

Optimal group testing designs for prevalence estimation combining imperfect and gold standard assays

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Abstract: We consider group testing studies where a relatively inexpensive but imperfect assay and a perfectly accurate but higher-priced assay are both available. The primary goal is to accurately estimate the prevalence of a trait of interest, with the error rates of the imperfect assay treated as nuisance parameters. Considering the costs for performing the two assays and enrolling subjects, we propose a D_s -optimal mixed design to provide maximal information about the prevalence. We show that extreme values for the cost of the perfect assay lead to designs in which only one of the two assays is used, but otherwise the optimal designs use both assays. We provide a guaranteed algorithm to efficiently build an optimal design on discrete design spaces. Our computational results also show the robustness of the proposed design.

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1. Introduction

Estimating the proportion of a population having a trait, for example, the prevalence of a disease, is an important objective in scientific research and is full of history. When the disease or the trait is rare and the individual samples can be pooled as a group sample to be tested simultaneously, group testing, also known as pooled testing, can be applied to save cost and to improve the estimation accuracy. The key assumption of conventional group testing is that the test result from a group sample is positive if and only if at least one individual in the group has the trait. Ever since [Dorfman \(1943\)](#), the group testing approach has found numerous applications, such as human and plant disease screening and surveillance ([Pilcher et al., 2005](#); [Liu et al., 2011](#); [Saá et al., 2018](#)), genetics studies ([Gastwirth, 2000](#)), and drug development ([Xie et al., 2001](#)).

Most theoretical studies on group testing only consider the setting where all tests are performed using the same assay. Some researchers make a simplified assumption that the test is perfect ([Hughes-Oliver and Swallow, 1994](#); [Hughes-Oliver and Rosenberger, 2000](#)) or that the testing error rates are known values ([Tu et al., 1995](#); [Liu et al., 2012](#)), while others allow the error rates to be estimated from the data ([Huang et al., 2017, 2020](#)).

In practice, the tests used in most group testing experiments are likely to have imperfect performance, and the error rates for the target population are unknown to the researchers. However, in some situations a gold standard assay, which is perfectly accurate but may be too expensive to be adopted widely, such as the Western-blot assay for HIV screening ([Delaney et al., 2006](#)), is available. [Zhang et al. \(2014\)](#) provided an optimal validation subsample design to efficiently estimate the unknown prevalence in their setting. Their main idea was that all group samples with a common size are tested by an inexpensive assay to provide a large amount of mixed information about the prevalence and the testing error rates. In addition, some samples were tested a second time using the gold standard to characterize the error rates, which improved the estimation and identification of the prevalence.

This work motivates us to consider the design problem under a more flexible set-up: (i) Our optimal designs are sought from among all possible designs, without any restriction on the number of different group sizes. (ii) We consider mixed designs based on three testing procedures: each group sample is tested either by only one of the two assays, or by both assays. (iii) We utilize the cost considerations as in [Huang et al. \(2020\)](#), that is, the relative costs for performing

assays and for enrolling subjects, and then we fix the total budget and control the numbers of tests and subjects through their costs. In particular, according to (iii), when prevalence estimation is the only interest, only the gold standard is used when its cost is sufficiently low, and only the regular assay is used when the cost of the gold standard is sufficiently high; besides these two extreme conditions, a mixed design of the three procedures should be adopted.

The outline of this paper is as follows. We introduce some statistical background in Section 2. In Section 3, we theoretically characterize a class of designs containing the optimal ones, and then we provide a search algorithm to obtain an optimal design in this class. We show some examples and discuss computation and other practical issues in Section 4. All proofs and technical details are given in Appendix A.

2. Modeling and cost framework

We refer to the cheaper, imperfect assay as the regular assay, and the higher-priced, perfect assay as the gold standard. The testing procedures based on only the regular assay, only the gold standard, or both assays are denoted as procedures R, G, and B respectively. Let $\theta = (p_0, p_1, p_2)^\top$, where p_0 is the prevalence, and p_1 and p_2 are respectively the true positive and true negative rates of the regular test. The parameters p_1 and p_2 are also known as sensitivity and specificity, respectively. We assume that $p_0 \in (0, 1)$, $p_1, p_2 \in (0.5, 1]$, the two types of testing errors of the regular test occur randomly with error rates $1 - p_1$ and $1 - p_2$, respectively, and there is no testing error for the gold standard. Hence, for the procedure based on only the regular assay, the positive response probability (either true or false positive) of a trial with group size x is

$$\pi_R(x) = \pi_R(x | \theta) = p_1 \{1 - (1 - p_0)^x\} + (1 - p_2)(1 - p_0)^x.$$

Similarly, for the procedure based on only the gold standard, the positive response probability of a trial with group size x is

$$\pi_G(x) = \pi_G(x | \theta) = 1 - (1 - p_0)^x.$$

Moreover, when both assays are applied to the same group sample, the probabilities of observing that the regular assay has a true negative, a false negative, a false positive, and a true positive are

$$\pi_B(x) = \pi_B(x | \theta) = (\pi_B^{00}(x), \pi_B^{01}(x), \pi_B^{10}(x), \pi_B^{11}(x))^\top,$$

where

$$\begin{aligned} \pi_B^{00}(x) &= p_2(1 - p_0)^x, & \pi_B^{01}(x) &= (1 - p_1)\{1 - (1 - p_0)^x\}, \\ \pi_B^{10}(x) &= (1 - p_2)(1 - p_0)^x, & \pi_B^{11}(x) &= p_1\{1 - (1 - p_0)^x\}. \end{aligned}$$

In practice, there are generally limits on the group sizes; therefore, we consider designs subject to a known group size constraint $1 \leq x_L \leq x \leq x_U < \infty$, where the limits on the group sizes are driven by practical considerations.

To introduce costs, we let the total budget be C , and we assume that the costs of performing an assay and enrolling a subject are c_{0P} and c_{1P} , respectively, where the testing procedure is $P = R, G, \text{ or } B$. In practice, these costs are known, with $c_{iR} \leq c_{iG} \leq c_{iB}$ for $i = 0, 1$. Without loss of generality, we set the cost for a regular individual test to satisfy the constraint $c_{0R} + c_{1R} = 1$, and the total budget C refers to how many trials with regular individual testing can be afforded. The cost function of a trial with group size x using procedure $P = R, G, \text{ or } B$ is denoted as

$$c_P(x) = c_{0P} + c_{1P}x. \tag{2.1}$$

When the gold standard is not available, the scenario with a fixed total number of trials (Liu et al., 2012; Zhang et al., 2014; Huang et al., 2017) is equivalent to setting $c_{0R} = 1$, and the scenario with a fixed total number of subjects (Tu et al., 1995; Liu et al., 2012; Zhang et al., 2014) is equivalent to setting $c_{0R} = 0$.

When the three testing procedures are all available, a mixed design can be utilized. Let $\mathcal{P} = \{R, G, B\}$ be the set of procedures. An experiment consists of n_{iP} trials with group size x_{iP} , where $x_{i_1P} \neq x_{i_2P}$ if $i_1 \neq i_2$, under procedure $P \in \mathcal{P}$ for $i = 1, \dots, k_P$. For such an experiment, we denote a mixed design ξ with total budget $C = \sum_{P \in \mathcal{P}} \sum_{i=1}^{k_P} n_{iP}c_P(x_{iP})$ as

$$\xi = \sum_{P \in \mathcal{P}} w_P \xi_P = \sum_{P \in \mathcal{P}} \sum_{i=1}^{k_P} w_{iP} A_{x_{iP}}^P, \tag{2.2}$$

where $w_{iP} = n_{iP}c_P(x_{iP})/C$ is the proportion of budget expended on x_{iP} , $w_P = \sum_{i=1}^{k_P} w_{iP}$ is the proportion of budget expended on procedure P , A_x^P refers to the single-point design with procedure P at size x , and $\xi_P = \sum_{i=1}^{k_P} (w_{iP}/w_P) A_{x_{iP}}^P$ refers to the sub-design under procedure P .

