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Bayesian Optimal Designs For Nonlinear Models With Three or Four Parameters

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Abstract. In design of experiments, optimal design is an important approach that maximizes the chances of experimental success. A- and D-optimality are well-known criteria for identifying optimal designs. In nonlinear models, these criteria depend on unknown parameters, complicating the design derivation. This paper uses the Bayesian method to address this, deriving A- and D-optimal designs for EMAX, log-linear, and LINEXP models with three or four parameters, using uniform priors. Optimal designs with minimum support points are obtained, with varying weights. These designs serve as benchmarks for evaluating practical alternative designs. Two alternatives were assessed, showing over 80% efficiency in most models compared to A- and D-optimal designs. The computations in this study were performed using a numerical nonlinear approach, specifically the NLPSolve method, which is included in the Optimization package in Maple software.

Keywords. A-optimality, D-optimality, Nonlinear model, Equivalence theorem.

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1 Introduction

Nonlinear regression models are increasingly used in biostatistics and pharmacology. Although extensive research has been conducted on applying these models to data analysis, progress in design selection has been relatively limited due to the complex nature of the corresponding nonlinear optimization problems. The precision of estimating the unknown parameters of the model depend on the design used in the experiment, and vice-versa (Khuri et al., 2006). Optimal designs can enhance the statistical inference regarding the quantities of interest by appropriately selecting the values of control variables. In this context, optimality criteria, primarily based on the information matrix, have been introduced (Silvey, 1980). Among the various optimality criteria, A- and D-optimality are two of the most widely used. In nonlinear models, the dependence of the information matrix on unknown parameters makes it challenging to directly determine the optimal design (Atkinson et al., 2007). A common approach is to use an assumed parameter value that leads to a locally optimal design (see Li and Balakrishnan (2011), Yang and Stufken (2012), Hu et al. (2015) and Feller et al. (2017), Hao and Yang (2020), Olamide et al. (2021), Zhu et al. (2021) and Gündüz (2023), among many others). However, locally optimal designs do not account for the uncertainty in the parameter values and may not be efficient for other parameter values. Dette et al. (2013) demonstrated that locally optimal designs are sensitive to the misspecification of the unknown parameter. To address this issue, a Bayesian approach, which assumes a prior distribution for the parameters, has been proposed. The Bayesian optimal design uses prior information, whether informative or historical, about the unknown parameters as the prior distribution. However, once the prior distribution is specified, no corrective measures are available within the Bayesian framework. The noninformative or subjective prior distribution reflects the uncertainty about the parameter values and is frequently used by researchers. For example, Burghaus and Dette (2014) studied Bayesian optimal designs using noninformative prior distributions. Furthermore, Goudarzi et al. (2021) extended this by considering the prior distribution as an unknown distribution belonging to a class of distribution functions, introducing nonparametric Bayesian optimal designs. In this study, we use the uniform prior distribution, which has been applied in a series of papers, including those by Abebe et al. (2014), Goos and Mylona (2018), Lukemire et al. (2019), among others. Recent studies on the use of Bayesian approaches to optimal designs include Kleinegesse and Gutmann (2020), Taylor et al. (2022), and Leng and Yin (2023).

Statistical modeling has a long history in clinical trials, tumor growth, dose-response modeling, and other areas; the EMAX, log-linear, and LINEXP models are widely used in these fields. Locally optimal designs for these models have been studied by Dette et al. (2010), Li and Balakrishnan (2011), Yang and Stufken (2012), and Hu et al. (2015). On the other hand, determining the optimal Bayesian design for nonlinear models with multiple parameters necessitates complex and challenging analytical solutions, ultimately leading to the reliance on numerical methods. We investigate Bayesian A- and D-optimal designs numerically for the EMAX, log-linear, and LINEXP models with three or four parameters. In the next section, we review the design criteria that define

the primary objectives of an experiment. We also examine the optimal design problem for the nonlinear models and review the three aforementioned models. In section 3, we focus on the Bayesian A- and D-optimal designs for the EMAX, log-linear and LINEXP regression models. Additionally, these designs were used to evaluate the merits of two alternative designs with equally spaced support points, one with uniform weights and the other with varying weights. The paper concludes with a summary of the findings and remarks in the final section.

