



On optimal fMRI designs for correlated errors

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ABSTRACT

Functional magnetic resonance imaging (fMRI) techniques involve studying the brain activity of an experimental subject in response to a mental stimulus, such as a picture or a video shown to the subject. The design problem in fMRI studies is to come up with the best sequence of stimuli to be shown to subjects which enables the precise estimation of the brain activity. In previous analytical studies concerning fMRI designs, it has been assumed that the errors are independent over time. The current state-of-the-art method to find optimal designs for the situations when the errors are correlated is to use the genetic algorithm. In this paper, we analytically obtain the optimal designs in a subclass for the situations when the errors over time are assumed to have an auto-regressive (AR) structure. Since such optimal designs might not exist, in practice, we advocate the use of what we call *g*-lag orthogonal designs. We show that these *g*-lag orthogonal designs perform reasonably well under a wide range of conditions under the models with correlated errors.

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1. Introduction

Functional magnetic resonance imaging (fMRI) measures cerebral blood flow, which is used as a surrogate for neuronal brain activity. When an area of the brain is stimulated, it leads to increased blood flow in that area. The fMRI uses the blood-oxygen-level-dependent (BOLD) contrast which is used to map neural activity in the brain of humans or other animals by imaging the change in blood flow (also known as, hemodynamic response) related to energy use by brain cells. Event-related functional magnetic resonance imaging (ER-fMRI) is a technique for studying brain activity in response to mental stimuli (for example, looking at pictures, watching a video, etc.). ER-fMRI is important and popular in neuroscience because this technique does not involve people to undergo brain surgery or to ingest substances or chemicals which may have harmful side-effects.

Experimental subjects are presented with a sequence of mental stimuli of one or more types and during this exposition, an MRI scanner repeatedly scans the subject's brain to collect a time series from each brain voxel. For each voxel, the observed time series represents the cumulative effects of the stimuli. The effect of a single stimulus is modeled by a Hemodynamic Response Function (HRF), which could be different for different voxels. Estimating the HRF is often the main interest in an fMRI experiment (Lazar, 2008). For design selection, we focus on estimation of the heights of the HRF at selected time points after onset.

In this paper, we consider fMRI studies with one type of stimulus and focus on estimating the HRF function. The design problem for fMRI studies with one type of stimulus is to understand which 0–1 sequence out of the 2^n sequences, where

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n is the length of the considered sequence, is the best sequence for estimating the HRF function. Considerations are based on a common model for fMRI studies that is discussed in Section 2.

Existing approaches for finding optimal fMRI designs mainly rely on computer search algorithms (Wager and Nichols, 2003; Kao et al., 2009a,b, for example). Recently, analytical results for stimuli of one or two types have been obtained (Kao, 2013, 2015, for example). To the best of our knowledge, the analytical results are only available for the situations when the observations are independent over time. Kao (2015), while discussing the analytical results for stimuli of two types, mentioned that the assumption of uncorrelated errors may sometimes be violated and it becomes important to find optimal designs for such situations analytically. The current state-of-the-art method to find the best designs is to use the genetic algorithm of Kao et al. (2009a). The algorithm can incorporate several models that occur in practice, and can handle the errors being temporally dependent. The designs provided by the algorithm are highly efficient but there is no surety that these designs are optimal.

In this paper, we study analytically obtaining highly efficient fMRI designs under the assumption of correlated errors. We start with the model that is considered in the papers with the assumption of independent errors (Kao, 2013, 2015) and introduce the correlated errors assuming an auto-regressive (AR) structure. Since it is quite hard to provide a general solution to the problem, we obtain the optimality results within a subclass of designs. In Sections 2 and 3, we discuss the model, information matrix, class of designs, optimal designs under our setup, and the definition of g -lag orthogonal designs. Since the optimal designs may not exist, in Section 4, we identify g -lag orthogonal designs that (a) are locally optimal when the correlation parameter is not too large, and (b) are highly efficient compared to the optimal designs obtained in this paper. Additionally, we propose a new construction method to obtain larger g -lag orthogonal designs from smaller designs which provides alternate designs to the ones available in the literature. It is possible to have non-orthogonal designs that are better than the ones we have advocated the use of. Using a genetic algorithm (GA), we study the efficiencies of g -lag orthogonal designs among all possible designs under the AR(1) structure. We identify g -lag orthogonal designs that perform well as long as the parameter of AR(1) structure is not too large (efficiencies higher than 0.90). In addition, we also identify efficient g -lag orthogonal designs for the AR(2) error structure, which sometimes is a more useful error structure in practice (Lenoski et al., 2008).

2. The model and the information matrix

An ordered sequence $(x_1, x_2, \dots, x_n)$ where $x_i \in \{0, 1\}$, $i = 1, \dots, n$ is an fMRI experimental design with one stimulus type occurring for at most n time points. The pre-specified time between successive time-points is called the inter-stimulus interval or ISI. When $x_i = 1$, the stimulus occurs at the i th time point for a brief time, say, 1 s, and when $x_i = 0$, no stimulus is shown at the i th time point and the subject is asked to rest or gaze at a fixed object.

The stimuli x_i 's are presented sequentially to an experimental subject while a BOLD signal is obtained at each brain voxel. The cumulative heights of the HRFs, that contribute to an fMRI time series, are observed at regular, discrete time points depending on the times at which scanning takes place. Since an HRF will return to baseline (cf. Zhang and Yu, 2008), the number of heights of an HRF that an fMRI time series provides information about depends on ISI, the time to repetition (TR) or time between two consecutive observations in an fMRI time series, and the time until the HRF returns to baseline. For details we refer to Kao and Stufken (2015). We assume that the number of heights for which information is collected is equal to k ($k < n$).

The assumption that the last $k - 1$ elements of the design also appear in the pre-period before the first valid MRI measurement, similar to the previous studies (Kao, 2013, 2015), is adopted here. The model that we consider is

$$y_i = \mu + \sum_{j=0}^{k-1} x_{i-j} h_{j+1} + \epsilon_i, \quad i = 1, \dots, n,$$

where μ is the general mean, h_{j+1} is the j th HRF height, and $x_{i-j} = x_{n+i-j}$. The model in matrix notation is then,

$$y = 1_n \mu + X\alpha + \epsilon, \quad (1)$$

where 1_n is a column vector of length n with all 1s, $y = (y_1, \dots, y_n)$, $\alpha = (h_1, \dots, h_k)$, and the design matrix

$$X = \begin{bmatrix} x_1 & x_n & x_{n-1} & \cdots & x_{n-k+2} \\ x_2 & x_1 & x_n & \cdots & x_{n-k+3} \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ x_n & x_{n-1} & x_{n-2} & \cdots & x_{n-k+1} \end{bmatrix}.$$

We assume that the errors $\epsilon = (\epsilon_1, \dots, \epsilon_n)$ are auto-correlated, following a circular AR(1) structure with parameter λ . That is, the variance-covariance matrix of ϵ is Σ such that

$$\Sigma^{-1} = \begin{bmatrix} 1 + \lambda^2 & -\lambda & 0 & \cdots & -\lambda \\ -\lambda & 1 + \lambda^2 & -\lambda & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ -\lambda & 0 & 0 & \cdots & 1 + \lambda^2 \end{bmatrix}.$$

A Toeplitz matrix is a matrix in which each descending diagonal from left to right is constant. One can denote a $n \times n$ Toeplitz matrix $A = (A_{u,v})$ by a generating vector of length $2n - 1$ with entries $(a_{n-1}, \dots, a_1, a_0, a_{-1}, \dots, a_{-(n-1)})$ where $A_{u,v} = a_{u-v}$, $u, v = 1, \dots, n$. For example, Σ^{-1} is a Toeplitz matrix with its generating vector being $(-\lambda, 0, \dots, -\lambda, 1 + \lambda^2, -\lambda, \dots, 0, -\lambda)$. Define H to be the Toeplitz matrix with the generating vector being $(0, 0, \dots, -\lambda, 1, 0, \dots, 0, -\lambda)$. Then, the information matrix of α , using the generalized least squares estimation, in the circular AR(1) model (1) for an arbitrary design equals

$$C = X^T H^T H X - \frac{1}{1_n^T H^T H 1_n} X^T H^T H 1_n 1_n^T H^T H X. \quad (2)$$

