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Standardized maximim *D*-optimal designs for enzyme kinetic inhibition models

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ABSTRACT

Locally optimal designs for nonlinear models require a single set of nominal values for the unknown parameters. An alternative is the maximin approach that allows the user to specify a range of values for each parameter of interest. However, the maximin approach is difficult because we first have to determine the locally optimal design for each set of nominal values before maximin types of optimal designs can be found via a nested optimization process. We show that particle swarm optimization (PSO) techniques can solve such complex optimization problems effectively. We demonstrate numerical results from PSO can help find, for the first time, formulae for standardized maximin *D*-optimal designs for nonlinear model with 3 or 4 parameters on the compact and nonnegative design space. Additionally, we show locally and standardized maximin *D*-optimal designs for inhibition models are not necessarily supported at a minimum number of points. To facilitate use of such designs, we create a web-based tool for practitioners to find tailor-made locally and standardized maximin optimal designs.

1. Introduction

One of the simplest and popular models to study enzyme kinetics is the 2-parameter Michaelis-Menten equation.

$$\upsilon = \eta(\theta, s) + \varepsilon = \frac{V_{\max} \cdot s}{km + s} + \varepsilon, \quad s \in X, \quad \theta = (V_{\max}, km)^{\top}.$$

Here s is the substrate concentration chosen from a user-selected range of concentrations, X, to observe the velocity of the reaction υ whose mean response is $\eta(\theta,s)$. The parameter km is the Michaelis-Menten constant which controls the rate of the reaction. Another parameter, $V_{\max}$, represents the rate of the enzyme kinetic reaction at the maximum substrate concentration. Each error term ε is assumed to be normally distributed with mean 0 and constant variance and errors are assumed to be independent. The design space X is assumed to be compact and is prespecified for the study.

Optimal design issues for the Michaelis-Menten model have been quite extensively studied in the literature, see for example [1–8], among others. Much of the work in the literature, including those just cited, requires a single best guess for the model parameters to construct locally *D*-optimal designs for estimating the parameters. This approach has drawbacks because previous studies or experts may not agree on a single best guess for the values of the model parameters. Because locally optimal designs can be sensitive to mis-specification of the nominal values for the model parameters, it is helpful to consider alternative design strategies.

Our approach is to first elicit a parameter space that includes all possible values of all the parameters in the mean function of the model. This space may be selected by the user or from opinions of experts. We then seek a design that maximizes the minimal determinant of the information matrix over this parameter space. The resulting optimal designs are called maximin *D*-optimal designs. They are also appealing because in practice, it is often easier to elicit a range of possible values for each model parameter than a prior distribution or a single best guess for the set of nominal values for the model parameters.

Maximin (or minimax) optimal designs were found by Refs. [9–12] and by Dette and his team, which includes [7,13], among several others. A drawback of maximin optimal designs for nonlinear models is that they are difficult to find both analytically and even numerically. Some attempts were made to find such designs under a more restricted setup. For example [11,12,14], found minimax *D*-optimal designs for the logistic model under various restrictions, such as searching only among the class of symmetrical balanced designs. Ref. [15] constructed maximin *D*-optimal designs for a bioassay study using the four-parameter logistic model. However, his approach was not based on theory and the optimal

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designs were found under a restrictive setting so that the resulting designs are not truly maximin optimal. To date, formulae for maximin optimal designs are available for simple models with up to 2 parameters and the derivation is specific to the model and not generalizable to even slightly different models. To our best knowledge, there is also no known algorithm that is guaranteed to generate the maximin optimal design in a general regression setting even for linear models.

A more complicated version of the maximin design criterion is a standardized version of the maximin criterion and seek a standardized maximin *D*-optimal design. The standardized criterion is especially meaningful when the magnitude of parameters in the model vary considerably [13]. Results not shown here suggest that standardized maximin optimal designs are generally more robust to mis-specification in the nominal values than maximin optimal designs. For this reason, we focus on finding standardized maximin optimal designs and not discuss maximin optimal designs further. Between the two types, standardized maximin *D*-optimal designs are clearly more technically difficult to study and determine and so less discussed. In our work, we test the capability of particle swarm optimization (PSO) to find these hard to find optimal designs for nonlinear models with more than two parameters and use the numerical results to develop formulae for the optimal designs.

PSO was proposed by Ref. [16] and is a member of the class of nature-inspired meta-heuristic algorithms. Such algorithms are increasingly used in various disciplines for general optimization purposes [17, 18]. Ref. [19] provides an overview of such algorithms. Our earlier successes using PSO to tackle simpler but different types of design problems [20–22] and [23] encouraged us to now test PSO algorithms further with more challenging design problems. An example of an application of PSO to tackle estimation problems is [24], who applied PSO to estimate parameters in a pharmacokinetic mixed effects nonlinear model.

Section 2 describes four nonlinear models used in enzyme kinetic studies and how PSO algorithm works in general. Section 3 presents PSO-generated standardized maximin *D*-optimal for estimating model parameters and show how PSO can help find formulae for the optimal designs among designs. Additionally, we show that not all standardized maximin optimal designs are minimally supported, i.e., designs with the number of support points equal to the number of parameters in the mean function. In particular, we produce a standardized maximin optimal design with 4 points for a 3-parameter inhibition model, thereby invalidating the assumption made in Ref. [25] that locally *D*-optimal designs for the inhibition models are minimally supported. Section 4 offers conclusions.

2. Standardized maximin optimal designs for enzyme inhibition kinetic models and PSO

This section first reviews a few ways to extend Michaelis-Menten model to study inhibition effects in enzyme kinetic reaction, different design criteria and design efficiency for estimating model parameters. Then we review particle swarm optimization (PSO) techniques in the context of finding optimal deigns.

2.1. Common inhibition models and design problems

Our inhibition models have either 3 or 4 parameters with two controllable variables, s for the substrate concentration and i for the inhibition amount. The design space X is the cartesian product of $S \times I$, where S is the interval $0 \le s_{\min} \le s \le s_{\max}$ and I is the interval $0 \le i_{\min} \le i \le i_{\max}$. Both the upper and lower bounds are user-selected and throughout, we assume that the vector of model parameters θ in the model belongs in a known region θ called the plausible region.

