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UNIVERSALLY OPTIMAL FMRI DESIGNS FOR COMPARING HEMODYNAMIC RESPONSE FUNCTIONS

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Abstract: We consider an experimental design problem in functional magnetic resonance imaging (fMRI), a dominant technology for studying brain activity in response to mental stimuli presented to the experimental subject. In contrast to previous studies, we develop analytical results on optimal designs for comparing hemodynamic response functions, each describing the effect of the corresponding type of stimulus. In particular, for studies with two stimulus types, we derive a sufficient condition for an fMRI design to be universally optimal, and show that designs constructed via m-sequences or Paley difference sets satisfy this sufficient condition.

Key words and phrases: Difference sets, experimental designs, Hadamard matrix, m-sequences, universal optimality.

1. Introduction

Experiments for studying functions of human brains via functional magnetic resonance imaging (fMRI) typically involve presenting to an experimental subject a sequence of brief mental stimuli of one or more types (e.g., pictures of familiar and unfamiliar faces). While the subject is exposed to the stimuli, an MRI scanner repeatedly scans the subject's brain to collect a time series from each brain voxel (three-dimensional imaging unit). These time series are analyzed to make statistical inference about brain activity in response to the stimuli. Typically, such an inference is made based on the hemodynamic response function (HRF), a function of time describing the noise-free change of the MRI measurements following a stimulus onset. The HRF can be viewed as the effect of the stimulus to the brain, and is often the main interest in an fMRI experiment. See Lazar (2008) for an overview of statistical analysis of fMRI data.

For experiments with two types of stimuli, comparing the HRFs helps to study the differences in their effects. For this common study objective, we seek an optimal fMRI design for yielding the most precise estimate of the contrast between the HRFs. Existing approaches for finding such optimal fMRI designs mainly rely on computer search algorithms (e.g., Wager and Nichols (2003); Kao et al. (2009a); Kao, Mandal and Stufken (2009b); Maus et al. (2010)). Analytical results, while important, are scarce. Recently, Kao (2013) conducted an analytical analysis on optimal designs for estimating individual HRFs. However, to our knowledge, analytical results are unavailable to guide the selection of designs for comparing HRFs.

Our study addresses this lack. For experiments with two stimulus types, we derive a sufficient condition for an fMRI design to be universally optimal (Kiefer (1975)) in comparing HRFs. We then provide designs that satisfy this sufficient condition. These designs can be used in fMRI studies or serve as benchmarks for evaluating other fMRI designs. In the next section, we describe our setting and main results on optimal fMRI designs. We then present some universally optimal fMRI designs in Section 3. The paper closes with a conclusion and a discussion in Section 4.

2. Main Results

An fMRI experimental designs with two stimulus types can be written as an ordered sequence $\boldsymbol{d} = (d_1, d_2, \ldots, d_N)$, where $d_n \in \{0, 1, 2\}$, $n = 1, \ldots, N$, and N is the number of time points where a stimulus can possibly occur. The pre-specified time between these time points is τ (e.g., 4 s). When $d_n = q > 0$, a qth-type stimulus occurs at the nth time point with a brief presentation duration (e.g., 1 s). With $d_n = 0$, no stimulus appears at the corresponding time point. During the time periods with no stimulus presentation, the subject is asked to rest or, say, gaze at a visual fixation when the experiment involves visual stimuli.

While being presented to the experimental subject, each stimulus gives rise to a hemodynamic response function, HRF, at each brain voxel responding to the stimulus. At the same voxel, the HRFs evoked by the stimuli of the same type are typically assumed to be the same across the experiment. With two stimulus types, a study objective of interest is often on comparing the two HRFs. This can be achieved by analyzing the MRI measurements collected every τ seconds from each voxel. Let y_n be the nth MRI measurement of the time series of a brain voxel, and $x_{q,n}$ be a 0-1 indicator which equals 1 when a qth-type stimulus is presented at time point n (i.e. $d_n = q$); $n = 1, \ldots, N$ and $q = 1, 2$. We follow previous studies (e.g., Kao (2013)) to consider a linear model with the assumption that the last $K - 1$ elements of the design also appear in the pre-period before the first valid MRI measurement, y_1:

$$y_n = \gamma + \sum_{k=0}^{K-1} \{x_{1,n-k} h_{1,k+1} + x_{2,n-k} h_{2,k+1}\} + \varepsilon_n, \ 1 \leq n \leq N. \tag{2.1}$$

Here, γ is an unknown parameter, $h_{q,k}$ is the kth HRF height evaluated at $(k-1)\tau$ seconds after an onset of a qth-type stimulus, $\varepsilon_1, \ldots, \varepsilon_N$ represent homoscedastic, uncorrelated noise, the integer K depends on the duration (e.g., 30 s) of the

HRF, and x_{n-k} is interpreted as x_{N+n-k} when $n \leq k$. Clearly, for any given fMRI design, we have $x_{1,n} + x_{2,n} \in \{0,1\}$ for all n.

