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An Efficient Way to Find Optimal Crossover Designs Using CVX for Precision Medicine

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Abstract

Crossover designs play an increasingly important role in precision medicine. We formulate the optimal crossover design problem as a convex optimization problem and demonstrate that the convex optimization package CVX is effective for searching a broad class of optimal crossover designs, including cases where analytical optimal crossover designs are unavailable. We also use CVX to search for N-of-1 trials frequently used in precision medicine and dual-objective optimal crossover designs to estimate treatment effects and carryover treatment effects with unequal interest. We provide CVX codes and as illustrations, use them to find optimal crossover designs under the A-optimality criterion.

Keywords: convex optimization, dual-objective optimal design, information matrix, N-of-1 trial, precision medicine, repeated measures design.

1. Introduction

Crossover designs allow each patient in the trial to receive different treatments over time and use the patient as control. Consequently, the within response variability is smaller,

providing a more accurate estimate of the treatment effect. Crossover designs are gaining importance in recent years because a variation of them include N-of-1 trials or single patient trials that focus on one patient where the main goal is to evaluate whether the treatment is effective for the individual rather than an average patient. In the last two decades or so, there is increasing interest in N-of-1 trials. Duan et al. (2013) raised awareness among clinicians and epidemiologists that N-of-1 trials are potentially useful for informing personalized treatment decisions for patients with chronic conditions. Nikles et al. (2005) discussed such trials in behavioral sciences and different medical settings and related issues, such as, the economics and ethics of such trials, statistical analysis of analyzing N-of-1 trials and how to report results to professional audiences. Scuffham et al. (2010) showed how N-of-1 trials can improve patient management and save costs and Kravitz et al. (2014) provided a user's handbook on implementing such trials. A systematic review of use of N-of-1 trials in the medical literature is Gabler et al. (2011) and Chen and Chen (2014) discussed several ways to analyze and compare results from N-of-1 trials.

These designs apply treatments like in a crossover fashion and their optimality properties have been studied in Kiefer (1974); Cheng and Wu (1980); Kershner and Federer (1981); Carriere and Reinsel (1992); Kunert and Stufken (2002) and Kunert and Stufken (2008), just to mention a few. Traditional crossover design models assume that the carryover effects last for only one period. Subject effects are typically considered fixed in the model and assume no carryover effects for observations in the first period. An alternative model, which has carryover effects in the first period as well, was proposed by giving patients a pre-period or baseline period (Kunert 1984; Afsarinejad 1988). More complex models for crossover studies have also been considered. Some models incorporated higher-order carryover effects (Bose and Mukherjee 2003) or assumed the carryover effects are proportional to the treatment effects (Kempton et al. 2001) or assumed interaction effects between the treatment effects and carryover effects (Sen and Mukerjee 1987). Mukhopadhyay and Saha (1983); Jones et al. (1992) and Carriere and Reinsel (1993) allowed random patient effects.

Optimal crossover designs are model-based and thus can be very sensitive to model assumptions. This means that a slight change in model assumption can result in a very different design and become sub-optimal with its optimality and efficiency varying substantially. In principle, the implemented design should be robust to both model assumptions and design criteria.

It is known that the two-treatment design AB, AA and the duals BA, BB is found to be universally optimal for two-period experiments, with the duality defined as the sequence that switches A and B with the same effect. Similarly, it is known that the two-sequence design ABB and its dual BAA and the four-sequence design $ABBA$, $AABB$ and the duals $BAAB$, $BBAA$ by switching the order are optimal for three- and four-period experiments; see for example, Carriere (1994) and Laska and Meisner (1985). However, as the model gets complex with important effects that need to be adjusted for, finding the optimal crossover design analytically becomes a challenging task.

The aim of this paper is to introduce the software called CVX, which is a disciplined optimization tool for solving convex optimization problems. It is widely used among engineering researchers to solve convex optimization problems but interestingly, it is

rarely used among statistics researchers. The software can be helpful because analytical description of crossover designs are only possible for relatively simple models and are not available for more complex models. There is also no dedicated software or commands in commercial statistical packages for finding them. To this end, we first show how to transform crossover design problems into convex optimization problems and then apply CVX to find different types of crossover designs. In particular, we first show results from CVX coincide with some of the known theoretical crossover designs in the literature before we apply CVX to solve crossover design problems where theoretical designs are unavailable.

