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Minimax optimal designs via particle swarm optimization methods

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Abstract Particle swarm optimization (PSO) techniques are widely used in applied fields to solve challenging optimization problems but they do not seem to have made an impact in mainstream statistical applications hitherto. PSO methods are popular because they are easy to implement and use, and seem increasingly capable of solving complicated problems without requiring any assumption on the objective function to be optimized. We modify PSO techniques to find minimax optimal designs, which have been notoriously challenging to find to date even for linear models, and show that the PSO methods can readily generate a variety of minimax optimal designs in a novel and interesting way, including adapting the algorithm to generate standardized maximin optimal designs.

Keywords Continuous optimal design · Equivalence theorem · Fisher information matrix · Standardized maximin optimality criterion · Regression model

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1 Introduction

Particle swarm optimization (PSO) is a population based stochastic optimization method inspired by social behavior of bird flocking or fish schooling and proposed by Eberhart and Kennedy (1995). In the last decade or so, PSO has singularly generated considerable interest in optimization circles as evident by its ever increasing applications in various disciplines. The importance and popularity of PSO can also be seen in the existence of many websites which provide PSO tutorials and PSO codes, track PSO development and applications in different fields. Some exemplary websites on PSO are http://www.swarmintelligence.org/index.php, http://www.particleswarm.info/ and http://www.cis.syr.edu/~mohan/pso/. Currently, there are at least 3 journals which have a focus theme on swarm intelligence and applications with a few more having an emphasis on the more general class of nature-inspired metaheuristic algorithms, of which PSO is a member. Nature-inspired metaheuristic algorithms have been rising in popularity in the optimization literature in the last 2 decades and in the last decade have dominated the optimization world compared with traditional mathematical optimization tools (Whitacre 2011a,b). Of particular note is Yang (2010), who saw a need to publish a second edition of his book on nature-inspired metaheuristic algorithms published less than 2 years earlier. This shows just how dynamic and rapidly expanding the field is. Clerc (2006) seems to be the first book devoted entirely to PSO and an updated overview of PSO methodology is available in Poli et al. (2007).

Interestingly, PSO has yet to make an impact in the statistical literature. We believe PSO methodology can be potentially useful in solving many statistical problems because ideas behind PSO are very simple and general yet requiring minimal or no assumption on the function to be optimized.

Our aim is to show that PSO methodology is effective in finding many types of optimal designs, including minimax optimal designs, which are notoriously difficult to find and study. This is because the design criterion is non-differentiable and there is no effective algorithm for finding such designs to date, even for linear models. Specifically, we demonstrate that PSO can readily generate different types of minimax optimal designs for linear and nonlinear models which agree with the few published results in the literature.

PSO is a stochastically iterative procedure for optimizing a function. The key advantages of this approach are that PSO is fast and flexible, there are few tuning parameters required of the algorithm and PSO codes can be easily written down generically to find optimal designs for a regression model. For more complicated problems, such as minimax design problems, the code will have to be modified appropriately. Generally, only the optimality criterion and the information matrix in the codes have to be changed to find an optimal design for another problem. We discuss this further in the exemplary pseudo MATLAB codes which we provide in Sect. 4 to generate the optimal designs.

In the next section, we provide the background. In Sect. 3, we demonstrate that PSO methodology can efficiently generate different types of minimax optimal designs for linear and nonlinear models. In Sect. 4, we provide computational and implementation details for our proposed PSO-based procedure. Section 5 shows that PSO methodology can be modified to find standardized maximin optimal designs. As illustrative examples, we construct such designs for enzyme kinetic models and Sect. 6 closes with a discussion.

2 Background

We focus on continuous designs which are treated as probability measures on a given design space X. This approach was proposed by Kiefer and his collection of voluminous work in this area is now documented in a single collection (Kiefer 1985). If a continuous design takes p_i proportion of the total observations at $x_i \in X, i = 1, 2, \ldots, k$, we denote it by ξ with $p_1 + p_2 + \cdots + p_k = 1$. Given a fixed sample size N, we implement ξ by taking roughly Np_i observations at $x_i, i = 1, 2, .., k$ subject to $Np_1 + Np_2 + \cdots + Np_k = N$. As Kiefer had shown, one can round each of the Np_i's to the nearest integer so that they sum to N without losing too much efficiency if the sample size is large. The proportion p_i is sometimes called the weight of the design at x_i. Continuous designs are practical to work with, along with many other advantages widely documented in design monographs, such as Fedorov (1972), Silvey (1980), Pázman (1986), Atkinson et al. (2007) and in Kiefer (1985).

Our setup assumes we have a statistical model defined on given compact design region X. The mean of the univariate response is modeled by a known function $g(x, \theta)$ apart from the values of the vector of parameters θ. We assume errors are normally and independently distributed, all with zero means and possibly unequal variances. The mean function $g(x, \theta)$ can be a linear or nonlinear function of θ and the set of independent variables x. Following convention, the value of the design ξ is measured by its Fisher information matrix defined to be the negative of the expectation of the matrix of second derivatives of the log-likelihood function. For example, consider the popular Michaelis–Menten model in the biological sciences given by

$$y = g(x, \theta) + \varepsilon = \frac{ax}{b + x} + \varepsilon, \quad x > 0,$$

where $a > 0$ denotes the maximal response possible and $b > 0$ is the value of x for which there is a half-maximal response. In practice, the design space is truncated to $X = [0, c]$ where c is a sufficiently large user-selected constant. If $\theta^\top = (a, b)$ and the errors ε are normally and independently distributed with means 0 and constant variance, the Fisher information matrix for a given design ξ is

$$\begin{aligned} I(\theta, \xi) &= \int \frac{\partial g(x, \theta)}{\partial \theta} \frac{\partial g(x, \theta)}{\partial \theta^T} \xi(dx) \\ &= \int \left(\frac{ax}{b + x}\right)^2 \begin{pmatrix} \frac{1}{a^2} & -\frac{1}{a(b+x)} \\ -\frac{1}{a(b+x)} & \frac{1}{(b+x)^2} \end{pmatrix} \xi(dx). \end{aligned}$$

For nonlinear models, such as the Michaelis–Menten model, the information matrix depends on the model parameters. For linear models, the information matrix does not depend on the model parameters and we denote it simply by $I(\xi)$.

Following convention, the optimality criterion is formulated as a convex function of the design and the optimal design is found by minimizing the criterion over all designs on the design space X. This means that for nonlinear models, the design criterion that we want to optimize contains unknown parameters. For example, to estimate parameters accurately, we minimize $\log |I(\theta, \xi)^{-1}|$ over all designs ξ on X (D-optimality). As such, a nominal value or best guess for θ is needed before the function can be optimized. The resulting D-optimal design depends on the nominal value and so it is called locally D-optimal. More generally, locally optimal designs require nominal values for the model parameters before optimal designs can be found. In addition, when the criterion is a convex function in ξ, this means that a standard directional derivative argument can be applied to produce an equivalence theorem which checks whether a given design is optimal among all designs on X. Details are available in the above cited design monographs.

Minimax optimal designs arise naturally when we wish to have protection against the worst case scenario. For example if the vector of model parameters is θ and Θ is a user-selected set of plausible values for θ, one may want to implement a minimax optimal design ξ^* defined by

$$\xi^* = \arg\min_{\xi}\max_{\theta\in\Theta}\log|I^{-1}(\theta,\xi)|, \quad (1)$$

where the minimization is over all designs on X. The optimal design provides some global protection against the worst case scenario by minimizing the maximal inefficiencies of the parameter estimates. Clearly, when Θ is a singleton set, the optimal minimax design is the same as the locally optimal design.

