Approximate c-Optimal Experimental Designs with Correlated Observations using Combinatorial Optimisation

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Abstract
We review the use of combinatorial optimisation algorithms to identify approximate c-optimal experimental designs when the assumed data generating process is a generalised linear mixed model and there is correlation both between and within experimental conditions. We show how the optimisation problem can be posed as a supermodular function minimisation problem for which algorithms have theoretical guarantees on their solutions. We compare the performance of four variants of these algorithms for a set of example design problems and also against multiplicative methods in the case where experimental conditions are uncorrelated. We show that a local search starting from either a random design or the output of a greedy algorithm provides good performance with the worst outputs having variance $< 10\%$ larger than the best output, and frequently better than $< 1\%$. We extend the algorithms to robust optimality and Bayesian c-optimality problems.

Keywords: optimal design, experimental design, algorithms, optimisation, GLMM

1 Introduction

We consider the question of how to identify a c-optimal design when the observations are correlated. In particular, we assume the data generating process can be described using a generalised linear mixed model (GLMM). For a $N \times 1$ vector of outcomes $y$, with an $N \times P$ matrix $X$ of covariates and a $N \times Q$ ‘design matrix’ for random effects $Z$, a GLMM can be written as:

$$y \sim F(h^{-1}(X\beta + Z\gamma), \omega)$$  \hspace{1cm} (1)

where $\beta$ are mean function parameters, $h(.)$ is a link function, $F(.)$ is a distribution function with scale parameter(s) $\phi$, and $\gamma \sim N(0, \Omega)$ is a vector of random effects with covariance matrix $\Omega$. Such models provide a flexible parametric approach to estimation of covariate effects when the observations are correlated, such as longitudinal designs (Zeger et al., 1988), cluster randomised trials (Hussey and Hughes, 2007), and geospatial statistical modelling (Diggle et al., 1998).

The covariance matrix of the observations $y$ is $\Sigma$. For the analyses in this article we use the approximation $\Sigma = W^{-1} + Z\Omega Z^T$, where $W$ is an $N \times N$ diagonal matrix with diagonal terms equal to the GLM iterated weights (Breslow and Clayton, 1993). For linear mixed models this approximation is exact. The information matrix for the mean function parameters is $M = X^T\Sigma^{-1}X$. 

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The c-optimality function that we aim to minimise is:

\[ f(M) = c^T M^{-1} c \]  

(2)

where \( c \) is a \( p \times 1 \) vector such that \( c \in \text{range}(M) \) to ensure estimability of \( c^T \beta \) (Pukelsheim, 1980). The vector \( c \) often has all elements equal to zero except for a one at the position corresponding to the treatment effect parameter of interest. It is generally not possible to identify exact optimal designs in this context, and we rely on approximations. We first discuss related approximate approaches before turning to the subject of this article: approximate c-optimal designs using combinatorial optimisation methods.

To provide some structure to the discussion we let \( Q = [X, Z] \) and \( Q_i \) refers to a row of a matrix \( Q \). We refer to an ‘observation’ as a a single row \( Q_i \), and an ‘experimental condition’ as the smallest set of observations that may or may not be included in the experiment. A ‘design space’ comprises all the possible experimental conditions in the experiment along with any relevant restrictions. We return to these definitions in more detail later. The design spaces we consider are discrete as they are comprised of a finite set of experimental conditions specified in advance. In some cases, it is assumed that discrete design points are formed by a uniform lattice over a continuous design space (e.g. Yang et al. (2013)), however we do not place any limitations on the set of points here.

Approximate optimisation methods often aim to solve a relaxed version of the optimisation problem. For designs with correlated observations one such approach is to identify the optimal ‘weights’ to place on each experimental condition or design point. These weights can be interpreted as an “amount of effort” to place on the observations in the design. Elfving’s Theorem is a classic result in theory of optimal designs based on this idea (Elfving, 1952, Ford et al., 1992, Studden, 2005). For iid observations (i.e. when \( \Sigma = \sigma^2 I \)) we can write the information matrix as the sum \( M = \sum_i X_i^T X_i \) for all observations \( i = 1, ..., R \). We can place a probability measure over the observations \( \phi = \{ (\phi_i, X_i) : i = 1, ..., R; \phi_i \in [0, 1] \} \) such that \( \phi \) defines an approximate experimental design, then the information matrix of the approximate design is \( M(\phi) = \sum_i X_i^T X_i \phi_i \). Elfving’s theorem provides a geometric characterisation of c-optimality and shows that an optimal design \( \phi \) lies at the intersection of the convex hull of the \( X_i \) and the vector defined by \( c \). Solutions can be obtained using linear programming methods (Harman and Jurik, 2008).

Holland-Letz et al. (2011), and relatedly Sagnol (2011), extended Elfving’s theorem to design spaces with experimental conditions with multiple correlated observations. Assuming still that there are \( R \) possible observations then we represent an experimental condition as \( e_j \subset \{ i \in \mathbb{N}, i \leq R \} \) for \( j = 1, ..., J \). Holland-Letz et al. (2011) and Sagnol (2011) examine designs in which there is no correlation between the experimental conditions allowing us to represent the information matrix as:

\[
M = X^T \Sigma^{-1} X = \sum_{j=1}^J X_{i \in e_j}^T \Sigma_{i \in e_j}^{-1} X_{i \in e_j}
\]  

(3)

where, in a slight abuse of notation we use \( \Sigma_{i \in e_j} \) to represent the submatrix of \( \Sigma \) formed using the rows and columns \( i \in e_j \). Equation 3 can be further reduced to \( \sum_j X_{i \in e_j}^T F F^T X_{i \in e_j} \) where \( F_j \) is a square root of the inverse covariance matrix \( \Sigma_{i \in e_j} \). A generalised approach to Elfving’s set follows and Sagnol (2011) shows that the optimal weights for each experimental condition can be solved using conic optimisation methods with a second order cone program. We refer to these approaches as ‘multiplicative’. Holland-Letz et al. (2012) provide an estimate on the lower bound of the efficiency of multiplicative methods. Prior approaches to optimal experimental designs with correlated observations relied on asymptotic arguments (Muller and Pázman, 2003, Näther, 1985, Sacks and Ylvisaker, 1968).

