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Locally Optimal Binary Crossover Designs

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Abstract

Optimal two-treatment, p period crossover designs for binary responses are determined. The optimal designs are obtained by minimizing the variance of the treatment contrast estimator over all possible allocations of n subjects to 2^p possible treatment sequences. An appropriate logistic regression model is postulated and the within subject covariances are modeled through a working correlation matrix. The marginal mean of the binary responses are fitted using generalized estimating equations. The efficiencies of some crossover designs for $p = 2, 3, 4$ periods are calculated. An equivalence theorem is provided to verify optimality of numerically obtained locally optimal designs.

Key words: Binary response; Generalized estimating equations; Logistic regression; Efficiency.

AMS Subject Classifications: MSC: 62K05

1. Introduction

In crossover trials, every experimental unit receives a sequence of treatments over different time periods. For the real life applications of crossover trials see *e.g.*, Jones and Kenward (2014) and Senn (2003). The problem of determining optimal designs for crossover trials has been studied quite extensively in recent years and we refer to Bose and Dey (2009) for a review of results on optimal crossover designs. However, most of the available results on optimal crossover designs relate to situations where the response variable is continuous (see Kershner and Federer (1981), Laska and Meisner (1985), Matthews (1987) and Carriere and Huang (2000) and the references therein). In clinical or pharmaceutical research, the outcome of interest is often binary in nature. While methods for analyzing binary data arising from crossover trials are available in Jones and Kenward (2014) and Senn (2003), the question of designing such studies in an optimal manner does not seem to have been addressed much in the literature. Waterhouse *et al.* (2006) considered crossover designs for binary response, where the treatments were taken to be continuous in nature and no period effects were considered in the model. Singh and Mukhopadhyay (2016) proposed optimal

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crossover Bayesian designs for the generalized linear models (GLMs). One of their case study was based on a four periods ($p = 4$) binary crossover design for four periods. Recently, Singh *et al.* (2020) proposed min–max crossover designs for the GLMs. Following the methodology proposed in Singh and Mukhopadhyay (2016), Jankar *et al.* (2020) proposed locally D-optimal designs for the GLMs. In comparison aforementioned references, the present article discusses the binary crossover design in greater details for $p = 2, 3, 4$ periods and two treatments. We discuss optimal designs for binary responses in a logistic regression framework.

Since the main interest lies in the estimation of the treatment effect, the designs proposed, minimize the variance of the estimator associated with the treatment effect. For a binary logistic model, the variance of the treatment effect estimator depends on the model parameters, to address the issue of parameter dependence, various intervals of model parameter are assumed and a subset of parameter values are selected from these intervals. In crossover studies the response at the current time period may have the effect of the treatment from the previous time period. This effect is refer to as the "carryover effect". Often the interest lies in estimating the carryover effect. Optimal crossover designs to estimate the carryover effect for the normal response are discussed in Laska and Meisner (1985) and Gondaliya and Divecha (2015). In our setting assuming that the carryover effect of a treatment lasts only to the next succeeding period, optimal designs for estimating the carryover effect are also discussed. A population average approach is utilized for the estimation of the model parameters. In this approach we treat the subject effects as a nuisance parameter and use the generalized estimating equations of Liang and Zeger (1986) to estimate the marginal means. The observations from each subject over different time points are assumed to be mutually correlated while the observations from different subjects are uncorrelated. The correlation between observations within subjects are modeled using a "working correlation structure". We study the effect of three working correlation structures, uncorrelated, equi-correlated and autoregressive (AR) on the designs chosen. The rest of the article is organised as foloows. In Section 2, we define the crossover logistic model for a binary response and discuss the estimation of the crossover model using generalized estimating equations. In Section 3, results on optimal two-treatment designs for 2, 3 and 4 periods are given. The optimally of numerically obtained locally optimal designs is verified using an equivalence theorem given in Section 3.5.

2. The Model and Estimation

Consider a crossover trial involving t treatments, n subjects and p periods. Suppose the response obtained from the jth subject is $\mathbf{Y}_j = (Y_{1j}, \ldots, Y_{pj})'$, where a prime denotes transposition. Instead of specifying a joint distribution of the repeated measurements we use a working GLM to describe the marginal distribution of Y_{ij} as (Liang and Zeger, 1986)

$$f(y_{ij}) = exp[\{y_{ij}\phi_{ij} - b(\phi_{ij}) + c(y_{ij})\}\psi].$$

For a binary random variable Y_{ij}, $\phi_{ij} = \log \dfrac{\mu_{ij}}{1-\mu_{ij}}$, $b(\phi_{ij}) = \log[1 + \exp\{\phi_{ij}\}]$, $c(y_{ij}) = 0$, and the scale parameter ψ is 1 (Robinson and Khuri, 2003). The mean of Y_{ij} is μ_{ij} and variance $\mu_{ij}(1 - \mu_{ij})$.

In a crossover setup, we model the marginal mean μ_{ij} using the population-average model

$$logit(\mu_{ij}) = \eta_{ij} = \mu + \beta_i + \tau_{d(i,j)} + \rho_{d(i-1,j)};\ i = 1\ \ldots, p,\ j = 1, \ldots, n, \tag{1}$$

where μ is the overall mean, β_i represents the effect of the ith period, τ_s is the treatment effect due to treatment s and ρ_s is the carryover effect due to treatment s, $s = 1, \ldots, t$. Throughout, $\mathbf{1}_u$ is a $u \times 1$ vector of all ones, I_u is the identity matrix of order u and 0_{ab} is an $a \times b$ null matrix. Also, we write $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$, $\boldsymbol{\tau} = (\tau_1, \ldots, \tau_t)'$ and $\boldsymbol{\rho} = (\rho_1, \ldots, \rho_t)'$. Since there is no carryover effect in the first period, we set $\rho_{d(0,j)} = 0$ for all j.

In matrix notation, the linear predictor corresponding to the jth subject, $\boldsymbol{\eta}_j = (\eta_{1j}, \ldots, \eta_{pj})'$, can be written as

$$\boldsymbol{\eta}_j = \mathbf{X}_j\boldsymbol{\theta}, \tag{2}$$

where $\boldsymbol{\theta} = (\mu, \boldsymbol{\beta}', \boldsymbol{\tau}', \boldsymbol{\rho}')'$. The design matrix is $\mathbf{X}_j = [\mathbf{1}_p\ P_j\ T_j\ F_j]$, where $P_j = I_p$; T_j is a $p \times t$ matrix with its (i, s)th entry equal to 1 if subject j receives the treatment effect of the treatment s in the ith period and zero otherwise; F_j is a $p \times t$ matrix with its (i, s)th entry equal to 1 if subject j receives the carryover effect of the treatment s in the ith period and zero otherwise. Note that the first row of F_j consists of all zeros since $\rho_{d(0,j)} = 0$ for all j.

Since we are working with the population–average model, the estimation of the model parameters can be done using the generalized estimating equation (GEE) approach proposed by Liang and Zeger (1986) and Zeger et al. (1988). The GEEs are utilized to estimate the parameters of GLM with a possible unknown correlation between outcomes. The resulting estimators are referred to as the GEE estimators. The GEE estimators are consistent even if the correlation structure is misspecified. It is assumed that measurements from the same subject in the p periods are correlated while observations from different subjects are uncorrelated. The dependencies between repeated observations from a subject are modeled using a "working correlation" matrix $C(\boldsymbol{\alpha})$ where $\boldsymbol{\alpha}$ is a vector of length s. If $C(\boldsymbol{\alpha})$ is the true correlation matrix of $\mathbf{Y}_j$, then

$$Cov[\mathbf{Y}_j] = D_j^{1/2}C(\boldsymbol{\alpha})D_j^{1/2}, \tag{3}$$

where $D_j = diag(\mu_{1j}(1 - \mu_{1j}), \ldots, \mu_{pj}(1 - \mu_{pj}))$. Let $W_j = D_j^{1/2}C(\boldsymbol{\alpha})D_j^{1/2}$.

