Efficiency nonminimally supported design for two parameters weighted exponential model

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Abstract. Minimally supported design is a design with the number of supported design equal to the number of parameters in the model. Locally D-optimal design for weighted exponential model is minimally supported design with uniform weight. The standardized variance of D-optimal design is less than or equal the number of parameters, and maximized the standardized variance at the supported designs. We construct an alternative design by adding one supported design. Nonminimally supported design is obtained from supported design of D-optimal design plus one supported design in three ways, by adding one of them, by adding the average of them or by adding one supported design around them. We compare nonminimally supported designs in terms efficiency, standardized variance, and propose design that are efficient and practically convenient for practitioners.

1. Introduction

In conducting research, researchers have an important problem are how to determine the supported design that must be tried so that it meets the optimallity criteria. One of the optimallity criteria is D-optimal. D-optimal design is a design with the aim is determining the supported designs and its proportion that must be tried so that the variance of parameter estimate is minimum. D-optimal design usually use minimally supported design (the number of supported design is same the number of parameters) with uniform weight [1,2]. Supported designs of D-optimal design are obtained by maximizing the determinant of information matrix. The aim of D-optimality is minimizing the variance of parameter estimate so that the parameters in the model are significant. D-optimal design is unique and depends on the model which we used. In nonlinear models to choose the supported design becomes complicated. This is because the elements of information matrix in the nonlinear model are a function of their parameters so researcher needs prior information about of the value of the parameters.

The curve of the weighted exponential distribution is unimodal, the curve from zero increase to the maximum point then decrease, and at a certain time it is relatively constant tends to zero. Usually weighted exponential model is used to describe the growth curve model. The exponential models with unimodal curves is widely used in several area including biology, chemistry, agriculture, animal husbandry, pharmacokinetics and pharmacodynamics. Gupta and Kundu [3] investigated the distribution function of weighted exponentials with two parameters, this probability density function as follows:

\[
f(x) = \frac{1+\beta}{\beta} e^{-\alpha x} (1 - e^{-\alpha x}), \quad x > 0, \quad \alpha, \beta > 0
\]
The curve of model (1) is unimodal, and the maximum point occurred at \( x = \frac{\ln(1+\beta)}{a\beta} \). Model in equation (1) is a nonlinear model.

D-optimal design for exponential model has been studied. There are many models that have been studied and each of them is used in different cases. In the homoscedastic case [4] investigated a model which is the additive of multiplication between exponential form and polynomials of degree \( n \). The other researcher, Hans and Chaloner [5] used an exponential model that was applied to pharmacokinetics, and the logarithm of the exponential model is applied to plasma HIV RNA. The application of D-optimal design in agriculture, legume growth analysis are investigated [6]. Atkinson [7] investigated D-optimal designs for exponential model and applied to determination of concentration drugs in the blood. Widiharih et al. [8] introduced d-optimal designs for weighted exponential and generalized exponential two parameters. After that Widiharih et. al. [9] developed their research to modified exponential model. There is a problem in computation, so the research is continued in computation area.

Based on the equation (1), and by adopting the curve shape and simplifying the model, we construct design for the two parameter weighted exponential as follows:

\[
y = e^{-\theta_1 x} (1 - e^{-\theta_2 x}) + \epsilon, \quad x \geq 0, \quad \theta_1, \theta_2 > 0
\]  

(2)

with homoscedastic errors assumption. The curve of model (2) is identical with the curve of model (1).

In this paper we develop nonminimally supported design of the model (2) by adding one supported design to minimally supported design that obtained from D-optimal design. We assume that all of supported designs have the uniform weight. Determinant of information matrix of model (2) for minimally and nonminimally supported design are calculated then determine the efficiency of nonminimally supported design.

