

Optimal treatment allocations for dose-ranging trials with binary outcomes

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Summary

We consider the construction of optimal designs for dose-ranging trials with multiple periods, where the outcome of the trial is considered to be a binary response. The carry-over effect of each dose from one period to the next is assumed to be proportional to the direct effect. We show that for a logistic regression model the efficiency of an optimal design is substantially greater than a balanced design. The optimal designs are also shown to be robust to misspecification of the value of the parameters.

Key Words: cross-over design; optimal design; dose-ranging trials; binary outcomes; proportional carry-over effect.

1 Introduction

The drug development process has seen a number of changes over the past 30 years. Many of these changes that are pertinent to the design of studies have been oriented to

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the development of more efficient design processes. From a pharmacological perspective, a major improvement in efficiency has been afforded by the integration of advanced statistical methodology into pharmacokinetic studies. Traditionally population pharmacokinetic studies were based on intensive sampling strategies, where the same number of blood samples (often greater than 12) were taken from each patient. Since the introduction of non-linear mixed effects modelling in the early 1980s (see for example Sheiner and Beal¹), unbalanced, ‘sparse’ designs have become common practice in population pharmacokinetic studies. For example, the number and timing of blood samples can vary from subject to subject, with some subjects providing few samples. In contrast to the flexibility now afforded to population pharmacokinetic (PK) studies, the design of cross-over trials with multiple treatment periods and treatment sequences are typically limited to balanced designs, where all individuals receive all treatments and block sequences are designed so that all treatments follow all other treatments at some stage, that is balanced with respect to carry-over effects. Recent research into the design of cross-over trials for PK studies can be found in Jones and Wang², Jones *et al.*³ and Jones and Wang⁴. They show that balanced designs are optimal for trials that have no carry-over effect, and for two treatments only. It is likely that sparse period and unbalanced designs will provide an efficient means in which to test the efficacy of a drug without the need for time consuming and expensive completely balanced designs. The aim of this paper is to assess different approaches to optimising treatment allocation in parallel and cross-over designed studies.

Section 2 introduces the model for a hypothetical drug with a binary response, and gives the information matrix for a cross-over design with two periods (which can be simplified for the single period case). Section 3 compares optimal and balanced parallel

designs (where each subject receives only one dose) in terms of their efficiency, and also considers optimal dose levels for a balanced allocation. In Section 4, another comparison of optimal and balanced allocations is given, this time for cross-over designs, where two doses are given to each subject. This is considered for two cases: where the amount of carry-over effect from one period to the next is known, and again when it is unknown. The sensitivity of these designs is also assessed. In Section 5, another comparison of optimal and balanced designs is carried out for hybrid designs, in which each subject receives either one or two doses. Sensitivity analyses are also presented for these designs. A final discussion of these designs is given in Section 6.

2 Model and information matrix

Consider a fictive drug, which elicits an all or nothing response: success or failure. For the purposes of this study the fictive drug is based on the triptan like 5-HT_{1D} agonists for the treatment of migraine (see for example Nestorov *et al.*⁵). In these scenarios it is assumed that the patients' response can be described by a binary outcome defined by treatment success (1) or failure (0) corresponding to alleviation or persistence of the migraine headache, respectively. We have assumed that there will be four dose levels: 0, 5, 10 and 20 units, each with a fixed probability of producing a success, dependent on the size of the dose(s) given. We aim to find the optimum allocation of dosage sequences (with a maximum of 2 doses per subject), and compare it to a balanced allocation.

The variation in the data arising from a cross-over trial is usually explained by an analysis-of-variance (ANOVA) model such as

$$Y_{kl} = \beta + \theta_{d[k,l]} + \lambda_{d[k,l-1]} + \rho_l + s_k + \varepsilon_{kl} \quad (1)$$

where Y_{kl} is the response of subject k in period l to dose (treatment) $d[k,l]$. $\theta_{d[k,l]}$ is the effect of dose $d[k,l]$, $\lambda_{d[k,l-1]}$ is the carry-over effect of the dose given in period $l-1$, ρ_l is the effect of period l , s_k is the effect of the k^{th} subject, β is the overall mean and ε_{kl} is the error term. It can be convenient to consider the carry-over effect of a dose as directly proportional to its direct effect, in which case $\lambda_{d[k,l-1]}$ would be written as $\alpha\theta_{d[k,l-1]}$. Another term that may be included in such a model is the interaction between subject and period effects.

In our case, we instead consider the response to be the overall performance of a particular sequence of doses. The subject and period effects are ignored. A number of references (including Robinson and Jewell⁶ and Yano *et al*⁷) support this model by showing that the inclusion of subject effects do not necessarily yield more precise estimates of the parameters of primary interest in logistic regression. We model this response after a sequence of two doses as a logistic regression (see Dobson⁸):

$$\text{logit}(\pi_{ij}) = \beta + \theta d_j + \alpha \theta d_i \quad (2)$$

where π_{ij} is the probability of success of dose d_i (in the first period) followed by dose d_j (in the second period). The four dose levels in our problem are $d_1 = 0$ units, $d_2 = 5$ units, $d_3 = 10$ units and $d_4 = 20$ units. In this model, the residual effect of a particular dose is considered to be directly proportional to its direct effect (see Kempton *et al.*⁹). The model parameters are β , θ and α where β is the intercept (zero dose or placebo), θ is the treatment effect of the drug and α is the proportionality factor for the carry-over effect.