Approximate approaches such as those described above are useful for designs where we include or exclude uncorrelated groups of observations. For example, studies where individuals can be observed at different time points, like pharmacokinetic studies and cohort studies, may wish to choose how to allocate \( m \) individuals to a set of alternative schedules of observation. Holland-Letz et al. (2012) consider examples of assigning individuals to different dose schedules in a pharmacokinetic study. Similarly, a cluster randomised trial with repeated measures can intervene in different clusters at different time points (Hemming et al., 2015). If all clusters receive either
and show that they typically perform much better than the bounds would suggest and identify the global optimum most of the time. We compare results from approximate and combinatorial algorithms in Section 4 and discuss extensions to robust optimal and Bayesian optimal designs in Sections 5 and 6, respectively.

2 Combinatorial specification of correlated designs

We re-specify the optimisation problem in terms of sets of observations. The set of all observations in the design space is $I := \{ i \in \mathbb{N}; i \leq R \}$, such that $i \in I$ is a row in the matrix $Q$, which contains all possible observations for our problem. As before, an experimental condition is a set of one or more observations:

$$e_j \subset I$$

then a design space consists of all permissible experimental conditions:

$$D := \{ e_j : j = 1, ..., J, e_j \in I \}$$

where the $e_j$ need not be unique. A design $d \subseteq D$ of size $n$ is then:

$$d := \{ e_j : e_j \in D; |d| \leq n \}$$

where the total number of observations in the design is $\sum_j |e_j| = n^*$. The c-optimal objective function $g : 2^d \to \mathbb{R}_{\geq 0}$ we consider is then:

$$g(d) = \begin{cases} c^T M_d^{-1} c & \text{for } M_d \text{ positive semi-definite} \\ k & \text{otherwise} \end{cases}$$

It is possible for a design not to produce a positive semi-definite information matrix, for example if it is too small, in which case we assume the variance to be some large value $k > \max_d g(d)$. Our optimisation problem is:

$$\min_{d \in D^n} g(d)$$

Equation (3) shows that when the observations in different experimental conditions are independent of one another then the information matrix can be written as a sum. We can derive a more general expression for the marginal change to the
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information matrix when observations are added. Let \(d'\) and \(d\) be two designs such that \(d' \subseteq d \subseteq D\) and \(d = d' \cup d''\). We let \(X_1\) and \(X_2\) be the covariate matrices for designs \(d'\) and \(d''\), respectively, and \(\Sigma_1\) and \(\Sigma_2\) be their covariance matrices. \(\Sigma_{12}\) is the covariance between the observations in designs \(d'\) and \(d''\). Then,

\[
M_d = \begin{bmatrix} X_1 \\ X_2 \end{bmatrix}^T \begin{bmatrix} \Sigma_1 & \Sigma_{12} \\ \Sigma_{12}^T & \Sigma_2 \end{bmatrix}^{-1} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix}
\]

\[
= \begin{bmatrix} X_1^T & X_2^T \end{bmatrix} \begin{bmatrix} \Sigma_1^{-1} - \Sigma_{12} \Sigma_{12}^T \Sigma_1^{-1} \Sigma_{12}^T S^{-1} \Sigma_{12} \Sigma_1^{-1} - S^{-1} \Sigma_{12} \Sigma_1^{-1} \\ -S^{-1} \Sigma_{12} \Sigma_1^{-1} \end{bmatrix} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix}
\]

\[
= X_1^T \Sigma_1^{-1} \Sigma_{12} \Sigma_1^{-1} \Sigma_{12} \Sigma_1^{-1} X_1 + X_2^T S^{-1} \Sigma_{12} \Sigma_1^{-1} X_1
\]

\[
= M_{d'} + \delta M_{d',d''}
\]

where \(S = (\Sigma_2 - \Sigma_{12} \Sigma_1^{-1} \Sigma_{12})\) is the Schur complement, which we assume is invertible, and we use \(\delta M_{d',d''}\) to represent the marginal change in the information matrix of \(M_d\) when the additional observations in \(d''\) are added. It is evident that if \(\Sigma_{12} = 0\) then \(\delta M_{d',d''}\) reduces to \(X_2^T \Sigma_2^{-1} X_2\) as in Equation (3). We also note that \(\delta M_{d',d''}\) is positive semi-definite such that \(M_d \succeq M_{d'}\) (where \(A \succeq B\) means \(A - B\) is positive semi-definite), which implies that \(g(d) \leq g(d')\) for \(d' \subseteq d\). Thus, the function \(g\) is monotonically decreasing whenever \(S\) is invertible.

Equation (9) also shows how we can achieve some computational efficiency with correlated observations. A naive optimisation approach that recalculated the information matrix for each design would require at least \(O(n^3)\) operations by needing to invert the covariance matrix each time. For discrete combinatorial approaches we can iteratively add or remove single observations at a time, i.e. moving from \(d\) to \(d/\{i\} \cup \{i'\}\) and \(i \neq i'\), so the calculation only requires \(O(|e_j| n^2)\) operations to add or remove an experimental condition through rank-1 up/down dates of the inverse covariance matrix (we provide the specific calculations in the supplementary material). Thus, there is some computational advantage to combinatorial approaches, particularly as \(n\) grows.

\[2.1 \text{Monotone Supermodular Minimisation} \]