2 Notations and preliminaries

Consider a nonlinear regression model where a univariate response y depends on a single regression variable x, which belongs to the design space $\mathcal{X} = [a, b]$, where $a < b$. The response y is assumed to be normally distributed with mean $\mu(x, \boldsymbol{\theta})$ and variance $\sigma^2 > 0$. Let $\boldsymbol{\theta} = (\theta_1, \theta_2, ..., \theta_p)$ be a $p \times 1$ vector of unknown parameters of interest in the mean response $\mu(x, \boldsymbol{\theta}) = E(Y|X = x)$. Without loss of generality, we assume the variance to be constant and equal to 1 (Dette and Neugebauer, 1996). Under the assumption that the mean response is differentiable with respect to $\boldsymbol{\theta}$, the Fisher information matrix for $\boldsymbol{\theta}$ at a design point x is defined as follows:(Fedorov and Hackl, 2012)

$$I(x, \boldsymbol{\theta}) = \frac{\partial}{\partial \boldsymbol{\theta}} \mu(x, \boldsymbol{\theta}) \frac{\partial}{\partial \boldsymbol{\theta}^T} \mu(x, \boldsymbol{\theta}).$$

Typically, approximate designs are employed to study optimality. In approximate design context, a design is a probability measure $\xi \in \Xi$, where Ξ is a class of probability measure on $\mathcal{X}$. An approximate design ξ can be represented as $\xi = \{(x_i, w_i), i = 1, 2, \ldots, k\}$, where $x_i \in \mathcal{X}$ are design points and $w_i \geq 0$, denote corresponding weights with $\sum_{i=1}^{k} w_i = 1$ (Kiefer, 1974). Assuming response variables are independent, the Fisher information matrix for $\boldsymbol{\theta}$ under design ξ is defined by $M(\xi, \boldsymbol{\theta}) = \sum_{i=1}^{k} w_i I(x_i, \boldsymbol{\theta})$ (Atkinson et al., 2007). If N observations are available, the quantities $w_i N$ are rounded to integers n_i such that $\sum_{i=1}^{k} n_i = N$ and the experimenter takes n_i observations at each point x_i, $i = 1, 2, ..., k$ (Pukelsheim and Rieder, 1992). The optimal design ξ^* is the design among all possible designs with d points in Ξ which optimizes a function of the information matrix. There are several optimality criteria such as D-, G-, A-optimality, etc. Here, we focus on the A- and D-optimality, whose some useful properties mentioned by Jones et al. (2021).

To address the dependence of the information matrix on the unknown parameters in nonlinear models, we utilize the Bayesian approach. Specifically, a design is called Bayesian optimal with respect to the prior π when the expectation of a concave(convex) function of the information matrix is maximized(minimized), as discussed in Dette and Neugebauer (1996), Abebe et al. (2014), Zohbi et al. (2016) and Prangle et al. (2023) among others.The A-optimal design minimizes the average variance of the estimated parameters, which is equivalent to minimizing the trace of the inverse of the information matrix across all possible designs $x \in \mathcal{X}$. The D-optimality criterion, on the other hand, seeks designs that maximize the determinant of the information matrix.

The Bayesian A- and D-optimal criteria, with respect to a prior distribution π on the parameter space Θ, by analogy with the non-Bayesian theory of optimal design, are defined as follows (Chaloner and Verdinelli, 1995):

$$\phi_A(\xi|\pi) = E(trace(M^{-1}(\xi,\boldsymbol{\theta}))) = \int_\Theta trace(M^{-1}(\xi,\boldsymbol{\theta}))\pi(\boldsymbol{\theta})d\boldsymbol{\theta}, \tag{2.1}$$

$$\phi_D(\xi|\pi) = E(\log(\det M(\xi,\boldsymbol{\theta}))) = \int_\Theta \log(\det M(\xi,\boldsymbol{\theta}))\pi(\boldsymbol{\theta})d\boldsymbol{\theta}, \tag{2.2}$$

where the information matrix is assumed to be a non-singular matrix, and π is a prior distribution for θ, based on pre-experiment and subjective knowledge. Firth and Hinde (1997) and Clyde and Chaloner (1996) demonstrated that the equivalence theorem holds for the Bayesian optimal criteria. In this context, the equivalence theorem for assessing the A- and D-optimality leads to the following forms:

$$d(x,\xi_A^*) = \int_\Theta [\frac{\partial}{\partial\boldsymbol{\theta}^T}\mu(x,\boldsymbol{\theta})M^{-2}(\xi_A^*,\boldsymbol{\theta})\frac{\partial}{\partial\boldsymbol{\theta}}\mu(x,\boldsymbol{\theta}) - trace(M^{-1}(\xi_A^*,\boldsymbol{\theta}))]\pi(\boldsymbol{\theta})d\boldsymbol{\theta} \geq 0,$$
$$d(x,\xi_D^*) = \int_\Theta \frac{\partial}{\partial\boldsymbol{\theta}^T}\mu(x,\boldsymbol{\theta})M^{-1}(\xi_D^*,\boldsymbol{\theta})\frac{\partial}{\partial\boldsymbol{\theta}}\mu(x,\boldsymbol{\theta})\pi(\boldsymbol{\theta})d\boldsymbol{\theta} \leq p,$$