For example, if a subject receives 20 units of the drug (d_4) followed by 5 units (d_2), we can model the probability of success (π_{42}) by

$$\begin{aligned}\text{logit}(\pi_{42}) &= \beta + \theta d_2 + \alpha \theta d_4 \\ &= \beta + 5\theta + 20\alpha\theta\end{aligned}\tag{3}$$

Although the carry over effect can be assumed to be negligible for pharmacokinetic studies if a sufficient washout period is included (as per Senn and Ezzet¹⁰), the same assumption is not necessarily valid for pharmacodynamic endpoints where changes in receptor availability, alteration in short and intermediate term homeostatic responses, and the potential for long term remodelling are plausible. The response of a subject after a single dose (with no previous doses) is also modelled by a logistic regression:

$$\text{logit}(\pi_i) = \beta + \theta d_i\tag{4}$$

where similarly π_i is the probability of success of dose d_i alone.

For each dose sequence (for example, dose d_i followed by dose d_j), observations are taken from the n_{ij} subjects, and the number of successes, r_{ij} , is recorded. The log-likelihood function is

$$\ell_2(\boldsymbol{\pi}_2; \mathbf{r}_2) = \sum_{i=1}^4 \sum_{j=1}^4 \left[r_{ij} \log\left(\frac{\pi_{ij}}{1 - \pi_{ij}}\right) + n_{ij} \log(1 - \pi_{ij}) + \log\left(\frac{n_{ij}}{r_{ij}}\right) \right]\tag{5}$$

where $\boldsymbol{\pi}_2 = (\pi_{11}, \dots, \pi_{14}, \dots, \pi_{44})$ and $\mathbf{r}_2 = (r_{11}, \dots, r_{14}, \dots, r_{44})$. The total sample size is given by $n = \sum_{i=1}^4 \sum_{j=1}^4 n_{ij}$.

Similarly, the log-likelihood function for a single dose (where we record r_i successes from n_i subjects for dose d_i) is given by

$$\ell_1(\boldsymbol{\pi}_1; \mathbf{r}_1) = \sum_{i=1}^4 \left[r_i \log\left(\frac{\pi_i}{1 - \pi_i}\right) + n_i \log(1 - \pi_i) + \log\left(\frac{n_i}{r_i}\right) \right]\tag{6}$$

where $\boldsymbol{\pi}_1 = (\pi_1, \dots, \pi_4)$ and $\mathbf{r}_1 = (r_1, \dots, r_4)$.

This gives rise to the $p \times p$ information matrix \mathbf{I} with elements

$$I_{ab} = \text{E} \left[-\frac{\partial^2 \ell_1}{\partial \gamma_a \partial \gamma_b} \right] + \text{E} \left[-\frac{\partial^2 \ell_2}{\partial \gamma_a \partial \gamma_b} \right], \quad a = 1, \dots, p; \quad b = 1, \dots, p \quad (7)$$

where the γ_a are the elements of $\boldsymbol{\gamma}$, the vector of parameters of interest. For example, if we are interested in estimating β , θ and α (as in a full cross-over design), then $\boldsymbol{\gamma} = (\beta, \theta, \alpha)^T$ and $p = 3$. Note that this includes the information for the $n_i = \sum_{j=1}^4 n_{ij}$ subjects who receive dose d_i followed by another dose, as well as those subjects only receiving one dose.

The optimality criterion we use to judge designs is D-optimality which is commonly used in optimal design for pharmacological studies. The D-optimal design will be the set of n_i and/or n_{ij} such that $|\mathbf{I}|$ is a maximum.

3 Parallel designs

3.1.1 Optimal and balanced parallel designs

Parallel design are those with only one dose per subject and so the model is simply the logistic model given in equation (4), as there are only single doses. The information matrix is given by the first term of equation (7), which is:

$$\begin{aligned} \mathbf{I} &= -\text{E} \begin{bmatrix} \frac{\partial^2 \ell_1}{\partial \beta^2} & \frac{\partial^2 \ell_1}{\partial \beta \partial \theta} \\ \frac{\partial^2 \ell_1}{\partial \theta \partial \beta} & \frac{\partial^2 \ell_1}{\partial \theta^2} \end{bmatrix} \\ &= \sum_{i=1}^4 \begin{bmatrix} n_i \pi_i (1 - \pi_i) & n_i d_i \pi_i (1 - \pi_i) \\ n_i d_i \pi_i (1 - \pi_i) & n_i d_i^2 \pi_i (1 - \pi_i) \end{bmatrix} \end{aligned} \quad (8)$$

where, $\pi_i = \frac{e^{\beta+\theta d_i}}{1 + e^{\beta+\theta d_i}}$.

The true values of β and θ are unknown, but are necessary for the calculation of \mathbf{I} . The values of these parameters may be chosen (estimated) from past experience or expert opinion. However, for the purposes of this investigation we selected $\beta = -1$ and $\theta = 0.3$. Later we consider how sensitive the optimal design is to the choice of parameter values.

The optimal parallel design for 96 subjects each receiving one of the four dose levels was found by an exhaustive search of all possible combinations. This optimal design and the balanced design are given in Table 1, along with their respective efficiencies (as described below). (For convenience we have set the number of subjects to be 96, this simplifies matters when dealing with cross-over designs as will be clear in later sections of the paper.) We shall see that this optimal allocation is supported by the optimal dose levels found in section 3.2.