The rest of the paper is organized as follows. In Section 2, we briefly describe the statistical setup and review optimal design ideas and methods. Section 3 reviews fundamentals of convex optimization. Section 4 shows how to formulate the optimal design problem into a convex optimization problem, and as an example, shows how to use CVX to find A-optimal crossover designs. In Section 5, we further demonstrate usefulness of CVX and report optimal crossover designs for a broader class of of models, including N-of-trials and dual-objective optimal crossover designs found from CVX. Section 6 discusses CVX codes, and Section 7 concludes with ideas for future work and stresses the relevance of our work to advance research in precision medicine.

2. Background

We denote a crossover design with t treatments and p periods by COD(t,p), where each subject receives a treatment sequence with p periods and any one of the t treatments can be assigned to the patient at each period. Let S be the number of distinct sequences; the maximum value of S is t^p. This is the number of all possible distinct sequences of treatments we need to consider when we design a crossover trial. Usually, there are replicates and some of the treatment sequences are used multiple times in the study; if the i^{th} sequence is replicated n_i times, then the total sample size is $n = \sum_{i=1}^{S} n_i$.

The linear model for modeling responses from the crossover design has the form

$$y_i = X_i\beta + \epsilon_i,$$

where $y_i \in R^p$ is the vector of responses from a subject assigned to the ith sequence. Suppose that there are k unknown parameters in the model, $X_i \in R^{p\times k}$ is the design matrix for the ith sequence, and $\beta \in R^k$ is the vector of the unknown parameters. Assuming the error terms have the covariance matrix Σ, then the information matrix of a design ξ that assigns n_i patients to the i^{th} distinct sequence of treatments is proportional to,

$$I(\xi) = \sum_{i=1}^{S} n_i X_i \Sigma^{-1} X_i^T.$$

These are exact design problems and they are extremely difficult to determine analytically. In practice, we determine approximate designs which are easier to determine by solving a convex optimization problem. Instead of determining the number of replicates n_i in the exact design problem, we find the optimal proportions for each distinct sequence in the design. Let n be the number of subjects in the experiment and and let $\xi_i = n_i/n$ which is the proportion of subjects assigned the i^th distinct sequence

of treatments. To implement an approximate design, we assign $n_i = n\xi_i$ subjects to treatment sequence i after rounding each n_i to the nearest non-negative integer where $n_1 + \ldots + n_S = n$. When n is large enough, the constraint can be relaxed to $\xi \in R_+^S$ and the $\xi_1 + \ldots + \xi_S = 1$. This relaxed design problem is often called the approximate experimental design problem.

Given an optimality criterion, we find a design that optimizes it among a selected class of designs. If it is among all k-point designs, it is an optimal k-point design and if it is optimal among all designs, it is a globally optimal design. Since the information matrix $I(\xi)$ measures the value of the design, optimality criteria are usually formulated as a function of the information matrix. For many common statistical problems, the optimality criteria are also formulated as a convex or concave function of the information matrices. For example, a design is D-optimal (ξ_D) if it maximizes the determinant of $I(\xi)$, i.e.,

$$\xi_D = arg\ max_\xi\ det\ I(\xi),$$

and a design is A-optimal (ξ_A) if it minimizes the trace of the inverse of the information matrix, i.e.,

$$\xi_A = arg\ min_\xi\ tr(I(\xi)^{-1})$$

and the optimization is over all designs on the given design space. Both criteria are used to estimate model parameters; a D-optimal design ensures the confidence ellipsoid for the parameters has minimal volume and an A-optimal design makes the confidence ellipsoid as small as possible by minimizing the sum of the lengths of the major axes of the ellipsoid. Another criterion is E-optimality that minimizes the maximum length of the major axes in the confidence ellipsoid. It is a minimax criterion, a non-differentiable and more difficult, and the hardest to find and to study analytically. Extensions of these criteria to estimate only a subset of the model parameters are available.