2. Material and Methods.

2.1 D-optimal Design for Nonlinear Model.

The nonlinear model is denote by:

\[
y = \eta(x, \theta) + \epsilon
\]  

(3)

with assumption independent \( \epsilon \sim N(0, \sigma^2) \). Based on this assumption so \( E(\epsilon) = 0 \), then

\[
E(Y|x) = \eta(x, \theta)
\]  

(4)

The aim of this paper is construct the design \( \xi \) containing the supported designs and their proportions. Designs \( \xi \) of \( p \) supported designs \((x_i, i = 1, 2, 3, \ldots, p)\) and their proportions \((w_i, i = 1, 2, 3, \ldots, p)\) is denoted by:

\[
\xi = \begin{pmatrix} x_1 & x_2 & \ldots & x_p \\ w_1 & w_2 & \ldots & w_p \end{pmatrix}
\]  

(5)

where: \( w_i = \frac{r_i}{n} \), \( r_i \) : number of observations of the supported design \( x_i \), \( n = \sum_{i=1}^{p} r_i \), \( \sum_{i=1}^{p} w_i = 1 \). Based on equation (4) and (5), can be construct the information matrix of design \( \xi \) for model (4) is:

\[
M(\xi, \theta) = \sum_{i=1}^{p} w_i \frac{\partial^2 \eta(x_i, \theta)}{\partial \theta^2} \frac{\partial \eta(x_i, \theta)}{\partial \theta} \tag{6}
\]

where \( h(x, \theta) = \frac{\partial \eta(x, \theta)}{\partial \theta} = (h_1(x, \theta), h_2(x, \theta), \ldots, h_k(x, \theta))^T \) is the vector of partial derivatives of the conditional expectation \( E(Y|x) \) with respect to the parameters \( \theta \). \( M(\xi, \theta) \) is \( k \times k \) \( (k : \text{number of parameters}) \) symmetric matrix [10]. Determination of D-optimal design by maximizing \( |M(\xi, \theta)| \), which is the determinant of the information matrix in equation (6). The standardized variance \( d(\xi, x) \) is [10]:

\[
d(\xi, x) = h^T(x, \theta) M^{-1}(\xi, \theta) h(x, \theta)
\]  

(7)

Determination of design \( \xi \) which satisfy D-optimality based on The Equivalence Theorem that can be written as follows[10]:

\[
\xi^* \text{ is D-optimal design } \Leftrightarrow d(\xi^*, x) \leq k
\]  

(8)
2.2 D-optimal Design for Weighted Exponential Model.

Consider the weighted exponential model in equation (2). Based on equation (3), we have
\[
\eta(x, \theta) = e^{-\theta_1 x} (1 - e^{-\theta_1 x})^{\theta_2}
\]
(9)
\[
h(x, \theta) = \frac{\partial \eta(x, \theta)}{\partial \theta} = \left(-xe^{-\theta_1 x} (1 - e^{-\theta_2 x})ight)
\]
\[xe^{-(\theta_1 + \theta_2)x}\]

We use minimally supported design with uniform weight, so the design \( \xi \) as follows:
\[
\xi = \begin{pmatrix} x_1 \\ 1/2 \\ x_2 \\ 1/2 \end{pmatrix}
\]
(10)
\[
M(\xi, \theta) = \begin{pmatrix} m_{11} & m_{12} \\ m_{12} & m_{22} \end{pmatrix}
\]

where:
\[
m_{11} = \frac{1}{2} \sum_{i=1}^{2} x_i e^{-2\theta_1 x_i} (1 - e^{-\theta_2 x_i})^2
\]
\[
m_{22} = \frac{1}{2} \sum_{i=1}^{2} x_i e^{-2(\theta_1 + \theta_2) x_i}
\]
\[
m_{12} = \frac{1}{2} \sum_{i=1}^{2} x_i e^{-(2\theta_1 + \theta_2) x_i} (1 - e^{-\theta_2 x_i})
\]

\[
|M(\xi, \theta)| \propto x_1^2 x_2^2 e^{-2\theta_1 (x_1 + x_2)} [(1 - e^{-\theta_2 x_1}) e^{-\theta_2 x_2} - (1 - e^{-\theta_2 x_2}) e^{-\theta_2 x_1}]^2
\]
(11)

Based on information of the value of \( \theta_1 \) and \( \theta_2 \), D-optimal design in equation (10) \( x_1, x_2 \) are obtained by maximizing \( |M(\xi, \theta)| \) in equation (11).