For such an experiment, let $y_{iR} \sim \text{binomial}(n_{iR}, \pi_R(x_{iR}))$ be the number of positive responses at x_{iR} for $i = 1, \dots, k_R$; let $y_{iG} \sim \text{binomial}(n_{iG}, \pi_G(x_{iG}))$ be the number of positive responses at x_{iG} for $i = 1, \dots, k_G$; and let $y_{iB} = (y_{iB}^{00}, y_{iB}^{01}, y_{iB}^{10}, y_{iB}^{11})^T \sim \text{multinomial}(n_{iB}, \pi_B(x_{iB}))$ be the number of true negative, false negative, false positive, and true positive responses at x_{iB} . Thus, after subtracting an unimportant additive constant, the log-likelihood function of θ under design ξ in equation (2.2) is a linear combination of the log-likelihood functions under the single-point designs

$$L(\theta) = C \sum_{P \in \mathcal{P}} \sum_{i=1}^{k_P} w_{iP} \ell_P(\theta | x_{iP}), \tag{2.3}$$

where

$$\ell_P(\theta | x_{iP}) = \frac{1}{c_P(x_{iP})} \left\{ \frac{y_{iP}}{n_{iP}} \log(\pi_P(x_{iP} | \theta)) + \left(1 - \frac{y_{iP}}{n_{iP}}\right) \log(1 - \pi_P(x_{iP} | \theta)) \right\}$$

for $P = R$ or G , and

$$\ell_B(\theta | x_{iB}) = \frac{1}{c_B(x_{iB})} \sum_{j, j'=0}^1 \left\{ \frac{y_{iB}^{jj'}}{n_{iB}} \log(\pi_B^{jj'}(x_{iB} | \theta)) \right\}.$$

The maximum likelihood estimate $\hat{\theta}$ is obtained by maximizing function (2.3), and the covariance matrix of $\hat{\theta}$ is asymptotically proportional to the inverse of the information matrix of ξ , which is a linear combination of the information matrices of the corresponding single-point designs,

$$M(\xi) = \sum_{P \in \mathcal{P}} \sum_{i=1}^{k_P} w_{iP} M(A_{x_{iP}}^P), \quad (2.4)$$

where

$$M(A_x^P) = M_P(x) = \lambda_P(x) f_P(x) f_P(x)^\top \quad \text{for } P = R, G,$$

$$M(A_x^B) = M_B(x) = \sum_{j=0}^2 \lambda_{Bj}(x) f_{Bj}(x) f_{Bj}(x)^\top,$$

with

$$\begin{aligned} \lambda_P(x) &= [c_P(x) \pi_P(x) \{1 - \pi_P(x)\}]^{-1} \quad \text{for } P = R, G, \\ \lambda_{B0}(x) &= [c_B(x) \pi_G(x) \{1 - \pi_G(x)\}]^{-1}, \\ \lambda_{B1}(x) &= \pi_G(x) \{c_B(x) p_1 (1 - p_1)\}^{-1}, \\ \lambda_{B2}(x) &= \{1 - \pi_G(x)\} \{c_B(x) p_2 (1 - p_2)\}^{-1}, \\ f_R(x) &= ((p_1 + p_2 - 1)x(1 - p_0)^{x-1}, 1 - (1 - p_0)^x, -(1 - p_0)^x)^\top, \\ f_G(x) &= f_{B0}(x) = (x(1 - p_0)^{x-1}, 0, 0)^\top, \\ f_{B1}(x) &= (0, 1, 0)^\top, \quad \text{and} \\ f_{B2}(x) &= (0, 0, 1)^\top. \end{aligned}$$

To precisely estimate the prevalence p_0 , we seek a design that minimizes the variance of \hat{p}_0 by the choice of k_P and (x_{iP}, w_{iP}) for $i = 1, \dots, k_P$ and $P \in \mathcal{P}$ under the cost constraint C and the design space constraint $[x_L, x_U]$. In design theory, the design corresponds to a D_s -optimal design (Atkinson et al., 2007, Chapter 10.3), which maximizes

$$\Phi_s\{M(\xi)\} = -\log \{M(\xi)^-\}_{11} \quad (2.5)$$

among all designs under which p_0 is estimable, where M^- is a generalized inverse of matrix M and M_{11} is its (1,1)-entry. From (2.4) and (2.5), the optimality of a design depends on the unknown parameters $\theta = (p_0, p_1, p_2)^\top$ and on the cost functions (2.1) as inverse weights, but is invariant to the total budget C .

3. D_s -optimal budget-constrained designs

In this section we theoretically characterize D_s -optimal budget-constrained designs via the approximate design framework proposed by Kiefer (1974). We first

consider the design space as the interval $[x_L, x_U]$ to obtain an overview of the behavior of these designs. Then we use these results to provide a guaranteed algorithm to obtain optimal designs supported on integers within $[x_L, x_U]$ for practical use.

Intuitively, when $c_G(x)$ is close to $c_R(x)$, one may prefer only to have gold standard tests, which means $k_B = k_R = 0$. In contrast, when $c_G(x)$ is much higher than $c_R(x)$, one may prefer only to have regular tests, and thus $k_B = k_G = 0$. Before addressing the relationship between cost functions and the best choice of $\{k_R, k_G, k_B\}$, we first define a valid design to be one where p_0 is estimable. We then provide a class Ξ of designs in which there exists a D_s -optimal design, with sharp upper bounds for the numbers of group sizes under the three procedures, where

$$\Xi = \{\xi : \xi \text{ is valid, } \max(k_R - 2, k_G, k_B) = 1\}.$$

The following proposition characterizes all valid designs and establishes that Ξ contains a D_s -optimal design. Its proof and other theoretical results are provided in Appendix A.

Proposition 3.1.

- (i) A design ξ is valid if and only if $\max(k_R - 2, k_G, k_B) \geq 1$.
- (ii) There exists a D_s -optimal design within Ξ .

Note that $k_R \geq 3$ or $k_B \geq 1$ yields a nonsingular information matrix. Now we partition Ξ into subclasses. For a nonempty subset of procedures $\mathcal{Q} \subseteq \mathcal{P}$, we state a design $\xi \in \Xi$ is a \mathcal{Q} -design if $k_p > 0$ for $p \in \mathcal{Q}$ and $k_{p'} = 0$ for $p' \notin \mathcal{Q}$. We denote that $\Xi_{\mathcal{Q}}$ is the collection of all \mathcal{Q} -designs. Therefore, Ξ is partitioned as $\{\Xi_R, \Xi_G, \Xi_B, \Xi_{RG}, \Xi_{RB}, \Xi_{GB}, \Xi_{RGB}\}$. We further state that a \mathcal{Q} -design $\xi_{\mathcal{Q}}$ is $D_s^{\mathcal{Q}}$ -optimal if it is D_s -optimal among all \mathcal{Q} -designs. Since D_s -optimality is equivalent to c -optimality with $c = (1, 0, 0)^T$ (Atkinson et al., 2007, Chapter 17.5), which minimizes the asymptotic variance of $c^T \hat{\theta}$, a D_s -optimal design must satisfy the generalized Elfving’s theorem (Dette and Holland-Letz, 2009). In the next theorem we show that we only need to search for a D_s -optimal design in Ξ_R, Ξ_G, Ξ_B , and Ξ_{RB} .