A common application of the minimax design criterion is in a dose response study where the goal is to find an extrapolation optimal design which provides the best inference on the mean responses over a known interval Z outside the dose interval X. If we have a heteroscedastic linear model with mean function $g(x)$ and $\lambda(x)$ is the assumed reciprocal variance of the response at dose x, then the variance of the fitted response at the point z is proportional to

$$v(z,\xi) = g^T(z)I(\xi)^{-1}g(z),$$

where

$$I(\xi) = \int \lambda(x)g(x)g^T(x)\xi(dx).$$

The best design for inference at the point z is the one that minimizes $v(z,\xi)$ among all designs ξ on X. However if we know there are several dose levels of interest and they are all in some pre-determined compact set Z, one may seek a design to minimize the maximal variance of the fitted responses on Z. Such a design criterion is also convex and one can use the following equivalence theorem: ξ^* is minimax optimal for extrapolation on Z if and only if there exists a probability measure μ^* on $A(\xi^*)$ such that for all x in X,

$$c(x,\mu^*,\xi^*) = \int_{A(\xi^*)} \lambda(x)r(x,u,\xi^*)\mu^*(du) - v(u,\xi^*) \le 0$$

with equality at the support points of ξ^*. Here, $A(\xi) = \{u \in Z|v(u,\xi) = \max_{z\in Z} v(z,\xi)\}$ and $r(x,u,\xi) = (g^T(x)I(\xi)^{-1}g(u))^2$. If X is one or two-dimensional, one may visually inspect the plot of $c(x,\mu^*,\xi^*)$ versus values of $x \in X$ to confirm the optimality of ξ^*. In what is to follow, we display such plots to verify the optimality of a design without reporting the measure μ^*. A formal proof of this equivalence theorem can be found in Berger et al. (2000) and further details on minimax optimal design problems are available in Wong (1992) and Wong and Cook (1993) with further examples in King and Wong (1998, 2000). Extensions to nonlinear models are straightforward if one assumes the mean response can be adequately approximated by a linear model via a first order Taylor Series expansion.

There are three points worth noting: (i) when Z is a singleton set, the probability measure μ^* is necessarily degenerate at Z and the resulting equivalence theorem reduces to one for checking whether a design is c-optimal, see Fedorov (1972) or Silvey (1980); (ii) equivalence theorems for minimax optimality criteria all have a form similar to the one shown above and they are more complicated because we need to work with the subgradient μ^*. A reference for subgradient is the full chapter called "The subgradient method" in Shor (1985). Finding the subgradient requires another set of optimization procedures which usually is more tricky to handle and this in part explains why minimax optimal designs are much harder to find than optimal designs under a differentiable criterion, and (iii) under the setup here, the convex design criterion allows us to derive a lower bound on the efficiency of any design (Pázman 1986). This implies that one can always assess how good a design is by providing its efficiency lower bound (without knowing the optimal design).

3 PSO-generated minimax optimal designs

Minimax optimal designs are notoriously difficult to find and we know of no algorithm to date which is guaranteed to find such optimal designs. Even for linear polynomial models with a few factors, recent papers acknowledge the difficulty of finding minimax optimal designs; see Rodriguez et al. (2010) and Johnson et al. (2011), who considered finding a G-optimal design to minimize the maximal variance of the fitted response across the design space. Optimal minimax designs for nonlinear models can be challenging even when there are just two parameters in the model; earlier attempts to solve such minimax problems have to impose constraints to simplify the optimization problem. For example, Sitter (1992) found minimax D-optimal designs for the two-parameter logistic model among designs which allocated equal numbers of observations at equally spaced points placed symmetrically about the location parameter. Similarly, Noubiap and Seidel (2000) found minimax optimal designs numerically among symmetric and balanced designs after noting that "by restricting the set of regarded designs in a suitable way, the minimax problem becomes numerically tractable in principle; nevertheless it is still a two-level problem requiring nested global optimization." In the same paper on p.152, the authors remark that "Unfortunately, the minimax procedure is, in general, numerically intractable".

We are therefore naturally interested in investigating whether the PSO methodology provides an effective way to find minimax optimal designs. Our examples in this section are confined to the scattered few minimax optimal designs reported in the literature, either numerically or analytically. The hope is that all optimal designs found by PSO agree with results in the literature and this would then suggest that the algorithm should also work well for problems whose minimax optimal designs are unknown. Of course, we can also confirm the optimality of the design found by the PSO

Table 1 Selected locally E-optimal designs for the Michaelis–Menten model found by PSO and from theory when the design space is $[0, \tilde{x}] = [0, 200]$

a	b	ξ_{PSO}		E-optimal designs	
100	150	46.520 (0.6925)	200 (0.3075)	45.510 (0.6927)	200 (0.3073)
100	100	38.152 (0.6770)	200 (0.3230)	38.150 (0.6769)	200 (0.3231)
100	50	24.783 (0.6171)	200 (0.3829)	24.780 (0.6171)	200 (0.3829)
100	10	6.516 (0.2600)	200 (0.7400)	6.515 (0.2600)	200 (0.7400)
100	1	0.701 (0.0222)	200 (0.9778)	0.701 (0.0220)	200 (0.9778)
10	150	46.497 (0.7071)	200 (0.2929)	46.510 (0.7070)	200 (0.2931)
10	100	38.142 (0.7068)	200 (0.2932)	38.150 (0.7068)	200 (0.2933)
10	50	24.778 (0.7058)	200 (0.2942)	24.780 (0.7058)	200 (0.2942)
10	10	6.515 (0.6837)	200 (0.3163)	6.515 (0.6838)	200 (0.3162)
10	1	0.701 (0.1882)	200 (0.8118)	0.701 (0.1881)	200 (0.8119)

Table shows the two support points with their weights in parentheses

using an equivalence theorem. Example 3 below is one such instance.

We selectively present three examples and briefly a fourth with two independent variables out of many successes we have had with PSO for finding different types of minimax optimal designs. One of the examples has a binary response and the rest have continuous responses. The first example seeks to find a locally E-optimal design which minimizes the maximum eigenvalue of the inverse of the Fisher information matrix. Example 2 seeks a best design for estimating parameters in a two-parameter logistic model when we have a priori a range of plausible values for each of the two parameters. The desired design is the one which maximizes the smallest determinant of the information matrix over all nominal values of the two parameters in the plausible region. Equivalently, this is the minimax optimal design which minimizes the maximum determinant of the inverse of the information matrix where the maximum is taken over all nominal values in the plausible region for the parameters. The numerically minimax optimal design for Example 2 was found by repeated guess work followed by confirmation with the equivalence theorem in King and Wong (2000) with the aid of Mathematica. We will compare their designs with our PSO-generated designs. The third example concerns a heteroscedastic quadratic model with a known efficiency function and we want to find a design to minimize the maximum variance of the fitted responses across a user-specified interval. The minimax optimal designs are unknown for this example and we will check the optimality of the PSO-generated design using an equivalence theorem.

The key tuning parameters in the PSO method are (i) flock size, i.e. number of particles (designs) to use in the search, (ii) the number of common support points these designs have, and (iii) the number of iterations allowed in the search process. Unless mentioned otherwise, we use the same values for these tuning parameters for the outer problem [e.g the minimization problem in Eq. (1)] and the inner problem [e.g the maximization problem in Eq. (1)]. We use default values for all other tuning parameters in the PSO codes which we programmed in MATLAB version R2010b. Section 4 provides information on these default values. All CPU computing times (in seconds) were from a Intel Core2 6300 computer with 5 GB RAM and operating system Ubuntu 64bit Linux with kernel 2.6.35-30.

Before we present our modified PSO method called Nested PSO in Sect. 4, we present four examples, with a bit more detail for the first example.

