Optimal and efficient crossover designs for comparing test treatments to a control treatment under various models

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Abstract

We study the optimality, efficiency, and robustness of crossover designs for comparing several test treatments to a control treatment. Since A-optimality is a natural criterion in this context, we establish lower bounds for the trace of the inverse of the information matrix for the test treatments versus control comparisons under various models. These bounds are then used to obtain lower bounds for efficiencies of a design under these models. Two algorithms, both guided by these efficiencies and results from optimal design theory, are proposed for obtaining efficient designs under the various models.

KEY WORDS: Crossover designs; Repeated measurements; Carryover effect; Balanced designs; A-optimal designs.

1 Introduction

Crossover designs are used in many clinical trials and other studies. In such studies, subjects receive a sequence of treatments, specified by the design, over successive periods of time. Treatments can then be compared using repeated measurements from the same subject and the individual subjects are used as blocks. Thus, between-subject variation is removed from the experimental error to increase the sensitivity of the experiment. Crossover designs also facilitate economical use of resources when a limited number of subjects is available for the study. In particular, they require fewer subjects than a parallel study for an equal number of treatment replications.

A disadvantage of crossover designs is the possibility that the effect of a treatment applied in one period may persist into the next period (carry-over effects). Ideally, an experiment that uses a crossover design will have sufficiently long wash-out periods between active treatment periods to make any carry-over effects negligible. This will, however,

* Supported by the National Science Foundation Grant DMS-0304661.

inevitably increase the duration of the experiment. Moreover, ethical reasons (how long can we deny a suffering patient treatment during a wash-out period?) and incomplete knowledge (how long is long enough for an effective wash-out period?) may result in inadequate wash-out periods. It is therefore prudent to use a design that, if needed, allows for efficient estimation of differences between treatment effects under a statistical model that includes carry-over effects. Section 2 will describe several models that have been proposed.

While these models are fairly simple (and possibly too simplistic), when, at the time of planning the experiment, it is difficult to postulate an appropriate model, it is prudent to select a design that allows for efficient estimation of treatment differences under a variety of these models. Hedayat and Stufken (2003) study the efficiencies of crossover designs under different models when all treatment comparisons are equally important. However, in many clinical trials the main goal of the experiment is to compare several test treatments to a control treatment or placebo. Optimal or efficient designs for the case that all treatment comparisons are equally important may not be efficient for comparing test treatments to a control treatment.

Universal optimality, which is the design optimality criterion most commonly used in the crossover design literature when all treatment comparisons are equally important, is inappropriate when comparing test treatments to a control treatment. An appealing optimality criterion for the latter is A-optimality. With A_d denoting the information matrix for $\theta = (\tau_1 - \tau_0, \ldots, \tau_t - \tau_0)'$ under design d, an A-optimal design minimizes $Tr(A_d^{-1})$ over all competing designs d. (Here and elsewhere, 0 denotes the control treatment and τ_i the effect of treatment i.) The criterion is appealing because an A-optimal design also minimizes $\sum_{i=1}^{t} Var_d(\hat{\tau}_i - \hat{\tau}_0)$ over d, where $\hat{\tau}_i - \hat{\tau}_0$ is the BLUE of $\tau_i - \tau_0$, $i = 1, \ldots, t$. Throughout this paper, A-optimality will be used as the optimality criterion. In order to find designs that are efficient under this criterion for a variety of models, we need to establish lower bounds for the efficiency of the designs under the A-criterion and we need to be able to generate efficient designs. This paper presents tools for doing this when $p \leq t + 1$, which is arguably the most important case that is assumed to hold throughout the paper.

The layout of the paper is as follows. The models to be considered will be presented in Section 2, while lower bounds for the trace of the inverse of the information matrices are established in Section 3. In Section 4, we introduce two simple but fast algorithms to construct robust designs, i.e., designs that are efficient under a variety of models.

2 Statistical models and notation

We will now present a number of statistical models for crossover designs when the response variable is continuous. While some of these models may only be useful for special situations,

others have received considerably more coverage in the literature.