Theorem 3.1. *There exists a D_s -optimal design with either $k_G = 0$ or $k_R + k_B = 0$.*

Theorem 3.1 greatly simplifies the problem by eliminating the need to consider three of the most difficult subclasses, namely Ξ_{RG}, Ξ_{GB} , and Ξ_{RGB} , among the seven. For the remaining four subclasses, we provide the corresponding optimal designs in three of them below, leaving only one subclass for further consideration. Now we characterize D_s^R -, D_s^G -, and D_s^B -optimal designs, respectively. Theorem 2 in Huang et al. (2020) provides the D_s^R -optimal design ξ_R^* which is a three-point design involving the smallest allowable group size x_L . Here we provide D_s^G - and D_s^B -optimal designs using the complete class approach (Yang and Stufken, 2012). Let $\xi_p^* = A_{x_p^*}^p$ be the single-point design at x_p^* with procedure $p = G$ or

B, where

$$x_P^* = \arg \max_{x \in [x_L, x_U]} \frac{x^2(1-p_0)^x}{(1-(1-p_0)^x)c_P(x)}. \quad (3.1)$$

We have the following proposition.

Proposition 3.2.

- (i) The design ξ_P^* is D_s^P -optimal for $P = G$ or B .
- (ii) The design ξ_G^* is at least as efficient as ξ_B^* in terms of the D_s -criterion (2.5).

Through Theorem 3.1, one of the three designs, ξ_R^* , ξ_G^* , and ξ_B^* , may be D_s -optimal among all valid designs. However, if none of them is, then there must exist an RB-design that is D_s -optimal. More explicitly, Theorem 3.1 and Proposition 3.2 show that either ξ_G^* or an optimal design in $\Xi_{R \oplus B} \equiv \Xi_R \cup \Xi_B \cup \Xi_{RB}$ is D_s -optimal among all valid designs, where the latter may be ξ_R^* , ξ_B^* , or an RB-design. Moreover, if ξ_B^* is optimal within $\Xi_{R \oplus B}$, then ξ_G^* must outperform all designs in $\Xi_{R \oplus B}$. Otherwise, we need to check whether ξ_G^* or an optimal design in $\Xi_{R \oplus B}$ performs better.

Furthermore, we state that a design $\xi \in \Xi_{R \oplus B}$ is $D_s^{R \oplus B}$ -optimal if it is D_s -optimal within $\Xi_{R \oplus B}$. Now we consider $D_s^{R \oplus B}$ -optimal designs. Proposition 3.1 implies that valid designs in $\Xi_{R \oplus B}$ have nonsingular information matrices. Therefore, it is convenient to utilize the general equivalence theorem (Kiefer, 1974) to check whether ξ_R^* , ξ_B^* , or an $R \oplus B$ -design is $D_s^{R \oplus B}$ -optimal. We first state some notations. For a design $\xi \in \Xi_{R \oplus B}$ and a single-point design A_x^P with procedure $P = R$ or B , we define the directional derivative of Φ_s at $M(\xi)$ in the direction $M(A_x^P)$ as

$$\begin{aligned} \phi_P(x, \xi) &= \lim_{\delta \rightarrow 0^+} \frac{1}{\delta} [\Phi_s\{M(\xi)\} - \Phi_s\{M((1-\delta)\xi + \delta A_x^P)\}] \\ &= \text{tr}\{M(\xi)^{-1}M(A_x^P)\} - \text{tr}\{\widetilde{M}(\xi)^{-1}\widetilde{M}(A_x^P)\} - 1, \end{aligned}$$

where \widetilde{M} is the 2×2 submatrix of M after deleting the first row and the first column. We have the following theorem based on the proof of the general equivalence theorem.

Theorem 3.2. A design $\xi \in \Xi_{R \oplus B}$ is $D_s^{R \oplus B}$ -optimal if and only if

$$\max_{P=R, B} \max_{x \in [x_L, x_U]} \phi_P(x, \xi) = 0.$$

Moreover, ξ_R^* is $D_s^{R \oplus B}$ -optimal if and only if $\max_x \phi_B(x, \xi_R^*) \leq 0$, and ξ_B^* is $D_s^{R \oplus B}$ -optimal if and only if $\max_x \phi_R(x, \xi_B^*) \leq 0$.

In practice, group testing designs can only be supported on integers. Above we provide some key properties of D_s -optimal designs supported on the interval $[x_L, x_U]$. Our proofs of Propositions 3.1(i) and 3.2, and of Theorems 3.1 and 3.2 still hold for the integer-valued design space $\Omega_{(i)} = \{x_L, \dots, x_U\}$. We state

that the $D_{s^{(I)}}$ -optimality is the D_s -optimality among integer-supported designs, where “(I)” stands for integers. A $D_{s^{(I)}}^R$ -optimal design, denoted as $\xi_R^{(I)}$, can be obtained from Algorithm 1 in Huang et al. (2020). Moreover, $D_{s^{(I)}}^G$ - and $D_{s^{(I)}}^B$ -optimal designs, $\xi_G^{(I)}$ and $\xi_B^{(I)}$, are respectively supported on the integers closest to x_G^* and x_B^* in (3.1) for $P = G$ or B . Therefore, using similar arguments as above, Theorem 3.1 and Proposition 3.2 show that either $\xi_G^{(I)}$ or a $D_{s^{(I)}}^{R\oplus B}$ -optimal design is $D_{s^{(I)}}$ -optimal among all designs supported on $\Omega_{(I)}$.

First we can utilize Theorem 3.2 to check whether $\xi_R^{(I)}$ or $\xi_B^{(I)}$ is $D_{s^{(I)}}^{R\oplus B}$ -optimal. If none of them is, we provide a guaranteed algorithm based on Theorem 3.2 to obtain a $D_{s^{(I)}}^{R\oplus B}$ -optimal design. For a design ξ and a procedure P , let $\tilde{\phi}_P(\xi) = \max_x \phi_P(x, \xi)$ and let $\tilde{x}_P(\xi)$ be the corresponding maximizer. The proposed algorithm is presented as follows.

Algorithm 3.1 Construct a $D_{s^{(I)}}^{R\oplus B}$ -optimal design $\xi_{R\oplus B}^{(I)}$.