Ref. [25] provided interpretation of the parameters in the 4 inhibition models, which all have two common parameters $V_{\max}$ and *km*. The competitive model and the noncompetitive models has a common third parameter *kic*. The uncompetitive model has a third parameter *kiu*. Both the parameters *kic* and *kiu* are called dissociation constants and are assumed to be positive. The mixed-type model contains all four parameters. These 4 inhibition models describe different behaviors of the inhibitor and they are:

Competitive Inhibition: This type of inhibitor will blocks the enzyme and make it unable to react with the substrate to form product. In this case, the inhibitor competes with the substrates for space on the enzyme.

$$v = \eta(\theta, s, i) + \varepsilon = \frac{V_{max} \cdot s}{km\left(1 + \frac{i}{kic}\right) + s} + \varepsilon, \quad (s, i) \in X = S \times I.$$

Uncompetitive Inhibition: The inhibitor binds to the enzyme-substrate complex and prevents the enzyme from turning substrate into product. The velocity equation is

$$v = \eta(\theta, s, i) + \varepsilon = \frac{V_{max} \cdot s}{km + s\left(1 + \frac{i}{kiu}\right)} + \varepsilon, \quad (s, i) \in X = S \times I.$$

Noncompetitive Inhibition: The inhibitor can be competitive or uncompetitive that either blocks the enzyme or binds to the enzyme-substrate complex. Neither of which can react to form product. The velocity equation is

$$v = \eta(\theta, s, i) + \varepsilon = \frac{V_{max} \cdot s}{(km + s)\left(1 + \frac{i}{kic}\right)} + \varepsilon, \quad (s, i) \in X = S \times I.$$

Mixed-type Inhibition Model: The mixed-type inhibition is a generalization of the noncompetitive model and it has 4 parameters. The velocity equation is

$$v = \eta(\theta, s, i) + \varepsilon = \frac{V_{max} \cdot s}{km\left(1 + \frac{i}{kic}\right) + s\left(1 + \frac{i}{kiu}\right)} + \varepsilon, \quad (s, i) \in X = S \times I.$$

We focus on approximate designs proposed by Kiefer in the late 1950's. Approximate designs are probability measures and after they are found they are rounded to an exact design for implementation. For instance, if $\xi = \{(\mathbf{x}_1, w_1), (\mathbf{x}_2, w_2), \ldots, (\mathbf{x}_q, w_q)\}$ is an approximate design with q points at $\mathbf{x}_j = (s_j, i_j)$, $j = 1, \ldots, q$ with corresponding weights $w_1, \ldots, w_q$, the implemented design takes nw_i number of observations at $\mathbf{x}_i$ to each nw_i is a rounded positive integer nearest to $n \times w_i$ and $nw_1 + nw_2 + \cdots + nw_q = n$. The worth of a design is measured by its Fisher information matrix, defined as the negative of the expectation of the second derivatives of the total log-likelihood function with respect to the model parameters. That is, given a design ξ, the information matrix for an inhibition model is

$$M(\xi, \theta) = \sum_{j=1}^{q} w_j f(s_j, i_j, \theta) f(s_j, i_j, \theta)^{\top},$$

where $f(s,i,\theta)$ is the gradient vector of $\eta(\theta,s,i)$, i.e. $f(s, i, \theta) = \frac{\partial \eta(\theta, s, i)}{\partial \theta}$.
For an optimality criterion, the design questions are the choice of the optimal value for q and the triplet $(s_j, i_j, w_j), j = 1, \ldots, q$, subject to $\sum_{j=1}^{q} w_i = 1$.

The four inhibition models are nonlinear models and so their information matrices $M(\xi,\theta)$ depend on the unknown model parameters θ. Consequently a design criterion formulated in terms of the information matrix depends on θ, prompting [26] to call designs that optimize such a criterion locally optimal. For example, if θ_0 is a vector of nominal values for θ, a locally *D*-optimal design ξ_{θ_0} is a design that maximizes

$$\Psi(\xi) = \log|M(\xi, \theta_0)|$$

among all designs on X. Here the nominal values for θ frequently comes

from a pilot study or from an expert's opinion.

Design efficiency measures how the design performs relative to the optimum. Different designs can be meaningfully compared using their criterion values or some function thereof. For example for *D*-optimality, we compare the performances of two designs ξ_1 and ξ_2 via the ratio of their determinants,

$$\left\{\frac{|M(\xi_1,\theta_0)|}{|M(\xi_2,\theta_0)|}\right\}^{1/p},$$

where p is the number of parameters in the mean function. When ξ_2 is the (locally) *D*-optimal design for θ_0, the above ratio becomes the *D*-efficiency of the design ξ_1. If the *D*-efficiency of ξ_1 is 0.5, the design ξ_1 has to be replicated twice to do as well as the *D*-optimal design.

The maximin approach requires that a known region θ for all plausible values of θ be specified in advance and the locally *D*-optimal design be available for each set of $\theta \in \theta$. Following Ref. [7], the standardized maximin *D*-optimal design ξ^*_{SM} maximizes the minimal efficiency among all possible efficiencies from assumed values of θ in θ and so is the design that maximizes

$$\Psi(\xi) = \min_{\theta\in\theta}\left\{\frac{|M(\xi,\theta)|}{\sup_\gamma |M(\gamma,\theta)|}\right\}^{1/p}, \quad (1)$$

where the denominator is the determinant of the information matrix of the locally *D*-optimal design for the specific parameter θ.