Our focus is on $\theta_k = h_{1,k} - h_{2,k}$, $k = 1, \ldots, K$, and we rewrite Model (2.1) as

$$y_n = \gamma + \sum_{k=0}^{K-1} \{a_{n,k}\xi_{k+1} + b_{n,k}\theta_{k+1}\} + \varepsilon_n,\ 1 \leq n \leq N, \tag{2.2}$$

where $a_{n,k} = (x_{1,n-k} + x_{2,n-k})/2$, $b_{n,k} = (x_{1,n-k} - x_{2,n-k})/2$, and $\xi_k = h_{1,k} + h_{2,k}$. We proceed to find a universally optimal design for inference on $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_K)'$ over the class $\mathfrak{D}_N$ of designs with N elements.

Definition 1. Let $\boldsymbol{\Phi}$ be a class of optimality criteria, ϕ, that are (a) real-valued, convex functions of non-negative definite matrices, (b) orthogonally invariant, $\phi(\boldsymbol{P}'\boldsymbol{A}\boldsymbol{P}) = \phi(\boldsymbol{A})$ for any orthogonal matrix $\boldsymbol{P}$ and non-negative definite matrix $\boldsymbol{A}$, and (c) nonincreasing, $\phi(\boldsymbol{A}_1) \leq \phi(\boldsymbol{A}_2)$ when $\boldsymbol{A}_1$, $\boldsymbol{A}_2$ and $\boldsymbol{A}_1 - \boldsymbol{A}_2$ are non-negative definite. A design is universally optimal if, for every $\phi \in \boldsymbol{\Phi}$, it minimizes $\phi(\boldsymbol{M}_d[\boldsymbol{\theta}])$ over $\mathfrak{D}_N$, where $\boldsymbol{M}_d[\boldsymbol{\theta}]$ is the information matrix of $\boldsymbol{\theta}$ for a given design $\boldsymbol{d}$.

A universally optimal design optimizes a large class of optimality criteria that includes the widely considered A- and D-optimality criteria, which aim respectively at minimizing the average variance and generalized variance of parameter estimates (e.g., Pukelsheim (1993)). For any design in $\mathfrak{D}_N$, let $n_k^{(pq)} = \#\{n \mid (d_{n-k}, d_n) = (q,p), n = 1, \ldots, N\}$ be the number of time points when a p is preceded by a q at a time distance k; here, d_{n-k} is set to d_{N+n-k} when $n \leq k$. Our result provides a sufficient condition for an fMRI design to be universally optimal. Some methods for constructing designs satisfying this sufficient condition are presented in the next section.

Theorem 1. *If there exists a design $\boldsymbol{d}^* \in \mathfrak{D}_N$ for which*

$$n_k^{(11)} = n_k^{(12)} = n_k^{(21)} = n_k^{(22)} = \frac{N}{4},\ 1 \leq k \leq K-1, \tag{2.3}$$

then $\boldsymbol{d}^*$ is universally optimal in $\mathfrak{D}_N$ for inference on $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_K)'$.

Proof. Let $n_q = \sum_{n=1}^N x_{q,n}$ be the number of occurrences of the qth-type stimulus in a design in $\mathfrak{D}_N$; $q = 1, 2$. For the design $\boldsymbol{d}^*$ satisfying (2.3), we have $n_1 = n_2 = N/2$, and $\sum_{n=1}^N b_{n,k} = \sum_{n=1}^N b_{n,k}a_{n,k} = \sum_{n=1}^N b_{n,k}a_{n,\ell} = \sum_{n=1}^N b_{n,k}b_{n,\ell} = 0$, $1 \leq k \neq \ell \leq K-1$, where $a_{n,k}$ and $b_{n,k}$ are as in (2.2). Thus, $\boldsymbol{d}^*$ allows estimation of each θ_k in Model (2.2) orthogonally to γ, $\xi_1, \ldots, \xi_K$, and θ_h for $h \neq k$. In addition, for any design in $\mathfrak{D}_N$, $\sum_{n=1}^N b_{n,k}^2 = (n_1 + n_2)/4 \leq N/4$ with equality being attained for the design $\boldsymbol{d}^*$. Consequently, the information matrix $\boldsymbol{M}_{d^*}[\boldsymbol{\theta}]$

is proportional to the identity matrix and $tr\{\boldsymbol{M}_{d^*}[\boldsymbol{\theta}]\} = \max_{d\in\mathfrak{D}_N} tr\{\boldsymbol{M}_d[\boldsymbol{\theta}]\}$. Following Proposition 1' of Kiefer (1975), the claimed universal optimality of $\boldsymbol{d}^*$ follows; see also, Kiefer and Wynn (1984).