For a repeated-measures model, Zeger *et al.* (1988, equation (3.1)) derived the generalized estimating equations (GEE) to be

$$\sum_{j=1}^{n} \frac{\partial \boldsymbol{\mu}_j'}{\partial \boldsymbol{\theta}} W_j^{-1}(\mathbf{Y}_j - \boldsymbol{\mu}_j) = 0,$$

where $\boldsymbol{\mu}_j = (\mu_{1j}, \ldots, \mu_{pj})'$. The asymptotic variance for the GEE estimator $\widehat{\boldsymbol{\theta}}$ (see Zeger *et al.*, 1988, equation (3.2)) is

$$Var(\widehat{\boldsymbol{\theta}}) = \left[\sum_{j=1}^{n} \frac{\partial \boldsymbol{\mu}_j'}{\partial \boldsymbol{\theta}} W_j^{-1} \frac{\partial \boldsymbol{\mu}_j}{\partial \boldsymbol{\theta}}\right]^{-1}, \tag{4}$$

if $Cov(\mathbf{Y}_j) = W_j$, *i.e.* the working correlation is same as the true correlation. However, if the true correlation structure varies from the "working correlation" structure, then $Var(\widehat{\boldsymbol{\theta}})$ is given by the sandwich formula (Zeger *et al.*, 1988, equation (3.2))

$$Var(\widehat{\boldsymbol{\theta}}) = A^{-1}BA^{-1},$$

where

$$A = \sum_{j=1}^{n} \frac{\partial \boldsymbol{\mu}_j'}{\partial \boldsymbol{\theta}} W_j^{-1} \frac{\partial \boldsymbol{\mu}_j}{\partial \boldsymbol{\theta}}, \quad \text{and} \quad B = \sum_{j=1}^{n} \frac{\partial \boldsymbol{\mu}_j'}{\partial \boldsymbol{\theta}} W_j^{-1} Cov(\mathbf{Y}_j) W_j^{-1} \frac{\partial \boldsymbol{\mu}_j}{\partial \boldsymbol{\theta}}.$$

For the crossover model (1), the ith element of $\frac{\partial \boldsymbol{\mu}_j}{\partial \boldsymbol{\theta}}$ is $\mathbf{x}_{ij}'\mu_{ij}(1-\mu_{ij})$, where $\mathbf{x}_{ij}'$ is the ith row of $\mathbf{X}_j$ for $i = 1, \ldots, p$.

Before introducing the design selection criterion, we list the main objectives of the paper with the help of the following example. Consider a trial reported by Senn (2003, page 127) wherein it was desired to study the effect of two drugs on 24 children aged 7 to 13 suffering from exercise-induced asthma. The two treatments were, a single dose of $12\mu g$ formoterol solution aerosol (treatment A) and a single dose of $200\mu g$ of salbutamol solution aerosol (treatment B). Each child was given both the treatments either in the order, AB or BA. The response variable was binary, taking value 1 if the drug was effective and 0 otherwise. An equal number of children were allocated to each treatment sequence, AB or BA. Several questions arise about the design used:

- Is the design with equal allocation to sequences $\{AB, BA\}$ optimal for the binary model? If not which is the optimal design?
- For continuous responses [Laska and Meisner (1985)], in a 2–periods 2–treatments (2×2) crossover study, proved that the design with equal allocation to treatment sequences $\{AB, BA\}$ is optimal when there are no carryover effects in the model. If the same design is used for binary model what is the efficiency loss, if any?
- In binary models design selection depends on the model parameters. What will be the effect of these parameters when selecting a crossover design?
- Will the design change in a binary model if we include carryover effects in the model?

Finding an exact optimal design (optimal number of subjects to the treatment sequences) which is associated with the integer optimization problem of a non-linear function is mathematically intractable. Instead to find optimal crossover designs for the binary model we use the approximate theory as in Laska and Meisner (1985) and Kushner (1997, 1998). For a review of results on optimal crossover designs using the approximate theory, we refer to Bose and Dey (2009, Chapter 4). An approximate/continuous crossover design with k treatment sequences can be expressed in the form of a probability measure as follows:

$$\zeta = \begin{Bmatrix} \boldsymbol{\omega}_1 & \boldsymbol{\omega}_2 & \ldots & \boldsymbol{\omega}_k \\ p_{\omega_1} & p_{\omega_2} & \ldots & p_{\omega_k} \end{Bmatrix},$$

where $\boldsymbol{\omega}_i \in \Omega$ (set of all permutations of t treatments of length p). Observe that Ω denotes the set of all possible treatment sequences of length p. Here $p_{\boldsymbol{\omega}_i}$ is the proportion of subjects assigned to treatment sequence $\boldsymbol{\omega}_i$. Fixing the number of subjects to n and periods to p, we determine the proportion of subjects assigned to a particular treatment sequence. We denote by n_ω the number of subjects assigned to sequence $\boldsymbol{\omega}$. Then, $n = \sum_{\boldsymbol{\omega}\in\Omega} n_\omega, n_\omega \geq 0$, $p_{\boldsymbol{\omega}_i} = n_{\boldsymbol{\omega}_i}/n \geq 0$ and $\sum_{i=1}^{k} p_{\boldsymbol{\omega}_i} = 1$, for $i = 1, \cdots, k$. Once an approximate optimal design is obtained, an exact design can be found by efficient rounding (Kiefer (1971), Pukelsheim and Rieder (1992)).

It follows from Lemma 4.2.1 in Bose and Dey (2009) that $T_{\boldsymbol{\omega}} = T_j$ and $F_{\boldsymbol{\omega}} = F_j$ for all j subjects assigned to a treatment sequence $\boldsymbol{\omega}$. This implies that $\mathbf{X}_j = \mathbf{X}_{\boldsymbol{\omega}}$. Since $np_{\boldsymbol{\omega}}$ subjects are assigned to sequence $\boldsymbol{\omega}$, the variance of $\widehat{\boldsymbol{\theta}}$ in (4) can be expressed as

$$Var_\zeta(\widehat{\boldsymbol{\theta}}) = U^{-1} = \left[\sum_{\boldsymbol{\omega}\in\Omega} np_{\boldsymbol{\omega}} \frac{\partial \boldsymbol{\mu}'_{\boldsymbol{\omega}}}{\partial \boldsymbol{\theta}} W_{\boldsymbol{\omega}}^{-1} \frac{\partial \boldsymbol{\mu}_{\boldsymbol{\omega}}}{\partial \boldsymbol{\theta}}\right]^{-1}. \tag{5}$$

For the estimation of the treatment effect, instead of working with the full variance-covariance matrix of $\widehat{\boldsymbol{\theta}}$ we concentrate on $Var(\widehat{\boldsymbol{\tau}})$ where,

$$Var_\zeta(\widehat{\boldsymbol{\tau}}) = HVar_\zeta(\widehat{\boldsymbol{\theta}})H', \tag{6}$$

where H is a $t \times m$ matrix given by $[0_{t1}, 0_{tp}, I_t, 0_{tt}]$ and m is the total number of parameters in $\boldsymbol{\theta}$.

A locally optimal design (LOD) ζ^* is one which minimizes the $\log(Var_\zeta(\widehat{\boldsymbol{\tau}}))$ with respect to p_w, when $\sum_{w\in\Omega} p_w = 1$ and $\omega \in \Omega$. Similarly, an LOD associated with the carryover effect can be obtained by minimizing $\log(Var_\zeta(\widehat{\boldsymbol{\rho}}))$. As an example, consider the case when $p = 3$ and $\Omega = \{AAA, AAB, ABB, ABA, BAB\ BAA, BBA, BBB\}$. An optimal design (approximate/continuous) is specified by the optimal proportions p^*_ω for each $\omega \in \Omega$ for which $Var_\zeta(\widehat{\boldsymbol{\tau}})$ is minimized with respect to these proportions. In other words, ζ^* determines the optimal proportion p^*_ω of the total observations assigned to the treatment sequences ω. Suppose,

$$\zeta^* = \begin{Bmatrix} AAA & AAB & ABB & ABA & BAB & BAA & BBA & BBB \\ 0.40 & 0 & 0 & 0.15 & 0.10 & 0.25 & 0 & 0.10 \end{Bmatrix},$$

Then the optimal design allocates 40% of subjects to treatment AAA, 15% to treatment ABA, 10% subjects to BAB and BBB, and 25% to BAA. No subjects are allocated to the treament sequences $\{AAB, ABB, BBA\}$. In equation (8) we note that the variance of the treatment effect estimator depends on the model parameters. Thus, the optimal design found by minimizing the variance of the treatment effect is parameter dependent and actually an LOD.

3. Two Treatment Crossover Trials: Results and Discussion

With two treatments of interest, the problem simplifies to minimizing the variance of the treatment contrast $\tau_1 - \tau_2$ to obtain optimal crossover designs. Reparameterizing

model (1) as in Singh and Mukhopadhyay (2016) and Laska and Meisner (1985), using $\tau = (\tau_1 - \tau_2)/2$ and $\rho = (\rho_1 - \rho_2)/2$ we get

$$logit(\mu_{ij}) = \mu + \beta P + \tau \Phi_{d(i,j)} + \rho \Phi_{d(i-1),j)}, \tag{7}$$

where P takes value 0 for period 1 and 1 for period 2, $\Phi_A = 1$,$\Phi_B = -1$ and $\Phi_{d(0,j)} = 0$.

For illustration we go back to the example in Section 2, where there are two treatments, A and B applied in two periods to each child. The design used involved the treatment sequences AB and BA, with equal allocation to each treatment sequence. Thus, the matrix $\mathbf{X}_{\boldsymbol{\omega}}$ depends on the treatment sequence $\boldsymbol{\omega} \in \Omega = \{AB, BA\}$. If the treatment sequence, for example is $\boldsymbol{\omega} = AB$, then

$$\mathbf{X}_{\boldsymbol{\omega}} = \begin{pmatrix} 1 & 0 & 1 & 0 \\ 1 & 1 & -1 & 1 \end{pmatrix}$$

In the following, we look at the performance of the design, $\{AB, BA\}$. Senn (2003) fitted a logistic model with no carryover effect to the data set and computed confidence intervals for the various components of $\boldsymbol{\theta}$. Using these intervals we investigate if the above two-period design is the best choice in the given situation. We also look at general situations for determining optimal designs when $p = 2, 3$ or 4 for two treatment case.