- 1: Obtain a $D_{s^{(I)}}^R$ -optimal design $\xi_R^{(I)}$. **If** $\tilde{\phi}_B(\xi_R^{(I)}) \leq 0$, **then** $\xi_{R\oplus B}^{(I)} \leftarrow \xi_R^{(I)}$ **and break**.
 - 2: Obtain a $D_{s^{(I)}}^B$ -optimal design $\xi_B^{(I)}$. **If** $\tilde{\phi}_R(\xi_B^{(I)}) \leq 0$, **then** $\xi_{R\oplus B}^{(I)} \leftarrow \xi_B^{(I)}$ **and break**.
 - 3: Obtain an initial design $\xi_{RB}^{(1)} = \{(X_R^{(1)}, X_B^{(1)}), (W_R^{(1)}, W_B^{(1)})\}$:
 - 3.1: support points $X_R^{(1)} = \{\tilde{x}_R(\xi_B^{(1)})\}$, and $X_B^{(1)} = \{x_B^{(1)}\}$;
 - 3.2: weights $(W_R^{(1)}, W_B^{(1)}) = \arg \max_{W_R, W_B} \Phi_s\{(X_R^{(1)}, X_B^{(1)}), (W_R, W_B)\}$.
 - 4: Let $i = 1$. **While** $\max\{\tilde{\phi}_R(\xi_{RB}^{(i)}), \tilde{\phi}_B(\xi_{RB}^{(i)})\} > 0$, **do**:
 - 4.1: **If** $\tilde{\phi}_R(\xi_{RB}^{(i)}) \geq \tilde{\phi}_B(\xi_{RB}^{(i)})$, **then** $X_R^{(i+1)} \leftarrow X_R^{(i)} \cup \{\tilde{x}_R(\xi_{RB}^{(i)})\}$ and $X_B^{(i+1)} \leftarrow X_B^{(i)}$, **else** $X_R^{(i+1)} \leftarrow X_R^{(i)}$ and $X_B^{(i+1)} \leftarrow X_B^{(i)} \cup \{\tilde{x}_B(\xi_{RB}^{(i)})\}$.
 - 4.2: Obtain $(W_R^{(i+1)}, W_B^{(i+1)}) = \arg \max_{W_R, W_B} \Phi_s\{(X_R^{(i+1)}, X_B^{(i+1)}), (W_R, W_B)\}$; delete those x having zero weight.
 - 4.3: Let $\xi_{RB}^{(i+1)} = \{(X_R^{(i+1)}, X_B^{(i+1)}), (W_R^{(i+1)}, W_B^{(i+1)})\}$; let $i \leftarrow i + 1$.
 - 5: $\xi_{R\oplus B}^{(I)} \leftarrow \xi_{RB}^{(i)}$. **End**.
-

Once we obtain a $D_{s^{(I)}}^{R\oplus B}$ -optimal design through Algorithm 3.1, we can compare it with $\xi_G^{(I)}$ to check which one is $D_{s^{(I)}}$ -optimal, using the algorithm below.

Algorithm 3.2 Construct a D_s -optimal design $\xi^{(I)}$.

- 1: Obtain $\xi_G^{(I)}$ and $\xi_{R\oplus B}^{(I)}$.
 - 2: **If** $\xi_{R\oplus B}^{(I)}$ has $X_R = \emptyset$ **then** $\xi^{(I)} \leftarrow \xi_G^{(I)}$ **and break**.
 - 3: **If** $\Psi_s(\xi_G^{(I)}) \geq \Psi_s(\xi_{R\oplus B}^{(I)})$ **then** $\xi^{(I)} \leftarrow \xi_G^{(I)}$ **else** $\xi^{(I)} \leftarrow \xi_{R\oplus B}^{(I)}$. **End**.
-

Theorems 3.1 and 3.2 guarantee that the design obtained by Algorithms 3.1 and 3.2 must be D_s -optimal. Algorithm 3.1 is guaranteed to terminate in a finite number of iterations, and it usually stops within ten iterations in our experience. The finite convergence of Algorithm 3.1 is due to its finite design space, and

the sequence of designs is strictly monotonic with respect to the D_s -criterion. Moreover, as a result of the convexity of the design criterion, this stepwise ascent algorithm converges to a global optimum. Note that these two algorithms which apply to discrete design spaces sometimes provide designs with more group sizes than stated in Proposition 3.1(ii), which applies to continuous design spaces. For example, in Section 4.2 we observe some optimal designs having two group sizes under procedure B, in contrast to the setting where $k_B \leq 1$ in Proposition 3.1(ii). This is because when an optimal value for the continuous design space is not an integer, and the two integers closest to it present roughly equal performance, the design including both integers may perform better than the designs including either one or the other.

Remark 3.1. In some practical situations only procedures R and G are available; for example, a group sample can only be tested once by either one of the two assays. Under this simpler setting, Theorem 3.1 indicates that a mixed design incorporating procedures R and G is not necessary. The better one between $\xi_R^{(1)}$ and $\xi_G^{(1)}$ with respect to the D_s -criterion is optimal.

Remark 3.2. For an approximate mixed design ξ and a given total budget C , the expected number of trials $n_{iP}^0 = Cw_{iP}/c_P(x_{iP})$ with group size x_{iP} under procedure P is not guaranteed to be an integer. For practical use, we obtain ξ with total budget C by implementing a two-step efficient rounding procedure for a budget-constrained design, introduced in Section 3.2 of Huang et al. (2020). More explicitly, we first allocate the budget to have $\lfloor n_{iP}^0 \rfloor$ trials with group size x_{iP} under procedure P, where $\lfloor x \rfloor$ is the largest integer not greater than x . Afterward, among all possible remaining budget allocations, we choose the one that minimizes the asymptotic variance of the prevalence estimate.

Remark 3.3. The above theoretical results rely on the assumption that each individual sample having the disease is independently Bernoulli distributed with prevalence p_0 . Although in practice, the sampling scheme is usually without replacement, the Bernoulli assumption is acceptable when the number of individuals in the study is smaller than a certain percentage of the population size, for instance, less than 20% (Christensen and Gardner, 2000).

4. Illustrative numerical examples

In this section we provide some numerical examples to study the performance of the $D_{s(i)}$ -optimal design when the working parameters may be moderately misspecified, and to investigate how multiple assays together with the cost settings affect the optimal designs. We consider the case where the working values of prevalence, true positive rate, and true negative rate are $\hat{\theta} = (\hat{p}_0, \hat{p}_1, \hat{p}_2)^\top = (0.06, 0.95, 0.95)^\top$, with group sizes in $[1, 50]$. We focus on the natural situation where the cost for performing both the regular and gold standard assays on a group sample is equal to the sum of the costs for performing the two assays separately, and where enrolling a subject for each procedure has identical costs. In this situation we only have two independent cost parameters $c_{0R} \in [0, 1]$

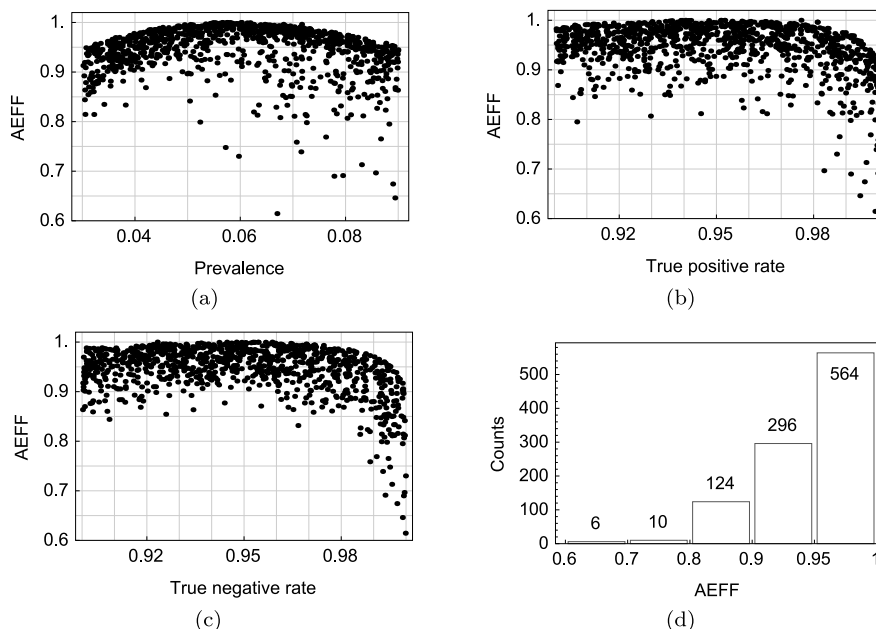


FIG 1. $AEFF(\tilde{\xi} | \theta)$ against different θ for 1000 draws. (a) $AEFF$ against the prevalence p_0 ; (b) $AEFF$ against the true positive rate p_1 ; (c) $AEFF$ against the true negative rate p_2 ; (d) summary of $AEFF$ for the 1000 draws.

and $c_{0G} \geq c_{0R}$, whereas the other cost parameters are $c_{0B} = c_{0R} + c_{0G}$ and $c_{1R} = c_{1G} = c_{1B} = 1 - c_{0R}$.

