Optimal design of mixture experiments for general blending models

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Abstract

Mixture models of the Scheffé polynomial class are standard in several scientific fields. For these models there is a vast literature on the optimal design of experiments to provide good estimates of the parameters with the use of minimal resources. Contrarily, the optimal design of experiments for general blending models, generalizing the class of Becker, have not been systematically addressed. Nevertheless, there are practical examples where the models relating the response variables, the parameters and the factors include nonlinear blending effects fall into a general form.

We propose a general formulation to find continuous and exact D– and A–optimal designs for general blending models. First, we consider designs to estimate the regression coefficients, and then extend the formulations to find locally optimal continuous designs for estimating both the coefficients and the power constants. The treatment relies on converting the Optimal Design of Experiments (ODoE) problem into an optimization problem of the Nonlinear Programming (or Mixed Integer Nonlinear Programming) class which includes the computation of

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the parameter sensitivities, the Cholesky decomposition of the Fisher Information Matrix and the equality constraint modeling the summation of component fractions to one. We apply the approach to quadratic and special cubic general blending models of the H_2 class of polynomials introduced by Becker, and to three examples of practical interest in combustion science and in the characterization of fuel properties.

Keywords: Model-based optimal designs, Blending models, Continuous designs, Exact designs, Mixture experiments.

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1. Motivation

In many mixtures, at least one component acts as a diluent, the properties of the mixture depending linearly on the amount of this component. In all but the simplest cases, the widely used polynomial models for mixtures introduced by Scheffé [1] do not have this desirable property. We provide algorithms for finding optimal experimental designs for models in which the blending can be linear, or can have some other general form specified by the parameters of a nonlinear model. Although our examples focus on these nonlinear models, our algorithm is general and can find efficient designs for polynomial mixture models and also for those with forms of nonlinearity in the mixture variables other than those exemplified here, including Generalized Linear Models (GLM's).

The optimal design of experiments (ODoE) is a well-established and increasingly important subfield of statistics. Running experiments is costly and users want to rein in costs without sacrificing the statistical efficiency of inferences. The literature on the construction of optimal experimental designs for specific models (of mechanistic or empirical nature) is extensive [2, 3, 4]. In ODoE, given a statistical model, a fixed total number of observations N and an optimality criterion, we seek the optimal number of design points, k, their locations from a pre-specified compact design space and the number of replicates at each design point subject to the constraint that the number of replicates sum to N. Such an optimal design provides maximal precision for statistical inference at minimum cost [5].

There are two types of design: large sample or *continuous designs* (also designated *approximate designs*) and small sample or *exact designs*. The former are essentially probability measures on the design space and are easier to find. In particular, when the optimality criterion is convex over the design space, we have a convex optimization problem [6] and there are algorithms for searching the optimal approximate designs, including analytical tools for studying their properties and confirming optimality of the design. In optimal exact design problems, the numbers of observations at design points are integers and they sum to N. Consequently, we do not have a convex optimization problem in general and, so, finding optimal exact designs is computationally more challenging than finding approximate optimal designs [7].

Herein we find D– and A–optimal experimental designs for general single-response models applied in mixture experiments

$$y = f(\mathbf{x}, \boldsymbol{\theta}) + \epsilon, \tag{1a}$$
$$\text{s.t. } \mathbf{1}_{n_x}^\intercal\, \mathbf{x} = 1, \tag{1b}$$
$$0 \leq \mathbf{x} \leq 1, \tag{1c}$$

where $f(\bullet) \in \mathbb{R}$ is a continuously differentiable function (with respect to parameters), $\mathbf{x} \in \mathbf{X} \subset \mathbb{R}^{n_x}$ is the set of *explanatory variables* (or control factors), $y \in \mathbb{R}$ the *response variable* that fully characterizes the results of the experiment, $\boldsymbol{\theta} \in \Theta \subset \mathbb{R}^{n_\theta}$ the set of parameters, $\mathbf{X} \equiv [0,\ 1]^{n_x}$, and Θ are compact domains of factors and parameters, respectively, n_x the number of control factors and n_θ the number of parameters to be estimated from the experiment. Further, ϵ is the observational error described by an independent and identically distributed (i.i.d.) random variable following the normal distribution $\mathcal{N}(0, \sigma_i)$, and $\mathbf{1}_{n_x}$ is the unitary column vector of size n_x. The model constraints (1b-1c) put additional complexity to the task of finding optimal designs of experiments as they are constraints of the design optimization problem. This issue can be overcome by solving the problem with up-to-date mathematical programming-based algorithms.

In (1) $x_i,\ i \in [\![n_x]\!]$ is the fraction of component i in the mixture and n_x the number of components. Scheffé polynomials with independent normally distributed errors are very often used to represent the responses of mixture experiments. Practically, they are built from regression polynomials by introducing the restrictions (1b-1c). Brown [8, §2.2.1] exemplifies the blending properties of the special second-order polynomial with $n_x = 3$

$$\mathbb{E}(y) = \sum_{i=1}^{3} \beta_i\, x_i + \beta_{1,2} x_1 x_2,$$

where $\mathbb{E}(y)$ is the expectation of y. For a fixed value of the ratio x_1/x_2, the value of $\mathbb{E}(y)$ is quadratic in x_3 as x_3 increases from 0 to 1.

Becker [9] introduced a class of homogenous models that generalizes the polynomial models to allow the representation of linear blending in the presence of an inert or additive component in the mixture. Cornell [10] provides examples of applications. Later, Becker [11] proposed the more general model

$$\mathbb{E}(y) = \sum_{i=1}^{n_x} \beta_i \, x_i + \sum_{i=1}^{n_x-1} \sum_{j=i}^{n_x} \beta_{i,j} \, h(x_i, x_j) \, (x_i + x_j) + \\ + \sum_{i=1}^{n_x-2} \sum_{j=i}^{n_x-1} \sum_{k=j}^{n_x} \beta_{i,j,k} \, h(x_i, x_j, x_k) \, (x_i + x_j + x_k), \tag{2}$$

where the $h(\bullet)$ for the H_2 class are

$$h(x_i, x_j, x_k) = \left(\frac{x_i}{x_i + x_j + x_k}\right)^{r_i} \left(\frac{x_j}{x_i + x_j + x_k}\right)^{r_j} \left(\frac{x_k}{x_i + x_j + x_k}\right)^{r_k} \tag{3a}$$

$$h(x_i, x_j) = \left(\frac{x_i}{x_i + x_j}\right)^{r_i} \left(\frac{x_j}{x_i + x_j}\right)^{r_j}. \tag{3b}$$

The coefficients r_i allow increased flexibility as they can be used for modeling variables described by ratios of proportions. Further generalization can be achieved when partial sums of components $(x_i + x_j)$ or $(x_i + x_j + x_k)$, are raised to powers $s_{i,j}$.

In this study, the quadratic and the special cubic models of the Becker [11] H_2 class of polynomials are further generalized. Various blending profiles are generated by raising the partial sums of fractions of interacting components (i, j) to powers $s_{i,j}$. As in Brown et al. [12], the generalized blending models considered in our study are: (i) quadratic general blending model (2-COMP)

$$\mathbb{E}(y) = \sum_{i=1}^{n_x} \beta_i x_i + \sum_{i=1}^{n_x-1} \sum_{j=i+1}^{n_x} \beta_{i,j} \, x_i^{r_{i,j}} \, x_j^{r_{j,i}}, \tag{4}$$

and (ii) special cubic general blending model (3-COMP)

$$\mathbb{E}(y) = \sum_{i=1}^{n_x} \beta_i x_i + \sum_{i=1}^{n_x-1} \sum_{j=i+1}^{n_x} \beta_{i,j} \, x_i^{r_{i,j}} \, x_j^{r_{j,i}} \, (x_i + x_j)^{s_{i,j} - r_{i,j} - r_{j,i}} + \\ + \sum_{i=1}^{n_x-2} \sum_{j=i+1}^{n_x-1} \sum_{k=j+1}^{n_x} \beta_{i,j,k} \, x_i^{r_{i,j,k}} \, x_j^{r_{j,k,i}} \, x_k^{r_{k,i,j}}. \tag{5}$$

An example of the flexibility in blending profiles that such models present is Brown et al. [12, Figure 1].

While the 2-COMP model includes 5 parameters (3 β's and 2 exponents), the 3-COMP model has 19 parameters (7 β's and 12 exponents). Both models omit the self-interaction terms as in Brown et al. [12]. Here, β_i, $\beta_{i,j}$ and $\beta_{i,j,k},\ i,\ j,\ k \in \{1, \cdots, n_x\}$ are the regression coefficients associated with linear, second-order and third-order interaction terms, respectively, and $r_{i,j},\ i,\ j \in \{1, \cdots, n_x\}$, $r_{i,j,k},\ i,\ j,\ k \in \{1, \cdots, n_x\}$, and $s_{i,j},\ i,\ j \in \{1, \cdots, n_x\}$ are exponents affecting the second and third order terms. The coefficients r and s are real numbers but in most of the practical cases they fall in $[-3,\ +3]$. Values close to 0 indicate the lack of sensitivity of the response to the respective base terms.

First in §4, we consider models linear in the parameters where the goal is to find optimal experimental designs for estimation of the parameters $\boldsymbol{\theta} \equiv \{\beta_i,\ \beta_{i,j},\ \beta_{i,j,k}\ :\ i,\ j,\ k \in \{1, \cdots, n_x\}\}$. Then, we extend the analysis to experimental designs to simultaneously estimate the regression coefficients and a subset of exponents, $\boldsymbol{\theta} \equiv \{\beta_i,\ \beta_{i,j},\ \beta_{i,j,k},\ r_{i,j},\ r_{i,j,k}\ :\ i,\ j,\ k \in \{1, \cdots, n_x\}\}$. This latter model is nonlinear and we will be interested in locally optimal designs.

1.1. Illustrative example

Spark Ignition engine performance is linked to knock phenomena which, in turn, depend on fuel resistance to auto-ignition, quantified by the octane number (*Research Octane Number* – RON and *Motor Octane Number* - MON). Fuel products must meet strict specifications in terms of RON, see European Commision [13]. The refining industry has to comply with both quality specifications and also stringent environmental regulations regarding emissions. To optimize its returns, the industry blends products of different specifications processed in different operation lines to assure that the specifications are met. These blending fractions have different compositions in terms of paraffin, olefin and aromatic components [14, 15]. The estimation of the properties of the mixture, such as the RON and Reid Vapor Pressure (RVP), based on the properties of the blending fractions, follow nonlinear mixing rules because of the group interactions, see Riazi [16] for the estimation of RON and Gary et al. [17] for the estimation of RVP. Thus, constructing adequate mathematical models for the estimation of mixture properties usually requires intensive experimental work. The most common experimental setup requires measuring the characteristics of mixtures of blending fractions with various compositions. Practically, there is substantial interest in finding optimal experimental designs to characterize general (nonlinear) blending models to predict mixture properties. Typically, these studies require a considerable amount of resources and experimental plans able to maximize the amount of information gathered for the available resources are highly desirable.