2.2. Particle swarm optimization

To find standardized maximin optimal designs numerically, we resort to particle swarm optimization (PSO) techniques. A main appeal of PSO is that it does not require assumptions on the problem for it to find the optimum. In particular, PSO can be used to optimize non-differentiable functions, such as the maximin or minimax optimality criteria. PSO came from studying animal behavior, such as when a flock of birds is looking for food on the ground. More specifically, the user first generates a flock of P birds, which are particles representing candidates of the optimal design. To find the optimal solution, the user also specifies the maximum number of iterations $t_{\max}$ for PSO to find the optimum. PSO then updates the position of the *jth* particle using equations (2) and (3) at each iteration t, $t = 1, \ldots, t_{\max}$. They relate its previous and current positions with its previous and current velocities as follows:

$$\mathbf{v}_j^{(t+1)} = \omega^{(t)}\mathbf{v}_j^{(t)} + c_1R_1 \otimes \left(\mathbf{x}_{j,L}^{(t)} - \mathbf{x}_j^{(t)}\right) + c_2R_2 \otimes \left(\mathbf{x}_G^{(t)} - \mathbf{x}_j^{(t)}\right), \quad (2)$$

$$\mathbf{x}_j^{(t+1)} = \mathbf{x}_j^{(t)} + \mathbf{v}_j^{(t+1)},\ j = 1, 2, \ldots, P. \quad (3)$$

In (2), $\otimes$ is the Hadamard product, i.e. denotes componentise multiplication, $\mathbf{v}_j^{(t+1)}$ is the velocity of the jth particle at the $(t+1)^{th}$ iteration and it has three components: its previous velocity $\mathbf{v}_j^{(t)}$ with which it flew to the current position $\mathbf{x}_j^{(t)}$ and $\mathbf{x}_{j,L}^{(t)}$ is local best position it has found so far. The flock shares information and decides on the global best position $\mathbf{x}_G^{(t)}$ among all the local best positions at the *tth* iteration. The tuning parameters are: (i) $\omega^{(t)}$ is the inertia weight which can be a constant, or a function of the iteration counter that keeps decreasing the effect of $\mathbf{v}_j^{(t)}$ during the updating procedure, (ii) c_1 and c_2 are the cognitive and the social parameters, respectively, and they guide the particle stochastic movement towards $\mathbf{x}_{j,L}^{(t)}$ and $\mathbf{x}_G^{(t)}$, (iii) R_1 and R_2 are two uniformly and independently random vectors from the interval [0, 1]. These represent the basic ideas of PSO but there are many other improvements that make it work better, see for example [16], and [19].

Our aim is to find an approximate design to maximize the criterion (1) in the multi-nested optimization problem using the modified nested PSO algorithm proposed by Ref. [23]. To fix ideas, we describe how PSO finds the standardized maximin optimal design when the locally optimal design is known. There are two layers of optimization: an outer loop and an inner loop. This means that we need to specify two sets of flock sizes and two numbers for the maximum number of iterations to run the PSO. Depending on the model and the type of optimal designs we wish to find, we may vary these four numbers as described in our applications. We keep the rest of the PSO tuning parameters in (2) fixed for all our computation. Specifically, for both the outer and inner loops, we let $\omega^{(t)}$ to be a linearly decreasing function in t with a starting weight of $\omega_0 = 0.95$ and a terminal weight of $\omega_1 = 0.2$ at the end of the first 80% of the maximum number of iterations $t_{\max}$. For the remaining 20% of the iterations, $\omega^{(t)}$ is set to be a constant with a value of 0.2. Throughout, we used the default values with $c_1 = c_2 = 2$. In practice, PSO searches are typically fast and if the sought optimal design is not found, usually a few more trials is required, with or without changes to the PSO algorithm.

3. Standardized maximin *D*-Optimal designs for inhibition models

We first review how we check optimality of a design among all designs on the given design space. We then present formulae for minimally supported standardized maximin optimal designs in Section 3.2, and in Section 3.3, we show such designs are not necessarily optimal among all designs. We conclude with a web-based tool for finding standardized maximin optimal designs.

3.1. Equivalence theorems and standardized maximin optimal designs

The maximin or standardized maximin criteria are concave over the set of all designs on the design space X and so equivalence theorems are available; see Ref. [27] or [28]. Such theorems are derived from directional derivative considerations and are useful to check whether a design is locally, maximin or standardized maximin *D*-optimal among all designs on X. For example, [8] showed that an approximate design ξ^*_{SM} is standardized maximin *D*-optimal if and only if there exists a probability measure μ on $A(\xi^*_{SM})$ such that for all $(s,i) \in X$, the directional derivative $d(s,i,\xi^*_{SM})$ of the criterion at ξ^*_{SM} in the direction of any point mass design $\delta_{(s,i)}$ has to satisfy

$$d(s,i,\xi^*_{SM}) = \int_{A(\xi^*_{SM})} f^{\top}(s,i,\theta)M^{-1}(\xi^*_{SM},\theta)f(s,i,\theta)\mu(d\theta) - p \le 0 \quad (4)$$

with equality at the support points of ξ^*_{SM}. Here $A(\xi)$ is the answering set

$$A(\xi) = \left\{\theta^* \in \theta \;\middle|\; \frac{|M(\xi,\theta^*)|}{sup_\gamma \quad |M(\gamma,\theta^*)|} = \min_{\theta\in\theta}\frac{|M(\xi,\theta)|}{sup_\gamma \quad |M(\gamma,\theta)|}\right\}, \quad (5)$$

and the vector function $f(s,i,\theta)$ is the gradient of the mean function $E(v)$ of one of the above models.

The equivalence theorem can be used to construct an efficiency lower bound for any design without knowing the optimum, see the monograph by Ref. [27]. This means that if an algorithm produces a design with a *D*-efficiency of at least 98%, the user may find it adequate for his or her purpose and terminate the algorithm to implement the design. For a regression model with p parameters, Atwood's efficiency lower bound is $p/(\lambda + p)$, where λ is the maximal value of the function on the left hand side of (4).

An equivalence theorem can also be used to find a formula for the optimal design for relatively simple models. This is done by substituting each support point of the optimal design in (4) and solving for the support points and weights from the resulting equations. We show here for the first time that it is possible to derive analytical formulae for standardized maximin optimal designs for a model with more than 2 nonlinear parameters. This is helpful for studying properties of the

optimal design, and in particular, its robustness to model assumptions.

Following Ref. [25], the nominal values for the parameters are $(V_{\max}, km, kic, kiu) = (7.2975, 4.3859, 2.5822, 5)$ and the design space is $X = S \times I = [0,30] \times [0,60]$. They reported locally D-optimal designs for three 3-parameter inhibition models and a fourth for mixed-type inhibition, which has an additional parameter. We assume each parameter has a known range of plausible values and to fix ideas, let the plausible region be $\theta = [km_L,km_U] \times [kic_L,kic_U] = [4,5] \times [2,3]$ for both the competitive and noncompetitive models, let $\theta = [km_L,km_U] \times [kiu_L, kiu_U] = [4,5] \times [4,5]$ for the uncompetitive model, and let θ is $[km_L, km_U] \times [kic_L,kic_U] \times [kiu_L,kiu_U] = [4,5] \times [2,3] \times [4,5]$ for the mixed-type model. We note that the optimal design does not depend on the parameter $V_{\max}$. Thus we can treat it as a fixed constant and will not include in our parameter vector.