The first model is the "traditional" first-order carryover effects model, first considered in the optimal design literature by Hedayat and Afsarinejad (1975). This model can be written as

$$Y_{dks} = \mu + \alpha_k + \beta_s + \tau_{d(k,s)} + \rho_{d(k-1,s)} + e_{ks}, \quad k = 1, \ldots, p; \ s = 1, \ldots, n, \tag{2.1}$$

where Y_{dks} denotes the response from subject s in period k to which treatment $d(k, s)$ was assigned. In this model μ is the general mean, α_k is the effect due to period k, β_s is the effect due to subject s, $\tau_{d(k,s)}$ is the direct treatment effect of treatment $d(k, s)$, and $\rho_{d(k-1,s)}$ is the carryover or residual effect of treatment $d(k-1, s)$. By convention, $\rho_{d(0,s)}$ is taken as 0, so that there is no carryover effect in the first period. All these effects are assumed to be fixed effects. The error terms e_{ks} are assumed to be independently normally distributed with mean 0 and variance σ^2.

Model (2.1), while commonly used in the optimal design literature, has been criticized for its simplistic view of the carryover effects. Recently another model, the self and mixed carryover effects model, was introduced by Afsarinejad and Hedayat (2002) and studied by Kunert and Stufken (2002, 2005). It allows each treatment to have two different carryover effects, one a self carryover effect (which applies if the carryover effect and direct treatment effect are from the same treatment) and the other a mixed carryover effect (which applies in all other cases). If there are only two treatments, this is a parameterization of the model that includes the direct by carryover interaction; for more than two treatments the model only captures part of that interaction, not requiring nearly as many parameters as for the full interaction model. Using the same notation as in Model (2.1), the self and mixed carryover effects model can be written as

$$\begin{aligned} Y_{dks} = \mu + \alpha_k + \beta_s + \tau_{d(k,s)} + (1 - \delta_{d(k,s),d(k-1,s)})\gamma_{d(k-1,s)} + \delta_{d(k,s),d(k-1,s)}\varphi_{d(k-1,s)} \\ + e_{ks}, \ k = 1, \ldots, p; \ s = 1, \ldots, n. \end{aligned} \tag{2.2}$$

In this model, $\gamma_{d(k-1,s)}$ and $\varphi_{d(k-1,s)}$ represent mixed and self carryover effects, respectively. $\delta_{d(k,s),d(k-1,s)}$ is an indicator variable that is 1 if $d(k, s) = d(k-1, s)$ and 0 otherwise. So a carryover effect will be either $\gamma_{d(k-1,s)}$ or $\varphi_{d(k-1,s)}$ depending on whether treatment $d(k-1, s)$ is followed by a different treatment or not. As in Model (2.1), there is no carryover effect in the first period, i.e., $\gamma_{d(0,s)} = \varphi_{d(0,s)} = 0$.

If washout periods are sufficiently long, we will not have to worry about carryover effects (cf. Senn, 2002). Other effects in Model (2.1) may turn out to be negligible for other situations. In any case, we would still want our design to be efficient for the estimation of differences in direct treatment effects. We will therefore also consider the following variations on Models (2.1) and (2.2), where each time $k = 1, \ldots, p$ and $s = 1, \ldots, n$.

No period effects:

$$Y_{dks} = \mu + \beta_s + \tau_{d(k,s)} + \rho_{d(k-1,s)} + e_{ks}, \tag{2.3}$$

No carryover effects:

$$Y_{dks} = \mu + \alpha_k + \beta_s + \tau_{d(k,s)} + e_{ks}, \tag{2.4}$$

No carryover and period effects:

$$Y_{dks} = \mu + \beta_s + \tau_{d(k,s)} + e_{ks}, \tag{2.5}$$

Only treatment effects:

$$Y_{dks} = \mu + \tau_{d(k,s)} + e_{ks}, \tag{2.6}$$

No subject effects:

$$Y_{dks} = \mu + \alpha_k + \tau_{d(k,s)} + \rho_{d(k-1,s)} + e_{ks}, \tag{2.7}$$

No carryover and subject effects:

$$Y_{dks} = \mu + \alpha_k + \tau_{d(k,s)} + e_{ks}, \tag{2.8}$$

No period and subject effects:

$$Y_{dks} = \mu + \tau_{d(k,s)} + \rho_{d(k-1,s)} + e_{ks}. \tag{2.9}$$

Observe that Models (2.4), (2.5), and (2.6) correspond to the two-way, one-way, and zero-way elimination models, respectively, with periods and subjects as blocking variables.