1.2. Algorithms for finding Optimal Experimental Designs

Over the last decades, algorithms have been developed and continually improved for generating different types of optimal designs for explicit algebraic models. Various numerical algorithms developed to construct such designs are based on exchange methods, originally proposed for the D–optimality criterion [18, 19, 20]. The numerical efficiency of these Wynn–Fedorov schemes has been improved by several authors, including Wu [21], Wu and Wynn [22], Pronzato [23] and Harman and Pronzato [24]. Some of these algorithms are reviewed, compared and discussed in Meyer and Nachtsheim [25] and Pronzato [26], among others. Another approach to finding continuous optimal designs is based on Multiplicative Algorithms, which have found broad application due to their simplicity [27]. The basic algorithm was proposed by Titterington [28] and later exploited in Pázman [29], Fellman [30], Pukelsheim and Torsney [31], Torsney and Mandal [32], Mandal and Torsney [33], Dette et al. [34], Torsney and Martín-Martín [35] and Yu [36, 37]. Recently, cocktail algorithms, that rely on both exchange and multiplicative algorithms, have been proposed [38], and improved [39].

Mathematical programming algorithms can currently solve complex, high–dimensional optimization problems, especially when they are convex and a self-concordant barrier is available for the constraints. Examples of applications of mathematical programming algorithms for finding continuous optimal designs are Linear Programming [40, 41, 42], Second-Order Conic Programming [43, 44], Semidefinite Programming (SDP) [45, 46, 47], Semi Infinite Programming (SIP) [48, 49], and Nonlinear Programming (NLP) [50, 51]. Applications based on procedures relying on metaheuristic optimization algorithms are also reported in the literature, see Heredia-Langner et al. [52] for Genetic Algorithms, Woods [53] for Simulated Annealing, Chen et al. [54] for Particle Swarm Optimization (PSO) and Masoudi et al. [55] for the Imperialist Competitive Algorithm, among others.

Applications of mathematical programming methods for finding optimal exact designs in a general regression setting are less numerous due to the additional numerical complexity. In Welch [56], the design space is discretized and a convex optimization algorithm based on branch and bound is used to ensure that the optimal numbers of replicates of the D–optimal exact designs are integers. Similarly, Harman and Filová [57] and Sagnol and Harman [44] used, respectively, Mixed-Integer Quadratic Programming (MIQP) and Mixed-Integer Second-Order Conic

Programming techniques (MISOCP) to find D–optimal exact designs. Both methods also require discretizing the design space, ensuring that the global optimal design is found on the discretized space. Esteban-Bravo et al. [58] showed that NLP formulations can be used to find unconstrained and constrained exact designs, and that Newton-based methods using Interior Point or Filter techniques performed well for the problem. Duarte et al. [59] formulated optimal exact design for D– and A–optimality criteria as a Mixed Integer Nonlinear Programming (MINLP) problem and solved it employing global and local MINLP solvers. Goos et al. [60] compared a variable neighborhood search (VNS) algorithm and a MINLP approach to tackle the problem of identifying D– and I–optimal designs for mixture experiments.

The optimal design of experiments for mixture models was studied in several references, see Cornell [10], Atkinson et al. [2], Sinha et al. [61] among others. For recent reviews the reader is referred to Piepel [62] and Goos et al. [63]. Various approaches to the construction of optimal designs for mixtures when the components are constrained have been proposed. For example Welch [64] used an exchange procedure on a candidate set of points generated from a grid of points including the extreme vertices and centroids of the polytope. Algorithms based on a coordinate-exchange algorithm and a hybrid thereof that take the mixture variables to be continuous over the polytope have been devised [65]. Approaches based on PSO were studied by Wong et al. [66]. Coetzer and Haines [67] proposed an approach that involves transforming the search for design points over a polytope to a search over a regular simplex with dimension equal to the number of vertices of the polytope. Syafitri et al. [68] proposed a VNS algorithm which Goos et al. [60] compare to a MINLP based formulations.

The approach in this study is grounded on mathematical programming. Our formulations lead to optimization problems of the NLP class for continuous designs, and MINLP class for exact designs, respectively, and those are solved numerically using specific algorithms. The equations representing the model, including the equality (1b), and the parametric sensitivities are embedded in the optimal design problem as additional constraints. The same holds for matrix algebra operations required for computing D– and A–optimality criteria. This strategy allows us to find optimal designs that satisfy the model equations and guarantees that all the solutions in the convergence process are feasible.

1.3. Novelty and organization

This paper contains three elements of novelty:

i. the application of systematic mathematical programming-based methodologies to find continuous and exact optimal designs of experiments for determining the regression coefficients in general (nonlinear) blending models based on Becker [11] H_2 class of polynomials;

ii. the provision of algebraic expressions for the D–optimal designs for two- and three-component models;

iii. the extension of the approaches to continuous designs for determining both the coefficients and exponents;

iv. the application of the methodologies to examples of practical interest.

The paper is organized as follows. Section 2 introduces the background and the notation used to formulate the problem, as well as the fundamentals of nonlinear and mixed integer nonlinear programming. Section 3 presents the mathematical programming formulations for finding continuous and approximate designs for general blending models. Section 4 applies the previous formulations to finding optimal designs. First, we consider continuous designs for determining the regression coefficients. Then, we determine exact optimal designs and locally optimal continuous designs for parameterizing the regression coefficients and some of the exponents. Finally, in §5 we test our formulation on three examples of practical interest. Section 6 offers a summary of the results obtained.

2. Notation and background

This section establishes the nomenclature used in the representation of the models. In §2.1 we present the experimental design problems outlined above. Then, in §2.2, we give an overview of the fundamentals of NLP and MINLP.

2.1. Optimal experimental design

Bold face lowercase letters represent vectors, bold face capital letters continuous domains, blackboard bold capital letters discrete domains and capital letters matrices. Finite sets containing ι elements are compactly represented by $[\![\iota]\!] \equiv \{1, \cdots, \iota\}$. The transpose operation of a matrix is represented by "$^\intercal$" and the trace of matrix by $\mathrm{tr}(\bullet)$.

We recall model (1) and consider a continuous design with K support points at $\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_K$. *Continuous designs* are used to represent experimental setups where $N \to +\infty$; consequently the weights vary continuously on $[0,\ 1]$ and represent the proportion of the total number of observations. Advantages of working with continuous designs are many, and there is a unified framework for finding optimal continuous designs for M-bODE problems when the design criterion is a convex function on the set of all approximate designs [69].

The weights at the support points are, respectively, $w_1, w_2, \dots, w_K$ where K is chosen by the user so that $K \geq n_\theta$. To implement the design for a total of N observations, we take roughly $N \times w_k$ observations at $\mathbf{x}_k$, $k \in [\![K]\!]$, subject to $N \times w_1 + \cdots + N \times w_K = N$, and each summand is an integer. For models with n_x control factors, we denote the k^{th} support point by $\mathbf{x}_k^\intercal = (x_{k,1}, \dots, x_{k,n_x})$ and represent the continuous design ξ^{cont} by K rows $(\mathbf{x}_k^\intercal, w_k),\ k \in [\![K]\!]$ with $\sum_{k=1}^{K} w_k = 1$. To discriminate between continuous and exact designs we use the superscript "cont" for the former, and the superscript "exact" for the later. Since the theoretical basis on optimal design of experiments was created for continuous designs, see [70, 71] among others, we also use this setup for presenting the basic concepts.

In what is to follow, we let $\Xi \equiv \mathbf{X}^K \times \Sigma$ be the space of feasible K-point designs over $\mathbf{X}$ where Σ is the $K-1$-simplex in the domain of weights $\Sigma = \{w_k:\ w_k \geq 0,\ \forall k \in [\![K]\!],\ \sum_{k=1}^{K} w_k = 1\}$.

The information resulting from an experimental design is measured by its FIM. The elements of the normalized FIM are the negative expectation of the second order derivatives of the log-likelihood of (1), $\mathcal{L}(\xi^{\text{cont}}, \boldsymbol{\theta})$, with respect to the parameters, given by

$$\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta}) = -\mathbb{E}\left[\frac{\partial}{\partial \boldsymbol{\theta}}\left(\frac{\partial \mathcal{L}(\xi^{\text{cont}})}{\partial \boldsymbol{\theta}^\intercal}\right)\right] = \int_{\xi^{\text{cont}} \in \Xi} M(\mathbf{x}, \boldsymbol{\theta})\ \mathrm{d}(\xi^{\text{cont}}) = \\ = \sum_{k=1}^{K} w_k\ M(\mathbf{x}_k, \boldsymbol{\theta}), \tag{6}$$

where $\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})$ is the *global* FIM from the design ξ^{cont}, $M(\mathbf{x}_k, \boldsymbol{\theta})$ is the *local* FIM from point $\mathbf{x}_k$. Let

$$\mathbf{h}(\mathbf{x}_k, \boldsymbol{\theta}) = \mathbb{E}\left[\frac{\partial \mathcal{L}(\xi^{\text{cont}})}{\partial \boldsymbol{\theta}}\right]_{\mathbf{x}_k} \tag{7}$$

be the first order derivative of the log-likelihood with respect to $\boldsymbol{\theta}$ at $\mathbf{x}_k$. Then, the local FIM's are obtained from

$$M(\mathbf{x}_k, \boldsymbol{\theta}) = \mathbf{h}(\mathbf{x}_k, \boldsymbol{\theta})\ [\mathbf{h}(\mathbf{x}_k, \boldsymbol{\theta})]^\intercal. \tag{8}$$

Herein, we focus on the class of design criteria proposed by Kiefer [6] where each member in the class, indexed by a parameter δ, is positively homogeneous and defined on the set of symmetric $n_\theta \times n_\theta$ semi-positive definite matrices given by

$$\Phi_\delta[\mathcal{M}(\xi^{\text{cont}})] = \left[\frac{1}{n_\theta}\ \text{tr}(\mathcal{M}(\xi^{\text{cont}})^\delta)\right]^{1/\delta}. \tag{9}$$

The maximization of Φ_δ for $\delta \neq 0$ is equivalent to minimizing $\text{tr}(\mathcal{M}(\xi^{\text{cont}})^\delta)$ when $\delta < 0$. Practically, Φ_δ becomes $[\text{tr}(\mathcal{M}(\xi^{\text{cont}})^{-1})]^{-1}$ for $\delta = -1$, which is A–optimality, and $[\det[\mathcal{M}(\xi^{\text{cont}})]]^{1/n_\theta}$ when $\delta \to 0$, which is D–optimality. These design criteria are suitable for estimating model parameters as they maximize the FIM in various ways. For the D–optimality criterion, the volume of the confidence region of $\boldsymbol{\theta}$ is proportional to $\det[\mathcal{M}^{-1/2}(\xi^{\text{cont}})]$. Then, maximizing the determinant (or a convenient convex function of the determinant) of the FIM leads to the smallest possible volume. Consequently, the ODoE problem can be cast as an optimization problem. For example, when $\boldsymbol{\theta}$ is fixed, the locally D– and A–optimal designs are respectively defined by

$$\xi_D^{\text{cont}} = \arg \max_{\xi^{\text{cont}} \in \Xi} \log \left\{\det[\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})]\right\}, \tag{10}$$

$$\xi_A^{\text{cont}} = \arg \min_{\xi^{\text{cont}} \in \Xi} \text{tr}[\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})^{-1}], \tag{11}$$

where the criteria (10-11) are $+\infty$ for designs with singular information matrices. Herein we limit our analysis to D– and A–optimal designs that are the most commonly used in practical applications.