As an illustration, we use PSO to find the standardized maximin D-optimal design for the competitive model when the locally D-optimal designs are available [25]. We first initiate a flock of candidate designs each with 3 design points, i.e. $q = 3$. This is a natural choice since there are 3 parameters in our model and usually a locally D-optimal design is minimally supported. For more complicated models, it is advantageous to search for the optimum using a flock each with a larger number of design points. This gives PSO more room to maneuver and frequently it is able to find the right number of points as it converges to the optimum, even in the case when the optimal design has fewer number of points than the number of parameters in the model. This is an appealing feature of PSO because many conventional algorithms require special handling of a singular information matrix during the iterative process. Our design criterion has two nested levels of optimization, an outer loop and an inner loop. The nested PSO settings for the outer loop are 256 particles and 200 iterations, and for the inner loop, there are 128 particles and 100 iterations.

Our PSO-generated standardized maximin D-optimal designs are quite similar to the locally D-optimal designs found by Ref. [25]. For example, under the given setup with $X = S \times I = [0,30] \times [0,60]$, the PSO-generated standardized maximin D-optimal design ξ_{PSO} for the competitive model has $s_2 = s_{\max}$ and $i_1 = i_2 = i_{\min}$ and its efficiency is 99%. The maximum value of the function $d(s,i,\xi_{PSO})$ is 0.0003, which is close to the expected value of 0 if the PSO-generated design is optimal. The PSO-generated standardized maximin optimal designs allowed us to make an informed conjecture on the theoretical optimal designs. In particular, the number and location of the support points enabled us to work with the equivalence theorem and established closed form formulae for the standardized maximin optimal designs. For example, using PSO results for the competitive inhibition model as an illustrative example, we conjectured that the standardized maximin optimal design has the form $\xi = \{(s_1,0,1/3),(30,0,1/3),(30,i_3,1/3)\}$, which is similar to the assumption made by Ref. [25]. Assuming that μ in (4) is equally supported at $(4,3)^\top$ and $(5,2)^\top$ in θ and imposing conditions required in the equivalence theorem, we then solved the resulting equations and arrived at $s_1 = 3.4429$ and $i_3 = 18.8944$.

A similar strategy produces other standardized maximin D-optimal designs. For example, consider the competitive inhibition model defined on 3 different design spaces: $X = [9,30] \times [0,60]$, $X = [0,30] \times [18,60]$ and $X = [9,30] \times [18,60]$. Table 1 displays the PSO-generated designs ξ_{PSO}'s and Fig. 1 shows the directional derivative function $d(s,i,\xi_{PSO})$ of each of these designs is close to what we expect if ξ_{PSO} is standardized maximin D-optimal. The table suggests that the sought optimal designs share the same structure shown in the previous paragraph. If we now impose the conditions required by the equivalence theorem and solve the resulting set of equations, we obtain the numerical standardized maximin D-optimal designs ξ^*_{SM} in Table 1 on these 3 design spaces.

3.2. Analytical results for minimally supported optimal designs

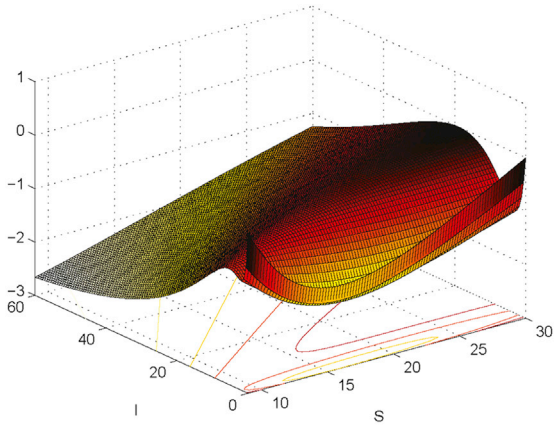
We now show how one may use the equivalence theorem and numerical results from PSO to obtain analytical description of the minimally supported standardized maximin D-optimal designs for the inhibition models. Closed-form formulae for optimal designs are desirable because they facilitate study of robustness properties of a design to model assumptions. A key difficulty in applying the equivalence theorem is the determination of the associate probability measure μ in (4). Even if our current design ξ is standardized maximin D-optimal, failure to find this probability measure μ will not enable us to claim the current design is optimal. An effective way to find the probability measure in (4) is therefore highly desirable but seems elusive to date.

Minimally supported optimal designs can be appealing in terms of time, labor and monetary savings for some studies. The availability of formulae for such optimal designs can greatly facilitate studying properties of the optimal designs. A disadvantage is that they cannot be used to check for model inadequacy. Another is that minimally supported optimal designs may not be optimal among all designs. We also determine in Section 3.3, for the first time, a standardized maximin optimal design for an inhibition model with more than 3 parameters.

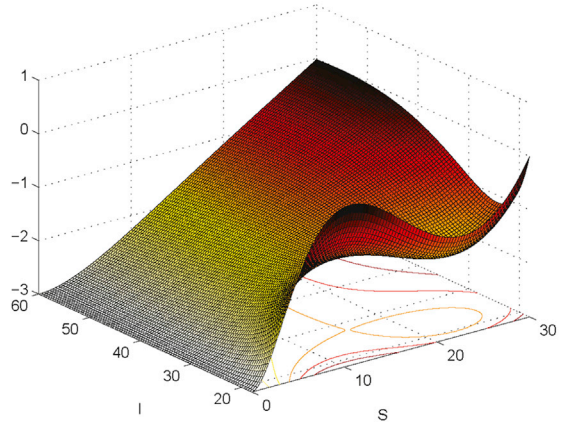
To obtain the closed-form description of the minimally supported standardized maximin optimal design or any other optimal design, guess work is required. The biggest problem is to guess correctly how many points are needed and where these points are. For instance, if the design space is symmetrical about 0, one hopes that the optimal design is also symmetric and so there are fewer number of variables that needs to be optimized in the design problem. Frequently, this means that equations

Table 1
Theoretical (ξ^*_{SM}) and the PSO-generated 3-point standardized maximin D-optimal designs (ξPSO) for the competitive model on different design spaces. The last column displays the Atwood's efficiency lower bounds [27] of the PSO-generated designs relative to the optimum.