where ξ_A^* and ξ_D^* represent A- and D-optimal designs, respectively. Similarly, $d(x,\xi_A^*)$ and $d(x,\xi_D^*)$ are known as the sensitivity function of a design under the A- and D-optimality criteria (Atkinson et al., 2007). Generally, the optimization of functions of the forms (2.1) and (2.2) must be performed numerically for many commonly used models and prior distributions. In this paper, we focus on Bayesian optimal designs for nonlinear models, including the EMAX, log-linear and LINEXP models, which are widely used in biology, medicine and pharmaceuticals. It should be noted that the theory and methods applied here are applicable to any nonlinear model.

2.1 Models

The EMAX, log-linear and LINEXP models are widely used in various applications, particularly in modeling tumor growth, and in studying the relationship between the response to a given drug dose and its effect (Meibohm and Derendorf, 1997; Boroujerdi, 2001; Demidenko, 2013),

- The EMAX model is often used to describe a dose-response relationship, where the mean response follows a nonlinear regression model as described by Boroujerdi (2001):

$$\mu(x,\boldsymbol{\theta}) = \theta_1 + \frac{\theta_2 x}{x+\theta_3}, \tag{2.3}$$

  where θ_1 denotes the effect of a placebo at the $x = 0$, $\theta_2 > 0$ represents the asymptotic maximum effect over the placebo and $\theta_3 > 0$ specifies the dose that gives

half of the asymptotic maximum effect. It is important to note that the Emax model can accommodate both an increase in effect ($\theta_2 > 0$) and a decrease in effect($\theta_2 < 0$) (Pinheiro et al., 2006). For this discussion, we assume an increasing effect model. In a dose-response relationship, it is often observed that the magnitude of the response increases with the dose until further increases in the dose no longer enhance the response. This maximum response is referred to as EMAX, and the dose corresponding to half of EMAX is denoted as θ_3. The vector of the partial derivatives is given by:

$$\frac{\partial}{\partial \boldsymbol{\theta}}\mu(x,\boldsymbol{\theta}) = (1, \frac{x}{x+\theta_3}, -\frac{\theta_2 x}{(x+\theta_3)^2}).$$

- The log-linear model is based on the assumption that the intensity of the response is linearly dependent on the logarithm of the dose, as follows:

$$\mu(x,\boldsymbol{\theta}) = \theta_1 + \theta_2 \log(x+\theta_3), \tag{2.4}$$

where θ_1 represents the placebo effect, θ_2 denotes the increase associated with $\log(x+\theta_3)$, and $\theta_3 > 0$ is an additive constant to address issues with the logarithm when the placebo response is zero. As with the EMAX model, an increasing effect ($\theta_2 > 0$) is assumed (Pinheiro et al., 2006). The vector of the partial derivatives is

$$\frac{\partial}{\partial \boldsymbol{\theta}}\mu(x,\boldsymbol{\theta}) = (1, \log(x+\theta_3), \frac{\theta_2}{x+\theta_3})$$

- The LINEXP model, proposed by Demidenko (2006), is used to describe tumor growth delay and regrowth data. It employs a nonlinear regression model to represent the natural logarithm of tumor volume as follows:

$$\mu(x,\boldsymbol{\theta}) = \theta_1 + \theta_2 e^{\theta_3 x} + \theta_4 x \tag{2.5}$$

where $x \in \mathcal{X}$ represents the single regression variable related to time. The parameter vector $\boldsymbol{\theta} = (\theta_1, \theta_2, \theta_3, \theta_4)$ is defined such that $\theta_1 + \theta_2$ represents the logarithm of the initial tumor volume, $\theta_3 < 0$ indicates the rate at which killed cells are washed out, and θ_4 denotes the final growth rate. The LINEXP model can describe either monotonic regrowth ($\theta_4 < \theta_3\theta_2$) or non-monotonic regrowth ($\theta_4 > \theta_3\theta_2$). For this model, the vector of the partial derivatives is given by:

$$\frac{\partial}{\partial \boldsymbol{\theta}}\mu(x,\boldsymbol{\theta}) = (1, e^{\theta_3 x}, \theta_2 x e^{\theta_3 x}, x)$$