We observe that

$$HX = \begin{bmatrix} x_1 - \lambda x_n & x_n - \lambda x_{n-1} & x_{n-1} - \lambda x_{n-2} & \cdots & x_{n-k+2} - \lambda x_{n-k+1} \\ x_2 - \lambda x_1 & x_1 - \lambda x_n & x_n - \lambda x_{n-1} & \cdots & x_{n-k+3} - \lambda x_{n-k+2} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ x_n - \lambda x_{n-1} & x_{n-1} - \lambda x_{n-2} & x_{n-2} - \lambda x_{n-3} & \cdots & x_{n-k+1} - \lambda x_{n-k} \end{bmatrix}.$$

Then, it is easy to see that $X^T H^T H X$ is a Toeplitz matrix with its generating vector as $(e_{k-1}, e_{k-2}, \dots, e_1, f, e_1, \dots, e_{k-2}, e_{k-1})$, where

$$f = \sum_{i=1}^n (x_i - \lambda x_{i-1})^2 = (1 + \lambda^2) \sum_{i=1}^n x_i^2 - 2\lambda \sum_{i=1}^n x_i x_{i-1}, \quad (3)$$

$$\begin{aligned} e_j &= \sum_{i=1}^n (x_i - \lambda x_{i-1})(x_{i-j} - \lambda x_{i-j-1}) \\ &= (1 + \lambda^2) \sum_{i=1}^n x_i x_{i-j} - \lambda \sum_{i=1}^n x_i x_{i-j+1} - \lambda \sum_{i=1}^n x_i x_{i-j-1}. \end{aligned} \quad (4)$$

We also note that $H 1_n = (1 - \lambda) 1_n$, and $1_n^T H^T H X = (1 - \lambda)^2 (\sum_{i=1}^n x_i) 1_k^T$. Therefore,

$$\frac{1}{1_n^T H^T H 1_n} X^T H^T H 1_n 1_n^T H^T H X = \frac{(1 - \lambda)^2}{n} \left(\sum_{i=1}^n x_i \right)^2 1_k 1_k^T. \quad (5)$$

Note that C is a $k \times k$ matrix, and from the expressions in (3), (4), and (5), it is immediately clear that C depends on the design only through the values of $\sum_{i=1}^n x_i x_{i-\ell}$ for $\ell = 0, 1, \dots, k$, with the value for $\ell = k$ only playing a role for correlated errors. For the case of uncorrelated errors, one of the sufficient conditions (Kao, 2013, Theorem 1) for a design to be universally optimal is that the design should have an equal number ($n/2$) of 1s and 0s. Therefore, we also use designs with $n/2$ stimuli as our starting point, and call such a design g -lag orthogonal if it also satisfies

$$\sum_{i=1}^n x_i x_{i-\ell} = \frac{n}{4}, \text{ for all } \ell = 1, \dots, g, \quad (6)$$

where the design is $(x_1, x_2, \dots, x_n)$ with $x_i \in \{0, 1\}$, $i = 1, \dots, n$. We use $\mathcal{D}(n, g)$ to denote the class of all g -lag orthogonal designs with $n/2$ stimuli. A $(k-1)$ -lag orthogonal design with $n/2$ stimuli is universally optimal for uncorrelated errors (see Kao, 2013, Theorem 1).

In the next section, we first obtain the information matrix of designs in $\mathcal{D}(n, k-1)$, and then obtain A -optimal designs in this subclass of designs.

3. Optimal designs in $\mathcal{D}(n, k-1)$

From (2), using (3), (4), (5) and (6), the information matrix for the fMRI designs in $\mathcal{D}(n, k-1)$, with the errors being correlated as AR(1) with parameter λ , is

$$C = \frac{n}{4} \begin{bmatrix} 1 + \lambda^2 & -\lambda & 0 & \cdots & b\lambda \\ -\lambda & 1 + \lambda^2 & -\lambda & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ b\lambda & 0 & 0 & \cdots & 1 + \lambda^2 \end{bmatrix}, \quad (7)$$

where

$$b = 1 - \frac{4}{n} \sum_{i=1}^n x_i x_{i-k}. \quad (8)$$

Note that the information matrix C is dependent on the design through b . Then, $\frac{4}{n}C$ is a Toeplitz matrix with its generating vector as $(b\lambda, 0, \dots, -\lambda, 1 + \lambda^2, -\lambda, \dots, 0, b\lambda)$. The designs in $\mathcal{D}(n, k-1)$ have $\sum_{i=1}^n x_i x_{i-k}$ equal to an integer between 0 and $\frac{n}{2}$, and therefore, the values of b lie between -1 and 1 . Now, we obtain the optimal values of b assuming b is a real number and then for finding the actual designs, one could use the nearest integer value of b .

We consider A -optimality as a criterion to find optimal designs. A design $d^* \in \mathcal{D}(n, k-1)$ is said to be A -optimal in $\mathcal{D}(n, k-1)$ if $\text{trace}(C_{d^*}^{-1}) \leq \text{trace}(C_d^{-1})$ for any other design $d \in \mathcal{D}(n, k-1)$. The following result, with a proof in the Appendix, gives an expression for the $\text{trace}(C_d^{-1})$ for a design $d \in \mathcal{D}(n, k-1)$, where C is as in (7).

Theorem 1. For a design $d \in \mathcal{D}(n, k-1)$ with $k \geq 3$ and a non-zero λ ,

$$\text{trace}(C_d^{-1}) = \frac{4}{n} \left(\frac{\sum_{i=1}^k \lambda^{2(k-i)} (i(k-i+1) - b^2(i-1)(k-i))}{\sum_{i=0}^k \lambda^{2i} + 2b\lambda^k - b^2 \sum_{i=1}^{k-1} \lambda^{2i}} \right).$$

Note that from (7), for $\lambda = 0$, $\text{trace}(C_d^{-1}) = \frac{4k}{n}$ for any design $d \in \mathcal{D}(n, k-1)$. Therefore, all designs are equivalent at $\lambda = 0$ and any design could be used.

To find the value of b corresponding to the A -optimal design, standard calculus results are used. The roots are obtained for the first derivative of $\text{trace}(C_d^{-1})$ in Theorem 1 with respect to b and then these roots are evaluated for their corresponding maxima or minima possibility. The first derivative of $\text{trace}(C_d^{-1})$ yields only two roots of b . The absolute value of one of these two roots is larger than 1, and the corresponding second derivative is strictly negative. The detailed proofs are given in the Appendix. The second derivative at the other root, however, is strictly positive. Therefore, if the absolute value of the other root is smaller than or equal to 1, then we have found the value of b corresponding to an A -optimal design. Theorem 3 gives the value of b for which $\text{trace}(C_d^{-1})$ is minimum among all designs $d \in \mathcal{D}(n, k-1)$. But, we first need to show that the value of b in Theorem 3 is a real number. This is done in Lemma 2, the proof of which is in the Appendix.

Both in Lemma 2 and Theorem 3 we will use the following notation: $c_1 = \sum_{i=1}^k i(k-i+1)\lambda^{2(k-i)}$, $c_2 = \sum_{i=1}^k (i-1)(k-i)\lambda^{2(k-i)}$, $c_3 = \sum_{i=0}^k \lambda^{2i}$, $c_4 = \lambda^k$, and $c_5 = \sum_{i=1}^{k-1} \lambda^{2i}$. Then, for a design $d \in \mathcal{D}(n, k-1)$, the value for $\text{trace}(C_d^{-1})$ in Theorem 1 can be written as

$$\text{trace}(C_d^{-1}) = \frac{4}{n} \left(\frac{c_1 - c_2 b^2}{c_3 + 2c_4 b - c_5 b^2} \right). \quad (9)$$

The value of the parameter λ lies between -1 and 1 . The quantities c_1 , c_2 , c_3 , and c_5 are all symmetric around $\lambda = 0$, that is, the values of c_1 , c_2 , c_3 , and c_5 are the same at $|\lambda|$ as at $-|\lambda|$. On the other hand, the value of c_4 at $|\lambda|$ is the negative of its value at $-|\lambda|$. These observations are helpful to simplify the proofs of Lemma 2 and Theorem 3.