The efficiency of the balanced design, compared to this optimal design, is given by

$\frac{|\mathbf{I}_{\text{par,bal}}|^{1/p}}{|\mathbf{I}_{\text{par,opt}}|^{1/p}} = 0.761$, where $p = 2$, the number of parameters in the model. This indicates

that the balanced design is 76.1% as efficient as the optimal design, that is 31 more treatments are required for the balanced design to provide the same information as the optimal design with 96 treatments.

3.1.2 Optimal and balanced parallel designs, linear dose intervals

We generally view the response in this model as the probability of success, which is non-linearly related to dose. However, it may be preferable to consider $\text{logit}(\pi_i)$ as the

response, which has a simple linear relationship to dose in our model. In this case, it would be more appropriate to use linear dose intervals, rather than those used previously (0, 5, 10, 20). Calculations were repeated using linear dose intervals (0, 5, 10, 15 units), and the results are shown in Table 2. As we see, there is no difference in the optimal design, with only a slight change in efficiency (the balanced design is now 84.1% as efficient as the optimal design). The improvement in efficiency of the balanced design was considered to be due to the closer proximity of the maximum dose level (15 units) to the optimal dose level (10 units), compared to the previous maximum of 20 units. In this light, it can be shown that a balanced allocation of the dose levels of 0, 5, 10 and 14 units will again be more efficient (given these dose levels, the balanced allocation is 85.7% as efficient as the optimal design).

3.2 Optimal dose levels for a balanced parallel design

Optimal dose levels for parallel designs were briefly considered. It is known that for simple logistic models such as the one used for this parallel design, the two optimal design points are given by those which correspond to the probabilities 0.178 and 0.824 (see Minkin¹¹).

We found that the optimal dosing scheme allocated half of the patients to a 0 unit dose, and the other half to a 9.32 unit dose. Note that only two doses are required to provide an optimal design for this model, which supports the optimal design found above, where half of the subjects receive a dose of 0 units, and the other half receive a dose of 10 units.

The logistic curve for this model is shown in Figure 1, with the two optimal doses marked with a circle. The probabilities are calculated by

$$\pi_i = \frac{e^{\beta+\alpha d_i}}{1 + e^{\beta+\alpha d_i}}. \quad (9)$$

These optimal doses do not correspond to the probabilities 0.178 and 0.824 as discussed above, as the lowest possible dose corresponds to a probability of 0.269. If we allow the doses to be negative, we find that the optimal doses do indeed correspond to the probabilities 0.178 and 0.824. We can also see the ‘placebo effect’ from the y -intercept in Figure 1. With these parameter values, a subject still has a 26.9% chance of success even if no active dose is administered.

4 Cross-over designs

4.1.1 Optimal and balanced cross-over designs, α known

Now consider cross-over designs as an alternative to parallel designs, where each subject receives two doses, and the carry-over effect α is assumed to be known. This case is quite artificial and is included as a comparator for the parallel design, where the carry-over effect cannot be estimated. As with the parallel designs, the total number of doses was fixed at 96, that is there are only 48 subjects.

Rather than working with discrete values for n_{ij} , for ease of computation approximate designs were considered, that is calculations were based on the proportion of subjects receiving each dose sequence rather than the number of subjects. Once the optimal approximate design is found, the corresponding exact design is found by multiplying these proportions by the total number of subjects, and rounding to the nearest integer.

The optimal design was found by using simulated annealing in the following algorithm.

1. An initial treatment allocation was chosen, for example a balanced design where each dose is followed by every other dose an equal number of times.
2. The allocations are altered by large amounts at first, accepting a high proportion of ‘bad’ changes, and accepting all ‘good’ changes.
3. As the algorithm progresses, decreasing alterations to the allocations are made, and fewer ‘bad’ changes are accepted.
4. When the size of the alterations becomes sufficiently small, the search is terminated.

Since α is considered in this example to be a fixed constant that is known then the information matrix is 2x2, with one row/column for each parameter of interest.

$$\begin{aligned}
\mathbf{I} &= -\mathbb{E} \begin{bmatrix} \frac{\partial^2 \ell_1}{\partial^2 \beta} & \frac{\partial^2 \ell_1}{\partial \beta \partial \theta} \\ \frac{\partial^2 \ell_1}{\partial \theta \partial \beta} & \frac{\partial^2 \ell_1}{\partial^2 \theta} \end{bmatrix} - \mathbb{E} \begin{bmatrix} \frac{\partial^2 \ell_2}{\partial^2 \beta} & \frac{\partial^2 \ell_2}{\partial \beta \partial \theta} \\ \frac{\partial^2 \ell_2}{\partial \theta \partial \beta} & \frac{\partial^2 \ell_2}{\partial^2 \theta} \end{bmatrix} \\
&= \sum_{i=1}^4 \begin{bmatrix} n_i \pi_i (1 - \pi_i) & n_i d_i \pi_i (1 - \pi_i) \\ n_i d_i \pi_i (1 - \pi_i) & n_i d_i^2 \pi_i (1 - \pi_i) \end{bmatrix} \\
&\quad + \sum_{i=1}^4 \sum_{j=1}^4 \begin{bmatrix} n_{ij} \pi_{ij} (1 - \pi_{ij}) & n_{ij} (d_j + \alpha d_i) \pi_{ij} (1 - \pi_{ij}) \\ n_{ij} (d_j + \alpha d_i) \pi_{ij} (1 - \pi_{ij}) & n_{ij} (d_j + \alpha d_i)^2 \pi_{ij} (1 - \pi_{ij}) \end{bmatrix}
\end{aligned} \tag{10}$$

Since \mathbf{I} is dependent on α , β and θ , it is necessary to specify or know their values in order to evaluate $|\mathbf{I}|$. The same values of the parameters were chosen, namely $\alpha = 0.25$, $\beta = -1$ and $\theta = 0.3$. The degree of sensitivity of the optimal design to these parameter values is investigated later. Assuming we have 48 subjects, and allocating 2 doses to each, the optimal design was determined and is displayed in Table 3.