3.1. Designs compared

An optimal design obtained by considering all possible treatment sequences associated with a p period model is denoted by $D^{(p)}$. For example when $p = 2$, $D^{(2)}$ is consists of the treatment sequences $\{AA, AB, BA, BB\} = \Omega$, with optimal proportions p^*_ω associated to the treatment sequence $\omega \in \Omega$. The designs that we consider are similar to those discussed by Laska and Meisner (1985) and Carriere and Huang (2000) and are listed below for $p = 2, 3$ and 4. The notation $D_i^{(p)}$ denotes ith design considered for a model with p time periods.

(i) $p = 2$:

$D_1^{(2)}$: AB and BA; $D_2^{(2)}$: AB, AA, BA and BB, with equal number of subjects assigned to each sequence. For normal responses, when there is no carryover effect, $D_1^{(2)}$ is an optimal design [Grizzle (1965)]. Design $D_2^{(2)}$ is shown to be universally optimal [Carriere and Reinsel (1992)].

(ii) $p = 3$:

$D_1^{(3)}$: ABB and BAA;

$D_2^{(3)}$: ABB, AAB, BAA and BBA;

$D_3^{(3)}$: ABB, ABA, BAA and BAB.

In designs $D_1^{(3)} - D_3^{(3)}$, each treatment sequence is allocated equally. These designs are shown to be optimal under different scenarios for normal responses. Under appropriate assumption on the within-subject correlation, Kershner (1986) and Laska *et al.* (1983) shown that $D_1^{(3)}$ is an universally optimal design. Optimality of designs $D_2^{(3)}$ and $D_3^{(3)}$ was investigated by

Laska *et al.* (1983), Ebbutt (1984), Matthews (1987), Carriere (1994), and Carriere and Huang (2000) for normal responses.

(iii) $p = 4$:

$D_1^{(4)}$: $AABB$, $BBAA$, $ABBA$ and $BAAB$;

$D_2^{(4)}$: $AABB$, $BBAA$;

$D_3^{(4)}$: $ABBA$, $BAAB$;

$D_4^{(4)}$: $ABAB$, $BABA$.

In designs $D_1^{(4)} - D_4^{(4)}$, each treatment sequence is allocated equally. The performances of these designs are investigated in Gondaliya and Divecha (2018).

For evaluating and comparing the above designs we define an efficiency measure as

$$\Gamma(\zeta) = \left(\frac{Var_{\zeta^*}(\widehat{\tau})}{Var_{\zeta}(\widehat{\tau})}\right)^{1/m}, \tag{8}$$

where ζ^* is the locally optimal crossover design and m is the number of unknown regression parameters in the model. Note that the efficiency in (8) defined for designs associated with the estimation of the treatment effect. Efficiency of designs associated with the estimation of the carryover effect can be defined by replacing $\widehat{\tau}$ with $\widehat{\rho}$ in (8).

3.2. Working correlation structures

We consider the uncorrelated, compound symmetric or, equi-correlated and the AR(1) structures for the correlation matrix $C(\boldsymbol{\alpha})$. Under the equi-correlated covariance structure, $C(\boldsymbol{\alpha}) = (1-\alpha)I_p + \alpha J_p$, where α is a scalar.

Under the AR(1) assumption the (i,j)th element c_{ij} fo $C(\boldsymbol{\alpha})$ is,

$$c_{ij} = \alpha^{|i-j|},\ i \neq j.$$

A Working Example: Here we present an example to illustrate the proposed methodology for obtaining the optimal proportions and compute design efficiency. Consider the case $p = 3$. We have used the reparametrized version of the model as described in Singh and Mukhopadhyay (2016). Let the estimates of the parameters be $\widehat{\boldsymbol{\theta}} = [\widehat{\mu}, \widehat{\beta}_1, \widehat{\beta}_2, \widehat{\tau}, \widehat{\rho}] = [0.5, 1.0, -1.0, -2.0, 1]$ and $\widehat{\alpha} = 0.1$. A compound symmetric correlation structure is assumed and $\Omega = \{AAA, ABB, ABA, AAB, BAA, BAB, BBA, BBB\}$. Optimal design (proportions) is obtained by minimizing the variance function given in equation (6) with respect to ζ. For the given parameter estimates and treatment sequences, LOD is,

$$\zeta^* = \begin{Bmatrix} AAA & ABB & ABA & AAB & BAA & BAB & BBA & BBB \\ 0 & 0.1865 & 0 & 0.1317 & 0.2068 & 0.1105 & 0.3645 & 0 \end{Bmatrix}$$

Observe that the above design uses treatment sequences $\{ABB, AAB, BAA, BAB, BBA\}$ with proportions of subjects $\{0.1865, 0.1317, 0.2068, 0.1105, 0.3645\}$, respectively. The efficient conversion of approximate design to an exact design can be done using the methods

given in Pukelsheim and Rieder (1992). Nearest integer approach is also one of the methods used and works quite well in most of the cases.

Suppose we are interested in comparing ζ^* with another design say

$$\zeta_A = \begin{Bmatrix} ABB & AAB & BAA & BBA \\ 1/4 & 1/4 & 1/4 & 1/4 \end{Bmatrix}$$

Design ζ_A distributes equal proportion of subjects to each treatment sequence considered. The values of $Var_{\zeta^*}(\widehat{\boldsymbol{\tau}}) = 3.7263$ and $Var_{\zeta_A}(\widehat{\boldsymbol{\tau}}) = 3.9778$. The design efficiency calculated using the formula given in equation (8) for $m = 6$ is 0.987.

Remark 1: It is clear that the expression of $Var_{\zeta}(\widehat{\boldsymbol{\theta}})$ given in (5) is a scalar multiple of n and the design efficiency is independent of n, *i.e.*, to compute the efficiency based on the formula (8), total number of observations (n) is not required.

Remark 2: Here and later in this article, design optimization is done using numerical techniques. In particular, we have used *fmincon* function of MATLAB R2014a. The function *fmincon* is used for nonlinear optimization under a constraint. These programs are available from authors upon request.

3.3. Parameter dependence

The variance of the treatment effect estimator depends on the model parameters and the optimal design found by minimizing the variance of the treatment effect is actually locally optimal. We have assumed that historical data from same study are available. Based on the historical data, using GEE approach the point estimate $\widehat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$ is obtained. A parameter space $\mathcal{B}$ for $\boldsymbol{\theta}$ is set up by taking Cartesian product of the confidence intervals of the individual parameters. For each period size p, the efficiencies of the designs listed in Section 3.1 are calculated as follows:

(a) An LOD ζ^* is obtained using $\widehat{\boldsymbol{\theta}}$. Suppose ζ^N denotes a competitive design listed in Section 3.1.

(b) From the parameter space $\mathcal{B}$, 5000 values of $\boldsymbol{\theta}$ are randomly generated. For each value of $\boldsymbol{\theta}$, the efficiency based on ζ^* and ζ^N is computed using (8). Thus, we shall have 5000 efficiencies values corresponding to 5000 values of $\boldsymbol{\theta}$.

(c) The performances of ζ^* and ζ^N are assessed through the box–plot of 5000 efficiencies values calculated in (b).

This allows us to study the robustness of the designs selected to the changes in the parameter values.

3.4. Results

LODs are computed for the following scenarios:

Scenario ID1: LOD for the estimation of the treatment effect (minimize the variance of the estimate of the parameter associated treatment effect) in the model with no carryover effects (NC). The working correlation structure is assumed to be independent (ID).

Scenario ID2: LOD for the estimation of the treatment effect when the carryover effect is included in the model (WC). The working correlation structure is assumed to be ID.

Scenario ID3: LOD for the estimation of the carry effect when the carryover effect is included in the model (WC). The working correlation structure is assumed to be ID.

Scenarios **CS1**, **CS2**, and **CS3** are same as scenarios **ID1**, **ID2**, and **ID3** except that the ID structure is replaced by CS correlation structure. Similarly, scenarios **AR1**, **AR2**, and **AR3** are same as scenarios **CS1**, **CS2**, and **CS3** except that the CS structure is replaced by an auto regressive (AR) correlation structure. In the subsequent sections, optimal proportions are denoted by a vector $\mathbf{p}^* = (p^*_{\omega_1}, \ldots, p^*_{\omega_s})'$, where $\omega_i \in \Omega$ for $i = 1, \ldots, s$, and s is the cardinality of Ω. A LOD ζ^* can be identify by $\mathbf{p}^*$ and the associated treatment sequences.

3.4.1. Two periods two treatment (2×2) crossover trials

For 2×2 binary trial, we used the data from a study reported in Jones and Kenward (2014) (Page 97, Table 2.36). The experiment was designed to assess the cerebrovascular deficiency. Two drugs (placebo and an active drug) given to subjects based on the treatment sequences $\{AB, BA\}$. The responses are recorded as abnormal (0) and normal (1) electrocardiogram readings. Based on the data, the point estimates of the model parameters and the 95% estimated confidence intervals are reported in Table 1. The estimated value of α is 0.1.

