OPTIMAL DESIGNS FOR BIVARIATE DOSE – RESPONSE EXPERIEMNTS

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Abstract

The methodology of R-optimal designs is used to obtain optimal experimental dose levels to improve the precision of model coefficient estimates in the bivariate dose-response experiments involving toxicity and efficacy. The optimal dose levels are obtained sequentially by utilizing the multiresponse R-optimal design methodology developed by Liu and Yue (2013).

Key Words: dose response curves, bivariate, optimal design, Bonferroni t-intervals , R - optimal

1 Introduction

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In the planning stage of a drug development study, the choice of dose level combinations that should be included in the experiment plays an essential role. This 'optimal' set of dose level combinations in statistical design theory is called a design, and each dose level combination is called a design point. There are many criteria in optimal design theory that can be used to select an optimal design. D–optimality is the criterion that is mostly used; it yields a set of design points or a set of dose level combinations that will improve the precision of the model parameter estimates. This improvement in parameter estimate precision will undoubtedly improve the predicted response for any given dose level combination. In fact, the D-optimality criterion is equivalent to the G-optimality criterion, which yields a set of design points that minimizes the maximum of the predicted response (Atkinson and Donev 1992, p. 97)

More specifically, a D-optimal design minimizes the volume of the confidence ellipsoid of the vector with unknown parameters (for example, Silvey 1980), However, as stated in Dette (1997), interpretation of an ellipsoid thus obtained is not easy, especially when the number of parameters in the model is more than 3. Therefore, as suggested by Dette (1997), construction of a common joint confidence region for the model parameters, based on Bonferroni t-intervals, may be more practical. If there are k model parameters to be estimated, such a confidence region will form a k-dimensional rectangle. Thus, an R - optimal design which minimizes the volume of such a k-dimensional rectangle may be a preferred alternative.

The purpose of this work is to develop a sequential procedure to obtain R - optimal designs for bivariate dose response studies that include toxicity and efficacy as

responses of interest. This work is based on the multiresponse extension of R - optimal designs developed by Liu and Yue (2013).

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Let

$$\underline{Y}_i^u = \underline{f}_i'(\underline{x}^u)\,\underline{\beta}_i + \underline{\varepsilon}_I \qquad i = 1,2, \quad u=1,2,\ldots,N. \qquad (1)$$

Here, $\underline{Y}_i$, i = 1,2 are the efficacy and toxicity response vectors of dimension N, where N is the number of trials, $\underline{x}^u = (x_1^u, x_2^u, \ldots, x_q^u)'$, u= 1,2, .. ., N represent the q dose combinations at N trials, $f_i(\underline{x})$ is a p_ix1 vector, representing a regression function of p_i terms, i=1,2 and $\underline{\theta}' = (\underline{\beta}_1', \underline{\beta}_2')'$ is the parameter vector of dimension $p = p_1 + p_2$. The least squares estimator of $\underline{\theta}$ is given by

$$\hat{\theta} = (\chi'\Sigma^{-1}\chi)^{-1}\chi'Y\,, \qquad (2)$$

where χ = Diag (X_1,X_2) is the design matrix, $X_i = (\underline{f}_i'(\underline{x}_1), \underline{f}_i'(\underline{x}_2), \ldots, \underline{f}_i'(\underline{x}_N))'$, i=1,2 , $Y = (Y_1', Y_2')'$, and Σ is the covariance matrix of efficacy and toxicity responses. Note that χ is a block diagonal matrix of dimension 2Nxp and X_1, X_2 are matrices of dimensions Nxp_1 and Nxp_2 respectively. Also, $\hat{\theta}' = (\underline{\hat{\beta}}_1', \underline{\hat{\beta}}_2')'$ and for a given set of N dose combinations, $\underline{x}_1, \underline{x}_2, \ldots, \underline{x}_N$, a discrete design can be defined as

$$t_N = \{(\underline{x}_1, w_1), (\underline{x}_2, w_2), \ldots, (\underline{x}_N, \underline{w}_N)\} \in T, \quad \text{where } 0 < w_i < 1, \ \sum_{i=1}^{N} w_i = 1, \ \underline{x}_i \in X \subset R_q. \qquad (3)$$