3.1 Example 1: E-optimal designs for the Michaelis–Menten model

The Michaelis–Menten model is one of the simplest and most widely used model in the biological sciences. Dette and Wong (1999) used a geometric argument based on the celebrated Elfving's theorem and constructed locally E-optimal designs for the model with two parameters $\theta^\top = (a, b)$. Such optimal designs are useful for making inference on θ by making the area of the confidence ellipsoid small in terms of minimizing the length of the longest principal axis. This is achieved by minimizing the larger of the two eigenvalues of the inverse of the information matrix over all designs on X. For a given θ, they showed that if the known design space is $X = [0, \tilde{x}]$ and $\tilde{z} = \tilde{x}/(b+\tilde{x})$, the locally E-optimal design is supported at $\tilde{x}$ and $\{(\sqrt{2} - 1)b\tilde{x}\}/\{(2 - \sqrt{2})\tilde{x} + b\}$ and the weight at the latter support point is

$$w = \frac{\sqrt{2}(a/b)^2(1-\tilde{z})\{\sqrt{2} - (4 - 2\sqrt{2})\tilde{z}\}}{2 + (a/b)^2\{\sqrt{2} - (4 - 2\sqrt{2})\tilde{z}\}^2}.$$

We use the Nested PSO procedure to be described in the next section to search for the locally 2-point E-optimal design using 128 particles and 100 iterations. Selected minimax optimal designs are shown in Table 1 along with the theoretical optimal designs reported in Dette and Wong (1999). All the PSO-generated designs are close to the theoretical

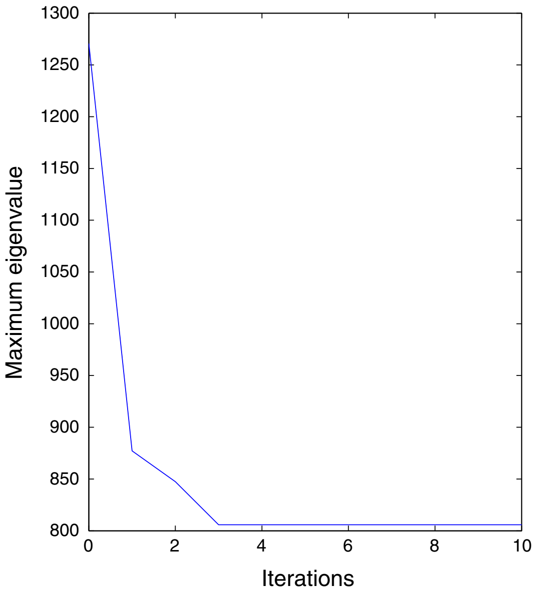


Fig. 1 Plot of the maximum eigenvalue of $I(\xi,\theta)^{-1}$ versus the iteration number in the nested PSO search in Example 1

E-optimal designs and for those which show a small discrepancy, the difference quickly vanishes when we increase the flock size or the number of iterations.

It is instructive to demonstrate the search process of the PSO method in a bit more detail for this example; similar demonstrations can be shown for the other examples as well. As an illustrative example, consider the case when $a = 100$ and $b = 150$ with 128 particles and 100 iterations. Figure 1 plots the "best" maximum eigenvalue of $I(\xi, \theta)$ over the first 10 iterations of the PSO procedure. Notice how quickly in just 3 iterations, PSO finds the smallest value of the larger of the two eigenvalues from information matrices generated by the θ's in Θ. Figure 2 shows the initial positions of the 128 randomly generated particles and how they move after the 1st, 5th and at the 10th iteration when they converged.

3.2 Example 2: a minimax D-optimal design for the two-parameter logistic regression model when we have plausible ranges for the two parameters

The widely used two-parameter logistic model assumes the probability of response is $p(x,\theta) = 1/\{1+\exp(-b(x-a))\}$ with $\theta^\top = (a, b)$. For a given design ξ, a direct calculation shows the Fisher information matrix to be

$$I(\theta,\xi) = \int \begin{pmatrix} b^2 p(x,\theta)(1-p(x,\theta)) & -b(x-a)p(x,\theta)(1-p(x,\theta)) \\ -b(x-a)p(x,\theta)(1-p(x,\theta)) & (x-a)^2 p(x,\theta)(1-p(x,\theta)) \end{pmatrix} d\xi(x).$$

Suppose now that instead of having nominal values for θ, we have a priori a known set Θ of plausible values for the two parameters a and b, i.e. $\theta \in \Theta$ and Θ is known. We wish to find a minimax D-optimal design ξ^* such that

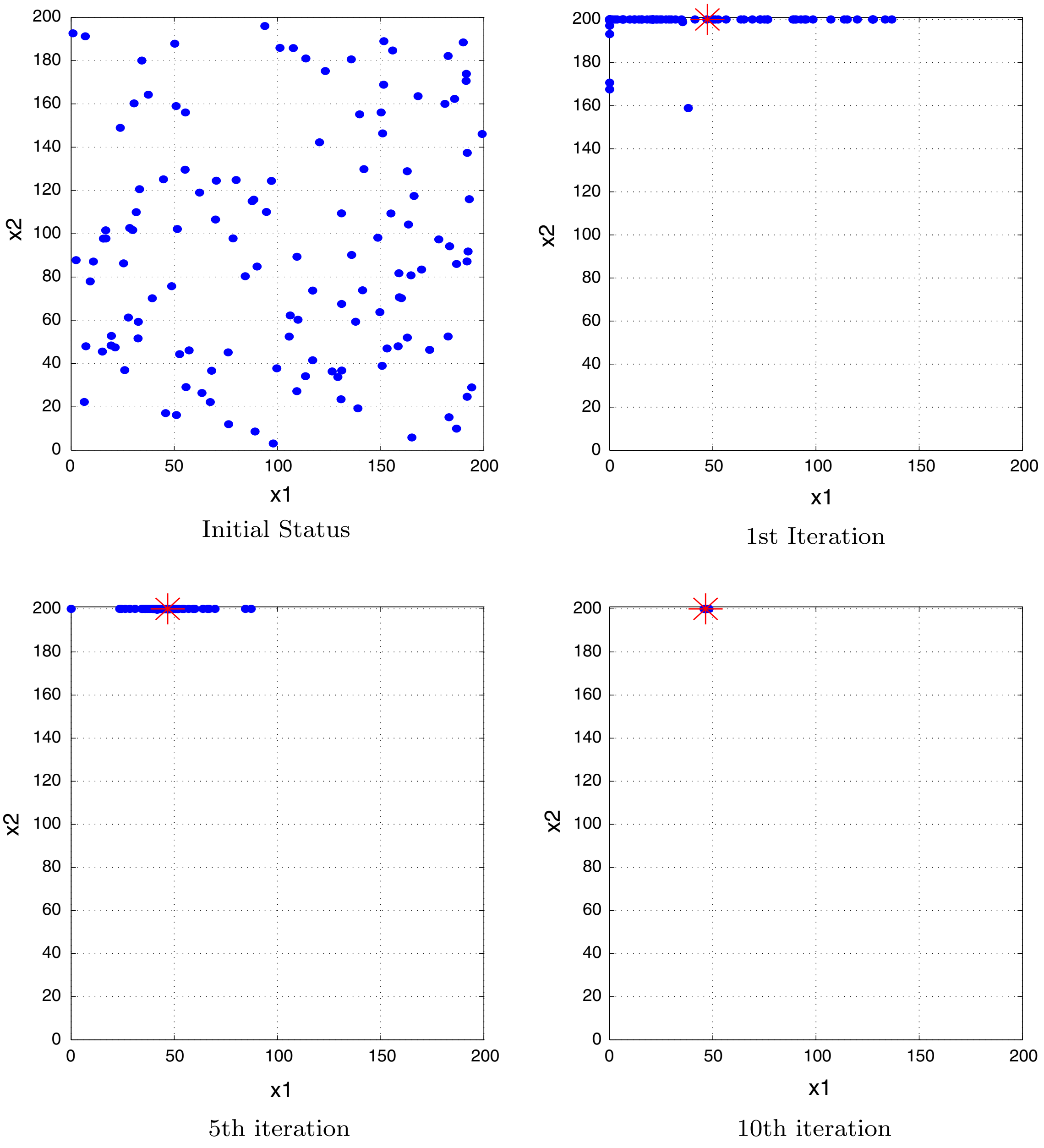
$$\xi^* = \arg\min_{\xi} \max_{\theta\in\Theta} \log(|I^{-1}(\theta,\xi)|),$$

where the minimization is over all designs on a given compact design set X. As mentioned above, this minimax optimal design reduces to a locally D-optimal design when Θ is a singleton set.

