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Optimum Mixture Designs for Binomial Two-Parameter Log-Logistic (LL2) Model with Mixture of Two Similar Compounds

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Abstract

The paper investigates the class of two-parameter log-logistic dose-response bioassay models in the binomial set-up. The dose is defined by the potency adjusted mixing proportions of two similar compounds. The aim is to investigate the D- and Ds- optimal mixture designs for estimating the full set of parameters or only the potency for a best guess of the parameter values. An indication has been given for finding the optimal design for the estimation of the mixture at which the probability of success attains a given value.

Keywords: dose-response experiment, log-logistic (LL2) model, mixture experiment,parameter estimation, D-optimality criterion, D_s-optimality criterion.

1. Introduction

Non-linear models find wide application in many areas of research, like agriculture, pharmaceutical, chemical, biomedical, pharmacokinetics, toxicology and clinical research etc., as they are found to be more reasonable and accurate than linear models for defining the processes. The non-linear dose-response models are in particular very useful in agricultural and medical research to approximate the relationship between the response and the concentration of a compound/drug. For similarly acting drugs or compounds, the effect of their mixture is given by the sum of the potency- adjusted doses or concentrations of the drugs/compounds, and the dose response models help to study the effect of the mixture on the response (cf. Loewe 1928). Some recent studies on dose response relationships have been made by Haas, Thayyar-Madabusi, Rose, and Gerba (2000), Liu, An, Johnson, and Lovett (2003), Nielsen, Welinder, Jönsson, Axmon, Rylander, and Skerfving (2001), Patel, Telesca, George, and Nel (2012), Hoelzer, Chen, Dennis, Evans, Pouillot, Silk, and Walls (2013), Holland-Letz and Kopp-Schneider (2018), to name a few.
Designs for the logistic class of model functions have been addressed at length in Finney (1978), Abdelbasit and Plackett (1983) and Meeker and Hahn (1977). Minkin (1987) investi-

gated optimal designs for binary data. Mathew and Sinha (2001) studied the optimal designs for binary data under logistic regression. Fedorov and Leonov (2001) discussed model oriented approach to finding optimum designs in dose-response experiments. Geometric and uniform designs in logistic dose response model under Gaussian and binomial settings have been discussed by O′Brien, Chooprateep, and Homkham (2009). D-optimal designs for three Poisson dose response models have been compared by Maloney, Simonsson, and Schaddelee (2003). Holland-Letz and Kopp-Schneider (2015) generated usable D-optimal experimental designs for dose response studies using three common dose response functions, namely log-logistic, log-normal and Weibull functions. For non-linear and binary logistic models see also Agresti (2012), Collett (2003).

In the existing literature on designs for parameter estimation in dose response models with two similar compounds or drugs, the amounts of the compounds have been taken as the covariates. However, it seems more logical to study the effects of the mixing proportions of the compounds on the response rather than the actual amounts. In the present paper, we consider modeling the response as a function of the potency adjusted mixing proportions of two similar compounds. We consider the cases where the two compounds are independent as well as when there is dependence. As sigmoidal models are extensively used in practice, we use the two parameter log-logistic (LL2) dose response function for binary data. We obtain the locally D- optimal design for estimating all the parameters of the model. We also find the D_s-optimal design for estimating the relative potency. Further, we indicate how to find the locally optimal design for the estimation of the mixing proportions at which the probability of success attains a given value in the absence of interaction effect.

2. Estimation in non-linear models

A general non-linear model is defined as $E(Y) = f(t, \theta)$ where Y denotes the response, t the vector of explanatory variables, θ the vector of unknown parameters and f a non-linear function of for a given t. In this situation, obtaining the optimal design for parameter estimation is rather challenging, especially as the designs depend on the unknown model parameter θ

