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# CVX based algorithms for constructing various optimal regression designs

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## ABSTRACT

CVX based numerical algorithms are widely and freely available for solving convex optimization problems but their applications to solve optimal design problems are limited. Using the CVX programs in MATLAB, we demonstrate their utility and flexibility over traditional algorithms in statistics for finding different types of optimal approximate designs under a convex criterion for nonlinear models. They are generally fast and easy to implement for any model and any convex optimality criterion. We derive theoretical properties of the algorithms and use them to generate new  $A$ -,  $c$ -,  $D$ - and  $E$ -optimal designs for various nonlinear models, including multi-stage and multi-objective optimal designs. We report properties of the optimal designs and provide sample CVX program codes for some of our examples that users can amend to find tailored optimal designs for their problems.

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# 1 Introduction

An algorithmic approach is a practical way to find optimal designs. There are many types of algorithms for computing optimal designs and they come with different assumptions. Historically, many of the algorithms are deterministic, meaning that repeated runs of the algorithm with the same input produce the same design when it stops using the same stopping criterion. Some algorithms have a proof of convergence to the optimum and others are ad-hoc or based on heuristics. The former includes traditional ones, like Fedorov-type and exchange-type of algorithms, developed mainly for linear models and more than 40 years ago. They are well described in several design monographs, such as Fedorov (1972) and Silvey (1980).

The traditional algorithms generally work well but can be problematic when there are many variables to optimize and the model is nonlinear. They may stall or break down because of the huge computational burden. For instance, Broudiscou et al. (1996) claimed that traditional algorithms in statistics for finding optimal designs cannot be used to find non-standard designs, such as asymmetrical  $D$ -optimal designs. They found the algorithms performed poorly, difficult to handle and ultimately abandoned them for genetic algorithms. Similarly, Royle (2002) reported that the traditional exchange algorithms are not practical for finding large spatial designs because they can be computationally prohibitive when the criterion is computationally expensive to evaluate or the design space is too large. More recent algorithms include multiplicative algorithms, cocktail algorithm (Yu, 2011) and an algorithm proposed by Yang et al. (2013), where they showed their algorithms outperformed several traditional algorithms for finding optimal designs in several ways. Mandal et al. (2015) provides a brief review of current numerical approaches for finding optimal designs, including metaheuristic algorithms.

Apart from the above mentioned deterministic algorithms, there are also mathematical programming methods that seem highly appropriate for finding optimal designs. For reasons that are not very clear, these tools are considerably less used

in statistics for finding optimal designs, until recently. Papp (2012) reviewed semi-definite programming as a tool for finding optimal designs and noted its stability and theoretical guarantee of the efficiency. Using mainly polynomial models, he showed that running times required for finding various optimal designs are negligible. Additionally, Duarte and Wong (2014) and Duarte et al. (2015) used semi-infinite programming tools to find optimal designs, and Cuervo et al. (2016) employed a programming method to find  $D$ -optimal designs for linear models with multiple constraints on the design space. Ye et al. (2017) and Wong et al. (2017) further demonstrated the utility of semi-definite programming to find various types of optimal designs for linear models, and Wong et al. (2018) found various types of optimal designs for multi-response multi-factor experiments for nonlinear models using theory along with semi-definite programming tools.

CVX based numerical algorithms are widely used in engineering and available in MATLAB for solving convex optimization problems. However, their applications to solve optimal design problems are limited. Gao and Zhou (2017) was probably the first to apply a CVX program to find optimal moments of  $D$ -optimal designs for polynomial and trigonometric regression models. Our main goal in this paper is to demonstrate key advantages CVX programs have over traditional methods in statistics for finding optimal designs, including two-stage designs or multi-objective optimal designs for any model. Additionally, we derive theoretical results helpful for studying properties of the optimal designs and the algorithms. In particular, we show a generalization of the scale invariance property of  $D$ -optimal designs and how the choice of the discretized points in the design space affect the quality of the generated design. We provide new optimal designs and also show CVX based algorithms can find multi-stage or multi-objective optimal designs.

Section 2 describes statistical background and Section 3 studies CVX based algorithms for constructing optimal designs, including conditions for checking whether a design is optimal among all designs on the selected design space. In Section 4 we derive several properties of the algorithms and the generated optimal designs, and

in Section 5 we present various applications. Section 6 proposes another CVX based algorithm for finding optimal designs for large design space and models with several covariates. Section 7 concludes with proofs in the Appendix. MATLAB codes for four examples are given in the Supplementary Material.

## 2 Background

Suppose we have a statistical model for studying the relationship between a response variable  $Y$  and a set of independent variables  $\mathbf{x}$  from a known compact set  $S \subset R^k$ , where  $k$  is the dimension of  $\mathbf{x}$ . Design issues concern selecting points from  $S$  in some optimal way to observe the responses. We assume there are resources to take  $n$  independent observations and the mean response at  $\mathbf{x}$  is  $f(\mathbf{x}, \boldsymbol{\theta})$ , where  $\boldsymbol{\theta}$  is a  $q$ -dimensional vector of unknown parameters in the model.

There are two types of designs: approximate and exact. We focus on approximate designs and denote such a design with  $m$  points by  $\xi = \{(\mathbf{x}_i, w_i), i = 1, \dots, m\}$ , where  $\mathbf{x}_1, \dots, \mathbf{x}_m \in S$ ,  $w_1, \dots, w_m$  are the corresponding weights that sum to unity. The implemented design takes roughly  $nw_i$  observations at  $\mathbf{x}_i$ ,  $i = 1, \dots, m$ , subject to  $nw_1 + \dots + nw_m = n$  after rounding each  $nw_i$  to a positive integer. Approximate designs are easier to study and find because there is a unified theory for finding them and confirming their optimality using equivalence theorems.

Following convention, the worth of a design is measured by its Fisher information matrix. We denote this matrix by  $\mathbf{I}_\xi(\boldsymbol{\theta}) = \sum_{i=1}^m w_i \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta})$ , where  $\mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta})$  is the information from an observation at  $\mathbf{x}_i$ . The asymptotic covariance matrix of the maximum likelihood estimator  $\hat{\boldsymbol{\theta}}$  of  $\boldsymbol{\theta}$  is proportional to the inverse matrix of  $\mathbf{I}_\xi(\boldsymbol{\theta})$ . Many optimality criteria are formulated as a convex function  $\Phi(\cdot)$  and the design sought is  $\xi^* = \arg \min_{\xi} \Phi(\mathbf{I}_\xi^{-1}(\boldsymbol{\theta}))$ , and the minimization is over all designs on  $S$ . Examples of  $\Phi$  are the determinant and the trace functions. For nonlinear models,  $\mathbf{I}_\xi(\boldsymbol{\theta})$  depends on the true value  $\boldsymbol{\theta}$  and  $\xi^*$  is called a locally optimal design, or simply

an optimal design.

Finding analytical solutions to optimal design problems for nonlinear models (NMs) and generalized linear models (GLMs) is challenging unless the model is simple. The problem is compounded when the model has several factors or the design space has complicated constraints or errors have a complex correlation structure. We believe this in part explains why the bulk of design work concerns models with one or two factors; see for example, Biedermann et al. (2006), Dassel and Rawlings (1988), Dette and Biedermann (2003), and Fang et al. (2006). This suggests that relying solely on an analytical approach to find optimal designs can be limiting, when we have a high dimensional nonlinear model. More effective and powerful algorithms are needed to find optimal designs for more complicated design problems. The next section presents our algorithms for finding various types of optimal designs and how they can be programmed to generate tailor made designs for the user.

### 3 CVX based algorithms

CVX is a modeling system, developed for solving disciplined convex optimization problems (Grant and Boyd, 2013), and it is available in MATLAB. CVX can solve several types of optimization problems, including linear and quadratic programming, second-order cone programming, semi-definite programming, and other complex convex optimization problems. There are various algorithms to solve convex optimization problems (Boyd and Vandenberghe, 2004), including steepest descent method and Newton's method for unconstrained minimization problems, Newton's method for minimization problems with equality constraints, and interior point methods for inequality constrained minimization problems. Here we briefly discuss interior point methods. Consider a minimization problem with two inequality constraints,

$$\begin{aligned} \min_{\mathbf{v}} g_0(\mathbf{v}) & \tag{1} \\ \text{subject to: } g_1(\mathbf{v}) \leq 0, g_2(\mathbf{v}) \leq 0, \mathbf{A}\mathbf{v} = \mathbf{b}, \end{aligned}$$

where  $\mathbf{v} = (v_1, \dots, v_{k_0})^\top$ ,  $\mathbf{A}$  is a  $l_0 \times k_0$  constant matrix with rank  $l_0$ ,  $\mathbf{b}$  is a constant vector, and  $g_0, g_1$  and  $g_2$  are convex and twice continuously differentiable functions from  $R^{k_0}$  to  $R$ .