4.1. Sensitivity analysis

Here we examine how moderately misspecified working parameters affect the performance of the proposed $D_{s(l)}$ -optimal design. We set $c_{0R} = 0.5$ and $c_{0G} = 10$. By Algorithm 3.2 with working parameters $\tilde{\theta} = (0.06, 0.95, 0.95)^\top$, we obtain a $D_{s(l)}$ -optimal design $\tilde{\xi}$ supported on group sizes 11 with procedure R and 14 with procedure B with weights 0.352 and 0.648, respectively. When the total budget $C = 8000$, by Remark 3.2, we implement $\tilde{\xi}$ as 470 trials with size 11 under R and 296 trials with size 14 under B. The performance of $\tilde{\xi}$ under a true value of θ is measured by the asymptotic efficiency

$$AEFF(\tilde{\xi} | \theta) = \frac{(M(\xi^*(\theta) | \theta)^-)_{11}}{(M(\tilde{\xi} | \theta)^-)_{11}} \in [0, 1],$$

where $\xi^*(\theta)$ is a $D_{s(l)}$ -optimal design under θ .

Suppose that the true value of θ comes from $\Theta = (0.03, 0.09) \times (0.9, 1)^2$, which covers $\tilde{\theta}$. Figure 1 shows the asymptotic efficiency of $\tilde{\xi}$ for θ drawn randomly

from Θ . Among the 1000 draws, the asymptotic efficiency of $\tilde{\xi}$ is always at least 60%, and is usually greater than 90% (860 draws), indicating that the design $\tilde{\xi}$ performs stably well. We also observe that the asymptotic efficiency decreases as the true prevalence remains away from the working prevalence, and as the true positive and true negative rates tend to one.

4.2. The role of multiple assays with cost considerations

Here we consider how the use of two assays together with cost constraints leads to different optimal designs than arise when either of these features is not present. We consider three different cases, with $c_{0R} = 1, 0.5$, or 0 respectively, and study how the optimal designs vary with c_{0G} . Three properties of variations concerning group sizes x_{iP} , weights (proportions of budget) w_{iP} , and relative numbers of trials n_{iP}^0/N , where $N = \sum_{i,P} n_{iP}^0$, for the design considered are presented in Figures 2, 3, and 4.

First, we consider the case with $c_{0R} = 1$, where subjects are cost-free. The properties of the proposed $D_{s(i)}$ -optimal designs for the selected c_{0G} are shown in Figure 2. As expected, a G-design and an R-design are optimal when c_{0G} is sufficiently low and sufficiently high, respectively, and an RB-design is optimal otherwise. When the gold standard assay is sufficiently cheap, in this example no more than twice the cost of a regular individual test, using only the gold standard assay is the optimal strategy, as it provides the most information about the prevalence. In contrast, when the gold standard assay is sufficiently expensive, at least 17 times the cost of a regular individual test in this example, it is optimal to run $\xi_R^{(i)}$ which only uses procedure R.

Besides these two extreme situations, a mixed design incorporating procedures R and B is optimal. In this case, the optimal design allocates more budget on procedure B, but more trials on procedure R. Moreover, a group size based on procedure R is close to the intermediate group size of $\xi_R^{(i)}$ which mainly provides information about the prevalence (Huang et al., 2017). In particular, when c_{0G} is moderately expensive ($c_{0G} \geq 7$ here), the optimal designs include the smallest group size x_L with procedure R, which provides cheap information about the true negative rate to identify the prevalence (Huang et al., 2020). Moreover, under such moderate c_{0G} the optimal group sizes for the two procedures are usually different, and there may be multiple group sizes for one procedure. This indicates that using a common group size for both procedures R and B may not be optimal when distinct sizes for different procedures are allowed.

Next, we consider the cases with $c_{0R} = 0.5$ or $c_{0R} = 0$, whereby in the latter case the regular assay is cost-free. The properties of the proposed $D_{s(i)}$ -optimal designs for the selected c_{0G} in these two cases are shown in Figures 3 and 4. We observe patterns similar to those in Figure 2, where the optimal design strategy as c_{0G} increases is to first use procedure G only, then use a mixed design with procedures R and B, and finally use procedure R only. In addition, as the subject cost, $c_{1R} = 1 - c_{0R}$, grows, the R-designs are not favored because they usually contain tests with extremely large group sizes (Huang et al., 2020).