A function \(g\) is called supermodular if:

\[
g(d \cup \{e_j\}) - g(d) \geq g(d' \cup \{e_j\}) - g(d')\]

for all \(d' \subseteq d\). That is, there are diminishing marginal reductions in the function with increasing size of the design. For our specific \(c\)-optimality problem, we can re-express this definition using Equation (9) as:

\[
c^T([M_{d'} + \delta M_{d',d''} + \delta M_{d',e_j}]^{-1} - [M_{d'} + \delta M_{d',d''}]^{-1})c \geq c^T([M_{d'} + \delta M_{d',e_j}]^{-1} - M_{d'}^{-1})c
\]

\[
c^T(M_{d'} + \delta M_{d',d''} + (M_{d'} + \delta M_{d',d''})\delta M_{d',e_j}^{-1}(M_{d'} + \delta M_{d',d''})^{-1})c \leq c^T(M_{d'} + M_{d'}\delta M_{d',e_j}^{-1} M_{d'})^{-1}c
\]
where the second line follows from Hua’s identity. Thus, the function is supermodular if:

\[
M_d \delta M_{d,e_j}^{-1} M_d' \delta M_{d',e_j} + (M_d + \delta M_{d,e}) \delta M_{d,e_j}^{-1} (M_d' + \delta M_{d',e'}) \Rightarrow \\
M_d' [\delta M_{d,e_j}^{-1} - \delta M_{d',e_j}^{-1}] M_d + \delta M_{d,e'} [\delta M_{d,e_j}^{-1} + \delta M_{d,e_j}^{-1}] M_d + 2 \delta M_{d,e_j}^{-1} \delta M_{d'^e_j} \delta M_{d,e'}' \geq 0
\]

(12)

One can see that this last line is generally satisfied if \( \delta M_{d,e_j} \geq \delta M_{d,e_j} \); i.e. that the marginal gain in information with the addition of \( e_j \) for the smaller design is larger than or equal to the gain for the bigger design. However, moderate deviations to this rule can still allow the condition to be satisfied. We do not provide a complete proof of when this condition is satisfied as it depends on a complex combination of the covariances between the different components of these designs and the values of their covariates, which may vary widely given the range of models captured by a GLMM formulation. We assume that for the relatively commonplace models we consider, including with strictly positive monotone decreasing covariance functions, that function \( g(\cdot) \) is supermodular as the elements of \( \Sigma_{12} \) are all greater than or equal to zero.

A function is called submodular if in Equation (10) the inequality is reversed. The maximisation of a submodular function is equivalent to the minimisation of a supermodular function (Sviridenko et al., 2017). The literature often discusses the former, but both problems have the same algorithms associated with finding approximate optimal solutions. There are two foundational algorithms with well defined theoretical guarantees for minimising (maximising) a monotone supermodular (submodular) functions. These algorithms map onto algorithms proposed by Wynn (1970) and Fedorov (1972) for identification of D-optimal (i.e. maximising \( \det(M) \)) experimental designs as we discuss below.

### 2.1.1 Local search

Algorithm 1 shows the local search algorithm. At each step of the algorithm, the optimal ‘neighbour’ is identified as the design with one experimental condition removed and a different one from the design space added. If this neighbouring design has a smaller variance than the current design, then it replaces the current design, otherwise the algorithm terminates. The evaluation of \( g \) scales as \( O(n^2) \) when the experimental conditions are correlated (see Supplementary Information), so the running time of this algorithm scales with \( O(n^2(n^2J - n^2)) \), as we have to evaluate adding all remaining elements in \( D \) for each element in \( \mathcal{D} \) up to a maximum of \( n \) times. When the experimental conditions are uncorrelated we can use Equation (3) to reduce the evaluation of the function for a neighbouring design to calculating the information matrix only for the experimental condition and adding/subtracting it, which scales as \( O(n^2) \) where \( n_e = \max_j |e_j| \); typically \( n_e << n \) so the computational complexity is significantly reduced.

Fedorov (1972) developed the first local search algorithm for D-optimal designs with independent observations; several variants were later proposed (Nguyen and Miller, 1992). Although there is presently no proof that such an approach converges to a D-optimal design. For general monotone supermodular function minimisation, we can consider the ‘optimality bound’; if \( d \) is the output of the local search algorithm and \( d^* \) is the global minimiser of the function, then the optimality bound is the upper bound of \( g(d)/g(d^*) \). Fisher et al. (1978) showed that under a cardinality constraint (such as \(|d| \leq n \)) the optimality bound is 3/2. Filmus and Ward (2014) improved this bound to \((1+1/e)\) by using an auxiliary function in place of \( g \) that excludes poor local optima. Feige (1998) showed that further improving these bounds is an NP-hard problem and Nemhauser and Wolsey (1978) showed that algorithms that improve on these bounds require an exponential number of function evaluations, rather than the polynomial number of the local search. In practice these algorithms may perform significantly better than the lower bounds would suggest, though there exists
little empirical evidence for the types of design we consider. Hooper et al. (2020) aimed to identify c-optimal cluster randomised trial designs based on a linear mixed model using a local search type approach (although they did not explicitly reference it as such) and assumed that the resulting designs were optimal. However, they did not clearly define a design space or experimental condition so their results are difficult to interpret.