Following King and Wong (2000), we assume that $\Theta = [a_L, a_U] \times [b_L, b_U]$, where a_L, a_U, b_L and b_U are the known limits of the lower and upper bounds for a and b. In King and Wong (2000), the numerically minimax D-optimal designs were found by first running the Fedorov-Wynn algorithm (Fedorov 1972). Invariably, the algorithm did not converge but provided clues on the number and locations of the support points of the optimal design. King and Wong (2000) then used the information along with the equivalence theorem to find the numerically minimax optimal design using Mathematica. A certain amount of guesswork was still necessary because not much was known of the subgradient μ^*. The process of finding the minimax optimal design was labor intensive and time consuming. We now use the nested PSO to find minimax optimal designs for two exemplary cases from King and Wong (2000) and compare results. For case (a), the design interval was non-symmetric and the number of particles for the inner loop is 64 and the number for the outer loop is 32. The outer iteration number was 100 and the inner iteration number was 50. In case (b), the design interval was symmetric and larger, and the number of inner particles is 256 and the number for the outer particles is 512. The outer iteration number is 200 and the inner iteration is 100. In both cases, the PSO generated designs were found quickly and a direct calculation shows both had at least 99.4 % efficiency.

Case a $\Theta = [0, 2.5] \times [1, 3]$ and $X = [-1, 4]$. The 4-point PSO-generated design ξ is supported at $-0.4230, 0.6164, 1.8836$ and 2.9230 and the weights at these points are $0.2481, 0.2519, 0.2519$ and 0.2481 respectively. This design is close to the one reported in King and Wong (2000) and Fig. 3a plots $c(x, \xi, \mu^*)$ versus $x \in X$ and visually confirms the design ξ found by PSO is nearly optimal or optimal.

Case b $\Theta = [0, 3.5] \times [1, 3.5]$ and $X = [-5, 5]$ (Example 3.2 in King and Wong (2000)). The 6-point PSO-generated design is supported at $-0.3504, 0.6075, 1.4146, 2.0854, 2.8925$ and 3.8504 and the weights at these points were $0.1799, 0.2151, 0.1050, 0.1050, 0.2151$ and 0.1799 respectively. This design is also close to the one reported in King and Wong (2000) and Fig. 3b similarly confirms that the design found by PSO is nearly optimal or optimal.



Initial Status

1st Iteration

5th iteration

10th iteration

Fig. 2 The movement of particles in the PSO search for the locally E-optimal design for the Michaelis–Menten model at various stages. The *red star* in each of the last *three plots* indicates the current best design. (Color figure online)

3.3 Example 3: a heteroscedastic minimax design for a quadratic polynomial model with an increasing efficiency function

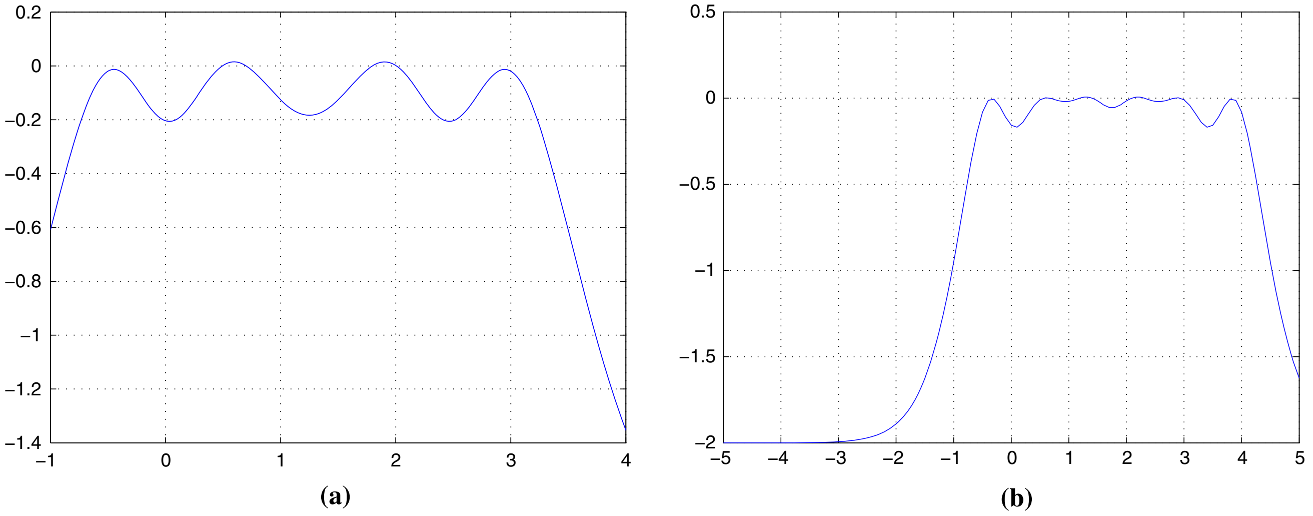
Consider heteroscedastic polynomial models on a given compact design space X that have the form

$$y(x) = g^\top(x)\beta + e(x)/\sqrt{\lambda(x)},$$

where $g^\top(x) = (1, x, \ldots, x^d)$, $\beta^\top = (\beta_0, \beta_1, \ldots, \beta_d)$ and $e(x)$ is a random error having mean 0 and constant variance σ^2. The function $\lambda(x)$ is a known positive real-valued continuous function defined on X and inversely proportional to the variance of the fitted response at x. All observations are assumed to be independent. Recalling that the variance of the fitted response at x using design ξ is proportional to $v(x, \xi) = g^\top(x)I^{-1}(\xi)g(x)$, the sought design is ξ^* defined by

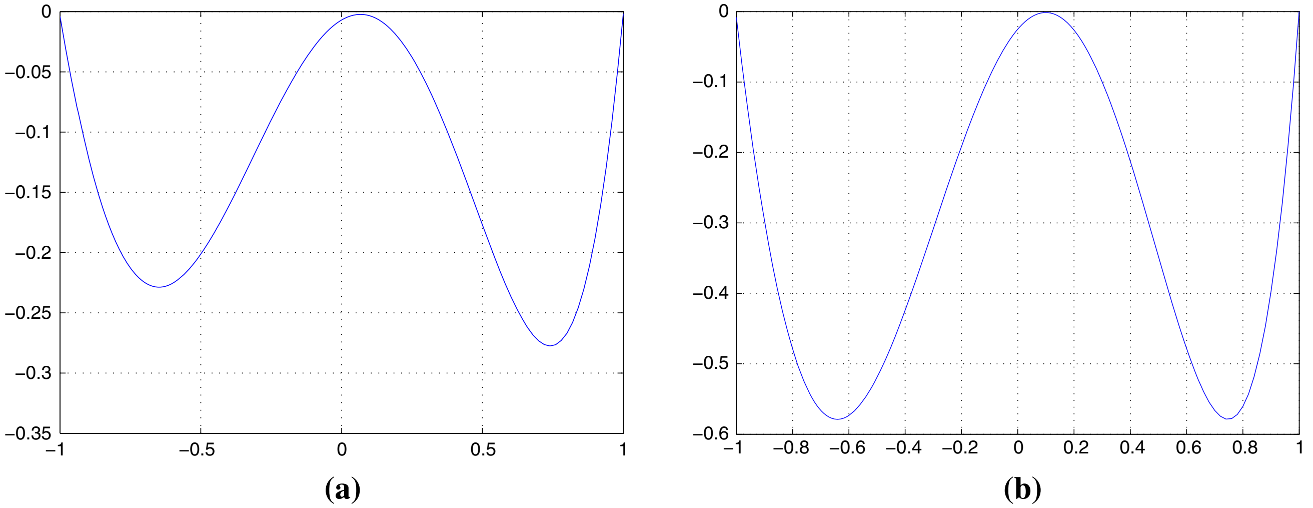
$$\xi^* = \arg\min_{\xi}\max_{x\in Z} v(x, \xi),$$

where the minimization is over all designs on X. Here Z is a compact set and pre-selected for prediction purposes, which may overlap with the design space X. When $Z = X$, this minimax design is called the G-optimal design (Wong and Cook



(a) **(b)**

Fig. 3 Plot of $c(x, \mu^*, \xi)$ versus x for Example 2 for case **a** $\Theta = [0, 2.5] \times [1, 3]$ and $X = [-1, 4]$; case **b** $\Theta = [0, 3.5] \times [1, 3.5]$ and $X = [-5, 5]$



(a) **(b)**

Fig. 4 Plot of $c(x, \mu^*, \xi)$ versus x over the design interval $X = [-1, 1]$ for the quadratic regression model with $\lambda(x) = 2x + 5$ in Example 3 for case **a** $Z = [-1, 1]$ and case **b** $Z = [1, 1.2]$

1993). King and Wong (1998), Brown and Wong (2000) and Chen et al. (2008) proposed algorithms and discussed computational issues for finding such designs in simple and quadratic models. Our experience with these proposed algorithms is that they may not work well for more complex models and a more complicated heteroscedastic structure. Accordingly, we applied Nested PSO and tested if it can find the minimax optimal design for the quadratic model with a monotonic increasing efficiency function when (a) $X = Z$ and (b) Z is outside of X. The first case corresponds to G-optimality and the second case corresponds to a design extrapolation problem where we want to make predictions outside the design space. The optimality of PSO-generated designs will be ascertained by equivalence theorems. In both cases, we used 128 particles and 100 iterations to find the minimax optimal designs.