Lemma 2. For a design $d \in \mathcal{D}(n, k-1)$ and for $0 < |\lambda| \leq 1$, it holds that

$$(c_1 c_5 - c_2 c_3)^2 > 4c_1 c_2 c_4^2 \quad \text{and} \quad c_1 c_5 > c_2 c_3,$$

where c_1 through c_5 are as defined before (9).

In Theorem 3, we find the optimal value of b (and call it b^*) for which $\text{trace}(C_d^{-1})$ is minimum among all designs $d \in \mathcal{D}(n, k-1)$. We note that the value of b^* at $|\lambda|$ is the negative of its value at $-|\lambda|$.

Theorem 3. For a design $d \in \mathcal{D}(n, k-1)$, the value of b corresponding to the A -optimal design under model (1) with $AR(1)$ error structure having the parameter λ is

$$b^* = \frac{(c_1 c_5 - c_2 c_3) - ((c_1 c_5 - c_2 c_3)^2 - 4c_1 c_2 c_4^2)^{\frac{1}{2}}}{2c_2 c_4},$$

where c_1 through c_5 are as defined before (9).

Proof. From (9), let $\text{trace}(C_d^{-1}) = \frac{4}{n} \left(\frac{c_1 - c_2 b^2}{c_3 + 2c_4 b - c_5 b^2} \right) = f(b)$. Differentiating it with respect to b and putting the first derivative equal to 0 yields two roots, $r_1 = \frac{s_1 - \sqrt{s_2}}{2s_3}$, and $r_2 = \frac{s_1 + \sqrt{s_2}}{2s_3}$, where $s_1 = c_1 c_5 - c_2 c_3$, $s_2 = s_1^2 - 4c_1 c_2 c_4^2$, and $s_3 = c_2 c_4$.

Let $f''(r_1)$ and $f''(r_2)$ denote the values of the second derivative of f with respect to b at the roots r_1 and r_2 , respectively. Simplifying these values at each of these two roots, we get

$$f''(r_1) = \frac{16\sqrt{s_2}s_3^4}{(-2c_5 s_2 + 2\sqrt{s_2}(c_5 s_1 - 2c_4 s_3))^2}, \quad f''(r_2) = \frac{-16\sqrt{s_2}s_3^4}{(2c_5 s_2 + 2\sqrt{s_2}(c_5 s_1 - 2c_4 s_3))^2}.$$

Also, for $k \geq 3$ and for non-zero λ , $c_2 > 0$, and $c_4^2 > 0$, therefore, $s_3^4 > 0$. To see that the denominator of $f''(r_1)$ is different from zero, we note that $(-2c_5 s_2 + 2\sqrt{s_2}(c_5 s_1 - 2c_4 s_3))^2 = 4s_2(c_5(s_1 - \sqrt{s_2}) - 2c_4 s_3)^2 = 4s_2(c_5 \frac{4c_1 c_2 c_4^2}{(s_1 + \sqrt{s_2})} - 2c_4^2 c_2)^2 =$

$\frac{16s_2c_2^2c_4^4}{(s_1+\sqrt{s_2})^2}(c_1c_5+c_2c_3-\sqrt{s_2})^2$, and since $s_2 < s_1^2$, we have that $\sqrt{s_2} < (c_1c_5 - c_2c_3) < c_1c_5 + c_2c_3$. Similarly, the denominator of $f''(r_2)$ is different from zero, because $(2c_5s_2 + 2\sqrt{s_2}(c_5s_1 - 2c_4s_3))^2 = \frac{16s_2c_2^2c_4^4}{(s_1-\sqrt{s_2})^2}(c_1c_5 + c_2c_3 + \sqrt{s_2})^2$. Now, if s_2 is also strictly positive, then r_1 and r_2 are points of local minima and maxima, respectively. From Lemma 2, we have that s_2 is strictly positive for non-zero λ . Hence, r_1 is the desired point where $\text{trace}(C_d^{-1})$ is minimum.

We now show that $|r_2| > 1$ and therefore outside the possible range of b . Since $c_2 = c_1 - k \sum_{i=1}^k \lambda^{2(k-i)}$, we have that $c_1 > c_2$. Now assume that $\lambda > 0$. Then since $c_4 \geq 0$, we have that $c_1c_4 \geq s_3$, or, in other words $s_2 = s_1^2 - 4c_1c_4s_3 \leq s_1^2 - 4s_3^2$. Then since, s_1, s_2 , and s_3 are all non-negative, we have that $s_1 - 2s_3 \geq \frac{s_2}{s_1+2s_3} \geq 0$. Then, $s_1 - 2s_3 + \sqrt{s_2} > 0$ implies that $\frac{s_1+\sqrt{s_2}}{2s_3} > 1$, or $r_2 > 1$. For the case, when $\lambda < 0$, we note that the value of r_2 at $|\lambda|$ is the negative of the value of r_2 at $-|\lambda|$. This implies that the absolute value of r_2 is always larger than 1.

By using Lemma 2, it is easy to see that the numerator of $r_1 = b^*$ is always a non-negative real number. We now show that $|r_1| < 1$. For $r_1 < 1$, it should hold that $(s_1 - 2s_3)^2 < s_2 = s_1^2 - 4c_1c_2c_4^2$ or that $s_3^2 - s_1s_3 + c_1c_2c_4^2 < 0$ or (since $s_3 > 0$) that $s_3 - s_1 + c_1c_4 < 0$. So, showing $r_1 < 1$ is equivalent to showing $c_1c_5 - c_2c_3 - c_2c_4 - c_1c_4 > 0$. Now, using the values of $c_i, i = 1, \dots, 5$ from the proof of Lemma 2, we get

$$c_1c_5 - c_2c_3 - c_2c_4 - c_1c_4 = -c_2(1 + \lambda^k)^2 + \frac{k\lambda^2(1 - \lambda^{2k})(1 - \lambda^{k-2})(1 + \lambda^k)}{(1 - \lambda^2)^2}.$$

Therefore, we need to show that

$$c_2 < \frac{k\lambda^2(1 - \lambda^k)(1 - \lambda^{k-2})}{(1 - \lambda^2)^2}.$$

Using the value of c_2 from the proof of Lemma 2, we, therefore, need to show that

$$k\lambda^{2k} - (k-2)\lambda^{2k+2} + (k-2)\lambda^2 - k\lambda^4 < k\lambda^2(1 - \lambda^k)(1 - \lambda^{k-2})(1 - \lambda^2),$$

or, upon simplifications, $2\lambda^{2k} - k\lambda^{k+2} + k\lambda^{k-2} - 2 < 0$. Now, say, $g(\lambda) = 2\lambda^{2k} - k\lambda^{k+2} + k\lambda^{k-2} - 2$. The derivative $g'(\lambda) = 4k\lambda^{2k-1} - k(k+2)\lambda^{k+1} + k(k-2)\lambda^{k-3} = \lambda^{k-3}(4k\lambda^{k+2} - k(k+2)\lambda^4 + k(k-2))$. That $4k\lambda^{k+2} - k(k+2)\lambda^4 + k(k-2) > 0$ follows because λ^x is convex in x . Then $r_1 < 1$ follows by noting that $g'(\lambda) > 0$ for $\lambda \in (0, 1)$, implying that $g(\lambda)$ is an increasing function. This, together with the fact that $g(1) = 0$ proves that $2\lambda^{2k} - k\lambda^{k+2} + k\lambda^{k-2} - 2 < 0$, or that, $r_1 < 1$. For the case, when $\lambda < 0$, we note that the value of r_1 at $|\lambda|$ is the negative of the value of r_1 at $-|\lambda|$. This implies that the absolute value of r_1 is always smaller than 1. ■

Within the class of $(k-1)$ -lag orthogonal designs, that is, in $\mathcal{D}(n, k-1)$, we obtained the value of an optimal b such that if the $(k-1)$ -lag orthogonal design additionally has the value of $\frac{4}{n} \sum_{i=1}^n x_i x_{i-k} = 1 - b^*$, then that design is the A-optimal design for the situations when the errors are correlated with a circular AR(1) structure.

We recognize the fact that a design with optimal b^* might not exist and even if it exists, it might be hard to find. In what follows, we consider the $(k-1)$ -lag orthogonal designs that additionally have $b = 0$ or $\sum_{i=1}^n x_i x_{i-k} = \frac{n}{4}$. Note that these designs are k -lag orthogonal designs from the definition in (6).