Here, X is the experimental region representing the acceptable dose ranges for the q drugs used in the study. Essentially, w_i, i=1,2, …, N are replication proportions of each $\underline{x}_i$ The information matrix associated with the design $t \in T$ is defined by

$$M(t, \Sigma) = \sum_{i=1}^{N} w_i\, \underline{f}_i'(\underline{x}_i)\, \Sigma^{-1}\, \underline{f}_i(\underline{x}_i). \qquad (4)$$

Furthermore

$$\Sigma = D\,(S_0 \otimes I_N)\, D, \qquad (5)$$

where $(S_0 \otimes I_N)$ is the matrix direct product of S_0 and I_N, D= Diag $(d_{11}\underline{I}_N \ d_{22}\,\underline{I}_N)$, in which d_{ii} are the standard deviations of efficacy and toxicity responses and

$$S_o = \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix}$$

is their correlation matrix.

3. R – optimal Designs

As stated by Dette (1997), a R - optimal design minimizes the volume of the p-dimensional rectangle based on Bonferroni t-intervals and this volume is proportional to $\prod_{i=1}^{p}(\chi'\Sigma^{-1}\chi)_{ii}^{-1}$. In design theory, this is analogous to minimizing $\prod_{i=1}^{p} M_{ii}^{-1}(t,\Sigma)$. Therefore a design $t^* \in T$ is said to be R-optimal if,

$$\psi(t^*,\Sigma) = \sup_{t\varepsilon T} \psi(t,\Sigma), \qquad (7)$$

where $\psi(t, \Sigma) = \prod_{i=1}^{p} M_{ii}^{-1}(t,\Sigma)$.

4. Construction of R-optimal Designs

It can be shown that

$$M^{-1}(t,\Sigma) = \begin{bmatrix} \{d_{11}(X_1'X_1 - \rho X_1'X_2(X_2'X_2)^{-1}X_2'X_1)\}^{-1} & \text{A} \\ \text{B} & \{d_{22}(X_2'X_2 - \rho X_2'X_1(X_1'X_1)^{-1}X_1'X_2)\}^{-1} \end{bmatrix}, \qquad (8)$$

where, as defined earlier $X_i = (\underline{f}_i'(\underline{x}_1), \underline{f}_i'(\underline{x}_2), .., \underline{f}_i'(\underline{x}_N))$, $t = \{(\underline{x}_1, w_1), (\underline{x}_2, w_2), \ldots, (x_N, \underline{x}_N)\}$, while A and B are the two off diagonal matrices. Hence

$$\psi(M(t,\Sigma)) = \prod_{i=1}^{p} M_{ii}^{-1}(t,\Sigma)$$

$$= d_{11}d_{22} \prod_{i=1}^{p_1} (M_1)_{ii}(t,\rho) \prod_{i=1}^{p_2} (M_2)_{ii}(t,\rho), \qquad (9)$$

where

$$M_1(t, \rho) = X_1^{'}X_1 - \rho X_1^{'}X_2(X_2^{'}X_2)^{-1}X_2^{'}X_1 \quad (10)$$

and

$$M_2(t, \rho)) = X_2^{'}X_2 - \rho X_2^{'}X_1(X_1^{'}X_1)^{-1}X_1^{'}X_2 . \quad (11)$$

Note that both matrices M_1 and M_2 depend only on the dose combinations that define t ∈ T and ρ is the correlation between efficacy and toxicity responses. Also, equation (9) indicates that $\psi[M(t, \Sigma)]$ does not depend on the sub matrices A and B and also that a choice of design depends on Σ, only on ρ via M_1 and M_2. Therefore, in the case when Σ is unknown, only ρ should be estimated. This can be done while obtaining R optimal design points sequentially. The estimate of ρ based on N design points, denoted $\tilde{\rho}_N$ can be calculated by first computing $\tilde{d}_{ij}^N$, the estimates of d_{ij} where

$$N\tilde{d}_{ij}^N = \sum_{u=1}^{N} (\underline{y}_i - \underline{f}_i'(\underline{x}^u)\tilde{\underline{\beta}}_i)' (\underline{y}_j - \underline{f}_j'(\underline{x}^u)\tilde{\underline{\beta}}_j), \quad (12)$$

and then use the formula

$$\tilde{\rho}_N = \frac{(\tilde{d}_{ij}^N)^2}{\tilde{d}_{ii}^N \tilde{d}_{jj}^N}, \quad i, j = 1,2 \quad (13)$$