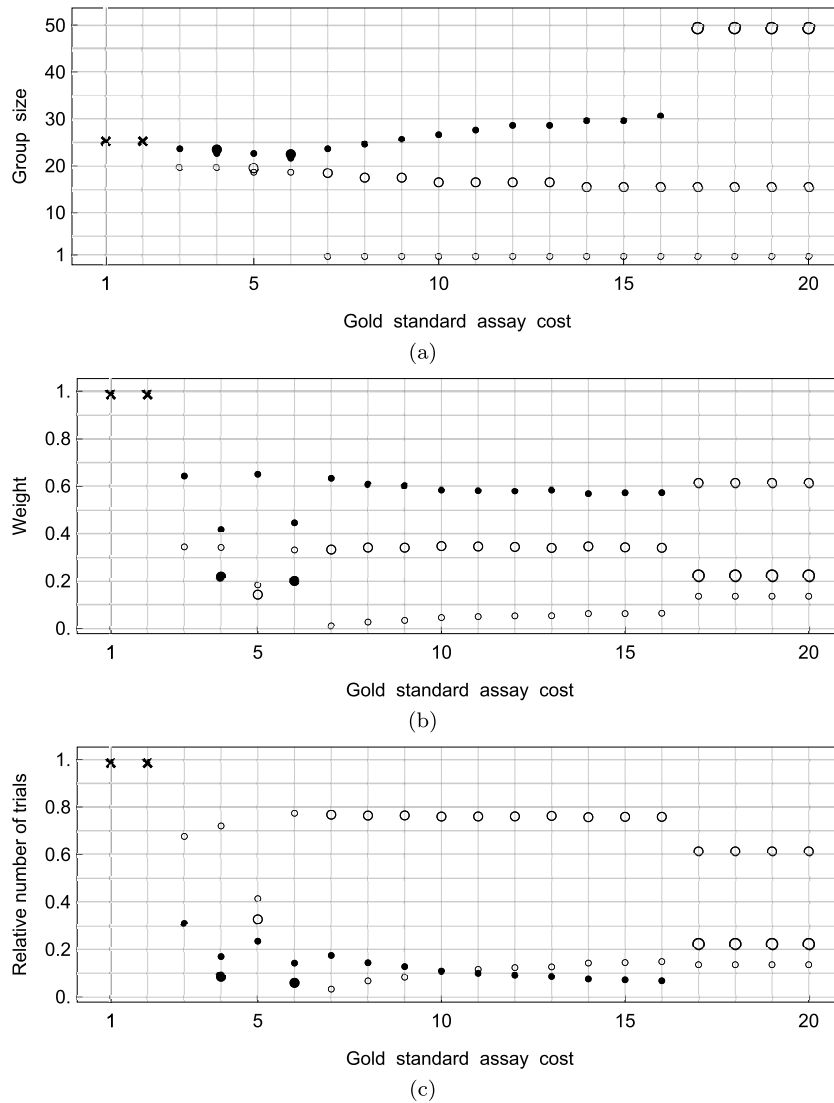


FIG 2. D_s -optimal designs against c_{0G} for $c_{0R} = 1$. Symbols (\circ , \times , \bullet) refer to group sizes under procedure R, G, and B, respectively; different sizes under the same symbol indicate different group sizes under the same procedure: (a) group sizes x_{iP} ; (b) weights w_{iP} ; (c) relative numbers of trials n_{iP}^0/N .

Through Figures 2, 3 and 4, a design based on only procedure R is optimal only when the gold standard assay is extremely expensive, $c_{0G} \geq 17, 180$, or 320 for the three cases considered here with subject cost $c_{1R} = 0, 0.5$, or 1, respectively. This indicates that as the subject costs grow, which is typical in modern studies involving human subjects, it is often worthwhile to develop a gold stan-

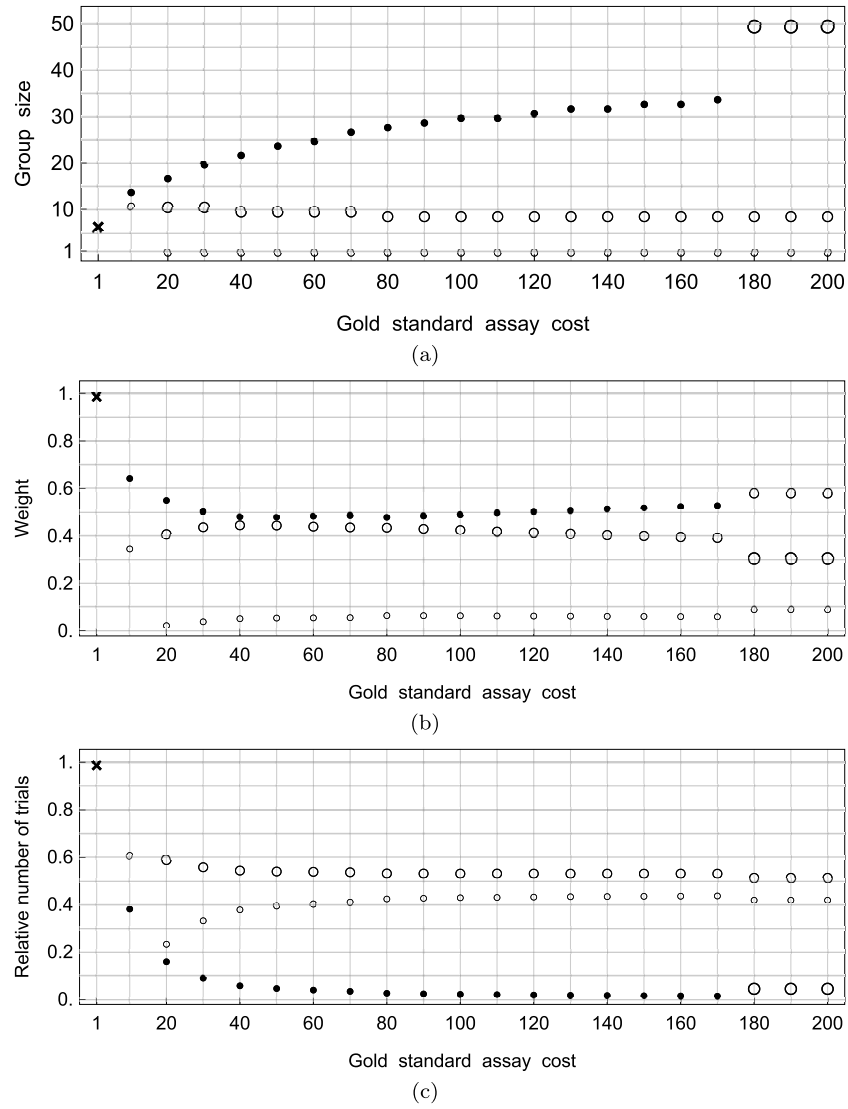


FIG 3. D_s -optimal designs against c_{0G} for $c_{0R} = 0.5$. Symbols (\circ , \times , \bullet) refer to group sizes under procedure R, G, and B, respectively; different sizes under the same symbol indicate different group sizes under the same procedure: (a) group sizes x_{iP} ; (b) weights w_{iP} ; (c) relative numbers of trials n_{iP}^0/N .

standard assay, even when the imperfect regular assay is cost-free. Our results show that mixed designs are often optimal and may substantially outperform single assay approaches.