For any n-point continuous design ξ , given by

$$\xi = \left\{ \begin{array}{cccc} t_1 & t_2 & \dots & t_n \\ w_1 & w_2 & \dots & w_n \end{array} \right\} \tag{1}$$

where $t_1, t_2, \dots, t_n$ are distinct support points of the design with masses $w_1, w_2, \dots, w_n$ respectively such that $w_i \geq 0$ for $1 \leq i \leq n, \sum_{i=1}^{n} w_i = 1$. Under the usual homoscedastic Gaussian condition, the information matrix of ξ is given by $M(\xi) = (F_1', F_2', \dots, F_n')\Omega\ (F_1', F_2', \dots, F_n')'$, where $F_i \equiv F(t_i, \theta) = \frac{\partial f(t_i,\theta)}{\partial \theta}, 1 \leq i \leq n, \Omega$ is a diagonal matrix with diagonal elements $w_1\sigma^2, w_2\sigma^2, \dots, w_n\sigma^2$, and σ^2 is the error variance. The asymptotic dispersion matrix of the least square estimator of θ is $M(\xi)$, will depend on θ. To overcome this drawback, one may (a) use a Bayesian strategy, (b) find locally optimal designs for given sets of parameter values, or (c) integrate the criterion function over the parameter space.

In the present paper, we consider locally optimum continuous designs. The general Equivalence Theorem of Kiefer and Wolfowitz (1960) enables checking of the optimality of a continuous design. The theorem states that a design ξ^* is D-optimal if the maximum value of $d(t, \xi^*, \theta) = F(t, \theta)'M^{-1}(\xi)F(t, \theta)$ over the design space, where $F(t, \theta) = \frac{\partial f(t,\theta)}{\partial \theta}$, is equal to the number of parameters to be estimated, and the maximum value is attained at the support points of ξ^* (cf. Whittle 1973). To estimate a subset $\theta^{(2)}$ of θ, where $\theta = (\theta^{(1)}|\theta^{(2)})'$, if one accordingly partitions $M(\xi)$ as

$$M(\xi) = \left[\begin{array}{cc} M_{11}(\xi) & M_{12}(\xi) \\ M_{21}(\xi) & M_{22}(\xi) \end{array} \right]$$

and $F(t,\theta)$ as $F(t,\theta)' = (F^{(1)}(t,\theta)'|F^{(2)}(t,\theta)')$, the D_s-optimal design maximizes $|M(\xi)|/|M_{11}(\xi)|$. By Equivalence Theorem, a design ξ^* is D_s-optimal if

$$d_s(t,\xi,\theta) = F(t,\theta)'M^{-1}(\xi^*)F(t,\theta) - F^{(1)}(t,\theta)'M_{11}^{-1}(\xi^*)F^{(1)}(t,\theta) \leq s, \text{ for all } t,\theta, \quad (2)$$

where $\theta^{(2)}$ contains s parameters. Equality holds at the support points of ξ^* (cf. Atkinson and Bogacka 1997).

We shall consider only non-singular designs.

3. Binary log-logistic (LL2) model for a mixture of similar drugs

Let us consider the response to be a binary variable, taking the value 1 or 0 according as an individual exhibits the attribute under study or not. For a given t, the effective dose of the mixture of two similar compounds, suppose n independent experiments are conducted, where each experiment has two possible outcomes success (presence of the attribute) and failure (absence of the attribute) - with success probability π.The distribution of the number of successes in n independent experiments therefore follows a binomial distribution with expectation and variance $n\pi$ and $n\pi(1-\pi)$, respectively. We define the mean response of an experiment by the two parameter logistic model, given by

$$E(Y) = \pi = \frac{1}{1+z(t)}, \quad (3)$$

where $z(t) = (\frac{t}{\theta_1})^{\theta_2}$ (cf. Tusto, O′Brien, and Tiensuwan 2016). Here θ_1, and θ_2 are the LD50 and slope parameter, respectively. We use the commonly used link function in a logistic regression, which is the logit function defined as

$$\eta(t) = ln(\frac{\pi}{1-\pi}).$$

Hence, our model is

$$\eta(t) = \theta_2[ln(\theta_1) - ln(t)]. \quad (4)$$

In the present study, we consider the mixing proportions $x = (x_1, x_2)$ of two similar compounds A and B. The mixing proportions x_1, x_2 satisfy the constraints $0 \leq x_1, x_2 \leq 1, x_1 + x_2 = 1$, and the effective dose t is the potency-adjusted mixing proportions of the two compounds. Attempt is made to find the optimal design for parameter estimation when