Here we consider the quadratic model with a monotonic increasing efficiency function $\lambda(x) = 2x + 5$. This is a more difficult problem than the case when we have a symmetric efficiency function because one can then exploit the symmetry of the design problem and reduce the dimension of the optimization problem. Specifically, we applied PSO to find an minimax optimal design when (a) $X = Z = [-1, 1]$ and (b) $X = [-1, 1]$ and $Z = [1, 1.2]$. For the first case, the PSO-generated 3-point design is supported at ±1 and 0.0777 with weight at 1 equal to 0.2126 and weight at -1 equal to 0.4928. In the second case, the PSO-generated 3-point design is supported at ±1 and 0.0967 with weight at 1 equal to 0.6667 and weight at -1 equal to 0.0768. The efficiency lower bounds for the PSO-generated designs are 0.9974 and 0.9975, respectively. Figure 4a is the graph of $c(x, \xi, \mu^*)$ for case (a) and Fig. 4b is the graph of $c(x, \xi, \mu^*)$

for case (b). They both visually confirm the optimality of the PSO-generated designs ξ.

We note that earlier work on optimal extrapolation designs for polynomial models were carried out in a series of papers by Kiefer and Wolfowitz (1964a,b, 1965) and Levine (1966), assuming the efficiency function $\lambda(x)$ was a constant. Under the homoscedastic model, they were able to obtain analytic results when $X = [-1, 1]$ and $Z = [e, f]$ for selected values of e and f, including results for non-polynomial regression problems involving Chebyshev systems. Spruill (1984, 1990) worked on similar problems where bias was factored into the criterion as well. Interest in such design problems continues to date, see Broniatowski and Celant (2007) for example. PSO was able to produce optimal designs reported in the above papers and for problems with a more general setup. Because of space consideration, we do not report here additional results from PSO for extrapolation minimax optimal designs.

3.4 Example 4: a linear model with two factors

Our final example shows PSO can also find minimax optimal designs for regression models with multiple variables. Consider a homoscedastic quadratic model with two variables given by

$$E(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2$$

on the design space $(x_1, x_2) \in X = [-1, 1]^2$ and we want to know how to take independent observations to minimize the maximum variance of the fitted response across X. We used 500 outer iterations with an outer flock size of 500 and 50 inner iterations with an inner flock size of 50 in our PSO search. The PSO-generated design from Algorithm 2 is supported at $(-0.0296, -1)$, $(-0.0015, 0.0099)$, $(0.0161, 1)$, $(1, -0.0342)$, $(1, -1)$, $(-1, 1)$, $(1, 1)$, $(-1, -1)$ and $(-1, -0.0225)$, and the corresponding weight distribution at these points is respectively given by 0.0815, 0.0962, 0.0790, 0.0801, 0.1454, 0.1468, 0.1464, 0.1443 and 0.0804.

How close is this 9-point design to the G-optimal design? Fig. 5 shows the plot of the directional derivative of the G-optimality criterion evaluated at the 9-point PSO-generated design and confirms visually that the the PSO-generated design is optimal or near to the G-optimal design. The model has homoscedastic errors and so the sought G-optimal design is also the D-optimal design (Kiefer and Wolfowitz 1960), which is always easier to find. This D or G-optimal design was reported in Farrell et al. (1968) and has weight 0.1458 at each of the 4 points $(\pm 1, \pm 1)$, weight 0.0802 at each of the 4 points $(\pm 1, 0)$ and $(0, \pm 1)$ and weight 0.0962 at the center point $(0, 0)$.

The maximal variances from the D-optimal design and the PSO-generated design are 6.000 and 6.002, respectively, providing a G-efficiency of 0.9997 or 99.97 % for the PSO-generated design.

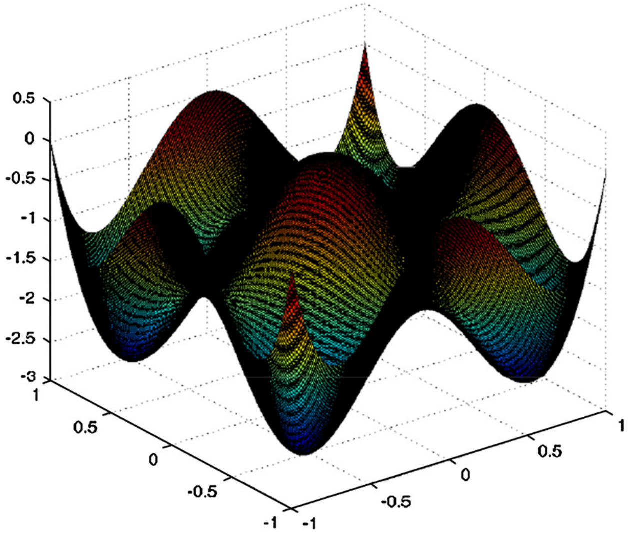


Fig. 5 Plot of the directional derivative of the G-optimality criterion evaluated at the 9-point PSO-generated design for the quadratic model with 2 variables

In the next section, we provide computational details for the PSO. As may have been already noticed in the above examples, a couple of the designs found by the PSO method appeared to be slightly numerically different from the theoretical optimal designs. Our experience is that the discrepancy can be entirely attributed to the choices for the tuning parameters. For simplicity, we used the same set of tuning parameters for all cases in the same example even though this may not be adequate for all the cases. Generally, when more particles and more iterations are used, the discrepancy disappears and PSO is more likely able to find the optimal design. Interestingly, when we used 256 particles and 500 iterations in Example 1, the discrepancy persisted even when we increased the iteration and particle numbers to the thousands. Further investigation revealed that the smaller support point of the theoretical optimal design in the first row of Table 1 calculated from the formula was wrongly reported and the correct value was the one found by PSO!

4 Computational and implementation details for PSO

PSO, proposed by Eberhart and Kennedy (1995), is an iterative method which can be generically and readily coded to simulate the behavior of a flock of birds in search for food. Before presenting our modified PSO algorithm for finding optimal minimax designs, we first describe how PSO works in its most basic for solving a minimization problem:

$$\min_{\mathbf{x} \in X} f(\mathbf{x}), \tag{2}$$

where X is a given compact domain and $f(\mathbf{x})$ is the objective function. We initialize PSO using a user-specified number, say n, randomly generated particles to search for the optimum over the search space. In our context, X is the design space, $f(\mathbf{x})$ is the design criterion formulated as a convex function of the information matrix and the particles are the flock of birds or search designs defined by their mass distributions and support points. If the model has k parameters in the mean function, it is typical to choose the initial flock of search designs to be those with k support points.