The value of the objective function for this allocation is $|\mathbf{I}_{\text{cross,opt}}| = 4,756.1$, the same as for the optimal parallel design. This was compared to a balanced design (given in Table 4).

Note that this balanced design has every treatment followed by every other treatment (but not itself) an equal number of times.

For this allocation, $|\mathbf{I}_{\text{cross,bal}}| = 2,349.8$. Note that this is different from the balanced parallel design since the model now introduces a carry-over effect from one period to the next. If the carry-over effect is set to zero (that is if $\alpha = 0$) then $|\mathbf{I}_{\text{cross,bal}}|$ is exactly the same as for the balanced parallel design. The algorithm was run with 10 different starting values and the same design was found each time, demonstrating the consistency of the algorithm.

The efficiency of this balanced design, compared to the optimal design, is given by

$$\frac{|\mathbf{I}_{\text{cross,bal}}|^{1/p}}{|\mathbf{I}_{\text{cross,opt}}|^{1/p}} = 0.703, \text{ where } p = 2. \text{ This means that balanced design is 70.3\% as efficient}$$

as the optimal design when α is known. Hence an additional 41 treatments would be required for a balanced design to provide the same information as the optimal design using only 96 treatments. Given α is a positive fixed constant of known value that yields a carryover effect that is proportional to the dose then the results are not surprising since the effects of the 1st period (dose = 0 units) will not confound the 2nd period.

4.1.2 Optimal and balanced cross-over designs, α unknown

Here we assume that α is an unknown parameter, that is we are now interested in estimating the carry-over effect, which is a situation that is more likely to occur. The

information matrix, \mathbf{I} , now incorporates a row and column corresponding to α , so it is a 3×3 matrix which depends on r_{ij} , the number of successes in the observed data (which is unknown).

To eliminate r_{ij} from \mathbf{I} , a first-order Taylor series approximation of $\text{logit}(\pi_{ij})$ (about $\alpha = \alpha^*$ and $\theta = \theta^*$) was used:

$$\text{logit}(\pi_{ij}) \approx \beta + (d_j + \alpha^* d_i) \theta + \theta^* d_i \alpha - \alpha^* \theta^* d_i. \quad (11)$$

This removes the nonlinearity in α and θ . α^* and θ^* are chosen as the same ‘guesses’ at the actual values of the parameters α and θ .

$$\begin{aligned} \mathbf{I} &= -\text{E} \begin{bmatrix} \frac{\partial^2 \ell_1}{\partial^2 \beta} & \frac{\partial^2 \ell_1}{\partial \beta \partial \theta} & \frac{\partial^2 \ell_1}{\partial \beta \partial \alpha} \\ \frac{\partial^2 \ell_1}{\partial \theta \partial \beta} & \frac{\partial^2 \ell_1}{\partial^2 \theta} & \frac{\partial^2 \ell_1}{\partial \theta \partial \alpha} \\ \frac{\partial^2 \ell_1}{\partial \alpha \partial \beta} & \frac{\partial^2 \ell_1}{\partial \alpha \partial \theta} & \frac{\partial^2 \ell_1}{\partial^2 \alpha} \end{bmatrix} - \text{E} \begin{bmatrix} \frac{\partial^2 \ell_2}{\partial^2 \beta} & \frac{\partial^2 \ell_2}{\partial \beta \partial \theta} & \frac{\partial^2 \ell_2}{\partial \beta \partial \alpha} \\ \frac{\partial^2 \ell_2}{\partial \theta \partial \beta} & \frac{\partial^2 \ell_2}{\partial^2 \theta} & \frac{\partial^2 \ell_2}{\partial \theta \partial \alpha} \\ \frac{\partial^2 \ell_2}{\partial \alpha \partial \beta} & \frac{\partial^2 \ell_2}{\partial \alpha \partial \theta} & \frac{\partial^2 \ell_2}{\partial^2 \alpha} \end{bmatrix} \\ &= \sum_{i=1}^4 \begin{bmatrix} n_i \pi_i (1 - \pi_i) & n_i d_i \pi_i (1 - \pi_i) & 0 \\ n_i d_i \pi_i (1 - \pi_i) & n_i d_i^2 \pi_i (1 - \pi_i) & 0 \\ 0 & 0 & 0 \end{bmatrix} \\ &+ \sum_{i=1}^4 \sum_{j=1}^4 \begin{bmatrix} n_{ij} \pi_{ij} (1 - \pi_{ij}) & n_{ij} (d_j + \alpha d_i) \pi_{ij} (1 - \pi_{ij}) & \theta n_{ij} d_i \pi_{ij} (1 - \pi_{ij}) \\ n_{ij} (d_j + \alpha d_i) \pi_{ij} (1 - \pi_{ij}) & n_{ij} (d_j + \alpha d_i)^2 \pi_{ij} (1 - \pi_{ij}) & \theta n_{ij} d_i (d_j + \alpha d_i) \pi_{ij} (1 - \pi_{ij}) \\ \theta n_{ij} d_i \pi_{ij} (1 - \pi_{ij}) & \theta n_{ij} d_i (d_j + \alpha d_i) \pi_{ij} (1 - \pi_{ij}) & \theta^2 n_{ij} d_i^2 \pi_{ij} (1 - \pi_{ij}) \end{bmatrix} \quad (12) \end{aligned}$$

The algorithm yielded the optimal design given in Table 5.

