CONSTRUCTION OF LOCALLY D-OPTIMAL DESIGN FOR MONOD MODEL USING RECURSIVE ALGORITHM

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ABSTRACT: *Construction of optimal design for nonlinear models involves optimization of certain function of Fisher information matrix which depends on unknown parameter(s) value(s). For a locally optimal design, the unknown parameter(s) are replaced by guess value(s) based on prior knowledge of the experimenter. If the guesses are not close enough to the actual parameter(s) value(s) the resulting design may not be optimal, robust and efficient. To address the problem of constructing inefficient designs based on miss guessed parameter value, we employed a new methodology that identify a subclass of designs with a simple format and restrict consideration to this subclass. A locally D-optimal design for Monod model that is supported at two design point was constructed within this subclass. This approach makes construction of optimal design easier because it specifies the optimum number of support points required for any design in question.*

KEYWORDS: Monod Model, Saturated Design, D-optimal Design, Fisher Information Matrix, Recursive Algorithm, Tylor Series.

INTRODUCTION

Monod model is one of the most widely used nonlinear models in biomedical and pharmaceutical sciences. It is also used in biochemistry, nutrition sciences and enzyme kinetic studies. The model is widely applied for describing microbial growth and substrate degradations in many kinds of applications (e.g., batch and continuous fermentation, activated sludge wastewater treatment, pharmacokinetics, plant physiology etc.) Despite its wide range applications in different fields, construction of optimal designs remains a biggest challenge to experimenters. This is of course not unconnected with the dependence of design support points on the unknown parameters of the Fisher information matrix. For a locally optimal design, the unknown parameter(s) are replaced by a guess value(s) based on prior knowledge of the experimenter. If the guesses are not close enough to the actual parameter(s) value(s) the resulting design may not be optimal, robust and efficient. To tackle the menace of constructing inefficient designs arising from miss guessed of parameter value, (Yang and Stufken, 2012) proposed identifying a subclass of designs with a simple format, so that one can restrict considerations to this subclass for any optimality problem. With a simple format, it would be relatively easy to derive an optimal design, analytically or numerically.

So our aim is to identify a subclass of design for Monod model so that for any design ξ that does not belong to this class, there exist a design ξ^* in the class that has an information matrix that dominates that

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of ξ in the Loewner ordering. Also ξ^* will not be worse than ξ for most of the commonly used optimality criteria and for many functions of the parameters. Furthermore, for the already identified subclass, D-optimality criterion and recursive algorithm would be used to determine the specific design support point.

This paper is organized and divided into the following sections. A brief review of literature on locally optimal designs is presented in Section two. Strategy and basic concept of methodology is presented in section three while section four is devoted to application of the methodology to Monod model. Lastly, a concluding remark is given in section five.

Locally Optimal Designs

The most commonly and simple approach to the problem of experimental designs for nonlinear models is locally optimal design that was introduced by Chernoff (1953). Under this set up, a best guess for the unknown parameters which often comes from the previous experimentation, pilot experiment, or simply a mere guess by the experimenter is been considered (Zhang, 2006). A better design can be chosen base on the selected design optimality criterion function evaluated at the guess value. This approach has received increasing attention and numerous contributions by several authors. Konstantinous and Dettea (2015) considered the construction of optimal designs for nonlinear regression models when there are measurement errors in the covariates and developed approximate design theory for the estimation of parameters using maximum likelihood and least-squares method of estimation.

Dette *et al(2010)* derived locally D- and EDρ-optimal designs for the exponential, log –linear and three-parameter emax models. For each model the locally D- and EDρ-optimal designs are supported at the same set of points, while the corresponding weights are different. They also demonstrate that locally D- and EDρ-optimal designs for the emax, log-linear and exponential models are relatively robust with respect to misspecification of the model parameters.

Wu and Stufken (2014) considered generalized linear models with a single-variable quadratic polynomial as the predictor under a popular family of optimality criteria and derive explicit expressions for some *D*-optimal designs. For unrestricted design region, optimal designs can be found within a subclass of designs based on a small support with symmetric structure. Gutiérrez et al (2014) gave explicit formulae for the construction of D-optimal designs as a function of the unknown parameters for the logistic regression model. Haines et al (2007) considered the construction of locally D-optimal design for logistic regression model with two explanatory variables, the variables are considered to be doses of two drugs and are thus constrained to be greater than or equal to zero with no interaction term in the model. The result shows that there are two patterns of *D*-optimal design that depend on model parameters based on 3 and 4 support points respectively. Other contributions can be found in Wang et al (2006), Rodriguez-Torreblanca and Rodriguez-Diaz (2007), Russell et al (2009), Dette et al (2001), Chang (2005a and 2005b), Dette *et al*(2006).