There are two key steps in interior point methods. The first step transforms the problem in (1) into an equality constrained problem by a logarithmic barrier function as follows,

$$\begin{aligned} \min_{\mathbf{v}} \quad & g_0(\mathbf{v}) - \frac{1}{\gamma} \sum_{i=1}^2 \log(-g_i(\mathbf{v})) \\ \text{subject to:} \quad & \mathbf{A}\mathbf{v} = \mathbf{b}, \end{aligned} \tag{2}$$

where  $-\sum_{i=1}^2 \log(-g_i(\mathbf{v}))$  is called a barrier function, and  $\gamma$  is a positive parameter. As  $\gamma \rightarrow \infty$ , the solution of problem (2) converges to that of problem (1).

The second step solves a sequence of problems in (2) defined by an increasing sequence of  $\gamma$ , say  $0 < \gamma^{(0)} < \gamma^{(1)} < \gamma^{(2)} < \dots$ . For a fixed  $\gamma$ , Newton's method or other methods can be applied to find a solution for problem (2). A barrier approach or path-following approach is then applied to solve the sequence of problems, using the solution for (2) with  $\gamma = \gamma^{(j)}$  as the starting point for (2) with  $\gamma = \gamma^{(j+1)}$ ,  $j = 0, 1, 2, \dots$ . Boyd and Vandenberghe (2004, Chapter 11) provide a detailed discussion about the choice of  $\gamma^{(j)}$ , stopping criteria and convergence analysis, which are carefully implemented in CVX. Other techniques such as solving dual problems and using sparsity features are also discussed to speed up the methods by reducing the number of variables. The dual problems for optimal design problems also provide interesting geometric interpretations for optimal designs and there are a few examples in Boyd and Vandenberghe (2004, Section 7.5). In summary the CVX system contains various optimization methods that are fully supported by theory.

The convex optimization problems need to be written in certain forms before they can be solved by CVX. The next subsection describes a few commonly used optimal design criteria and how they may be formulated in ways that CVX can optimize directly after the design space is discretized by the user into a set  $S_N$  of  $N$  grid points from which optimal design points are selected by CVX. The number  $N$

is also user-selected and can be very large. Frequently, the  $N$  grid points are equally spaced throughout the set  $S$  and there is a new proposal to use grid set that adapts after each iteration (Duarte et al., 2018). In Section 3.2 we present CVX algorithms and conditions for checking whether the CVX-generated designs are optimal.

### 3.1 Optimality criteria

Given a statistical model, the error distribution, and a discretized design space,  $S_N = \{\mathbf{x}_1, \dots, \mathbf{x}_N\}$ , we denote an approximate design on  $S_N$  by  $\xi_N = \{(\mathbf{x}_i, w_i), i = 1, \dots, N\}$  where the weight vector at these points,  $\mathbf{w} = (w_1, \dots, w_N)^\top$ , satisfies

$$w_i \geq 0, \quad i = 1, \dots, N, \quad \sum_{i=1}^N w_i = 1. \quad (3)$$

Given a design criterion, the optimization problem is to determine points in  $S_N$  that receive a positive weight and become support points of the optimal design. Berger and Wong (2009) provide details for several optimality criteria. For  $D$ -optimality, which is the most widely used criterion, we minimize the objective function

$$\mathcal{L}_D(\xi_N) = -\log(\det(\mathbf{I}_{\xi_N}(\boldsymbol{\theta}))), \quad (4)$$

or

$$\mathcal{L}'_D(\xi_N) = -(\det(\mathbf{I}_{\xi_N}(\boldsymbol{\theta})))^{1/q}, \quad (5)$$

over all vectors  $\mathbf{w}$  satisfying (3).

Other criteria include  $A$ -,  $A_s$ -,  $c$ -,  $I$ - and  $L$ -optimality. Like  $D$ -optimality, each of these criteria can be formulated as a convex function of  $\mathbf{w}$ . Collectively, these criteria are embedded in the following class of objective functions and our goal then is to find a weight distribution on  $S_N$  that optimizes the criterion,

$$\mathcal{L}_{AC}(\xi_N) = \text{trace}(\mathbf{C}^\top \mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}) \mathbf{C}), \quad (6)$$

where the choice of the  $q \times l$  matrix  $\mathbf{C}$  with  $l \leq q$  determines the optimality criterion. For singular  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta})$ ,  $\mathcal{L}_D(\xi_N)$  and  $\mathcal{L}_{AC}(\xi_N)$  are defined to be  $+\infty$ .

It is important that  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta})$  is linear in  $\mathbf{w}$ , so  $\mathcal{L}_D(\xi_N)$ ,  $\mathcal{L}'_D(\xi_N)$  and  $\mathcal{L}_{AC}(\xi_N)$  are convex functions of  $\mathbf{w}$  (Boyd and Vandenberghe, 2004, Bose and Mukerjee, 2015). We then apply CVX to find optimal designs after writing the convex optimization problem in a general form:

$$\begin{aligned} \min_{\mathbf{w}} \mathcal{L}(\xi_N) & \tag{7} \\ \text{subject to: } w_i \geq 0, \quad i = 1, \dots, N, \quad \sum_{i=1}^N w_i = 1, \end{aligned}$$

where  $\mathcal{L}(\xi_N)$  can be  $\mathcal{L}_D(\xi_N)$ ,  $\mathcal{L}'_D(\xi_N)$ ,  $\mathcal{L}_{AC}(\xi_N)$ , or other convex functions of  $\mathbf{w}$  discussed later in Section 4.4.

### 3.2 Algorithm I

We propose an algorithm to construct optimal designs via CVX as follows.

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**Algorithm I: Computing optimal designs via CVX in MATLAB**

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Step (i): Input parameter value for  $\boldsymbol{\theta}$  and design points  $\mathbf{x}_1, \dots, \mathbf{x}_N$ .

Step (ii): Compute the  $q \times q$  information matrices  $\mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta})$  at each  $\mathbf{x}_i$  for  $i = 1, \dots, N$ .

Step (iii): Use CVX to solve problem (7) for  $\mathbf{w}$  and denote the solution by  $\hat{\mathbf{w}}$ .

Step (iv): Check optimality of  $\hat{\mathbf{w}}$ .

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This algorithm is simple and can be applied to any model and various optimality criteria. Steps (i) and (ii) depend on the model and design space, while the design criterion is specified in Step (iii) through the objective function  $\mathcal{L}(\xi_N)$  in problem (7). In Step (iv), we verify if the numerical result  $\hat{\mathbf{w}}$  is an optimal design.

Similar to Bose and Mukerjee (2015) and Wong et al. (2017), the optimality conditions are stated in Lemma 1 below. Let  $\xi_N^*$  be the optimal design with weight vector  $\hat{\mathbf{w}}$ , let  $h_{T_i}(\hat{\mathbf{w}}) = \text{trace} \left( \mathbf{C}^\top \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}) \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}) - \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}) \right) \mathbf{C} \right)$ , and let  $h_{D_i}(\hat{\mathbf{w}}) = \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}) \right) - q$ ,  $i = 1, \dots, N$ . The latter two functions

represent the negative directional derivative of the criterion evaluated at  $\xi_N^*$  in the direction of the degenerate design at  $\mathbf{x}_i$ .

**Lemma 1.** *The optimality conditions are:*

(i)  $\xi_N^*$  is a  $D$ -optimal design on  $S_N$  if and only if it satisfies  $h_{Di}(\hat{\mathbf{w}}) \leq 0$ , for all  $i = 1, \dots, N$ ;

(ii)  $\xi_N^*$  is an optimal design that minimizes  $\mathcal{L}_{AC}(\xi_N)$  on  $S_N$  if and only if it satisfies  $h_{Ti}(\hat{\mathbf{w}}) \leq 0$ , for all  $i = 1, \dots, N$ .