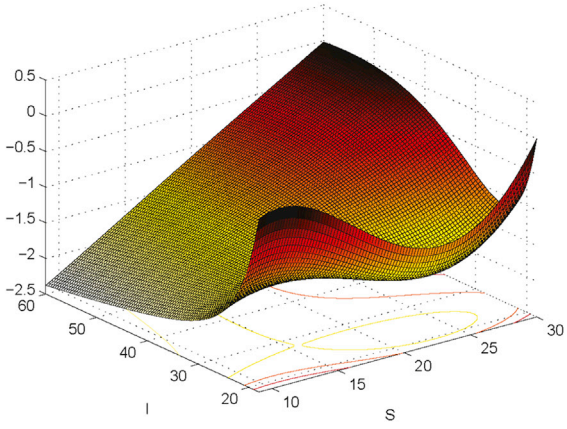
Design space $= X = S \times I$		Support point weight			D-efficiency
$X = [9,30] \times [0,60]$	ξ_{PSO}	$\begin{pmatrix} 9.0000 \\ 0.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 0.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 18.8940 \end{pmatrix}$	99.99%
		0.3333	0.3333	0.3334	
	ξ^*_{SM}	$\begin{pmatrix} 9.0000 \\ 0.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 0.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 18.8944 \end{pmatrix}$	100.00%
		1/3	1/3	1/3	
$X = [0,30] \times [18,60]$	ξ_{PSO}	$\begin{pmatrix} 10.6440 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 55.2719 \end{pmatrix}$	99.99%
		0.3333	0.3333	0.3334	
	ξ^*_{SM}	$\begin{pmatrix} 10.6363 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 55.3095 \end{pmatrix}$	100.00%
		1/3	1/3	1/3	
$X = [9,30] \times [18,60]$	ξ_{PSO}	$\begin{pmatrix} 10.6451 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 55.2748 \end{pmatrix}$	99.99%
		0.3333	0.3333	0.3334	
	ξ^*_{SM}	$\begin{pmatrix} 10.6363 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 18.0000 \end{pmatrix}$	$\begin{pmatrix} 30.0000 \\ 55.3095 \end{pmatrix}$	100.00%
		1/3	1/3	1/3	



(a) $S \times I = [9, 30] \times [0, 60]$



(b) $S \times I = [0, 30] \times [18, 60]$



(c) $S \times I = [9, 30] \times [18, 60]$

Figure 1. Directional derivative of the standardized maximin *D*-optimality criterion evaluated at the PSO-generated design for the competitive inhibition model for the 3 design spaces.

emanating from the equivalence theorem have to be solved, with one equation for each of the posited design point of the optimal design. In addition, one typically has to find roots of additional equations derived from taking derivatives of the directional derivative function and setting them equal to zero at the "interior" support points of the design to ensure all conditions in the equivalence theorem are satisfied.

To fix ideas, consider finding the formula for the standardized maximin *D*-optimal design for the competitive inhibition model on the design space $X = [s_{\min}, s_{\max}] \times [i_{\min}, i_{\max}]$ and both $s_{\min}$ and $i_{\min}$ are nonnegative. From PSO numerical results, we conjectured that the standardized maximin optimal design ξ is a 3-point equally weighted design with the following properties: one of its support points is at the extreme ends of the two concentrations, one support point is at $(s_1, i_{\min})$ and the third is at (s_3,i_3). Further numerical search indicates that, according to the definition of answering set in (5), the minimal efficiency of the standardized maximin *D*-optimal design occurs at the corner points of θ. For example, if one plots the *D*-efficiencies of the standardized maximin *D*-optimal design for the first case in Table 1 when the parameter space is [4,5] × [2,3], it can be shown that the efficiencies attain their minimum at two corner points, $\theta_1^* = (km_L, kic_U)$ and $\theta_2^* = (km_U, kic_L)$. Accordingly, based on the equivalence theorem, we solve the minimization problem:

$$\min_{\alpha_1,\alpha_2} \quad \sum_{k=1}^{3}\left(\sum_{j=1,2}\alpha_j f^{\top}\left(s_k, i_k, \theta_j^*\right) M\left(\xi, \theta_j^*\right)^{-1} f\left(s_k, i_k, \theta_j^*\right) - 3\right)^2,$$

with the constraints that $\alpha_1, \alpha_2 \in [0, 1]$ and $\alpha_1 + \alpha_2 = 1$. Our experience is that the numerical solutions are $\alpha_1 = \alpha_2 = 0.5$ for this and many other problems with different design spaces and parameter spaces. Our conjecture is that the associate probability measure for the optimal design is equally supported at two points in the answering set θ_1^* and θ_2^*, i.e. $A(\xi) = \{\theta_1^*, \theta_2^*\}$. A direct calculation shows that the directional derivative of the standardized maximin criterion evaluated at a design ξ in the direction of the degenerate design at (s,i) is

$$\begin{aligned} d(s, i, \xi) = {} & 0.5 f^{\top}(s, i, \theta_1^*) M\left(\xi, \theta_1^*\right)^{-1} f\left(s, i, \theta_1^*\right) \\ & + 0.5 f^{\top}\left(s, i, \theta_2^*\right) M\left(\xi, \theta_2^*\right)^{-1} f\left(s, i, \theta_2^*\right) - 3. \end{aligned}$$

Imposing conditions from the equivalence theorem that must be satisfied for an optimal design lead to requiring that

$$\frac{d}{\mathrm{d}s} d(s, i, \xi)|_{s=s_1, i=i_{\min}} = 0, \quad \frac{d}{\mathrm{d}s} d(s, i, \xi)|_{s=s_3, i=i_3} = 0 \quad \text{and} \quad \frac{d}{\mathrm{d}i} d(s, i, \xi)|_{s=s_3, i=i_3} = 0.$$

The solutions of these equations are displayed below.