So far there is limited work on design issues related to Monod model despite its wide range applications in different fields most especially in relation to the newly improved statistical techniques. To this end, we proposed to investigate optimal design problems for this important model. Specifically, functional algebraic-approach would be used to construct locally D-optimal design for the aforementioned model, where Taylor expansion would be used for the numerical calculation of the locally D-optimal designs via recursive algorithm.

Strategy

Suppose we make n observations $y_1, \ldots, y_n$; from an experiment with $x_1, \ldots, x_n$; explanatory variables. Let's the data be modeled by nonlinear relationship of the form:

$$y_i = \eta(x_i, \theta) + \epsilon_i, \epsilon_i \sim \mathcal{N}(0, \sigma^2), i = 1,2, \ldots n \qquad (3.1)$$

Where

$\eta(x_i, \theta)$ is the regression function, θ is the vector of $rx1$ unknown parameters and ϵ_i is the random error component. Note that both θ and ϵ_i are independent and identically distributed. In addition, suppose we have $t < n$ distinct design point and lets x_i occurs $m_i$times among the points $x_1, \ldots, x_n$, in what follows, each of the point x_i is associated with weight coefficient (proportion of observation at i[th] design point), $w_i = m_i/n$. Here we require that $0 \le w_i \le 1; i = 1,2, \ldots, t$ and $\sum_{i=1}^{t} w_i = 1$.

Define a discrete probability measure, ξ as

$$\xi = \begin{pmatrix} x_1, & \ldots & , x_t \\ w_1, & \ldots, & w_t \end{pmatrix} \qquad (3.2)$$

Then the matrix,

$$M(\xi, \theta) = \sum_{i=1}^{t} w_i f(x_i, \theta) f^T(x_i, \theta) \qquad (3.3)$$

is called Fisher information matrix of the design ξ.

where

$$f(x, \theta) = \left(\frac{\partial \eta(x, \theta)}{\theta_1}, \ldots, \frac{\partial \eta(x, \theta)}{\theta_r} \right)^T$$

is the vector of partial derivatives of $\eta(x, \theta)$ with respect to θ

The asymptotic variance-covariance matrix of the least squares estimator, $\hat{\theta}$ is given by

$$V_{\hat{\theta}} = \frac{\sigma^2}{n} \{M(\xi, \theta)\}^{-1}$$

We are interested in the optimal choice of a design among the available classes of designs in the design space, $\chi \subseteq \mathcal{R}$, where $\mathcal{R} = (0,1)$ is the design region/interval such that $V_{\hat{\theta}}$ is minimized.

If an information matrix of any nonlinear model, discrete or continuous can be transform to matrices of the form as in equation 3.4 and 3.5 respectively, then, a subclass of design can be determine with information matrix that dominates that of all other designs in terms of Loewner ordering.

$$M(\xi, \theta) = G^T(a, b) H_\xi(a, b) G(a, b) \qquad 3.4$$

Where

$$H_\xi(a, b) = \begin{bmatrix} \sum_{i=1}^{t} w_{i\vartheta_1(h_i)} & \sum_{i=1}^{t} w_{i\vartheta_2(h_i)} \\ \sum_{i=1}^{t} w_{i\vartheta_2(h_i)} & \sum_{i=1}^{t} w_{i\vartheta_3(h_i)} \end{bmatrix} \qquad 3.5$$

is a matrix that depends on design ξ through $w_i's\ and\ h_i's$ and on (a,b) through the $h_i's$, while $G(a,b)$is a matrix that depends on (a,b) only.
In this paper we consider Monod model and the information matrix have been verified to conform to the transformed matrices of equation 3.4 and 3.5, details of the verification is presented below.
Consider Monod model given by

$$Y_i = \frac{ax_i}{b+x_i} + \epsilon_i$$

Where

$Y_1, \dots Y_N$ are experimental results and $[a,b] \in \theta$ are positive integers(parameters). a is defined as supremum of the function and b is the value of x at which half supremum of the function is reached.