(a) $t = x_1 + \rho x_2$, where there is no interaction between A and B, and ρ denotes the potency of B relative to A. This is the Finney$_3$ model for no interaction;

(b) $t = x_1 + \rho x_2 + \delta\sqrt{\rho x_1 x_2}$ where interaction is present between A and B, ρ denotes the potency of B relative to A and δ is the coefficient of synergism. This model, used for modelling synergy, is the so-called Finney$_5$ model.

It may be noted that 100t % defines the effective concentration in view of B in 100 units of the mixture.

As the D-optimality criterion involves the unknown parameters, we find locally D-optimal designs for parameter estimation for specified values of the unknown parameters. This approach is acceptable under the assumption that the experimenter has some knowledge about the parameter values. We also investigate the locally D$_s$-optimal designs for estimating the relative potency ρ, which in many circumstances is of sole interest. Optimum design for the estimation of x at which the probability of success, π, takes a particular value is also discussed. It may be noted that the values of x at which $\pi = 0.5$, 0.75, 0.95 are referred to as LD50, LD75 and LD95, respectively and find importance in reliability and bioassay experiments.

4. Optimum designs

In this section we discuss locally D- and D_s- optimal designs for estimation of whole or partial set of parameters in the model (3) for the two forms of t, the effective dose, indicated in Section 3.

4.1. $t = x_1 + \rho x_2$

Consider a continuous design ξ , given by (1), where $t_i = x_{1i}+\rho x_{2i}$, $x_i = (x_{i1}, x_{i2})$, $x_{i1}, x_{i2} \geq 0$, $x_{i1} + x_{i2} = 1$. The information matrix of ξ for estimation of $\theta = (\theta_1, \theta_2, \rho)$ in model (3) is given by $M(\xi) = F'\Omega F$, where

$$F = \begin{bmatrix} \frac{\partial\eta(t_1)}{\partial\theta_1} & \frac{\partial\eta(t_1)}{\partial\theta_2} & \frac{\partial\eta(t_1)}{\partial\rho} \\ \frac{\partial\eta(t_2)}{\partial\theta_1} & \frac{\partial\eta(t_2)}{\partial\theta_2} & \frac{\partial\eta(t_2)}{\partial\rho} \\ \dots & \dots & \dots \\ \frac{\partial\eta(t_n)}{\partial\theta_1} & \frac{\partial\eta(t_n)}{\partial\theta_2} & \frac{\partial\eta(t_n)}{\partial\rho} \end{bmatrix}$$

and $\Omega = diag(w_1\pi_1(1-\pi_1), w_2\pi_2(1-\pi_2), \dots, w_n\pi_n(1-\pi_n))$. Hence, writting $a_i = w_i\pi_i(1-\pi_i) = w_i\frac{(t_i/\theta_1)^{\theta_2}}{[1+(t_i/\theta_1)^{\theta_2}]^2}$, $1 \leq i \leq n$, (cf. equation (3), we have

$$M(\xi) = \begin{bmatrix} (\frac{\theta_2}{\theta 1})^2\sum_{i=1}^n a_i & -\frac{\theta_2}{\theta_1}\sum_{i=1}^n a_i ln(\frac{t_i}{\theta_1}) & -\frac{\theta_2^2}{\theta_1}\sum_{i=1}^n a_i\frac{x_{i2}}{t_i} \\ -\frac{\theta_2}{\theta_1}\sum_{i=1}^n a_i ln(\frac{t_i}{\theta_1}) & \sum_{i=1}^n a_i\{ln(\frac{t_i}{\theta_1})\}^2 & \theta_2\sum_{i=1}^n a_i(\frac{x_{i2}}{t_i})ln(\frac{t_i}{\theta_1}) \\ -\frac{\theta_2^2}{\theta_1}\sum_{i=1}^n a_i\frac{x_{i2}}{t_i} & \theta_2\sum_{i=1}^n a_i(\frac{x_{i2}}{t_i})ln(\frac{t_i}{\theta_1}) & \theta_2^2\sum_{i=1}^n a_i(\frac{x_{i2}}{t_i})^2 \end{bmatrix}.$$