$$s_1^* = \max\left\{s_{min}, \frac{-[\text{Comp:A}] + \sqrt{[\text{Comp:A}] \times [\text{Comp:B}]}}{[\text{Comp:C}]}\right\},$$

$$s_3^* = \max\left\{s_{min}, \min\left\{\sqrt{\frac{km_L km_U (kic_L + i_{max})(kic_U + i_{max})}{kic_L kic_U}}, s_{max}\right\}\right\},$$

$$i_3^* = \min\left\{i_{min} + \sqrt{\frac{[\text{Comp:B}]}{km_L km_U}}, i_{max}\right\},$$

where

$$\begin{aligned}
[\text{Comp:A}] &= km_L km_U (kic_L + i_{min})(kic_U + i_{min}),\\
[\text{Comp:B}] &= [km_U (kic_L + i_{min}) + kic_L s_{max}] \times [km_L (kic_U + i_{min}) + kic_U s_{max}],\\
[\text{Comp:C}] &= km_U kic_U (kic_L + i_{min}) + km_L kic_L (kic_U + i_{min}) + kic_L kic_U s_{max}.
\end{aligned}$$

These provide the interior support points of the optimal design for the competitive inhibit model, including the standardized maximin optimal designs and the associate measures for the other inhibition models. Clearly, when the plausible region becomes a singleton set, for example when $km_L = km_U$, $kic_L = kic_U$ and $kiu_L = kiu_U$, the formulae reduce to those for locally *D*-optimal designs in Ref. [25]. Table 2 displays the support structures for each type of inhibition models and, the mathematical formulae of these four standardized maximin optimal designs are shown in the supplementary material.

3.3. Minimally supported designs may not be optimal designs

In this subsection, we show that standardized maximin optimal designs are not necessarily minimally supported designs. With the help of PSO, we were able to disprove an assumption that locally *D*-optimal designs for the inhibition models are always minimally supported. Ref. [25] found formulae for the locally *D*-optimal designs for the inhibition models by assuming that all such designs are equally supported at the minimal number of points. We show here that for certain parameter configurations, locally *D*-optimal designs have 3 or more points. To fix ideas, we use the noncompetitive inhibition model as an illustrative example.

It is assumed in Ref. [25] that when

$$s_{min} \geq \frac{s_{max} km}{s_{max} + 2km} \quad \text{and} \quad kic + 2i_{min} \geq i_{max}, \tag{6}$$

the locally *D*-optimal design for the model is equally supported at $(s_{\min}, i_{\min})$, $(s_{\max}, i_{\min})$ and $(s_{\max}, i_{\max})$. However, this assumption is invalid. For instance, suppose that the design space is [15,30] × [30,60] and the nominal values for the parameters are $\theta = (4, 2)^\top$. It is easy to check that the parameter configuration satisfies the conditions in (6) and a direct calculation shows that the design ξ_{L-3pt} is equally supported at (30,30), (15,30) and (30,60). This design was reported to be locally *D*-optimal in Ref. [25]. However, according to the directional derivative function of the locally *D*-optimal criterion at ξ, which is, $d_\theta(s,i,\xi) = f(s,i,\theta)^\top M^{-1}(\xi,\theta) f(s,i,\theta) - 3$, Fig. 2(a) shows $d_\theta(s,i,\xi_{L-3pt})$ has a maximum value of 0.9042 at the corner point (15,60), and the Atwood's efficiency lower bound [27] of ξ_{L-3pt} is 76.84%. Thus, the design ξ_{L-3pt} is not locally *D*-optimal among all designs on the given design space. In addition to find ξ_{L-3pt} by the analytical results in Ref. [25], we also tried to generate the corresponding optimal design by the PSO algorithm. The numerical generator provided an identical design as ξ_{L-3pt} even when we doubled the swarm size and the number of iterations. Therefore, we conjecture that the optimal design with this parameter configuration might not always be minimally supported.

We applied the PSO algorithm with 256 particles and 200 iterations and the PSO-generated 4-point design is

$$\xi_{L-4pt} = \left\{ \begin{pmatrix} 15.0000 \\ 30.0000 \\ 0.3069 \end{pmatrix} \begin{pmatrix} 30.0000 \\ 30.0000 \\ 0.3164 \end{pmatrix} \begin{pmatrix} 30.0000 \\ 60.0000 \\ 0.2542 \end{pmatrix} \begin{pmatrix} 15.0000 \\ 55.0958 \\ 0.1225 \end{pmatrix} \right\}$$

Fig. 2(b) shows the directional derivative function $d_\theta(s,i,\xi_{L-4pt})$ has a maximum value 0.0002 with equality at the four support points. This confirms that the PSO-generated 4-point design is locally *D*-optimal design for all practical purposes. Further calculation shows that the determinant of the information matrix for ξ_{L-4pt} is about 5.37% larger than that from the three-point design, ξ_{L-3pt}, which was erroneously claimed to be locally *D*-optimal in Ref. [25].

What is the standardized maximin *D*-optimal design for the noncompetitive inhibition model when the true values of the parameters (*km*,*kic*) are believed to lie in inside [4,5] × [2,3]? From the results in Section 3.2, the theoretical support points are (15,30), (30,30) and (30,60), because $15 = s_1 = s_{\min} > s_1^*$ and $60 = i_3 = i_{\max} < i_3^*$. We denote this 3-point design as $\xi_{SMM-3pt}$. To check $\xi_{SMM-3pt}$ is optimal or not, the maximum value of $d(s,i,\xi_{SMM-3pt})$ in (4) should be less than or equal to 0. However, it is easy to verify that its maximal value is 0.8527, and so this 3-point design is not standardized maximin *D*-optimal. A direct calculation shows the Atwood's efficiency lower bound of $\xi_{SMM-3pt}$ is 77.87%. Fig. 3(a) shows the directional derivative function of the standardized maximin criterion at this 3-point design and suggests that the standardized maximin design has four points which is similar in structure to the locally *D*-optimal design.