$\varepsilon_1, \dots \varepsilon_N$ are independent and identically distributed random values (experimental errors) with zero mean and variance $\sigma^2 > 0$ and $x_1, \dots x_N \in [0,1]$ are observation points.

let $h_i = ax_i/(b+x_i),\ \vartheta_1(h_i) = h_i^2,\ \vartheta_2(h_i) = h_i^3,\ \vartheta_3(h_i) = h_i^4$ (3.6)
and

$$G(a,b) = \begin{bmatrix} 1/a & -1/b \\ 0 & 1/ab \end{bmatrix} \quad (3.7)$$

Substituting equation (3.5) and (3.7) in to equation (3.4), we get

$$M(\xi,\theta) = G^T(a,b)H_\xi(a,b)G(a,b) = \begin{bmatrix} 1/a & 0 \\ -1/b & 1/ab \end{bmatrix} \begin{bmatrix} \sum_{i=1}^{t} w_{i\vartheta_1(h_i)} & \sum_{i=1}^{t} w_{i\vartheta_2(h_i)} \\ \sum_{i=1}^{t} w_{i\vartheta_2(h_i)} & \sum_{i=1}^{t} w_{i\vartheta_3(h_i)} \end{bmatrix} \begin{bmatrix} 1/a & -1/b \\ 0 & 1/ab \end{bmatrix}$$

$$M(\xi,\theta) = \sum_{i=1}^{t} w_i \begin{bmatrix} 1/a & 0 \\ -1/b & 1/ab \end{bmatrix} \begin{bmatrix} \vartheta_1(h_i) & \vartheta_2(h_i) \\ \vartheta_2(h_i) & \vartheta_3(h_i) \end{bmatrix} \begin{bmatrix} 1/a & -1/b \\ 0 & 1/ab \end{bmatrix} \quad (3.8)$$

$$M(\xi,\theta) = \sum_{i=1}^{t} w_i \begin{bmatrix} 1/a & 0 \\ -1/b & 1/ab \end{bmatrix} \begin{bmatrix} \frac{a^2 {x_i}^2}{(b+x_i)^2} & \frac{a^3 {x_i}^3}{(b+x_i)^3} \\ \frac{a^3 {x_i}^3}{(b+x_i)^3} & \frac{a^4 {x_i}^4}{(b+x_i)^4} \end{bmatrix} \begin{bmatrix} 1/a & -1/b \\ 0 & 1/ab \end{bmatrix}$$

$$M(\xi,\theta) = \sum\nolimits_{i=1}^{t} w_i \begin{bmatrix} \frac{{x_i}^2}{(b+x_i)^2} & \frac{-a{x_i}^2}{(b+x_i)^3} \\ \frac{-a{x_i}^2}{(b+x_i)^3} & \frac{a^2{x_i}^2}{(b+x_i)^4} \end{bmatrix} \quad (3.9)$$

Now consider the untransformed information matrix, equation (3.3),

$$M(\xi,\theta)=\sum_{i=1}^{t} w_i f(x_i,\theta) f^T(x_i,\theta),\ \ where\ f(x_i,\theta)=\left(\frac{\partial\eta(x_i,\theta)}{\partial\theta_1},\dots,\frac{\partial\eta(x_i,\theta)}{\partial\theta_r}\right)^T$$

Therefore,

$$M(\xi,\theta)=\sum_{i=1}^{t} w_i \begin{bmatrix}\frac{x_i}{(b+x_i)}\\ \frac{-ax_i}{(b+x_i)^2}\end{bmatrix}\begin{bmatrix}\frac{x_i}{(b+x_i)} & \frac{-ax_i}{(b+x_i)^2}\end{bmatrix}=\sum\nolimits_{i=1}^{t} w_i \begin{bmatrix}\frac{x_i{}^2}{(b+x_i)^2} & \frac{-ax_i{}^2}{(b+x_i)^3}\\ \frac{-ax_i{}^2}{(b+x_i)^3} & \frac{a^2x_i{}^2}{(b+x_i)^4}\end{bmatrix} \quad (3.10)$$

■

Clearly, equation (3.9) and (3.10) are equivalent.

Having successfully verified the equivalences of our design information matrices, we shall now show the mechanism and strategy for a general nonlinear models under certain conditions that there exists a subclass of designs such that for any given design ξ, there exists a design ξ^* in this subclass such that $M_{\xi^*}(\theta)\geq M_{\xi}(\theta)$.