Optimization problems are pervasive in research. Some special classes of optimization problems, such as least squares and linear programming problems, can be numerically solved quite efficiently. Convex optimization is a wider class of optimization problems than linear programming problems. After interior-point methods were developed in the 1980s to solve linear programming problems, researches realized these methods could be used for convex optimization problems as well. Some classes of convex optimization problems can be solved numerically efficiently, just as the linear programming problems are (Boyd et al. (2004)).

In the next section, we review convex optimization problems and show our approximate optimal design problems can be formulated as convex optimization problems so that we can use CVX to solve crossover design problems where analytical solutions are not available. We assume the objective function or the optimality criterion is a convex or concave function of $I(\xi)$ with ξ subject to $\xi_1 + \ldots + \xi_S = 1$. If there are constraints, we assume that they are also convex (or concave) functions.

3. Convex Optimization

3.1. Convex Sets

A set C is convex if for any two points $x, y \in C$ and any $\alpha \in [0,1]$, we have $\alpha x + (1-\alpha)y \in C$. We denote the set of symmetric $n \times n$ matrices by S^n, and denote the set of symmetric positive semidefinite matrices by $S^n_+ = \{X \in S^n | X \succeq 0\}$, where $X \succeq 0$ denotes the matrix X is positive semidefinite. Similarly, we denote the set of symmetric positive definite matrices by $S^n_{++} = \{X \in S^n | X \succ 0\}$, where $X \succ 0$ denotes X is a positive definite matrix. Manifestly, S^n, S^n_+ and S^n_{++} are all convex sets.

3.2. Convex Functions

A function $f : R^n \to R$ is convex if the domain, $\mathbf{dom} f$, is a convex set and if for all $x, y \in \mathbf{dom} f$ and any $\alpha \in [0,1]$, we have

$$f(\alpha x + (1-\alpha)y) \leq \alpha f(x) + (1-\alpha) f(y).$$

We say f is concave if $-f$ is convex. If f is convex and also concave, then f is an affine function.

Some examples of convex or concave functions defined on S^n_{++} are,

- $f(X) = tr(X^{-1})$ is convex on S^n_{++};
- $f(X) = \log\det X$ is concave on S^n_{++}.

A function $f : R^m \to S^n$ is matrix convex if for any $x, y \in \mathbf{dom} f$ and any $\alpha \in [0,1]$, we have

$$f(\alpha x + (1-\alpha)y) \preceq \alpha f(x) + (1-\alpha) f(y),$$

where the matrix inequality $X \preceq Y$ means $Y - X \succeq 0$ or $Y - X \in S^n_+$.

3.3. Conditions on Composition Functions to Preserve Convexity

Consider the function f is a composition of h and g, i.e., $f(x) = h \circ g(x)$, where $g, h : R \to R$. According to the second derivative rule, a function is convex if and only if its second derivative is non-negative, and a function is concave if and only if its second derivative is non-positive. Taking the second derivative of $f(x)$, we have,

$$f''(x) = h''(g(x))(g'(x))^2 + h'(g(x))g''(x),$$

which gives the conditions on h and g, such that the composition preserves the convexity.

- If h is convex and nondecreasing, and g is convex, then f is convex.
- If h is convex and nonincreasing, and g is concave, then f is convex.
- If h is concave and nondecreasing, and g is concave, then f is concave.
- If h is concave and nonincreasing, and g is convex, then f is concave.

The results can be generalized to more complicated composition, such as when $h : R^k \to R$ and $g : R^n \to R^k$ (Boyd et al. (2004)).

4. Constructing A-optimal Crossover Designs

We now construct crossover designs belonging to the class COD(t,p). Given an assumed linear model with k parameters, let $X_i \in R^{p\times k}$, $i = 1, 2, \cdots, S$, be the fixed design matrix corresponding the the i^{th} treatment sequence. The information matrix for the whole design ξ with S distinct treatment sequences is proportional to

$$I(\xi) = \sum_{i=1}^{S} \xi_i X_i \Sigma^{-1} X_i^T.$$

Clearly, the matrix $I(\xi) \succeq 0$ and we first assume that $I(\xi) \succ 0$ in this section; the case when the information matrix is singular is discussed in section 5. We also have the obvious constraints that the weights ξ_is are positive and they sum to unity. We write the constraint as $\mathbf{1}^T\xi = 1$.