The two basic equations that drive movement for the ith particle in the PSO algorithm in its search to optimize an objective function $f(\mathbf{x})$ is as follows. At times t and $t+1$, the movement of particle i is governed by

$$\mathbf{w}_i^{t+1} = \theta_t \mathbf{w}_i^t + \gamma_1 \alpha_1 (\mathbf{p}_i - \mathbf{x}_i^t) + \gamma_2 \alpha_2 (\mathbf{p}_g - \mathbf{x}_i^t), \tag{3}$$

and

$$\mathbf{x}_i^{t+1} = \mathbf{x}_i^t + \mathbf{w}_i^{t+1}. \tag{4}$$

Here, $\mathbf{w}_i^t$ and $\mathbf{x}_i^t$ are, respectively, the velocity and the current position for the ith particle at time t. The initial velocity $\mathbf{w}_i^0$ is set to be zero. The inertia weight θ_t modulates the influence of the former velocity and can be a constant or a decreasing function with values between 0 and 1. For example, Eberhart and Shi (2000) used a linearly decreasing function over the specified time range with an initial value 0.9 and end value of 0.4. The vector $\mathbf{p}_i$ is the personal best (optimal) position attained by the ith particle up to time t and the vector $\mathbf{p}_g$ is the global best (optimal) position attained among all particles up to time t. This means that up to time t, the personal best for particle i is $pbest_i = f(\mathbf{p}_i)$ and $gbest = f(\mathbf{p}_g)$. The two random vectors in the PSO algorithm are α_1 and α_2 and their components are usually taken to be independent random variables from $U(0,1)$. Note that in Eq. (3), the product in the last two terms is Hadamard product. The constant γ_1 is the cognitive learning factor and γ_2 is the social learning factor. These two constants determine how each particle moves toward its own personal best position or overall global best position. The default values for these two constants in the PSO codes are $\gamma_1 = \gamma_2 = 2$ and they really seem to work well in practice for nearly all problems which we have investigated so far. Further details are in Chatterjee and Siarry (2006), Fan and Chang (2007) and Shi and Eberhart (1998a,b).

The particles' movements along various paths are clamped to a user-specified maximum velocity $\mathbf{w}_{max}$. After updating the velocity $\mathbf{w}_i$ via (3), if a certain component of $\mathbf{w}_i$ exceeds the corresponding component of $\mathbf{w}_{max}$, the component velocity will be limited to the corresponding component value of $\mathbf{w}_{max}$. In our implementation, we set $\mathbf{w}_{max} = 100 \cdot \mathbf{1}$, where $\mathbf{1}$ is the unit vector.

Algorithm 1 ***PSO for the minimization problem (2)***

```
(A1a)  Initialize particles
       (A1a.1)  Choose initial position $\mathbf{x}_i$ and velocity $\mathbf{w}_i$ for particle i, for $i = 1, \ldots, n$.
       (A1a.2)  Calculate fitness values $f(\mathbf{x}_i)$.
       (A1a.3)  Determine local and global best positions $\mathbf{p}_i$ and $\mathbf{p}_g$.
(A1b)  Repeat until stopping criteria are satisfied.
       (A1b.1)  Calculate each particle velocity using equation (3).
       (A1b.2)  Update each particle position using equation (4).
       (A1b.3)  Calculate fitness values $f(\mathbf{x}_i)$.
       (A1b.4)  Update best positions $\mathbf{p}_i$ and $\mathbf{p}_g$ and best values $pbest_i$ and $gbest$.
(A1c)  Output $\mathbf{p}_g$ and $gbest$.
```

To find minimax optimal designs, we modified Algorithm 1 and call the modified PSO method nested PSO because it involves double optimization, one after the other. More generally, let $g(u, v)$ be a given function defined on two compact spaces $\mathcal{U}$ and $\mathcal{V}$. Minimax optimization problems have the form:

$$\min_{\mathbf{u}\in\mathcal{U}} \max_{\mathbf{v}\in\mathcal{V}} g(\mathbf{u}, \mathbf{v}) \equiv \min_{\mathbf{u}\in\mathcal{U}} f_{outer}(\mathbf{u}) \equiv \min_{\mathbf{u}\in\mathcal{U}} \left[\max_{\mathbf{v}\in\mathcal{V}} f_{inner}(\mathbf{v}) \right], \tag{5}$$

where

$$f_{outer}(\mathbf{u}) = \max_{\mathbf{v}\in\mathcal{V}} f_{inner}(\mathbf{v}), \tag{6}$$

and, for fixed $\mathbf{u}$,

$$f_{inner}(\mathbf{v}) = g(\mathbf{u}, \mathbf{v}). \tag{7}$$

We call functions $f_{outer}(\mathbf{u})$ and $f_{inner}(\mathbf{v})$ the outer and inner objective functions respectively. Note that the maximization problem (6) is equivalent to the minimization problem

$$\min_{\mathbf{v}\in\mathcal{V}} [-f_{inner}(\mathbf{v})],$$

which can be solved by Algorithm 1. For our design problems, we set $g(u, v)$, $\mathcal{U}$ and $\mathcal{V}$ appropriately. For instance, for G-optimality, we let $\mathcal{U}$ be the set of all designs defined on X, let $\mathcal{V} = X$ and let $g(\mathbf{u}, \mathbf{v})$ be the variance of the fitted response at $\mathbf{v}$ for design $\mathbf{u}$. The same setup is used for Example 3, except that we now replace $\mathcal{V} = X$ by $\mathcal{V} = Z$. The minimax design problem is now formulated as a nested (or double) minimization problem and solved using Algorithm 2, which in essence is Algorithm 1 applied twice, once to the outer function and another to the inner function.

Algorithm 2 *Nested PSO for the minimax problem (5)*

```
(A2a) Initialize particles
    (A2a.1) Choose initial position $\mathbf{x}_i$ and velocity $\mathbf{w}_i$ for particle i, for $i = 1, \ldots, n$.
    (A2a.2) Calculate fitness values $f_{outer}(\mathbf{x}_i)$ by solving (6) via Algorithm 1.
    (A2a.3) Determine local and global best positions $\mathbf{p}_i$ and $\mathbf{p}_g$.
(A2b) Repeat until stopping criteria are satisfied.
    (A2b.1) Calculate each particle velocity using equation (3).
    (A2b.2) Update each particle position using equation (4).
    (A2b.3) Calculate fitness values $f_{outer}(\mathbf{x}_i)$ by solving (6) via Algorithm 1.
    (A2b.4) Update best positions $\mathbf{p}_i$ and $\mathbf{p}_g$ and best values $pbest_i$ and $gbest$.
(A2c) Output $\mathbf{p}_g$ and $gbest$.
```

To apply the Nested PSO to solve minimax design problems we use Example 3 as an illustrative example and set $f_{outer}(\xi) = \max_{z \in Z} v(z, \xi)$ which is first computed via PSO for each fixed ξ. The optimal design is then found by another PSO by treating each particle as a design ξ represented as $(x_1, \ldots, x_k, p_1, \ldots, p_k)^\top$, where $x_i, i = 1, \ldots, k$ are the support points in the design space and $p_i, i = 1, \ldots, k$ are the corresponding weights with $1 > p_i > 0$ and $\sum_{i=1}^{k} p_i = 1$.

All minimax optimal designs in Sect. 3 were found using Algorithm 2. In the supplementary material, we provide open PSO codes which implement Algorithm 2 and demonstrate how to use a MATLAB toolbox to obtain a G-optimal design for an illustrative case when we have a simple linear model and the efficiency function is $\lambda(x) = x + 5$ defined on $X = [-1, 1]$. We also show how the codes can be readily amended to find different optimal designs under various setups.

In the next section, we show the flexibility of the PSO methodology by finding standardized maximin optimal designs for a class of nonlinear models. Maximin optimal designs are similar in spirit to minimax optimal designs in terms of interpretation and construction via PSO. Standardized maximin or minimax optimal designs were proposed by Dette and Biedermann (2003) to make locally optimal designs more robust against mis-specification of the set of nominal values for the model parameters.