Denoting the test treatments by 1, 2, ..., t and the control treatment by 0, we use the notation:

n_{dis}: the number of times that treatment i is assigned to subject s

$\widetilde{n}_{dis}$: the number of times that treatment i is assigned to subject s in the first $p-1$ periods

l_{dik}: the number of times treatment i is used in period k

m_{dij}: the number of times treatment i is immediately preceded by treatment j

r_{di}: the replication of treatment i

$\widetilde{r}_{di}$: the replication of treatment i in the first $p-1$ periods of the design

$\Omega_{t+1,n,p}$: all designs based on $t+1$ treatments (denoted by $0, \ldots t$) for n subjects and p periods

$\Omega^1_{t+1,n,p}$: the subclass of $\Omega_{t+1,n,p}$ in which the control treatment appears equally often in each period

$\Omega^2_{t+1,n,p}$: the subclass of $\Omega^1_{t+1,n,p}$ in which no treatment is immediately followed by itself

We also define $z_d = \sum_{s=1}^{n} \sum_{i=1}^{t} (n_{dis} - 1)^+$. Here, $m^+ = \max(m, 0)$.

3 Efficiency bounds for designs under the various models

The purpose of this section is to identify lower bounds for the trace of A_d^{-1}, where A_d is the information matrix for $(\tau_1 - \tau_0, \ldots, \tau_t - \tau_0)'$. These design-independent bounds will either apply to all designs in $\Omega_{t+1,n,p}$ or to all designs in a subclass. While designs that achieve these bounds do not always exist (this depends on the values of t, n and p), the bounds are always useful to obtain lower bounds for the efficiencies of existing designs. We will study this problem here for all the models introduced in Section 2.

3.1 Model (2.1)

Hedayat and Yang (2005) establish the following optimality result in $\Omega^2_{t+1,n,p}$.

Theorem 1. *For $p \leq t+1$, a design $d^* \in \Omega^2_{t+1,n,p}$ is A-optimal in $\Omega^2_{t+1,n,p}$ if d^* is a totally balanced test-control incomplete crossover design and $Tr(A_{d^*}^{-1})$ is equal to*

$$\min_{r_{d0}} \left(\frac{t(t-1)^2 p}{x_1} + \frac{tp}{y_1} \right), \tag{3.1}$$

where

$$\begin{aligned} x_1 &= t(p-1)(np - r_{d0}) - p(r_{d0} - \frac{1}{p} \min_{\delta} \sum_{s=1}^{n} n_{d0s}^2) - \\ &\qquad \frac{[nt(p-1) - t\widetilde{r}_{d0} - \min_\delta \sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s}]^2}{n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \min_\delta \sum_{s=1}^n \widetilde{n}_{d0s}^2} \end{aligned}$$

and

$$y_1 = p(r_{d0} - \frac{1}{p} \min_{\delta} \sum_{s=1}^{n} n_{d0s}^2) - \frac{n(p-1)(\min_\delta \sum_{s=1}^n n_{d0s}\widetilde{n}_{d0s})^2}{np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\min_\delta \sum_{s=1}^n \widetilde{n}_{d0s}^2}.$$

For a given design $d \in \Omega^2_{t+1,n,p}$, the minimizations in the expressions for x_1 and y_1 are over all designs $\delta \in \Omega^2_{t+1,n,p}$ with $r_{\delta 0} = r_{d0}$. For designs in $\Omega^2_{t+1,n,p}$, since all these minima are a function of r_{d0}, t, n and p only and since $\widetilde{r}_{d0} = (p-1)r_{d0}/p$, the minimization in (3.1) is a numerical minimization over possible values of r_{d0} rather than over all designs in $\Omega^2_{t+1,n,p}$.