When the design criterion is convex (which is the case for the above criteria), the global optimality of a design ξ^{cont} in $\mathbf{X}$ can be verified using an equivalence theorem based on the consideration of the directional derivative of the objective function [71, 20, 72, 6, 73, 3]. For instance, if we let $\boldsymbol{\delta}_x$ be the degenerate design at the point $\mathbf{x} \in \mathbf{X}$, the equivalence theorems for D– and A–optimality are as follow: (i) ξ_D^{cont} is D–optimal if and only if

$$\text{tr}\left\{[\mathcal{M}(\xi_D^{\text{cont}}, \boldsymbol{\theta})]^{-1}\ M(\boldsymbol{\delta}_{\mathbf{x}})\right\} - n_\theta \leq 0, \quad \forall \mathbf{x} \in \mathbf{X}; \tag{12}$$

(ii) ξ_A^{cont} is globally A–optimal if and only if

$$\text{tr}\left\{[\mathcal{M}(\xi_A^{\text{cont}}, \boldsymbol{\theta})]^{-2}\ M(\boldsymbol{\delta}_{\mathbf{x}}, \boldsymbol{\theta})\right\} - \text{tr}\left\{[\mathcal{M}(\xi_A^{\text{cont}}, \boldsymbol{\theta})]^{-1}\right\} \leq 0, \quad \forall \mathbf{x} \in \mathbf{X}. \tag{13}$$

We call the functions on the left side of the inequalities (12-13) *dispersion functions* and denote them by $\Psi(\mathbf{x}|\xi^{\text{cont}})$. To compare the D–optimal efficiency, an indicator of the information content extracted from two different designs, say ξ_D^{cont} and ξ_D^{ref}, where the latter one is the reference, we use

$$\text{Eff}_D = \left\{ \frac{\det[\mathcal{M}(\xi_D^{\text{cont}}, \boldsymbol{\theta})]}{\det[\mathcal{M}(\xi_D^{\text{ref}}, \boldsymbol{\theta})]} \right\}^{1/n_\theta}, \tag{14}$$

and, similarly, for the A–optimality criterion, the efficiency of ξ_A^{cont} relative to ξ_A^{ref} is defined by

$$\text{Eff}_A = \frac{\text{tr}[\mathcal{M}^{-1}(\xi_A^{\text{ref}}, \boldsymbol{\theta})]}{\text{tr}[\mathcal{M}^{-1}(\xi_A^{\text{cont}}, \boldsymbol{\theta})]}. \tag{15}$$

Now, we extend the theoretical framework to exact designs. The design space $\mathbf{X}$ is a known compact domain from which the design points are selected to observe the N outcomes. Here, ξ^{exact} is a $K-$point exact design supported at $\mathbf{x}_1, \cdots, \mathbf{x}_k, \cdots, \mathbf{x}_K$ in $\mathbf{X}$ with n_k replicates at $\mathbf{x}_k$ subject to $\sum_{k=1}^K n_k = N$. Henceforth, we assume the number K of support points in the design sought is user specified, and an initial estimate for K is the number of parameters in the model, n_θ. In what follows, let $\mathbf{n}$ be the vector of all possible replicates at the design points, let $\Omega_k^N = \{n_k : \ 0 \leq n_k < N, \ \sum_{k=1}^K n_k = N, \ 1 \leq k \leq K\}$ and let $\Xi_K^N \equiv \mathbf{X}^K \times \Omega_K^N$ be the set of all $K-$point feasible designs on $\mathbf{X}$. We assume $K \geq n_\theta$; otherwise, there are not enough support points to estimate all model parameters. Also, the number of support points is pre-specified by the user which is sometimes not the case in practice.

2.2. Nonlinear Programming and Mixed-Integer Nonlinear Programming

In this section we introduce the fundamentals of Nonlinear Programming and Mixed-Integer Nonlinear Programming (MINLP). NLP is used to solve the design problems (10-11) and seeks to find the global optimum $\mathbf{x}$ of a convex or nonconvex nonlinear function $f : \mathbf{X} \mapsto \mathbb{R}$ in a compact domain $\mathbf{X}$ with possibly nonlinear constraints. The general structure of the NLP problems is:

$$\min_{\mathbf{x} \in \mathbf{X}} f(\mathbf{x}) \tag{16a}$$

$$\text{s.t. } \mathbf{g}(\mathbf{x}) \leq \mathbf{0} \tag{16b}$$

$$\mathbf{h}(\mathbf{x}) = \mathbf{0}, \tag{16c}$$

where (16b) represents a set of r_i inequalities, and (16c) represents a set of r_e equality constraints. The functions $f(\mathbf{x})$, $\mathbf{g}(\mathbf{x})$ and $\mathbf{h}(\mathbf{x})$ are twice differentiable.

In our context, the variable $\mathbf{x} \in \mathbf{X}$ includes the location of the support points as well as the weights quantifying the relative effort required at each one. By construction $\mathbf{X}$ in (16a) is closed which is what we have for Ξ.

Nested and gradient projection methods are commonly used to solve NLP problems. Some examples are the General Reduced Gradient (GRG) [74, 75] and the Trust-Region [76] algorithms. Other methods are Sequential Quadratic Programming (SQP) [77] and the Interior-Point (IP) [78]. Ruszczyński [79] provides an overview of NLP algorithms.

MINLP is used for solving the exact design problems introduced in §3.3. MINLP is class of mathematical programming problems where the objective or some of the constraints are nonlinear and some of the decision variables are constrained to integer values. To optimize a function of n_x continuous variables, $\mathbf{x}$, and n_y discrete variables, $\mathbf{y}$, the general form of a MINLP is

$$\min_{\mathbf{x},\mathbf{y}} f(\mathbf{x},\mathbf{y}) \tag{17a}$$

$$\text{s.t. } \mathbf{g}(\mathbf{x},\mathbf{y}) \leq \mathbf{0} \tag{17b}$$

$$\mathbf{h}(\mathbf{x},\mathbf{y}) = \mathbf{0} \tag{17c}$$

$$\mathbf{x} \in \mathbf{X},\ \mathbf{y} \in \mathbf{Y}. \tag{17d}$$

As before, the function (17b) represents a set of r_i inequalities and (17c) a set of equality constraints, $\mathbf{X}$ is a compact set containing continuous variables $\mathbf{x}$, $\mathbf{Y}$ contains the discrete variables $\mathbf{y}$ and (17a) is the objective function.

Some common algorithms to solve mixed-integer nonlinear programs are the outer-approximation method [80], the branch and bound method [81] and the extended cutting plane method [82]. Floudas [83] reviews the fundamentals of using MINLP to solve optimization problems and notes that traditional MINLP algorithms guarantee the global optima under certain convexity assumptions.

Optimal design problems may have multiple local optima. To guarantee that a global optimum is found, a global solver such as `BARON` must be employed. This implements deterministic global optimization algorithms that combine spatial branch-and-bound procedures and bound tightening methods via constraint propagation and interval analysis in a *branch-and-reduce* technique [84]. Sahinidis [85] showed that these techniques work quite well under fairly general assumptions. In our formulations, those assumptions are satisfied by construction as all decision variables are bounded. However, global optimization solvers still require a long computational time compared to local solvers [86], and this may limit their utilization to small and average sized problems.

A way to reduce the CPU time needed is to use a local MINLP solver, such as, SBB [87], for handling exact design problems. SBB uses CONOPT as a NLP solver to handle the relaxed nonlinear programs [74] and CPLEX to solve the mixed-integer linear programs [87].

3. Formulations for optimal design of experiments

This section introduces NLP formulations for finding $K-$point, continuous D–, and A–optimal designs for general blending models. In Sections 3.1 and 3.2, we respectively present the formulations for finding continuous D– and A–optimal designs. In Section 3.3, we adapt the formulations to determine exact D– and A–optimal designs. Section 3.4 provides implementation details.

3.1. Continuous D–optimal designs

A formulation for finding D–optimal continuous designs on Ξ is defined in (10).

To maximize $\log\left(\det[\mathcal{M}(\xi^{\text{cont}},\boldsymbol{\theta})]\right)$, we apply the Cholesky decomposition to the global FIM; that is

$$\mathcal{M}(\xi^{\text{cont}},\boldsymbol{\theta}) = \mathcal{U}^{\intercal}(\xi^{\text{cont}},\boldsymbol{\theta})\,\mathcal{U}(\xi^{\text{cont}},\boldsymbol{\theta}), \tag{18}$$

where $\mathcal{U}(\xi^{\text{cont}},\boldsymbol{\theta})$ is an upper triangular matrix and has positive diagonal elements $u_{i,i}$ when the FIM is positive definite. It follows that

$$\det(\mathcal{M}(\xi^{\text{cont}},\boldsymbol{\theta})) = \prod_{i=1}^{n_\theta} u_{i,i}^2, \tag{19}$$

and $\log[\det(\mathcal{M}(\xi^{\text{cont}},\boldsymbol{\theta}))] = 2\sum_{i=1}^{n_\theta}\log(u_{i,i})$. Then, maximizing $\det(\mathcal{M}(\xi^{\text{cont}},\boldsymbol{\theta}))$ is equivalent to maximizing the sum of the logarithms of the diagonal elements of $\mathcal{U}(\xi^{\text{cont}},\boldsymbol{\theta})$.

Let $m_{i,j},\ i,\ j \in [\![n_\theta]\!]$ be the $(i,j)^{\text{th}}$ element of the global FIM $\mathcal{M}(\xi^{\text{cont}},\boldsymbol{\theta})$ and $u_{i,j}$ the $(i,j)^{\text{th}}$ element of $\mathcal{U}(\xi^{\text{cont}},\boldsymbol{\theta})$. The formulation for finding a locally D–optimal continuous design is

$$\max_{\mathbf{x},\mathbf{w}} \sum_{i=1}^{n_\theta} \log(u_{i,i}) \tag{20a}$$

$$\text{s.t.}\mathbf{1}_{n_x}^{\intercal}\,\mathbf{x}_k = 1, \qquad k \in [\![K]\!] \tag{20b}$$

$$\text{Equations (7-8)} \tag{20c}$$

$$m_{i,j} = \sum_{k=1}^{K} w_k \, m_{i,j,k}^{\text{loc}}, \quad i,\ j \in [\![n_\theta]\!] \tag{20d}$$

$$m_{i,j} = \sum_{l=1}^{n_\theta} u_{l,i} u_{l,j}, \quad i,\ j \in [\![n_\theta]\!],\ i \le j \tag{20e}$$

$$u_{i,i} \ge \zeta, \quad i \in [\![n_\theta]\!] \tag{20f}$$

$$u_{i,j} = 0, \quad i,\ j \in [\![n_\theta]\!],\ i \ge j+1 \tag{20g}$$

$$m_{i,i} \ge u_{i,j}^2, \quad i, j \in [\![n_\theta]\!] \tag{20h}$$

$$\sum_{k=1}^{K} w_k = 1 \tag{20i}$$

$$\mathbf{x} \in \mathbf{X}^K,\ \mathbf{w} \in \Sigma.$$

Here, ζ is a small positive constant to ensure that the FIM is positive definite. For all examples in §4, $\zeta = 1 \times 10^{-5}$. Equation (20c) is the set of equations used to determine the sensitivity coefficients, equation (20b) assures that the fraction of the components sums to 1 for all the support points (see (1b)), equation (20d) follows from (6), (20e) represents the Cholesky decomposition, (20f) guarantees that all diagonal elements of $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ are positive and (20g) assures that $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ is upper triangular. Equation (20h) is a numerical stability condition imposed on the Cholesky factorization of positive semidefinite matrices [88, Theorem 4.2.8] and the constraint (20i) restricts the sum of weights to 1.