3 Bayesian optimal design and efficiency

In this section, Bayesian D-optimal designs for nonlinear regression models described by (2.3), (2.4) and (2.5) are considered. Note that the vectors of partial derivatives of these models do not include θ_1; thus, the designs are not sensitive to θ_1. From

a theoretical perspective, the number of support points for a design can range from p to $p(p+1)/2$, as indicated by Carathéodory's theorem. In this paper, the number of support points was found to be equal to the number of model parameters, p. In the design optimization problem, when the number of support points equals to the number of model parameters, the design is said to be saturated. This phenomenon was first demonstrated in a celebrated paper by De la Garza (1954), who showed that for a polynomial regression model with degree $(p-1)$, any optimal design can be based on at most p points. Khuri et al. (2006) illustrated this phenomenon in the context of a nonlinear regression model with locally optimal designs. Burghaus and Dette (2014) used the theory of canonical moments to derive optimal saturated designs with respect to noninformative priors for polynomial models. Several authors, including Dette and Wong (1996), Yang (2010), Yang and Stufken (2009), Yang and Stufken (2012) and Hu et al. (2015), have investigated saturated designs, with the latter paper developing tools to find such optimal designs and proving their uniqueness under mild conditions. In optimization design problems, when it is known that the optimal design is saturated, both numerical and analytical calculations are significantly simplified. However, for nonlinear and complex models involving multiple parameters and a dispersed prior distributions, obtaining analytical solutions becomes highly challenging. In such cases, numerical optimization methods are typically the only feasible approach. Nevertheless, the following theorem demonstrates that Bayesian A- and D-optimal designs for the three models depend only on one of the parameters and its associated distribution, while the remaining parameters do not influence the optimal designs.

Theorem 3.1. *The Bayesian A- and D-optimal designs on the design space $\mathcal{X} = [a, b]$ for the EMAX, loglinear and LINEXP models depend only on θ_3. π_1 and π_2 were considered as arbitrary prior distributions for θ_2 and θ_3, respectively.*

Proof. We provide the proof of D-optimality for the log-linear model as an example. Proofs for both A- and D-optimality for all models, based on similar reasoning, are available upon request from the author. Let $\xi = \{(x_i, w_i), i = 1, 2, \ldots, k\}$ denote a Bayesian D-optimal design, where $k \geq 3$. This condition is necessary since the information matrix of a Bayesian D-optimal design is required to be nonsingular (Chaloner and Larntz (1989)). For simplicity, we consider $k = 3$, and the proof for other values of k follows a similar approach. Based on the definition of the information matrix, standard calculations show that finding the D-optimal design depends solely on θ_3. Specifically, using the natural logarithm base, we have:

$$\phi_D(\xi|\pi) =$$

$$\int_{\Theta_3}\int_{\Theta_2} \ln\Big(\frac{-1}{(x_1+\theta_3)^2(x_2+\theta_3)^2(x_3+\theta_3)^2}\Big[w_1\,(w_1+w_2-1)w_2\,{\theta_2}^2((x_2-x_3)(x_1+\theta_3)\ln(x_1+$$

$$\theta_3) - (x_2+\theta_3)(x_1-x_3)\ln(x_2+\theta_3) + \ln(x_3+\theta_3)(x_3+\theta_3)(x_1-x_2))^2\Big]\Big)\pi_1(\theta_2)\pi_2(\theta_3)d\theta_2 d\theta_3 =$$

$$\Big(\int_{\Theta_2} \ln({\theta_2}^2)\pi_1(\theta_2)d\theta_2\Big)\int_{\Theta_3} \ln\Big(\frac{-1}{(x_1+\theta_3)^2(x_2+\theta_3)^2(x_3+\theta_3)^2}\Big[w_1\,(w_1+w_2-1)w_2\,((x_2-$$

$$x_3)(x_1+\theta_3)\ln(x_1+\theta_3) - (x_2+\theta_3)(x_1-x_3)\ln(x_2+\theta_3) + \ln(x_3+\theta_3)(x_3+\theta_3)(x_1-x_2))^2\Big]\Big)\pi_2(\theta_3)d\theta_3.$$

As observed, the integral involving θ_2 does not affect the determination of x's and w's. Therefore, the optimal design depends solely on θ_3. □

The general equivalence theorem for Bayesian optimality criteria, such as A- and D-optimality, can be derived under suitable regularity conditions (Chaloner and Larntz, 1989). To verify the design optimality for the models, we adopt this general equivalence theorem. In the following, we present the Bayesian A- and D-optimal designs obtained using equations (2.1) and (2.2). We consider the design space $\mathcal{X} = [0, 10]$ and use a uniform prior distribution for the unknown parameters. Dette and Sperlich (1994), Mukhopadhyay and Haines (1995), Dette and Neugebauer (1996), and Braess and Dette (2007) consider nonlinear models with a single parameter and derive analytical expressions for the weights and design points for the optimal Bayesian design. However, for models with more than one parameter and a dispersed prior distribution, obtaining analytical results is extremely challenging, and numerical optimization remains the only viable approach. Since an analytical solution is not available, we employ numerical optimization methods. Specifically, we use the Clenshaw–Curtis quadrature method for numerical integration, which expands the integrand in terms of Chebyshev polynomials. All numerical calculations in this paper are implemented using Maple software.