The proof of Lemma 1 is omitted; it is similar to the proof of Lemma 2 in Wong et al. (2017). In practice, conditions in Lemma 1 are replaced by

$$h_{Di}(\hat{\mathbf{w}}) \leq \delta \text{ or } h_{Ti}(\hat{\mathbf{w}}) \leq \delta, \text{ for all } i = 1, \dots, N, \quad (8)$$

where  $\delta$  is a small positive number, say  $10^{-4}$ ; see Bose and Mukerjee (2015).

To compare two designs  $\xi^1$  and  $\xi^2$ , we use two efficiency measures:  $\text{Eff}_D(\xi^1, \xi^2) = \frac{\mathcal{L}'_D(\xi^1)}{\mathcal{L}'_D(\xi^2)}$  for  $D$ -optimality, and  $\text{Eff}_{AC}(\xi^1, \xi^2) = \frac{\mathcal{L}_{AC}(\xi^2)}{\mathcal{L}_{AC}(\xi^1)}$  for  $AC$ -optimality. If  $\text{Eff}_D(\xi^1, \xi^2) < 1$ ,  $\xi^2$  is more  $D$ -efficient than  $\xi^1$ . Likewise if  $\text{Eff}_{AC}(\xi^1, \xi^2) < 1$ ,  $\xi^2$  is more  $AC$ -efficient than  $\xi^1$ .

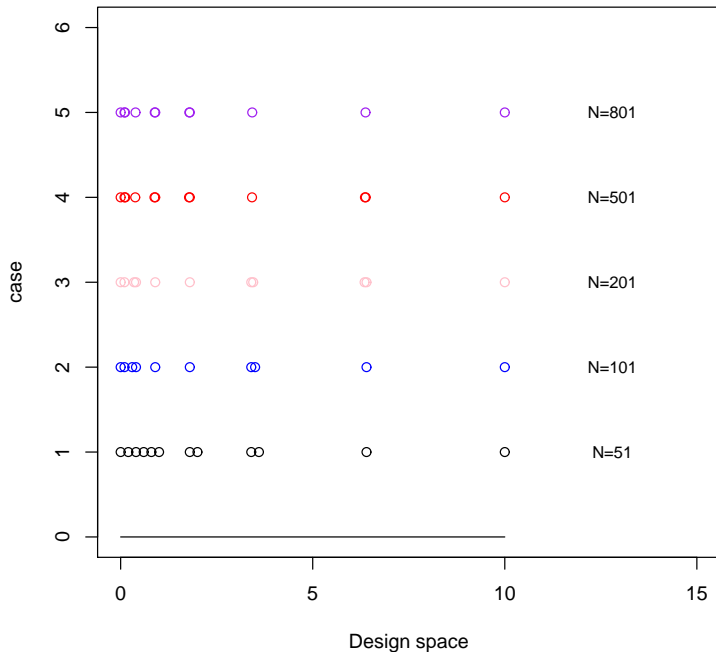
### 3.3 Programming in MATLAB

Example 1 illustrates how we implement Algorithm I in MATLAB to find optimal designs for a model frequently used in biological sciences. All computation times reported in the paper are from a PC equipped with an Intel(R) Core(TM)2 Quad CPU Q9550@2.83GHz.

**Example 1.** Consider the  $K$ -compartmental model given by

$$E(Y) = f(x, \boldsymbol{\theta}) = \sum_{j=1}^K \theta_j \exp(-\theta_{K+j}x), \quad x \geq 0, \quad 0 < \theta_{K+1} < \theta_{K+2} < \dots < \theta_{2K}.$$

Figure 1: Support points of the  $D$ -optimal designs for various values of grid size  $N$



Our goal is to compute  $D$ -optimal designs for the model on a user-selected discrete design space  $S_N \subset [a, b]$ . Here we use  $N$  equally spaced points, given by  $x_i = a + (b - a)(i - 1)/(N - 1)$ ,  $i = 1, \dots, N$ , which is commonly used. For this model, we have  $\mathbf{I}_x(\boldsymbol{\theta}) = \frac{\partial f(x, \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \left( \frac{\partial f(x, \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right)^\top$ . Earlier results for this model include those from Dette et al. (2006), who noted that the  $D$ -optimal designs do not depend on the true values of  $\theta_1, \dots, \theta_K$  and found the number of the support points in the  $D$ -optimal designs when  $K \leq 3$ . The derivation of the optimal design becomes very challenging when  $K \geq 4$ , as the information matrix approaches singularity.

Our MATLAB program that implements Algorithm I for this problem is given in the Supplementary Material, and it can find  $D$ -optimal designs for  $K \geq 4$ . The output of the program gives the support points of the  $D$ -optimal design and their positive weights, the value of the function  $-\mathcal{L}'_D(\xi_N)$ , the computation time and the maximum value of  $h_{Di}(\hat{\mathbf{w}})$  in (8). For  $K \leq 3$ , our results are consistent with those

Figure 2: Plot of  $d(x, \boldsymbol{\theta})$  versus  $x$  for the CVX-generated design with  $N = 801$

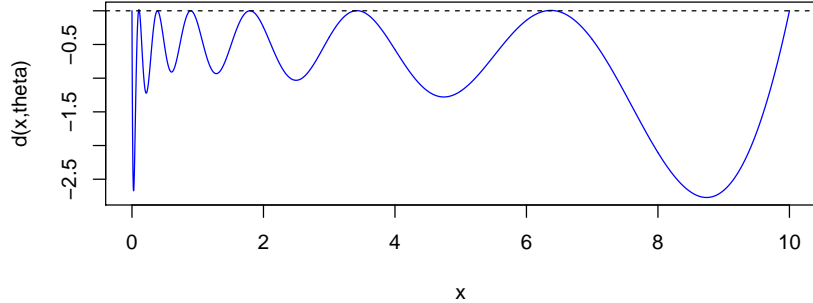


Table 1: Results for Example 1 with  $K = 4$  and  $S = [0, 10]$

Algorithm I	$N = 51$		$N = 101$		$N = 201$		$N = 501$		$N = 801$		
time (sec.)	0.8892		1.1388		1.7784		1.9188		3.2292		
$-\mathcal{L}'_D(\xi_N^*)$	0.0034		0.0037		0.0037		0.0037		0.0037		
$\text{Eff}_D(\xi_N^*, \xi_{801}^*)$	0.9295		0.9973		0.9973		1.0000		1.0000		
$\xi_{801}^*$											
support points	0.0000	0.1000	0.1125	0.3875	0.8875	0.9000	1.7875	1.8000	3.4250	6.3750	10.0000
weights	0.1250	0.0032	0.1218	0.1250	0.0369	0.0881	0.0854	0.0396	0.1250	0.1250	0.1250

in Dette et al. (2006). Our results for  $K = 4$  are new, and Figure 1 shows the  $D$ -optimal designs when  $(\theta_5, \dots, \theta_8) = (0.1, 0.6, 2.3, 5.5)$  and  $S_N \subset [0, 10]$  for different values of  $N$ . As  $N$  gets large, the support points are clustered around 8 points including the two boundary points 0 and 10. Let  $d(x, \boldsymbol{\theta}) = \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}) \mathbf{I}_x(\boldsymbol{\theta}) \right) - q$  and Figure 2 checks the conditions in (8) by the plot of  $d(x, \boldsymbol{\theta})$  versus  $x$  for  $N = 801$ . We observe that  $d(x, \boldsymbol{\theta}) \leq 0$  for all  $x \in [0, 10]$ , so the design found by our MATLAB program is  $D$ -optimal. Table 1 presents the computation time, objective function,  $D$ -efficiency and the optimal design for  $N = 801$ . These results indicate that Algorithm I is fast and effective for finding optimal designs, and the optimal designs are highly efficient for a moderate value of  $N$ .

## 4 Properties of Algorithm I and optimal designs

We provide more details and discuss several important issues related to the computation using Algorithm I, including a convergence result, scale transformation of design space, transformation of the information matrix, and multi-stage and multi-objective designs.

### 4.1 Convergence result

Let  $S$  be a given compact set. The set  $S_N (\subset S)$  is formed by Cartesian product of equally spaced points in each design variable. Let  $\xi^c$  be the optimal design on  $S$  and let  $\xi_N^*$  be the optimal design on  $S_N$ , found by solving problem (7). Yang et al. (2013, Theorem 5) derived an efficiency lower bound for any continuous design on a discretized design space  $S_N$ . We have the following result for  $\xi_N^*$  as  $N \rightarrow \infty$ .

