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Order-of-addition mixture experiments

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ABSTRACT
In a mixture experiment, m components are mixed to produce a response. The total amount of the mixture is a constant. Existing literature on mixture designs ignores the order of addition of the mixture components. This paper considers the Order-of-Addition (OofA) mixture experiment, where the response depends on both the mixture proportions of components and their order of addition. Empirical study demonstrates that if mixture-order interactions exist, then the optimal mixture proportions identified by traditional models may be misleading. Full Mixture OofA designs are created which ensure orthogonality between mixture model terms and addition order effects. These designs allow for the estimation of (1) typical mixture model parameters and (2) order-of-addition effects. Moreover, models which include both main effects and key mixture-order interactions are introduced.

KEYWORDS
Design of experiments; pairwise ordering model; response surface design

1. Introduction

In a mixture experiment, there are m components that are mixed together in a fixed total amount to produce a response y. It is typically assumed that the response only depends on the proportion of each ingredient that is included in the mixture. Let $x_1, \ldots, x_m$ represent the proportions of the m components, with $0 \le x_i \le 1$ for $i = 1, \ldots, m$ and $\sum_i x_i = 1$. The objective of a mixture experiment is to find values of the mixture component proportions $x_1, \ldots, x_m$ that optimize (maximize or minimize) the response y. Alternatively, the objective can be to choose $x_1, \ldots, x_m$ to match a target response T. Note that the mixture components take values in the $(m-1)$ dimensional simplex $\mathcal{S} = \{(x_1, \ldots, x_m) \in [0,1] | \sum_i x_i = 1\}$.

Here, we are not only concerned with the mixture proportions $x_1, \ldots, x_m$, but their addition order as well. It is assumed that these m components are being added one at a time. Thus, there are $m!$ possible orderings of these components to consider. This is an Order-of-Addition (OofA) problem, where the response y may depend on the order in which the components $x_1, \ldots, x_m$ have been added, as well as possible mixture-order interactions. In general, there are many scientific applications where the order of the components produces an effect on the response. Ding et al. (2015) provides an example in the field of combinatorial drug therapy, where both the ratio and order of three drugs were examined for treatement of oral cancer. Another example of order of addition in bioengineering is provided by Chandrasekaran, Bhartiya, and Wangikar (2006), where the efficiency of synthesis of carbonate products depended on the order of addition of alcohols.

1.1. Existing research on OofA

Most of the existing work on the OofA problem is on the Pair-Wise Ordering (PWO) model, which was introduced by Van Nostrand (1995). It was officially called the Pair-Wise Ordering (PWO) model in Voelkel (2019). Notation from Lin and Peng (2019) will be used here. Suppose that there are m components $1, 2, \ldots, m$ and a permutation is represented by $\mathbf{a} = (a_1, \ldots, a_m)^T$. Let $\mathcal{P}$ be the set of all pairs (j, k) where $1 \le j < k \le m$. Let jk denote the pair (j, k). The PWO factor for all $jk \in \mathcal{P}$ is defined as

$$z_{jk}(\mathbf{a}) = \begin{cases} 1 & \text{if } j \text{ precedes } k \text{ in } \mathbf{a} \\ -1 & \text{if } k \text{ precedes } j \text{ in } \mathbf{a} \end{cases} \quad [1]$$

So if $\mathbf{a} = (3,1,2)$ then $z_{12}(\mathbf{a}) = 1, z_{13}(\mathbf{a}) = -1, z_{23}(\mathbf{a}) = -1$. The PWO factors must obey the transitive property, i.e., if $z_{ij}(\mathbf{a}) = 1$ and $z_{jk}(\mathbf{a}) = 1$, then it must be true that $z_{ik}(\mathbf{a}) = 1$. Thus, certain

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combinations are impossible, such as $z_{12}(\mathbf{a}) = 1, z_{13}(\mathbf{a}) = -1, z_{23}(\mathbf{a}) = 1$. Let $\tau(\mathbf{a})$ be the expected response given permutation $\mathbf{a}$. The PWO model is

$$\tau(\mathbf{a}) = \beta_0 + \sum_{jk \in \mathcal{S}} z_{jk}(\mathbf{a})\beta_{jk} \quad [2]$$

A parameter estimate $\hat{\beta}_{jk}$ indicates how the pairwise order of components j and k impacts the expected response. If certain parameters were identified as significant, then these parameters would provide clues to help determine the optimal order. In Lin and Peng (2019), topological sorting methods are discussed for finding the optimal order given the output of the PWO model. There are also several results concerning the optimality of PWO designs (and fractional designs). Let the moment matrix $\mathbf{M}$ be defined as $\mathbf{M} = \mathbf{X}^{\mathbf{T}}\mathbf{X}/n$, where n is the number of runs in the PWO design (the unreplicated full design would have $n = m!$). Peng, Mukerjee, and Lin (2019) showed that the full design (with moment matrix $\mathbf{M_f}$) is optimal for $D-, A-, E-$, and $M.S.-$ criteria (as well as for any criteria that is concave and signed permutation invariant). Peng, Mukerjee, and Lin (2019) also showed that a fractional PWO design is optimal iff it has the same moment matrix $\mathbf{M_f}$ as the full design, and they showed a systematic way to construct some optimal fractional and even minimal-point PWO designs. See also Chen, Mukerjee, and Lin (2020), Winker, Chen, and Lin (2020), and Zhao, Lin, and Liu (2020).

1.2. Mixture designs

Here, three common types of designs are reviewed: the simplex-lattice design, the simplex-centroid design, and the extreme vertices design. We use these designs from Cornell (1990) for the purpose of illustration. More complicated designs and models may be applied in a similar manner.