Suppose the full vector of model parameters β can be partitioned into two components $(\theta', \psi')'$, where θ is the vector of parameters of interest and ψ is the vector of nuisance parameters. Then, we partition the information matrix $I(\xi)$ in the following form

$$I(\xi) = \begin{bmatrix} I_1 & I_2 \\ I_2^T & I_3 \end{bmatrix},$$

where $I_1 \in R^{k'\times k'}$ and $I_3 \in R^{(k-k')\times(k-k')}$. Since $I(\xi) \succ 0$, we have $I_1 \succ 0$ and $I_3 \succ 0$. The information matrix for θ adjusted by ψ is

$$I_\theta = I_1 - I_2^T I_3^{-1} I_2.$$

The matrix I_θ is called the Schur complement of I_3 in $I(\xi)$ and since $I(\xi) \succ 0$, it can be shown that $I_\theta \succ 0$. To find an A-optimal design for estimating a subset of the model parameters, namely θ, the design we seek is the one that minimizes $\mathbf{tr}\ I_\theta^{-1}$ over all designs of interest on the design space.

We next show that the above optimization problem is a convex optimization problem. To this end, let $I \in S_{++}^k$ and partition it as

$$I = \begin{bmatrix} I_1 & I_2 \\ I_2^T & I_3 \end{bmatrix},$$

where $I_1 \in S^{k'}$ and let $SC(I) : S_{++}^k \to S_{++}^{k'}$,

$$SC(I) = I_1 - I_2^T I_3^{-1} I_2.$$

Lemma 1. The function $SC(I)$ is matrix concave in S_{++}^k.

Proof: To prove lemma 1, we recall a matrix fractional function defined for a convex function (Boyd et al. 2004) and use the fact that the function $f : R^n \times S^n \to R$, defined as

$$f(x, Y) = x^T Y^{-1} x$$

is convex on $\mathbf{dom}f = R^n \times S^n_{++}$.

Define a function $g : S^{k'}_{++} \times R^{k' \times (k-k')} \times S^{k-k'}_{++}$ by

$$\begin{aligned} g(I_1, I_2, I_3) &= \nu^T (I_1 - I_2^T I_3^{-1} I_2)\nu \\ &= \nu^T I_1 \nu - (I_2\nu)^T I_3^{-1}(I_2\nu) \\ &= \nu^T I_1 \nu - f(I_2\nu, I_3). \end{aligned}$$

Since $-f$ is concave, the g is a concave function of I_2, I_3 plus an affine function of I_1. Therefore, the g is a concave function of I_1, I_2, I_3. This implies that, for any $I_a, I_b \in S^n_{++}$, with their partitions $(I_{a1}, I_{a2}, I_{a3}), (I_{b1}, I_{b2}, I_{b3}) \in \mathbf{dom}g$ and any $\alpha \in [0, 1]$, we have, $g(\alpha I_{a1} + (1-\alpha)I_{b1}, \alpha I_{a2} + (1-\alpha)I_{b2}, \alpha I_{a3} + (1-\alpha)I_{b3}) \geq \alpha g(I_{a1}, I_{a2}, I_{a3}) + (1-\alpha)g(I_{b1}, I_{b2}, I_{b3})$. It follows that $\nu^T SC(\alpha I_a + (1-\alpha)I_b)\nu \geq \nu^T(\alpha SC(I_a) + (1-\alpha SC(I_b)))\nu$, or

$$SC(\alpha I_a + (1-\alpha)I_b) \succeq \alpha SC(I_a) + (1 - \alpha SC(I_b)).$$

Hence, $SC(I)$ is matrix concave of I on S^k_{++} and the result of Lemma 1 follows.

Lemma 2. The composition $SC \circ I$ is a concave function of ξ.