We refer the reader to Hedayat and Yang (2005) for the definition of a totally balanced test-control incomplete crossover design, who also give examples of such designs that are optimal in $\Omega^2_{t+1,n,p}$ for $p = 3$, 4, and 5, $t = p-1$,..., 9, and certain values of n.

Hedayat and Yang (2004) considered the larger class $\Omega^1_{t+1,n,p}$, where the same treatment can appear in consecutive periods. Through tedious algebra, they obtained a lower bound for $Tr(A_d^{-1})$ in this larger class, and found that, in general, optimal designs in the subclass $\Omega^2_{t+1,n,p}$ may no longer be optimal in the larger class, but are still highly efficient.

To formulate this bound for $\Omega^1_{t+1,n,p}$, let Γ_d be the set of all treatment sequences with the control treatment in the last period, and define $\Psi_d = \sum_{s\in\Gamma_d} \widetilde{n}_{d0s}$. Furthermore, define

$$A(t,n,p) = \min_{r_{d0},\Psi_d,m_{d00},z_d} \left(\frac{t(t-1)^2 p}{x_2} + \frac{tp}{y_2} \right), \tag{3.2}$$

where

$$\begin{aligned} x_2 &= t(p-1)(np - r_{d0}) - 2tz_d - p(r_{d0} - \frac{1}{p}\min_\delta \sum_{s=1}^n n_{\delta 0s}^2) \\ &\quad - \frac{[t(p-1)(n-z_d) - t\widetilde{r}_{d0} - (\min_\delta \sum_{s=1}^n n_{\delta 0s}\widetilde{n}_{\delta 0s} - pm_{d00})]^2}{n(p-1)(pt-t-1) - (pt-t+p-2)\widetilde{r}_{d0} + \min_\delta \sum_{s=1}^n \widetilde{n}_{\delta 0s}^2} \end{aligned} \tag{3.3}$$

and

$$y_2 = p(r_{d0} - \frac{1}{p}\min_\delta \sum_{s=1}^n n_{\delta 0s}^2) - \frac{n(p-1)(\min_\delta \sum_{s=1}^n n_{\delta 0s}\widetilde{n}_{\delta 0s} - pm_{d00})^2}{np(p-1)\widetilde{r}_{d0} - \widetilde{r}_{d0}^2 - n(p-1)\min_\delta \sum_{s=1}^n \widetilde{n}_{\delta 0s}^2}. \tag{3.4}$$

For a given design $d \in \Omega^1_{t+1,n,p}$, the minima that appear in the expressions in (3.3) and (3.4) are over all designs $\delta \in \Omega^1_{t+1,n,p}$ with $r_{\delta 0} = r_{d0}$, $\Psi_\delta = \Psi_d$ and $m_{\delta 00} = m_{d00}$. All of these minima depend only on r_{d0}, Ψ_d, m_{d00}, t, n and p. We also note that $\widetilde{r}_{d0} = (p-1)r_{d0}/p$ for designs in $\Omega^1_{t+1,n,p}$, which is used in the computations for (3.2). The minimization in (3.2) is not accomplished by considering all possible designs (there are simply too many), but by a numerical minimization over the possible ranges of the four parameters r_{d0}, Ψ_d, m_{d00}, and z_d.

Theorem 2. *Let $n \geq p(p-1)/2$. For any design $d \in \Omega^1_{t+1,n,p}$, we have*

$$Tr(A_d^{-1}) \geq A(t,n,p). \tag{3.5}$$

Hedayat and Yang (2004) have a restriction on t in their formulation of our Theorem 2, which turns out to be unnecessary.

3.2 Models (2.2) and (2.3)

The self and mixed carryover effects model is more complicated than the traditional model. However, efficiency bounds for Model (2.1) are also useful for Model (2.2). Writing $Y_d = (Y_{d11}, Y_{d21}, \ldots, Y_{dpn})'$, $\alpha = (\alpha_1, \ldots, \alpha_p)'$, $\beta = (\beta_1, \ldots, \beta_n)'$, $\tau = (\tau_0, \ldots, \tau_t)'$, $\gamma = (\gamma_0, \ldots, \gamma_t)'$, $\varphi = (\varphi_0, \ldots, \varphi_t)'$, $e = (e_{11}, e_{21}, \ldots, e_{pn})'$, $P = 1_n \otimes I_p$, and $U = I_n \otimes 1_p$, the self and mixed carryover effects model can be written as

$$Y_d = \mu 1 + P\alpha + U\beta + T_d\tau + M_d\gamma + S_d\varphi + e,$$

where T_d is the design matrix for the direct treatments, M_d the design matrix for the mixed carryover effects, and S_d the design matrix for the self carryover effects. Note that M_d and S_d are determined by T_d.