**Theorem 1.** *If all the elements of  $\mathbf{I}_x(\boldsymbol{\theta})$  are bounded and continuous functions of  $\mathbf{x} \in S$ , then  $\mathcal{L}(\xi_N^*) \rightarrow \mathcal{L}(\xi^c)$  as  $N \rightarrow \infty$ .*

The proof of Theorem 1 is in the Appendix. The sequence of designs  $\xi_N^*$  may also converge to  $\xi^c$  in distribution. In Example 1,  $\mathcal{L}(\xi_N^*)$  converges as  $N$  gets large, and the support points shown in Figure 1 seem to converge to the 8 points in  $\xi_{801}^*$ .

### 4.2 Scale transformation of design space

$D$ -optimal designs for NMs and GLMs are usually not scale invariant. We derive a general relationship between  $D$ -optimal designs and the design spaces for various models. To fix ideas, let  $\xi^*(S_N, \boldsymbol{\theta})$  be the  $D$ -optimal design on the design space  $S_N$  with true model parameter value  $\boldsymbol{\theta}$ . Let  $\mathbf{V} = \text{diag}(s_1, \dots, s_k)$  be a  $k \times k$  diagonal matrix with  $s_j > 0$  ( $j = 1, \dots, k$ ) and let  $S_N^V = \{\mathbf{V}\mathbf{x}_1, \dots, \mathbf{V}\mathbf{x}_N\}$  be the transformed design space. This transformation scales each design variable  $x_j$  by a factor  $s_j$ , for  $j = 1, \dots, k$ .

**Theorem 2.** Suppose  $\xi^*(S_N, \boldsymbol{\theta}) = \{(\mathbf{x}_i^*, w_i^*), i = 1, \dots, m\}$  is a  $D$ -optimal design for a model with parameter value  $\boldsymbol{\theta}$  on  $S_N$ . If there exists a constant  $q \times q$  nonsingular matrix  $\mathbf{T}$  (not depending on  $\mathbf{x}$  and  $\boldsymbol{\theta}$ ) and parameter value  $\boldsymbol{\theta}^V$  such that

$$\mathbf{I}_{\mathbf{V}\mathbf{x}}(\boldsymbol{\theta}^V) = \mathbf{T} \mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta}) \mathbf{T}^\top, \quad \text{for all } \mathbf{x} \in S_N, \quad (9)$$

then  $\xi^*(S_N^V, \boldsymbol{\theta}^V) = \{(\mathbf{V}\mathbf{x}_i^*, w_i^*), i = 1, \dots, m\}$  is a  $D$ -optimal design for the model with parameter value  $\boldsymbol{\theta}^V$  on design space  $S_N^V$ .

The proof of Theorem 2 is in the Appendix. The result is a generalization of the scale invariance property in linear models and can be applied to any model. For linear models,  $\mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta})$  does not depend on parameter  $\boldsymbol{\theta}$ , so the condition in (9) becomes  $\mathbf{I}_{\mathbf{V}\mathbf{x}}(\boldsymbol{\theta}) = \mathbf{T} \mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta}) \mathbf{T}^\top$  and the result in Theorem 2 becomes a scale invariance property of  $D$ -optimal designs. For NMs and GLMs, the  $D$ -optimal designs on  $S_N$  and  $S_N^V$  are related through different parameter values:  $\boldsymbol{\theta}$  and  $\boldsymbol{\theta}^V$ . Our experience is that (9) holds for many models and matrix  $\mathbf{T}$  is usually diagonal and depends on the scale matrix  $\mathbf{V}$ . Example 2 below illustrates some of these ideas. In Section 4.3 and Example 3 we use Theorem 2 to handle the situation when we have an ill-conditioned information matrix.

**Example 2.** Consider the logistic model with two variables and an interaction term, and the probability of a response is

$$P(\mathbf{x}, \boldsymbol{\theta}) = \frac{\exp(\theta_0 + \theta_1 x_1 + \theta_2 x_2 + \theta_3 x_1 x_2)}{1 + \exp(\theta_0 + \theta_1 x_1 + \theta_2 x_2 + \theta_3 x_1 x_2)}, \quad 0 \leq x_1 \leq b_1, \quad 0 \leq x_2 \leq b_2,$$

where  $\boldsymbol{\theta} = (\theta_0, \dots, \theta_3)^\top$  is the parameter vector. We use  $N_1$  and  $N_2$  equally spaced grid points from  $[0, b_1]$  and  $[0, b_2]$ , respectively, to form  $S_N$  with  $N = N_1 N_2$ . A direct calculation shows the information matrix for this model at a single observation is

$$\mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta}) = \frac{\exp(\mathbf{z}^\top \boldsymbol{\theta})}{(1 + \exp(\mathbf{z}^\top \boldsymbol{\theta}))^2} \mathbf{z} \mathbf{z}^\top, \quad \text{with } \mathbf{z} = (1, x_1, x_2, x_1 x_2)^\top.$$

Let  $\mathbf{V} = \text{diag}(s_1, s_2)$ ,  $\boldsymbol{\theta}^V = (\theta_0, \frac{\theta_1}{s_1}, \frac{\theta_2}{s_2}, \frac{\theta_3}{s_1 s_2})^\top$  and let  $\mathbf{T} = \text{diag}(1, s_1, s_2, s_1 s_2)$ . It is easy to verify that (9) holds, and the same is true when  $k > 2$  and there are several interaction terms in the model.

### 4.3 Transformation on the information matrix

Sometimes the information matrix is ill-conditioned and computational problems can arise. Consequently, the optimal design problem in (7) with objective function involving  $\mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta})$  may not be easy to solve. For such situations, we suggest to decompose the information matrix and write it as  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta}) = \mathbf{D} \mathbf{B} \mathbf{D}^\top$  before feeding it into Algorithm I, where  $\mathbf{B}$  and  $\mathbf{D}$  are  $q \times q$  nonsingular matrices. This strategy is especially helpful if it is easier to find  $\mathbf{D}^{-1}$  and  $\mathbf{B}^{-1}$  numerically than  $\mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta})$ . For many models, scaling the design space can result in a different form of  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta})$ , and by (9) we have  $\mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta}) = \mathbf{T}^{-1} \mathbf{I}_{\mathbf{V}_{\mathbf{x}}}(\boldsymbol{\theta}^V) \mathbf{T}^{-\top}$ , which leads to  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta}) = \mathbf{T}^{-1} \left( \sum_{i=1}^N w_i \mathbf{I}_{\mathbf{V}_{\mathbf{x}_i}}(\boldsymbol{\theta}^V) \right) \mathbf{T}^{-\top}$ . Our strategy is to work with the inverse of  $\left( \sum_{i=1}^N w_i \mathbf{I}_{\mathbf{V}_{\mathbf{x}_i}}(\boldsymbol{\theta}^V) \right)$  in Algorithm I. There are other transformations that can be used, such as a simple one that scales  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta})$  by a constant factor for all the elements in the matrix. The transformations discussed here can be applied to all optimality criteria, even though equation (9) is developed to show a property of  $D$ -optimal designs. We now show that an appropriate transformation on the information matrix can help find  $c$ -optimal designs effectively in Example 3.