Proof: The information matrix $I(\xi)$ can be considered as an affine function of ξ, $I : R^S \to S^k_{++}$, i.e., $I : R^S \to S^n_{++}$ is an affine function. So, for any $\xi_1, \xi_2 \in R^S$ and any $\alpha \in [0, 1]$, we have

$$I(\alpha\xi_1 + (1-\alpha)\xi_2) = \alpha I(\xi_1) + (1-\alpha)I(\xi_2).$$

Therefore,

$$\begin{aligned} SC \circ I(\alpha\xi_1 + (1-\alpha)\xi_2) & \\ &= SC(I(\alpha\xi_1 + (1-\alpha)\xi_2)) \\ &= SC(\alpha I(\xi_1) + (1-\alpha)I(\xi_2)) \\ &\geq \alpha SC \circ I(\xi_1) + (1-\alpha)SC \circ I(\xi_2) \end{aligned}$$

and Lemma 2 holds.

The next two lemmas hold because the conditions preserve the convexity introduced in section 3.3.

Lemma 3. $h(I_\theta) = tr(I_\theta^{-1}) : S^{k'}_{++} \to R$ is convex and decreasing.

Lemma 4. The composition $h \circ SC \circ I$ is a convex function of ξ.

It follows from Lemma 4 that finding an A-optimal design is a convex optimization problem. We next discuss how such problems can be solved numerically and in an efficient manner.

5. Optimal CVX-generated Crossover Designs

In this section, we show how we solve 2 and 3-treatment optimal crossover design problems using programs in Matlab with CVX, which is a package for solving convex optimization programs (Boyd et al. 2004). All numerical solutions in this paper show a duality gap of zero (up to machine precision), certifying their global optimality. In other words, CVX finds the best approximate design.

We first assume the model of interest is the traditional model with a first-order residual effect and errors are equicorrelated with the within-subject correlation $\rho = 0.5$, unless stated otherwise. We also discuss and construct dual-objective crossover designs and optimal N-of-trial designs crucial for precision medicine.

Most of our demonstrations in this section are two-treatment crossover designs but we also show in our last example in the next subsection that CVX has the capability to extend to cases with 3 or more treatments. To fix ideas, we focus on A-optimal designs in this paper.

In a two-treatment crossover design, the parameters of interest can be constructed as the contrast of the two treatment effects and the contrast of the two carryover effects. Since the information matrix for treatment effect contrast or carryover effect contrast is a scalar, we note that all our A-optimal designs for a two-treatment crossover trial also D-optimal and E-optimal.

5.1. Optimal Crossover Designs with Two and Three-treatment and Various Periods for Estimating Treatment Effect

Optimal designs have been well developed for two-treatment p-period crossover trials (Laska and Meisner 1985). It is known that if $p = 2$, the design AA, AB, BB, BA with equal number of subjects per sequence is an optimal design for treatment effect. When $p = 3$, the design built up of the sequence ABB and its dual is optimal. For $p = 4$, according to Cheng and Wu (1980), the strongly balanced designs are universally optimal.

We next use CVX to generate optimal crossover designs to estimate the two-treatment effects and let the period effects and carryover effects be nuisance parameters. Tables (1), (2) and (3) display, respectively, the optimal design sequences and their optimal weights when the crossover trial has 2, 3 and 4 periods.

Table 1: Optimal design for treatment effect in COD(2,2).

AA	AB	BA	BB
0.2500	0.2500	0.2500	0.2500

Table 2: Optimal design for treatment effect in COD(2,3).

ABB	BAA
0.5000	0.5000

The numerical solutions agree with the known results, verifying that CVX is able to successfully produce the same optimal designs derived from theoretical considerations or reported elsewhere.

Table 3: Optimal design for treatment effect in COD(2,4).

ABBA	ABAB	AABB	BBAA	BABA	BAAB
0.1042	0.0729	0.3229	0.3229	0.0729	0.1042

CVX can also generate optimal crossover designs, that are not readily available from the literature or they are too challenging to construct from theory. This is particularly true when we have unstructured, special or general error structures, complex models or designs with more than 2 treatments. However, there is no increased complexity to find them using CVX after we cast the design problem into a convex optimization problem. For example, a direct application of CVX produces Table (4) that gives the optimal crossover design with 5-periods and assuming an auto-correlated error structure. Table (5) shows another example of the optimal crossover design found from CVX with an unstructured general error structure under the self and mixed carryover effect model (Kunert and Stufken 2002). This application assumes that the carryover effects not only depend on the treatment assigned to the previous period but also depend on the treatment administered currently in a mixed or parallel fashion.