To start with let, $\vartheta_1(h),\vartheta_2(h),\dots,\vartheta_k(h)$ be k functions defined on [A,B]. Throughout this paper, we have the following assumptions:

(i) $\vartheta_1(h),\vartheta_2(h),\dots,\vartheta_k(h)$ are infinity differentiable;

(ii) $f_{l,l}$ has no zero value on [A,B].

Here, $f_{l,t}$ $1\leq t\leq k, t\leq 1\leq k$ are defined as follows:

$$f_{l,t}(h)=\begin{cases}\vartheta_l'(h), & t=1, l=1,\dots,k\\ \left(\frac{f_{l,t-1}(h)}{f_{t-1,t-1}(h)}\right)', & 2\leq t\leq k, t\leq l\leq k\end{cases}$$

Theorem 3.1

For any nonlinear regression model, suppose the information matrix can be expressed as in (3.4) and $\mathrm{h_i}\in[\mathrm{A},\mathrm{B}]$. Rename all distinct $\vartheta_{\mathrm{lt}}, 1\leq \mathrm{l}\leq \mathrm{t}\leq \mathrm{p}$ to $\vartheta_1,\vartheta_2,\dots,\vartheta_{\mathrm{k}}$ such that (i)ϑ_{k} is one of $\vartheta_{\mathrm{ll}}, 1\leq \mathrm{l}\leq \mathrm{p}$ and (ii)there is no $\vartheta_{\mathrm{lt}}=\vartheta_{\mathrm{k}}$ for $1<\mathrm{t}$. Let $\Psi(\mathrm{h})=\prod_{\mathrm{l=1}}^{\mathrm{k}}\mathrm{f_{l,l}}(\mathrm{c})$, $\mathrm{h}\in[\mathrm{A},\mathrm{B}]$. For any given design ξ, there exist a design ξ^*, such that $\mathrm{M}_{\xi^*}(\theta)\geq \mathrm{M}_{\xi}(\theta)$. Note that ξ^* depends on different situations.

i. When k is odd and $\Psi(h)<0,\xi^*$ is based on at most $(\mathrm{k}+1)/2$ points including point A.
ii. When k is odd and $\Psi(h)>0,\xi^*$ is based on at most $(\mathrm{k}+1)/2$ points including point B.
iii. When k is even and $\Psi(h)>0,\xi^*$ is based on at most $(\mathrm{k}/2)+1$ points including points A and B.
iv. When k is even and $\Psi(h)<0,\xi^*$ is based on at most $\mathrm{k}/2$ points.

For a two parameter model with $k=3$, the conditions in (i) and (ii) of theorem 3.1 above can be narrowed down to the following important result.

Lemma 3.1: The functions $\vartheta_1(h), \vartheta_2(h),\ \vartheta_3(h)$ are called type I functions on $[A, B]$ if the following conditions holds

i) $\vartheta_1(h), \vartheta_2(h),\ \vartheta_3(h)$ are continuous functions on $[A, B]$ that are three times differentiable on $(A, B]$

ii) $\vartheta_1'(h)\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\left(\left(\frac{\vartheta_3'(h)}{\vartheta_1'(h)}\right)' \Big/ \left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\right)' < 0\ for\ h \in (A, B] and$

iii) $lim_{h\downarrow A}\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\left(\vartheta_1(A) - \vartheta_1(h)\right) = 0$

Where A is finite and B could be $+\infty$.

Also we can say that the functions $\vartheta_1(h), \vartheta_2(h),\ \vartheta_3(h)$ are functions of type II on $[A, B]$ if

i) $\vartheta_1(h), \vartheta_2(h),\ \vartheta_3(h)$ are continuous functions $[A, B]$ that are three times differentiable on $[A, B)$

ii) $\vartheta_1'(h)\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\left(\left(\frac{\vartheta_3'(h)}{\vartheta_1'(h)}\right)' \Big/ \left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\right)' > 0\ for\ h \in [A, B) and$

iii) $lim_{h\downarrow B}\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\left(\vartheta_1(B) - \vartheta_1(h)\right) = 0$

In this case A could be $-\infty$ and B is finite.