1.2.1. Simplex-lattice design

The $\{m, l\}$ simplex lattice design, called the $\{q, m\}$ simplex lattice design by Cornell (1990), is a design for m components and a polynomial model of degree l for the response surface. It uses design points of the form $x_i = 0, \frac{1}{l}, \frac{1}{l}, \frac{2}{l}, \ldots 1$. The design consists of all possible combinations of the of these x_i that produce points in the simplex $\mathcal{S}$.

1.2.2. Simplex-centroid design

The simplex-centroid design, also covered in Cornell (1990), has a total of $2^m - 1$ design points. The design points are generated as follows. Start by taking all m permutations of the point $(1, 0, \ldots, 0)$. Then, take all $\binom{m}{2}$ permutations of $(1/2, 1/2, 0, \ldots, 0)$, all $\binom{m}{3}$ permutations of $(1/3, 1/3, 1/3, 0, \ldots, 0)$, and so on until one reaches the point $(1/m, \ldots, 1/m)$, which is the centroid.

1.2.3. Extreme vertices design

Sometimes, there are constraints placed on the mixture proportions. For example, practical concerns might make it so the first component must be between 10% and 80%. In this case, we assume that there are single-component constraints $0 \le L_i \le X_i \le U_i \le 1$, for $i = 1, 2, \ldots, m$. In this case, the region of interest is not the entire simplex, but a polyhedron that lies within the simplex. This design uses the vertices of the polyhedron, in addition to points positioned on the center of any faces of the region and an overall centroid. These points can be systematically identified by several procedures, such as the XVERT algorithm provided by Snee and Marquardt (1974).

In these experiments, it is often sufficient to use a second-order polynomial to model the response surface:

$$\eta = \sum_{i=1}^{m} \beta_i x_i + \sum_{i<j} \beta_{ij} x_i x_j \quad [3]$$

where η represents the response surface and the x_i is the value taken by the i^{th} mixture component. The model has no intercept term due to the constraint that $\sum_i x_i = 1$.

1.3. The OofA mixture experiment

The OofA mixture experiment is a mixture experiment where the researchers are also concerned that the order in which components are added into the mixture has an effect on the response. In such studies, the response surface would be a function of both the mixture proportions $x_1, \ldots, x_m$ and their order of addition. In this experiment, there are three goals of interest: (1) Determine whether the order-of-addition of the components has a statistically significant effect on the response; (2) Determine whether the mixture components have a statistically significant effect on the response; (3) Find the settings (i.e., mixture proportions and ordering) that gives an optimal response; i.e., a response that is either maximized, minimized, or matches a target value T. The focus here is on how to incorporate OofA designs into mixture models. For more details, see Section 2.1, where the OofA Mixture problem is formally stated.

It is important to study the OofA Mixture experiment. There are studies that use mixture experiments which acknowledge that the order of addition of the mixture components can have an impact on the response. As an example, Sljivic-Ivanovic et al. (2015) studied how applying $m=3$ sorbents in a mixture impacted the removal of ions from aqueous solutions. They concluded that the order of addition was indeed significant. It should also be noted that they conducted separate experiments for the mixture proportions and the order of addition; they used an extreme vertices design to examine the mixture proportions, and they ran all $m!=6$ orderings with fixed mixture proportions to study the order of addition. Another example is given by Voelkel and Gallagher (2019), where the effect of the order of addition of mixture components (e.g. binder resins, flow and leveling additives) on the viscosity of automotive paint coatings was studied. In this study, any mixture components involved were held constant, so it is not possible to infer whether the mixture proportions had an effect on the response. While it might seem practical to hold the mixture proportions constant to study the order of addition, it should be noted that doing so makes it impossible to determine if there is interaction between the order of addition and the mixture proportions. It is therefore useful to construct designs where both the order of addition and the mixture proportions are varied, so that experimenters can determine whether the response changes for particular combinations of addition orders and mixture proportions.

The outline of the paper is as follows. In Section 2, we discuss the construction of a design for the OofA Mixture experiment and models for this problem. Section 3 shows an example of these models. Section 4 gives the results of a simulation study. Section 5 provides a conclusion.

2. Proposed method

In this section, we first formulate the OofA Mixture problem; i.e. show how to construct designs for this problem and how to model the response surface.

2.1. Problem formulation

Suppose that there are m components that will be added into a mixture with a fixed total amount to produce a continuous response y. Let $x_1, \ldots, x_m$ be the proportions of each component that are included in the mixture. Let $\mathcal{A}$ be the set of all permutations of $(1, 2, \ldots, m)$ and $\mathcal{S} = \{(x_1, \ldots, x_m) \in [0,1] | \sum_i x_i = 1\}$ or a sub-region of this simplex determined by single-component constraints. In the OofA Mixture experiment, it is assumed that the response depends on both the mixture proportions and their order of addition. This can be expressed as

$$y = f(\mathbf{x}, \mathbf{a}) + \epsilon$$

where $\epsilon \sim N(0, \sigma^2), \mathbf{x} \in \mathcal{S},$ and $\mathbf{a} \in \mathcal{A}$. There are two goals to keep in mind when designing an OofA mixture experiment. First, the experimental design should ensure that effects only due to mixture components (pure mixture effects) have low correlation with effects that involve the order of addition. It is desirable for these effects to be orthogonal, but this may not always be the case. In Appendix A, we prove that these effects are indeed orthogonal if the full design from Section 2.2 is used. Appendices are included in the supplementary material. Second, the design and accompanying model should allow us to find the optimal mixture proportions and ordering. In the case of finding a maximum (or a minimum), the optimal proportions and ordering are

$$(\mathbf{x}^*, \mathbf{a}^*) = \arg\ \max_{\mathbf{x},\mathbf{a}} f(\mathbf{x}, \mathbf{a}) \\ \text{subject to} \quad \mathbf{a} \in \mathcal{A} \quad \text{and} \quad \mathbf{x} \in \mathcal{S}$$