Since the optimal designs may not always be feasible in practice, they serve as a benchmark for formulating implementable designs, ensuring minimal efficiency loss. We consider two alternative designs and evaluate the relative efficiencies with respect to ϕ-optimal design ξ^*. This is defined as $(\phi(\xi^*)/\phi(\xi))^{1/p}$, where p is the number of parameters. Given that the design space is a closed interval, a p-point equally spaced design on $\mathcal{X} = [a, b]$ is defined at the points $x_i = a + (b-a)(i-1)/p$. We explore two methods for determining the weights of these support points. The first method involves assigning uniform weights to all support points, resulting in a design known as the equally spaced and uniformly weighted (ESUW) design. In the second method, the endpoints of the design space are given a weight that is half the weight of the inner point(s) within the interval. We refer to this type of design as an equally spaced and symmetrically weighted (ESSW) design (Li and Balakrishnan, 2011).

3.1 Bayesian optimal designs for EMAX model

In this section, we investigate the Bayesian A- and D-optimal designs for the three-parameter EMAX model, as described in equation (2.3). For this purpose, we use a

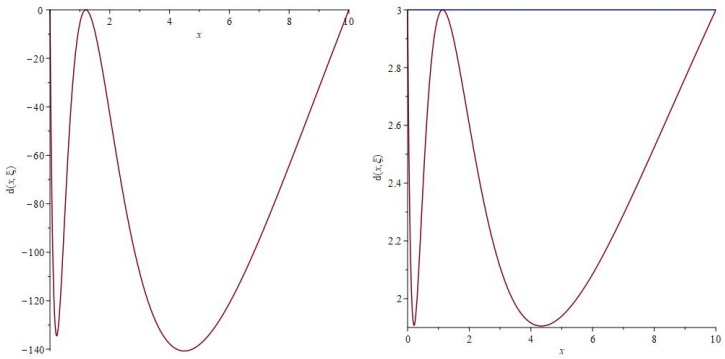

Figure 1: The plot of $d(x, \xi^*)$ functions for EMAX model when $\theta_2, \theta_3 \sim U(1, 2)$, Bayesian A-optimal(left hand) and Bayesian D-optimal(right hand).

Table 1: Bayesian optimal designs for EMAX model on $\mathcal{X} = [0, 10]$

prior for θ_2	prior for θ_3	Design	D-optimal design	A-optimal design
$U(1,2)$	$U(1,2)$	x	(0.0, 1.135, 10)	(0.000, 1.198, 10.00)
		w	(1/3, 1/3, 1/3)	(0.260, 0.476, 0.264)
	$U(1,5)$	x	(0.0, 1.755, 10)	(0.000, 2.165, 10.00)
		w	(1/3, 1/3, 1/3)	(0.250, 0.495, 0.255)
	$U(1,8)$	x	(0.0, 2.170, 10)	(0.000, 2.774, 10.00)
		w	(1/3, 1/3, 1/3)	(0.250, 0.498, 0.252)
	$U(1,10)$	x	(0.0, 2.380, 10)	(0.000, 3.059, 10.00)
		w	(1/3, 1/3, 1/3)	(0.250, 0.499, 0.251)
	$U(1,15)$	x	(0.0, 2.780, 10)	(0.000, 3.536, 10.00)
		w	(1/3, 1/3, 1/3)	(0.250, 0.500, 0.250)
	$U(1,20)$	x	(0.0, 3.059, 10)	(0.000, 3.827, 10.00)
		w	(1/3, 1/3, 1/3)	(0.250, 0.500, 0.250)

uniform prior distribution $U(\alpha, \beta)$ for each parameter. The prediction function $d(x, \xi^*)$ is depicted in Figure 1. It is observed that the Bayesian optimal design results in only three points, including the boundary points.