To find the 4-point standardized maximin *D*-optimal design, we modified the nested PSO to solve the 3-layer optimization problem. The first is to find the locally *D*-optimal design for each set of parameter values when the corresponding analytical results of 3-point designs in Ref. [25] is not locally *D*-optimal verified by the equivalence theorem. In the second step, PSO searches for point or points in the parameter space that produce the extremum in the inner optimization problem in (1). The third step uses another PSO to determine the standardized maximin design that maximizes the criterion. Because the whole process requires extensive computational time, it is frequently helpful to fix some parameters. For our example, we fix the first 3 design points at the 3 corner points, (15,30), (30,30) and (30,60), and set the fourth point as $(15,i_4)$. Therefore, the unknown components in our design structure are i_4 and

Table 2
Anticipated structure of equally weighted 3- and 4-point standardized maximin D-optimal designs on design space $S \times I = [s_{\min}, s_{\max}] \times [i_{\min}, i_{\max}]$ and the answering sets A(ξ) with the associate measure μ(θ) for the 4 inhibition models.

Inhibition model	Design structure				Answering sets with associate measure			
Competitive	$\begin{pmatrix} s_1 \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_3 \\ i_3 \end{pmatrix}$		$\begin{pmatrix} km_L \\ kic_U \end{pmatrix}$	$\begin{pmatrix} km_U \\ kic_L \end{pmatrix}$		
Uncompetitive	$\begin{pmatrix} s_1 \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_3 \end{pmatrix}$		$\begin{pmatrix} km_L \\ kiu_L \end{pmatrix}$	$\begin{pmatrix} km_U \\ kiu_U \end{pmatrix}$		
Noncompetitive	$\begin{pmatrix} s_1 \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_3 \end{pmatrix}$		$\begin{pmatrix} km_L \\ kic_L \end{pmatrix}$	$\begin{pmatrix} km_L \\ kic_U \end{pmatrix}$	$\begin{pmatrix} km_U \\ kic_L \end{pmatrix}$	$\begin{pmatrix} km_U \\ kic_U \end{pmatrix}$
Mixed-type	$\begin{pmatrix} s_1 \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_2 \\ i_2 \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_{\min} \end{pmatrix}$	$\begin{pmatrix} s_{\max} \\ i_4 \end{pmatrix}$	$\begin{pmatrix} km_L \\ kic_U \\ kiu_U \end{pmatrix}$	$\begin{pmatrix} km_U \\ kic_L \\ kiu_L \end{pmatrix}$		

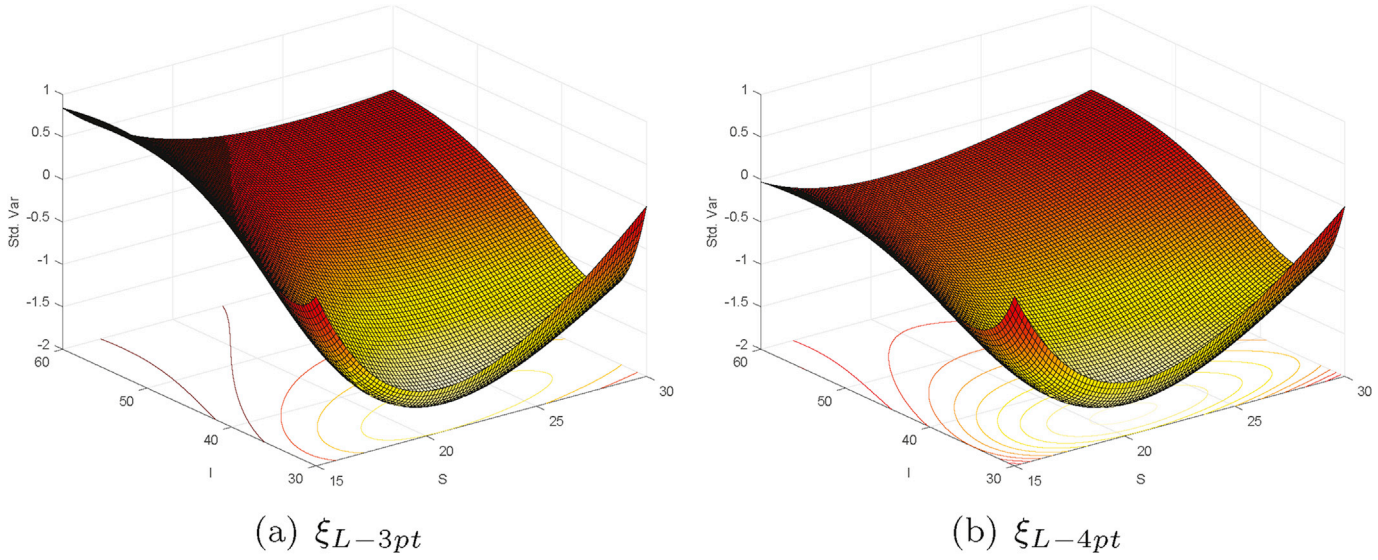


Figure 2. Plots of the directional derivative of the *D*-optimality criterion at the 3-point design ξ_{L-3pt} (a) and 4-point locally *D*-optimal design ξ_{L-4pt} (b) for the noncompetitive inhibition model with parameter vector (*km*,*kic*) = (4,2) on the design space $S \times I = [15,30] \times [30,60]$.