5 Standardized maximin optimal designs for enzyme inhibition kinetic models

The two-parameter Michaelis–Menten model in Example 1 is commonly used enzyme kinetics studies. There are four popular extensions of the Michaelis–Menten model used to further identify the types of inhibition process involved in the enzyme-inhibitor system. These nonlinear models have three or four parameters and their mean velocity functions are

Competitive inhibition model:

$$\upsilon = \frac{VS}{K_m(1 + \frac{I}{K_{ic}}) + S}; \tag{8}$$

Noncompetitive inhibition model:

$$\upsilon = \frac{VS}{(K_m + S)(1 + \frac{I}{K_{ic}})}; \tag{9}$$

Uncompetitive inhibition model:

$$\upsilon = \frac{VS}{K_m + S(1 + \frac{I}{K_{iu}})}; \tag{10}$$

Mixed inhibition model:

$$\upsilon = \frac{VS}{K_m(1 + \frac{I}{K_{ic}}) + S(1 + \frac{I}{K_{iu}})}. \tag{11}$$

Here S and I are the two design variables denoting the concentration of the substrate and the inhibitor concentration respectively. The model parameters are V, K_m, K_{ic}, K_{iu}, and Bogacka et al. (2011) found locally D-optimal designs for these four enzyme inhibition kinetic models. The locally D-optimal designs do not depend on V because this parameter enters the four models linearly. Thus we only consider the parameter vector $\theta = (K_m, K_{ic}, K_{iu})^\top$.

We now use the nested PSO algorithm to find standardized maximin D-optimal designs for these models. Let ξ_θ^* be the locally D-optimal design with respect to the parameter θ and let Θ be a known set containing plausible values of θ. The goal here is to seek an optimal design which maximizes the design criterion $\Phi(\xi)$, where

$$\Phi(\xi) = \min_{\theta \in \Theta} \frac{|I(\xi, \theta)|}{|I(\xi_\theta^*, \theta)|}.$$

We follow the set up in Bogacka et al. (2011) where the design space for the two variables $\mathbf{x} = (S, I)$ is $X = [0, 30] \times [0, 60]$ and the range set Θ of possible values for $\theta = (K_m, K_{ic}, K_{iu})^\top$ is $[4, 5] \times [2, 3] \times [4, 5]$, which includes the nominal values used in their study for an application using the Competitive Inhibition model.

Table 2 The nested PSO-generated standardized maximin D-optimal designs for the four inhibition models using the following PSO parameters: number of particles in the outer (inner) loop = 256 (128), number of iterations in the outer (inner) loop = 200 (100) and $\gamma_1 = \gamma_2 = 2$

Type	ξ_{PSO}				Lower bound of efficiency (%)
Competitive inhibition model	$\begin{pmatrix}3.4445\\0.0000\end{pmatrix}$ 0.3333	$\begin{pmatrix}30.0000\\0.0000\end{pmatrix}$ 0.3333	$\begin{pmatrix}30.0000\\18.8982\end{pmatrix}$ 0.3334		99.99
Noncompetitive inhibition model	$\begin{pmatrix}3.4429\\0.0000\end{pmatrix}$ 0.3333	$\begin{pmatrix}30.0000\\0.0000\end{pmatrix}$ 0.3333	$\begin{pmatrix}30.0000\\2.4495\end{pmatrix}$ 0.3334		99.99
Uncompetitive inhibition model	$\begin{pmatrix}3.4461\\0.0000\end{pmatrix}$ 0.3333	$\begin{pmatrix}30.0000\\0.0000\end{pmatrix}$ 0.3334	$\begin{pmatrix}30.0000\\5.1383\end{pmatrix}$ 0.3333		99.99
Mixed inhibition model	$\begin{pmatrix}3.4406\\0.0000\end{pmatrix}$ 0.2503	$\begin{pmatrix}4.2835\\3.1445\end{pmatrix}$ 0.2498	$\begin{pmatrix}30.0000\\0.0000\end{pmatrix}$ 0.2501	$\begin{pmatrix}30.0000\\4.0191\end{pmatrix}$ 0.2498	99.92

Table 3 Standardized maximin D-optimal designs for the four kinds of inhibition models

Type	ξ^*_{ci}			
Competitive inhibition model	$\begin{pmatrix}3.4429\\0\end{pmatrix}$ 1/3	$\begin{pmatrix}30\\0\end{pmatrix}$ 1/3	$\begin{pmatrix}30\\18.8944\end{pmatrix}$ 1/3	
Noncompetitive inhibition model	$\begin{pmatrix}3.4429\\0\end{pmatrix}$ 1/3	$\begin{pmatrix}30\\0\end{pmatrix}$ 1/3	$\begin{pmatrix}30\\2.4495\end{pmatrix}$ 1/3	
Uncompetitive inhibition model	$\begin{pmatrix}3.4429\\0\end{pmatrix}$ 1/3	$\begin{pmatrix}30\\0\end{pmatrix}$ 1/3	$\begin{pmatrix}30\\5.1424\end{pmatrix}$ 1/3	
Mixed inhibition model	$\begin{pmatrix}3.4429\\0\end{pmatrix}$ 1/4	$\begin{pmatrix}4.2943\\3.1231\end{pmatrix}$ 1/4	$\begin{pmatrix}30\\0\end{pmatrix}$ 1/4	$\begin{pmatrix}30\\4.0199\end{pmatrix}$ 1/4

The nested PSO-generated standardized maximin optimal designs are shown in Table 2 along with their efficiency lower bounds. For each of these design ξ, the bound is given by

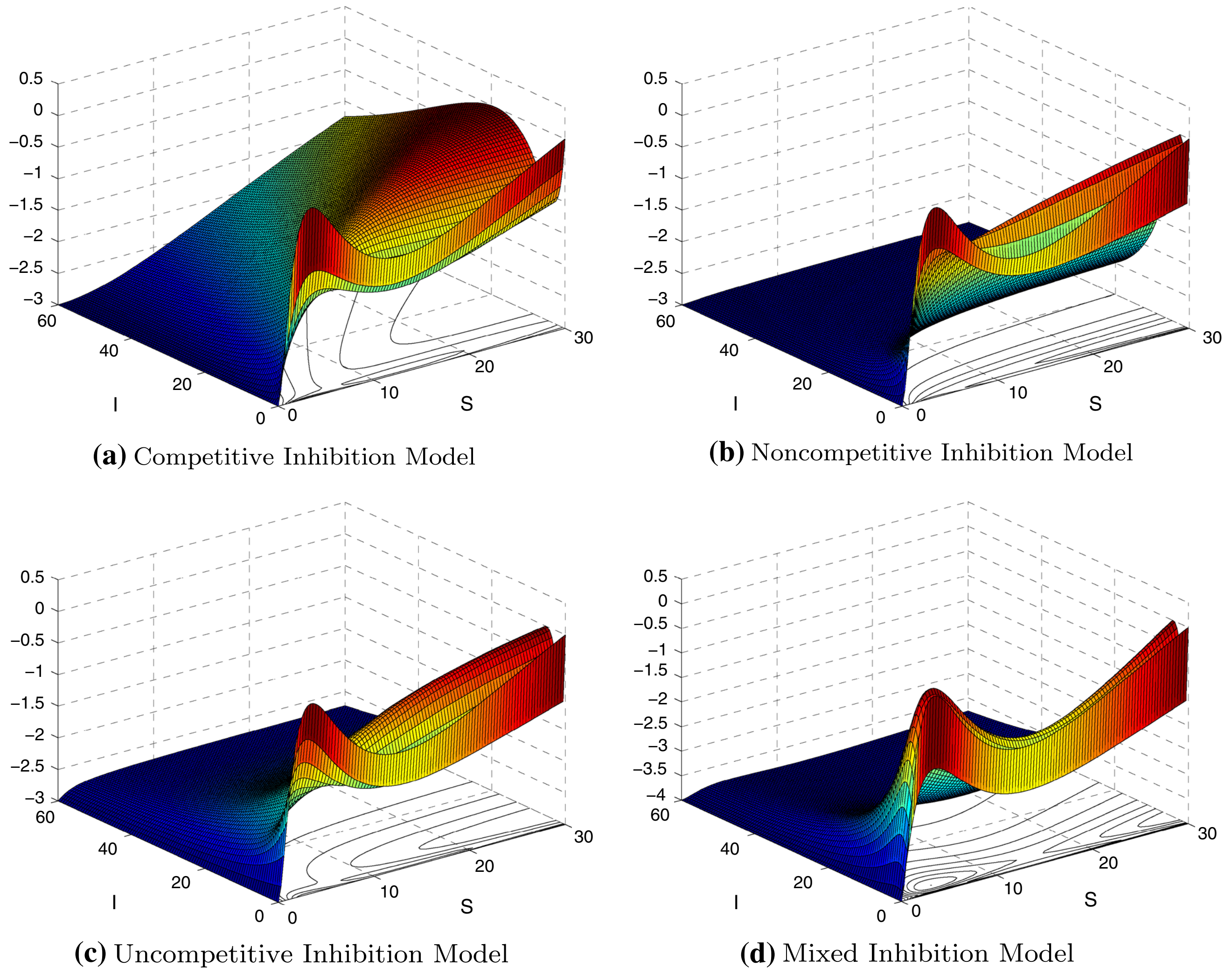
$$\frac{p}{\max_{x\in X}\int_{A(\xi)}\frac{\partial g(x,\theta)^\top}{\partial\theta}I(\xi,\theta)^{-1}\frac{\partial g(x,\theta)}{\partial\theta}\mu(d\theta)},$$