Table 1: Estimated 95% confidence intervals of the model parameters in a 2×2 binary crossover trial. The point estimates are the middle points of the associated confidence intervals

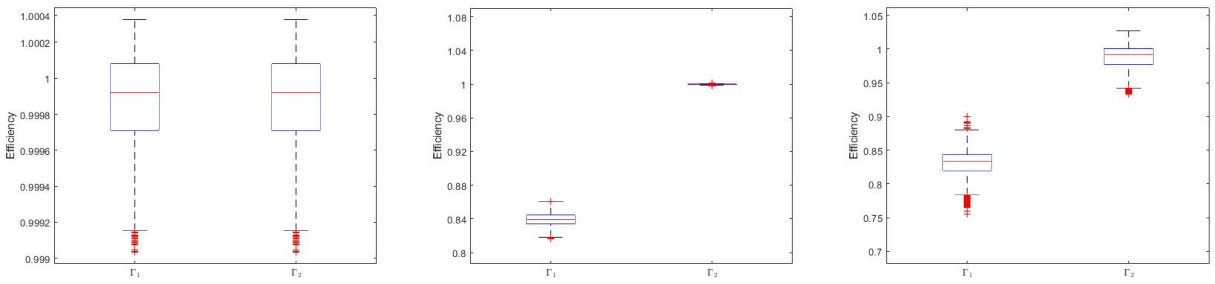
Model	μ	β	τ	ρ
NC	[0.2997, 1.1253]	[-0.5600, 0.2012]	[-0.0572, 0.3238]	·
WC	[0.2976, 1.1364]	[-0.5652, 0.1952]	[-0.1924, 0.6464]	[-0.5441, 0.9141]

LODs for the binary 2×2 trial under scenarios ID1, ID2, ID3, CS1, CS2 and CS3 are computed based the point estimate $\widehat{\boldsymbol{\theta}}$ reported in Table 1. The parameter space to compute the efficiencies is made up the Cartesian product of the interval estimates of the model parameters (given in Table 1). The optimal proportions are reported for the following sequence of treatments: $\{AB, AA, BA, BB\}$.

Scenario ID1: The optimal proportions are obtained as $\mathbf{p}^* = (0.2513, 0.2601, 0.2486, 0.2400)'$. Thus, LOD ζ^* is close to $D_2^{(2)}$. From Figure 1(a), it can be observed that the performances of ζ^*, $D_1^{(2)}$ and $D_2^{(2)}$ are similar. For normal responses, $D_2^{(2)}$ is an optimal design [see Laska and Meisner (1985)].

Scenario ID2: LOD consists of the optimal proportions $\mathbf{p}^* = (0.2436, 0.2633, 0.2514, 0.2418)'$. Design $D_2^{(2)}$ is as efficient as ζ^* whereas $D_1^{(2)}$ performs worst (see Figure 1(b)). Design $D_2^{(2)}$ is an optimal design for normal responses.

Scenario ID3: The vector of optimal proportions is $\mathbf{p}^* = (0.5070, 0, 0, 0.4930)'$. Observing Figure 1(c), it can be concluded that LOD ζ^* is slightly better than $D_2^{(2)}$ since the median efficiency of $D_2^{(2)}$ compared with ζ^* is less than 1. The performance of $D_1^{(2)}$ is worst.



(a) **(b)** **(c)**

Figure 1: Binary 2×2 crossover trials with independent correlation structure. The efficiencies of design $D^{(2)}$ when compared to $D_1^{(2)}$ and $D_2^{(2)}$ are denoted by "Γ_1" and "Γ_2" respectively and given as box–plots. The red line indicates the median and the red dots the outliers. (a) Scenario ID1 (b) Scenario ID2 (c) Scenario ID3

Scenario CS1: Optimal proportions assigned by LOD ζ^* are $\mathbf{p}^* = (0.5011, 0, 0.4989, 0)'$. LOD is very close to $D_1^{(2)}$ which is optimal for normal responses. From the efficiency box–plots (see Figure 2 (a)) it is observed that ζ^* and $D_1^{(2)}$ are equally efficient. The performance of $D_2^{(2)}$ is not satisfactory.

Scenario CS2: LOD ζ^* assigns the proportions $\mathbf{p}^* = (0.2435, 0.2632, 0.2515, 0.2419)'$. LOD is very similar to $D_2^{(2)}$. The performance of ζ^* is similar to $D_2^{(2)}$ whereas $D_1^{(2)}$ perform poorly (see Figure 2 (b)).

Scenario CS3: Optimal proportions are $\mathbf{p}^* = (0.4763, 0.0319, 0, 0.4919)'$. Thus LOD assigns approximately all the proportions to the sequences AB and BB. The efficiency plot (Figure 2 (c)) shows that design $D_2^{(2)}$ is as efficient as ζ^*.

In the above three scenarios (CS1, CS2 and CS3) the correlation parameter α is assumed to take value 0.1. We have repeated the above exercise with $\alpha = 0.4$ and computed the efficiencies. The efficiency plots are depicted in Figure 2 (d), (e) and (f) for scenarios CS1,

CS2 and CS3 respectively. From these plots it is observed that the ranking of designs based on the efficiency remain unchanged for the higher correlation value.

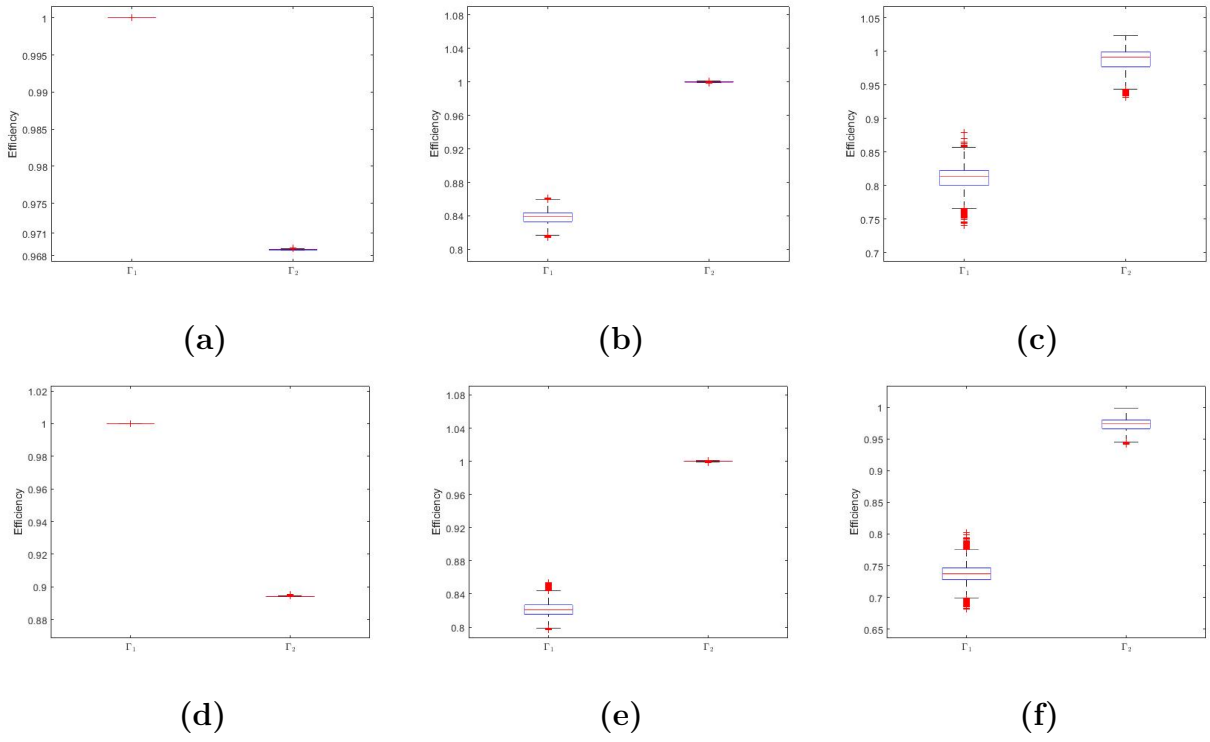


Figure 2: Binary 2×2 crossover trials with CS correlation structure. The efficiencies of design $D^{(2)}$ when compared to $D_1^{(2)}$ and $D_2^{(2)}$ are denoted by "Γ_1" and "Γ_2" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario CS1 with $\alpha = 0.1$ (b) Scenario CS2 with $\alpha = 0.1$ (c) Scenario CS3 with $\alpha = 0.1$ (d) Scenario CS1 with $\alpha = 0.4$ (e) Scenario CS2 with $\alpha = 0.4$ (f) Scenario CS3 with $\alpha = 0.4$

3.4.2. Three periods two treatment (3×2) crossover trials

The reparameterized version of model (1) for a 3×2 crossover trial is written as

$$logit(\mu_{ij}) = \mu + \beta_1 P_1 + \beta_2 P_2 + \tau \Phi_{d(i,j)} + \rho \Phi_{d(i-1,j)},$$

where where (P_1, P_2) takes values (0,0), (1,0), and (0,1) for the period 1, 2, and 3 respectively.