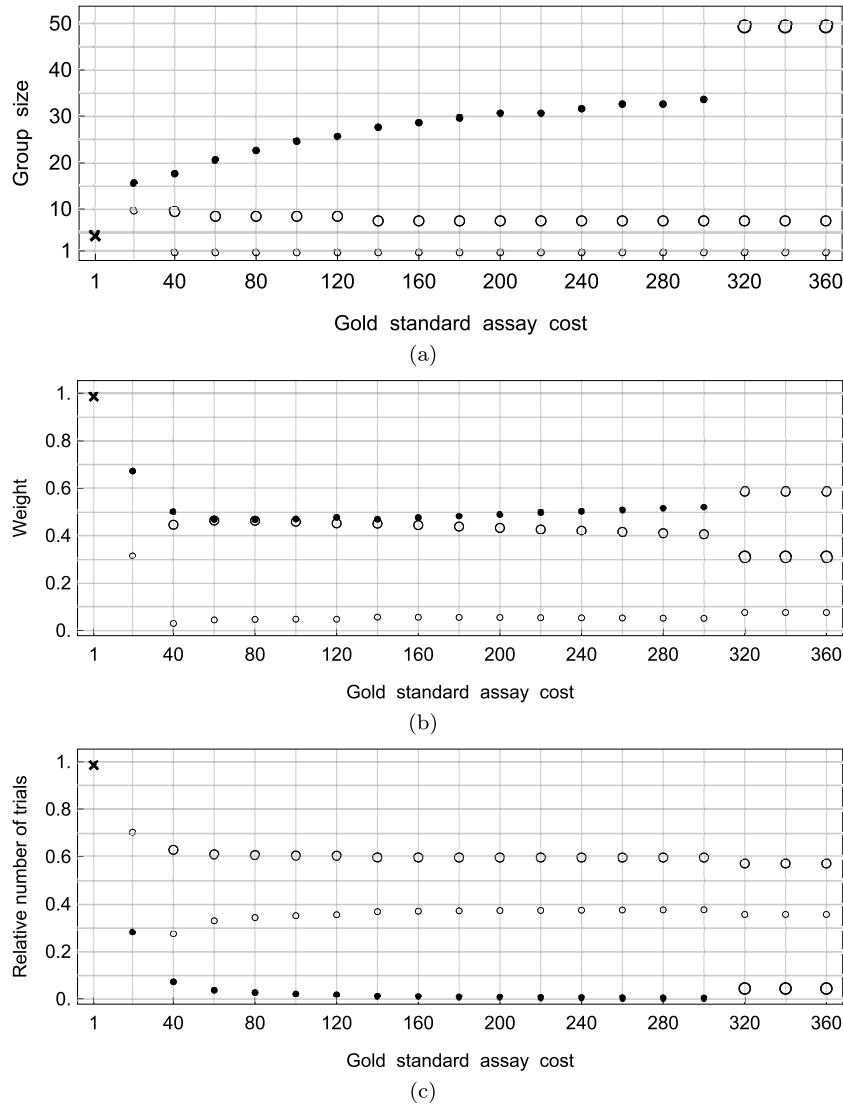


FIG 4. D_s -optimal designs against c_{0G} for $c_{0R} = 0$. Symbols (o, x, ●) refer to group sizes under procedure R, G, and B, respectively; different sizes under the same symbol indicate different group sizes under the same procedure: (a) group sizes x_{iP} ; (b) weights w_{iP} ; (c) relative numbers of trials n_{iP}^0/N .

Appendix A: Supporting and technical materials

Here we provide the technical details of the propositions and theorems in the main text. In Section A.1 we present some supporting materials mainly based on the complete class approach. In Section A.2 we provide the technical proofs of the propositions and theorems.

A.1. Supporting materials

Firstly we provide the complete class results for procedures G and B based on the framework in [Yang and Stufken \(2012\)](#). The design ξ_1 is said to be at least as informative as ξ_0 under the Löwner ordering, denoted by $\xi_1 \leq_L \xi_0$, if $M(\xi_0) - M(\xi_1)$ is nonnegative definite. Moreover, we state that a class of designs $\Xi_{B1} \subset \Xi_{B0} = \{\xi : k_B > 0, k_R = k_G = 0\}$ is a complete class under procedure B if for an arbitrary design $\xi_0 \in \Xi_{B0}$, there exists a $\xi_1 \in \Xi_{B1}$ such that $\xi_0 \leq_L \xi_1$. Now we present the following results.

Proposition A.1.

- (i) For an arbitrary $x \in [x_L, x_U]$, $A_x^G \leq_L A_{x_G^*}^G$.
- (ii) The class of designs $\Xi_B = \{\xi : k_B = 1, k_R = k_G = 0\}$ is complete under procedure B.

Proof. For (i), note that the information matrix of A_x^G can be written as $M(A_x^G) = \nu(x)e_1e_1^\top$, where $e_1 = (1, 0, 0)^\top$ and

$$\nu(x) = \frac{x^2(1-p_0)^{x-2}}{(1-(1-p_0)^x)c_G(x)}.$$

Therefore, by the definition of x_G^* , we have that $\forall x$, $A_x^G \leq_L A_{x_G^*}^G$.

We prove (ii) using the complete class framework of [Yang and Stufken \(2012\)](#). We first consider the case with $c_{1B} = 0$. The information matrix of a design $\xi_B = \{(x_i, w_i)\}_{i=1}^{k_B} \in \Xi_{B0}$ can be written as

$$M(\xi_B) = P(\theta) \left(\sum_{i=1}^{k_B} M_1(\theta; r_i) \right) P(\theta)^\top, \quad (\text{A.1})$$

where $r_i = (1-p_0)^{x_i} \in (0, 1)$, $P(\theta)$ does not depend on x_i , and $M_1(\theta; r)$ is a diagonal matrix with elements $(b_0(r), b_1(r) - b_2(r), b_2(r))$, where

$$b_0(r) = \frac{\log(r)^2 r}{1-r}, \quad b_1(r) = 1, \quad \text{and} \quad b_2(r) = r.$$

Let $h_{1,1}(r) = \frac{d}{dr} b_2(r)$, $h_{2,1}(r) = \frac{d}{dr} b_0(r)$, and $h_{2,2}(r) = \frac{d}{dr} \frac{h_{2,1}(r)}{h_{1,1}(r)}$, then we have that

$$-h_{1,1}(r) \times h_{2,2}(r) = \frac{-2(1-r+\log(r))(1-r+r\log(r))}{r(1-r)^3} > 0$$

for all $r \in (0, 1)$. Therefore, by Theorem 2(d) in [Yang and Stufken \(2012\)](#) and the proof thereof, for arbitrary $r_1 < r_2 \in (0, 1)$ and $w \in (0, 1)$, there exists an $r_0 \in (r_1, r_2)$ such that

$$b_2(r_0) = wb_2(r_1) + (1-w)b_2(r_2) \quad \text{and} \quad b_0(r_0) > wb_0(r_1) + (1-w)b_0(r_2).$$

Therefore, Ξ_B is a complete class with respect to procedure B.

Next we consider the case with $c_{1B} > 0$. The information matrix of a design $\xi_B = \{(x_i, w_i)\}_{i=1}^{k_B}$ can also be written as in (A.1). However, now the elements of the core diagonal matrix $M_1(\theta; r)$ are respectively

$$b_0(r) = \frac{\log(r)^2 r}{(c' - \log(r))(1 - r)}, \quad b_1(r) = \frac{1}{c' - \log(r)}, \quad \text{and} \quad b_2(r) = \frac{r}{c' - \log(r)},$$

for $c' = c_{0B}/c_{1B} \geq 0$. In this case $P(\theta)$ is different from that in the $c_{1B} = 0$ case, and still does not depend on x_i . Now let

$$h_{1,1}(r) = \frac{d}{dr} b_2(r), \quad H_{2,1}(r) = \frac{d}{dr} \begin{pmatrix} b_1(r) & 0 \\ 0 & b_0(r) \end{pmatrix},$$

and $H_{2,2}(r) = \frac{d}{dr} \frac{H_{2,1}(r)}{h_{1,1}(r)}$.

Therefore, if $-h_{1,1}(r) \times H_{2,2}(r)$ is positive definite, we can use similar arguments as when $c_{1B} = 0$ to show that Ξ_B is a complete class with respect to procedure B.

Now we prove that $-h_{1,1}(r) \times H_{2,2}(r)$ is positive definite. We have

$$-h_{1,1}(r) \times H_{2,2}(r) = \begin{pmatrix} h_1(r) & 0 \\ 0 & h_2(r) \end{pmatrix},$$

where

$$h_1(r) = \frac{1}{r^2(c' - \log(r))(1 + c' - \log(r))} > 0, \forall r \in (0, 1),$$

and

$$h_2(r) = \frac{-2(1 + c')(1 - r + \log(r))(1 - r + r \log(r)) - (\log(r))^2(r - 2 + r^2 - 2r \log(r))}{r(1 - r)^3(c' - \log(r))(1 + c' - \log(r))},$$

where its denominator is positive, and the numerator, denoted by h_3 , is also positive by the following arguments. For $r \in (0, 1)$, since

$$\frac{\partial}{\partial c'} h_3(r) = -2(1 - r + \log(r))(1 - r + r \log(r)) > 0 \quad \text{and} \quad \frac{\partial}{\partial c'} h_3(1) = 0,$$

we have that $\frac{\partial}{\partial c'} h_3(r) > 0$ for $c' \geq 0$. Hence,

$$h_3(r) \geq h_3(r) |_{c'=0} = h_{31}(r) + h_{32}(r) > 0,$$

where

$$h_{31}(r) = -2(1 - r)^2 - (1 + r)(2 - 2r + r \log(r)) \log(r) > 0,$$

$$h_{32}(r) = 2(1 - r + r \log(r))(\log(r))^2 > 0. \quad \square$$

A.2. Technical proofs of the propositions and theorems

Proof of Proposition 3.1. To prove (i), let $c = (1, 0, 0)^\top$, and recall that p_0 is estimable under a design ξ if and only if $c \in \text{range}(M(\xi))$. For the necessity, we only need to show that the design is not valid when $k_R \leq 2$ and $k_G = k_B = 0$. The proof comes from Lemma 1 of Huang et al. (2020) and is omitted.