Application

4.1.1 Determination of Required Number of Support Points for Monod Model

To identify the number of support points needed for the construction of optimal design, we have to check the form of the function as specified in lemma 3.1. Basically, there are three conditions for verifying whether a function is of type I or type II; to verify the first condition, it means to show that $\vartheta_1(h)$, $\vartheta_2(h)$, $\vartheta_3(h)$ are continuous functions $[A, B]$ that are three times differentiable on $[A, B)$

Now,

$$\vartheta_1(h_i) = h_i^2 = (ax_i/(b + x_i))^2$$
$$\Rightarrow \vartheta_1'(h_i) = 2(ax_i/(b + x_i)), \quad \vartheta_1''(h_i) = 2 \quad and \quad \vartheta_1'''(h_i) = 0$$

also,

$$\vartheta_2(h_i) = h_i^3 = (ax_i/(b + x_i))^3$$
$$\Rightarrow \vartheta_2'(h_i) = 3(ax_i/(b + x_i))^2, \qquad \vartheta_2''(h_i) = 6(ax_i/(b + x_i)) \quad and \quad \vartheta_2'''(h_i) = 6$$

and

$$\vartheta_3(h_i) = h_i^4 = (ax_i/(b + x_i))^4$$
$$\Rightarrow \vartheta_3'(h_i) = 4(ax_i/(b + x_i))^3, \vartheta_3''(h_i) = 12(ax_i/(b + x_i))^2 and\ \vartheta_2'''(h_i) = 24(ax_i/(b + x_i))$$

By definition of continuity and differentiability, all differentiable functions are continuous but, the convers is not always true. From the above findings we can see that the condition of continuity and differentiability has been met. It is important to note that differentiability in the interval, [A, B) means that the function is defined for every point in [A, B).

To verify the second condition, we need to show that

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$$\vartheta_1'(h)\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\left(\left(\frac{\vartheta_3'(h)}{\vartheta_1'(h)}\right)'\Big/\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\right)' > 0 \; for\; h \in [A, B)$$

Consider,

$$\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)' = \left(\frac{3(ax_i/(b+x_i))^2}{2(ax_i/(b+x_i))}\right)' = \frac{3}{2}$$

$$\left(\frac{\vartheta_3'(h)}{\vartheta_1'(h)}\right)' = \left(\frac{4(ax_i/(b+x_i))^3}{2(ax_i/(b+x_i))}\right)' = 4(ax_i/(b+x_i))$$

and

$$\left(\left(\frac{\vartheta_3'(h)}{\vartheta_1'(h)}\right)'\Big/\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\right)' = \left(\frac{4(ax_i/(b+x_i))}{\frac{3}{2}}\right)' = \frac{8}{3}$$

$$\Rightarrow \vartheta_1'(h)\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\left(\left(\frac{\vartheta_3'(h)}{\vartheta_1'(h)}\right)'\Big/\left(\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\right)'\right)' = 2(ax_i/(b+x_i))\left(\frac{8}{2}\right) = 8(ax_i/(b+x_i)) > 0$$

Next is to check for the last condition which is given as

$$lim_{h\downarrow B}\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\big(\vartheta_1(B) - \vartheta_1(h)\big) = 0$$

$$\frac{\vartheta_2'(h)}{\vartheta_1'(h)}\big(\vartheta_1(B) - \vartheta_1(h)\big) = \frac{3(ax_i/(b+x_i))^2}{2(ax_i/(b+x_i))}\big(\vartheta_1(B) - \vartheta_1(h)\big)$$

$$lim_{h\downarrow B}\frac{3(ax_i/(b+x_i))^2}{2(ax_i/(b+x_i))}\big(\vartheta_1(B) - \vartheta_1(h)\big) = \frac{3(ax_i/(b+x_i))^2}{2(ax_i/(b+x_i))}\big(\vartheta_1(B) - \vartheta_1(B)\big) = 0$$

Having verified that the function is a type II function, then for any given k, we can use theorem 3.1 and draw necessary conclusions about the minimum number of support points required and the inclusion of the boundary point as design support point. Obviously, for $k = 3$, we have two support points and one of which is the boundary point, B. The next important task will be the determination of the other support point, the lower boundary support point.