Algorithm 1 Local search algorithm

Let \( d_0 \) be size \( n \) design
Set \( \delta = 1 \) and \( d \leftarrow d_0 \)
while \( \delta < 0 \) do
    for all element \( e_j \in d \) and \( e_{j'} \in D/d \) do
        Calculate \( g(d/\{e_j\} \cup \{e_{j'}\}) \)
    end for
    Set \( d' \leftarrow \text{argmin}_{j,j'} g(d/\{e_j\} \cup \{e_{j'}\}) \)
    \( \delta = g(d') - g(d) \)
    if \( \delta > 0 \) then \( d \leftarrow d' \)
end if
end while

2.1.2 Greedy search

Algorithm 2 shows the greedy algorithm. We start from the empty set \( (s = 0) \) and at each step of the algorithm add the experimental condition that has the largest marginal increase in the objective function. The optimality bound for this algorithm is \( (1 + 1/e) \) (Nemhauser and Wolsey, 1978), and it scales as \( O(Jn^2) \), or \( O(Jn^3) \) when the experimental conditions are uncorrelated. Fedorov (1972) proposed a variant of this algorithm for D-optimal designs, often called a sequential algorithm, in which observations are sequentially added to an existing design until a convergence criterion identifying D-optimality is reached. Fedorov showed this algorithm produced a D-optimal design for linear models without cardinality constraint. Accelerated (or adaptive) greedy algorithms provide significant computational improvements on the standard greedy algorithm by avoiding recomputation of the objective function (Robertazzi and Schwartz, 1989). Accelerated greedy algorithms have been used in experimental design, designing sensor networks, and other problems (Guo et al., 2019, Yang et al., 2019, Zou et al., 2016). We do not consider the accelerated algorithm here as we aim to first consider whether the greedy algorithm performs well for c-optimal experimental design.

Yang et al. (2013) developed a continuous sequential/greedy algorithm to identify optimal designs for generalised linear models under a range optimality criteria. They discretised the design space using a regular lattice and showed convergence to optimal designs as the number of lattice cells grows. Variants and combinations of these methods have also been proposed, for example, the ‘Cocktail algorithm’ combines a sequential algorithm with two other algorithms in each step to find D-optimal designs (Yu, 2011), although there are few examples for c-optimality.

Algorithm 2 Greedy search algorithm

Let \( d \) be a non-degenerate design of size \( s < n \)
Set \( k = 0 \)
while \( k \leq n \) do
    for all element \( e_j \in D/d \) do
        Calculate \( g(d \cup \{e_j\}) \)
    end for
    Set \( d' \leftarrow \text{argmin}_{e_j} g(d \cup \{e_j\}) \)
    \( \delta = g(d') - g(d) \)
    if \( \delta > 0 \) then \( d \leftarrow d' \)
end if
end while

For general monotone supermodular function minimisation, the greedy algorithm should start from the empty set and sequentially add elements. However, for the c-optimal design problem this would fail, as the information matrix would not be positive definite. We would require \( p \) or more observations to ensure the design was not degenerate and both the covariance and information matrices were positive semi-definite. The starting design of size \( p \) may therefore affect the quality of the solution output from the algorithm and we no longer have theoretical guarantees about its performance. However, it may be able to provide a useful starting point for the local search algorithm and reduce the computational effort required. Other authors have used the output from the greedy algorithm as an input to the local search algorithm in other settings (e.g. Filmus and Ward (2014)). We can therefore identify four alternative combination algorithms:
• *Algorithm I* Local search algorithm starting from a randomly chosen design of size \( n \);
• *Algorithm II* Local search algorithm starting from a randomly chosen design of size \( p \leq s < n \), followed by greedy algorithm, followed by a local search;
• *Algorithm III* Local search algorithm starting from a randomly chosen design of size \( p \leq s < n \), followed by greedy algorithm;
• *Algorithm IV* Greedy algorithm starting from a randomly chosen design of size \( p \leq s < n \), followed by a local search algorithm.

The running time of the greedy algorithm is smaller than that of the local search algorithm but the quality of its solutions may be inferior to those from other algorithm variants. In the following sections we aim to compare the performance of these algorithms, compare them to approximate optimal designs where use cases overlap, and extend the algorithms to robust and Bayesian optimal designs.

### 3 Comparative performance

#### 3.1 Comparison of Algorithms

Our first empirical analysis is a direct comparison of the four algorithms described above. We compare them in two areas: range of solutions and computational complexity. For the former, we run the algorithm 1,000 times across all four algorithms for each of the applied examples described below. Within each run we determine the range of variance of the designs from each algorithm (where by ‘variance’ we refer to the value of \( c^T M^{-1} c \)). The ratio of the variance of the worst design from each algorithm to the maximum across all four algorithms, and the proportion of designs with variance equal to the minimum. To assess computational complexity we report the range of the number of times the function \( g \) is evaluated within each run of each algorithm. We do not systematically report running times as these are heavily dependent on system architecture, operating systems, compilers, and so forth. We coded the algorithms in C++ as efficiently as we could, but there may of course be more efficient means of implementing them. A comparison of the number of calls to the function provides an indication of relative computational complexity. We make all these algorithms available as part of the glmmr package for R.

#### 3.2 Applied Examples

We describe three example optimal design problems below for the comparison of the algorithms.

**A) Cluster randomised trial with unequal cluster-period sizes.** Figure 1 describes a design space for a cluster randomised trial with repeated measures. Each cell is a cluster-period within which we can observe individuals. We consider two related design problems. Individuals are cross-sectionally sampled within each cluster-period. There are \( K = 6 \) clusters and \( T = 5 \) total time periods arranged as per Figure 1. The assumed mean function for an observation \( i \) in cluster \( k \) at time \( t \) is:

\[
\mu_i(k,t) = \beta_0 \Delta_{ct} + \beta_1 \tau_t + \epsilon_{ct}
\]

where \( \Delta_{ct} \) is a treatment indicator equal to one if the cell has the intervention and zero otherwise as shown in Figure 1, \( \tau_t \) are \( T \) time-period indicators (so we do not include an intercept). The random effects terms \( \epsilon_{kt} \) are defined by the covariance function:

\[
Cov(\epsilon_{kt}, \epsilon_{k't'}) = \begin{cases} 
\sigma_1^2 & \text{if } k = k', t = t' \\
\sigma_2^2 & \text{if } k = k', t \neq t' \\
0 & \text{otherwise}
\end{cases}
\]

which defines a compound symmetric covariance matrix with cluster and cluster-period group
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membership random effects (Hemming et al., 2015, Hussey and Hughes, 2007). We specify a linear model with normal distribution, identity link function, and scale parameter $\sigma^2 = 1$. We set $\sigma_1^2 = 0.04$ and $\sigma_2^2 = 0.01$, which is equivalent to an intraclass correlation coefficient of 0.05 and a cluster autocorrelation coefficient of 0.8 in standard cluster trials terminology, and $\beta_0 = \beta_1 = 0$. We specify a maximum number of individuals per cluster-period of 10, and aim to identify an optimal design of 100 individuals (out of a possible 300); an experimental condition is a single observation from an individual. We set $c = (1, 0, ..., 0)^T$.