where p is the number of the parameters in the mean function, $A(\xi)=\{\theta\in\Theta|\Phi(\xi)=\text{eff}_\theta(\xi)^2\}, \text{eff}_\theta(\xi)=(|I(\xi,\theta)|/|I(\xi^*_\theta,\theta)|)^{1/2}$ and μ is the probability measure defined on $A(\xi)$ which minimizes the denominator; see Wong and Cook (1993) or Dette and Biedermann (2003) for details. For instance, for the mixed inhibition model we have $g(x,\theta) = \upsilon = VS/(K_m(1+\frac{I}{K_{ic}})+S(1+\frac{I}{K_{iu}}))$ and $p = 4$. Table 2 shows that all the designs found by the nested PSO are at least 99.9 % efficient and so they are all very close to the theoretical standardized maximin optimal designs.

To find the maximin optimal designs, one notes that the maximin criterion is a concave function on the space of designs on X and so conditions from an equivalence theorem can be applied. For example, consider the competitive inhibition (ci) model where Table 2 suggests the optimal design ξ^*_{ci} should be an equally weighted design with the following structure:

$$\xi^*_{ci} = \begin{pmatrix}\begin{pmatrix}S_1\\0\end{pmatrix} & \begin{pmatrix}30\\0\end{pmatrix} & \begin{pmatrix}30\\I_3\end{pmatrix}\\ 1/3 & 1/3 & 1/3\end{pmatrix}.$$

One could also conjecture that when we have the maximin optimal design ξ^*, the measure μ^* is equally supported at $(4,3)^\top$ and $(5,2)^\top$ in the parameter space. This conjecture comes from the best design found by the nested PSO. The requirements of the equivalence theorem then provide us with equations to solve for S_1 and I_3. In this case, the solutions are $S_1 = 3.4429$ and $I_3 = 18.8944$. Both values are close to the design points shown in Table 2 and the design displayed in Table 3 for this model is the standardized maximin optimal design. Similarly, the other designs found using hints from the generated designs shown in Table 3 are also standardized maximin optimal for the other 3 models. The plots of the directional derivatives for the maximin criterion for these 4 designs in Fig. 6 confirm their optimality.



(a) Competitive Inhibition Model

(b) Noncompetitive Inhibition Model

(c) Uncompetitive Inhibition Model

(d) Mixed Inhibition Model

Fig. 6 Plots of the directional derivatives of the standardized maximin D-optimality criterion evaluated at the PSO-generated designs for the four inhibition models

6 Discussion

Given rapidly rising costs of experimentation, optimal design ideas take on an increasingly important role. A well designed study is able to answer scientific questions accurately and with minimum cost. It is therefore not surprising that optimal experimental designs continue to find increasingly more applications in different fields and novel applications are continually seen in traditional areas, see Berger (2005), for example.

Computer algorithms have played and will continue to play an important role in our search of optimal designs. They are usually sequential in nature and typically involve the addition of a carefully selected new design point to the current design by mixing them appropriately to form a new design. The generated design accumulates many points or clusters of points as the algorithm proceeds and judicious rules for collapsing points into distinct points is required. The weights typically used in popular algorithms such as Fedorov's algorithm for finding optimal designs to combine designs from each successive iterations are between 0 and 1 and have the following properties: (a) their sum is infinity and (b) the sum of squares of each term is finite. One common choice for the weight at the kth iteration is $1/k$, where $\sum_{l=1}^{\infty} 1/k = \infty$ and $\sum_{l=1}^{\infty} 1/k^2 < \infty$. Both conditions help ensure successful termination of the algorithm.

Stopping rules are employed to decide when to terminate the search; they typically require either a maximum number of iterations allowed or when the change in the value of the optimality criterion in successive searches is negligible according to a user-selected tolerance level. An example of such an algorithm is the noted Fedorov-Wynn algorithm which is still popular after more than 3 decades of use. Details and exemplary codes for generating D- and c-optimal designs can be found in design monographs like Silvey (1980) and Fedorov (1972). Several modified versions of the Fedorov-

Wynn algorithm have been proposed and we refer to them as the Fedorov-Wynn types of algorithms.

A main difference between PSO and the popular Fedorov-Wynn types of algorithms is that PSO uses many particles (designs) right from the start to cover the design space before searching for the optimum, whereas the Fedorov-Wynn types of algorithms use only one starting design. This means that a poor choice of the starting design in the Fedorov-Wynn algorithm may require a relatively long time for it to get near the optimum. In contrast, PSO's uses many particles to search for the optimum at any one time by sharing information among the search particles. In addition, PSO is flexible and easy to implement; our experience is that only the number of iterations and flock size seem to affect PSO's ability to find the optimal design.; all other tuning parameters in the PSO do not seem to matter, and so we set them all equal to their default values. In this sense, PSO compares favorably with other algorithms like genetic algorithms which can depend sensitively on the tuning parameters. In sum, our experience with PSO agrees with findings reported in the literature.

To get a sense of computing time which nested PSO required to run through a search, we revisit Example 1 for the Michaelis–Menten model. For brevity, we consider an illustrative case when the model parameters are $(a, b)^\top = (100, 150)$ and we use different numbers of particles and iterations. When the iteration number is fixed at 100, and the number of particles is 128, 256, 512, 1024 and 2048, the search took 0.87, 1.65, 3.16, 6.32 and 12.58 s respectively. When the number of particles is fixed at 128, and the iteration number is 200, 500 and 1,000, the PSO search time is 1.68, 4.13 and 8.05 s respectively. In all cases, the generated designs agree up to 5 decimal places in terms of both weights and design points. Clearly larger flock size requires more time to partake in the sharing of information and larger numbers of iterations require longer time.

In summary, PSO is a novel and powerful method to generate different types of optimal experimental designs. We continue to have other successes not all reported here when we applied PSO to find A, c or D-optimal designs for nonlinear models with 3 or more parameters. Each time PSO would find and confirm the results in the literature usually in a few seconds of CPU time. We have also verified that PSO is able to generate D-optimal designs for Scheffe's quadratic polynomial mixture models up to 8 factors with a hundred or more variables to be optimized.

PSO methodology has potential for finding other types of optimal designs. We have two areas for future work. The first is to apply PSO to find multiple-objective optimal designs. Such designs are more attractive because studies typically have several goals and not all of them may be of equal interest. Multiple-objective optimal designs are discussed extensively with examples in Cook and Wong (1994), Huang and Wong (1998), Zhu and Wong (2000, 2001). The second area for future work is to apply PSO to find optimal designs under a non-convex criterion, where we no longer have an equivalence theorem to confirm whether a design is optimal or not. Our latest results include modifying PSO in a novel way to find balanced optimal supersaturated designs, which have a very different setup than the one considered here. The design space is discrete and because we allow more factors than have been considered in the literature, the optimization problem is high dimensional. Other examples of optimal designs under non-convex objective functions are exact optimal designs, replication free optimal designs, minimum bias designs or designs which minimize the mean square error. We plan to apply PSO methodology to find these types of optimal designs and hope to report results in the near future.

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