4. Optimality and construction of g -lag orthogonal designs

The next result shows that g -lag orthogonal designs (with $g = k$) are locally A-optimal for estimation under model (1) with AR(1) error structure.

Theorem 4. A design $d_0 \in \mathcal{D}(n, k-1)$ which is also k -lag orthogonal, i.e., which has $b = 0$, is locally-A-optimal in $\mathcal{D}(n, k-1)$ under model (1) with AR(1) error structure when the parameter λ is in a neighborhood of 0.

Proof. For a design $d \in \mathcal{D}(n, k-1)$, from Theorem 1, let $\text{trace}(C_d^{-1}) = f(\lambda, b)$. Consider the function $h(\lambda, b) = f(\lambda, b) - f(\lambda, 0)$. From simple algebra, it can be seen that $h(0, b) = 0$, $\frac{\partial h(\lambda, b)}{\partial \lambda} = 0$ at $\lambda = 0$, but the second derivative of $h(\lambda, b)$ at $\lambda = 0$ is $\frac{\partial^2 h(\lambda, b)}{\partial \lambda^2} > 0$. ■

The efficiency of a design $d \in \mathcal{D}(n, k-1)$ with respect to a design d^* is defined as

$$\text{eff}_d = \frac{\text{trace}(C_{d^*}^{-1})}{\text{trace}(C_d^{-1})}. \quad (10)$$

Considering d^* in (10) to be an optimal fMRI design in $\mathcal{D}(n, k-1)$ with $b = b^*$ as obtained in Theorem 3, in Fig. 1(a), efficiencies of k -lag orthogonal designs are plotted for $\lambda \in [-1, 1]$ and for specific values of $k = 3, \dots, 6$, and in Fig. 1(b) the box-plots of efficiencies of k -lag orthogonal designs are displayed for $k = 3, \dots, 15$ where each box-plot is over the values of $\lambda \in [-1, 1]$. From the figure, we note that k -lag orthogonal designs remain highly efficient as k increases, irrespective of the value of λ . Additionally, as λ inches closer to 0, k -lag orthogonal designs are more efficient, and even optimal for small enough λ . For example, for $|\lambda| \leq 0.4$, the efficiencies are at least 0.95. Similarly, for $k \geq 4$, the efficiencies

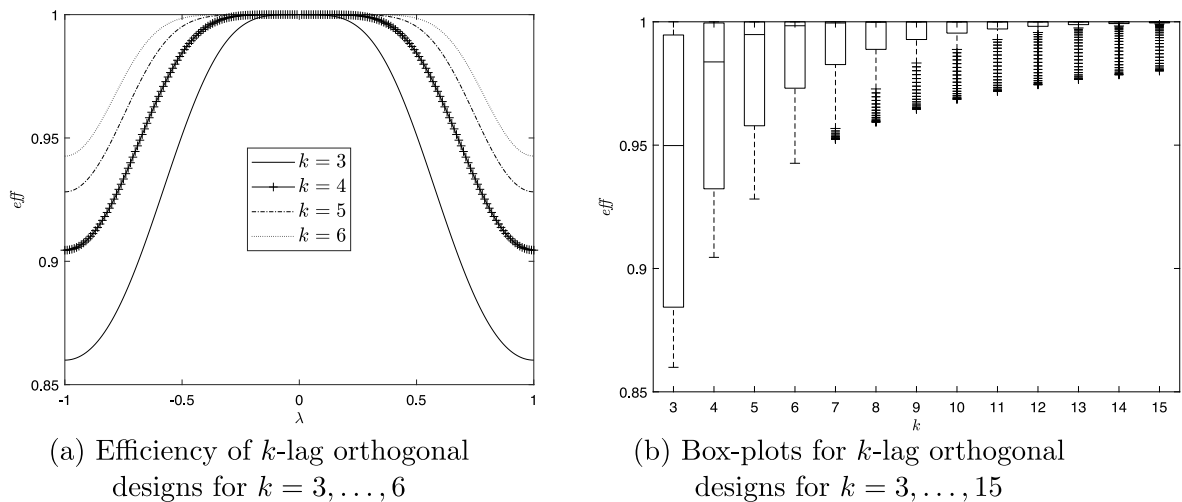


Fig. 1. Efficiency charts for k -lag orthogonal designs.

are at least 0.9, and the efficiencies are always larger than 0.95 provided that k is greater than 6. Since we do not know whether d^* exists, the efficiencies calculated using (10) are, in fact, lower bounds for the efficiencies.

We now provide a construction method to obtain g -lag orthogonal fMRI designs with larger n from such designs with smaller n . Note that for $g = k - 1$, these designs are universally optimal under the model (1) with uncorrelated error structure for estimating k HRF heights. For $g = k$, these designs are locally A -optimal under the model (1) with AR(1) error structure as in Theorem 4.

Theorem 5. For $n_1 \geq g_1$ and $n_2 \geq g_2$, let $d_1 = (x_1^1, \dots, x_{n_1}^1)$ and $d_2 = (x_1^2, \dots, x_{n_2}^2)$ be g_1 -lag and g_2 -lag orthogonal designs for a single stimulus type, respectively. With $g = \min(g_1, g_2)$, the design $d^+ = (d_1, d_2)$ is a g -lag orthogonal design provided that either (i) $x_u^1 = x_u^2$ for $u = 1, \dots, g$, or (ii) $x_{n_1-v}^1 = x_{n_2-v}^2$ for $v = 0, \dots, g - 1$.

For the proof, from the definition of d^+ , it is easily seen that, for $\ell = 1, \dots, g$, the value of $\sum_i x_i x_{i-\ell}$ for d^+ is equal to the sum of the values for d_1 and d_2 if condition (i) or (ii) holds. That d^+ is g -lag orthogonal follows now since d_1 and d_2 are.

Theorem 5 provides alternate orthogonal designs for certain values of n and g to the ones available in the literature (Kao, 2015; Lin et al., 2017). Lemma 3.8 of Lin et al. (2017) also constructs larger orthogonal designs by repeating copies of the same design. This is a special case of Theorem 5, but may be less desirable if patients can memorize the earlier pattern and start behaving differently. In such situations, our Theorem 5 may provide an alternate construction. For example, a design with $n = 128$ and $g = 14$ can be constructed using Theorem 5 from the two designs d_1 with $n_1 = 36$, $g_1 = 14$ and d_2 with $n_2 = 92$, $g_2 = 14$ of Lin et al. (2017). The design d^+ is given as (1111101000011010010001001100011101010110100000110010000001111101110111001011010011000111010111110100001101001000100110001110101).

5. Performance against non-orthogonal designs

We have obtained the conditions for a design to be A -optimal when the errors are correlated with the AR(1) structure within the class of $(k - 1)$ -lag orthogonal designs, $\mathcal{D}(n, k - 1)$. Because such designs with an optimal b^* may not exist, we showed that k -lag orthogonal designs perform reasonably well, that is, have high efficiencies within this class $\mathcal{D}(n, k - 1)$. However, it is possible to have designs that fall outside $\mathcal{D}(n, k - 1)$. For example, one may obtain such designs using the genetic algorithm (GA) of Kao et al. (2009a). Using the genetic algorithm, we obtained the designs for the parameters provided in Table 1 for the λ values equal to 0.1, 0.3, and 0.5 and for n between 100 and 200. We chose these parameters (n and g) because we know that g -lag orthogonal designs exist for these parameters (Lin et al., 2017). From Table 1, we see that for a small $\lambda = 0.1$, there are times when an orthogonal design performs better than the design obtained via genetic algorithm (efficiencies exceeding 1). As λ increases, the designs obtained by the genetic algorithm are better than the k -lag orthogonal designs but the relative efficiencies of k -lag orthogonal designs remain higher than 0.90.