In order to estimate θ , a non-singular continuous design should have at least three distinct support points. As algebraic derivation is rather tedious, we carry out a thorough numerical investigation which shows that for given parameter values, the D-optimal design has support points at the two extreme points and one or two points in-between. Table 1 gives the support points of the D-optimal design in-between the extreme points for some combinations of the parameter values. The optimal masses of the support points are found to be all equal, that is 1/3 for a three-point design and 1/4 for four-point design. The optimality of the designs have been verified using the Equivalence Theorem.

Table 1: Optimal support points besides the extreme points in the D-Optimum designs for estimation of θ for some combinations of the parameter values.

θ_1	ρ \ θ_2	0.2	0.5	1	3.0
0.2	0.05	(0.2529, 0.7471)	(0.3862, 0.6138)	(0.4603, 0.5397)	(0.6761,0.3239)
	0.5	(0.2464, 0.7536)	(0.3801, 0.6199)	(0.4813, 0.5187)	(0.6904, 0.3096)
	2	(0.1863, 0.8137)	(0.3219, 0.6781)	(0.4706, 0.5294)	(0.7739, 0.2261)
2	0.05	(0.2531, 0.7469)	(0.3863, 0.6137)	(0.4999, 0.5001) (0.6498, 0.3502)	(0.4999,0.5001)
	0.5	(0.2681, 0.7319)	(0.3916, 0.6084)	(0.4832, 0.5168)	(0.6746, 0.3254)
	2	(0.4130, 0.5870)	(0.4516, 0.5484)	(0.4907, 0.5093)	(0.6551, 0.3449)

Remark. *For almost all combinations of the parameter values considered, the D-optimal design is found to be a saturated design.*

When interest lies in estimating only the relative potency ρ, we note that $d_s(t, \xi, \theta)$ given by (2), can be written as a very complicated function in x_1. However, to estimate ρ, it is essential to also estimate θ_1 and θ_2, as is evident from the model (4). In view of this, the optimum design should have at least three support points. As in the earlier case, it is not possible to

Table 2: D_s- optimum design for estimation of ρ in mixture of two similar compounds.

θ_1	ρ \ θ_2	0.2	0.5	1	2.0
0.2	0.05	(0,1)	(0,1)	(0,1)	(0,1)
		0.2828	**0.2644**	**0.2807**	**0.2358**
		(1, 0)	(1 ,0)	(1, 0)	(1, 0)
		0.2173	**0.2357**	**0.2491**	**0.2643**
		(0.2529, 0.7471)	(0.3862, 0.6138)	(0.4002, 0.598)	(0.6138, 0.3862)
		0.4999	**0.4999**	**0.4702**	**0.4999**
	1	(0,1)	(0,1)	(0,1)	(0,1)
		0.2731	**0.2542**	**0.2725**	**0.2539**
		(1, 0)	(1 ,0)	(1, 0)	(1, 0)
		0.2463	**0.2496**	**0.2569**	**0.2499**
		(0.2274, 0.7726)	(0.3639, 0.6361)	(0.4478, 0.5522)	(0.6439, 0.3561)
		0.4806	**0.4962**	**0.4706**	**0.4962**
2	0.05	(0,1)	(0,1)	(0,1)	(0,1)
		0.2830	**0.2644**	**0.2212**	**0.2356**
		(1, 0)	(1 ,0)	(1, 0)	(1, 0)
		0.2171	**0.2356**	**0.3287**	**0.2644**
		(0.2531, 0.7469)	(0.3863, 0.6137)	(0.4306, 0.5694)	(0.6137, 0.3863)
		0.4999	**0.5000**	**0.4501**	**0.5000**
	1	(0,1)	(0,1)	(0,1)	(0,1)
		0.3245	**0.2766**	**0.2799**	**0.2337**
		(1, 0)	(1 ,0)	(1, 0)	(1, 0)
		0.1952	**0.2272**	**0.2495**	**0.2700**
		(0.3058, 0.6942)	(0.4062, 0.5938)	(0.4004, 0.5996)	(0.6065, 0.3935)
		0.4803	**0.4962**	**0.4706**	**0.4963**

(The bold figures below the support points are the corresponding masses.)

algebraically study the nature of the support points. A numerical study has been done, and the optimality of the designs thus obtained have been verified using Equivalence Theorem.