**Example 3.** Guess et al. (1977) proposed a Probit like dose response model to ascertain the probability that an animal will have a type of cancer tumor as the dose of a compound varies. This postulated probability as a function of the dose  $x$  assumes all the coefficients in the model are non-negative and is given by  $P(x, \boldsymbol{\theta}) = 1 - \exp(-(\theta_0 + \theta_1 x + \theta_2 x^2 + \theta_3 x^3))$ ,  $x \in [0, b]$ . Hoel and Jennrich (1979) used theory and found  $c$ -optimal designs for estimating the excess probability  $P(t, \boldsymbol{\theta}) - P(0, \boldsymbol{\theta})$  of an animal developing cancer if it is continuously exposed to a carcinogenic compound at dose  $t$ , and  $P(0, \boldsymbol{\theta})$  is the probability due to background sources. We applied Algorithm I and were able to confirm the results in Hoel and Jennrich (1979) for the case when  $t = 0.5$  by computing the  $c$ -optimal for estimating  $g_1(\boldsymbol{\theta}) = P(0.5, \boldsymbol{\theta}) - P(0, \boldsymbol{\theta})$  when  $b = 500$ . Frequently, differences between scalar quantities are measured by their difference or their ratio and usually the former is simpler to estimate and draw inference. Our CVX based program is flexible in that if we wish

Table 2: c-optimal designs for Example 3 with  $\boldsymbol{\theta} = (0.01, 0.000267377, 0, 0)^\top$

$N$	time (sec.)	optimal design				$\mathcal{L}_{AC}(\xi_N^*)$	$\text{Eff}_{AC}(\xi_N^*, \xi_{5001}^*)$	
estimating $g_1(\boldsymbol{\theta})$								
6	0.9828	support points	0.0000	100.0000	300.0000	500.0000	$1.1142 \times 10^{-5}$	0.9190
		weights	0.2315	0.5364	0.1887	0.0434		
51	0.5928	support points	0.0000	80.0000	340.0000	500.0000	$1.0252 \times 10^{-5}$	0.9988
		weights	0.2739	0.5359	0.1414	0.0488		
501	1.6068	support points	0.0000	83.0000	342.0000	500.0000	$1.0240 \times 10^{-5}$	1.0000
		weights	0.2668	0.5324	0.1488	0.0520		
5001	11.5288	support points	0.0000	82.6000	342.4000	500.0000	$1.0240 \times 10^{-5}$	1.0000
		weights	0.2677	0.5325	0.1479	0.0519		
estimating $g_2(\boldsymbol{\theta})$								
6	1.2168	support points	0.0000	100.0000	300.0000	500.0000	0.2192	0.9416
		weights	0.4493	0.3844	0.1352	0.0311		
51	1.0764	support points	0.0000	80.0000	340.0000	500.0000	0.2065	0.9992
		weights	0.4859	0.3794	0.1001	0.0346		
501	1.7316	support points	0.0000	83.0000	342.0000	500.0000	0.2064	1.0000
		weights	0.4810	0.3769	0.1053	0.0368		
5001	11.8561	support points	0.0000	82.6000	342.4000	500.0000	0.2064	1.0000
		weights	0.4815	0.3770	0.1048	0.0367		

to estimate the ratio of the two quantities, Algorithm I can directly find the optimal design for estimating  $g_2(\boldsymbol{\theta}) = P(0.5, \boldsymbol{\theta})/P(0, \boldsymbol{\theta})$  with the same set of nominal values. Table 2 shows selected optimal designs for these two objectives for various values of  $N$ . The optimal designs for estimating  $g_2(\boldsymbol{\theta})$  are new. All the optimal designs have 4 support points with unequal weights. Algorithm I is fast, taking about 11 seconds when  $N = 5001$ . For this problem, we transformed the objective function by rescaling the variable  $x$  appropriately using  $x' = x/b$ . The detailed transformation and the MATLAB codes are given in the Supplementary Material.

#### 4.4 Two-stage designs and multi-objective designs

Algorithm I can also be used to find other types of optimal designs, including multi-stage and multi-objective designs. In multi-stage design, let  $\xi_0$  be the first stage

design, let  $\xi_N$  be the design at the next stage, and let  $n_0$  and  $n_1$  be the number of observations to be taken at the first and second stages, respectively. The combined design is denoted by  $\xi_0 + \xi_N$ , which is defined in Yang et al. (2013). The information matrix of the combined design is  $\mathbf{I}_{\xi_0 + \xi_N}(\boldsymbol{\theta}) = \frac{n_0}{n_0 + n_1} \mathbf{I}_{\xi_0}(\boldsymbol{\theta}) + \frac{n_1}{n_0 + n_1} \mathbf{I}_{\xi_N}(\boldsymbol{\theta})$ . The commonly used criteria can be formed similarly as in (4), (5), or (6) by replacing the information matrix  $\mathbf{I}_{\xi_N}(\boldsymbol{\theta})$  by  $\mathbf{I}_{\xi_0 + \xi_N}(\boldsymbol{\theta})$  to find an one-stage design.

An alternative is that, given the first stage design, we want to improve it in the second stage design by minimizing the objective function over all second-stage designs  $\xi_N$  to find the optimal designs. For fixed sample sizes  $n_0$  and  $n_1$  in the multi-stage design problem, we note that  $\mathbf{I}_{\xi_0 + \xi_N}(\boldsymbol{\theta})$  is still linear in  $\mathbf{w}$  and Algorithm I can be directly applied for finding multi-stage optimal designs. In addition, this two-stage design approach can be easily extended to construct sequential designs.

Our optimal designs depend on the true value of  $\boldsymbol{\theta}$ , which is frequently unknown in practice. Nominal values are needed and even though they can come from previous studies, they may not agree. Because a wrong set of nominal values can produce very inefficient designs, a multiple-objective optimal design is helpful to incorporate the uncertainty in each set of the nominal values. To fix ideas, suppose there are two possible nominal values,  $\boldsymbol{\theta}^*$  and  $\boldsymbol{\theta}^{**}$  for  $\boldsymbol{\theta}$  and we wish to design a study so that the implemented design is efficient regardless which of the two sets of nominal values is valid. One approach is to modify objective functions in (4) and (6) as follows:

$$\begin{aligned}\mathcal{L}_D^\alpha(\xi_N) &= -(1 - \alpha) \log(\det(\mathbf{I}_{\xi_N}(\boldsymbol{\theta}^*))) - \alpha \log(\det(\mathbf{I}_{\xi_N}(\boldsymbol{\theta}^{**}))), \\ \mathcal{L}_{AC}^\alpha(\xi_N) &= (1 - \alpha) \text{trace}(\mathbf{C}^\top \mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}^*) \mathbf{C}) + \alpha \text{trace}(\mathbf{C}^\top \mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}^{**}) \mathbf{C}),\end{aligned}$$

where  $\alpha$  is a user-selected number in  $[0, 1]$  and reflects the strength of belief which set is closer to the truth.

When  $\alpha = 0$  we only use the information obtained from assuming  $\boldsymbol{\theta}^*$ , and when  $\alpha = 1$  we only use the information from  $\boldsymbol{\theta}^{**}$ . If there are more than two possible values of  $\boldsymbol{\theta}$  to be considered, weighted average objective functions can be defined similarly. Since  $\mathcal{L}_D^\alpha(\xi_N)$  and  $\mathcal{L}_{AC}^\alpha(\xi_N)$  are still convex functions of  $\mathbf{w}$ , we modify

Algorithm I slightly for finding optimal designs: in Step (i) we input two parameter values  $\boldsymbol{\theta}^*$  and  $\boldsymbol{\theta}^{**}$  and design points  $\mathbf{x}_1, \dots, \mathbf{x}_N$ , in Step (ii) we compute  $\mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^*)$  and  $\mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^{**})$  for each  $i$ , and Steps (iii) and (iv) are the same. The conditions in Lemma 1 are now changed to verify if a design is a multi-objective optimal design as follows.

**Theorem 3.** *For a user-selected choice of  $N$ ,  $S_N \subset S$  and  $\alpha$  in  $[0, 1]$ ,*

(i) *the design  $\xi_N^*$  is optimal for minimizing  $\mathcal{L}_D^\alpha(\xi_N)$  on  $S_N$ , if and only if it satisfies, for all  $i = 1, \dots, N$ ,*

$$(1 - \alpha) \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^*) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^*) \right) + \alpha \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^{**}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^{**}) \right) - q \leq 0;$$

(ii) *the design  $\xi_N^*$  is optimal for minimizing  $\mathcal{L}_{AC}^\alpha(\xi_N)$  on  $S_N$ , if and only if it satisfies, for all  $i = 1, \dots, N$ ,*

$$(1 - \alpha) \text{trace} \left( \mathbf{C}^\top \left[ \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^*) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^*) \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^*) - \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^*) \right] \mathbf{C} \right) + \\ \alpha \text{trace} \left( \mathbf{C}^\top \left[ \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^{**}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^{**}) \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^{**}) - \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^{**}) \right] \mathbf{C} \right) \leq 0.$$