B) Cluster randomised trial with equal cluster-period sizes. The design space in Figure 1 is expanded to $K = 10$ clusters and $T = 9$ periods with the same staggered intervention initiation. Individuals are again assumed to be cross-sectionally sampled and we assume the same mean function specification as Equation (13). We modify the covariance function to an autoregressive specification:

$$\text{Cov}(\epsilon_{kt}, \epsilon_{k't'}) = \begin{cases} \sigma_1^2 \lambda^{|t-t'|} & \text{if } k = k' \\ 0 & \text{otherwise} \end{cases}$$

where we set $\lambda = 0.6$. We now assume an experimental condition is a whole cluster period of 10 individual observations, and aim to find an optimal design of 10 cluster-periods. We set $c = (1, 0, ..., 0)^T$.

C) Geospatial sampling to estimate non-linear intervention effects. Our design space is a unit-square $A = [0,1]^2$. The space is divided into a regular $25 \times 25$ lattice, where observations are made at the cell centroids $a \in A$. In the second time period an intervention is added at the point $z = (0.5, 0.5)$. The mean function at location $a$ is specified as:

$$\mu(a) = \beta_0 + \beta_1 \exp(-\beta_2 |a - z|) + \epsilon_a$$

To accomodate the non-linear mean function in the framework described above we use a first-order approximation to the information matrix (following Holland-Letz et al. (2011, 2012) and others):

$$M_d = F^T \Sigma^{-1} F$$

where the first column of $F$ is a vector of ones, the second column is $\partial \mu / \partial \beta_1 = \exp(-\beta_2 |a - z|)$, and the third column is $\partial \mu / \partial \beta_2 = -\beta_1 |a - z| \exp(-\beta_2 |a - z|)$. We set $\beta_0 = 1$, $\beta_1 = \ln(2)$, and $\beta_2 = 4$. We specify a Poisson distribution with log link function. Finally, we specify an exponential covariance function:

$$\text{Cov}(\epsilon_a, \epsilon_{a'}) = 0.25 \exp(-4|a - a'|)$$

Our aim is to find an optimal design of size $n = 100$ (of a total possible 625). We set $c = (0, 1, 0.1)^T$.

3.3 Results

Table 1 reports the results from the algorithms for each of the examples. Algorithms I and IV, which end with a local search and start either randomly or from a greedy search, respectively for I to IV, provided the best performance in terms of the ratio of the worst design to the best and the proportion of outputs equal to the best design. Algorithm IV required fewer operations (between 25% and 75% of Algorithm I). For example $A$, the majority of outputs from Algorithms I, II, and IV were the best design, but for $B$ only 10%, 3%, 0%, and 14% were, respectively, with the figures dropping to $< 1\%$ for example $C$. However, for algorithms I and IV in example $C$ the variance of the worst design from the algorithm was within 0.01% of the best design. Algorithm III did not produce the best observed design in any of the examples. Figure 2 shows optimal designs for each example. To provide an indication of running time on the machine used to run the analyses (Intel Core i7-9700K, 32GB RAM, Windows 10, gcc compiler), algorithm IV for Example $A$ took $\sim 0.1s$, $B$ took $\sim 2s$, and $C$ took $\sim 120s$.

4 Comparison with Approximate Optimisation

An approximate design is characterised by a probability measure over unique experimental conditions $\phi = \{(\phi_j, \epsilon_j) : j = 1, ..., J; \phi_j \in [0,1]; \sum_j \phi_j = 1\}$ where $\phi_j$ are the weights associated with each experimental condition. These weights can be identified for design spaces with uncorrelated experimental conditions (Holland-Letz et al., 2012, Sagnol, 2011). However, there
| Ex | Algo. | Var. (range) | Min. ratio | Prop. min | F evaluations |
|----|-------|--------------|------------|-----------|---------------|
| A | I | (0.043, 0.043) | 1.0001 | 0.85 | (32,070, 48,960) |
| A | II | (0.043, 0.043) | 1.0028 | 0.58 | (10,830, 19,710) |
| A | III | (0.045, 0.047) | 1.1098 | 0.00 | (3,240, 4,440) |
| A | IV | (0.043, 0.043) | 1.0005 | 0.60 | (6,990, 18,180) |
| B | I | (0.088, 0.089) | 1.0181 | 0.10 | (23,400, 43,200) |
| B | II | (0.088, 0.096) | 1.1075 | 0.03 | (14,400, 35,100) |
| B | III | (0.096, 0.107) | 1.2109 | 0.00 | (2,700, 9,000) |
| B | IV | (0.088, 0.088) | 1.0048 | 0.14 | (11,700, 35,100) |
| C | I | (1.754, 1.755) | 1.000 | 0.00 | (4.125M, 5.937M) |
| C | II | (1.754, 1.761) | 1.004 | 0.00 | (887,500, 1.957M) |
| C | III | (1.754, 1.762) | 1.005 | 0.00 | (67,500, 105,500) |
| C | IV | (1.754, 1.754) | 1.000 | 0.01 | (810,000, 2.123M) |

Table 1 Results from the four algorithms on the three examples. Table headings are: Var. = variance, Min. ratio is the ratio of the worst output of the algorithm to the best design from all four algorithms across all runs in the example, Prop. max is the proportion of outputs from each algorithm equal to the best possible design within each example, and F evaluations is the range of the number of function calls for each algorithm and example.