3.2. Continuous A–optimal design

Now, we introduce the formulation to determine A–optimal continuous designs modeled by (11). The optimization problem requires inverting $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$, potentially a numerically unstable operation when the FIM is ill-conditioned. To avoid the explicit computation of the inverse matrix, we apply the Cholesky decomposition to invert the upper diagonal matrix $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ that results from the decomposition of $\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})$; the rationale is that inverting an upper triangular matrix obtained by Cholesky factorization is numerically more stable than inverting the original matrix [89]. The procedure has three steps that are handled simultaneously within the optimization problem: (i) apply the Cholesky decomposition to the FIM, cf. §3.1; (ii) invert the upper triangular matrix $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ using the relation $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})\, \mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta}) = I_{n_\theta}$, where I_{n_θ} is the n_θ–dimensional identity matrix; and (iii) compute $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$ via $\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$, i.e. $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta}) = \mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta}) \times [\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})]^\intercal$ [89], and, finally, compute $\text{tr}[\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})]$.

Let $\overline{m}_{i,j}$ be the $(i,j)^{\text{th}}$ entry of $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$ and $\overline{u}_{i,j}$ be the $(i,j)^{\text{th}}$ entry of $\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$ where $i,\ j \in [\![n_\theta]\!]$. By construction, $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ is positive definite and invertible if all the diagonal elements are positive. The same holds for $\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$. Step (i) is the Cholesky decomposition of the FIM represented by (20e) and the second step corresponds to inverting $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ formulated as:

$$\begin{cases} \sum_{l=1}^{n_\theta} u_{i,l}\, \overline{u}_{l,j} = 1 & \text{if } i = j \\ \sum_{l=1}^{n_\theta} u_{i,l}\, \overline{u}_{l,j} = 0 & \text{if } i \neq j, \end{cases} \tag{21}$$

with step (iii) represented by

$$\overline{m}_{i,j} = \sum_{l=1}^{n_\theta} \overline{u}_{i,l} \overline{u}_{l,j}, \quad i,\ j \in [\![n_\theta]\!],\ i \leq j. \tag{22}$$

A–optimal designs minimize $\operatorname{tr}(\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta}))$ or equivalently, minimize the sum of all $\overline{m}_{i,i},\ i \in [\![n_\theta]\!]$. The complete NLP for computing A–optimal designs is

$$\min_{\mathbf{x},\mathbf{w}} \sum_{i=1}^{n_\theta} \overline{m}_{i,i} \tag{23a}$$

$$\text{s.t. } \mathbf{1}_{n_x}^{\intercal}\, \mathbf{x}_k = 1, \quad k \in [\![K]\!] \tag{23b}$$

$$\text{Equations (7-8)} \tag{23c}$$

$$m_{i,j} = \sum_{k=1}^{K} w_k\, m_{i,j,k}^{\text{loc}}, \quad i,\ j \in [\![n_\theta]\!] \tag{23d}$$

$$m_{i,j} = \sum_{l=1}^{n_\theta} u_{l,i} u_{l,j}, \quad i,\ j \in [\![n_\theta]\!],\ i \leq j \tag{23e}$$

$$\sum_{l=1}^{n_\theta} u_{i,l}\, \overline{u}_{l,j} = 1, \quad i,\ j \in [\![n_\theta]\!],\ i = j \tag{23f}$$

$$\sum_{l=1}^{n_\theta} u_{i,l}\, \overline{u}_{l,j} = 0, \quad i,\ j \in [\![n_\theta]\!],\ i \neq j \tag{23g}$$

$$\overline{m}_{i,j} = \sum_{l=1}^{n_\theta} \overline{u}_{i,l} \overline{u}_{l,j}, \quad i,\ j \in [\![n_\theta]\!],\ i \leq j \tag{23h}$$

$$u_{i,i} \geq \zeta, \quad i \in [\![n_\theta]\!] \tag{23i}$$

$$\overline{u}_{i,i} \geq \zeta, \quad i \in [\![n_\theta]\!] \tag{23j}$$

$$u_{i,j} = 0, \quad i,\ j \in [\![n_\theta]\!],\ i \geq j+1 \tag{23k}$$
$$\overline{u}_{i,j} = 0, \quad i,\ j \in [\![n_\theta]\!],\ i \geq j+1 \tag{23l}$$
$$\overline{m}_{i,j} = \overline{m}_{j,i}, \quad i,\ j \in [\![n_\theta]\!],\ i \leq j-1 \tag{23m}$$
$$m_{i,i} \geq u_{i,j}^2, \quad i,j \in [\![n_\theta]\!] \tag{23n}$$
$$\overline{m}_{i,i} \geq \overline{u}_{i,j}^2, \quad i,j \in [\![n_\theta]\!] \tag{23o}$$
$$\sum_{k=1}^{K} w_k = 1 \tag{23p}$$
$$\mathbf{x} \in \mathbf{X}^K,\ \mathbf{w} \in \Sigma.$$

Equations (23b, 23c, 23d, 23e, 23i, 23k, 23n) and (23p) are similar to those in the D–optimal design formulation. Equations (23f-23g) reflect the relationship (21) and generate $\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$, equation (23h) captures the constraint (22) to produce $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$ and equations (23k) and (23l), respectively, impose the lower triangular structure of $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ and $\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$. Equation (23m) ensures the symmetry of $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$ and equations (23i) and (23j), respectively, ensure that the diagonal elements of $\mathcal{U}(\xi^{\text{cont}}, \boldsymbol{\theta})$ and $\mathcal{U}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$ are positive. The conditions (23n) and (23o) are the numerical stability insurance for the Cholesky factorization of $\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})$ and $\mathcal{M}^{-1}(\xi^{\text{cont}}, \boldsymbol{\theta})$, respectively. The symmetry of the FIM and its inverse are guaranteed by (23d) and (23m), respectively.

3.3. Exact D– and A–optimal designs

Modifications in problems (20) and (23) required to find exact D– and A–optimal designs are overviewed next.

The resulting optimization problems are of Mixed-Integer Nonlinear Programming class [59]. Specifically, the design problems are non-convex and the mathematical tools to check optimality do not exist. The adaptation only requires replacing (20d) and (23d) by

$$m_{i,j} = \sum_{k=1}^{K} \frac{n_k}{N}\, m_{i,j,k}^{\text{loc}}, \quad i,\ j \in [\![n_\theta]\!] \tag{24}$$

and (20i) and (23p) by

$$\sum_{k=1}^{K} n_k = N. \tag{25}$$

Finally, we recall that exact optimal design problems include the decision variable $\mathbf{n}$ instead of $\mathbf{w}$, and $\mathbf{n} \in [\![N]\!]^K \subset \mathbb{N}^K$.

3.4. Implementation aspects

Here we detail the implementation aspects related to the numerical approach for solving the optimal design problem.

The continuous optimal design problems are solved with formulations (20) and (23), respectively. For such a purpose, they are coded in `The General Algebraic Modeling System` environment, commonly known by the initials `GAMS` [90] which is a general modeling system that supports mathematical programming applications in several areas. Upon execution, the code describing the mathematical program is automatically compiled, symbolically transcribed into a set of numerical structures, and all information regarding the gradient and matrix Hessian is generated using the automatic differentiation tool and made available to the solver. For solving both problems, the NLP solver `CONOPT` is used, which employs the Generalized Reduced Gradient (GRG) algorithm [74].

For the exact optimal design problems in §3.3 we set the number of experiments, N, and use the MINLP solver `SBB` which uses a branch and bound algorithm combined with a NLP solver – `CONOPT`. The absolute and relative tolerances of the solvers were set equal to 1×10^{-5} and 1×10^{-6}, respectively; the absolute tolerance is equal to ζ which is the minimum value allowed for the diagonal entries in the FIM so that it is positive definite.

To reduce CPU time, we provide *consistent initial* guesses to the NLP solver. This means that the initial solution $\xi^{(0)}$ has to be consistent, i.e., it satisfies all constraints of the problem [91]. To construct $\xi^{(0)}$, we first choose a point centrally located in $\mathbf{X}$ and then select the other grid points using the relation $\mathbf{x}_i = \mathbf{x}_{i-1} + \Delta\mathbf{x}$ where $\Delta\mathbf{x} = (\max \mathbf{x} - \min \mathbf{x})/(K-1)$ and K is the number of support points selected by the user. The replicates are then distributed so that the weights w_i are all equal to $1/K$. Next, we compute the elemental and the global FIM for $\xi^{(0)}$, $\mathcal{U}^\intercal(\xi^{(0)}, \boldsymbol{\theta})$ and $\mathcal{M}^{-1}(\xi^{(0)}, \boldsymbol{\theta})$ and let the solver iterate until it converges to the optimum. To construct consistent initial solutions for the MINLP problems for finding exact designs we use the continuous optimal design to determine the (integer) number of replicates at each support point assuring that $\sum_{i=1}^{K} n_i = N$ with $n_i = \text{round}(N\, w_i)$ and $\text{round}(\bullet)$ being the rounding operation to the nearest integer. Then, the elemental and global FIM's are computed as well as all other required information.

All computations in §4 used an Intel Core i7 machine running a 64 bits Windows 10 operating system with a $2.80\,\text{GHz}$ processor.

4. Results

This section presents D– and A–optimal designs calculated employing the formulations derived in §3. In Section 4.1 we consider continuous D– and A–optimal designs and use the formulations in §3.1 and §3.2, respectively. Section 4.2 reports exact D– and A–optimal designs; the formulation in §3.3 is used. Finally, Section 4.3 presents continuous locally D– and A–optimal designs for parameterizing both the β's and the exponents and uses the formulations in §3.1 and §3.2. All the designs presented in the following sections were obtained with the number of support points equal to the number of parameters, i.e. $K = n_\theta$. We check that this is the optimal number of support points.

The optima reported for each design in all the tables are for $\log[\det(\mathcal{M}(\xi, \boldsymbol{\theta}))]$ and $\mathrm{tr}[\mathcal{M}^{-1}(\xi, \boldsymbol{\theta})]$ for D– and A–optimality criteria, respectively (note the first is a maximizer and the second a minimizer). The efficiency of D– and A–optimal designs is determined from (14) and (15). We call a design *uniformly distributed* when the weights of all support points are equal to $1/n_\theta$. To help in the interpretation of the results, each of the columns of the optimal designs is for a support point; the first n_x lines correspond to component fractions in the mixture and the last line is for the corresponding weight (or number of replicates).

To demonstrate the generality of the proposed formulations we use both the 2-COMP and 3-COMP models and two sets of exponent parameters. Finding the locally D– and A–optimal designs in §4.3 requires specifying some of the values of the regression coefficients, $\boldsymbol{\beta}$. In all cases we set them to unitary values. For clarification purposes let us call $\boldsymbol{\theta}^{\text{fit,model}}$ the set of parameters that are to be estimated from the experimental design, and $\boldsymbol{\theta}^{\text{fix,model}}$ the set of parameters taken as fixed or known; the superscript "fit" is for estimation, "fix" is for fixed and "model" is for the model description. We note that $n_\theta = \mathrm{card}(\boldsymbol{\theta}^{\text{fit,model}})$. Section 4.3 reports continuous locally optimal designs for nonlinear models. Those were obtained by fixing $\boldsymbol{\theta}^{\text{fit,model}}$ to a singleton point in Θ.