4.2. $t = x_1 + \rho x_2 + \delta\left(\rho x_1 x_2\right)^{1/2}$

In this situation, for the estimation of the parameters of the model (4), the information matrix of a continuous design ξ has the following form:

$$M(\xi) = \begin{bmatrix} (\frac{\theta_2}{\theta_1})^2 \sum_{i=1}^{n} a_i & -\frac{\theta_2}{\theta_1} \sum_{i=1}^{n} a_i ln(\frac{t_i}{\theta_1}) & -\frac{\theta_2^2}{\theta_1} \sum_{i=1}^{n} a_i \frac{x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}}{t_i} & -\frac{\theta_2^2}{\theta_1} \sum_{i=1}^{n} a_i \frac{\sqrt{\rho x_{i1}x_{i2}}}{t_i} \\ -\frac{\theta_2}{\theta_1} \sum_{i=1}^{n} a_i ln(\frac{t_i}{\theta_1}) & \sum_{i=1}^{n} a_i \{ln(\frac{t_i}{\theta_1})\}^2 & \theta_2 \sum_{i=1}^{n} a_i (\frac{x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}}{t_i}) ln(\frac{t_i}{\theta_1}) & \theta_2 \sum_{i=1}^{n} a_i ln(\frac{t_i}{\theta_1}) \frac{\sqrt{\rho x_{i1}x_{i2}}}{t_i} \\ -\frac{\theta_2^2}{\theta_1} \sum_{i=1}^{n} a_i \frac{x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}}{t_i} & \theta_2 \sum_{i=1}^{n} a_i (\frac{x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}}{t_i}) ln(\frac{t_i}{\theta_1}) & \theta_2^2 \sum_{i=1}^{n} a_i (\frac{x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}}{t_i})^2 & {\theta_2}^2 \sum_{i=1}^{n} a_i (x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}) \frac{\sqrt{\rho x_{i1}x_{i2}}}{t_i^2} \\ -\frac{\theta_2^2}{\theta_1} \sum_{i=1}^{n} a_i \frac{\sqrt{\rho x_{i1}x_{i2}}}{t_i} & \theta_2 \sum_{i=1}^{n} a_i ln(\frac{t_i}{\theta_1}) \frac{\sqrt{\rho x_{i1}x_{i2}}}{t_i} & {\theta_2}^2 \sum_{i=1}^{n} a_i (x_{i2} + \frac{\delta\sqrt{x_{i1}x_{i2}}}{2\sqrt{\rho}}) \frac{\sqrt{\rho x_{i1}x_{i2}}}{t_i^2} & \theta_2^2 \sum_{i=1}^{n} a_i \frac{\rho x_{i1}x_{i2}}{t_i} \end{bmatrix}$$

Here interaction is present between the two similar compounds, and $\theta = (\theta_1, \theta_2, \rho, \delta)$ is the vector of unknown parameters. It is difficult to find the D-optimal design algebraically. Numerical computation, however, shows that the D- optimal design for estimating θ is a four-point design with support at the extreme points and two points in-between, and the mass at each point is 0.25. The optimal support points in-between the extreme points are shown in Table 3 for some combinations of the parameter values.

For the estimation of only ρ, we argue as in the previous sub-section and search for the optimal design within the class of designs with at least four support points, since one also has to estimate $(\theta_1, \theta_2, \delta)$ in order to estimate ρ.