2.3 Algorithm to construct nonminimally supported design and their efficiency.

The algorithm of constructing nonminimally supported design.

a. Determine the minimally supported design \((x_1, x_2)\) for model (2), by maximized:
\[
|M(\xi, \theta)| \propto x_1^2 x_2^2 e^{-2\theta_1 (x_1 + x_2)} [(1 - e^{-\theta_2 x_1}) e^{-\theta_2 x_2} - (1 - e^{-\theta_2 x_2}) e^{-\theta_2 x_1}]^2
\]
(12)

b. Based on step (a) we can find \( x_1, x_2 \) and the value of \( |M(\xi, \theta)| \) (determinant of minimally supported design).

c. Construct on minimally supported design by adding one supported design \((x_3)\) in three ways design as follows:
   I. \( x_3 \) is taken one of \( x_1 \) or \( x_2 \)
   II. \( x_3 \) is taken of average \( x_1 \) and \( x_2 \)
   III. \( x_3 \) is taken randomly around \( x_1 \), \( x_2 \) and their average.
The efficiency nonminimally supported design.

The efficiency nonminimally supported design based on the value of determinant information matrix. At first determine the determinant of information matrix $|M(\xi, \theta)|$ for all alternatif nonminimally supported design which we have been constructed. The information matrix as follows:

$$
M(\xi, \theta) = \begin{bmatrix}
m_{11} & m_{12} \\
m_{12} & m_{22}
\end{bmatrix}
$$

where:

$$
m_{11} = \frac{1}{3} \sum_{i=1}^{3} x_i^2 e^{-2\theta_1 x_i (1 - e^{-\theta_2 x_i})^2}
$$

$$
m_{22} = \frac{1}{3} \sum_{i=1}^{3} x_i^2 e^{-2(\theta_1 + \theta_2) x_i}
$$

$$
m_{12} = \frac{1}{3} \sum_{i=1}^{3} -x_i^2 e^{-(2\theta_1 + \theta_2) x_i (1 - e^{-\theta_2 x_i})}
$$

$$
|M(\xi, \theta)| = m_{11}m_{22} - m_{12}^2
$$

The formula of efficiency as follows:

$$
Eff = \frac{|M(\xi, \theta)| \text{ of nonminimally supported design}}{|M(\xi, \theta)| \text{ of minimally supported design}}
$$

3. Results and Discussions

Consider model (2):

$$
y = e^{-\theta_1 x (1 - e^{-\theta_2 x})} + \varepsilon, \quad x \geq 0, \quad \theta_1, \theta_2 > 0
$$

Model (2) has a unimodal curve, the maximum point occurs at point

$$
x = \frac{\ln(1 + \theta_2)}{\theta_1}
$$

The curve of model (2) for $\theta_1 = 0.1$ at several of $\theta_2$ and for $\theta_2 = 0.5$ at several of $\theta_1$ are presented in Figure 1 and Figure 2.

**Figure 1.** The curve of model (2) at several of $\theta_2$ for $\theta_1 = 0.1$

**Figure 2.** The curve of model (2) at several of $\theta_1$ for $\theta_2 = 0.5$
Based on Figure 1, if $\theta_1$ fixed and several of $\theta_2$ is closer, then each curve has maximum relatively different. Based on Figure 2, if $\theta_2$ fixed and several of $\theta_1$ each curve has different maximum too.

In this paper we construct nonminimally supported design with prior information of $\theta_1 = 1, \theta_2 = 0.5$, and $\theta_1 = 1, \theta_2 = 2$, the design region is $[0, 5$]

1. Minimally supported design based on (11) as follows:

Table 1. Minimally Supported Design Model (2) for $\theta_1 = 1, \theta_2 = 0.5$, and $\theta_1 = 1, \theta_2 = 2$, the Design Region is $[0, 5$]

| $\theta_1$ | $\theta_2$ | $x_1$   | $x_2$               | $|M(\xi, \theta)|$ |
|------------|------------|---------|---------------------|-------------------|
| 1          | 0.5        | 0.504652| 1.92887             | 0.0002856         |
| 1          | 2          | 0.305797| 1.37013             | 0.0003511         |

2. Adding one supported design ($x_3$) from Table 1 in three ways design, the result is presented in Table 2.

I. $x_3$ is taken one of $x_1$, or $x_2$  
II. $x_3$ is taken of average $x_1$ and $x_2$  
III. $x_3$ is taken randomly around $x_1$, $x_2$ and their average

Nonminimally supported design model (2) for $\theta_1 = 1, \theta_2 = 0.5$, and $\theta_1 = 1, \theta_2 = 2$ the design region is $[0, 5$] is presented in Table (2).