In the case of matching a target value T, the optimal proportions and ordering are

$$(\mathbf{x}^*, \mathbf{a}^*) = \arg\ \min_{\mathbf{x},\mathbf{a}} \ (f(\mathbf{x}, \mathbf{a}) - T)^2 \\ \text{subject to} \quad \mathbf{a} \in \mathcal{A} \quad \text{and} \quad \mathbf{x} \in \mathcal{S}$$

The above are constrained optimization problems, since the optimal $\mathbf{x}^*$ must lie in the simplex, and the optimal ordering must be a valid permutation of $(1, 2, \ldots, m)$. For the purpose of this initial research we focus on maximizing or minimizing the response, as the problem of matching a target T is essentially minimizing a function of the response.

2.2. Construction of the full design matrix

In this section, an OofA Mixture design that can be constructed based on a simplex design is introduced. Let $\mathcal{P} = \{jk \mid j, k \in (1, \ldots, m), \quad j < k\}$ and $\mathcal{S}$ be an $(m-1)$ dimensional simplex. Then for $x \in \mathcal{S}, jk \in \mathcal{P}$, and a permutation a of $(1, \ldots, m)$, define the modified PWO variables

$$z_{jk}(x, a) = \begin{cases} 1 & x_j, x_k \neq 0 \quad \text{and } j \text{ is before } k \text{ in } a \\ 0 & x_j = 0 \text{ or } x_k = 0 \\ -1 & x_j, x_k \neq 0 \quad \text{and } j \text{ is after } k \text{ in } a \end{cases}$$

These modified PWO variables describe the ordering of the nonzero mixture components. The Simplex

Table 1. OofA simplex lattice design, $m = 3, l = 3$.

x_1	x_2	x_3	z_{12}	z_{13}	z_{23}
1.00	0.00	0.00	0.00	0.00	0.00
0.00	1.00	0.00	0.00	0.00	0.00
0.00	0.00	1.00	0.00	0.00	0.00
0.33	0.67	0.00	1.00	0.00	0.00
0.33	0.67	0.00	−1.00	0.00	0.00
0.67	0.33	0.00	1.00	0.00	0.00
0.67	0.33	0.00	−1.00	0.00	0.00
0.33	0.00	0.67	0.00	1.00	0.00
0.33	0.00	0.67	0.00	−1.00	0.00
0.67	0.00	0.33	0.00	1.00	0.00
0.67	0.00	0.33	0.00	−1.00	0.00
0.00	0.33	0.67	0.00	0.00	1.00
0.00	0.33	0.67	0.00	0.00	−1.00
0.00	0.67	0.33	0.00	0.00	1.00
0.00	0.67	0.33	0.00	0.00	−1.00
0.33	0.33	0.33	1.00	1.00	1.00
0.33	0.33	0.33	1.00	1.00	−1.00
0.33	0.33	0.33	1.00	−1.00	−1.00
0.33	0.33	0.33	−1.00	−1.00	−1.00
0.33	0.33	0.33	−1.00	−1.00	1.00
0.33	0.33	0.33	−1.00	1.00	1.00

Lattice and Simplex Centroid designs include many points in the simplex where some mixture proportions are not used (e.g. vertices). This modification to the PWO variables ensures that orderings are not assigned to components that are absent from a particular run of the design. It should be noted that the above modified PWO variables are only different from the traditional PWO indicators if some of the mixture components are zero. For example, if $x = (0.5, 0.5, 0)$ and $a = (1, 2, 3)$, then $z_{12}(x, a) = 1$, but $z_{13}(x, a) = z_{23}(x, a) = 0$. Using these modified PWO variables, it is possible to construct a design matrix using Algorithm 1.

Algorithm 1: Generate Full OofA Mixture Design Matrix

Create a simplex design for m components, $\mathbf{SD(m)}$.
Initialize a design matrix $\mathbf{D}$.
for *each row x of* $\mathbf{SD(m)}$ **do**
  Let k be the number of nonzero components of x.
  Replicate x $k!$ times (including the original row).
  Associate each replicate with a unique ordering a of the k nonzero components of x.
  For each replicate, represent its ordering a using a row vector z of $\binom{m}{2}$ modified PWO variables $z_{jk}(x, a)$ for each $jk \in \mathcal{P}$.
end
Stack the rows x (and their replicates) into a matrix $\mathbf{X}$.
Stack the rows z into a matrix $\mathbf{Z}$.
return $\mathbf{D} = (\mathbf{X}, \mathbf{Z})$

Algorithm 1 uses an existing mixture design $\mathbf{SD(m)}$ as an input. Each row of $\mathbf{SD(m)}$ is replicated once for every possible ordering of the nonzero components. Each replicate is then assigned an addition order in terms of the modified PWO variables. The designs generated by Algorithm 1 are called "full" designs because, for each row of $\mathbf{SD(m)}$, they include one run for every possible ordering of the nonzero mixture components. For example, an OofA Mixture design constructed using a Simplex Lattice Design for $m = 3, l = 3$ is shown in Table 1.

In general, the number of rows N in $\mathbf{D}$ for the Full OofA Simplex Centroid Design is

$$N = m + \binom{m}{2}2! + \binom{m}{3}3! + \ldots + \binom{m}{m-1}(m-1)! + m!.$$

So N grows very quickly with m when $\mathbf{D}$ is constructed from the Simplex Centroid Design. It should be noted that the previous algorithm is a general framework; the rows x do not have to be drawn from the Simplex Centroid Design. They can be drawn from any unreplicated mixture design (e.g. Simplex Lattice). If there are single-component constraints, the rows may be drawn from an extreme vertices design. If the constrained region is in the interior of the simplex, the modified PWO variables will reduce to the PWO variables from Peng, Mukerjee, and Lin (2019).