Table 4 gives the optimum designs for estimating ρ for some combinations of the parameter

Table 3: Optimal support points besides the extreme points in the D-optimal designs for estimation of $\theta = (\theta_1, \theta_2, \rho, \delta)$ in two-component mixture

δ	ρ \ (θ_1, θ_2)	0.2	0.5	1	3.0
0.5	(0.2, 0.05)	(0.1476, 0.8524)	(0.1542, 0.8458)	(0.0568, 0.9432)	(0.2079, 0.7921)
		(0.7983, 0.2017)	(0.7746, 0.2254)	(0.4999, 0.5001)	(0.8408, 0.1592)
	(0.2, 0.5)	(0.1453,0.8547)	(0.1499, 0.8501)	(0.0587, 0.9413)	(0.2193 , 0.7807)
		(0.7954, 0.2046)	(0.7706,0.2294)	(0.5134, 0.4866)	(0.8540 , 0.1460)
	(2, 0.05)	(0.1499, 0.8501)	(0.1546, 0.8454)	(0.0594, 0.9406)	(0.2076, 0.7924)
		(0.8005, 0.1995)	(0.7740, 0.2260)	(0.5130, 0.4870)	(0.8407, 0.1593)
	(2.0,0.5)	(0.1600, 0.8400)	(0.1860, 0.8140)	(0.0571, 0.9429)	(0.2085, 0.7915)
		(0.8032, 0.1968)	(0.7703, 0.2297)	(0.5000, 0.5000)	(0.8397, 0.1603)
-0.5	(0.2, 0.05)	(0.0541, 0.9459)	(0.1381, 0.8619)	(0.0901, 0.9099)	(0.5016, 0.4984)
		(0.3737, 0.6263)	(0.6251, 0.3749)	(0.5126, 0.4874)	(0.9124, 0.0876)
	(0.2, 0.5)	(0.0537, 0.9463)	(0.1369, 0.8631)	(0.0916, 0.9084)	(0.5203, 0.4797)
		(0.3664, 0.6336)	(0.6180, 0.3820)	(0.5128, 0.4872)	(0.9147, 0.0853)
	(2, 0.05)	(0.0541, 0.9459)	(0.1382, 0.8618)	(0.0935, 0.9065)	(0.5014, 0.4986)
		(0.3740, 0.6260)	(0.6252, 0.3748)	(0.5230,0.4770)	(0.9124, 0.0876)
	(2.0, 0.5)	(0.0566, 0.9434)	(0.1373, 0.8627)	(0.0893, 0.9107)	(0.4989, 0.5011)
		(0.3930, 0.6070)	(0.6399, 0.3601)	(0.5125, 0.4875)	(0.9117, 0.0883)

values. It is observed that the D_s-optimal design is a four-point or five-point design with unequal masses for every combination of the model parameters.

Remark. *It is interesting to note that for given θ_2, the support points and the corresponding masses when $\theta_1 = 0.2$ and $\theta_1 = 2, 0$ are quite close to one another in most cases. Further, except for one combination of the parameters, the optimal design is a four-point design.*

5. Optimal designs for the estimation of the mixing proportions for a given π

Let us consider model (4) with $t = x_1 + \rho x_2$. Suppose we wish to estimate $x_0 = (x_{10}, x_{20})'$ such that $\pi t = \pi_0$. For such a π_0, we have $x_{20} = \theta_1 \frac{e^{\frac{-\eta_0}{\theta_2}} - 1}{(\rho - 1)}$ where $\eta(t) = ln \frac{\pi_0}{1-\pi_0} = \eta_0$, say. Since $0 \leq x_{20} \leq 1$,we must have $0 \leq \frac{e^{\frac{-\eta_0}{\theta_2}} - 1}{(\rho - 1)} \leq \frac{1}{\theta_1}$ This clearly indicates that, for any given set of values of $(\theta_1, \theta_2, \rho)$, π may not take the desired value in [0, 1].
For an n-point continuous design ξ with moment matrix $M(\xi)$, the variance of $\hat{x}_{20}$ is given by