Table (6) provides yet a further example of an optimal crossover design with 3 treatments, 3-periods and errors are equicorrelated with an illustrative value of $\rho = 0.5$.

Table 4: Optimal design for estimating treatment effect in COD(2,5) and errors are auto-correlated errors with $\rho = 0.4$.

AABBA	ABAAB	ABBAB	BAABA	BABBA	BBAAB
0.3552	0.0724	0.0724	0.0724	0.0724	0.3552

Table 5: Optimal design for estimating the treatment effect in COD(2,4) assuming a general error structure defined by a randomly generated symmetric positive semi-definite matrix given by

$$\begin{bmatrix} 1.0000 & 0.4023 & 0.2805 & 0.1746 \\ 0.4023 & 1.0000 & 0.2290 & 0.2158 \\ 0.2805 & 0.2290 & 1.0000 & 0.1864 \\ 0.1746 & 0.2158 & 0.1864 & 1.0000 \end{bmatrix}.$$

ABAA	ABBA	BAAB	BABB
0.4365	0.0635	0.0635	0.4365

Table 6: Optimal design for estimating the treatment effect in COD(3,3) and errors are equicorrelated with $\rho = 0.5$.

ABB	ABC	ACB	ACC	BAA	BAC	BCA	BCC	CAB	CBA
0.1675	0.0843	0.1023	0.0339	0.1675	0.0843	0.1023	0.0339	0.1121	0.1121

5.2. Dual-objective Optimal Designs in COD(2,2)

Not all studies have only one single agreed upon objective. For instance, the researcher may want to estimate model parameters and also make inference on the mean response at an extrapoloated does in a dose response at the same time. Similarly, in crossover designs, parameters corresponding to carryover effects and parameters corresponding to the direct effects may have differential interests to the researcher.

In this section, we consider optimal two-treatment two-period CODs with dual objectives. When within-subject correlation is not equal to zero, the optimal design for direct treatment effect and the optimal design for carryover effect are not identical. For example, the traditional optimal design for estimating the direct treatment effect has an equal number of subjects in each of the treatment sequences AA, AB, BB, BA. Table (1) shows corresponding results from CVX, along with Table (7) for CVX-generated] designs for estimating carryover effects.

Table 7: Optimal design for carryover effect in COD(2,2).

AA	AB	BA	BB
0.3750	0.1250	0.1250	0.3750

When both treatment effect and carryover effect are of interest, we find the optimal two-objective crossover design by optimizing a convex sum of the objective functions for the direct treatment effect and the carryover effect. The weight is a user-selected tuning parameter in the convex combination that represents the relative importance of the two objectives. Specifically, we want to find an approximate design that minimizes

$$\alpha \mathbf{tr} I_{\theta_1}^{-1} + (1-\alpha)\mathbf{tr} I_{\theta_2}^{-1}$$

and subject to $\xi \succeq 0$, $\mathbf{1}^T\xi = 1$. Since a convex combination of convex functions is again a convex function, we apply the same technique for finding a single objective optimal design to find the two-objective optimal design. Table (8) shows the compound optimal design for estimating the direct treatment effect and the carryover effect when $\alpha = 0.5$. For other values of α, representing different levels of interest in the two objectives, the corresponding designs are readily generated by CVX. Clearly, larger values of α signifies greater interest in the first objective for estimating θ_1.

Table 8: Compound optimal design for treatment and carryover effect in COD(2,2), $\rho = 0.5$ and $\alpha = 0.5$.

AA	AB	BA	BB
0.2914	0.2086	0.2086	0.2914

Table (8) displays the optimal crossover trial when we want to estimate both the direct and carryover treatments effects. The two objectives need not be of equal interest and their relative importance is reflected in the choice of the value $\alpha \in [0, 1]$. If α takes on either of the extreme values, we obtain the single objective designs shown in Tables (1) and (7). The technical details for constructing a dual-objective optimal crossover design parallel to that the approach in Cook and Wong (1994).