As m increases, the run size of the full design also grows quickly for the Simplex Lattice design, and even more so for the extreme vertices design. In the case of strict financial limitations on the number of runs, the full OofA Mixture design can be used as a list of candidate points for a smaller design of size $n < N$. Modern statistical packages can be used to choose n of the N rows that maximize an optimality criterion, such as such as D-optimality, which maximizes the determinant of the information matrix. For instance, this can be done using the R package AlgDesign by Wheeler (2019). In cases where the number of mixture components is large, enumerating a set of candidate points may be burdensome, as such a set would be quite large. This subset of n rows is not guaranteed to be the optimal design, but these designs generally have desirable optimality criteria.

2.3. Models for OofA mixture

In this section, we construct models for the pairwise ordering and mixture component effects. First, an additive model is considered, i.e., a model with no interactions between the mixture terms and the ordering:

$$y = \mathbf{X}\beta + \mathbf{Z}\delta + \epsilon \quad [4]$$

where $\epsilon \sim N(0, \sigma^2 I)$, β contains the coefficients for the mixture model, δ contains the coefficients for the PWO model, and $\mathbf{X}, \mathbf{Z}$ are as defined in Algorithm 1. Model (4) is useful for identifying significant mixture or order main effects. However, if there is concern that the mixture effects depend on the addition order (or vice-versa), then Model (4) should be compared with a model that includes mixture-order interactions. Consider the following more general model:

$$y(\mathbf{x}, \mathbf{z}) = \eta(\mathbf{x}) + g(\mathbf{x}, \mathbf{z}) + \epsilon \quad [5]$$

where $\eta(\mathbf{x})$ models the response surface in terms of the mixture proportions, and $g(\mathbf{x}, \mathbf{z})$ is a function of both the mixture proportions and their order. Technically, Model (5) is a generalization of Model (4), i.e. take $\eta(\mathbf{x}) = \mathbf{X}\beta$ and $g(\mathbf{x}, \mathbf{z}) = \mathbf{Z}\delta$. However, with Model (5), interaction terms may now be included. For instance, consider:

$$\begin{aligned} y(\mathbf{x}, \mathbf{z}) = \sum_{i=1}^{m} \beta_i x_i + \sum_{i<j} \beta_{ij} x_i x_j + \sum_{k<l} \delta_{kl} z_{kl} \\ + \sum_{i} \sum_{k<l} \gamma_{kl}^{i} x_i z_{kl} + \epsilon \end{aligned} \quad [6]$$

where γ_{kl}^{i} represents the effect of the interaction between mixture proportion x_i and the order of components x_k, x_l. Model (6) is an instance of Model (5), where

$$\eta(\mathbf{x}) = \sum_{i=1}^{m} \beta_i x_i + \sum_{i<j} \beta_{ij} x_i x_j \ ,$$

$$g(\mathbf{x}, \mathbf{z}) = \sum_{k<l} \delta_{kl} z_{kl} + \sum_{i} \sum_{k<l} \gamma_{kl}^{i} x_i z_{kl}$$

Model (6) only includes "first order" interactions; i.e., interactions between single mixture proportions and PWO variables. It can be modified to include higher-order interactions, though this will clearly increase the number of parameters to estimate. In general, Model (6) will include $m + 2\binom{m}{2} + m\binom{m}{2}$ parameters. Another major flaw with Model (6) is that its model matrix will not have full rank. To see this, note that $z_{kl} = (x_1 + \ldots + x_m) z_{kl} = x_1 z_{kl} + \ldots + x_m z_{kl}$. So, each of the "main effects" z_{kl} can be written as a linear combination of the terms $x_1 z_{kl}, \ldots x_m z_{kl}$, so the columns of the resulting model matrix will be linearly dependent. This problem can be remedied in one of two ways. The first is by following methodology from Cornell (1990) and fitting a modification of Model (6):

$$\begin{aligned} \eta(\mathbf{x}) = \sum_{i=1}^{m} \beta_i x_i + \sum_{i<j} \beta_{ij} x_i x_j \quad , \quad g(\mathbf{x}, \mathbf{z}) \\ = \sum_{i} \sum_{k<l} \gamma_{kl}^{i} x_i z_{kl} \end{aligned} \quad [7]$$

Model (7) does not explicitly model the main effect of the order components; it models the effect of the order components only through their interactions with the mixture proportions. This is very similar to the form of the mixture models with process variables as shown in Chapter 7 of Cornell (1990). This "reduced" model only has $m + \binom{m}{2} + m\binom{m}{2}$ parameters. The second way to remedy this problem is to place restrictions on certain model parameters. When $m \geq 3$, assume that $\gamma_{kl}^{i} = 0$ if $i \neq k$ and $i \neq l$. In this case, the model becomes

$$\begin{aligned} \eta(\mathbf{x}) = \sum_{i=1}^{m} \beta_i x_i + \sum_{i<j} \beta_{ij} x_i x_j \ , \\ g(\mathbf{x}, \mathbf{z}) = \sum_{k<l} \delta_{kl} z_{kl} + \sum_{i} \sum_{k<l,\, i=k,\, l} \gamma_{kl}^{i} x_i z_{kl} \end{aligned} \quad [8]$$

Model (8) includes both the main PWO effects and some of their interactions with the mixture proportions. Specifically, the assumption $\gamma_{kl}^{i} = 0$ means that a mixture proportion only interacts with the pairwise orderings that it takes part in. For example, under Model (8), if $m = 3$ then mixture component 1 is may interact with z_{12} and z_{13}, but not z_{23}.