For 2-COMP model $\boldsymbol{\theta}^{\text{fit,2-COMP}} \equiv \{\beta_1, \beta_2, \beta_{1,2}\}$, and $\boldsymbol{\theta}^{\text{fix,2-COMP}} \equiv \{r_{1,2}, r_{2,1}\}$. Two singletons are considered for simulating $\boldsymbol{\theta}^{\text{fix,2-COMP}}$: (i) the first is denoted $\Theta_1^{\text{2-COMP}} \equiv \{0.72\} \times \{0.72\}$; and (ii) the second is $\Theta_2^{\text{2-COMP}} \equiv \{1.0\} \times \{0.5\}$. In turn, for 3-COMP model the set of parameters for estimation in §4.1 and §4.2 is $\boldsymbol{\theta}^{\text{fit,3-COMP}} \equiv \{\beta_1, \beta_2, \beta_3, \beta_{1,2}, \beta_{1,3}, \beta_{2,3}, \beta_{1,2,3}\}$, and the set of fixed parameters is $\boldsymbol{\theta}^{\text{fix,3-COMP}} \equiv \{r_{1,2}, r_{1,3}, r_{2,3}, r_{2,1}, r_{3,1}, r_{3,2}, r_{1,2,3}, r_{2,3,1}, r_{3,1,2}, s_{1,2}, s_{1,3}, s_{2,3}\}$. Two singletons are also considered for the values of $\boldsymbol{\theta}^{\text{fix,3-COMP}}$: (i) $\Theta_1^{\text{3-COMP}} \equiv \{0.8\} \times \{0.4\} \times \{0.8\} \times \{1.2\} \times \{0.6\} \times \{1.2\} \times \{0.9\} \times \{0.9\} \times \{1.2\} \times \{3.0\} \times \{3.0\} \times \{3.0\}$; and (ii) $\Theta_2^{\text{3-COMP}} \equiv \{0.36\} \times \{0.24\} \times \{0.45\} \times \{1.68\} \times \{0.96\} \times \{1.54\} \times$

$\{1.2\} \times \{1.2\} \times \{0.6\} \times \{2.6\} \times \{2.0\} \times \{2.0\}$. Since the models considered in §4.1 and §4.2 are linear, the optimal designs do not require setting $\boldsymbol{\theta}^{\text{fit,2-COMP}}$ or $\boldsymbol{\theta}^{\text{fit,3-COMP}}$. In contrast, the designs in §4.3 require the specification of a singleton point for the parameters to be estimated.

4.1. Continuous optimal designs

Here we present the approximate optimal designs for 2-COMP and 3-COMP models, respectively.

Table 1 presents the continuous optimal designs for 2-COMP model and Table 2 for the 3-COMP model. As expected, the D–optimal designs are uniformly distributed. All the D– and A–optimal designs include the support points corresponding to pure components. We set the number of support points for these designs to $K = 2^{n_x} - 1$ and observe that n_x of them are for experiments with pure components. The location of the remaining $K - n_x$ support points vary as do their weights in A–optimal designs. For the D–optmality criterion the center support point that is $(x_1, x_2) = (r_{1,2}/(r_{1,2} + r_{2,1}), r_{2,1}/(r_{1,2} + r_{2,1}))$; this result is verified using analytical algebra in Appendix A, where we extend the result to D–optimal design of experiments for 3-COMP model using symbolic algebra. Here, the D–optimal design is uniform and formed by 7 support points: (i) three of them are $(1, 0, 0)$, $(0, 1, 0)$ and $(0, 0, 1)$; (ii) three of them are on the axis (i.e., each one is a mixture of only two components), and they are $(x_1, x_2, x_3) = (r_{1,2}/(r_{1,2} + r_{2,1}), r_{2,1}/(r_{1,2} + r_{2,1}), 0)$, $(x_1, x_2, x_3) = (r_{1,3}/(r_{1,3} + r_{3,1}), 0, r_{3,1}/(r_{1,3}+r_{3,1}))$ and $(x_1, x_2, x_3) = (0, r_{2,3}/(r_{2,3}+r_{3,2}), r_{3,2}/(r_{2,3}+r_{3,2}))$; and (iii) the center is $(x_1, x_2, x_3) = (r_{1,2,3}/(r_{1,2,3} + r_{2,3,1} + r_{3,1,2}), r_{2,3,1}/(r_{1,2,3} + r_{2,3,1} + r_{3,1,2}), r_{3,1,2}/(r_{1,2,3} + r_{2,3,1} + r_{3,1,2}))$.

The results for the 3-COMP models show one support point formed by a mixture of all components and n_x points involving mixtures of two components. In all cases the D–optimal designs obtained for 2-COMP and 3-COMP agree with the theoretical results.

[Table 1 about here.]

[Table 2 about here.]

The optimizer convergence ensures the global optimality of all the designs obtained in §4.1 and §4.3. Nonetheless, the optimality of designs was checked graphically by plotting the dispersion function (see (12) and (13) for D– and A–optimality, respectively) and validating the equivalence theorems. Here, for demonstration purposes we consider the continuous D– and A–optimal designs for 3-COMP model for singleton $\Theta_1^{\text{3-COMP}}$ (first line of the Table 2). The display in the domain $\mathbb{X} \equiv \{(x_1, x_2) : \ x_1 + x_2 \leq 1, \ 0 \leq x_1, x_2 \leq 1, \ x_3 = 1 - x_1 - x_2\}$ is shown in Figure 1. Figure 1(a) shows the dispersion function for the D–optimal design and Figure 1(b) is for A–optimality. In both cases the dispersion function is bounded from above by zero and is maximized at the support points, so the designs are indeed optimal. Similar plots were constructed for all continuous designs obtained and all satisfy the optimality conditions.

[Figure 1 about here.]

4.2. Exact optimal designs

This Section reports the exact optimal designs for 2-COMP and 3-COMP models obtained with the formulation in §3.3.

The designs were obtained for $N = 3 \times n_\theta$; thus, $N = 9$ for 2-COMP model and 21 for 3-COMP model. Table 3 shows the exact optimal designs for 2-COMP model, and Table 4 for the 3-COMP model. The D–optimal designs for both 2-COMP and 3-COMP models are also uniform and coincide with the approximate designs obtained in §4.1. The reason is that the number of experiments, N, is a multiple of the number of support points and $n_i/N = w_i, \ i \in [\![K]\!]$. In contrast, the A–optimal designs are not uniform and there are support points at which $n_i/N \neq w_i$.

[Table 3 about here.]

To compare the efficiency of the exact designs relative to approximate designs we use Equations (14) and (15). The reference designs, ξ^{ref}, are those obtained in §4.1 for similar models and parameters; see Tables 1 and 2. For all the D–optimal designs the optima of exact and approximate designs are equal; consequently, the efficiency of exact designs is $100\,\%$. The efficiency of the A–optimal design for the 2-COMP model and $\Theta_1^{\text{2-COMP}}$ (see Table 3) is $98.09\,\%$; for $\Theta_2^{\text{2-COMP}}$ is $99.98\,\%$. For 3-COMP model, considering the singleton $\Theta_1^{\text{3-COMP}}$ (see Table 4) the efficiency is $98.90\,\%$. Finally, for the second set of parameters ($\Theta_2^{\text{3-COMP}}$) the efficiency is $99.30\,\%$. In all cases the efficiency of exact designs is high.

[Table 4 about here.]

4.3. *Continuous locally optimal designs for finding the regression coefficients and exponents*

This section extends the results in §4.1 to optimal designs to fit both the linear regression coefficients (β's) and some of the exponents in the mixture model (r's). Contrarily to models considered in previous sections, the models are nonlinear (w.r.t. some of the parameters), and we find locally optimal designs. For 2-COMP model the set of parameters to estimate is $\boldsymbol{\theta}_{\text{ext}}^{\text{fit,2-COMP}} \equiv \{\beta_1, \beta_2, \beta_3, \beta_{1,2}, r_{1,2}, r_{2,1}\}$, and for 3-COMP model is $\boldsymbol{\theta}_{\text{ext}}^{\text{fit,3-COMP}} \equiv \{\beta_1, \beta_2, \beta_3, \beta_{1,2}, \beta_{1,3}, \beta_{2,3}, \beta_{1,2,3}, r_{1,2}, r_{1,3}, r_{2,3}, r_{2,1}, r_{3,1}, r_{3,2}, r_{1,2,3}, r_{2,3,1}, r_{3,1,2}\}$; the subscript "ext" is used for designate the extended set of parameters. The set of fixed parameters is empty for 2-COMP model, and is $\boldsymbol{\theta}^{\text{fix,3-COMP}} \equiv \{s_{1,2}, s_{1,3}, s_{2,3}\}$ for the 3-COMP model. For the 3-COMP model we again obtained designs for two singletons. To distinguish the values of the parameters to be estimated from those that are fixed, we encapsulate the former in singletons $\boldsymbol{\theta}_{\text{ext}}^{\text{fit,2-COMP}}$ and $\boldsymbol{\theta}_{\text{ext}}^{\text{fit,3-COMP}}$, respectively, and the latter in singletons $\Theta_{\text{ext}}^{\text{fix,2-COMP}}$ which is empty, and $\Theta_{\text{ext}}^{\text{fix,3-COMP}}$. The computation of locally optimal designs requires setting the values of the regression coefficients $\boldsymbol{\beta}$ because the derivatives $\partial\mathcal{L}(\xi^{\text{cont}})/\partial\mathbf{r}^\intercal$ depend on them, and we use 1.0 in all cases. For clarity, the singletons used for finding the optimal designs addressed in this Section are listed in Table 5.

[Table 5 about here.]

Table 6 reports the locally optimal designs for 2-COMP model and Table 7 for 3-COMP model. We notice that the number of support points is 5 in the former case and 16 in the second for a model with 19 parameters, so that the experimental plans obtained do not allow fitting the vector s's involved in the model as exponents. The reason for fixing the parameters s is that the FIM is nearly singular and its inversion required by A–optimality becomes numerically unstable. Typically, this trend indicates that the model is unidentifiable, or at least includes a set of unidentifiable parameters.

[Table 6 about here.]

[Table 7 about here.]

5. Application to realistic examples

We now apply the formulation to three practical problems from the fields of combustion science and gasoline characterization. All examples were chosen to demonstrate that, in practice, general blending models may have application in laboratory experiments. The structure used for tabulating ξ^* is similar to that employed in the previous examples; the first n_x lines contains the levels of the control variables for all support points, and the last the weight of the corresponding support point. The global optimality of the designs presented in this section was checked plotting the dispersion functions as in §4, and they were all demonstrated to be globally optimal. In all cases, we report the optimal designs for finding the regression coefficients.

The first and second examples represent flammability metrics used to characterize the ignition properties of mixtures of kinds of natural litter on forest floors that may sustain forest fires [92]. Here, x_1 is the fraction of cladodes (leaf-like stems), x_2 the fraction of other small components such as bark fragments and dry woody fruits, x_3 the fraction of twigs, x_4 the fraction of leaves and x_5 the fraction of decomposed material. One of the flammability metrics proposed by Gormley et al. [92] is bulk density for which the model is

$$\mathbb{E}(y) = \sum_{i=1}^{5} \beta_i\, x_i + \beta_6\, \frac{x_1\, x_2^{0.5}}{x_1 + x_2 + 0.001} + \beta_7\, x_2^3\, x_3^3. \tag{26}$$

The second metric is Residual Mass Fraction (RMF), when the model is

$$\mathbb{E}(y) = \beta_1\, x_2 + \beta_2\, x_3 + \beta_3\, x_4 + \beta_4\, \frac{x_1^3\, x_2^{1.5}}{(x_1 + x_2 + 0.001)^3} + \beta_5\, x_1^3\, x_2^3. \tag{27}$$

The RMF is independent of x_5, so the experimental designs have only four regressors and the summation constraint is $\sum_{i=1}^{4} x_i = 1$. We also note that both models include terms $x_1 + x_2$ in the denominator. To prevent the occurrence of $\mathbb{E}(y) \to +\infty$ when $x_1 + x_2 \to 0$ a constant equal to 0.001 is added; in both cases $s_{i,j} - r_{i,j} - r_{j,i} = 0$.