5.3. Optimal N-of-1 Trial Designs

For two-treatment multi-crossover single-patient trials, a general N-of-1 design can have multiple AB or BA crossover pairs in a sequence of treatments for within-patient comparisons. In addition to within patient-based evidence of a treatment contrast, it may also be desirable to obtain a population average effect of treatments. Aggregating the series of N-of-1 trials can give such an estimate of the average effect. Li et al. (2022) provides background information and relationship among on N-of-1 trials and crossover designs.

In the following, we apply convex optimization to search for, say, optimal six- and eight-period designs in N-of-1 trials for estimating the treatment effect under the traditional model. Table (9) and (10) display the optimal designs found from CVX.

Table 9: Optimal six-period N-of-1 trials with uncorrelated errors.

ABBAAB	BAABBA
0.5000	0.5000

Table 10: Optimal eight-period N-of-1 trials with eqicorrelated errors.

ABBAABBA	BAABBAAB
0.5000	0.5000

Table 11: Optimal 8-period N-of-1 trials with auto-correlated errors and $\rho = 0.5$.

ABABABAB	0.0029
ABABABBA	0.0044
ABABBAAB	0.0087
ABABBABA	0.0044
ABBAABAB	0.0087
ABBAABBA	**0.4579**
ABBABAAB	0.0087
ABBABABA	0.0044
BAABABAB	0.0044
BAABABBA	0.0087
BAABBAAB	**0.4579**
BAABBABA	0.0087
BABAABAB	0.0044
BABAABBA	0.0087
BABABAAB	0.0044
BABABABA	0.0029

We observe from Tables (9) and (10) that the optimal design in N-of-1 trials under the traditional model has treatment sequences with alternating crossover pairs AB and BA. This is consistent with the theoretical results of the optimal two-treatment N-of-1 trials.

Table (11) gives the optimal N-of-1 design under the traditional model with auto-correlated errors. As discussed in the optimal two-treatment N-of-1 trials, it is challenging to construct optimal N-of-1 design with auto-correlated errors analytically. However, as seen here, CVX generates the optimal design easily. The results in the Table (11) suggest that $ABBAABBA$ or $BAABBAAB$ is the option for a nearly optimal N-of-1 design. The weights for other sequences are not zero, implying that the sequences other than $ABBAABBA$ and $BAABBAAB$ may also be included to obtain an optimal aggregate N-of-1 design where $N > 1$. Extended multi-period N-of-1 designs over eight periods can be similarly constructed efficiently using CVX.

6. CVX Codes for Finding Optimal Crossover Designs in Matlab

Matlab is a widely used package for scientific computation and it has, as an option, CVX as well. This section shows how Matlab uses the CVX package to construct the A-optimal crossover designs shown in the previous section. Additional applications to solve convex optimization problems using CVX are available in Grant et al. (2009).

The following Matlab codes can be used to obtain optimal designs in Table (1), (2), (3), (4), (5), (6),(9), (10) and (11). Once the user provides the input variables (e.g., V, Sinvhalf, tauid, etc.), the below core program generates the sought optimal crossover design without further changes.

```
cvx_begin
    variable m(poolsize);
    variable X(length(tauid), length(tauid)) symmetric;
    r=repmat(m,1,p)';
    r=r(:);
    M=diag(r);
    Xd=V*Sinvhalf*M*Sinvhalf*V';
    A=Xd(tauid,tauid);
    B=Xd(tauid,taucomplement)';
    C=Xd(taucomplement,taucomplement);

    minimize(trace(X))
    subject to
    [A, B', eye(size(A, 1));
     B, C, zeros(size(C, 1), size(A, 2));
     eye(size(A, 1)), zeros(size(A, 2), size(C, 1)), X] == ...
        semidefinite(2 * size(A, 1) + size(B, 1));
    m >= 0;
    sum(m) == 1;
cvx_end
```

The set of codes starts with "cvx_begin" and ends with "cvx_end". In between, the convex optimization problem is defined. The variable statement defines a vector "m" and its length, denoted as "poolsize", is the total number of all candidate sequences

in an crossover design. The "V" denotes the design matrix for all candidate design sequences and "Sinvhalf" denotes $\Sigma^{-\frac{1}{2}}$.