With an estimable model of the general form (5), the optimal proportions and order $\mathbf{x}^*, \mathbf{a}^*$ and response y^* can be found. This is done by finding the mixture proportions that produce a minimum (or maximum) response for each possible order, and then finding the overall minimum response (or maximum) across the orders. Obviously, this is not ideal for larger m; rather, this algorithm simply outlines a brute force approach for finding an optimal value. Note that if the objective of optimization is to match a target T, then it is sufficient to minimize $(\hat{f}(\mathbf{x}, \mathbf{a}) - T)^2$ instead of $\hat{f}(\mathbf{x}, \mathbf{a})$.

2.3.1. Identifiability for Model (7) or (8)

If Model (7) or (8) is applied to an OofA Mixture design that is generated from a Simplex-Centroid design, then the resulting model matrix will also not be full rank. In the OofA Simplex-Centroid design, if x_j and x_k are mixture proportions for components j and k and z_{jk} is the indicator for the ordering of x_j and x_k, then notice that $x_j z_{jk} = x_k z_{jk}$. This is true because each row in the Simplex-Centroid design that

Table 2. Overall ANOVA results for the OofA mixture model.

	Source	SS	df	MS	Fstat	p value
1	Mixture	211.9692	6	35.3282	134.2938	4.9052e-27
2	Order	3.4716	3	1.1572	4.3989	8.4958e-03
3	Error	11.838	45	0.2631		

satisfies $x_j \neq 0, x_k \neq 0$ must have $x_j = x_k$; otherwise, $z_{jk} = 0$, which preserves the equality. Since $x_j z_{jk} = x_k z_{jk}$, then some of the parameters in Model (7) or (8) will not be identifiable. Thus, for identifiability, it is required that for a simplex design SD, the set of design points $\{x \in SD \mid \quad x_j \neq 0, x_k \neq 0, x_j \neq x_k, jk \in \mathcal{P}\}$ is non empty. This requirement is satisfied by several Simplex-Lattice Designs (e.g. {3,3} Simplex Lattice).

3. Example

This example is based on the classical fish patty dataset in Cornell (1990). In this dataset, the response y is the texture of the fish patties, which is measured in grams of force required to puncture the surface of a patty. The fish patties were mixtures of three components: mullet (x_1), sheepshead (x_2), and croaker (x_3). The original dataset included three process variables: temperature (z_1), oven time (z_2), and frying time (z_3). Each of the process variables were coded to have evels $\{-1, 1\}$. The original design was a simplex-centroid design that was run for each of the 2^3 combinations of the three process variables. The original dataset is provided in Appendix B.

To illustrate the use of the OofA models given in Section 2.3, the process variables z_1, z_2, and z_3 were replaced with the modified PWO variables z_{12}, z_{13}, and z_{23}, respectively. This is simply for the sake of illustration of the methods. In the case where certain components were not used, the corresponding PWO variables were set to 0. There were two rows where the PWO indicator variables represented an impossible ordering, e.g. $(1, -1, 1)$; these two rows (51 and 54) were removed from the dataset.

In the original problem, objectives of the analysis included studying how the process variables impacted the response, as well as the mixture proportions. Additionally, it was desirable for the texture of the fish patties to be between 2.0 and 3.5. Similar objectives are considered in this modified problem. Aims of this analysis will be to see whether the OofA of the mixture components (and the mixture proportions) impacts the response and to see how both OofA and mixture proportions affect the response. Finally, a target value of $T = 2.75$ (the midpoint of 2.0 and 3.5) was considered as an "optimal" texture value. Initially

Table 3. Parameter estimates for the OofA mixture models.

	Model (4)			Model (9)		
Term	Estimate	Std. Error	t value	Estimate	Std. Error	t value
x_1	2.8630	0.1808	15.838	2.8630	0.1863	15.3636
x_2	1.0730	0.1808	5.936	1.0730	0.1863	5.7579
x_3	2.0005	0.1808	11.067	2.0005	0.1863	10.7351
z_{12}	0.1030	0.1405	0.733	0.0075	0.8768	0.0086
z_{13}	0.4726	0.1405	3.365	0.0900	0.8768	0.1027
z_{23}	−0.1064	0.1405	−0.757	−0.1800	0.8768	−0.2053
x_1x_2	−0.9444	0.8405	−1.124	−0.9444	0.8665	−1.0900
x_1x_3	−0.8044	0.8405	−0.957	−0.8044	0.8665	−0.9284
x_2x_3	0.3856	0.8405	0.459	0.3856	0.8665	0.4450
x_1z_{12}				0.2475	1.9427	0.1274
x_2z_{23}				0.1950	1.9427	0.1004
x_3z_{13}				0.9000	1.9427	0.4633

the additive Model (4) was fit to the data, and an ANOVA was used to determine if the mixture or the order had a significant effect on the response. These results are summarized in Table 2. Using a significance level of $\alpha = 0.05$, it is clear that both the mixture proportions and the order of addition have a significant effect on the texture of the fish patties.

Model (4) was compared to Model (9), which is provided below.

$$\eta(\mathbf{x}) = \sum_{i=1}^{3} \beta_i x_i + \sum_{i<j} \beta_{ij} x_i x_j,$$
$$g(\mathbf{x}, \mathbf{z}) = \sum_{k<l} \delta_{kl} z_{kl} + \gamma_{12}^{1} x_1 z_{12} + \gamma_{23}^{2} x_2 z_{23} + \gamma_{13}^{3} x_3 z_{13} \tag{9}$$

We note that the omission of the mixture-order interactions $x_1 z_{13}, x_2 z_{12}$, and $x_3 z_{23}$ in Model (9) ensures identifiability; otherwise, we would see that $x_j z_{jk} = x_k z_{jk}$ and the model matrix would not be full rank. The parameter estimates for Models (4) and (9) are given in Table 3.