Finally, we consider the 7-parameter linear (w.r.t parameters) model proposed by Yuan et al. [93] to represent the RON of Toluene Reference Fuels (TRFs) blended with Ethanol. Here, x_1 is the mole fraction of isooctane, x_2 the mole fraction of n-heptane, x_3 mole fraction of toluene and x_4 the mole fraction of ethanol. The model is

$$\mathbb{E}(y) = \sum_{i=1}^{4} \beta_i\, x_i + \beta_5\, x_1\, x_4 + \beta_6\, x_3\, x_4 + \beta_7\, x_2\, x_4\, (x_2 - x_4). \tag{28}$$

Model (28) does not quite fall into the general class of blending models addressed in this study, but still illustrates the use of the method in designing mixture experiments for nonlinear models in the regressors, including the additional complexity of dealing with negative elements in the FIM. Table 8 reports the continuous optimal designs for fitting the parameters of models (26-28). The D–optimal designs are uniform and all involve experiments with pure components. Table 9 is for exact optimal designs obtained with $N = 3\, n_\theta$. The D–optimal efficiencies of the exact designs using the continuous designs for reference are again $100\,\%$. Since the A–optimal designs are not uniform, the A–optimal efficiencies determined with Eq. (15) are not $100\,\%$. For model (26) the value is $87.90\,\%$, $88.14\,\%$ for model (27), and $98.09\,\%$ for model (28). In all cases the efficiency of the exact designs is relatively high.

[Table 8 about here.]

[Table 9 about here.]

6. Conclusions

We have considered the continuous and exact optimal design of experiments for general blending models for mixtures using mathematical programming-based approaches. We have addressed specifically the quadratic and special cubic blending models of the Becker [11] H_2 class of polynomials. These models allow a large degree of generalization in describing nonlinear blending effects. This class of design problems presents additional computational issues due to non-linearity of terms and the requirement that the support points form a simplex in the space of component concentrations.

Our formulations address the D– and A–optimality criteria and includes: (i) the generation of the sensitivity coefficients; (ii) the Cholesky decomposition of the global FIM; and (iii) the computation of the determinant of FIM (or the trace of its inverse) within the optimization problem which is of NLP class for continuous optimal designs and MINLP class for exact optimal designs. The constraint representing the summation of fractions to one is included in the optimization problem as an additional equality.

We found continuous optimal designs for parametrizing the regression coefficients for two- and three-component general blending models in §4.1 and locally optimal designs for parametrizing both the regression coefficients and some of the power coefficients in §4.3. The former models are linear with respect to the parameters while the latter are nonlinear. Additionally, we also obtained (i) exact optimal designs for parametrizing the regression coefficients (in §4.2); and (ii) continuous and exact designs for three examples of practical interest found in literature, see §5. The efficiency of exact designs relative to equivalent continuous designs is relatively high, being $100\,\%$ for D–optimality criterion and a correctly chosen size of the experiment. Further, the continuous D-optimal designs obtained for linear models are in agreement with theoretical results. In Appendix A we generalize the theoretical form of continuous D–optimal designs for (linear in parameters) 2- and 3-COMP models. These general forms serve to assess the accuracy of designs obtained numerically.

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Appendix A

A.1. Construction of D–optimal designs for 2-COMP model

It is possible to make some analytical progress with the D-optimal design for the two–component model. Let us assume that the set of support points of the design is

$$\begin{pmatrix}1\\0\end{pmatrix}, \begin{pmatrix}0\\1\end{pmatrix}, \begin{pmatrix}x\\1-x\end{pmatrix}.$$

Then, the vectors $\mathbf{h}(\mathbf{x}_k, \boldsymbol{\theta})$ are

$$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}x\\1-x\\x^{r_{1,2}}(1-x)^{r_{2,1}}\end{pmatrix},$$

where x is the fraction of component 1.

Now, considering the design is uniform ($w_k = 1/3,\ k \in [\![K]\!]$), the local FIMs are obtained with Eq. (8), and aggregated into the global FIM, $\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})$, using (6). Under such conditions the optimality criterion is $\det[\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})]$ which is differentiable and strictly convex in $[0, 1]$. The necessary conditions for establishing global optimality are (i) $\nabla_x \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})] = 0$; and (ii) $\nabla_x^2 \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})]$ being a semidefinite positive matrix; where $\nabla_x \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})]$ is the gradient and $\nabla_x^2 \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})]$ the Hessian matrix. In this specific case $\det[\mathcal{M}(\xi^{\text{cont}}, \boldsymbol{\theta})] = 1/27\ x^{2r_{1,2}}\ (1-x)^{2r_{2,1}}$.

To find the design maximizing the objective function $\xi^{\text{cont},*}$ we use the necessary condition (i). Thus, the value of x is obtained solving a nonlinear algebraic equation resulting from $\nabla_x \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})] = 2/27\ x^{2r_{1,2}-1}\ (1-x)^{2r_{2,1}-1}\ (r_{1,2}\ (1-x) + r_{2,1}\ x) = 0$. This equation is satisfied for (i) $x = 0$; (ii) $x = 1$; and (iii) $x = r_{1,2}/(r_{1,2} + r_{2,1})$. Then, the third design point in the optimal design is $x_1 = r_{1,2}/(r_{1,2} + r_{2,1})$ and $x_2 = r_{2,1}/(r_{1,2} + r_{2,1})$. Substituting this result in the 1×1 Hessian matrix we observe that it is always positive, and this design is globally optimum. There is a clear relationship to the optimal designs for 3–COMP; the support points for mixtures of two-components in 3–COMP model are expected to follow the rule established for 2-component models.

A.2. Construction of D–optimal designs for 3-COMP model

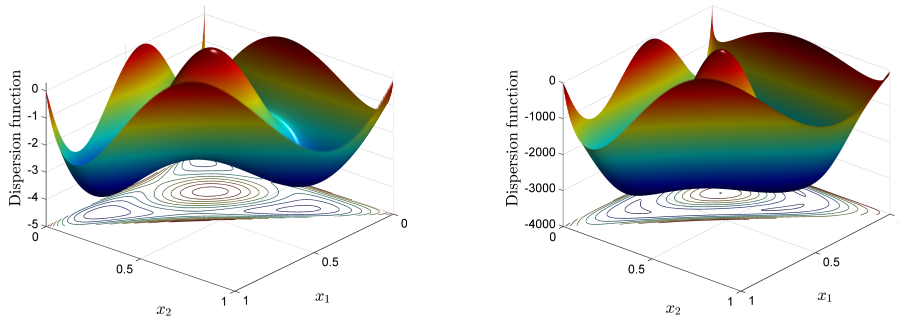
Now we extend the strategy to three-component models. Let $s_{i,j} = r_{i,j} + r_{j,i},\ i \in [\![2]\!],\ j > i$; the set of support points of the design is

$$\begin{pmatrix}1\\0\\0\end{pmatrix},\ \begin{pmatrix}0\\1\\0\end{pmatrix},\ \begin{pmatrix}0\\0\\1\end{pmatrix},\begin{pmatrix}x_{4,1}\\1-x_{4,1}\\0\end{pmatrix},\ \begin{pmatrix}x_{5,1}\\0\\1-x_{5,1}\end{pmatrix},\ \begin{pmatrix}0\\x_{6,1}\\1-x_{6,1}\end{pmatrix},\ \begin{pmatrix}x_{7,1}\\x_{7,2}\\1-x_{7,1}-x_{7,2}\end{pmatrix}.$$

Conversely, the vectors $\mathbf{h}(\mathbf{x}_k, \boldsymbol{\theta})$ are

$$\begin{pmatrix}1\\0\\0\\0\\0\\0\\0\end{pmatrix},\ \begin{pmatrix}0\\1\\0\\0\\0\\0\\0\end{pmatrix},\ \begin{pmatrix}0\\0\\1\\0\\0\\0\\0\end{pmatrix},\ \begin{pmatrix}x_{4,1}\\1-x_{4,1}\\0\\x_{4,1}^{r_{1,2}}\ (1-x_{4,1})^{r_{2,1}}\\0\\0\\0\end{pmatrix},\ \begin{pmatrix}x_{5,1}\\0\\1-x_{5,1}\\0\\x_{5,1}^{r_{1,3}}\ (1-x_{5,1})^{r_{3,1}}\\0\\0\end{pmatrix},$$
$$\begin{pmatrix}0\\x_{6,1}\\1-x_{6,1}\\0\\0\\x_{6,1}^{r_{2,3}}\ (1-x_{6,1})^{r_{3,2}}\\0\end{pmatrix},\ \begin{pmatrix}x_{7,1}\\x_{7,2}\\1-x_{7,1}-x_{7,2}\\x_{7,1}^{r_{1,2}}\ x_{7,2}^{r_{2,1}}\\x_{7,1}^{r_{1,3}}\ (1-x_{7,1}-x_{7,2})^{r_{3,1}}\\x_{7,2}^{r_{2,3}}\ (1-x_{7,1}-x_{7,2})^{r_{3,2}}\\x_{7,1}^{r_{1,2,3}}\ x_{7,2}^{r_{2,3,1}}\ (1-x_{7,1}-x_{7,2})^{r_{3,1,2}}\end{pmatrix}.$$

Let the weights be $w_k = 1/7,\ k \in [\![K]\!]$ and the vector $\mathbf{x} = \big(x_{4,1},\ x_{5,1},\ x_{6,1},\ x_{7,1},\ x_{7,2}\big)^{\intercal}$ include the unknowns of the design problem. The optimality criterion is strictly convex in $[0, 1]^5$. Again, the necessary conditions for establishing local optimality are (i) $\nabla_{\mathbf{x}} \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})] = 0$; and (ii) $\nabla^2_{\mathbf{x}} \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})]$ being a semidefinite positive matrix. Consequently, the values of $\mathbf{x}$ are obtained solving a set of 5 nonlinear algebraic equations, i.e. $\nabla_{\mathbf{x}} \det[\mathcal{M}(\xi^{\text{cont},*}, \boldsymbol{\theta})] = 0$. The problem was solved employing symbolic algebra and we obtain $x_{4,1} = r_{1,2}/(r_{1,2}+r_{2,1})$, $x_{5,1} = r_{1,3}/(r_{1,3}+r_{3,1})$, $x_{6,1} = r_{2,3}/(r_{2,3}+r_{3,2})$, $x_{7,1} = r_{1,2,3}/(r_{1,2,3}+r_{2,3,1}+r_{3,1,2})$ and $x_{7,2} = r_{2,3,1}/(r_{1,2,3}+r_{2,3,1}+r_{3,1,2})$. Afterwards, the semidefinite positiveness of the solution was confirmed.