Fig. 2 Optimal designs for examples A-C. The 0 and 1 labels in the top row indicate the treatment status of the cluster period.
are several methods for converting proportions to integer counts that sum to a given total, which is known as the apportionment problem. The problem was famously identified for converting popular vote totals in states into numbers of seats in the US House of Representatives; the solutions are named after their proposers (Balinski and Young, 2002). We compare the performance of approximate design algorithms with different apportionment methods to the best performing combinatorial method from the previous section, the local search with greedy start. For a given set of weights $\phi_j$ and a target total of number of experimental conditions $n$ in the design, the methods for determining the number of each experimental condition $n_j$ such that $\sum_j n_j = n$, are:

1. **Hamilton’s method** Let $\pi_j = n \ast \phi_j$, we assign $\lfloor \pi_j \rfloor$ of each experimental condition. The remaining total is filled by the experimental conditions with the largest remainders $|\pi_j - \lfloor \pi_j \rfloor|$ until we have $n$ experimental conditions.

2. **Divisor methods** Start with all $n_j = 0$ and let $\pi_j = n \ast \phi_j$. Proceeding iteratively, we choose the next experimental condition in the design to be that with $\max_j \pi_j / \alpha(n_j)$, for which we update the total until the condition $\sum_j n_j = n$ is met.
   
   (a) **Jefferson’s method** $\alpha(n_j) = n_j + 1$
   
   (b) **Webster’s method** $\alpha(n_j) = n_j + 0.5$
   
   (c) **Adam’s method** $\alpha(n_j) = n_j$. Initially we include one of each experimental condition with $\pi_j > 0$.

To identify the optimal approximate design $\phi$ we use the second-order cone program proposed by Sagnol (2011). We consider the following optimal design problem.

**D) Hybrid cluster randomised trial designs.** Returning to the cluster trial design space shown in Figure 1, we now consider an experimental condition to be a whole row, i.e. a collection of five cluster-periods each with ten cross-sectionally sampled individuals in. We wish to include $K$ clusters in the design, each of which may be assigned to any of the experimental conditions, and consider $K = 6$ to $K = 30$. We use the mean function as Equation (13) and the autoregressive covariance function specified by Equation (15). The experimental conditions are uncorrelated with one another. This design problem was considered by Girling and Hemming (2016).

The optimal weights for the six experimental conditions from the weighting method are $(0.412, 0.048, 0.040, 0.040, 0.048, 0.412)$. Figure 3 presents the relative variances of the designs resulting from each of the rounding procedures alongside the best and worst designs resulting from using a local search algorithm. For this example, the local search converged to the same design on every iteration so the best and worst values are equal, for each sample size this was also the minimum variance across all methods. For the different rounding methods, Hamilton’s method performed best at every sample size and found the optimal design for even values of the sample size. Adam’s method performed worst for sample sizes less than 12 clusters, after which Jefferson’s method generally performed worst.

## 5 Robust optimal designs

The analysis and discussion so far has been based on the assumption that the correct model specification is known. However, this is typically an unrealistic assumption, and it is well known that an optimal design for one model may perform very poorly for an alternative model. We consider a model robust optimal design criterion that is amenable to combinatorial optimisation. Following Dette (1993), we assume that the “true” model belongs to a known class of GLMMs. We can define a model with the collection $G = (F, h, Q, \Theta, c)$ where $\Theta$ are the parameters that define the covariance function and the scale parameter for the distribution. The class of models is then

$$G_U = \{G_1, ..., G_U\}$$

The vector $\rho = (\rho_1, ..., \rho_U)$ with $\rho > 0$ is then called a prior for the class $G$ with the values reflecting the belief about the relative probability or adequacy of each model. The objective function (7) can be written for a specific model as $g_u(d) = g(d; G_u)$ and we can define the robust objective function as:

$$h(d) = \sum_{u=1}^{U} \rho_u g_u(d)$$
Dette (1993) provides a geometric characterisation of this approach for c-optimal designs with uncorrelated observations, building on similar work for D-optimal designs. The objective function (20) is also monotone submodular since

$$\sum_{u=1}^{U} \rho_u g_h(d) = \sum_{u=1}^{U} \rho_u [g_h(d) - g_h(d')] \leq \sum_{u=1}^{U} \rho_u [g_h(d) - g_h(d')]$$

and

$$\sum_{u=1}^{U} \rho_u g_h(d) \geq \sum_{u=1}^{U} \rho_u g_h(d') \text{ for } d' \subseteq d$$

if all the $g_u$ are themselves monotone submodular. We can thus employ the local and greedy search approaches described above. A design minimising (20) is then said to be optimal for $G_U$ over the prior $\rho$. We note that other robust specifications such as minimax ($h(d) = \max_u g_u(d)$) are not supermodular, so we do not consider them here.

We extend the examples A to C used described in Section 3.2 to robust optimal design problems.

E) Cluster randomised trial with unequal cluster-period sizes and unknown covariance parameters. As example A but with the covariance parameters $(\sigma_1^2, \sigma_2^2)$ unknown. The range of possible values we consider are $((0.045,0.05), (0.04,0.01), (0.03,0.02), (0.095,0.005), (0.008,0.002), (0.003,0.002))$ with uniform prior probabilities of 1/6 on each design.

F) Cluster randomised trial with equal cluster-period sizes and unknown covariance parameters. As example B but with the mean function parameters and covariance parameter $(\beta_0, \beta_1, \lambda)$ unknown. The range of possible values we consider are $(((0,...,0),0.0.6), ((-1,...,-1),0.0.6), ((-1,...,-1),0.5,0.6), ((0,...,0),0.0.9), ((-1,...,-1),0.0.9), ((-1,...,-1),0.5,0.9))$ again with uniform prior probabilities of 1/6 on each design.

G) Geospatial sampling with unknown nonlinear intervention effects. As example C but with $\beta_2$ unknown. We consider values $\beta_2 = 4.6$ with prior probabilities (0.5, 0.5).