Table 1 presents the results for several uniform distributions of θ_3; with $\theta_2 \sim U(1, 2)$. According to the aforementioned theorem, θ_2 does not affect the D-optimal design. The results show that the Bayesian A- and D-optimal designs are saturated designs. Both designs include the boundary points, i.e. $\xi^* = \{(a, w_1), (x^*, w_2), (b, w_3)\}$. As the uncertainty in the prior distribution of θ_3 increases, x^* also increases. For the D-optimal design, when $\theta_3 \sim U(1, 2)$, $x^* = 1.135$, and when $\theta_3 \sim U(1, 20)$, x^* increases to 3.059. Additionally, in the D-optimal design, the points have the same weights. For the A-optimal design, increasing the uncertainty in the prior distribution of θ_3 from $U(1, 2)$ to $U(1, 20)$, results in an increase in x^* from 1.198 to 3.827. The boundary points in A-optimal designs have similar weights and are less than the weight of the other point, x^*. Table 2 shows the efficiencies of ESUW and ESSW designs under various prior distributions for θ_3. The D-efficiency of the p-point ESUW and ESSW designs is

Table 2: D- and A-efficiency(%) for EMAX model; $\theta_2 \sim U(1,2)$

θ_3		$U(1,2)$	$U(1,5)$	$U(1,8)$	$U(1,10)$	$U(1,15)$	$U(1,20)$
p-point ESUW design	D-eff	92.5	96.3	97.7	98.2	98.9	99.5
	A-eff	52.4	72.9	81.0	84.7	89.7	91.9
p-point ESSW design	D-eff	91.9	95.8	97.2	97.7	98.4	98.8
	A-eff	53.0	73.0	83.3	87.3	92.8	95.4

higher than their A-efficiency. Additionally, as the uncertainty in the parameter (θ_3) increases, the efficiency of these designs improves. . This improvement is attributed to the fact that the midpoint of the support points for A- and D-optimal designs (x^*) moves closer to the center of the design space as uncertainty increases. This relationship is illustrated in Table 1. In such scenarios, a design with equally spaced support points can serve as a good approximation for the support points of the A- and D-optimal designs. However, the efficiency of these equally spaced designs, particularly in terms of A-efficiency, decreases significantly when the range of θ_3 is more concentrated.

3.2 Bayesian optimal designs for log-linear model

With reference to (2.4), the sensitivity functions $d(x, \xi^*)$ are shown in Figure 2.

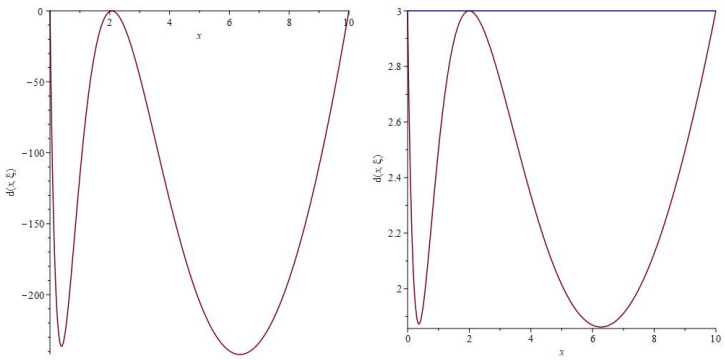

Figure 2: The plot of $d(x, \xi^*)$ functions for log-linear model when $\theta_2, \theta_3 \sim U(1,2)$, Bayesian A-optimal(left hand) and Bayesian D-optimal(right hand)

For further details, Table 3 presents the Bayesian optimal design for various uniform prior regions of θ_3. As before, the optimal designs do not depend on θ_1 and include the boundary points of the design space. According to the theorem, A- and D-optimal designs are not influenced by θ_2. As the uncertainty in θ_3 increases, x^* also increases for D-optimal designs. for example, when the distribution of θ_3 is $U(1,2)$, x^* is 1.997, and when it changes to $U(1,20)$, x^* increases to 3.656. This behavior is clearly observed in A-optimality designs as well. In this case, the weights for D-optimal designs are equal, whereas for A-optimal designs, the boundary points have similar weights, approximately half of the weight of x^*.