While the most studied error structure in past studies has been an AR(1) structure, several authors have also worked on more complicated error structures such as AR(2) models (Lenoski et al., 2008), ARMA models (Lindquist, 2008), and AR(p) models with $p \geq 2$ (Worsley et al., 2002). All of these models are shown to be useful when analyzing the correlated noise in fMRI data. In particular, it has been claimed that AR(2) structure often provides better results compared to AR(1)

Table 1Relative efficiencies of g -lag orthogonal designs to GA designs for $100 \leq n \leq 200$, AR(1) structure, and $k = g$.

n	g	$eff(\lambda = 0.1)$	$eff(\lambda = 0.3)$	$eff(\lambda = 0.5)$
100	13	1.0080	0.9826	0.9174
104	19	1.0392	0.9999	0.9529
108	13	1.0098	0.9856	0.9276
112	22	1.0290	0.9943	0.9448
116	13	1.0104	0.9763	0.9379
120	16	1.0143	1.0081	0.9124
124	13	1.0033	0.9882	0.9106
128	13	1.0009	0.9803	0.9228
132	15	1.0035	0.9875	0.9173
136	13	1.0005	0.9782	0.9212
140	13	1.0047	0.9769	0.9118
144	16	1.0033	0.9818	0.9069
148	13	1.0049	0.9802	0.9184
152	13	1.0039	0.9810	0.9192
156	19	1.0122	0.9850	0.9219
160	16	1.0054	0.9772	0.9143
164	13	1.0041	0.9691	0.9165
168	22	1.0128	0.9895	0.9310
172	13	1.0018	0.9739	0.9031
176	15	1.0011	0.9754	0.9078
180	13	1.0016	0.9748	0.9056
184	13	1.0083	0.9727	0.9220
188	13	1.0075	0.9807	0.9101
192	16	1.0026	0.9851	0.9186
196	13	1.0037	0.9731	0.9078
200	16	1.0009	0.9821	0.9178

and ARMA models (Lenoski et al., 2008). The inverse of the variance–covariance matrix Σ of ϵ corresponding to an AR(2) structure with known parameters λ_1 and λ_2 is

$$\begin{bmatrix} 1 + \lambda_1^2 + \lambda_2^2 & -\lambda_1 + \lambda_1\lambda_2 & -\lambda_2 & 0 & \cdots & 0 & -\lambda_2 & -\lambda_1 + \lambda_1\lambda_2 \\ -\lambda_1 + \lambda_1\lambda_2 & 1 + \lambda_1^2 + \lambda_2^2 & -\lambda_1 + \lambda_1\lambda_2 & -\lambda_2 & 0 & \cdots & 0 & -\lambda_2 \\ -\lambda_2 & -\lambda_1 + \lambda_1\lambda_2 & 1 + \lambda_1^2 + \lambda_2^2 & -\lambda_1 + \lambda_1\lambda_2 & -\lambda_2 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ -\lambda_1 + \lambda_1\lambda_2 & -\lambda_2 & 0 & \cdots & 0 & \cdots & -\lambda_1 + \lambda_1\lambda_2 & 1 + \lambda_1^2 + \lambda_2^2 \end{bmatrix}.$$

Given that k -lag orthogonal designs are highly efficient as long as the parameter of AR(1) structure is not too large, we now evaluate the performance of g -lag designs under the AR(2) structure. We again obtain the best designs from the GA algorithm using AR(2) error structure and use those designs as the benchmark designs. Using the same methodology as for the AR(1) error structure, we observed that the information matrix for AR(2) error structure depends on the design via two terms $\sum_{i=1}^n x_i x_{i-k}$ and $\sum_{i=1}^n x_i x_{i-k-1}$. Since the information matrix under AR(1) error structure was only dependent on the design via $\sum_{i=1}^n x_i x_{i-k}$, we saw that designs in $\mathcal{D}(n, k-1)$ which additionally have $\sum_{i=1}^n x_i x_{i-k} = n/4$ or, equivalently, $b = 0$ perform reasonably well, and hence, we now extend the same notion to the AR(2) error structure. For estimating the k HRF heights in a model where the error has AR(2) error structure, designs in $\mathcal{D}(n, k-1)$ with additional properties $\sum_{i=1}^n x_i x_{i-k} = n/4$ and $\sum_{i=1}^n x_i x_{i-k-1} = n/4$ are expected to perform well. That implies that we expect that a $(k+1)$ -lag orthogonal design would perform good for estimating the k HRF heights in a model where errors have an AR(2) error structure. For the parameters where we know that a g -lag orthogonal design exists (same n and g as in Table 1), we now evaluate the efficiencies of actual g -lag orthogonal design against GA design for the models where one can only estimate up to $k = g - 1$ HRF heights. These efficiencies are then listed in Table 2, for specific values of $\lambda_1 = \{0.1, 0.3, 0.5\}$ and $\lambda_2 = \{0.1, 0.3\}$, while keeping the values of n and g the same as in Table 1. We observe that as long as the parameters for AR(2) structure are not too large, these g -lag orthogonal designs remain highly efficient (the efficiencies are greater than 0.75). Therefore, in conclusion, g -lag orthogonal designs perform reasonably well with errors assuming both the AR(1) correlation structure (when interest is in the estimation of $k = g$ HRF heights) and AR(2) correlation structure (when interest is in the estimation of $k = g - 1$ HRF heights).

For the results in the paper, we restrict ourselves to designs with n divisible by 4. We also made efficiency comparisons with other designs in literature such as circulant almost orthogonal array (CAOA) designs of Lin et al. (2017) with $n = 4t+2$ for any positive t . Our comparison resulted in a similar conclusion. For smaller values of λ parameter, even though CAO designs might sometimes perform better than the g -lag orthogonal designs, one does not lose too much on efficiency with the use of g -lag orthogonal designs.

Table 2Relative efficiencies of g -lag orthogonal designs to GA designs for $100 \leq n \leq 200$, AR(2) structure, and $k = g - 1$.

n	g	$eff(\lambda_1 = 0.1, \lambda_2 = 0.1)$	$eff(\lambda_1 = 0.1, \lambda_2 = 0.3)$	$eff(\lambda_1 = 0.3, \lambda_2 = 0.1)$	$eff(\lambda_1 = 0.3, \lambda_2 = 0.3)$	$eff(\lambda_1 = 0.5, \lambda_2 = 0.1)$	$eff(\lambda_1 = 0.5, \lambda_2 = 0.3)$
100	13	1.0079	0.9825	0.9695	0.9354	0.8925	0.8075
104	19	1.0322	0.9837	0.968	0.9356	0.9029	0.7782
108	13	0.9980	0.9956	0.9744	0.9306	0.8951	0.8048
112	22	1.0359	0.9916	0.9876	0.9456	0.9173	0.7960
116	13	1.0076	0.9844	0.9764	0.9399	0.8932	0.8082
120	16	1.0183	0.9901	0.9825	0.9237	0.8926	0.7961
124	13	1.0056	0.9791	0.9640	0.9247	0.8929	0.8223
128	13	0.9999	0.9817	0.9655	0.9276	0.8935	0.8211
132	15	0.9984	0.9808	0.9605	0.9248	0.8893	0.7960
136	13	1.0002	0.9826	0.9649	0.9303	0.8845	0.8264
140	13	0.9976	0.9871	0.9692	0.9237	0.8933	0.8121
144	16	1.0028	0.9735	0.9701	0.9219	0.8852	0.8054
148	13	1.0051	0.9782	0.9645	0.9262	0.8978	0.8141
152	13	0.9986	0.9818	0.9659	0.9290	0.8885	0.7979
156	19	1.0097	0.9803	0.9641	0.9298	0.8994	0.7767
160	16	1.0015	0.9838	0.9677	0.9417	0.8896	0.8036
164	13	0.9986	0.9836	0.9623	0.9347	0.8956	0.7987
168	22	1.0089	1.0007	0.9640	0.9296	0.8878	0.7703
172	13	0.9971	0.9819	0.9640	0.9289	0.8946	0.8030
176	15	1.0036	0.9826	0.9709	0.9167	0.9045	0.8166
180	13	0.9986	0.9742	0.9652	0.9227	0.8857	0.8079
184	13	1.0002	0.9798	0.9684	0.9263	0.8941	0.8173
188	13	0.9980	0.9786	0.9654	0.9222	0.8877	0.8215
192	16	0.9987	0.9766	0.9657	0.9246	0.8802	0.8005
196	13	0.9976	0.9853	0.9623	0.9270	0.8873	0.7998
200	16	0.9989	0.9796	0.9602	0.9184	0.8908	0.7852

6. Conclusions

Event-related fMRI studies are an important tool for studying brain activity in response to stimuli. In such studies, a subject is given a sequence of stimuli with the objective of discovering how this activates different parts of the brain. As with experiments in other fields, the choice of design matters in terms of the information that one obtains from the experiment. In this setting, a design consists of the sequence of stimuli to be given to the subject.