4.1.2 Dependence of Support Point on the Unknown Parameter Value

Consider the information matrix of the design given in equation 3.10

$$M(\xi,\theta) = \sum_{i=1}^{t} w_i \begin{pmatrix} \frac{{x_i}^2}{(b+x_i)^2} & \frac{-a{x_i}^2}{(b+x_i)^3} \\ \frac{-a{x_i}^2}{(b+x_i)^3} & \frac{a^2{x_i}^2}{(b+x_i)^4} \end{pmatrix}$$

If a D-optimal design is minimally supported, then it is easy to see that it has uniform weights on all support points. As a result, one has to determine only the r support points. On the other hand, if it is not

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known that the D-optimal design is minimally supported, then one is faced with the task of determining the support points and the corresponding weights (probabilities) of the design, so the determination of a D-optimal design is considerably easier when it is minimally supported. From the above important result, $for\ k = 3, then\ t = 2$, this implies that the design saturated/minimally supported. As mentioned above, for a saturated design (a design whose number of support point is equal to the model parameters) the weight coefficient at both design point are equal. This implies $w_i = {}^1\!/_2\ ; i = 1, 2$. Now, $M(\xi, \theta)$ reduces to

$$M(\xi,\theta) = \frac{1}{2}\begin{pmatrix} \frac{x_1{}^2}{(b+x_1)^2} + \frac{x_2{}^2}{(b+x_2)^2} & \frac{-ax_1{}^2}{(b+x_1)^3} + \frac{-ax_2{}^2}{(b+x_2)^3} \\ \frac{-ax_1{}^2}{(b+x_1)^3} + \frac{-ax_2{}^2}{(b+x_2)^3} & \frac{a^2x_1{}^2}{(b+x_1)^4} + \frac{a^2x_2{}^2}{(b+x_2)^4} \end{pmatrix}$$

For a locally *D*-optimal design, determinant of the information matrix is important and must be determine.

$$|M(\xi,\theta)| = \frac{ax_1{}^2x_2{}^2}{4}\left[\frac{1}{(b+x_1)^2(b+x_2)^4} + \frac{1}{(b+x_1)^4(b+x_2)^2} - \frac{2}{(b+x_1)^3(b+x_2)^3}\right]$$

$$|M(\xi,\theta)| = \frac{ax_1{}^2x_2{}^2}{4(b+x_1)^4(b+x_2)^4} = [(b+x_1)^2 + (b+x_2)^2 - 2(b+x_1)(b+x_2)]$$

$$|M(\xi,\theta)| = \frac{ax_1{}^2x_2{}^2}{4(b+x_1)^4(b+x_2)^4}[x_1{}^2 + x_2{}^2 - 2x_1x_2]$$

$$|M(\xi,\theta)| = \frac{ax_1{}^2x_2{}^2}{4(b+x_1)^4(b+x_2)^4}(x_2 - x_1)^2 \qquad (4.1)$$

Observe that the parameter, a, has been factored out as such it does not affect the optimization of the design, hence we can fix it at 1. In addition, the upper support point, x_2 which is regarded as the upper boundary point, B, is also fixed at 1. Therefore, the problem reduces to approximating the lower bound of *X* such that (4.1) is a maximum.

Imposing the condition $a = x_2 = 1$ we get

$$|M(\xi,\theta)| = \frac{x_1{}^2(1-x_1)^2}{4(b+x_1)^4(b+1)^4} \qquad 4.2$$

optimization of 4.2 with respect to x_1 is equivalent to optimizing $\frac{x_1{}^2(1-x_1)^2}{4(b+x_1)^4}$. Therefore, 4.2 reduces to

$$|M(\xi,\theta)| = \frac{x_1{}^2(1-x_1)^2}{4(b+x_1)^4}$$

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Taking the log of both sides we get

$$\log(|M(\xi,\theta)|) = log\frac{1}{4} + 2logx_1 + 2log(1-x_1) - 4log(b+x_1)$$

Taking the partial derivatives with respect to x_1 we have

$$\frac{\partial \log(|M(\xi,\theta)|)}{\partial x_1} = \frac{2}{x_1} - \frac{2}{(1-x_1)} - \frac{4}{(b+x_1)} = 0$$

$$x_1 = \frac{b}{(2b+1)} \qquad 4.3$$

Equation (4.3) shows clearly the dependence of support point on the unknown parameter value, *b*

Now the design in (3.2) becomes

$$\hat{\xi} = \begin{bmatrix} \frac{b}{(2b+1)} & 1 \\ \frac{1}{2} & \frac{1}{2} \end{bmatrix}$$

4.1.3 Determination of Lower Support Point Using Recursive Algorithm

The function $g(x_1, b) = (2b+1)x_1 - b = 0$ is called the gradient of the objective function.

for $b_0 = 0.75$, $x_0 = \frac{0.75}{(2(0.75)+1)} = 0.3$

since we are able to established/found an optimal design x_0 with respect to b_0 then we can use recursive algorithm as in (Dette et al (2001)) to find an approximate optimal experimental design $x_1(b)$ for different values of *b* provided the Jacobian of the function exist.