5.1 Results

The top panel of Table 2 reports the output of the algorithms and Figure 4 shows a approximate optimal designs for each example. As before, algorithms I and IV generally provide the best performance in terms of the ratio between the worst design and best design across all algorithms, although the results were comparable for Example F. However, in all cases very few (<1%) of algorithm outputs produced the best design, although all designs had 10% greater variance except for algorithms II and III for Example E.

Computational effort increased linearly with the number of designs in each design problem with the local search with random start requiring the most evaluations of the objective function.

6 Bayesian c-Optimality

We can further extend the ideas presented in this paper to Bayesian optimal experimental design. We assume the likelihood of the model remains...
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| Ex | Algo. | Var. (range) | Max. ratio | Prop. min | F evaluations |
|----|-------|--------------|------------|-----------|---------------|
| D  | I     | (0.042, 0.043) | 1.0032     | 0.00      | (202,680, 307,980) |
| D  | II    | (0.042, 0.044) | 1.0409     | 0.01      | (55,440, 120,960)  |
| D  | III   | (0.044, 0.047) | 1.1129     | 0.00      | (22,320, 33,840)   |
| D  | IV    | (0.042, 0.044) | 1.0377     | 0.00      | (32,940, 113,220)  |
| E  | I     | (0.087, 0.092) | 1.0723     | 0.00      | (172,800, 291,600) |
| E  | II    | (0.086, 0.107) | 1.2511     | 0.00      | (113,400, 253,800) |
| E  | III   | (0.099, 0.133) | 1.5442     | 0.00      | (21,600, 64,800)   |
| E  | IV    | (0.084, 0.089) | 1.0547     | 0.01      | (81,000, 232,200)  |
| F  | I     | (1.20, 1.20)   | 1.02       | 0.00      | (9.875M, 13.500M)  |
| F  | II    | (1.17, 1.20)   | 1.02       | 0.01      | (1.860M, 4.735M)   |
| F  | III   | (1.17, 1.20)   | 1.02       | 0.00      | (215,000, 265,000) |
| F  | IV    | (1.20, 1.20)   | 1.03       | 0.00      | (2.115M, 4.990M)   |
| G  | I     | (0.039, 0.039) | 1.0907     | 0.01      | (470,400, 754,080) |
| G  | II    | (0.040, 0.041) | 1.0814     | 0.00      | (138,720, 420,000) |
| G  | III   | (0.042, 0.043) | 1.0249     | 0.01      | (55,680, 144,000)  |
| G  | IV    | (0.039, 0.041) | 1.0394     | 0.00      | (65,760, 341,760)  |

Table 2: Results from the four algorithms for the robust and Bayesian examples. Table headings are: Var. = variance, Min. ratio is the ratio of the worst output of the algorithm to the best design from all four algorithms across all runs in the example, Prop. max is the proportion of outputs from each algorithm equal to the best possible design within each example, and F evaluations is the range of the number of function calls for each algorithm and example.

the same as Equation (1) but we add prior distributions for the model parameters. We specify the prior \( \beta \sim N(0, V_0) \) where \( V_0 \) is a covariance matrix, and that \( \Theta \sim F_\alpha \) where \( F_\alpha \) is an appropriate multivariate distribution. The aim in Bayesian optimal design is to maximise a utility function. Chaloner and Verdinelli (1995) comprehensively review Bayesian experimental design criteria and utility function and show the equivalent Bayesian c-optimality function to be:

\[
U(d) = \int \int (c^T [M_d(\beta, \Theta)+V_0]^{-1} c)p(\Theta)p(\beta)d\Theta d\beta \tag{21}
\]

where we have explicitly shown the dependence of the information matrix on the parameters. \( U(d) \) simplifies to the term in brackets under a linear model. Computation of (21) is difficult and expensive. We can use a Riemann sum approximation of this integral by partitioning the prior of \((\beta, \Theta)\) into \(K\) discrete cells \([\beta_k, \beta_{k+1}] \cup [\Theta_k, \Theta_{k+1}]\) each with volume \(V_k\):

\[
U(d) \approx \sum_{k=1}^{K} (c^T \tilde{M}_d(\beta_k^*, \Theta_k^*)^{-1} c)p(\Theta_k^*)p(\beta_k^*)V_k \tag{22}
\]

where \( \tilde{M}(d; \beta_k, \Theta_k) = M(d; \beta_k, \Theta_k) + V_0 \), and \((\beta_k^*, \Theta_k^*) \in [\beta_k, \beta_{k+1}] \cup [\Theta_k, \Theta_{k+1}]\). Equation (22) is now in the same form as the robust objective function in Equation (20) with weights \(p(\Theta_k^*)p(\beta_k^*)V_k\). We provide an example of a Bayesian version of example A.

H) Cluster randomised trial with unequal cluster-period sizes and unknown covariance parameters. As example A but we specify the priors \( \frac{\sigma^2_1}{\sigma^2_1+\sigma^2_2} \sim \text{Unif}(0, 0.05) \) and \( \frac{\sigma^2_1}{\sigma^2_1+\sigma^2_2} \sim \text{Unif}(0.5, 0.95) \). The priors for the parameters \( \beta \) are all set at \( N(0, 1) \). We set \( K = 16 \) and set the values of the cell limits \( \Theta_k \) using the points at the quantiles \([0, 0.25, 0.5, 0.75, 1]\) of both marginal prior distributions.