Our work is inspired by [Kao \(2015\)](#), who showed that, for a single stimulus type, $(k - 1)$ -lag orthogonal designs are universally optimal for estimation of k HRF parameters if the errors in model (1) are independent. The primary question addressed in our work focuses on identifying optimal and efficient designs for the same setting, except that we use the more realistic assumption of an autoregressive error structure.

For an AR(1) error structure, it turns out that different $(k - 1)$ -lag orthogonal designs can have different information matrices for estimation of the k HRF parameters, and that these matrices depend in general on the parameter λ . For a fixed value of λ , [Theorem 3](#) identifies the best design in the class of $(k - 1)$ -lag orthogonal designs under the A -optimality criterion. Such a design may be called locally A -optimal for that fixed value of λ . Whether such designs actually exist is unclear, but their value under the A -optimality criterion can be used as a benchmark in obtaining the efficiency of other designs. We do this for k -lag orthogonal designs, which have an information matrix under the AR(1) error structure that is only dependent on λ . It turns out that these k -lag orthogonal designs are highly efficient for most values of λ , and even A -optimal for values of λ in a neighborhood of 0. Moreover, provided that λ is not too large, the k -lag orthogonal designs remain highly efficient when compared to non-orthogonal designs, which is seen by comparing them to designs obtained by a genetic algorithm. We also note that $(k + 1)$ -lag orthogonal designs are highly efficient for smaller values of the parameters under an AR(2) error structure. While the information matrices for $(k - 1)$ -lag and k -lag orthogonal designs depend on the design as well as the parameters, all $(k + 1)$ -lag orthogonal designs have the same information matrix that is dependent only on these parameters.

While not shown here, in general we expect $(k + p - 1)$ -lag orthogonal designs to perform well under an AR(p) error structure, if the parameters are not too large.

Since g -lag orthogonal designs play such a central role in our considerations and recommendations, we also provide a method for the construction of larger g -lag orthogonal designs from smaller designs of this type. Our method gives alternate designs to the ones available in the literature. This is still a wide-open research area. For a given length n of the design, what is the maximal value of g for which a g -lag orthogonal design exists? General answers may remain elusive, but clever construction methods for g -lag orthogonal designs might be able to improve the best values that are currently available.

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Appendix

A Hankel matrix H_ℓ is a square matrix in which each ascending skew-diagonal from left to right is constant. If J_ℓ is a $\ell \times \ell$ matrix such that the elements of the main NE-SW diagonal are ones and the rest of the elements are zeros, then a Hankel matrix could be obtained corresponding to its Toeplitz matrix. In what follows, we assume that $H_\ell = T_\ell J_\ell$, where T_ℓ is a Toeplitz matrix. Let, e_1, e_ℓ, z , and y be column vectors of length ℓ such that $e_1 = (1 \ 0_{\ell-1})^T$, $e_\ell = (0_{\ell-1} \ 1)^T$, $z = (z_0, \dots, z_{\ell-1})^T$, $y = (y_0, \dots, y_{\ell-1})^T$.

Lemma A.1 (Formula 5 of [Glasa, 2002](#)). Let $H_\ell = T_\ell J_\ell$ be a $\ell \times \ell$ Hankel matrix. Also, let $T_\ell z = e_1$, and $T_\ell y = e_\ell$, and $z_0 \neq 0$. Then, the inversion of the Hankel matrix is given by

$$H_\ell^{-1} = \frac{1}{z_0} \begin{bmatrix} z_{\ell-1} & z_{\ell-2} & \cdots & z_0 \\ \vdots & \vdots & \vdots & 0 \\ z_1 & z_0 & 0 & 0 \\ z_0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} y_{\ell-1} & y_{\ell-2} & \cdots & y_0 \\ 0 & y_{\ell-1} & \cdots & y_1 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & y_{\ell-1} \end{bmatrix} - \frac{1}{z_0} \begin{bmatrix} y_{\ell-2} & \cdots & y_0 & 0 \\ \vdots & \vdots & \vdots & 0 \\ y_0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} 0 & z_{\ell-1} & \cdots & z_1 \\ 0 & 0 & \cdots & z_2 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 \end{bmatrix}$$

Lemma A.2. Let $H_\ell = T_\ell J_\ell$ be a $\ell \times \ell$ Hankel matrix and T_ℓ be the corresponding Toeplitz matrix. Additionally, let $T_\ell z = e_1$, and $T_\ell y = e_\ell$, and $z_0 \neq 0$. Then

$$\text{trace}(T_\ell^{-1}) = \begin{cases} \ell y_{\ell-1} + \frac{1}{z_0} \sum_{u=1}^{\frac{\ell}{2}-1} (\ell - 2u)(z_u y_{\ell-1-u} - z_{\ell-u} y_{u-1}) & \text{for } \ell \text{ even,} \\ \ell y_{\ell-1} + \frac{1}{z_0} \sum_{u=1}^{\frac{\ell-1}{2}} (\ell - 2u)(z_u y_{\ell-1-u} - z_{\ell-u} y_{u-1}) & \text{for } \ell \text{ odd.} \end{cases}$$

Proof. Since $J_\ell = J_\ell^{-1}$, we have that $T_\ell^{-1} = J_\ell H_\ell^{-1}$, and then it is not very hard to see that $\text{trace}(T_\ell^{-1})$ would be the sum of the entries of NE-SW diagonal of H_ℓ^{-1} . The sum of the entries of NE-SW diagonal of the first product of two matrices in [Lemma A.1](#) is $\sum_{u=0}^{\ell-1} (u+1)z_{\ell-1-u}y_u$. The sum of the entries of NE-SW diagonal of the second product of two matrices in [Lemma A.1](#) is $\sum_{u=1}^{\ell-1} u y_{\ell-1-u} z_u$. Then,

$$\text{trace}(T_\ell^{-1}) = \frac{1}{z_0} \sum_{u=0}^{\ell-1} (u+1)z_{\ell-1-u}y_u - \frac{1}{z_0} \sum_{u=1}^{\ell-1} u y_{\ell-1-u} z_u.$$

Upon rearrangements, and simplification, we get the required result. ■

For the information matrix C in [\(7\)](#), the Toeplitz matrix $\frac{4}{n}C$ has the generating vector as $(b\lambda, 0, \dots, -\lambda, 1 + \lambda^2, -\lambda, \dots, 0, b\lambda)$, that is, the matrix is

$$\begin{bmatrix} 1 + \lambda^2 & -\lambda & 0 & \cdots & b\lambda \\ -\lambda & 1 + \lambda^2 & -\lambda & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ b\lambda & 0 & 0 & \cdots & 1 + \lambda^2 \end{bmatrix}. \quad (\text{A.1})$$

The proof of the following lemma follows upon application of any equation solving technique like Gauss Jordan elimination, triangularization, etc.

Lemma A.3. Let $h = \sum_{i=0}^k \lambda^{2i} + 2b\lambda^k - b^2 \sum_{i=1}^{k-1} \lambda^{2i}$. Then, with T_k denoting the matrix in [\(A.1\)](#) and $e_1 = (1 \ 0_{k-1})^T$, a solution $z = (z_0, \dots, z_{k-1})^T$ for $T_k z = e_1$ is given by the following:

Case (i) For k even, $s = 0, \dots, (\frac{k}{2} - 1)$:

$$z_{2s} = \frac{1}{h} \sum_{u=s}^{k-s-1} \lambda^{2u} - \frac{b}{h} \sum_{u=\frac{k}{2}-s}^{\frac{k}{2}+s-1} \lambda^{2u}, \quad \text{and} \quad z_{2s+1} = \frac{1}{h} \sum_{u=s+1}^{k-s-1} \lambda^{2u-1} - \frac{b}{h} \sum_{u=\frac{k}{2}-s}^{\frac{k}{2}+s} \lambda^{2u-1}.$$