(a) (b)

Figure 1: Dispersion functions for the continuous optimal designs for 3-COMP model for: (a) D–optimal design; (b) A–optimal design. Set of parameters to estimate: $\boldsymbol{\theta}^{\text{fit,3-COMP}}$. Fixed Parameters: $\Theta_1^{\text{3-COMP}} \equiv \{0.8\} \times \{0.4\} \times \{0.8\} \times \{1.2\} \times \{0.6\} \times \{1.2\} \times \{0.9\} \times \{0.9\} \times \{1.2\} \times \{3.0\} \times \{3.0\} \times \{3.0\}$.

Table 1: Continuous optimal designs for 2-COMP model (Set of parameters to estimate: $\boldsymbol{\theta}^{\text{fit,2-COMP}}$).

Criterion	Design	Optimum
	Fixed Parameters: $\Theta_1^{\text{2-COMP}} \equiv \{0.72\} \times \{0.72\}$	
D–	$\begin{pmatrix} 0.0000 & 0.5000 & 1.0000 \\ 1.0000 & 0.5000 & 0.0000 \\ 0.3333 & 0.3333 & 0.3333 \end{pmatrix}$	-2.6461
A–	$\begin{pmatrix} 0.0000 & 0.5000 & 1.0000 \\ 1.0000 & 0.5000 & 0.0000 \\ 0.2770 & 0.4460 & 0.2770 \end{pmatrix}$	37.0137
	Fixed Parameters: $\Theta_2^{\text{2-COMP}} \equiv \{1.0\} \times \{0.5\}$	
D–	$\begin{pmatrix} 0.0000 & 0.6667 & 1.0000 \\ 1.0000 & 0.3333 & 0.0000 \\ 0.3333 & 0.3333 & 0.3333 \end{pmatrix}$	-2.6027
A–	$\begin{pmatrix} 0.0000 & 0.6507 & 1.0000 \\ 1.0000 & 0.3493 & 0.0000 \\ 0.2283 & 0.4395 & 0.3322 \end{pmatrix}$	35.0063

Table 2: Continuous optimal designs for 3-COMP model (Set of parameters to estimate: $\boldsymbol{\theta}^{\text{fit,3-COMP}}$).

Criterion	Design	Optimum
	Fixed Parameters: $\Theta_1^{\text{3-COMP}} \equiv \{0.8\} \times \{0.4\} \times \{0.8\} \times \{1.2\} \times \{0.6\} \times \{1.2\} \times \{0.9\} \times \times \{0.9\} \times \{1.2\} \times \{3.0\} \times \{3.0\} \times \{3.0\}$	
D–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.3000 & 0.0000 & 0.4000 & 0.4000 & 1.0000 \\ 1.0000 & 0.4000 & 0.3000 & 0.0000 & 0.6000 & 0.0000 & 0.0000 \\ 0.0000 & 0.6000 & 0.4000 & 1.0000 & 0.0000 & 0.6000 & 0.0000 \\ 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 \end{pmatrix}$	-13.4424
A–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.0002 & 0.4224 & 0.4915 & 0.3059 & 1.0000 \\ 0.0000 & 1.0000 & 0.4194 & 0.5775 & 0.0000 & 0.3090 & 0.0000 \\ 1.0000 & 0.0000 & 0.5804 & 0.0001 & 0.5085 & 0.3851 & 0.0000 \\ 0.0451 & 0.0518 & 0.1590 & 0.1172 & 0.1477 & 0.4376 & 0.0418 \end{pmatrix}$	3.6084×10^3
	Fixed Parameters: $\Theta_2^{\text{3-COMP}} \equiv \{0.36\} \times \{0.24\} \times \{0.45\} \times \{1.68\} \times \{0.96\} \times \{1.54\} \times \{1.2\} \times \times \{1.2\} \times \{0.6\} \times \{2.6\} \times \{2.0\} \times \{2.0\}$	
D–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.1765 & 0.4000 & 0.2000 & 0.0000 & 1.0000 \\ 1.0000 & 0.2261 & 0.8235 & 0.4000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.7739 & 0.0000 & 0.2000 & 0.8000 & 1.0000 & 0.0000 \\ 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 \end{pmatrix}$	-12.5903
A–	$\begin{pmatrix} 0.0000 & 0.3943 & 0.0107 & 0.4322 & 0.2622 & 0.0000 & 1.0000 \\ 1.0000 & 0.4060 & 0.2651 & 0.0016 & 0.7378 & 0.0000 & 0.0000 \\ 0.0000 & 0.1998 & 0.7242 & 0.5661 & 0.0000 & 1.0000 & 0.0000 \\ 0.0615 & 0.4422 & 0.0892 & 0.0913 & 0.1702 & 0.0434 & 0.1022 \end{pmatrix}$	2.8942×10^3

Table 3: Exact optimal designs for 2-COMP model (Set of parameters to estimate: $\boldsymbol{\theta}^{\text{fit,2-COMP}}$).

Criterion	Design	Optimum
	Fixed Parameters: $\Theta_1^{\text{2-COMP}} \equiv \{0.72\} \times \{0.72\}$	
D–	$\begin{pmatrix} 0.0000 & 0.5000 & 1.0000 \\ 1.0000 & 0.5000 & 0.0000 \\ 3 & 3 & 3 \end{pmatrix}$	-2.6461
A–	$\begin{pmatrix} 0.0000 & 0.5241 & 1.0000 \\ 1.0000 & 0.4759 & 0.0000 \\ 2 & 4 & 3 \end{pmatrix}$	37.7332
	Fixed Parameters: $\Theta_2^{\text{2-COMP}} \equiv \{1.0\} \times \{0.5\}$	
D–	$\begin{pmatrix} 0.0000 & 0.6667 & 1.0000 \\ 1.0000 & 0.3333 & 0.0000 \\ 3 & 3 & 3 \end{pmatrix}$	-2.6027
A–	$\begin{pmatrix} 0.0000 & 0.6521 & 1.0000 \\ 1.0000 & 0.3479 & 0.0000 \\ 2 & 4 & 3 \end{pmatrix}$	35.0138

Table 4: Exact optimal designs for 3-COMP model (Set of parameters to estimate: $\boldsymbol{\theta}^{\text{fit,3-COMP}}$).

Criterion	Design	Optimum
	Fixed Parameters: $\Theta_1^{\text{3-COMP}} \equiv \{0.8\} \times \{0.4\} \times \{0.8\} \times \{1.2\} \times \{0.6\} \times \{1.2\} \times \{0.9\} \times$ $\times \{0.9\} \times \{1.2\} \times \{3.0\} \times \{3.0\} \times \{3.0\}$	
D–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.3000 & 0.0000 & 0.4000 & 0.4000 & 1.0000 \\ 1.0000 & 0.4000 & 0.3000 & 0.0000 & 0.6000 & 0.0000 & 0.0000 \\ 0.0000 & 0.6000 & 0.4000 & 1.0000 & 0.0000 & 0.6000 & 0.0000 \\ 3 & 3 & 3 & 3 & 3 & 3 & 3 \end{pmatrix}$	-13.4424
A–	$\begin{pmatrix} 0.0000 & 0.0002 & 0.2977 & 0.0000 & 0.4206 & 0.4795 & 1.0000 \\ 1.0000 & 0.4220 & 0.3082 & 0.0000 & 0.5793 & 0.0000 & 0.0000 \\ 0.0000 & 0.5778 & 0.3942 & 1.0000 & 0.0001 & 0.5205 & 0.0000 \\ 1 & 4 & 9 & 1 & 2 & 3 & 1 \end{pmatrix}$	3.6482×10^3
	Fixed Parameters: $\Theta_2^{\text{3-COMP}} \equiv \{0.36\} \times \{0.24\} \times \{0.45\} \times \{1.68\} \times \{0.96\} \times \{1.54\} \times \{1.2\} \times$ $\times \{1.2\} \times \{0.6\} \times \{2.6\} \times \{2.0\} \times \{2.0\}$	
D–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.1765 & 0.4000 & 0.2000 & 0.0000 & 1.0000 \\ 1.0000 & 0.2261 & 0.8235 & 0.4000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.7739 & 0.0000 & 0.2000 & 0.8000 & 1.0000 & 0.0000 \\ 3 & 3 & 3 & 3 & 3 & 3 & 3 \end{pmatrix}$	-12.5903
A–	$\begin{pmatrix} 0.0000 & 0.2771 & 0.0095 & 0.0000 & 0.3921 & 0.4472 & 1.0000 \\ 1.0000 & 0.7229 & 0.2781 & 0.0000 & 0.4094 & 0.0011 & 0.0000 \\ 0.0000 & 0.0000 & 0.7124 & 1.0000 & 0.1986 & 0.5517 & 0.0000 \\ 1 & 4 & 2 & 1 & 9 & 2 & 2 \end{pmatrix}$	2.9147×10^3

Table 5: Singletons used for used for finding the optimal designs to fit both the linear regression coefficients (β's) and some of the exponents in the mixture model (r's).

Model	Case	Singleton	Values
2-COMP	1	$\Theta^{\text{fit,2-COMP}}_{1,\text{ext}}$	$\{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.72\} \times \{0.72\}$
		$\Theta^{\text{fix,2-COMP}}_{\text{ext}}$	$\emptyset$
	2	$\Theta^{\text{fit,2-COMP}}_{2,\text{ext}}$	$\{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.5\}$
		$\Theta^{\text{fix,2-COMP}}_{\text{ext}}$	$\emptyset$
3-COMP	1	$\Theta^{\text{fit,3-COMP}}_{1,\text{ext}}$	$\{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.8\} \times \{0.4\}\times$ $\times\{0.8\} \times \{1.2\} \times \{0.6\} \times \{1.2\} \times \{0.9\} \times \{0.9\} \times \{1.2\}$
		$\Theta^{\text{fix,3-COMP}}_{1,\text{ext}}$	$\{3.0\} \times \{3.0\} \times \{3.0\}$
	2	$\Theta^{\text{fit,3-COMP}}_{2,\text{ext}}$	$\{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.36\} \times \{0.24\}\times$ $\times\{0.45\} \times \{1.68\} \times \{0.96\} \times \{1.54\} \times \{1.2\} \times \{1.2\} \times \{0.6\}$
		$\Theta^{\text{fix,3-COMP}}_{2,\text{ext}}$	$\{2.6\} \times \{2.0\} \times \{2.0\}$

Table 6: Continuous locally optimal designs for 2-COMP model (Set of parameters to estimate: $\boldsymbol{\theta}_{\text{ext}}^{\text{fit,2-COMP}}$).