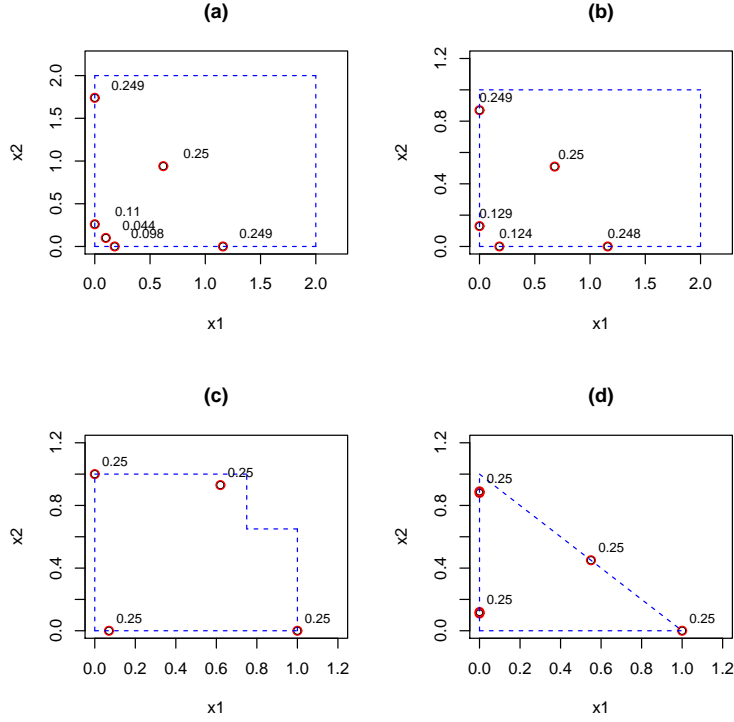
The proof of Theorem 3 is deferred to the Appendix. For practical applications, we relax the conditions in Theorem 3 the same way as we did in (8).

## 5 Applications

We now apply Algorithm I to find different types of optimal designs for various models including situations when the design space is irregularly shaped or models with several design variables.

Much of the design space assumed in the literature is the prototype cuboid or similar form. Sometimes irregularly shaped design spaces arise in practice. Design problems for an irregularly shaped design space can pose additional theoretical challenges. Using Example 4 as an example, we show that Algorithm I can find optimal designs for a logistic model with two factors on various design spaces.

Figure 3:  $D$ -optimal designs for Example 4 on various design spaces bounded by the dotted lines. The support points and weights are indicated by the circles and numbers, respectively. In (a) and (c),  $\boldsymbol{\theta} = (-2, 3, 2, 1)^\top$ ; in (b) and (d)  $\boldsymbol{\theta} = (-2, 3, 4, 1)^\top$ .



**Example 4.** We revisit Example 2 with the model now defined on design spaces in Figure 3. Design spaces in (a) and (b) are regularly shaped and those in (c) and (d) are irregularly shaped. We discretize interval  $[0, 1]$  with 101 equally spaced points for each factor space, so  $S_N$  contains  $N = 101^2, 101^2, 9326$ , and 5151 points, respectively, for the design spaces in (a), (b), (c) and (d). Figure 3 displays the support points and the weights of  $D$ -optimal designs. It shows that the number of support points in the  $D$ -optimal designs for this model depends on the nominal value of  $\boldsymbol{\theta}$  and the shape of the design space. For these design spaces the number of support points is 4, 5, or 6.

**Example 5.** This is an application with several design variables (large  $k$  and  $q$ ) in Yang et al. (2011), who studied a logistic model with multiple design variables and

Table 3:  $A$ - and  $D$ -optimal designs for Example 5 found by Algorithm I

	$k = q - 1$	$N = 2^k$	No. of points in $\xi_N^*$	objective function	time (sec.)
$D$ -optimality				$\mathcal{L}'_D(\xi_N^*)$	
	7	128	8	-0.0200	0.8580
	10	1024	22	-0.0176	8.7205
	12	4096	33	-0.0383	55.6876
	13	8192	45	-0.0465	247.5268
$A$ -optimality				$\frac{1}{q} \text{trace}(\mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}))$	
	7	128	10	139.0272	1.0296
	10	1024	31	173.9662	8.9233
	12	4096	43	77.8354	54.2804
	13	8192	57	63.7061	251.7388

no interactions. A direct calculation shows that the information matrix is

$$\mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta}) = \frac{\exp(\theta_0 + \theta_1 x_1 + \cdots + \theta_k x_k)}{(1 + \exp(\theta_0 + \theta_1 x_1 + \cdots + \theta_k x_k))^2} \begin{pmatrix} 1 \\ \mathbf{x} \end{pmatrix} (1 \ \mathbf{x}^\top), \quad \text{with } \mathbf{x}^\top = (x_1, \dots, x_k).$$

Yang et al. (2011) studied optimal designs based on  $2^k$  support points with each variable taking two points at  $-1$  and  $+1$ . In particular, when  $k+1$  is a multiple of 4, the minimum number of support points can be as small as  $k+1$  and a procedure is proposed to construct such designs. When  $k+1$  is not a multiple of 4, the minimum number of support points can be much larger than  $k+1$ . In this case, Algorithm I can be directly applied to find optimal designs on  $S_N$  including all the  $2^k$  points. For  $k=7$ , Algorithm I finds a  $D$ -optimal design with 8 support points with equal weight, which is the smallest number of support points to make the information matrix nonsingular. In the Supplementary Material, a 10-point  $A$ -optimal design for  $k=7$  variables is presented. The computation is very fast for  $k \leq 13$  even though  $N = 2^{13} = 8192$  is quite large. Table 3 lists the number of support points of the  $A$ - and  $D$ -optimal designs and the computation time.

**Example 6.** This example computes  $D$ - and  $E$ -optimal designs for the logistic model with 7 covariates  $x_1, \dots, x_7$  and 4 interaction terms:  $x_1 x_2, x_1 x_3, x_1 x_4$  and  $x_1 x_5$ . The design space is  $S = [-1, +1]^7$  and we discretize the design space of each variable  $x_j$  by dividing it into  $N_j$  equally spaced grid points in  $[-1, +1]$ ,  $j = 1, \dots, 7$ ,

Table 4:  $D$ - and  $E$ -optimal designs for the logistic model with  $k = 7$ ,  $q = 12$  and  $\boldsymbol{\theta} = (1.0, -6.0, 5.79, 0.25, 3.15, -0.9, -1.2, 2.06, -0.5, -1.08, 0.65, 0.01)^\top$ . The notation  $\lambda_{min}$  denotes the smallest eigenvalue of the matrix in brackets.

Design space $S_N$	No. of points in $\xi_N^*$	objective function	time (sec.)
$N = N_1 \times N_2 \times \dots \times N_7$		$D$ -optimality $\mathcal{L}'_D(\xi_N^*)$	
$N = 2^7$	21	-0.0905	1.5532
$N = 3^7$	32	-0.1246	11.7313
$N = 5 \times 5 \times 5 \times 2 \times 2 \times 2 \times 3$	37	-0.1254	20.8573
$N = 5 \times 5 \times 5 \times 5 \times 2 \times 2 \times 3$	40	-0.1256	98.1325
		$E$ -optimality $\lambda_{min}(\mathbf{I}_{\xi_N^*}(\boldsymbol{\theta}))$	
$N = 2^7$	14	0.0036	1.3104
$N = 3^7$	16	0.0049	7.2696
$N = 5 \times 5 \times 5 \times 2 \times 2 \times 2 \times 3$	22	0.0049	19.6093
$N = 5 \times 5 \times 5 \times 5 \times 2 \times 2 \times 3$	17	0.0049	91.3367

so that  $S_N$  has  $N = N_1 N_2 \dots N_7$  points. We have used various combinations of grid points in  $S_N$  and apply Algorithm I for finding optimal designs. Representative results for  $D$ - and  $E$ -optimal designs are in Table 4. From Table 4, the optimal designs on  $S_N$  with  $N = 2^7$  are only 72.6% and 72.1% efficient as those with  $N = 3^7$  for  $D$ - and  $E$ -optimality criteria, respectively. When  $N > 3^7$ , the efficiency of the optimal designs increases very little in this example. We also notice that the number of support points in the  $E$ -optimal designs is smaller than that in the  $D$ -optimal designs. When the theoretical results for optimal designs are extremely hard to derive for the logistic model with several covariates and interaction terms, Algorithm I can easily find the optimal designs on various  $S_N$ .