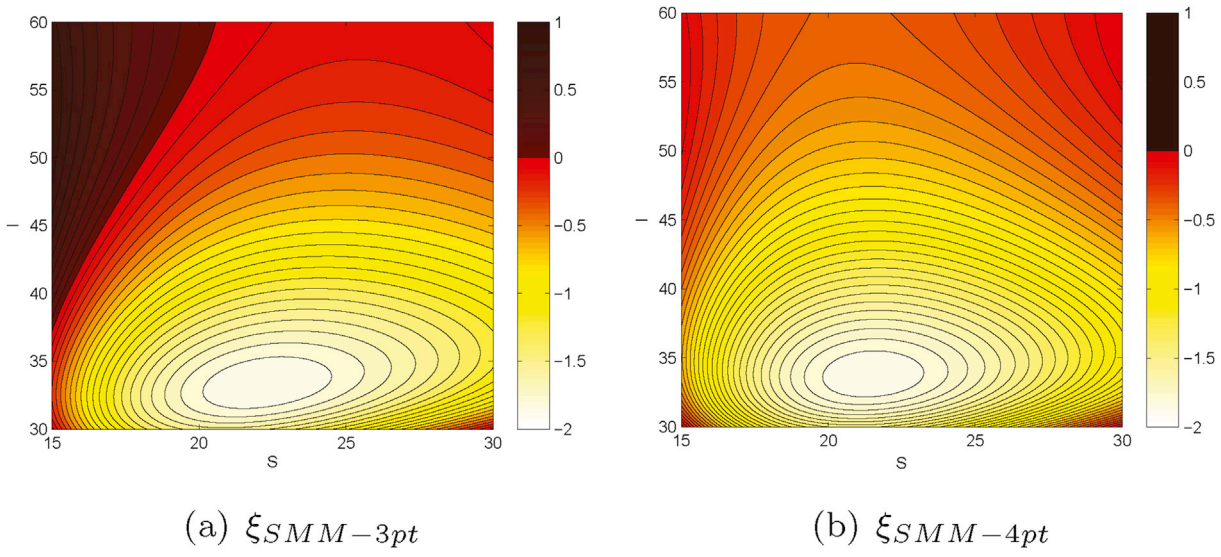


Figure 3. Contour plots of the directional derivatives of the *D*-optimality criterion at $\xi_{SMM-3pt}$ (a) confirming that the 3-point design is not standardized maximin *D*-optimal, and, $\xi_{SMM-4pt}$ (b) which is standardized maximin *D*-optimal for the non-competitive inhibition model.

four corresponding design weights, $w_1, \ldots, w_4$. To apply this 3-layer nested PSO, we choose 25, 10 and 64 particles for outer loop, inner loop optimizations and locally *D*-optimal design search with 200, 50 and 32 iterations respectively. The best standardized maximin *D*-optimal design we found is

$$\xi_{SMM-4pt} = \left\{ \begin{pmatrix} 15.0000 \\ 30.0000 \\ 0.3066 \end{pmatrix} \begin{pmatrix} 30.0000 \\ 30.0000 \\ 0.3175 \end{pmatrix} \begin{pmatrix} 30.0000 \\ 60.0000 \\ 0.2586 \end{pmatrix} \begin{pmatrix} 15.0000 \\ 55.2155 \\ 0.1173 \end{pmatrix} \right\}$$

For this 4-point design, the maximal value of the directional derivative function over the design space is 0.0051 and a direct calculation shows the *D*-efficiency of this design is at least 99.83% by Atwood's method [27]. The plot of the its directional derivative function is shown in Fig. 3(b).

Since the fourth design point in the best design we found is close to the corner point, we fixed the four corner points as the four design points and applied the 3-layer nested PSO with the same setups to search only for the best weights, w_1,w_2,w_3 and w_4. The PSO-generated design is

$$\xi_{SMM-4pt-W} = \left\{ \begin{pmatrix} 15.0000 \\ 30.0000 \\ 0.3111 \end{pmatrix} \begin{pmatrix} 30.0000 \\ 30.0000 \\ 0.3163 \end{pmatrix} \begin{pmatrix} 30.0000 \\ 60.0000 \\ 0.2571 \end{pmatrix} \begin{pmatrix} 15.0000 \\ 60.0000 \\ 0.1155 \end{pmatrix} \right\}$$

and the maximal value of the directional derivative function of the standardized maximin criterion at $\xi_{SMM-4pt-W}$ is 0.0286, implying that the PSO-generated design has at least 99.06% *D*-efficiency by Atwood's efficiency lower bound [27]. The upshot is that the two PSO-generated 4-point designs, $\xi_{SMM-4pt}$ and $\xi_{SMM-4pt-W}$, are nearly standardized maximin *D*-optimal since their *D*-efficiencies are above 99% and higher than that of the 3-point design, $\xi_{SMM-3pt}$.

3.4. A web-based tool

We provide a web-based tool to facilitate practitioners implement

tailor-made standardized maximin optimal designs for inhibition models. There is currently no software for generating such optimal designs. Our web-based tool provides researchers with additional design options and facilitate comparing performances of standardized maximin optimal designs with their competitors.

Our web-based tool is in the form of a shiny package in R software available at https://pingyangchen.shinyapps.io/stdmmoptdesigninhibition. By default this app finds 3-point designs for the competitive, noncompetitive and uncompetitive inhibition models, and a 4-point designs for the mixed-type inhibition model on the pre-specified design spaces and parameter space.

When the search terminates, we display the PSO-generated design, the computing time required and its *D*-efficiency lower bound. On average, the online app takes about 9 min to find the standardized maximin *D*-optimal designs shown in Table 1 by using 256 particles and 200 iterations for the outer loop, and, 128 particles and 100 iterations for the inner loop. If desired, the site also displays the plot to confirm optimality of the generated design. If the graph satisfies the conditions in the equivalence theorem in (4), the generated design is standardized *D*-maximin optimal; otherwise it is not.

Finding the standardized maximin optimal designs for nonlinear models are challenging and time consuming. For this reason, our code limits the user to find locally *D*-optimal designs up to 8 support points. For more complicated models, we recommend the user downloads our codes from the GitHub repository at https://github.com/PingYangChen/stdmmOptDesignInhibition and make appropriate changes to the code. There is also an option to specify whether a minimally supported design is sought. The complete set of instructions for using our codes are available from this GitHub repository.

4. Conclusions

Standardized maximin or standardized minimax *D*-optimal designs and even their simpler versions maximin or minimax *D*-optimal designs for nonlinear models are difficult to find and study because such design problems have a non-differentiable criterion and require multiple levels of optimization. Our work shows that use of a nature-inspired metaheuristic algorithm can generate such maximin optimal designs for inhibition models. The structure of the numerical optimal designs enables us to derive the formula of the standardized maximin design that are helpful for studying further properties of the optimal designs. We also provide a web-based tool to facilitate practitioners generate tailor-made maximin or standardized maximin optimal designs after they input parameters for their specific design problem. The performance of various designs can be compared on the website as well. For example, our numerical results suggest that standardized maximin optimal designs are generally less sensitive to maximin optimal designs when there is misspecification of the nominal values. Supporting numerical results are omitted for space consideration but interested reader can request them from the first author.

Our approach of using PSO to find standardized maximin optimal designs and, if desired, their analytical forms are not limited to inhibition models and standardized maximin optimal designs considered here. It can be broadly applied to find and compare other types of hard-to-find optimal designs for different models. We hope our work will stimulate greater interest in use of nature-inspired metaheuristic algorithms to solve statistical optimization problems.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.chemolab.2017.08.009.

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