Using a similar notation, the traditional model can be written as

$$Y_d = \mu 1 + P\alpha + U\beta + T_d\tau + F_d\rho + e,$$

where F_d is the design matrix for the carryover effects. Since $F_d = M_d + S_d$, we have that $\mathcal{C}(P|U|F_d) \subset \mathcal{C}(P|U|M_d|S_d)$. Here $\mathcal{C}(X)$ denotes the column space of the matrix X. If we write $A_d^{2.2}$ for the information matrix of $(\tau_1 - \tau_0, \ldots, \tau_t - \tau_0)'$ under the self and mixed carryover effects model, then it follows that $A_d^{2.2} \leq A_d$ (in the Loewner order) for any design d, and that

$$Tr\left((A_d^{2.2})^{-1}\right) \geq Tr(A_d^{-1}). \tag{3.6}$$

Consequently, a lower bound for $Tr(A_d^{-1})$ is also valid for $Tr\left((A_d^{2.2})^{-1}\right)$ and can therefore be used for computing efficiency bounds for designs under Model (2.2).

Note that if $d \in \Omega^2_{t+1,n,p}$, then S_d is the zero matrix and $F_d = M_d$. Hence for such designs $A_d^{2.2}$ and A_d are identical, so that equality holds in (3.6).

Turning to Model (2.3), the without period effects model, for design d we denote the information matrix for $(\tau_1 - \tau_0, \ldots, \tau_t - \tau_0)'$ under this model by $A_d^{2.3}$. The lower bounds in Theorems 1 and 2 are actually based on bounds for $Tr\left((A_d^{2.3})^{-1}\right)$ (see Hedayat and Yang, 2004, 2005) and can therefore immediately be applied to Model (2.3).

3.3 Models (2.4) and (2.5)

Model (2.4), the two-way elimination model with subject and period effects as block effects, and Model (2.5), the one-way elimination model with subject effects as block effects, can be written as

$$Y_d = \mu 1 + P\alpha + U\beta + T_d\tau + e$$

and

$$Y_d = \mu 1 + U\beta + T_d\tau + e,$$

respectively. With $A_d^{2.4}$ and $A_d^{2.5}$ as the information matrices for $(\tau_1 - \tau_0, \ldots, \tau_t - \tau_0)'$ under these two models, we have by an argument analogous to that in Subsection 3.2, that $Tr\left((A_d^{2.4})^{-1}\right) \geq Tr\left((A_d^{2.5})^{-1}\right)$. Consequently, a lower bound for $Tr\left((A_d^{2.5})^{-1}\right)$ is also a lower bound for $Tr\left((A_d^{2.4})^{-1}\right)$, and we cannot do better in general because there are optimal designs for which $A_d^{2.4} = A_d^{2.5}$. Majumdar and Notz (1983), studying the one-way elimination model, derive the following lower bound, which we will use for both models in this section:

$$\min_d Tr\left((A_d^{2.5})^{-1}\right) = \min_{x,z}\{g(x,z) : x = 0, \ldots, [p/2] - 1; z = 1, \ldots, n\}, \tag{3.7}$$

where

$$g(x,z)=\frac{t(t-1)^2p}{ntp(p-1)-(nx+z)(pt-t+p)+nx^2+2xz+z}+\frac{tp}{p(nx+z)-(nx^2+2xz+z)}.$$