Figure 1 shows side-by-side contour plots for Models (4) and (9), respectively. We note that the shape of the contours for the right panel is different from the left panel due to the interaction terms that are included in Model (9). This implies that when the interaction model is used, there is potential for optimal points to lie in different regions. In Figure 2, the same models are compared, but the order is changed to (1)–(3). The shape of the contours in each plot still differs in terms of gaps between the contours. In all of these cases, the contours have an upward trend when moving toward the right side of the simplex. Additionally, comparing the right panels in Figures 1 and 2 shows that when the order of addition changes, the shape of the contours change as well. However, a nested F-test between Models (4) and (9) revealed that the additional interaction terms in Model (9) were not statistically significant (p-value = 0.9509).

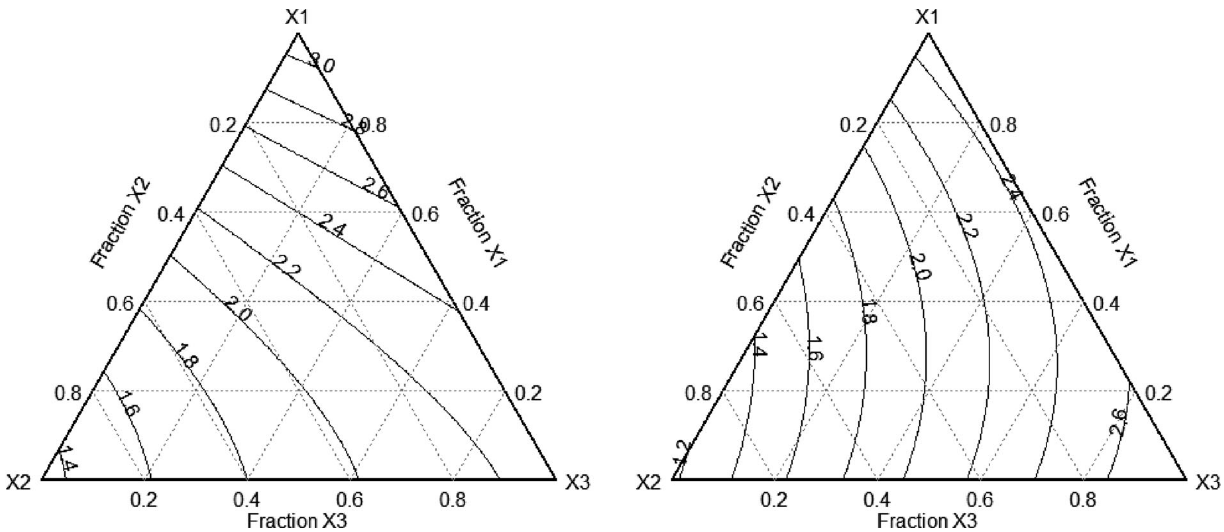

Figure 1. Comparison of Models With and Without Interaction Terms for ordering (1–3). Left: Contour plot for Model (4), which has no mixture-order interaction terms. Right: Contour plot for Model (9), which has mixture-order interaction terms.

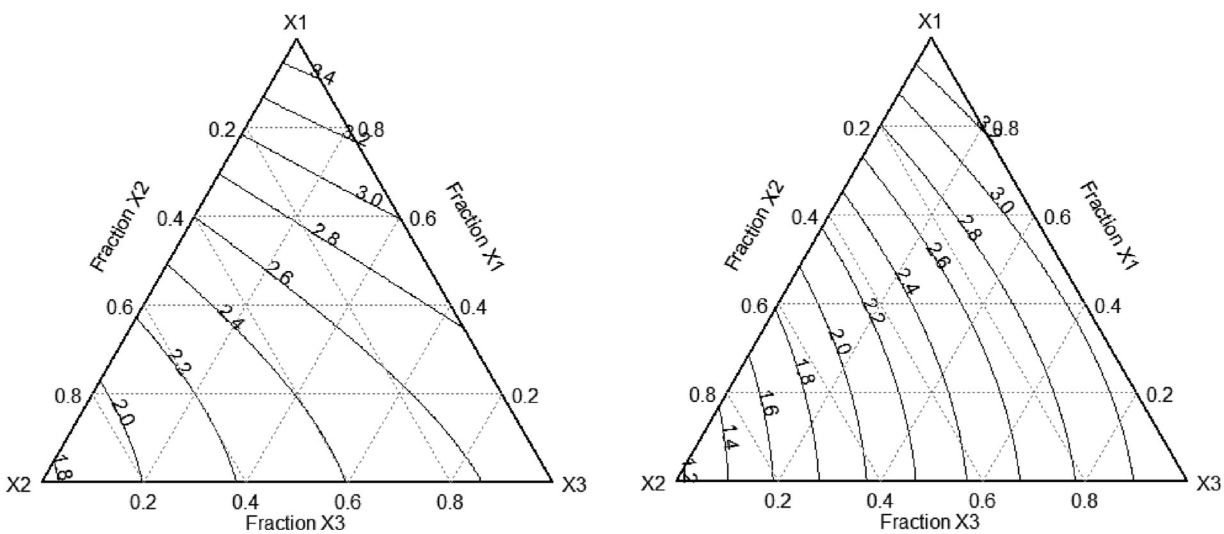

Figure 2. Comparison of Models With and Without Interaction Terms for ordering (1–3). Left: Contour plot for Model (4), which has no mixture-order interaction terms. Right: Contour plot for Model (9), which has mixture-order interaction terms.