Now we prove sufficiency. When $k_B \geq 1$, $M(\xi)$ is nonsingular and therefore $c \in \text{range}(M(\xi))$. When $k_G \geq 1$, the information matrix of ξ contains $w_G M(\xi_G)$ which is proportional to cc^\top , and thus $c \in \text{range}(M(\xi))$. To prove that $k_R \geq 3$ implies $M(\xi)$ is nonsingular, it is sufficient to show that for arbitrary $1 \leq x_1 < x_2 < x_3$, $\Gamma = (f_R(x_1), f_R(x_2), f_R(x_3))$ is nonsingular, where $\Gamma = \Gamma_0 \Gamma_1$ with

$$\Gamma_0 = \begin{pmatrix} \frac{p_1+p_2-1}{1-p_0} & 0 & 0 \\ 0 & -1 & 1 \\ 0 & -1 & 0 \end{pmatrix}$$

and $\Gamma_1 = \begin{pmatrix} x_1(1-p_0)^{x_1} & x_2(1-p_0)^{x_2} & x_3(1-p_0)^{x_3} \\ (1-p_0)^{x_1} & (1-p_0)^{x_2} & (1-p_0)^{x_3} \\ 1 & 1 & 1 \end{pmatrix}$.

Because $a_1 + a_2(1-p_0)^x + a_3x(1-p_0)^x$ has at most 2 real roots (Karlin and Studden, 1966, page 10) for $(a_1, a_2, a_3) \in \mathfrak{R}^3 \setminus (0, 0, 0)$, we have that $\{s_1, s_2(1-p_0)^x, s_3x(1-p_0)^x\}$ is a Tchebyshev system for some $s_i = \pm 1$ (Karlin and Studden, 1966, page 22, Theorem 4.1). Therefore, $|\Gamma_1| \neq 0$ (Karlin and Studden, 1966, page 1, Definition 1.1), and this completes the proof.

We prove part (ii) as follows. First, use the general equivalence theorem to show that k_R of a D_s -optimal design cannot be greater than 3, which is identical to part (i) of Theorem 2 in Huang et al. (2020) and is therefore omitted. Moreover, Proposition A.1 implies that $k_G \leq 1$ and $k_B \leq 1$ are sufficient to ensure the existence of a D_s -optimal design by the complete class approach under the Löwner ordering (Yang and Stufken, 2012).

Proof of Theorem 3.1. This theorem is proved by the generalized Elfving's theorem (Dette and Holland-Letz, 2009, Theorem 3). If there is a D_s -optimal design, denoted by $\xi = w_R \xi_R + w_G \xi_G + w_B \xi_B$, with $k_R + k_B \geq 1$ and $k_G \geq 1$, then ξ_G and $w'_R \xi_R + w'_B \xi_B$ are D_s -optimal, where $w'_P = \frac{w_P}{w_R + w_B}$ for procedures $P = R$ or B .

Let $\mu_P(x) = \lambda_P(x)^{1/2} f_P(x)$ for $P = R, G, B0, B1$, or $B2$. By Elfving's theorem, because ξ is also c -optimal with $c = (1, 0, 0)^\top$, there exists $\delta_{iP} = \pm 1$ for $i = 1, \dots, k_P$, procedure $P = R$ or G , and exists δ_{iBj} for $j = 0, 1, 2$ with $\sum_{j=0}^2 \delta_{iBj}^2 = 1$ for $i = 1, \dots, k_B$, such that the Elfving's representation of ξ ,

$$\sum_{i=1}^{k_R} w_{iR} \delta_{iR} \mu_R(x_{iR}) + \sum_{i=1}^{k_G} w_{iG} \delta_{iG} \mu_G(x_{iG}) + \sum_{i=1}^{k_B} w_{iB} \sum_{j=0}^2 \delta_{iBj} \mu_{Bj}(x_{iB}) = \gamma c,$$

lies on the boundary of the generalized Elfving set \mathcal{E} for some $\gamma > 0$.

Because $\mu_G(x) \propto c$ for all x , we have that both of the two designs ξ_G and $w'_R \xi_R + w'_B \xi_B$ must have their Elfving's representations lying in the direction of c . Therefore, it must be the case that the two representations are both equal to γc , which means that the two designs are both D_s -optimal.

Proof of Proposition 3.2. Proposition A.1(i) directly shows that ξ_G^* is D_s^G -optimal. By Proposition A.1(ii), there exists a group size x such that A_x^B is D_s^B -optimal. By maximizing $\Phi_s\{M(A_x^B)\}$, we get that x_B^* is the optimal group size. Finally, because

$$\Psi_s\{M(A_{x_B^*}^B)\} \leq \Psi_s\{M(A_{x_B^*}^G)\} \leq \Psi_s\{M(A_{x_G^*}^G)\},$$

we have the desired result.

Proof of Theorem 3.2. Note that all designs in $\Xi_{R \oplus B}$ have a nonsingular information matrix. If ξ_1 is $D_s^{R \oplus B}$ -optimal, then for an arbitrary group size x and procedure $P = R$ or B , the directional derivative of Φ_s at $M(\xi)$ in the direction $M(A_x^P)$ must have $\phi_P(x, \xi) \leq 0$; otherwise there exists a $\delta_0 > 0$ such that $\xi_2 = (1 - \delta_0)\xi_1 + \delta_0 A_x^P \in \Xi_{R \oplus B}$ and $\Phi_s\{M(\xi_2)\} - \Phi_s\{M(\xi_1)\} > 0$, which makes a contradiction.

On the other hand, if ξ_1 is not $D_s^{R \oplus B}$ -optimal, then there exists another design ξ_2 such that $\Phi_s\{M(\xi_2)\} - \Phi_s\{M(\xi_1)\} > 0$. Because $M(\xi_2)$ is a linear combination of the information matrices of its support points under the corresponding procedures, we have that

$$\begin{aligned} 0 &< \lim_{\delta \rightarrow 0^+} \frac{1}{\delta} [\Phi_s\{M(\xi_1)\} - \Phi_s\{M(\xi_2)\}] \\ &= \text{tr}\{M(\xi_1)^{-1}M(\xi_2)\} - \text{tr}\{\tilde{M}(\xi_1)^{-1}\tilde{M}(\xi_2)\} - 1 \\ &= \sum_{P=R,B} \sum_{i=1}^{k_P} \phi_P(x_{iP}^{(2)}, \xi_1), \end{aligned}$$

where $x_{iP}^{(2)}$ s are the group sizes in ξ_2 . Therefore, there must exist some $\phi_P(x_{iP}^{(2)}, \xi_1) > 0$.

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