3.4 Models (2.6), (2.7), (2.8) and (2.9)

We will use a common lower bound for these four models without subject effects. While the models may not be very plausible, we include them for completeness. By similar arguments as used in the previous subsections, it follows immediately that $Tr\left((A_d^{2.6})^{-1}\right)$ is a lower bound for the trace of the information matrix under each of the other three models. Moreover, it can be shown that $Tr\left((A_{d^*}^{2.6})^{-1}\right) = Tr\left((A_{d^*}^{2.7})^{-1}\right)= Tr\left((A_{d^*}^{2.8})^{-1}\right) = Tr\left((A_{d^*}^{2.9})^{-1}\right)$ if design d^* satisfies the following two conditions: (i) $l_{d^*ik}=r_{d^*i}/p$, for $i=0,\ldots,t$ and $k=1,\ldots,p$ (ii) $m_{d^*ij}=\frac{1}{np}r_{d^*i}\widetilde{r}_{d^*j}$ for $0\le i,j\le t$. Such designs do exist, as is shown by the following example:

1	1	1	2	2	2	3	3	3	4	4	4	0	0	0	0	0	0
1	2	3	2	3	4	3	4	0	4	0	0	0	0	1	0	1	2
4	0	0	0	1	2	2	1	2	3	4	0	3	3	0	4	0	1

A lower bound for Model (2.6), the zero-way elimination model, is (see Hedayat, Jacroux and Majumdar, 1988) given by:

$$\begin{aligned}&\min_d Tr\left((A_d^{2.6})^{-1}\right)\\ &\quad=\min_x\{\frac{t}{x}+\frac{t-np+x+t\lfloor\frac{np-x}{t}\rfloor}{\lfloor\frac{np-x}{t}\rfloor}+\frac{np-x-t\lfloor\frac{np-x}{t}\rfloor}{\lfloor\frac{np-x}{t}\rfloor+1},x=1,\ldots,np-t\},\end{aligned}\tag{3.8}$$

4 Obtaining efficient designs

Hedayat and Yang (2005) identified optimal designs under Model (2.2) in $\Omega^2_{t+1,n,p}$ by using Theorem 1. However, such designs exist only for selected values of t, n, and p. With the bounds derived in this paper, we can easily obtain lower bounds for the efficiency of a non-optimal design, whether in $\Omega^1_{t+1,n,p}$ or $\Omega^2_{t+1,n,p}$, and not only for one specific model. The efficiency of a design d in a class of designs is defined as $100\times Tr(B_{d^*}^{-1})/Tr(B_d^{-1})$ %, where d^* is the A-optimal design in the class and B_d is the appropriate information matrix for design d. Lower bounds for this efficiency are obtained by replacing $Tr(B_{d^*}^{-1})$ with the lower bounds in Section 3. For most models we compute the efficiency bounds in $\Omega_{t+1,n,p}$; for Models (2.1), (2.2) and (2.3) we will do it in the classes $\Omega^1_{t+1,n,p}$ or $\Omega^2_{t+1,n,p}$ since we don't have a sharp bound for the entire class.

If an experimenter has a particular design in mind, lower bounds can be computed easily in this way. If there is no candidate design, then, irrespective of the values of t, n

and p, the two algorithms presented in this section are useful for generating designs that are efficient under a variety of models, including those presented in this paper. Underlying these algorithms is the premise that totally balanced test-control incomplete crossover designs (see Theorem 1) are highly efficient under most of the models studied here. These designs play therefore a critical role in the algorithms, and the theme of the algorithms is not to stray too far from such designs.

Both of the algorithms have been made available (coded in SAS) by one of the authors (MY) at http://www.missouri.edu/∼yangmi/programs.html, along with instructions on how to use them. For both algorithms it must hold that $p = 3, 4$ or 5, and $t = p-1, \ldots, 9$, while n can be any integer greater than or equal to t. These constraints on the parameters cover the most important cases.

User inputs for both algorithms are t, n and p. The output consists of a design in $\Omega_{t,n,p}$ and efficiency bounds for that design under the various models discussed in this paper.

Algorithm I consists of the following four steps:

(i) For the input values of t and p, a value $\widetilde{n}$ is found so that an optimal design in $\Omega^2_{t+1,\widetilde{n},p}$, say d^* is available. The sequences of d^* will be used to construct the requested design.