For this allocation/design, $|\mathbf{I}_{\text{cross,opt}}| = 333,110$. Now that α is included in the information matrix, the equivalent balanced design gave a determinant of $|\mathbf{I}_{\text{cross,bal}}| =$

116,140, which has an efficiency of $\frac{|\mathbf{I}_{\text{bal}}|^{1/p}}{|\mathbf{I}_{\text{opt}}|^{1/p}} = 0.704$ (note that $p = 3$ for this case). So

the balanced design here is 70.4% as efficient as the optimal design. Again, this means that an extra 41 treatments would be required for a balanced design to match the information given by the balanced design with 96 treatments. The algorithm was run from a number of different starting values and consistently found the same optimal design. Interpretation of this design is more complex, but in essence the information from a given design can be considered as arising from the sum of the products of the information matrix for each of the elementary designs with the number of subjects allocated to that elementary design. In this example, three elementary designs were identified: 0 units followed by 10 units, 0 followed by 0 units and the maximum dose (in this case 20 units) followed by 0 units. It will be seen that these elementary designs travel through the subsequent analyses, but the proportion of patients assigned to each elementary design may change. Although the elementary designs cannot be considered in isolation, as they are jointly estimated, it can be seen that they each provide information about different parameters; 1) the same doses are allocated which provide precise estimates of θ (0 units followed by 10 units) without confounding by the carryover effect; 2) additional doses are allocated to improve the precision of the estimate of the intercept β (0 followed by 0 units), and 3) additional dose levels have been allocated for estimation of α (20 units followed by 0 units).

4.1.3 Optimal and balanced cross-over designs, linear dose range

As for our parallel designs, calculations for cross-over designs were repeated based on a linear dose range (0, 5, 10, 15 units). The optimal design is given in Table 6. The balanced design was found to be 74.7% as efficient as the optimal design. Again we see only a marginal change in this efficiency. However, the optimal design does vary

slightly in this case, where more observations are required in the highest dose level in the first period in order to estimate the carry-over effect.

4.2 *Alternative optimality criterion*

Although we believe that it is often useful to estimate the carry-over effect, this may not always be the case. Hence we consider D_S -optimality, where we are only interested in estimating a subset of the parameters (in this case, β and θ).

To investigate D_S -optimality in the cross-over designs, the information matrix was partitioned:

$$I = \begin{bmatrix} I_{11} & I_{12} \\ I_{21} & I_{22} \end{bmatrix}$$

I_{11} relates to the two parameters of interest (β and θ), I_{22} relates to the carry-over effect, treated as a nuisance parameter. To find the D_S -optimal design, we maximised $|I_{11} - I_{12}I_{22}^{-1}I_{21}|$. Interestingly, this yields the same design as we found when we treated α as known, i.e. all 48 subjects receive 0 units followed by 10 units (shown in Table 3).

4.3 *Sensitivity analysis*

To investigate the sensitivity of these designs to the choice of the parameter values, we calculated a sensitivity index (S.I.) for each parameter. This method of sensitivity analysis is given in Nestorov¹². For a parameter γ_i the S.I. is given by

$$\text{S.I.}(\gamma_i) = \frac{\partial |\mathbf{I}|}{\partial \gamma_i} \cdot \frac{\gamma_i}{|\mathbf{I}|} \quad (13)$$

The S.I. for each parameter for both the balanced design and optimal design (with α unknown) is given in Table 7. The greater the magnitude of the S.I. (regardless of sign),

the more sensitive $|\mathbf{I}|$ is to the choice of the parameter value. We see that for each parameter the balanced design is more sensitive than the optimal design.

As a further examination of the sensitivity of these designs, the plots in Figure 2 show the value of $|\mathbf{I}|$ when the true parameter values differ from the values used to find the optimal design. For this purpose we used a marginal sensitivity analysis, where all parameter values were fixed except for the one under investigation. The plots show how the ratio of $D(\gamma)$ to $D_{\text{opt}}(\gamma)$ (raised to the power of $1/p$) varies for different values of γ , where γ is one of α , β or θ , while the other parameters are held at their assumed values. $D(\cdot)$ refers to the determinant of the information matrix for the given design and $D_{\text{opt}}(\cdot)$ is the determinant of the information matrix for the optimal design. We see from plots (a) and (b) in Figure 2, that for β and α , the optimal design is always more efficient than the balanced design for a wide range of parameter values. However, if the true value of θ was larger than about 0.7 (in which case the true value of the parameter would be 233% of the expected value), we can see that the balanced design becomes more efficient than this optimal design.