Table 4. Mixture proportions and orderings with a response matching the target of $T = 2.75$.

Model (4)		Model (9)	
$\mathbf{x}^*$	$\mathbf{a}^*$	$\mathbf{x}^*$	$\mathbf{a}^*$
(0.603,0.054,0.343)	(1,2,3)	(0.611,0.003,0.385)	(1,2,3)
(0.469,0.161,0.370)	(1,2,3)	(0.399, 0.167, 0.434)	(1,3,2)
(0.767,0.033,0.200)	(2,1,3)	(0.838, 0.078, 0.083)	(3,1,2)
		(0.026, 0.020, 0.954)	(2,1,3)

This does not mean that the interaction terms are unimportant, as they may have important practical interpretations. Furthermore, other interaction models may have a better fit. For example, if we fit Model (9) without the OofA main effect terms $\gamma_{kl}z_{kl}$, then the resulting model has lower AIC (90.92 vs 91.29,96.85) and BIC (110.8 vs 111.18,122.71) than Models (4) and (9), respectively.

By examining all possible orders, we found the mixture and order settings that gave the closest patty texture to the target of $T = 2.75$ for both models. For both models, there were multiple combinations of the mixture and order that gave a predicted response nearly equal to T (within 10^{-10}). These are summarized in Table 4. It should be noted that for the ordering (1)–(3), the value of $\mathbf{x}^*$ for Model (4) is quite different than it is under Model (9). Careful consideration should be taken when deciding which of these points to use. For example, it may not be practical to have a mixture proportion as low as 0.003, so one should carefully consider if the first optimal point for Model (9) is a reasonable choice.

The purpose of this example is to both demonstrate how OofA Mixture models can be used and also to show the impact of including interaction terms in an OofA Mixture model. The inclusion of interaction terms in this example altered the shape of the contours. This resulted in different optimal points for the models with and without interaction when the objective was hitting a target response value.

4. Simulation study

Simulations were conducted to compare the optimal mixture proportions produced by the pure mixture Model (3) to those produced by the interaction Model (7) under various scenarios. The aim was to maximize the response. In the simulations, the optimization of the response was done in R using the package Rsolnp; see Ghalanos and Theussl (2012). Two settings (denoted Mixture-1, Mixture-2) were used to generate the parameters for the response surface, and another two settings (denoted Order-1, Order-2) were used to generate the parameters for the interaction effects in Model (7). Mixture data was simulated with $m=3$, 4, 5 components under Model (7). All of the scenarios used normal errors with constant variance σ^2. Simulations were run for $\sigma^2=0.05$ and 1. In all cases the optimal ordering was to place the components in ascending order.

- **Mixture-1 (Edge):** The optimal point lies on the edge of the simplex between x_1 and x_2. In this case, the parameters for the response surface were $\beta_1=4, \beta_2=2, \beta_i=1$ for $i=3,4,\ldots,m$, and $\beta_{ij}=\beta_i\beta_j$ for $i<j$. For example, when $m=3$, $\beta=(3,3,1,9,3,3)$.
- **Mixture-2 (Center):** The optimal point lies near the center of the simplex. In this case, the parameters for the response surface were $\beta_i=3$ for $i=1,\ldots,m$ and $\beta_{ij}=\beta_i\beta_j-i+j$. When $m=3$, $\beta=(3,3,3,7,8,7)$.
- **Order-1 (Constant):** "Constant" means that the interaction terms were the same for each $kl\in\mathcal{P}$ across i, i.e. $\gamma^i_{kl}=\gamma_{kl}$. The interaction effects are $\gamma_{12}=1,\gamma_{13}=2,\ldots,\gamma_{m-1,m}=\binom{m}{2}$, e.g. for $m=3$, $\gamma=(1,2,3,1,2,3,1,2,3)$.
- **Order-2 (Varying):** "Varying," means that the interaction terms were not constant across i for each $kl\in\mathcal{P}$. In this case, $\gamma^i_{kl}=i/1,i/2,\ldots,i/\binom{m}{2}$. For example, when $m=3$, $\gamma=(1,1/2,1/3,2,1,1/3,3,3/2,1)$.

By varying the number of mixture components, error variance (small vs large), and the mixture settings (edge vs center) and the order settings (constant vs varying), a total of 24 cases were examined. This allows a more informed conclusion to be made about how well the optimal proportions given under the mixture-only Model (3) compare to those found using the interaction Model (7). Mixture-1 setting represents the case where the mixture surface has an optimal point on the edge of the simplex; without loss of generality, this was taken to be the edge between components x_1 and x_2. Mixture-2 setting represents the case where the optimal point is near the center of the simplex. Order-1 setting is established so that the interaction effects are the same for each $kl\in\mathcal{P}$, whereas in Order-2 setting, these interaction effects are allowed to vary.

Table 5. Optimal proportions, order, and response from simulation, $m=3$, $\sigma^2=0.05$.

m	Mixture	Order	Model	$\mathbf{x}^*$	$\mathbf{a}^*$	y^*
3	1	1	(3)	(0.658,0.342,0)	NA	5.076
			(7)	(0.754,0.211,0.036)	(1–3)	10.719
		2	(3)	(0.645,0.355,0)	NA	5.293
			(7)	(0.436,0.373,0.191)	(1–3)	7.729
	2	1	(3)	(0.341,0.284,0.375)	NA	6.550
			(7)	(0.276,0.294,0.43)	(1–3)	12.61
		2	(3)	(0.333,0.316,0.351)	NA	6.345
			(7)	(0.081,0.410,0.509)	(1–3)	10.512

Table 5 shows the optimal mixture proportions $\mathbf{x}^*$, optimal ordering, and maximum response y^* for $m=3$ and $\sigma^2=0.05$. The remaining cases are shown in Appendix C. In all cases, the optimal proportions found using Model (3) differed from those found using Model (7). For example, when $m=3$, in the case of Mixture-1 and Order-2, Model (3) places the optimal point on the edge of the simplex, while Model (7) places the optimal point closer to the interior of the simplex. This case is shown in Figure 3.