$$\begin{aligned} Var(\hat{x}_{20}) &= \left(\frac{\partial x_{20}}{\partial \theta_1}, \frac{\partial x_{20}}{\partial \theta_2}, \frac{\partial x_{20}}{\partial \rho}) M(\xi)^{-1} (\frac{\partial x_{20}}{\partial \theta_1}, \frac{\partial x_{20}}{\partial \theta_2}, \frac{\partial x_{20}}{\partial \rho}\right)' \\ &= \frac{1}{(\rho-1)^2} \left[e^{\frac{-2\eta_0}{\theta_2}} m^{11} - 2\frac{\theta_1 \eta_0}{\theta_2^2} e^{\frac{-2\eta_0}{\theta_2}} m^{12} + \frac{\theta_1^2 \eta_0^2}{\theta_2^4} e^{\frac{-2\eta_0}{\theta_2}} m^{22} - 2\frac{e^{\frac{-\eta_0}{\theta_2}} (\theta_1 e^{\frac{-\eta_0}{\theta_2}} - 1)}{(\rho - 1)} m^{13} \right. \\ &\quad \left. -2\frac{\theta_1 \eta_0 e^{\frac{-\eta_0}{\theta_2}} (\theta_1 e^{\frac{-\eta_0}{\theta_2}} - 1)}{\theta_2^2 (\rho - 1)} m^{23} + \frac{(\theta_1 e^{\frac{-\eta_0}{\theta_2}} - 1)^2}{(\rho - 1)^2} m^{33} \right], \end{aligned}$$

where $M(\xi)^{-1} = ((m^{ij}))$
The locally optimum design for estimating x_0 is then obtained by minimizing $Var(\hat{x}_{20})$ for given values of $(\theta_1, \theta_2, \rho, \pi_0)$. It is interesting to note that the optimal designs are special cases of the c-optimal designs.