## 6 Another CVX based algorithm

When there are many design variables in the model, the number of grid points needed to cover the design space can be huge. If  $N$  is huge, say  $N > 10,000$ , Algorithm I may be slow or fail to find the optimal designs. For this situation, we recommend modifying Algorithm I to speed up the algorithm. For given  $\boldsymbol{\theta}$  and  $S_N$  we define

function,  $\Delta(\mathbf{x}, \xi_N) = \text{trace}(\mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}) \mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta})) - q$  for  $D$ -optimality, or

$$\Delta(\mathbf{x}, \xi_N) = \text{trace}(\mathbf{C}^\top \mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}) \mathbf{I}_{\mathbf{x}}(\boldsymbol{\theta}) \mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}) \mathbf{C}) - \text{trace}(\mathbf{C}^\top \mathbf{I}_{\xi_N}^{-1}(\boldsymbol{\theta}) \mathbf{C})$$

for the criterion in (6). From Lemma 1,  $\xi_N^*$  is optimal if and only if  $\Delta(\mathbf{x}_i, \xi_N^*) \leq 0$  for all  $i = 1, \dots, N$ .

Yang et al. (2013) proposed a 3-step general algorithm to find  $\xi_N^*$  with the following steps:

- Step (I): Start with a small subset  $S^{(0)} \subset S_N$ . Usually  $N_0$  is much smaller than  $N$ , but larger than  $k$ . Set  $t = 0$ .
- Step (II): Compute optimal weights for the support points in  $S^{(t)}$  and denote the optimal design on  $S^{(t)}$  as  $\xi^{(t)}$ . Update  $S^{(t)}$  by removing those points with zero weights, and
- Step (III): Find  $\mathbf{x}_t^* = \arg \max_{\mathbf{x} \in S_N} \Delta(\mathbf{x}, \xi^{(t)})$ . If  $\Delta(\mathbf{x}_t^*, \xi^{(t)}) < \delta$  (a prespecified small positive number), then  $\xi^{(t)}$  is the desired optimal design. Otherwise, set  $t = t + 1$  and  $S^{(t+1)} = S^{(t)} \cup \{\mathbf{x}_t^*\}$  and go to Step (II).

Step (II) is accomplished by using Newton's iterative method to obtain the optimal weights. There are two practical issues with this algorithm. First, the user needs to feed the first and second derivatives of  $\mathcal{L}(\xi_{N_t})$  with respect to the vector of weights  $\mathbf{w} = (w_1, \dots, w_{N_t})^\top$  to the codes for each iteration. Here  $N_t$  is the number of design points in  $S^{(t)}$ , and  $w_1, \dots, w_{N_t}$  are the weights in  $\xi_{N_t}$ . This task can be both laborious and complex, especially when the model is complicated. The second problem is that the Newton's iteration procedure does not guarantee to find the optimal weights and further, sometimes the weights can become negative and violate the conditions in (3).

To overcome these issues, we develop a fast CVX based algorithm by combining CVX with the algorithm proposed by Yang et al. (2013). The key is to recognize that Step (II) above is similar to solving an optimization problem in (7). Our experience is that if we use CVX instead of the Newton's iterative method in Step (II), we optimize

the weights effectively without the issues related to Newton iteration procedure. The combined algorithm is outlined as follows.

**Algorithm II: Iterative procedure using CVX**

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Step (I): It is the same as in Step (I) of Yang et al. (2013).  $N_0$  points in  $S^{(0)}$  can be randomly selected from  $S_N$  or uniformly distributed on  $S_N$ .

Step (II): Use CVX to compute optimal weights for the support points in  $S^{(t)}$  and denote the optimal design on  $S^{(t)}$  as  $\xi^{(t)}$ . Update  $S^{(t)}$  by removing those points with zero weights.

Step (III): It is the same as in Step (III) of Yang et al. (2013).

---

We follow Steps (ii) and (iii) of Algorithm I to implement Step (II) of Algorithm II. Algorithm II is very fast and can find optimal designs on  $S_N$  with huge  $N$ . In Algorithm I we use CVX to compute optimal weights for all the points in  $S_N$ , which can be slow when we have a high dimensional design problem and  $N$  is huge. At each iteration in Algorithm II, we use CVX to compute the optimal weights for all the points in  $S^{(t)}$ . Since  $S^{(t)}$  usually has a small number of points, this is the main reason that Algorithm II can handle a large number of grid points. Using Algorithm II we have computed optimal designs on  $S_N$  with  $N$  as large as  $10^6$ .

Table 5 compares the computation times required by Algorithms I and II for finding the optimal design in Example 1 in Yang et al. (2013) using various values of  $N$ . When Algorithm I takes too long to produce the design, we only report the results for Algorithm II. From Table 5, we observe that Algorithm I is faster than Algorithm II when  $N \leq 1,000$ , and Algorithm II is much faster than Algorithm I when  $N \geq 10,000$ . In addition, the ratio of computation time of Algorithm II to  $N$  decreases as  $N$  increases, which makes Algorithm II very efficient for large  $N$ . We tried to code the algorithm in Yang et al. (2013) in the software R and its resulting performance was very slower. We recognize that our codes were implemented on different platforms and on computers with different capabilities and so it is problematic to have a truly fair comparison.

Table 5: Computation times of ALGI (Algorithm I) and ALGII (Algorithm II)

Computation time (sec.)	<i>D</i> -optimal design		<i>A</i> -optimal design	
	ALGI	ALGII	ALGI	ALGII
$N = 500$	1.1312	6.0937	1.3740	3.4109
$N = 1,000$	2.0932	7.1963	2.1478	3.7916
$N = 5,000$	10.9751	8.7841	11.0433	4.2915
$N = 10,000$	33.7330	9.7546	34.1228	5.2793
$N = 20,000$	123.2608	11.0105	123.3329	5.6068
$N = 50,000$		16.9809		8.4723
$N = 100,000$		28.6356		15.3243
$N = 1,000,000$		203.2512		99.5638

## 7 Conclusion

Our paper provides theoretical insights into optimal designs found on a discretized design space and the theoretical optimal designs on the continuous design space. We study invariance properties of the optimal designs we found for nonlinear models and GLMs, including relationships between optimal designs found on different design space and how effective transformation of the information matrix can help us find the optimal design. We also recommend strategies when scaling issues arise due to either a large design space or wildly varying magnitudes of the elements in the information matrix that make it ill-conditioned. We emphasize that algorithms are important tools for finding optimal designs for complex models and they should be fast, flexible and easy to use.

We show that CVX based algorithms are very useful tools for finding optimal designs. In particular, they are fast and flexible. Our Algorithms I and II easily find various types of optimal designs for any model on a user-selected discretized design space  $S_N$ . Algorithm I is effective and fast for  $N < 10,000$  and we recommend Algorithm II when  $N \geq 10,000$ . Our experience is that we often do not require a large value of  $N$  to obtain a highly efficient design and so we believe Algorithm I suffices in practice. We close by noting that there is a version of CVX in R called CVXR that solves convex optimization problems. Our experience is that at this

time, this program works very slow compared with the MATLAB codes but we note that CVXR is currently pending an update.

## Supplementary Material

Four MATLAB programs are provided for computing  $D$ -,  $c$ -,  $A$ - and  $E$ -optimal designs in Examples 1, 3, 5 and 6. We also give the detailed scale transformation of the objective function in Example 3 and an  $A$ -optimal design in Example 5.

## Appendix: Proofs

**Proof of Theorem 1:** Let  $\mathbf{x}_1^c, \dots, \mathbf{x}_m^c \in S$  be the support points of  $\xi^c$  and let the optimal weights be  $w_1^c, \dots, w_m^c$ . From the construction of  $S_N (\subset S)$ , there exists a sequence of distinct points,  $\mathbf{u}_1^{(N)}, \dots, \mathbf{u}_m^{(N)}$  in  $S_N$ , such that  $\lim_{N \rightarrow \infty} \mathbf{u}_j^{(N)} = \mathbf{x}_j^c$  for  $j = 1, \dots, m$ . For each  $N$ , define a distribution  $\xi_N^1$  with  $m$  support points,  $\mathbf{u}_1^{(N)}, \dots, \mathbf{u}_m^{(N)}$ , and weights as,  $w_1^c, \dots, w_m^c$ , respectively. Then we have, for each  $N$ ,

$$\mathcal{L}(\xi^c) \leq \mathcal{L}(\xi_N^*) \leq \mathcal{L}(\xi_N^1),$$

since  $\xi^c$  is the optimal design on  $S$ ,  $\xi_N^*$  is the optimal design on  $S_N \subset S$  and  $\xi_N^1$  is a design on  $S_N$ . As  $N \rightarrow \infty$ ,  $\xi_N^1$  converges to  $\xi^c$  in distribution by the definition of  $\xi_N^1$ . If all the elements of  $\mathbf{I}_{\mathbf{x}}$  are bounded and continuous functions of  $\mathbf{x} \in S$ , we have  $\mathbf{I}_{\xi_N^1}(\boldsymbol{\theta})$  converges to  $\mathbf{I}_{\xi^c}(\boldsymbol{\theta})$  and  $\mathcal{L}(\xi_N^1)$  converges to  $\mathcal{L}(\xi^c)$ , which implies that  $\mathcal{L}(\xi_N^*)$  converges to  $\mathcal{L}(\xi^c)$ .  $\square$