(see Wijesinha 1984). Now, to develop a sequential procedure to obtain R – optimal design points, the following theorem proved by Liu and Yue (2012) can be utilized.

Equivalence Theorem

A design t ϵ T is R-optimal if and only if

$$\psi(M(t,\rho)) = p, \quad \text{where}$$

$$\Phi(\underline{x},t, \rho) = sup_{xi \in X} \text{trace}\left\{ M^{-1}(t) X_0^{'} . X_0 M^{-1}(t) \sum_{i=0}^{p} \frac{e_i e_i^{'}}{e_i^{'} M^{-1} e_i} \right\}, \quad (14)$$

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where X_0 = diag [$\underline{f}_1(\underline{x})$, $\underline{f}_2(\underline{x})$], $\underline{x} \in X$ and e_i denotes the ith unit vector in Rp.

5. Sequential Construction of R - optimal Designs

1. Start with an initial design. $t_{N0} = \{ (\underline{x}_1, w_1), (\underline{x}_2, w_2), \ldots, (x_{N0}, \underline{w}_{N0})\} \in T$ with N_0 design points,

2. Compute $\tilde{\rho}_{N0}$ using equation (13) and design points in t_{N0}.

3. Obtain a new design point $\underline{x}_{N0+1}$, by computing $\Phi(x, t_{N0}, \tilde{\rho}_{N0})$ over $\underline{x} \in X$.

4. Compute $\tilde{\rho}_{N0+1}$ using equation (13) and design points in

$$t_{N0+1} = \{ (\underline{x}_1, \frac{N_0 w_1}{N_0+1}), (\underline{x}_2, \frac{N_0 w_2}{N_0+1}), \ldots, (x_{N0}, \frac{N_0 w_{N_0+1}}{N_0+1}), (x_{N_0+1}, \frac{1}{N_0+1})\} \in T .$$

Here, $0 < w_i < 1$, $\sum_{i=1}^{N} w_i = 1$, $\underline{x}_i \in X \subset R_q$..

5. Once t_N is constructed,

   - compute $\tilde{\rho}_N$ using equation (13) and design points in t_N.
   - obtain a new design point $\underline{x}_{N+1}$, by computing $\Phi(x, t_N, \tilde{\rho}_N)$ over $\underline{x} \in X$.

Here, $t_N = \{ (\underline{x}_1, w_1), (\underline{x}_2, w_2), \ldots, (x_N, \underline{w}_N)\} \in T$, where $0 < w_i < 1$, $\sum_{i=1}^{N} w_i = 1$, $\underline{x}_i \in X \subset R_q$..

6. Continue until

$$\varphi(x, t_{N'}, \rho) - p < \delta.$$

where δ is a sufficiently small number chosen beforehand and $N' > N_0$.

The design $t_{N'}$ thus obtained is an approximate R - optimal design.

6. Conclusion

In this work, a sequential procedure is developed to obtain R-optimal designs for bivariate dose response linear models with continuous responses. It should be noted that the same procedure can be also applied for bivariate logistic models with

binary responses, by transforming the binary responses to the corresponding logit functions.

Compared to D-optimal designs, R-optimal designs are more practically useful since for large number of parameters, the interpretation of the optimal ellipsoid of the parameters obtained via D -optimal designs is somewhat difficult. Furthermore, the fact that bivariate models typically contain a greater number of parameters than a single response model is another reason why R -optimal designs may be preferable to D – optimal designs in bivariate models.

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