Table 4: Optimum design for estimation of ρ in two- component mixture

δ	ρ \ (θ_1, θ_2)	0.2	0.5	1	3.0
0.5	(0.2, 0.05)	(0, 1) **0.0961** (1, 0) **0.2921** (0.1823, 0.8177) **0.2079** (0.8171, 0.1829) **0.4039**	(0, 1) **0.1557** (1 ,0) **0.2391** (0.1459, 0.8541) **0.2609** (0.8008, 0.1992) **0.3443**	(0, 1) **0.5247** (1, 0) **0.4382** (0.4410, 0.5590) **0.0002** (0.8339, 0.1661) **0.0369**	(0, 1) **0.2775** (1, 0) **0.1157** (0.1840, 0.8160) **0.3843** (0.8311, 0.1689) **0.2225**
	(0.2, 0.5)	(0, 1) **0.0933** (1, 0) **0.2950** (0.1792, 0.8208) **0.2037** (0.8121, 0.1879) **0.4080**	(0, 1) **0.1520** (1 ,0) **0.2410** (0.1422, 0.8578) **0.2583** (0.7979, 0.2021) **0.3487**	(0, 1) **0.4162** (1, 0) **0.4131** (0.1381, 0.8619) **0.0761** (0.8676, 0.1324) **0.0946**	(0, 1) **0.2838** (1, 0) **0.1076** (0.1908, 0.8092) **0.3933** (0.8384, 0.1616) **0.2153**
	(2, 0.05)	(0, 1) **0.0962** (1, 0) **0.2921** (0.1824, 0.8176) **0.2079** (0.8172, 0.1828) **0.4038**	(0, 1) **0.1558** (1 ,0) **0.2391** (0.1460, 0.8534) **0.2609** (0.8009, 0.1991) **0.3442**	(0, 1) **0.3683** (1, 0) **0.5427** (0.0002, 0.9998) **0.0753** (0.7553, 0.2447) **0.0137**	(0, 1) **0.2775** (1, 0) **0.1158** (0.1839, 0.8161) **0.3872** (0.8310 0.1690) **0.2225**
	(2, 0.5)	(0, 1) **0.1037** (1, 0) **0.2875** (0.1889, 0.8111) **0.2110** (0.8215, 0.1785) **0.3977**	(0, 1) **0.1591** (1 ,0) **0.2375** (0.1492, 0.8508) **0.2619** (0.8026, 0.1974) **0.3415**	(0, 1) **0.4091** (1, 0) **0.4090** (0.1337, 0.8663) **0.0831** (0.3234, 0.6766) **0.0016** (0.8653, 0.1347) **0.0972**	(0, 1) **0.2773** (1, 0) **0.1167** (0.1844,0.8156) **0.3842** (0.8303 0.1697) **0.2218**
-0.5	(0.2, 0.05)	(0, 1) **0.1785** (1, 0) **0.1528** (0.0468, 0.9532) **0.3473** (0.3949, 0.6051) **0.3214**	(0, 1) **0.1746** (1 ,0) **0.1819** (0.1241, 0.8759) **0.3181** (0.6525, 0.3475) **0.3254**	(0, 1) **0.3185** (1, 0) **0.3182** (0.0096, 0.9904) **0.1840** (0.9819, 0.0181) **0.1793**	(0, 1) **0.1614** (1, 0) **0.1852** (0.4787, 0.5213) **0.3147** (0.9234 0.0766) **0.3387**
	(0.2, 0.5)	(0, 1) **0.1773** (1, 0) **0.1590** (0.0463, 0.9537) **0.3446** (0.3877, 0.6123) **0.3171**	(0, 1) **0.1739** (1 ,0) **0.1862** (0.1230, 0.8770) **0.3148** (0.6463, 0.3537) **0.3251**	(0, 1) **0.3189** (1, 0) **0.3084** (0.0237, 0.9763) **0.1804** (0.9793, 0.0207) **0.1923**	(0, 1) **0.1712** (1, 0) **0.1828** (0.4937, 0.5063) **0.3152** (0.9254, 0.0746) **0.3308**
	(2, 0.05)	(0, 1) **0.1786** (1, 0) **0.1527** (0.0468, 0.9532) **0.3474** (0.3951, 0.6049) **0.3213**	(0, 1) **0.1747** (1 ,0) **0.1818** (0.1241, 0.8759) **0.3182** (0.6527, 0.3473) **0.3253**	(0, 1) **0.3135** (1, 0) **0.3140** (0.0333, 0.9667) **0.1848** (0.9669, 0.0331) **0.1877**	(0, 1) **0.1613** (1, 0) **0.1852** (0.4785, 0.5215) **0.3147** (0.9234, 0.0766) **0.3388**
	(2, 0.5)	(0, 1) **0.1802** (1, 0) **0.1458** (0.0489, 0.9511) **0.3578** (0.4102, 0.5898) **0.3162**	(0, 1) **0.1750** (1 ,0) **0.1787** (0.1253, 0.8747) **0.3234** (0.6585, 0.3415) **0.3239**	(0, 1) **0.3239** (1, 0) **0.3144** (0.0306, 0.9694) **0.1749** (0.9698, 0.0302) **0.1868**	(0, 1) **0.1613** (1, 0) **0.1853** (0.4768, 0.5232) **0.3127** (0.9229, 0.0771) **0.3407**

(The bold figures below the support points are the corresponding masses.)

6. Conclusion

The paper studies the problem of finding the most efficient design in a dose-response experiment with binary response. The effective dose is a potency adjusted mixture of two similar compounds. The response function is assumed to be two-parameter log-logistic, where the mixing proportions of the compounds are taken as the covariates. The paper addresses the cases where there is no interaction as well as when interaction is present between the compounds, and determines locally D-optimal designs for parameter estimation. The designs are obtained by numerical optimization and verified using Equivalence Theorem. The optimal designs when the only parameter of interest is the relative potency of a compound have also been investigated. The paper also indicates how to find the optimum design for estimating the mixing proportions to get a specified probability of an individual having the trait under study. Interesting results have been obtained through numerical investigation, the most striking being that for the D_s-optimal designs to estimate the relative potency (ρ) when interaction exists between the compounds, in most cases the design points and their masses are quite close to one another when the coefficient of synergism (δ) the slope parameter θ_2 and $\rho(\neq 1)$ are fixed but the LD50 (θ_1) changes from 0.2 to 2.0.

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