5 Hybrid designs

Finally, we consider a hybrid type of design, where some subjects receive one dose and some receive two, that is a mixture of the parallel and cross-over designs. Since we are working with approximate designs, we can optimise the proportion of subjects receiving multiple doses at the same time as we optimise the actual allocations.

5.1 Optimal and balanced hybrid designs

The above algorithm was modified to consider both parallel and cross-over components. A number of different initial designs were considered as starting points for the algorithm which resulted in a number of different ‘optimal’ designs, each with identical values of $|\mathbf{I}_{\text{hyb,opt}}|$ of 333,110. A few of these designs are presented (in Table 8). Note that these designs are identical in terms of the determinant associated with the proportional allocation of treatments. However, due to rounding to the nearest integer (to give the actual allocations that would be used), the determinants vary slightly from 333,110. Indeed, due to the rounding process, even the total number of doses varies slightly from 96 in two of these designs.

The notion of a ‘balanced’ hybrid design is difficult to define. With 96 doses in total, there are 5 possible balanced designs that we can consider. The general form of these designs is given in Table 11. Note that $x = 0$ gives the balanced parallel design, and $x = 4$ gives the balanced cross-over design.

These balanced designs are summarised in terms of their efficiencies (comparing to the optimal value of the determinant given above) in Table 12.

If we consider the optimal design given in Table 10, with 48 single doses and 24 double doses, it would perhaps be sensible to compare this to the balanced design with $x = 2$, which also has 48 single doses and 24 double doses. The efficiency of this balanced design compared to this optimal design is 61.4%. This means that a balanced design would require an additional 61 treatments to match the information given by the optimal design with 96 treatments.

5.2 Sensitivity analysis

The S.I. for each parameter for each of the five balanced hybrid designs above and the third optimal hybrid design (from Table 10) is given in Table 13.

We see again that for each parameter, the balanced designs are more sensitive than the optimal design. Also, the optimal hybrid design has exactly the same sensitivity index for each parameter as the optimal cross-over design. The balanced hybrid design with $x = 4$ is exactly the same as the balanced cross-over design, so naturally the sensitivity indices are also equal in both cases. For the balanced ($x = 0$) design, the information matrix is singular and therefore the determinant is zero, so the sensitivity index is not defined.

Sensitivity plots for the optimal hybrid design given in Table 10 were generated in the same way as the sensitivity plots for the full cross-over designs, and are presented in Figure 3. Again, as for the full cross-over designs, we see that for β and α , the optimal design is always more efficient than the balanced design for a wide range of parameter values given in the plots. The balanced hybrid design is again more efficient than the optimal design only when the true value of θ was higher than about 0.7.

6 Discussion

We have shown that for a model with proportional carry-over effects and binary outcomes, an optimal allocation of treatments is significantly more efficient than a balanced allocation, whether we are considering parallel designs, cross-over designs or a combination of both in a hybrid design. Further, it appears in light of the sensitivity analyses performed that the optimal designs are quite robust against parameter misspecification, and given that often experimenters have a reasonable idea of the prior

distribution of the parameters, the results here are of practical value. They present experimenters with the potential of savings in terms of number of patients in an experiment without any loss in efficiency. In addition to savings in terms of number of patients, the work here highlights that optimal designs may offer greater flexibility to the sponsor since with the hybrid designs not all patients are required to receive both periods of treatments while these designs retain the advantages of the cross-over structure.

Although these findings are currently of theoretical interest only, at this stage, they do have significant potential for application in early phase IIa studies where significant PK data and some PD data may already be available and optimization of first or second use in patients could be optimized further. The final design may well be a composite of the optimal design (perhaps even a hybrid design) and additional design points to ensure that the important clinical questions can be answered. If the outcome of the study is a proof of concept, i.e. that the drug works, then accurate characterization of the dose-response relationship is vital to optimise later phase IIb studies.

To illustrate this, we considered ‘split’ designs for both parallel and cross-over designs, where half of the design points were taken from the balanced design, and the other half were taken from the optimal design. For example, the split parallel design consisted of 12 patients in each dose group from the balanced design, plus an extra 24 patients in the 0 unit and 10 unit group from the optimal design, to give allocations of 36, 12, 36 and 12 patients in the 0, 5, 10 and 20 unit groups, respectively. As expected, the efficiencies of these designs were roughly halfway between the balanced and optimal efficiencies (88.8% and 87.3% for the split parallel and cross-over designs, respectively).

This work has limited itself to discussion of parameter estimation for a specific model. There is a need for more generalised designs that may be near optimal for a number of alternative plausible structural models and ranges of parameter values and that also confers optimal conditions for model discrimination. We intend to extend the work to these designs and the consideration of more complex non-linear pharmacokinetic and pharmacodynamic models, such as compartmental models and also to other types of carry-over effects.

Tables

Table 1 Dose allocations for parallel designs.

Dose	0	5	10	20	Eff
Balanced Allocation	24	24	24	24	0.761
Optimal Allocation	48	0	48	0	1.000

Table 2 Dose allocations for parallel designs, linear dose range.

Dose	0	5	10	15	Eff
Balanced Allocation	24	24	24	24	0.841
Optimal Allocation	48	0	48	0	1.000

Table 3 Optimal cross-over design, α known.

		2 nd dose			
		0	5	10	20
1 st dose	0	0	0	48	0
	5	0	0	0	0
	10	0	0	0	0
	20	0	0	0	0

Table 4 Balanced cross-over design.