6.1 Results

The lower panel of Table 2 reports the results for the Bayesian example and Figure 4 shows an approximate optimal design for this problem. Similar to the robust optimality examples, very few of the outputs of the algorithm were the best design. The ratio of the worst to the best design was < 10% for all algorithms.
7 Conclusion

The identification of exact c-optimal designs is only possible for the simplest experiments. Different methods of approximation have been proposed for more complex scenarios. For designs with correlated observations, we considered four variants of approximate combinatorial algorithms for supermodular function minimisation. The theoretical upper optimality bound for these algorithms is \( (1 + e^{-1}) \approx 1.37 \), however, for the examples we considered the performance is significantly better for two of the algorithms. For the two best performing algorithms (I and IV), local searches starting from either a random position or the output of the greedy algorithm, we did not observe a design worse than 1.1 times the best design. However, the output of the greedy search was often a poor approximation and in one example the worst design was worse than the theoretical lower bound of a ‘proper’ greedy algorithm. Given the need for a non-degenerate design, we cannot start from the empty set, which removes theoretical guarantees on optimality bounds. Overall, algorithm IV is the preferred algorithm as it provides similar performance to algorithm I but with less computational effort. In all cases, it would be recommended to run the algorithm several times and take the best design.

We cannot guarantee that the optimal design was included in the output of any of the algorithms especially for designs where the variances from similar designs may be within a rounding error of one another. However, our comparison with other approximate optimal design methods provides some reassurance. For designs with correlated observations but with uncorrelated experimental conditions, deriving weights using multiplicative methods for each experimental condition provides one method of approximating an optimal design (Holland-Letz et al., 2011, Sagnol, 2011).
We showed that the quality of the approximation can depend on the method used to round the weights to exact numbers of experimental conditions. Combinatorial approaches can achieve similar or better designs in these cases.

Many design problems are not inherently discrete; however, we can discretise the design space by specifying a set of design points (Yang et al., 2013). In these cases there is a trade-off between quality of the approximation and computational effort. Such an approach is often taken in studies with assumed complex GLMM data generating processes. For example, in geospatial statistical applications with a point process, where the underlying model assumes a latent Gaussian field with fixed covariate effects, a computational grid is used to facilitate computation (Diggle et al., 2013). The algorithms described here can be used for geospatial applications. For sampling across an area to estimate prevalence under an assumed geospatial model there are a variety of proposed schemes in the literature (Chipeta et al., 2017), however for more complex applications like estimating prevalence under an assumed complex GLMM data generating processes. For example, in geospatial statistics with assumed complex GLMM the inverse covariance matrix of the design can be described by GLMMs, such as cluster randomised trials or spatio-temporal sampling schemes in the literature (Chipeta et al., 2017), however for more complex applications like estimating mean function parameters, combinatorial algorithms provide a new method where optimal designs to support their planning.

Optimal designs may sometimes be impractical or difficult to implement. However, being able to identify approximately optimal designs provides a benchmark against which to justify proposed experiments. Many types of study that can be described by GLMMs, such as cluster randomised trials or spatio-temporal sampling across an area, can be significant and expensive undertakings. Combinatorial optimisation methods provide a means of identifying near-optimal or optimal designs to support their planning.

Appendix A  Rank-1 down/up dating to remove/add observations

A.1 Removing an observation

For a design $d$ with $m$ observations with inverse covariance matrix $\Sigma_d^{-1}$ we can obtain the inverse of the covariance matrix of the design with one observation removed $d' = d/\{i\}$, $\Sigma_{d'}^{-1}$ as follows. Without loss of generality we assume that the observation to be removed is the last row/column of $\Sigma_d^{-1}$. We can write $\Sigma_d^{-1}$ as

$$\Sigma_d^{-1} = \begin{pmatrix} C & d' \\ d'^T & e \end{pmatrix}$$  \hspace{1cm} (A1)

where $C$ is the $(m-1) \times (m-1)$ principal submatrix of $B$, $d$ is a column vector of length $(m-1)$ and $e$ is a scalar. Then,

$$G = \Sigma_{d/\{i\}}^{-1} = C - dd^T/e$$  \hspace{1cm} (A2)

A.2 Adding an observation

For a design $d$ with $m$ observations with inverse covariance matrix $\Sigma_d^{-1}$, we aim now to obtain the inverse covariance matrix of the design $d' = d \cup \{i'\}$. Recall that $Z$ is a $R \times Q$ design effect matrix with each row corresponding to a possible observation. We want to generate $H^{-1} = \Sigma^{-1}_{d'}$. Note that:

$$H = \Sigma_{d'} = \begin{pmatrix} G^{-1} & f \\ f^T & h \end{pmatrix}$$  \hspace{1cm} (A3)

where $f = Z_{i \in d} D Z_i'$ is the column vector corresponding to the elements of $\Sigma = W^{-1} + Z DZ^T$ with rows in the current design and column corresponding to $i'$, and $h$ is the scalar $W_{i',i'}^{-1} + Z_i D Z_i'^T$. Also now define:

$$H^* = \begin{pmatrix} \Sigma_d & 0 \\ 0 & h \end{pmatrix}$$  \hspace{1cm} (A4)

so that

$$H^{*-1} = \begin{pmatrix} \Sigma^{-1}_d & 0 \\ 0 & 1/h \end{pmatrix}$$  \hspace{1cm} (A5)

and

$$H^{**} = \begin{pmatrix} \Sigma_d & f \\ 0 & h \end{pmatrix}$$  \hspace{1cm} (A6)

and $u = (f^T, 0)^T$ and $v = (0, ..., 0, 1)^T$, both of which are length $m$ column vectors. So we can get $H^{**}$ from $H^*$ using a rank-1 update as $H^{**} = H^* + uv^T$ and similarly $H = H^{**} + vu^T$. Using the Sherman-Morison formula:

$$H^{**-1} = H^{*-1} - \frac{H^{*-1}uv^TH^{*-1}}{1 + vu^TH^{*-1}u}$$  \hspace{1cm} (A7)

and

$$H^{-1} = H^{**-1} - \frac{H^{**-1}vu^TH^{**-1}}{1 + u^TH^{**-1}v}$$  \hspace{1cm} (A8)
So we have calculated the updated inverse with only matrix-vector multiplication, which is $O(n^2)$.

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