For the estimation of the confidence intervals we used the data set given in Example 3 of Morrey (1989). The estimated confidence intervals and the point estimates are presented in Table 2. The optimal proportions are reported in the following sequences of treatments: $\{ABB, ABA, AAB, BAA, BAB, BBA, AAA, BBB\}$. LODs are calculated based on the point estimates of the parameters reported in 2. In the computations of efficiency values, the parameter space is made up the Cartesian product of the confidence intervals of the parameters given in Table 2.

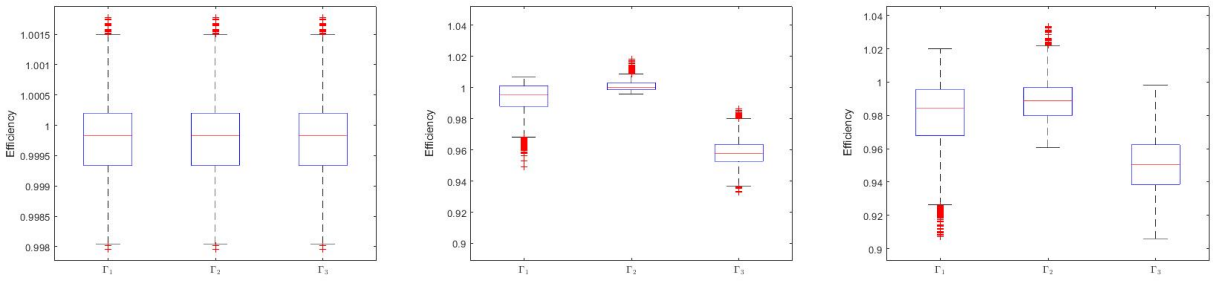
Table 2: Estimated 95% confidence intervals of the model parameters in a 3×2 binary crossover trial. The point estimates are the middle points of the associated confidence intervals

Correlation	Model	ν	β_1	β_2	τ
CS	NC	[-0.8185, 0.4045]	[-0.6396, 1.0616]	[-1.1237, 0.4717]	[0.1021, 0.7959]
	WC	[-0.8210, 0.3978]	[-0.5991, 1.0233]	[-1.3311, 0.4557]	[0.1178, 0.8488]
AR	NC	[-0.8231, 0.4019]	[-0.6334, 1.0620]	[-1.1162, 0.4764]	[0.0722, 0.7814]
	WC	[-0.8216, 0.3976]	[-0.5984, 1.0244]	[-1.3308, 0.4568]	[0.1175, 0.8505]
		ρ			
CS	NC	·			
	WC	[0.0976, 0.9564]			
AR	NC	·			
	WC	[0.0988, 0.9652]			

Scenario ID1: When there is no carryover effect, LOD ζ^* assigns the optimal proportions $\mathbf{p}^* = (0.1288, 0.1154, 0.1289, 0.1203, 0.1356, 0.1202, 0.1155, 0.1354)'$. Thus, ζ^* utilizes all the treatment sequences. Observing the box-plots depicted in Figure 3 (a), it is concluded that ζ^* is as efficient as $D_i^{(3)}$, for $i = 1, 2, 3$.

Scenario ID2: The vector of the optimal proportions is $\mathbf{p}^* = (0.3716, 0, 0.0428, 0.3398, 0.0791, 0, 0.0751, 0.0916)'$. More than 70% observations are assigned the sequence ABB and its dual. In terms of efficiency, design $D_2^{(3)}$ is as efficient as ζ^* followed by $D_1^{(3)}$ (see Figure 3 (b)). Design $D_3^{(3)}$ performs worst.

Scenario ID3: The optimal proportions are $\mathbf{p}^* = (0, 0.2558, 0, 0.2458, 0, 0.2549, 0.2435, 0)'$. In this case, the conclusion is same as in scenario ID2 (see Figure 3 (c)).



(a) **(b)** **(c)**

Figure 3: Binary 3×2 crossover trials with independent correlation structure. The efficiencies of design $\zeta^* = D^{(3)}$ when compared to $D_1^{(3)}$, $D_2^{(3)}$ and $D_3^{(3)}$ are denoted by "Γ_1", "Γ_2" and "Γ_3" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario ID1 (b) Scenario ID2 (c) Scenario ID3

Scenario CS1: LOD ζ^* chooses the treatment sequences with weights $\mathbf{p}^* = (0.0319, 0.4553, 0, 0, 0.4980, 0.0145, 0, 0)'$. Thus, more than 95% of subjects are assigned to the sequence ABA and its dual BAB. In terms of efficiency, ζ^* is as efficient as $D_3^{(3)}$ (less wider spread of the box–plot) followed by $D_1^{(3)}$ and $D_2^{(3)}$ (see Figure 4 (a)).

Scenario CS2: The optimal proportions are $\mathbf{p}^* = (0.3344, 0, 0.1891, 0.3588, 0, 0.1177, 0, 0)'$. Thus, LOD is positively supported only on the treatment sequences ABB, ABA and their duals BAA and BAB with more than 68% proportion only to ABB and its dual. For normal responses, optimal design equally assigns subjects to ABB and its dual. From Figure 4 (b), it is observed that $D_2^{(3)}$ is best in terms of the efficiency closely followed by $D_1^{(3)}$. Design $D_3^{(3)}$ performs worst.

Scenario CS3: LOD ζ^* is consist of the optimal proportions $\mathbf{p}^* = (0.4219, 0.0845, 0, 0.4441, 0, 0.0223, 0, 0.0272)'$. Thus ζ^* assigns more than 85% subjects to the sequence ABB and its dual. The efficiency plot (Figure 4 (c)) shows that only $D_1^{(3)}$ has satisfactory performance.

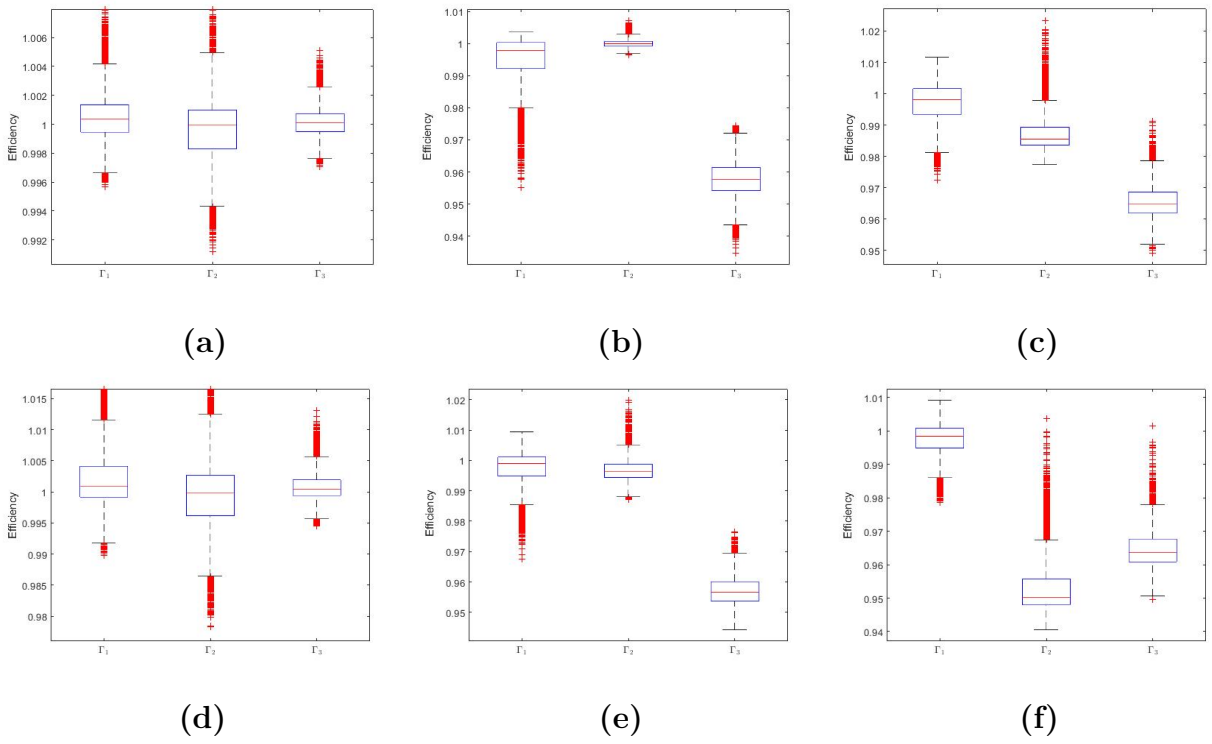


Figure 4: Binary 3×2 crossover trials with CS correlation structure. The efficiencies of design $\zeta^* = D^{(3)}$ when compared to $D_1^{(3)}$, $D_2^{(3)}$ and $D_3^{(3)}$ are denoted by "Γ_1", "Γ_2" and "Γ_3" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario CS1 with $\alpha = 0.1$ (b) Scenario CS2 with $\alpha = 0.1$ (c) Scenario CS3 with $\alpha = 0.1$ (d) Scenario CS1 with $\alpha = 0.4$ (e) Scenario CS2 with $\alpha = 0.4$ (f) Scenario CS3 with $\alpha = 0.4$

The above three scenarios (CS1, CS2 and CS3) are done based on the correlation

parameter $\alpha = 0.1$. We have repeated the above exercise with $\alpha = 0.4$ and computed the efficiencies. The efficiency plots are depicted in Figure 4 (d), (e) and (f) for scenarios CS1, CS2 and CS3 respectively. From these plots it is observed that the ranking of designs based on the efficiency remain unchanged for the higher correlation expect in scenario CS3. In Scenario CS3 an increase in α worsen the the performance of $D_2^{(3)}$.