		2 nd dose			
		0	5	10	20
1 st dose	0	0	4	4	4
	5	4	0	4	4
	10	4	4	0	4
	20	4	4	4	0

Table 5 Optimal cross-over design, α unknown.

		2 nd dose			
		0	5	10	20
1 st dose	0	2	0	27	0
	5	0	0	0	0
	10	0	0	0	0
	20	19	0	0	0

Table 6 Optimal cross-over design, linear dose range.

		2 nd dose			
		0	5	10	15
1 st dose	0	7	0	18	0
	5	0	0	0	0
	10	0	0	0	0
	15	23	0	0	0

Table 7 Sensitivity analysis of designs with α unknown.

Design	S.I.(β)	S.I.(θ)	S.I.(α)
Balanced	0.85842	-2.0142	-0.66440
Optimal	0.57058	-1.2145	-0.34759

Table 8 Hybrid design, 16 single doses, 41 double doses ($n = 98$, actual determinant = 354,380)

Single doses:					Multiple doses:					
					2 nd dose					
Dose	0	5	10	20						
Allocation	4	0	12	0	1 st dose	0	6	0	16	0
						5	0	0	0	0
						10	0	0	0	0
						20	19	0	0	0

Table 9 Hybrid design, 31 single doses, 33 double doses ($n = 97$, actual determinant = 343,490)

Single doses:					Multiple doses:					
					2 nd dose					
Dose	0	5	10	20						
Allocation	15	0	16	0	1 st dose	0	2	0	12	0
						5	0	0	0	0
						10	0	0	0	0
						20	19	0	0	0

Table 10 Hybrid design, 48 single doses, 24 double doses ($n = 96$, actual determinant = 332,990)

Single doses:					Multiple doses:					
					2 nd dose					
Dose	0	5	10	20						
Allocation	22	0	26	0	1 st dose	0	4	0	1	0
						5	0	0	0	0
						10	0	0	0	0
						20	19	0	0	0

Table 11 Possible balanced hybrid design, where $x = 0, 1, 2, 3, 4$ and $y = 24 - 6x$.

Single doses:					Multiple doses:					
					2 nd dose					
Dose	0	5	10	20						
Allocation	y	y	y	y	1 st dose	0	0	x	x	x
						5	x	0	x	x
						10	x	x	0	x
						20	x	x	x	0

Table 12 Comparison of 5 hybrid balanced designs.

x	# single doses	# double doses	Eff
0	96	0	0.000 ¹
1	72	12	0.508
2	48	24	0.614
3	36	36	0.672
4	0	48	0.704

Table 13 Sensitivity analysis of hybrid designs.

Design	S.I.(β)	S.I.(θ)	S.I.(α)
Balanced ($x = 0$)	N/A	N/A	N/A
Balanced ($x = 1$)	0.75618	-1.8021	-0.54883
Balanced ($x = 2$)	0.78607	-1.8657	-0.58441
Balanced ($x = 3$)	0.81978	-1.9358	-0.62277
Balanced ($x = 4$)	0.85842	-2.0142	-0.66440
Optimal	0.57058	-1.2145	-0.34759

¹ Note that this determinant is zero since α cannot be estimated with this design.

Legend for figures

Figure 1. Optimal dose levels and their corresponding probabilities. The open circles represent the dose, probability pairs that are optimal should any dose be able to be administered.

Figure 2. Effect of varying (a) β , (b) θ and (c) α , for the full cross-over designs. The efficiency of the balanced design is given by the solid line and the optimal design by the dashed line.

Figure 3. Effect of varying (a) β , (b) θ and (c) α , for the hybrid designs. The efficiency of the balanced design is given by the solid line and the optimal design by the dashed line.