Based on Table (1) and (2), shows that minimally supported design is the highest value for determinant of information matrix. The highest efficiency for nonminimally supported design is design I, $x_3$ is taken one of $x_1$ or $x_2$. The standardized variance $(d(\xi, x))$ for minimally supported design is less than or equal two, while the standardized variance $(d(\xi, x))$ for nonminimally supported design is less than or equal three. Therefore, Design I is the practical design we recmend over other alternatives for nonminimally supported design due to its high efficiency.

Table 2. Nonminimally Supported Design Model (2) for $\theta_1 = 1, \theta_2 = 0.5$, and $\theta_1 = 1, \theta_2 = 2$ the Design Region is $[0, 5$]

| $\theta_1$ | $\theta_2$ | $x_1$   | $x_2$ | $x_3$       | $|M(\xi, \theta)|$ | Efficiency |
|------------|------------|---------|-------|-------------|-------------------|------------|
| 1          | 0.5        | 0.504652| 1.92887| 0.50465     | 0.0002539         | 0.890712   |
|            |            |         | 1.92887| 0.0002539   | 0.890712         |
|            |            |         | 1.21676| 0.0002296   | 0.805730         |
|            |            |         | 0.40465| 0.0002489   | 0.873232         |
|            |            |         | 0.30465| 0.0002308   | 0.809986         |
|            |            |         | 0.20465| 0.0001975   | 0.692989         |
|            |            |         | 0.60465| 0.0002505   | 0.879053         |
|            |            |         | 0.70465| 0.0002435   | 0.854246         |
|            |            |         | 0.80465| 0.0002361   | 0.828274         |
|            |            |         | 2.02887| 0.0002532   | 0.888312         |
|            |            |         | 2.12887| 0.0002512   | 0.881305         |
|            |            |         | 2.22887| 0.0002480   | 0.870126         |
|            |            |         | 1.82887| 0.0002532   | 0.888284         |
As an illustration of the application practically, Rusdiana et. Al. [11] did research in pharmacokinetics. Six patient received Fenilpropanol Hidroclorida 50 mg orally. The following Fenilpropanol Hidroclorida in plasma (μg/ml) versus time (hour) is obtained. Data set is presented in Table 3.

Table 3. Fenilpropanol Hidroclorida in Plasma (μg/ml) for Six Patient in Several Time.

| Time (hour) | 1  | 2  | 3  | 4  | 5  | 6  |
|------------|----|----|----|----|----|----|
| 0.25       | 0.163 | 0.035 | 0.039 | 0.040 | 0.069 | 0.069 |
| 0.50       | 0.201 | 0.059 | 0.071 | 0.218 | 0.280 | 0.158 |
| 0.75       | 0.247 | 0.163 | 0.150 | 0.250 | 0.313 | 0.221 |
| 1.00       | 0.292 | 0.241 | 0.191 | 0.264 | 0.350 | 0.266 |
| 1.50       | 0.333 | 0.285 | 0.228 | 0.302 | 0.373 | 0.293 |
| 2.00       | 0.401 | 0.249 | 0.172 | 0.331 | 0.352 | 0.235 |
| 3.00       | 0.281 | 0.152 | 0.140 | 0.281 | 0.303 | 0.202 |
| 4.00       | 0.157 | 0.094 | 0.115 | 0.198 | 0.168 | 0.168 |
| 5.00       | 0.119 | 0.080 | 0.094 | 0.130 | 0.089 | 0.130 |
| 6.00       | 0.060 | 0.080 | 0.087 | 0.063 | 0.063 | 0.107 |
| 8.00       | 0.045 | 0.072 | 0.057 | 0.052 | 0.057 | 0.078 |
| 10.00      | 0.037 | 0.056 | 0.050 | 0.042 | 0.051 | 0.067 |
| 12.00      | 0.028 | 0.045 | 0.040 | 0.032 | 0.042 | 0.055 |

The scatterplot of the data set in Table 3 is presented in Figure 3.
Parameters estimate and T test of parameters are presented in Table 4. The value of Adj.R\textsuperscript{sq} is 0.8328.