Scenario AR1: In this case LOD utilizes only two treatment sequences ABA and BAB with approximately equal proportion of subjects. A design with equal proportions of subjects in ABA and BAB is optimal for normal responses. The efficiencies of all designs $D_i^{(3)}$, $i = 1, 2, 3$ compared with LOD are less than 1 (see Figure 5 (a)). Thus, the performances of any of $D_i^{(3)}$'s are not satisfactory.

Scenario AR2: Optimal proportions are obtained as $\mathbf{p}^* = (0.3922, 0, 0.1012, 0.4153, 0.0229, 0, 0, 0.0684)'$. LOD ζ^* assigns more than 80% subjects to the sequence ABB and its dual. Design $D_2^{(3)}$ is comparably as efficient as ζ^* followed by $D_1^{(3)}$ (see Figure 5 (b)). The performance of design $D_3^{(3)}$ is not satisfactory.

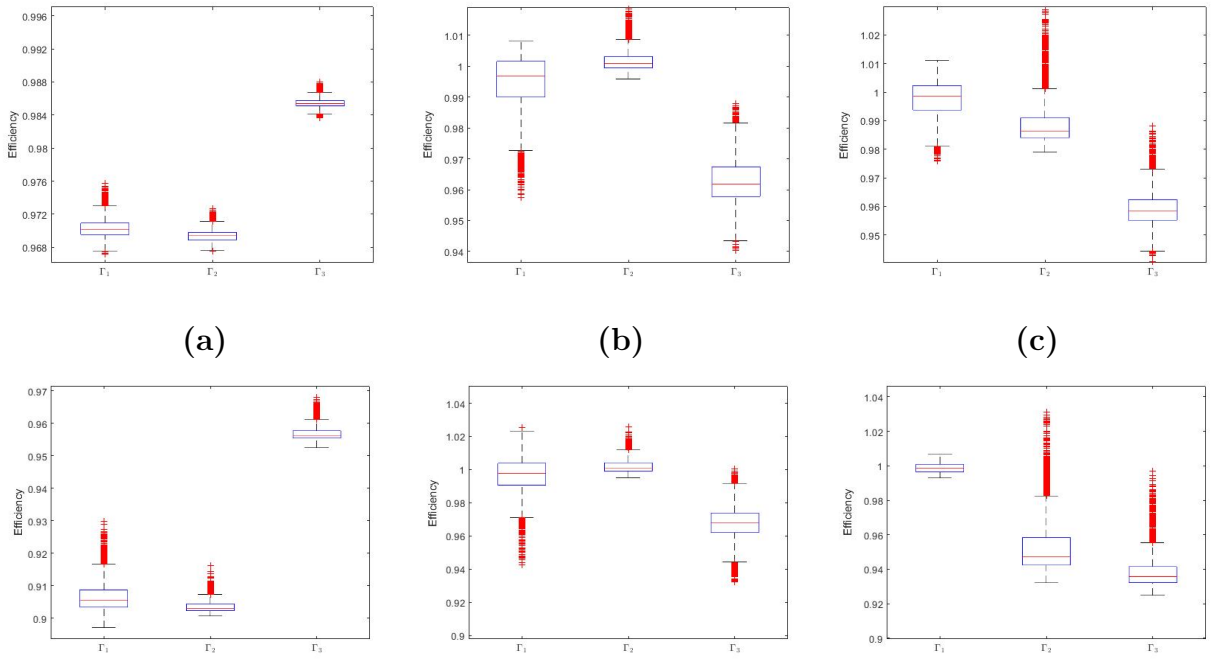


Figure 5: Binary 3×2 crossover trials with AR correlation structure. The efficiencies of design $\zeta^* = D^{(3)}$ when compared to $D_1^{(3)}$, $D_2^{(3)}$ and $D_3^{(3)}$ are denoted by "Γ_1", "Γ_2" and "Γ_3" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario AR1 with $\alpha = 0.1$ (b) Scenario AR2 with $\alpha = 0.1$ (c) Scenario AR3 with $\alpha = 0.1$ (d) Scenario AR1 with $\alpha = 0.4$ (e) Scenario AR2 with $\alpha = 0.4$ (f) Scenario AR3 with $\alpha = 0.4$

Scenario AR3: LOD ζ^* is consist of the optimal proportions $\mathbf{p}^* = (0.4663, 0.0370, 0, 0.4349, 0,$

$0.0217, 0, 0.0401)'$. LOD assigns more than 90% subjects to the sequence ABB and its dual BAA. Efficiency plots (see Figure 5 (c)) shows that only $D_1^{(3)}$ is as efficient as ζ^*.

When $\alpha = 0.4$, the efficiency plots are depicted in Figure 5 (d), (e) and (f) for scenarios AR1, AR2 and AR3 respectively. It is observed that the efficiency wise ranking of designs remain unchanged.

3.4.3. Four periods two treatment (4×2) crossover trials

We analyse the two treatment double blinded crossover data reported in McKnight and Van Den Eeden (1993). The study was designed to examine whether aspartame causes headaches in subjects who believe they experience aspartame-induced headaches. The run-in period was 7 days followed by a wash-out day repeated for 4 periods. Three doses per day of Both aspartame (A) 30 $mg/kg/day$, and placebo (B) were given to the subjects. There were four possible ordering of the treatments ($ABAB$, $ABBA$, $BABA$, $BAAB$). The response y takes values 0 if the number of days with headache is less than 2 and is equal to 1 if the number of days with headache is greater than or equal to 2.After removing the dropouts, the data for 21 subjects is given in Table 3.

The reparameterized version of model (1) for a 4×2 crossover trial is written as

$$logit(\mu_{ij}) = \mu + \beta_1 P_1 + \beta_2 P_2 + \beta_3 P_3 + \tau \Phi_{d(i,j)} + \rho \Phi_{d(i-1,j)},$$

where where (P_1, P_2, P_3) takes values (0,0,0), (1,0,0), (0,1,0) and (0,0,1) for the period 1, 2, 3 and 4 respectively.

The estimated confidence intervals and the point estimates based on the data from Table 3 are presented in Table 4. LODs are calculated based on the point estimates of the parameters reported in 4. Optimal proportions ($\mathbf{p}^*$) for all scenarios are reported in Table 5. In the computation of the efficiency, the parameter space is made of the Cartesian products of the confidence intervals of the parameters given in Table 4.

Table 3: Treatment order and corresponding Response of each period

Treatment order	period 1	period 2	period 3	period 4
$ABAB$	0	1	0	0
$ABAB$	1	1	1	1
$ABAB$	0	0	0	0
$ABAB$	1	1	1	1
$ABAB$	1	0	1	0
$ABBA$	0	1	0	0
$ABBA$	1	1	1	1
$ABBA$	0	0	1	0
$ABBA$	0	0	0	0
$ABBA$	1	1	1	1
$ABBA$	0	0	0	0
$BABA$	0	1	1	1
$BABA$	0	0	0	0
$BABA$	1	0	0	0
$BABA$	1	0	0	1
$BABA$	0	0	0	1
$BABA$	1	1	0	1
$BAAB$	0	0	0	0
$BAAB$	0	0	0	0
$BAAB$	0	1	0	0
$BAAB$	1	1	0	0

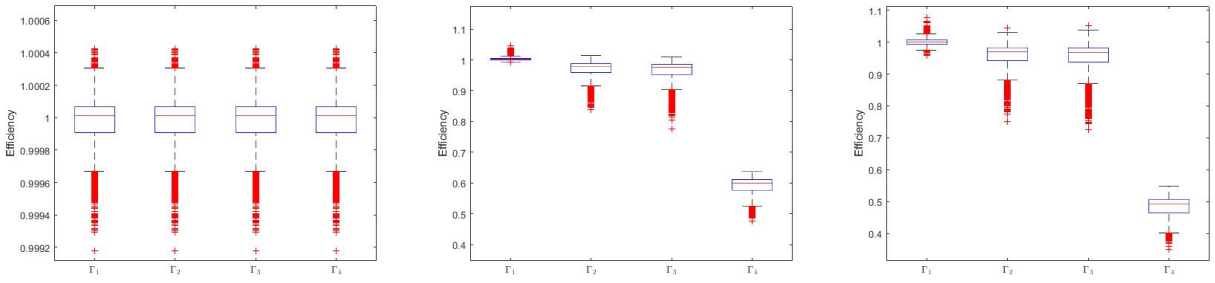
Table 4: Estimated 95% confidence intervals of the model parameters in a 4×2 binary crossover trial. The point estimates are the middle points of the associated confidence intervals

Correlation	Model	ν	β_1	β_2	β_3
CS	NC	[-1.160, 0.570]	[-0.683, 1.453]	[-1.381 , 0.615]	[-1.050, 0.640]
	WC	[-1.129, 0.623]	[-0.684, 1.492]	[-1.518, 0.466]	[-1.133, 0.603]
AR	NC	[-1.161, 0.563]	[-0.685, 1.455]	[-1.374, 0.618]	[-1.057, 0.641]
	WC	[-1.141, 0.615]	[-0.671, 1.493]	[-1.498, 0.462]	[-1.117, 0.615]
		τ	ρ		
CS	NC	[-0.227, 0.447]	·		
	WC	[-0.566, 0.280]	[-1.012, 0.045]		
AR	NC	[-0.242, 0.498]	·		
	WC	[-0.638, 0.318]	[-1.047, 0.109]		

Scenario ID1: In this case LOD ζ^* utilizes all the treatment sequences except $AAAA$ and its dual (see Table 5). Observing Figure 6 (a) it is concluded that all designs are equally efficient.