For this problem, the Jacobian of the function is given by

$$J = \frac{\partial(2b+1)x_1 - b}{\partial x_1} \Big|_{b=b_0}$$

$$J = 2(0.75) + 1 = 2.5$$

Using the relation,

$$\xi^*(s+1, \tau_0) = -J^{-1}(\tau_0)\frac{1}{(s+1)!}\left(\frac{d}{d\tau}\right)^{s+1} g\left(\xi^*_{(s)}(\tau), \tau\right) \text{, for s} = 0,1,2, \ldots$$

$when\ s = 0,$

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$$\frac{d}{db}(2b+1)x_1 - b = 2x_1 - 1 = -0.4$$

$$\Rightarrow \xi^*(1,0.75) = -\frac{(-0.4)}{2.5} = 0.16$$

and

${\xi^*}_{(s)}(\tau) = \xi^*(\tau_0) + \sum_{k=1}^{s} \xi^*(\mathrm{k}, \tau_0)(\tau - \tau_0)^k$ is obtained as

$${\xi^*}_{(0)}(\mathrm{b}) = 0.3 + 0.16(b - 0.75)$$

$when\ s = 1,$

$$\xi^*(2,0.75) = -\frac{1}{2.5}\left(\frac{d}{d\mathrm{b}}\right)^2 g(0.3 + 0.16(b - 0.75), \mathrm{b})$$

$g(0.3 + 0.16(b - 0.75), \mathrm{b}) = [0.3 + 0.16(b - 0.75)](2b + 1) - b$

$\frac{d}{d\mathrm{b}} g(0.3 + 0.16(b - 0.75), \mathrm{b}) = \frac{d}{d\mathrm{b}}(0.32b^2 - 0.48b + 0.18) = 0.64b - 0.48$

$\left(\frac{d}{d\mathrm{b}}\right)^2 g(0.3 + 0.16(b - 0.75), \mathrm{b}) = 0.64$

So

$$\xi^*(2,0.75) = -\frac{1}{2.5}\left(\frac{1}{2!}\right) 0.64 = -0.128$$

$$\Rightarrow {\xi^*}_{(1)}(\mathrm{b}) = 0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2$$

$when\ s = 2,$

$$\xi^*(3,0.75) = -\frac{1}{2.5}\left(\frac{d}{d\mathrm{b}}\right)^3 g(0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2, \mathrm{b})$$

$g(0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2, \mathrm{b}) =$

$$[(0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2)](2b + 1) - b$$

Now,

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$$\frac{d}{d\mathrm{b}} g(0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2, \mathrm{b}) = [-0.48 + 0.64b - 0.256(b - 0.75)^2 - 0.256(b - 0.75)(2b + 1)]$$

$$\left(\frac{d}{d\mathrm{b}}\right)^2 g(0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2, \mathrm{b}) = [0.64 - 0.512(b - 0.75) - 0.256(2b - 1.5) + (2b + 1)]$$

$$\left(\frac{d}{d\mathrm{b}}\right)^3 g(0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2, \mathrm{b}) = -1.536$$

$$\xi^*(3{,}0.75) = -\frac{1}{2.5} x \frac{1}{3!}(-1.536) = 0.1024$$

$$\Rightarrow \xi^*{}_{(2)}(\mathrm{b}) = 0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2 + 0.1024(b - 0.75)^3$$

when $s = 3$,

$$\xi^*(3{,}0.75) = -\frac{1}{2.5} x \frac{1}{4!}(8.19) = -0.1364$$

$$\Rightarrow \xi^*{}_{(3)}(\mathrm{b}) = 0.3 + 0.16(b - 0.75) - 0.128(b - 0.75)^2 + 0.1024(b - 0.75)^3 - 0.1364(b - 0.75)^4 \qquad 4.4$$

From the above computation we can deduce that for a given value of *b*, the lower support point can be approximated by the polynomial in equation 4.4 above.

CONCLUSION

In this paper, we have proved that the support points of locally D-optimal designs for Monod model are dependent on the guess parameter value, in addition the design is shown to be minimally supported (saturated) at two design points including *B*, the upper boundary point. We also proposed the use of Taylor series to approximate the lower support points for Monod model.

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