**Proof of Theorem 2:** From (9) we have

$$\mathbf{I}_{\xi(S_N^V, \boldsymbol{\theta}^V)}(\boldsymbol{\theta}^V) = \sum_{i=1}^N w_i \mathbf{I}_{\mathbf{V}_{\mathbf{x}_i}}(\boldsymbol{\theta}^V) = \mathbf{T} \left( \sum_{i=1}^N w_i \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}) \right) \mathbf{T}^\top = \mathbf{T} \mathbf{I}_{\xi(S_N, \boldsymbol{\theta})}(\boldsymbol{\theta}) \mathbf{T}^\top,$$

so minimizing  $-\det \left( \mathbf{I}_{\xi(S_N^V, \boldsymbol{\theta}^V)}(\boldsymbol{\theta}^V) \right)$  over  $\mathbf{w}$  is equivalent to minimizing  $-\det \left( \mathbf{I}_{\xi(S_N, \boldsymbol{\theta})}(\boldsymbol{\theta}) \right)$  over  $\mathbf{w}$ . This implies that if  $\xi^*(S_N, \boldsymbol{\theta}) = \{(\mathbf{x}_i^*, w_i^*), i = 1, \dots, m\}$  is a  $D$ -optimal

design for parameter  $\boldsymbol{\theta}$  on  $S_N$ , then  $\xi^*(S_N^V, \boldsymbol{\theta}^V) = \{(\mathbf{V}\mathbf{x}_i^*, w_i^*), i = 1, \dots, m\}$  is a  $D$ -optimal design for parameter  $\boldsymbol{\theta}^V$  on design space  $S_N^V$ .  $\square$

**Proof of Theorem 3:** (i) By considering the directional derivative of  $\mathcal{L}_D(\xi_N)$  in (4) at  $\xi_N^*$  in the direction of  $x_i$ , we obtain  $\sum_{i=1}^N w_i \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}) - I_q \right) \leq 0$ , for all  $\mathbf{w}$ , where  $I_q$  is the  $q \times q$  identity matrix. Applying this result to the objective function  $\mathcal{L}_D^\alpha(\xi_N)$ , we have, for all  $\mathbf{w}$ ,

$$(1-\alpha) \sum_{i=1}^N w_i \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^*) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^*) - I_q \right) + \alpha \sum_{i=1}^N w_i \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^{**}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^{**}) - I_q \right) \leq 0,$$

which leads to

$$\sum_{i=1}^N w_i \left[ (1-\alpha) \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^*) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^*) \right) + \alpha \text{trace} \left( \mathbf{I}_{\xi_N^*}^{-1}(\boldsymbol{\theta}^{**}) \mathbf{I}_{\mathbf{x}_i}(\boldsymbol{\theta}^{**}) \right) - q \right] \leq 0.$$

This implies the result in part (i). The proof of part (ii) is similar and is omitted.

$\square$

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## References

- Berger, M.P.F. & Wong, W.K. (2009). *An Introduction to Optimal Designs for Social and Biomedical Research*. Wiley, Chichester, UK.
- Biedermann, S., Dette, H. & Zhu, W. (2006). Optimal designs for dose-response models with restricted design spaces. *Journal of the American Statistical Association*, 101, 747-759.

- Bose, M. & Mukerjee, R. (2015). Optimal design measures under asymmetric errors, with application to binary design points. *Journal of Statistical Planning and Inference*, 159, 28-36.
- Boyd, S. & Vandenberghe, L. (2004). *Convex Optimization*. Cambridge University Press, New York.
- Broudiscou, A., Leardi, R. & Phan-Tan-Luu, R. (1996). Genetic algorithm as a tool for selection of  $D$ -optimal design. *Chemometrics and Intelligent Laboratory Systems*, 35, 105-116.
- Cuervo, D.P., Goos, P. & Sorensen, K. (2016). Optimal design of large-scale screening experiments: a critical look at the coordinate-exchange algorithm. *Statistics and Computing*, 26, 15-28.
- Dassel, K.A. & Rawlings, J.O. (1988). Experimental design strategy for the Weibull dose response model. *Environmental Pollution*, 53, 333-349.
- Dette, H. & Biedermann, S. (2003). Robust and efficient designs for the Michaelis-Menten model. *Journal of the American Statistical Association*, 98, 679-686.
- Dette, H., Melas, V.B. & Wong, W.K. (2006). Locally  $D$ -optimal designs for exponential regression models. *Statistica Sinica*, 16, 789-803.
- Duarte, B.P.M. & Wong, W.K. (2014). A semi-infinite programming based algorithm for finding minimax optimal designs for nonlinear models. *Statistics and Computing*, 24, 1063-1080.
- Duarte, B.P.M., Wong, W.K. & Atkinson, A.C. (2015). A semi-infinite programming based algorithm for determining  $T$ -optimum designs for model discrimination. *Journal of Multivariate Analysis*, 135, 11-24.
- Duarte, B.P.M., Wong, W.K. & Dette, H. (2018). Adaptive grid semi-definite programming for finding optimum designs. *Statistics and Computing*, 28, 441-460.
- Fang, Z., Wiens, D.P. & Wu, Z. (2006). Locally  $D$ -optimal designs for multistage models and heteroscedastic polynomial regression models. *Journal of Statistical Planning and Inference*, 136, 4059-4070.
- Fedorov, V.V. (1972). *Theory of Optimal Experiments*. Academic Press, New York.
- Gao, L.L. & Zhou, J. (2017).  $D$ -optimal designs based on the second-order least squares estimator. *Statistical Papers*, 58, 77-94.
- Guess, H., Crump, K. & Peto, R. (1977). Uncertainty estimates for low-dose-rate extrapolations of animal carcinogenicity data. *Cancer Research*, 37, 3475-3483.
- Grant, M.C. & Boyd, S.P. (2013). *The CVX Users Guide*. Release 2.0 (beta), CVX Research, Inc. Stanford University.
- Hoel, P.G. & Jennrich, R.I. (1979). Optimal designs for dose response experiments in cancer research. *Biometrika*, 66, 307-316.

- Mandal, A., Wong, W.K. & Yu, Y. (2015). Algorithmic searches for optimal designs in *Handbook of Design and Analysis of Experiments* (eds: Dean, A., Morris, M., Stufken, J. and Bingham, D.), 755-784, Chapman & Hall/CRC.
- Papp, D. (2012). Optimal designs for rational function regression. *Journal of the American Statistical Association*, 107, 400-411.
- Royle, J. A. (2002). Exchange algorithms for constructing large spatial designs. *Journal of Statistical Planning and Inference*, 100, 121-134.
- Silvey, S.D. (1980). *Optimal Design*. Chapman and Hall, London.
- Wong, W.K., Yin, Y. & Zhou, J. (2017). Using SeDuMi to find various optimal designs for regression models. *Statistical Papers*, 1-21, DOI 10.1007/s00362-017-0887-7.
- Wong, W.K., Yin, Y. & Zhou, J. (2018). Optimal designs for multi-response nonlinear regression models with several factors via semi-definite programming. *Journal of Computational and Graphical Statistics*. In press. DOI:10.1080/10618600.2018.1476250.
- Yang, M., Biedermann, S. & Tang, E. (2013). On optimal designs for nonlinear models: a general and efficient algorithm. *Journal of the American Statistical Association*, 108, 1411-1420.
- Yang, M., Zhang, B. & Huang, S. (2011). Optimal designs for generalized linear models with multiple design variables. *Statistica Sinica*, 21, 1415-1430.
- Ye, J.J., Zhou, J. & Zhou, W. (2017). Computing A-optimal and E-optimal designs for regression models via semidefinite programming. *Communications in Statistics - Simulation and Computation*, 46, 2011-2024.
- Yu, Y. (2011). D-optimal designs via a cocktail algorithm. *Statistics and Computing*, 21, 475-481.