In general, the simulations show that if the addition order of the mixture components has an effect on the response, then the optimal mixture proportions $\mathbf{x}^*$ and optimal response y^* found by the simplex model may be misleading. The simulations demonstrate that if there are interactions between mixture and addition order, then the optimal proportions $\mathbf{x}^*$ occur at different locations in the simplex than in traditional models. Based on these observations, it is recommended to initially fit the additive Model (4) to determine whether the order of addition is significant. If so, then it is recommended to compare fit of the additive model and Model (7) or (8) to determine whether there are significant interactions between mixture proportions and pairwise order.

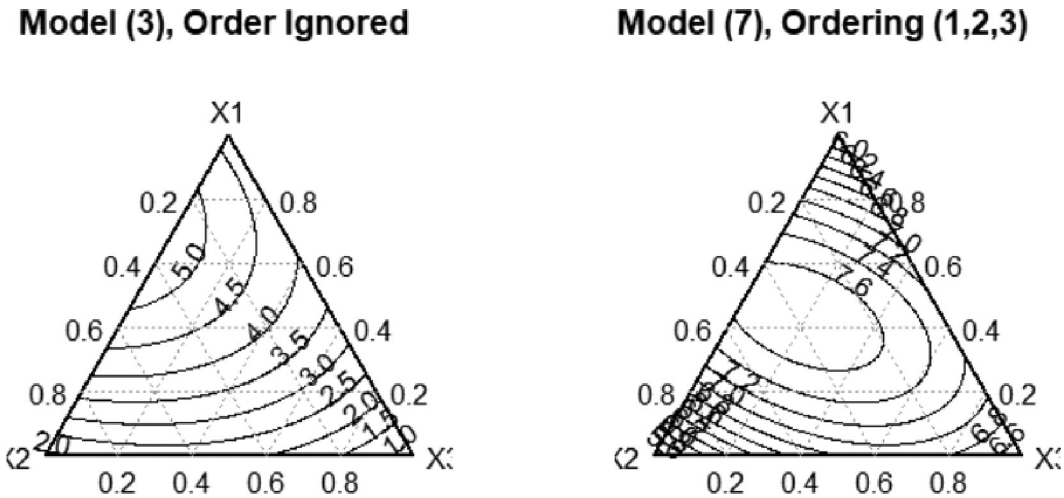

Figure 3. Comparison of Models, $m = 3$, Mixture Setting 1, Order Setting 2. Left: The response surface using Model (3). Right: The response surface using Model (7).

5. Conclusion

This paper introduced a new OofA Mixture experiment and provided a framework for an OofA analysis in traditional mixture designs. Full designs for this experiment were constructed. These designs ensure orthogonality between the simplex design parameters and pairwise ordering effects, as well as mixture-order interaction effects. Under an identifiability condition, two general models that allow for interactions between mixture and order were discussed. The designs presented in this paper can be used to determine whether the order and the mixture have a significant effect on the response. Finally, empirical evidence from simulations indicated that if there is significant interaction between order and mixture, then the optimal mixture proportions found by traditional models may be misleading.

It would be ideal to apply these methods to datasets where both the mixture proportions and addition order are varied, but traditional simplex designs do not do the latter. Thus, many papers on mixture experiments either ignore the order of addition, randomize the mixing order, or choose a constant mixing order. To the best of our knowledge, there are currently no published articles or datasets that vary both the order of addition and the mixture components in the same experiment.

It should be acknowledged that this paper provides initial steps for designing experiments for the OofA Mixture problem. There are many ways this work may be extended. Primarily, more work is needed to reduce the run size. The full designs presented in this paper are not intended for use for large m. Rather, it would be ideal to identify a fraction of these full designs that are $D-$ optimal, as was done in Peng, Mukerjee, and Lin (2019) for the case of the general OofA problem. Similarly, it is of interest to see if the OofA Orthogonal Arrays in Voelkel and Gallagher (2019) can be used to reduce the run size. On this same note, future work in this area is needed to identify optimal designs in this setting, ideally with regard to $D-$ optimality and other popular criteria. For instance, Goos, Jones, and Syafitri (2016) studied the construction of exact and continuous $I-$ optimal mixture designs, which minimize the average prediction variance over the experimental region. It would be both useful and intriguing to study $I-$ optimality in the context of OofA mixture designs. Another area of future research regards constrained mixture components. In real scenarios, it is likely that the mixture proportions will have at least single component constraints $0 \leq L_i \leq x_i \leq U_i \leq 1$ for each $i = 1, \ldots, m$. In this situation, the experimental region is not the full simplex, but a polyhedron that lies within the simplex. In this scenario, the Simplex Lattice and Centroid designs cannot be used, and one must rely on algorithms to construct an optimal design with a small run size. The same restriction clearly applies to OofA mixture designs, and it is of great importance to deal with this problem in the future.

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Disclosure statement

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Supplementary materials

MixOofAR.zip: A .zip file containing the modified Fish Patty data and two R files that are used to produce Tables 2–5 and Figures 1–3.

Appendix A: Proofs of some theoretical results for the designs presented in Section 2.

Appendix B: The original data from Cornell's fish patty experiment, and another example using Food Science data (Aidoo, Afoakwa, and Dewettinck 2014).

Appendix C: Additional simulation results from Section 4.

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