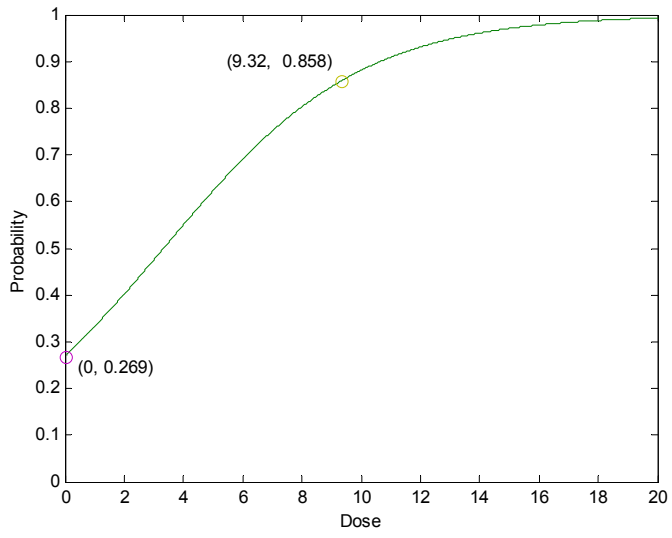


Figure 1

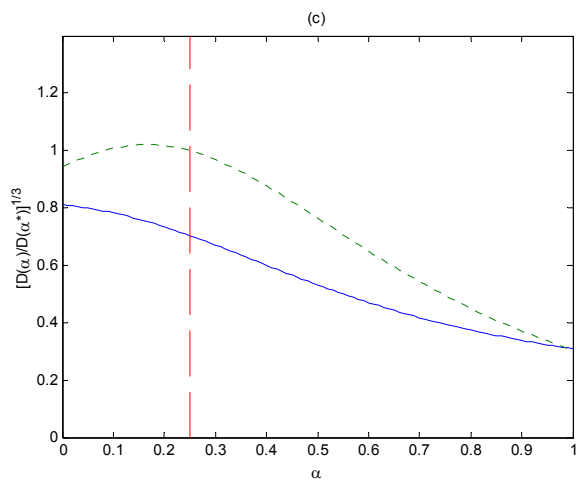
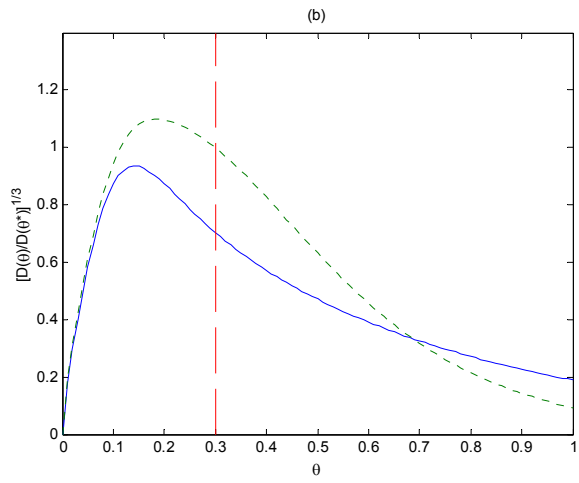
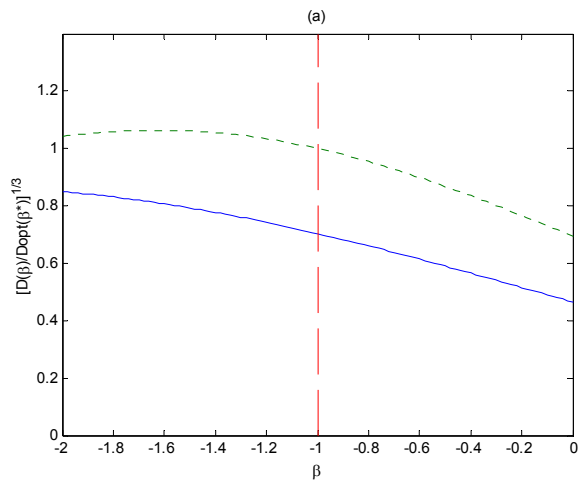


Figure 2

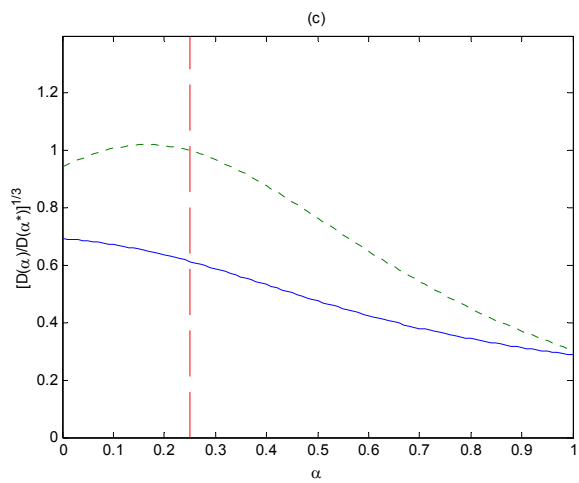
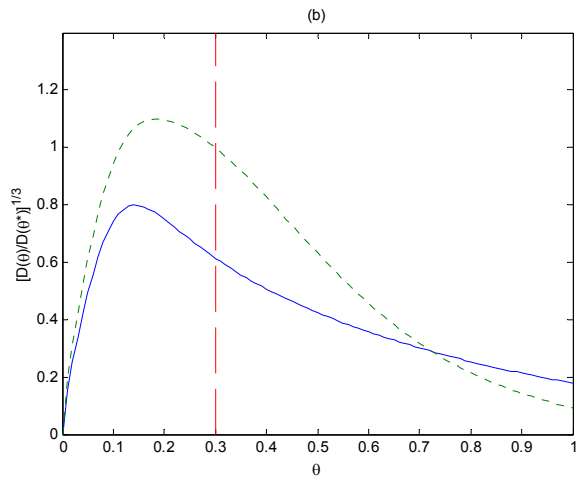
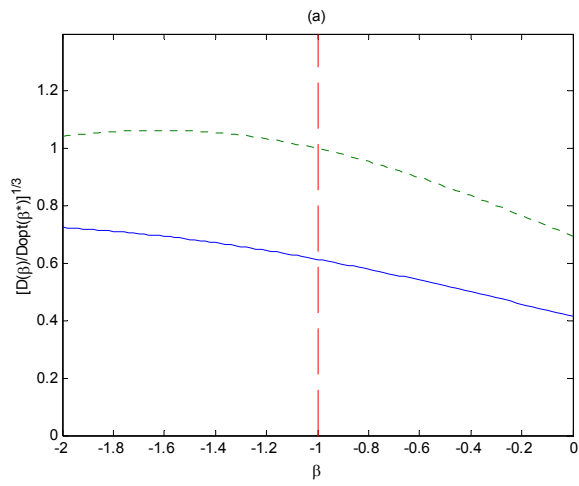


Figure 3

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