Table 4 presents the A- and D-efficiencies of the ESUW and ESSW designs for the

Table 3: Bayesian optimal designs for log-linear model on $\mathcal{X} = [0, 10]$

prior for θ_2	prior for θ_3	Design	D-optimal design	A-optimal design
$U(1,2)$	$U(1,2)$	x	(0.0, 1.997, 10)	(0.000, 2.071, 10.00)
		w	(1/3, 1/3, 1/3)	(0.245, 0.518, 0.237)
	$U(1,5)$	x	(0.0, 2.627, 10)	(0.000, 2.987, 10.00)
		w	(1/3, 1/3, 1/3)	(0.259, 0.503, 0.238)
	$U(1,8)$	x	(0.0, 2.991, 10)	(0.000, 3.472, 10.00)
		w	(1/3, 1/3, 1/3)	(0.260, 0.501, 0.239)
	$U(1,10)$	x	(0.0, 3.165, 10)	(0.000, 3.682, 10.00)
		w	(1/3, 1/3, 1/3)	(0.261, 0.500, 0.239)
	$U(1,15)$	x	(0.0, 3.473, 10)	(0.000, 4.018, 10.00)
		w	(1/3, 1/3, 1/3)	(0.259, 0.500, 0.241)
	$U(1,20)$	x	(0.0, 3.656, 10)	(0.000, 4.217, 10.00)
		w	(1/3, 1/3, 1/3)	(0.258, 0.500, 0.242)

Table 4: D- and A-efficiency(%) for log-linear model; $\theta_2 \sim U(1,2)$

θ_3		$U(1,2)$	$U(1,5)$	$U(1,8)$	$U(1,10)$	$U(1,15)$	$U(1,20)$
p-point ESUW design	D-eff	95.3	98.1	98.8	99.1	99.5	99.8
	A-eff	72.2	84.7	89.5	91.2	93.4	94.4
p-point ESSW design	D-eff	94.4	97.4	98.3	98.6	99.0	99.3
	A-eff	74.3	87.6	92.8	94.7	97.0	98.1

designs listed in Table 3. With increasing uncertainty in θ_3, both A- and D-efficiency improve, which can be attributed to the similarity between the distribution of support points in the Bayesian designs and the ESUW design. It appears that the ESUW design provides a suitable approximation for the D-optimal design, while the ESSW design offers a more appropriate approximation for the A-optimal design.

3.3 Bayesian optimal designs for LINEXP model

In this section, we examine the Bayesian A- and D-optimal designs for the LINEXP model as described in equation (2.5). Since the information matrix does not involved θ_1 and θ_4, the optimal designs are independent of these parameters, and according to the mentioned theorem, the optimal designs do not depend on θ_2 either. The sensitivity function $d(x, \xi^*)$ is illustrated in Figure 3. The A- and D-optimal designs for various prior distributions are summarized in Table 5. Both optimality criteria have led to distinct 4-point designs. As the uncertainty of θ_3 increases, the value of the middle points of the D-optimal design decreases; For example, when $\theta_3 \sim U(-2,-1)$, the support points $(0, 0.628, 3.088, 10)$ are obtained, and when $\theta_3 \sim U(-6,-1)$, the support points $(0, 0.408, 2.488, 10)$ are obtained. We also observe that this trend is also established for the A-optimal design, as we change the uniform from $U(-2,-1)$ to $U(-6,-1)$, again the support points change from $(0, 0.573, 3.127, 10)$ to $(0, 0.225, 1.895, 10)$. Unlike the Bayesian D-optimal designs, the A-optimal designs have support points with varying weights. In the A-optimal design, boundary points receive the lowest weight, and as the

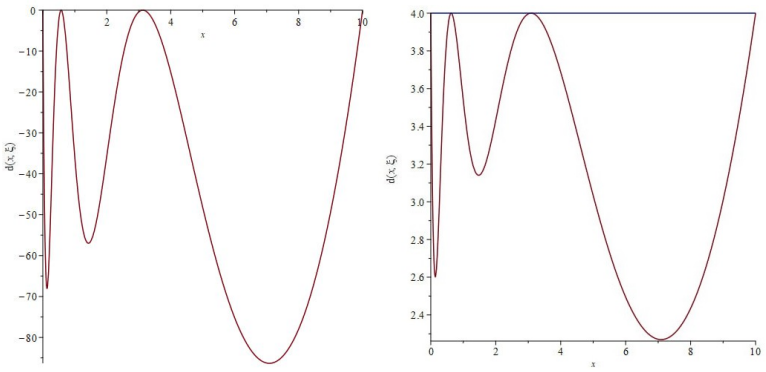

Figure 3: The plot of $d(x, \xi^*)$ functions for LINEXP model when $\theta_2 \sim U(1,2), \theta_3 \sim U(-2,-1)$, Bayesian A-optimal(left hand) and Bayesian D-optimal(right hand)