(ii) Let $\lambda = \lfloor \frac{n}{\widetilde{n}} \rfloor$. If $\lambda > 0$, form a starting design by taking λ copies of each sequence in d^*. If $\lambda = 0$, take a starting design d that consists of a small number of sequences, say t, selected from d^* so that it has the maximum efficiency under Model (2.1).

(iii) Add one sequence to the design constructed so far. This sequence is selected from d^* so that it maximizes the efficiency of the resulting design under Model (2.1).

(iv) If the number of sequences in the constructed design is less than n, repeat step (iii).

While Algorithm I is based on Model (2.1), it may not generate an optimal design under that model. The efficiencies suggest however that it is almost always highly efficient, and not only under Model (2.1). An advantage of Algorithm I is that, due its simplicity, it is very fast even when n is large.

As an example, suppose we are interested in a design for comparing 4 test treatments to a control on 20 subjects in 3 periods. The design obtained by Algorithm I is the following:

0	2	4	1	3	0	1	3	0	2	4	0	0	1	0	0	3	4	2	4
1	4	2	0	0	3	0	0	3	3	1	1	3	2	2	4	4	3	0	0
4	0	0	3	4	1	2	1	2	0	0	3	4	0	1	2	0	0	3	1

For this design, the efficiency lower bounds under Models (2.1) and (2.2) are 98.7% in $\Omega^2_{4+1,20,3}$ and 98.3% in $\Omega^1_{4+1,20,3}$, respectively; under Models (2.4), (2.5), (2.6), (2.3), (2.7), (2.8), and (2.9) the lower bounds are 99.0%, 99.5%, 99.7%, 98.5%, 89.0%, 99.3%, and 89.2% respectively. Here, the efficiency under Model (2.3) is in $\Omega^1_{4+1,20,3}$. Hence, with the possible exception of Models (2.7) and (2.9), the efficiencies of this design are very high.

Under the latter models, which both include carryover effects but no subject effects, a good design tends to have each treatment immediately followed by itself at some occasions. This does not happen at all for designs constructed by Algorithm I.

Algorithm I works nevertheless remarkably well. The efficiency bounds are usually quite high, though they tend to be a bit lower for small values of n (especially when n happens to be smaller than $\widetilde{n}$). One reason for this is that the bounds are based on approximate design theory, and that, for smaller n, there is possibly NO design that comes close to attaining them. Hence the bounds are conservative, and the constructed design is possibly much better than suggested by the bounds. A second reason can be that Algorithm I is just not as effective for small n. For that reason we developed a second algorithm, Algorithm II. This is a 5-step algorithm, in which steps (i), (ii) and (iv) are identical as for Algorithm I. Step (iii) is modified as follows:

(iii) Add two sequences to the design constructed so far, both from d^*, so that the resulting design has maximum efficiency. Next, again using design efficiency as the criterion, delete the 'worst' sequence from the resulting design.

Hence, just as for Algorithm I, step (iii) of Algorithm II also increases the size of the design by one sequence, but it facilitates the deletion of sequences that looked good at one time but that appear to be the weakest link now.

Once a design of n sequences has been obtained, Algorithm II still tries to improve the design by the following fifth step:

(v) Replace a sequence from the current design by a sequence from d^* so that the increase in efficiency is maximized. This step is repeated until improvements in efficiency are smaller than a pre-set value, say 0.001.

For the second algorithm, the efficiencies in steps (iii) and (v) need not be based on Model (2.1) alone. Based on user input, they can be based on a weighted average of the efficiencies under Models (2.1), (2.2) and (2.4). This can especially be important for small n. For example, for $t = 5$, $p = 3$, and $n = 6$, if we use the weights 1, 0, 0 for Models (2.1), (2.2), and 2.4), respectively, the design constructed by Algorithm II has efficiency 65% under Models (2.1) and (2.2) in $\Omega^2_{5+1,6,3}$ and 70% under Model (2.4). If we use the weights 0, 0, 1 for the three models then we obtain a design that has efficiency 15% under Models (2.1) and (2.2) in $\Omega^2_{5+1,6,3}$ and 89% under Model (2.4).

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