Case (ii) For k odd, $s = 0, \dots, (\frac{k-3}{2})$

$$z_{2s} = \frac{1}{h} \sum_{u=s}^{k-s-1} \lambda^{2u} - \frac{b}{h} \sum_{u=\frac{k-1}{2}-s}^{\frac{k-1}{2}+s-1} \lambda^{2u+1}, \quad z_{2s+1} = \frac{1}{h} \sum_{u=s+1}^{k-s-1} \lambda^{2u-1} - \frac{b}{h} \sum_{u=\frac{k-1}{2}-s}^{\frac{k-1}{2}+s} \lambda^{2u}, \quad \text{and}$$

$$z_{k-1} = \frac{1}{h} \lambda^{k-1} - \frac{b}{z} \sum_{u=0}^{k-2} \lambda^{2u+1}.$$

Lemma A.4. With T_k denoting the matrix in (A.1) and $T_k z = e_1$, and $T_k y = e_k$, where $e_1 = (1 \ 0_{k-1})^T$, and $e_k = (0_{k-1} \ 1)^T$, we have that

$$z_u = y_{k-u-1} \quad \text{for all } u = 0, \dots, k-1.$$

Proof. Substitute $z_u = y_{k-u-1}$, for all $u = 0, \dots, k-1$ in each of the k equations corresponding to $T_k z = e_1$; call these first set of k equations. Also, call the k equations corresponding to $T_k y = e_k$ the second set of equations. It is then simple to see that the first equation from first set is same as the last equation of the second set, similarly second equation from the first set is equal to the second last equation of the second set, and so on. This completes the proof. ■

The following is a corollary to Lemma A.2 using Lemma A.4.

Corollary A.1. For the information matrix C in (7), and $\frac{4}{n}Cz = e_1$ with $e_1 = (1 \ 0_{k-1})^T$ and $z = (z_0, \dots, z_{k-1})^T$, it holds that

$$\frac{n}{4} \text{trace}(C^{-1}) = \begin{cases} kz_0 + \frac{1}{z_0} \sum_{u=1}^{\frac{k}{2}-1} (k-2u)(z_u^2 - z_{k-u}^2) & \text{for } k \text{ even,} \\ kz_0 + \frac{1}{z_0} \sum_{u=1}^{\frac{k-1}{2}} (k-2u)(z_u^2 - z_{k-u}^2) & \text{for } k \text{ odd.} \end{cases}$$

We are now ready to provide the proof of Theorem 1 by substituting the values of z as obtained in Lemma A.3 in Corollary A.1.

Proof of Theorem 1. We divide the proof into two cases based on the value of k .

Case when k is even: We first find the values for $(z_u^2 - z_{k-u}^2)$ for $u = 1, \dots, \frac{k}{2} - 1$. Note that if u is even, then $k-u$ is even, and if u is odd, then $k-u$ is odd. Consider u to be odd first. Then $(z_u^2 - z_{k-u}^2) = (z_{2s+1}^2 - z_{2(\frac{k}{2}-s-1)+1}^2)$. Then, from Lemma A.3,

$$z_{2s+1} + z_{2(\frac{k}{2}-s-1)+1} = \frac{(1-b)}{h} \left(\sum_{\ell=s+1}^{k-s-1} \lambda^{2\ell-1} + \sum_{\ell=\frac{k}{2}-s}^{\frac{k}{2}+s} \lambda^{2\ell-1} \right).$$

Or,

$$z_{2s+1} + z_{2(\frac{k}{2}-s-1)+1} = \frac{(1-b)\lambda^{2s+1}}{h} \left(\sum_{\ell=0}^{k-2s-2} \lambda^{2\ell} + \sum_{\ell=\frac{k}{2}-2s-1}^{\frac{k}{2}-1} \lambda^{2\ell} \right).$$

Note that, the terms from $\lambda^{2(\frac{k}{2}-2s-1)}, \dots, \lambda^{2(\frac{k}{2}-1)}$ come twice and the rest of the terms come once. Divide the terms into two sets $\lambda^{2(0)}, \dots, \lambda^{2(\frac{k}{2}-1)}$, and $\lambda^{2(\frac{k}{2}-2s-1)}, \dots, \lambda^{2(k-2s-2)}$. The second set of terms is the same as the first set except having a multiple of $\lambda^{2(\frac{k}{2}-2s-1)}$ in each term. Therefore, we get,

$$z_{2s+1} + z_{2(\frac{k}{2}-s-1)+1} = \frac{(1-b)\lambda^{2s+1}(1+\lambda^{(k-4s-2)})}{h} \left(\sum_{\ell=0}^{\frac{k}{2}-1} \lambda^{2\ell} \right).$$

Now, similarly, subtracting the common terms and dividing the remaining terms into two appropriate sets, we get,

$$z_{2s+1} - z_{2(\frac{k}{2}-s-1)+1} = \frac{(1+b)\lambda^{2s+1}(1+\lambda^k)}{h} \left(\sum_{\ell=0}^{\frac{k}{2}-2s-2} \lambda^{2\ell} \right).$$

Also, note that $z_0 = \frac{1}{h}(1+\lambda^k) \sum_{\ell=0}^{\frac{k}{2}-1} \lambda^{2\ell}$, and $(1+\lambda^{(k-4s-2)})(\sum_{\ell=0}^{\frac{k}{2}-2s-2} \lambda^{2\ell}) = \sum_{\ell=0}^{k-4s-3} \lambda^{2\ell}$. Therefore, we have,

$$z_{2s+1}^2 - z_{2(\frac{k}{2}-s-1)+1}^2 = \frac{z_0(1-b^2)\lambda^{4s+2}(\sum_{\ell=0}^{k-4s-3} \lambda^{2\ell})}{h}.$$

Or, in other words,

$$z_u^2 - z_{k-u}^2 = \frac{z_0(1-b^2)\lambda^{2u}(\sum_{\ell=0}^{k-2u-1} \lambda^{2\ell})}{h}. \quad (\text{A.2})$$

It is then not too hard to see that for u even, as well, we get,

$$z_u^2 - z_{k-u}^2 = z_{2s}^2 - z_{2(\frac{k}{2}-s)}^2 = \frac{z_0(1-b^2)\lambda^{4s}(\sum_{\ell=0}^{k-4s-1} \lambda^{2\ell})}{h} = \frac{z_0(1-b^2)\lambda^{2u}(\sum_{\ell=0}^{k-2u-1} \lambda^{2\ell})}{h}. \quad (\text{A.3})$$

Now, from [Corollary A.1](#), for k even, $\frac{n}{4}\text{trace}(C^{-1}) = kz_0 + \frac{1}{z_0} \sum_{u=1}^{\frac{k}{2}-1} (k-2u)(z_u^2 - z_{k-u}^2)$. And, from [\(A.2\)](#) and [\(A.3\)](#), after summing the terms, we get

$$\frac{1}{z_0} \sum_{u=1}^{\frac{k}{2}-1} (k-2u)(z_u^2 - z_{k-u}^2) = \frac{(1-b^2)}{h} \sum_{u=1}^{\frac{k}{2}-1} (k-2u)\lambda^{2u} \left(\sum_{\ell=0}^{k-2u-1} \lambda^{2\ell} \right).$$

Or, in other words,

$$\frac{n}{4}\text{trace}(C^{-1}) = \frac{1}{h} \left(\sum_{u=0}^{\frac{k}{2}-1} (k-2u) \left(\sum_{\ell=u}^{k-u-1} \lambda^{2\ell} \right) - b^2 \sum_{u=1}^{\frac{k}{2}-1} (k-2u) \left(\sum_{\ell=u}^{k-u-1} \lambda^{2\ell} \right) \right). \quad (\text{A.4})$$

Now, consider the terms in the first part of Eq. [\(A.4\)](#) and note that for $\ell = 1, \dots, \frac{k}{2}$, the term $\lambda^{2(k-\ell)}$ comes ℓ times with the multiplying factors $(k-2\ell+2), (k-2\ell+4), \dots, k$. Rewrite the term in terms of summations on ℓ and then use the sum of arithmetic series on ℓ terms with the first term being $(k-2(\ell-1))$ and with the common difference of 2, for $\ell = 1, \dots, \frac{k}{2}$. Similarly, for $\ell = \frac{k}{2}+1, \dots, k$, the term $\lambda^{2(k-\ell)}$ comes $k-\ell+1$ times with the multiplying factors $2\ell-k, 2\ell-k+2, \dots, k$. Rewrite the term in terms of summations on ℓ and then use the sum of arithmetic series on ℓ terms with the first term being $2\ell-k$ and with the common difference of 2, for $\ell = \frac{k}{2}+1, \dots, k$. We then get,

$$\sum_{u=0}^{\frac{k}{2}-1} (k-2u) \left(\sum_{\ell=u}^{k-u-1} \lambda^{2\ell} \right) = \sum_{\ell=1}^k \left(\ell(k-\ell+1) \lambda^{2(k-\ell)} \right).$$