Table 5: Bayesian optimal designs for LINEXP model on $\mathcal{X} = [0, 10]$

prior for θ_2	prior for θ_3	Design	D-optimal design	A-optimal design
$U(1,2)$	$U(-2,-1)$	x	(0, 0.628, 3.088, 10)	(0.000, 0.573, 3.127, 10.00)
		w	(1/4, 1/4, 1/4, 1/4)	(0.173, 0.353, 0.372, 0.102)
	$U(-3,-1)$	x	(0, 0.535, 2.832, 10)	(0.000, 0.419, 2.621, 10.00)
		w	(1/4, 1/4, 1/4, 1/4)	(0.181, 0.390, 0.350, 0.079)
	$U(-4,-1)$	x	(0, 0.472, 2.657, 10)	(0.000, 0.326, 2.288, 10.00)
		w	(1/4, 1/4, 1/4, 1/4)	(0.185, 0.411, 0.338, 0.066)
	$U(-5,-1)$	x	(0, 0.433, 2.553, 10)	(0.000, 0.267, 2.060, 10.00)
		w	(1/4, 1/4, 1/4, 1/4)	(0.190, 0.422, 0.330, 0.058)
	$U(-6,-1)$	x	(0, 0.408, 2.488, 10)	(0.000, 0.225, 1.895, 10.00)
		w	(1/4, 1/4, 1/4, 1/4)	(0.192, 0.530, 0.225, 0.053)
	$U(-6,-2)$	x	(0, 0.288, 1.809, 10)	(0.000, 0.212, 1.556, 10.00)
		w	(1/4, 1/4, 1/4, 1/4)	(0.189, 0.445, 0.324, 0.042)

Table 6: D- and A-efficiency(%) for LINEXP model; $\theta_2 \sim U(1,2)$

θ_3		$U(-2,-1)$	$U(-3,-1)$	$U(-4,-1)$	$U(-5,-1)$	$U(-6,-1)$	$U(-6,-2)$
p-point ESUW design	D-eff	63.7	58.7	56.9	56.1	55.8	24.2
	A-eff	49.7	23.9	11.0	4.6	1.9	1.8
p-point ESSW design	D-eff	60.1	55.4	53.7	53.0	52.6	22.8
	A-eff	52.2	25.2	11.2	4.8	2.1	1.9

uncertainty in the prior distribution increases, the end support point receives the least weight. Table 6 provides the efficiencies of ESUW and ESSW designs for the LINEXP model. It is evident that as the uncertainty in the prior distribution of θ_3 increases, the efficiency of both designs decreases. This decrease is due to the middle points moving closer to the lower bound of the design space as the uncertainty grows. The decline in A-efficiency is more pronounced than that in D-efficiency, to the point where efficiency is significantly reduced when $\theta_3 \sim U(-4,-1)$ and with increased dispersion. This suggests that the ESUW and ESSW designs are not appropriate approximations

for Bayesian A- and D-optimal designs in the LINEXP model.

4 Concluding remarks

In this paper, we studied Bayesian A- and D-optimal designs for the three-parameter EMAX and log-linear models, and four-parameter LINEXP model. These models are frequently used in dose-response studies for new compound and in analyzing tumor growth delay and regrowth data. To address the challenge posed by the dependence of optimality criteria on unknown parameters of the model, we employed a Bayesian approach with a uniform prior distribution. This method captures all available information regarding parameter uncertainty. Although the examined models included 3 or 4 parameters, for all models, only one parameter influenced optimal Bayesian designs. Our findings indicate that the obtained optimal designs are saturated, and an increase in the uncertainty of the prior distribution of the effective parameter did not affect the number of support points. Specifically, the D-optimal designs feature uniform weights, while A-optimal designs have varying weights, with middle point(s) receiving more weight compared to boundary points. The general equivalence theorem was used to validate the optimality of these designs.

A number of authors have observed that for Bayesian D-optimal designs, the more diffuse the prior on the model parameters, the larger the required number of support points for the optimal design. However, our results for the EMAX, log-linear, and LINEXP models, as described by (2.3), (2.4), and (2.5), do not strictly align with this observation, particularly regarding the uniform prior on the parameters.

We evaluated the efficiency of commonly used designs, such as the equally spaced and uniformly weighted (ESUW) design and equally spaced and symmetrically weighted (ESSW) design. Most of the resulting designs achieved high efficiencies (more than 80%), except for the LINEXP model. The reduced efficiency in the LINEXP model is attributed to the middle point(s) shifting towards the lower end of the design space, making the distribution of support points more asymmetric as parameter uncertainty increases.

Due to the lack of analytical solutions for some integrals, we used a numerical method, namely Clenshaw–Curtis quadrature method. We make use of a nonlinear optimization programming with Maple software to get the results. In the Bayesian approach, the choice of the prior is challenging and may involve uncertainty. To address this uncertainty regarding an assumed prior, the nonparametric Bayesian approach is proposed. The authors hope report the new works in this context in the near future.

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