Table 4. Parameters Estimate and T test of Data Set in Table 3.

| Parameter | Estimate | Approx. Std Error | t-value | P-value |
|-----------|----------|-------------------|---------|---------|
| \( \theta_1 \) | 0.396792 | 0.0142 | 27.89 | <0.0001 |
| \( \theta_2 \) | 0.544692 | 0.0276 | 19.73 | <0.0001 |

Based on Table 4, we have the model:

\[
\hat{y} = e^{-0.396792x}(1 - e^{0.544692x})
\]  

Model in equation (13) has maximum of Fenilpropanol Hidroclorida in plasma 0.308 \( \mu \text{g/ml} \) at 1.59 hour. The curve of model in equation (13) is presented in Figure 4.

D-optimal design based on the value of parameters, the supported designs are 0.93 and 3.86 hour with proportion \( \frac{1}{3} \) and \( \frac{1}{3} \) respectively. Based on algorithm nonminimally supported design in 2.3, we suggest for another researcher which have the same problem, the supported designs are 0.93 and 3.86 hour with proportion \( \frac{1}{3} \) and \( \frac{2}{3} \) respectively to construct the model as an alternative of D-optimal design.

4. Conclusion and Future Work.
Minimally supported design with uniform weight has the highest determinant of inormation matrix. The highest efficiency for nonminimally supported design is design I, \( x_3 \) is taken one of \( x_1 \) or \( x_2 \).
Design I is the practical design we recommend over other alternatives for nonminimally supported design due to its high efficiency.

In the next investigation, it will be better to do the GUI MATLAB to make it easier for users to determine the nonminimally supported design.

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References

[1] Li G and Majumdar D 2008 D-optimal Designs for Logistic Models with Three and Four Parameters Journal of Statistical Planning and Inference 138 1950-1959
[2] Dette H and Pepelyshev A 2008 Efficient Experimental Designs for Sigmoidal Growth Models Journal of Statistical Planning and Inference 138 2 - 17
[3] Gupta R D and Kundu D A 2009 A New class of weighted exponential distribution Statistics 43 621-634
[4] Antille G, Dette H and Weinberg A 2003 A note on optimal design in weighted polynomial regression for the classical efficiency function Journal of Statistical Planning and Inference 113 285-292
[5] Han C and Chaloner K 2001 D and c-optimal design for exponential regression models used in viral dynamics and other application The Annals of Statistic 29(2) 585-601
[6] Dette H, Melas VB and Wong WK 2006 Locally D-optimal design for exponential regression models Statistica Sinica 16 789-803
[7] Atkinson A C 2008 Examples of the use an equivalence theorem in constructing optimum experimental designs for random effects nonlinear regression models Journal of Statistical Planning and Inference 138 2595-2606
[8] Widiharih T, Haryatmi S and Gunardi 2013 D-optimal designs for weighted exponential and generalized exponential models Applied Mathematical Sciences 7(22) 1067-1079
[9] Widiharih T, Haryatmi S and Gunardi 2016 D-optimal designs for modified exponential models with three parameters, Journal Model Assisted Statistics and Application 11 153-169
[10] Widiharih T, Rusgiyono A, Sudarno, Mukid M A and Prahutama A 2019 Locally D-optimal design for weighted exponential model and its computation Journal of Physics: conference series, 1217 012097.
[11] Rusdiana T, Sjub F and Asyarie S 2009 Interaksi farmakokinetic kombinasi obat paracetamol dan fenilpropanolamin hidroklorida sebagai komponen obat flu http:pustaka.unpad.ac.id/wo-content/uploads/2009/02/interaksi-farmakokinetic.pdf