Scenario ID2: LOD ζ^* assigns more than 80% observations to the sequences $AABB$, $AABA$ and their duals. Design $D_1^{(4)}$ is as efficient as ζ^* whereas $D_4^{(4)}$ perform worst (see Figure 6 (b)).

Scenario ID3: More than 85% observations are assigned to the sequences $BAAB$ and $ABBB$. Design $D_1^{(4)}$ is as efficient as LOD (see Figure 6 (c)). Performance of $D_4^{(4)}$ is worst.



(a) **(b)** **(c)**

Figure 6: Binary 4×2 crossover trials with independent correlation structure. The efficiencies of design $\zeta^* = D^{(4)}$ when compared to $D_1^{(4)}$, $D_2^{(4)}$, $D_3^{(4)}$ and $D_4^{(4)}$ are denoted by "Γ_1", "Γ_2", "Γ_3" and "Γ_4" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario ID1 (b) Scenario ID2 (c) Scenario ID3

Scenario CS1: LOD ζ^* equally assigns more than 94% observations to the sequence $ABBA$ and its dual. When $\alpha = 0.4$, then also, LOD utilizes $ABBA$ and its dual with more 96% observations assigned to them. Design $D_3^{(4)}$ is as efficient as ζ^* (see Figures 7 (a) and (d)).

Scenario CS2: In this case LOD assigns more than 90% observations to the sequences $AABB$, $ABAB$ and their duals. LOD is not affected by change in α from 0.1 to 0.4. Design $D_1^{(4)}$ is most efficient when compared to others with respect to LOD (see Figure 7 (b) and (e)). Note that $D_1^{(4)}$ is an optimal design for normal responses.

Scenario CS3: LOD ζ^* utilizes only the following sequences $\{AABB, BAAB, ABBB, BAAA\}$. SImilar to scenario CS2, in this case $D_1^{(4)}$ is as efficient as ζ^* (see Figure 7 (c) and (f)).

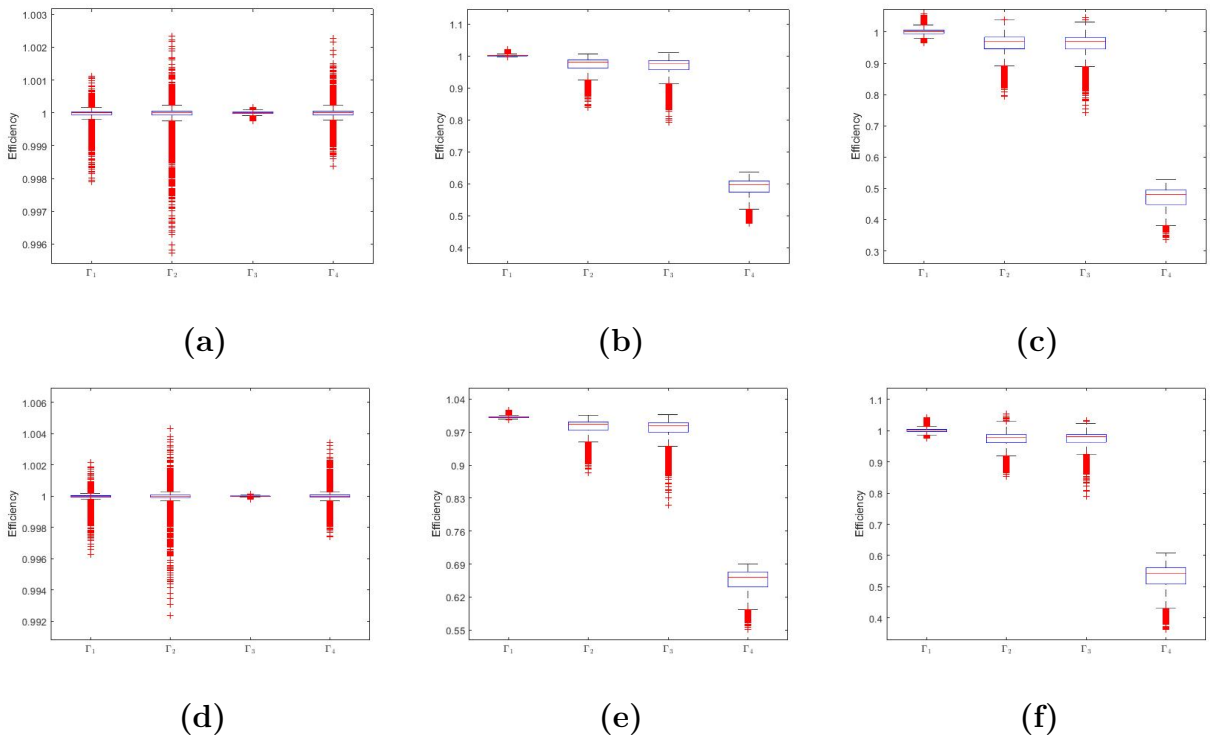


Figure 7: Binary 4×2 crossover trials with CS structure. The efficiencies of design $\zeta^* = D^{(4)}$ when compared to $D_1^{(4)}$, $D_2^{(4)}$, $D_3^{(4)}$ and $D_4^{(4)}$ are denoted by "Γ_1", "Γ_2", "Γ_3" and "Γ_4" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario CS1 with $\alpha = 0.1$ (b) Scenario CS2 with $\alpha = 0.1$ (c) Scenario CS3 with $\alpha = 0.1$ (d) Scenario CS1 with $\alpha = 0.4$ (e) Scenario CS2 with $\alpha = 0.4$ (f) Scenario CS3 with $\alpha = 0.4$

Scenario AR1: LOD assigns approximately equal observations only to the sequence $ABAB$ and its dual. LOD is as efficient as $D_4^{(4)}$ (see Figure 8 (a) and (d)) which is an optimal design for normal responses.

Scenario AR2: When $\alpha = 0.1$, LOD assigns more than 80% observations to the sequences $AABB$, $BABB$ and their duals. However, when $\alpha = 0.4$, ζ^* utilizes $AABB$, $ABBA$ and

their duals with approximately all the observations assigned to them. Design $D_1^{(4)}$ is as efficient as ζ^* (see Figure 8 (b) and (e)).

Scenario AR3: Approximately all the observations assigned to $AABB$, $BABB$ and their duals. Design $D_1^{(4)}$ is as efficient as ζ^* (see Figure 8 (c) and (f)).

