The columns of $\mathbf{P}$ matrix are labelled as $z_{12}, z_{13}, z_{14}, z_{15}, z_{23}, z_{24}, z_{25}, z_{34}, z_{35}$ and z_{45} in the respective order. Consider the synergistic pair (z_{25}, z_{35}) and the frequencies of z_{23} along with the symbol, it is clear that some balance properties are followed as in Table 3.

Table 3: The frequencies of two-tuples of an OofA-OA(12,5,2)

Two-tuples (z_{25}, z_{35})	z_{23}	Frequency
$++$	$+$	2
$++$	$-$	2
$+-$	$+$	2
$-+$	$-$	2
$--$	$+$	2
$--$	$-$	2

It is very interesting to see that this property exists for any OofA-OA. According to Zhao *et al.* (2021), when an OofA-OA is projected onto any $s(\geq 4)$ components, all the $s!$ orders occur equal number of times. Even though, the OofA-OA given in example 2 does not obey order balance property as specified in Zhao *et al.* (2021), balancing of frequency of two-tuples given in Theorem 2 is satisfied. In other words, this property can be utilized to check if a given fractional OofA design is OofA-OA even if it does not satisfy the order balance property.

5. Concluding remarks

Being PWO model as the most promising and acceptable model for OofA problems, the fractional designs under this model which are optimal with regard to any popular optimality criteria has been of considerable interest to the researchers. The OofA-OA is such a fractional design under this model that satisfies D-, A-, M.S.- and χ^2- optimality criteria. In this scenario, we propose a systematic method of constructing OofA-OA having $m + 1$ components from an existing OofA-OA with m components. As the resulting design is OofA-OA, it retains efficiency, optimality and balance property. The proposed method is easy to understand and lacks complexity for the construction. However, the run size of the proposed OofA-OA is a fixed number and is not flexible. Hence, we advise future research on systematic construction of OofA-OA with flexible run sizes for which OofA-OA exists. We further introduce a balance property which is applicable to any OofA-OA even if it does not obey the order balance property.

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Conflict of interest

The authors do not have any financial or non-financial conflict of interest to declare for the research work included in this article.

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