It can similarly be shown that

$$\sum_{u=1}^{\frac{k}{2}-1} (k-2u) \left(\sum_{\ell=u}^{k-u-1} \lambda^{2\ell} \right) = \sum_{\ell=1}^k \left((\ell-1)(k-\ell) \lambda^{2(k-\ell)} \right).$$

Therefore, for k even,

$$\frac{n}{4}\text{trace}(C^{-1}) = \frac{1}{h} \left(\sum_{\ell=1}^k \lambda^{2(k-\ell)} (\ell(k-\ell+1) - (\ell-1)(k-\ell)) \right). \quad (\text{A.5})$$

Case when k is odd: Following the similar methodology as above, we first find the values for $(z_u^2 - z_{k-u}^2)$ for $u = 1, \dots, \frac{k}{2}-1$. Note that if u is even, then $k-u$ is odd, and if u is odd, then $k-u$ is even. Consider u to be odd first. Then $(z_u^2 - z_{k-u}^2) = (z_{2s+1}^2 - z_{2(\frac{k-1}{2}-s)}^2)$. Then, from [Lemma A.3](#),

$$z_{2s+1}^2 - z_{2(\frac{k-1}{2}-s)}^2 = \frac{(1-b)}{h} \left(\sum_{\ell=s+1}^{k-s-1} \lambda^{2\ell-1} + \sum_{\ell=\frac{k-1}{2}-s}^{\frac{k-1}{2}+s} \lambda^{2\ell} \right).$$

Or,

$$z_{2s+1}^2 - z_{2(\frac{k-1}{2}-s)}^2 = \frac{(1-b)\lambda^{2s+1}}{h} \left(\sum_{\ell=0}^{k-1} \lambda^{\ell} \right) \left(\sum_{\ell=0}^{k-4s-3} (-\lambda)^{\ell} \right).$$

Similarly, we have,

$$z_{2s+1}^2 - z_{2(\frac{k-1}{2}-s)}^2 = \frac{(1+b)\lambda^{2s+1}}{h} \left(\sum_{\ell=0}^{k-1} (-\lambda)^{\ell} \right) \left(\sum_{\ell=0}^{k-4s-3} \lambda^{\ell} \right).$$

Also, note that $z_0 = \frac{1}{h} (\sum_{\ell=0}^{k-1} \lambda^{\ell}) (\sum_{\ell=0}^{k-1} (-\lambda)^{\ell})$, and $(\sum_{\ell=0}^{k-4s-3} \lambda^{\ell}) (\sum_{\ell=0}^{k-4s-3} (-\lambda)^{\ell}) = \sum_{\ell=0}^{k-4s-3} \lambda^{2\ell}$. Therefore, we have,

$$z_{2s+1}^2 - z_{2(\frac{k-1}{2}-s)}^2 = \frac{z_0(1-b^2)\lambda^{4s+2}(\sum_{u=0}^{k-4s-3} \lambda^{2u})}{h}.$$

Or, in other words,

$$z_u^2 - z_{k-u}^2 = \frac{z_0(1-b^2)\lambda^{2u}(\sum_{\ell=0}^{k-2u-1} \lambda^{2\ell})}{h}. \quad (\text{A.6})$$

It is then not too hard to see that for u even, as well, we get,

$$z_u^2 - z_{k-u}^2 = z_{2s}^2 - z_{2(\frac{k-1}{2}-s)+1}^2 = \frac{z_0(1-b^2)\lambda^{2u}(\sum_{\ell=0}^{k-2u-1} \lambda^{2\ell})}{h}. \quad (\text{A.7})$$

Now, from [Corollary A.1](#), for k odd, $\frac{n}{4}\text{trace}(C^{-1}) = kz_0 + \frac{1}{z_0} \sum_{u=1}^{\frac{k-1}{2}} (k-2u)(z_u^2 - z_{k-u}^2)$. And, from [\(A.6\)](#), and [\(A.7\)](#), after summing the terms, we get

$$\frac{1}{z_0} \sum_{u=1}^{\frac{k-1}{2}} (k-2u)(z_u^2 - z_{k-u}^2) = \frac{(1-b^2)}{h} \sum_{u=1}^{\frac{k-1}{2}} (k-2u) \left(\sum_{\ell=0}^{k-2u-1} \lambda^{2(u+\ell)} \right).$$

Then, on similar lines as above, it can be shown that the trace expression in the statement holds for k odd as well. ■

Proof of Lemma 2. Let $s_1 = c_1c_5 - c_2c_3$, and $s_2 = s_1^2 - 4c_1c_2c_4^2$. Then, we have to prove that $s_1 > 0$ and $s_2 > 0$. Note that the values of s_1 and s_2 are the same at $|\lambda|$ as at $-|\lambda|$. This is why, for the purposes of the proof, we can restrict ourselves to $0 < \lambda \leq 1$.

We first note that at $\lambda = 1$, we have $c_1 = k(k+1)(k+2)/6$, $c_2 = c_1 - k^2 = k(k-1)(k-2)/6$, $c_3 = k+1$, $c_4 = 1$, and $c_5 = k-1$. Then, $s_1 = 2k(k^2-1)/3$, and $s_2 = k^4(k^2-1)/3$. Therefore, at $\lambda = 1$, for $k > 1$, both s_1 and s_2 are positive.

We now consider the case when $\lambda \in (0, 1)$. It is easy to see that $c_2 = c_1 - \frac{k(1-\lambda^{2k})}{1-\lambda^2}$. Also, after using the arithmetic-geometric sums, we see that

$$\begin{aligned} c_1 &= \frac{1}{(1-\lambda^2)^3} ((k+2)\lambda^{2k+2} - k\lambda^{2k+4} + k - (k+2)\lambda^2) \\ c_2 &= \frac{1}{(1-\lambda^2)^3} (k\lambda^{2k} - (k-2)\lambda^{2k+2} + (k-2)\lambda^2 - k\lambda^4) \\ c_3 &= \frac{1 - \lambda^{2k+2}}{1 - \lambda^2} \\ c_5 &= \frac{\lambda^2 - \lambda^{2k}}{1 - \lambda^2}. \end{aligned}$$

Upon simplification, we get that

$$\begin{aligned} s_1 &= \frac{2\lambda^2}{(1-\lambda^2)^3} (1 - \lambda^{4k} - k\lambda^{2k-2}(1 - \lambda^4)) \\ s_2 &= \frac{4\lambda^4(1 - \lambda^{2k})^2}{(1-\lambda^2)^6} ((1 - \lambda^{2k})^2 - k^2\lambda^{2k-2}(1 - \lambda^2)^2). \end{aligned}$$

Now, s_2 can be further simplified to

$$s_2 = \frac{4\lambda^4(1 - \lambda^{2k})^2}{(1-\lambda^2)^6} (1 - \lambda^{2k} + k\lambda^{k-1}(1 - \lambda^2))(1 - \lambda^{2k} - k\lambda^{k-1}(1 - \lambda^2)).$$

If we prove that $1 - x^k - kx^{\frac{k-1}{2}}(1-x) > 0$ for $x \in (0, 1)$, then it will follow that $s_1 > 0$ (by taking $x = \lambda^4$) and $s_2 > 0$ (by taking $x = \lambda^2$). Obviously, since $\lambda \in (0, 1)$, then $\lambda^2 \in (0, 1)$, and $\lambda^4 \in (0, 1)$.

We observe that $1 - x^k - kx^{\frac{k-1}{2}}(1-x) > 0$ for $x \in (0, 1)$ is equivalent to $(1-x)(\sum_{i=0}^{k-1} x^i - kx^{\frac{k-1}{2}}) > 0$. From simple convexity argument, it is true that $\sum_{i=0}^{k-1} x^{a_i} > kx^{\frac{k-1}{2}}$ provided that $\sum a_i = k(k-1)/2$ and that a_i 's are not equal. This completes the proof. ■

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