Next, the information matrix and the Schur complement are calculated. The indices "tauid" and "taucomplement" are determined by the partitioning of the design matrix for calculating the Schur complement matrix for the direct treatment effect. The "tauid" is the index for the direct treatment effect and the "taucomplement" is the index for the other parameters.

The objective function of the optimization problem is to maximize the trace of the Schur complement under the conditions that the vector "m" is non-negative and it sums to unity. The outcome vector "m", which maximizes the trace of the Schur complement, indicates the proportion of each of the candidate sequences for an A-optimal design.

To extend the application and obtain the optimal designs in Tables (7) and (8), the objective function can be changed from Schur complement of the direct treatment effect to the linear combination of the Schur complement matrices of the direct treatment effect and the carryover effect. To find dual-objective optimal crosssover designs in this paper, the Matlab codes are directly modified as follows:

```
cvx_begin
    variable m(poolsize);
    variable X(length(tauid), length(tauid)) symmetric;
    variable Y(length(gammaid), length(gammaid)) symmetric;
    r = repmat(m, 1, p)';
    r = r(:);
    M = diag(r);
    Xd = V * Sinvhalf * M * Sinvhalf * V';
    Atau = Xd(tauid,tauid);
    Btau = Xd(tauid,taucomplement)';
    Ctau = Xd(taucomplement,taucomplement);
    Agamma = Xd(gammaid,gammaid);
    Bgamma = Xd(gammaid,gammacomplement)';
    Cgamma = Xd(gammacomplement,gammacomplement);

    minimize(alpha*trace(X) + (1-alpha)*trace(Y))
    subject to
    [Atau, Btau', eye(size(Atau, 1));
    Btau, Ctau, zeros(size(Ctau, 1), size(Atau, 2));
    eye(size(Atau, 1)), zeros(size(Atau, 2), size(Ctau, 1)), X] == ...
    semidefinite(2 * size(Atau, 1) + size(Btau, 1));
    [Agamma, Bgamma', eye(size(Agamma, 1));
    Bgamma, Cgamma, zeros(size(Cgamma, 1), size(Agamma, 2));
    eye(size(Agamma, 1)), zeros(size(Agamma, 2), size(Cgamma, 1)), Y] == ...
    semidefinite(2 * size(Agamma, 1) + size(Bgamma, 1));
    m >= 0;
    sum(m) == 1;
cvx_end
```

The indices "gammaid" and "gammacomplement" are determined by partitioning the

design matrix for calculating the Schur complement matrix for the carryover effect. We note that in this Matlab application, when "alpha" is set to 0, it produces the optimal designs in Table (7) and when "alpha" is set to 0.5, it produces the optimal designs in Table (8).

7. Discussion

We have shown how CVX can solve crossover optimal design problems quickly and effectively once the objective function and other constraints are formulated as a convex optimization problem. For the few cases we used to demonstrate, the CVX results are identical to the theoretical crossover designs reported in the literature.

We close with a note that we may apply CVX to tackle more complicated design problems. Consider the case when the information matrix is singular. To handle this case, we first generate a matrix fractional function on $R^n \times S_+^n$. If we could prove that the convexity holds for the matrix fractional function on $R^n \times S_+^n$, i.e., $f(x, Y) = x^T Y^- x$ is convex, then we can have more general results for more design problem with positive semidefinite information matrices, instead of positive definite information matrices.

We can also use CVX to solve convex optimization problems with other criteria or use CVX to generate optimal crossover designs when we have generalized linear models, including cases when we have discrete response experimental design problems. The task should be feasible with CVX as long as the objective function is formulated as a convex or concave functional. Other recent examples of using CVX to solve various design problems, including multiple-objective optimal design problems are available in Wong et al. (2019); Wong and Zhou (2019) and Wong and Zhou (2022). In summary, we believe the new use of CVX to search for optimal crossover designs and N-of-1 trails for more complicated models will undoubtedly advance research in precision medicine (Schork 2015; Davidson et al. 2018).

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