Criterion	Design	Optimum
	Fitted Parameters: $\Theta_{1,\text{ext}}^{\text{fit,2-COMP}} \equiv \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.72\} \times \{0.72\}$ Fixed Parameters: $\Theta_{1,\text{ext}}^{\text{fix,2-COMP}} \equiv \emptyset$	
D–	$\begin{pmatrix} 0.0000 & 0.0914 & 0.5000 & 0.9086 & 1.0000 \\ 1.0000 & 0.9086 & 0.5000 & 0.0914 & 0.0000 \\ 0.2000 & 0.2000 & 0.2000 & 0.2000 & 0.2000 \end{pmatrix}$	-7.6765
A–	$\begin{pmatrix} 0.0000 & 0.0711 & 0.5000 & 0.9289 & 1.0000 \\ 1.0000 & 0.9289 & 0.5000 & 0.0711 & 0.0000 \\ 0.1332 & 0.2359 & 0.2617 & 0.2359 & 0.1332 \end{pmatrix}$	572.4961
	Fitted Parameters: $\Theta_{2,\text{ext}}^{\text{fit,2-COMP}} \equiv \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.5\}$ Fixed Parameters: $\Theta_{2,\text{ext}}^{\text{fix,2-COMP}} \equiv \emptyset$	
D–	$\begin{pmatrix} 0.0000 & 0.1944 & 0.6676 & 0.9684 & 1.0000 \\ 1.0000 & 0.8056 & 0.3324 & 0.0316 & 0.0000 \\ 0.2000 & 0.2000 & 0.2000 & 0.2000 & 0.2000 \end{pmatrix}$	-7.5415
A–	$\begin{pmatrix} 0.0000 & 0.1628 & 0.6581 & 0.9766 & 1.0000 \\ 1.0000 & 0.8372 & 0.3419 & 0.0234 & 0.0000 \\ 0.1598 & 0.2607 & 0.2564 & 0.2151 & 0.1080 \end{pmatrix}$	566.1355

Table 7: Continuous locally optimal designs for 3-COMP model (Set of parameters to estmate: $\boldsymbol{\theta}_{\text{ext}}^{\text{fit,3-COMP}}$).

Criterion	Design	Optimum
	Fitted Parameters: $\Theta_{1,\text{ext}}^{\text{fit,3-COMP}} \equiv \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.8\} \times \{0.4\} \times$ $\times \{0.8\} \times \{1.2\} \times \{0.6\} \times \{1.2\} \times \{0.9\} \times \{0.9\} \times \{1.2\}$ Fixed Parameters: $\Theta_{1,\text{ext}}^{\text{fix,3-COMP}} \equiv \{3.0\} \times \{3.0\} \times \{3.0\}$	
D–	$\left(\begin{array}{cccccccc} 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.4068 & 0.0297 & 0.4375 & 0.0000 \\ 0.0000 & 1.0000 & 0.3999 & 0.0790 & 0.0689 & 0.0000 & 0.4376 & 0.8034 \\ 1.0000 & 0.0000 & 0.6000 & 0.9210 & 0.5243 & 0.9703 & 0.1249 & 0.1966 \\ 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 \\ \hline 0.4087 & 0.2997 & 0.0790 & 0.0689 & 0.3999 & 0.8034 & 0.9104 & 1.0000 \\ 0.0000 & 0.2997 & 0.9210 & 0.4068 & 0.6000 & 0.1966 & 0.0000 & 0.0000 \\ 0.5913 & 0.4006 & 0.0000 & 0.5244 & 0.0000 & 0.0000 & 0.0896 & 0.0000 \\ 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 \end{array}\right)$	-49.3166
A–	$\left(\begin{array}{cccccccc} 0.0001 & 0.0000 & 0.0000 & 0.3037 & 1.0000 & 0.0460 & 0.4924 & 0.0529 \\ 0.4292 & 0.0000 & 0.7685 & 0.3004 & 0.0000 & 0.0000 & 0.0000 & 0.4153 \\ 0.5708 & 1.0000 & 0.2315 & 0.3959 & 0.0000 & 0.9540 & 0.5076 & 0.5318 \\ 0.0607 & 0.0209 & 0.0343 & 0.1881 & 0.0153 & 0.0126 & 0.0719 & 0.1381 \\ \hline 0.0000 & 0.4191 & 0.8235 & 0.4182 & 0.7818 & 0.0008 & 0.4862 & 0.0865 \\ 1.0000 & 0.5808 & 0.0000 & 0.4830 & 0.2165 & 0.0833 & 0.0515 & 0.9135 \\ 0.0000 & 0.0001 & 0.1765 & 0.0988 & 0.0016 & 0.9160 & 0.4623 & 0.0000 \\ 0.0220 & 0.0628 & 0.0221 & 0.1351 & 0.0265 & 0.0248 & 0.1434 & 0.0214 \end{array}\right)$	4.5346×10^5
	Fitted Parameters: $\Theta_{2,\text{ext}}^{\text{fit,3-COMP}} \equiv \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{1.0\} \times \{0.36\} \times \{0.24\} \times$ $\times \{0.45\} \times \{1.68\} \times \{0.96\} \times \{1.54\} \times \{1.2\} \times \{1.2\} \times \{0.6\}$ Fixed Parameters: $\Theta_{2,\text{ext}}^{\text{fix,3-COMP}} \equiv \{2.6\} \times \{2.0\} \times \{2.0\}$	
D–	$\left(\begin{array}{cccccccc} 0.0000 & 0.0000 & 0.0000 & 0.0003 & 0.0055 & 0.0136 & 0.0571 & 0.0571 \\ 0.0284 & 1.0000 & 0.6500 & 0.0000 & 0.2239 & 0.0115 & 0.6559 & 0.9429 \\ 0.9716 & 0.0000 & 0.3500 & 0.9996 & 0.7706 & 0.9749 & 0.2870 & 0.0000 \\ 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 \\ \hline 0.2275 & 0.2988 & 0.2988 & 0.5116 & 0.6180 & 0.6180 & 0.7666 & 1.0000 \\ 0.0000 & 0.4868 & 0.7000 & 0.1495 & 0.3820 & 0.3479 & 0.0001 & 0.0000 \\ 0.7725 & 0.2143 & 0.0012 & 0.3389 & 0.0000 & 0.0341 & 0.2334 & 0.0000 \\ 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 & 0.0625 \end{array}\right)$	-47.5488
A–	$\left(\begin{array}{cccccccc} 0.0000 & 0.0272 & 0.0180 & 0.1781 & 0.0124 & 0.0013 & 0.8321 & 0.8321 \\ 0.0001 & 0.4684 & 0.9816 & 0.0000 & 0.0000 & 0.0048 & 0.0000 & 0.0000 \\ 0.9999 & 0.5043 & 0.0004 & 0.8219 & 0.9876 & 0.9939 & 0.1679 & 0.1679 \\ 0.0181 & 0.0100 & 0.0751 & 0.0403 & 0.0100 & 0.0139 & 0.1194 & 0.0100 \\ \hline 0.2093 & 0.7172 & 0.9982 & 0.8321 & 0.5233 & 0.6230 & 0.0028 & 0.3710 \\ 0.7843 & 0.2827 & 0.0018 & 0.0000 & 0.4767 & 0.1111 & 0.3776 & 0.3050 \\ 0.0064 & 0.0000 & 0.0000 & 0.1679 & 0.0000 & 0.2658 & 0.6197 & 0.3240 \\ 0.1284 & 0.1347 & 0.0638 & 0.0100 & 0.1554 & 0.1213 & 0.0185 & 0.0712 \end{array}\right)$	3.1584×10^5

Table 8: Continuous optimal designs for finding the regression coefficients for models (26-28).

Model	Criterion	Design	Optimum
(26)	D–	$\begin{pmatrix} 0.0000 & 1.0000 & 0.6667 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.0000 & 0.3333 & 0.0000 & 0.0000 & 0.5000 & 1.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.5000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 \end{pmatrix}$	-11.9253
	A–	$\begin{pmatrix} 0.0000 & 1.0000 & 0.5796 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.0000 & 0.4204 & 0.0000 & 0.0000 & 0.5000 & 1.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.5000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0074 & 0.0137 & 0.0198 & 0.0074 & 0.2379 & 0.4756 & 0.2381 \end{pmatrix}$	1.8105×10^4
(27)	D–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.4937 & 0.8762 & 0.0000 \\ 0.0000 & 0.0000 & 0.5063 & 0.1238 & 1.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.2000 & 0.2000 & 0.2000 & 0.2000 & 0.2000 \end{pmatrix}$	-9.6570
	A–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.4824 & 0.8960 & 0.0000 \\ 0.0000 & 0.0000 & 0.5176 & 0.1040 & 1.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0082 & 0.0082 & 0.5357 & 0.1900 & 0.2580 \end{pmatrix}$	1.4917×10^4
(28)	D–	$\begin{pmatrix} 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.5000 \\ 0.2377 & 0.0000 & 0.0000 & 0.8873 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.5000 & 1.0000 & 0.0000 \\ 0.7623 & 0.0000 & 1.0000 & 0.1127 & 0.5000 & 0.0000 & 0.5000 \\ 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 & 0.1429 \end{pmatrix}$	-11.8587
	A–	$\begin{pmatrix} 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.4582 \\ 0.2492 & 0.0000 & 0.0000 & 0.7584 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.4582 & 1.0000 & 0.0000 \\ 0.7508 & 0.0000 & 1.0000 & 0.2416 & 0.5418 & 0.0000 & 0.5418 \\ 0.2735 & 0.0712 & 0.2155 & 0.0953 & 0.1366 & 0.0712 & 0.1366 \end{pmatrix}$	8.6923×10^2

Table 9: Exact optimal designs for finding the regression coefficients for models (26-28), $N = 3\, n_\theta$.

Model	Criterion	Design	Optimum
(26)	D–	$\begin{pmatrix} 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.6667 \\ 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.5000 & 0.0000 & 0.3333 \\ 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.5000 & 0.0000 & 0.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.0000 \\ 3 & 3 & 3 & 3 & 3 & 3 & 3 \end{pmatrix}$	-11.9253
	A–	$\begin{pmatrix} 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.6091 & 0.0000 \\ 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.3909 & 0.5000 \\ 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.5000 \\ 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 \\ 1 & 4 & 4 & 1 & 1 & 1 & 9 \end{pmatrix}$	2.0597×10^4
(27)	D–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.4937 & 0.8762 & 0.0000 \\ 0.0000 & 0.0000 & 0.5063 & 0.1238 & 1.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.0000 \\ 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.0000 \\ 3 & 3 & 3 & 3 & 3 \end{pmatrix}$	-9.6570
	A–	$\begin{pmatrix} 0.0000 & 0.0000 & 0.4900 & 0.8903 & 0.0000 \\ 0.0000 & 0.0000 & 0.5100 & 0.1029 & 1.0000 \\ 1.0000 & 0.0000 & 0.0000 & 0.0034 & 0.0000 \\ 0.0000 & 1.0000 & 0.0000 & 0.0034 & 0.0000 \\ 1 & 1 & 7 & 3 & 3 \end{pmatrix}$	1.6824×10^4
(28)	D–	$\begin{pmatrix} 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.5000 & 0.0000 & 0.0000 \\ 0.0000 & 1.0000 & 0.0000 & 0.1127 & 0.0000 & 0.0000 & 0.7623 \\ 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.5000 & 0.0000 \\ 0.0000 & 0.0000 & 0.0000 & 0.8873 & 0.5000 & 0.5000 & 0.2377 \\ 3 & 3 & 3 & 3 & 3 & 3 & 3 \end{pmatrix}$	-11.8587
	A–	$\begin{pmatrix} 1.0000 & 0.0000 & 0.0000 & 0.0000 & 0.4744 & 0.0000 & 0.0000 \\ 0.0000 & 0.7553 & 0.0000 & 0.0000 & 0.0000 & 0.0000 & 0.2517 \\ 0.0000 & 0.0000 & 1.0000 & 0.0000 & 0.0000 & 0.4744 & 0.0000 \\ 0.0000 & 0.2447 & 0.0000 & 1.0000 & 0.5256 & 0.5256 & 0.7483 \\ 2 & 2 & 2 & 4 & 3 & 3 & 5 \end{pmatrix}$	8.8670×10^2