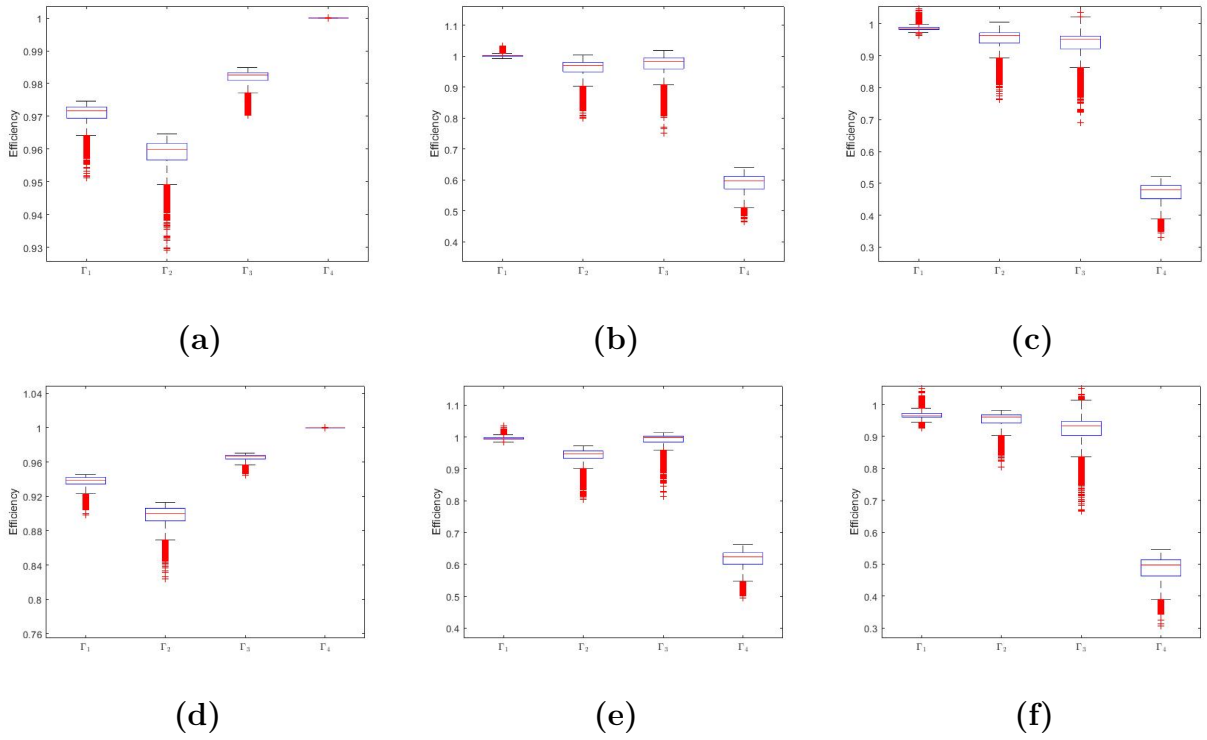


Figure 8: Binary 4×2 crossover trials with AR structure. The efficiencies of design $\zeta^* = D^{(4)}$ when compared to $D_1^{(4)}$, $D_2^{(4)}$, $D_3^{(4)}$ and $D_4^{(4)}$ are denoted by "Γ_1", "Γ_2", "Γ_3" and "Γ_4" respectively and given as boxplots. The red line indicates the median and the red dots the outliers. (a) Scenario AR1 with $\alpha = 0.1$ (b) Scenario AR2 with $\alpha = 0.1$ (c) Scenario AR3 with $\alpha = 0.1$ (d) Scenario AR1 with $\alpha = 0.4$ (e) Scenario AR2 with $\alpha = 0.4$ (f) Scenario AR3 with $\alpha = 0.4$

Table 5: Optimal proportion ($\mathbf{p}^*$) for 4×2 crossover trials

				$\alpha = 0.1$					
Sequence	ID1	ID2	ID3	CS1	CS2	CS3	AR1	AR2	AR3
$AABB$	0.0730	0.2251	0.0219	0.0081	0.3530	0.0614	0	0.2096	0.2015
$BBAA$	0.0698	0.1363	0	0	0.3415	0	0	0.2427	0.2007
$ABBA$	0.0710	0.0152	0	0.4771	0.0884	0	0	0.1235	0
$BAAB$	0.0717	0	0.4503	0.4786	0	0.4338	0	0	0
$ABAB$	0.0704	0.0168	0	0.0153	0.0930	0	0.4977	0	0
$BABA$	0.0723	0	0	0.0189	0.1240	0	0.5023	0.0021	0
$ABBB$	0.0739	0.0153	0.4153	0	0	0.4302	0	0	0
$BABB$	0.0754	0	0.0310	0	0	0	0	0.2427	0.2772
$BBAB$	0.0726	0.2490	0	0	0	0	0	0	0
$BBBA$	0.0732	0.1027	0.0139	0	0	0	0	0	0
$BAAA$	0.0690	0	0	0	0	0.0744	0	0	0.0290
$ABAA$	0.0679	0.0158	0	0	0	0	0	0.1771	0.2917
$AABA$	0.0702	0.2235	0	0	0	0	0	0.0021	0
$AAAB$	0.0696	0	0.0670	0	0	0	0	0	0
$AAAA$	0	0	0	0	0	0	0	0	0
$BBBB$	0	0	0	0	0	0	0	0	0

	$\alpha = 0.4$					
	CS1	CS2	CS3	AR1	AR2	AR3
$AABB$	0.0072	0.3538	0.0592	0	0.1253	0.1999
$BBAA$	0.0012	0.3423	0	0	0.1119	0.2240
$ABBA$	0.4842	0.0889	0	0	0.3732	0
$BAAB$	0.4857	0	0.3696	0	0.3644	0
$ABAB$	0.0091	0.0918	0	0.4973	0	0
$BABA$	0.0127	0.1232	0	0.5027	0	0
$ABBB$	0	0	0.4311	0	0	0
$BABB$	0	0	0	0	0	0.2838
$BBAB$	0	0	0	0	0.0251	0
$BBBA$	0	0	0	0	0	0
$BAAA$	0	0	0.1400	0	0	0
$ABAA$	0	0	0	0	0	0.2923
$AABA$	0	0	0	0	0	0
$AAAB$	0	0	0	0	0	0
$AAAA$	0	0	0	0	0	0
$BBBB$	0	0	0	0	0	0

3.5. An equivalence theorem

For the linear regression models equivalence theorems were developed by Whittle (1973) and Kiefer (1974). For the GLMs, equivalence theorem for the Bayesian setup was discussed in Chaloner and Larntz (1989). Optimality of min–max crossover designs for the binary response model was verified by an equivalence theorem discussed in Singh *et al.* (2020). Singh and Mukhopadhyay (2016) provided an equivalence theorem to confirm the optimality of numerically obtained crossover designs for the GLMs. In this section we provide an equivalence theorem which can be utilized to verify the optimality of the LODs obtained in this article.

Let the design space be defined as a unit simplex $\boldsymbol{\Xi} = \{\mathbf{p}' = (p_{\omega_1}, \ldots, p_{\omega_s}) : \sum_{i=1}^{s} p_{\omega_i} = 1, \text{ and } 0 \leq p_{\omega_i} \leq 1\}$. Note that $Var_{\zeta}(\widehat{\boldsymbol{\theta}})$ given in (5) depends on $\mathbf{p}$ via ζ. Therefore, $Var_{\zeta}(\widehat{\boldsymbol{\theta}})$ can be represented as $Var_{\zeta(\mathbf{p})}(\widehat{\boldsymbol{\tau}})$. Suppose the interest is in estimating a estimable linear function of the parameters say $\lambda = L'\boldsymbol{\theta}$, where L is a $m \times s$ matrix, m is the length of the vector $\boldsymbol{\theta}$, and $s \leq m$. The information matrix of λ is given by $C = (L'Var_{\zeta(\mathbf{p})}(\widehat{\boldsymbol{\theta}})L)^{-1}$.

Theorem 1: A locally optimal design $\zeta^* \equiv \zeta(\mathbf{p}^*)$ at $\boldsymbol{\theta} = \boldsymbol{\theta}_0$ obtained as

$$\zeta^* = \min_{\mathbf{p} \in \boldsymbol{\Xi}} \log(Det(L'Var_{\zeta(\boldsymbol{p})}(\widehat{\boldsymbol{\theta}})L))$$

satisfies the condition

$$trace\{Var_{\zeta^*}(\widehat{\boldsymbol{\theta}})LCL'Var_{\zeta^*}(\widehat{\boldsymbol{\theta}})(Var_{\zeta_\omega}(\widehat{\boldsymbol{\theta}}))^{-1}\} \leq s, \quad \text{for all } \omega \in \Omega, \tag{9}$$

where $Var_{\zeta_\omega}(\widehat{\boldsymbol{\theta}})$ is the variance with respect to the design ζ_ω having unit mass at single treatment sequence ω. Equality holds in (9) if the treatment sequence ω is included in ζ^* with positive probability.

The proof of Theorem 1 follows from Theorem 1 of Pettersson, H. (2005) and Theorem 2.1 of Müller, C. H. and Pázman, A. (1998).

4. Summary

Crossover designs for two treatments and binary responses are determined for $p = 2, 3, 4$. Since these designs depend on the model parameters, various intervals estimated from the data sets based on the historical studies are considered and LODs are found in each case. Within subject correlation is modelled using working correlation matrix assuming: independent, compound symmetric and auto–regressive structures. LODs are compared with designs optimal for normal responses in each case.

In Table 6 we list designs optimal for normal responses which are as efficient as locally optimal designs obtained in this article under various scenarios.

Table 6: Efficient designs

Periods	ID1	ID2	ID3	CS1	CS2	CS3	AR1	AR2	AR3
2	$\{D_i^{(2)} : i = 1, 2\}$	$D_2^{(2)}$	$D_2^{(2)}$	$D_1^{(2)}$	$D_2^{(2)}$	$D_2^{(2)}$			
3	$\{D_i^{(3)} : i = 1, 2, 3\}$	$D_2^{(3)}$	$D_2^{(3)}$	$\{D_i^{(3)} : i = 1, 2\}$	$D_2^{(3)}$	$D_1^{(3)}$	$D_3^{(3)}$	$D_2^{(3)}$	$D_1^{(3)}$
4	$\{D_i^{(4)} : i = 1, \ldots, 4\}$	$D_1^{(4)}$	$D_1^{(4)}$	$\{D_i^{(4)} : i = 1, 2, 3, 4\}$	$D_1^{(4)}$	$D_1^{(4)}$	$D_4^{(4)}$	$D_4^{(4)}$	$D_1^{(4)}$

In conclusion it clear from the numerical studies that the results in the logistic regression case are quite similar to the available results in the continuous case in most of the scenarios.

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