3. Universally Optimal Designs

3.1. Extended m-sequences

We construct universally optimal designs for comparing two HRFs by modifying the binary extended m-sequences considered in Kao (2013). A binary m-sequence of length $2^r - 1$ can be obtained by a linear recurrence relation $t_{n+r} = a_1 t_{n+r-1} + a_2 t_{n+r-2} + \cdots + a_r t_n \pmod 2$ with a specified nonzero initial r-tuple $(t_1, \ldots, t_r)$. Here, r is an integer and $a_1, \ldots, a_r \in \{0, 1\}$ are coefficients that are determined by a primitive polynomial $f(x) = x^r - a_1 x^{r-1} - a_2 x^{r-2} - \cdots - a_r$ over the finite field $GF(2)$ of order 2. A binary extended m-sequence, which is a de Bruijn sequence (Golomb and Gong (2005)), can be obtained by inserting a 0 to any run of $r-1$ zeros in a binary m-sequence. For $1 \le k \le r-1$, we have $n_k^{(11)} = n_k^{(10)} = n_k^{(01)} = n_k^{(00)} = 2^{r-2}$ in a binary extended m-sequence of length 2^r; see also Kao (2013).

Theorem 2. *Let $\boldsymbol{t} = (t_1, \ldots, t_N)$ be a binary extended m-sequence with $N = 2^K$, and let $\boldsymbol{d} = (d_1, \ldots, d_N)$ satisfy $d_n = t_n + 1$. The design $\boldsymbol{d}$ is universally optimal for comparing HRFs of length K.*

3.2. Paley-difference sets

Another method for obtaining a universally optimal design for comparing two HRFs is by using difference sets. See, e.g, Jungnickel and Pott (1999) for an overview of difference sets. Let $\mathbb{Z}_\nu = \{0, \ldots, \nu - 1\}$ and $(\mathbb{Z}_\nu, +)$ be a cyclic group under addition modulo ν for a prime power ν.

Definition 2. A (ν, κ, λ)-difference set in $(\mathbb{Z}_\nu, +)$ is a κ-subset, $\boldsymbol{s} = \{s_1, \ldots, s_\kappa\}$, of $\mathbb{Z}_\nu$ such that the multiset $\{s_i - s_j \pmod \nu) \mid s_i, s_j \in \boldsymbol{s}, s_i \ne s_j\}$ contains every nonzero element of $\mathbb{Z}_\nu$ exactly λ times.

For convenience, the elements in the difference sets considered here are arranged in an ascending order. When $N - 1 = 3 \pmod 4$ is a prime, we construct fMRI designs of length N by using Paley $(N-1, N/2-1, N/4-1)$-difference sets, $\boldsymbol{s}$ (Paley (1933)). Such an $\boldsymbol{s}$ contains all the nonzero quadratic residues in $\mathbb{Z}_{N-1}$; $\boldsymbol{s} = \{x^2 \pmod{N-1} \mid x = 1, \ldots, N/2 - 1\}$. In this $\boldsymbol{s}$, we identity the longest run of consecutive integers, and use G and s_{i_1} to denote the number of elements and the last element of this run, respectively. We then obtain another difference set, $\boldsymbol{s}^\pi = \boldsymbol{s} + \pi \pmod{N-1}$, by adding π modulo $N-1$ to every

Table 1. Selected universally optimal fMRI designs of length N for comparing two HRFs of length $K \leq G + 1$.

N	G	design
68	6	1 2 2 1 2 2 2 1 2 1 1 1 2 1 1 2 2 2 2 2 2 1 2 1 2 2 2 2 1 1 1 2 2 1 1 2 1 2 1 1 2 2 1 2 2 1 2 1 2 2 1 1 2 2 2 1 1 1 1 2 1 2 1 1 1 1 1 1
132	8	1 2 2 2 2 2 2 2 2 1 1 2 1 2 2 1 1 2 2 1 2 2 2 2 1 2 1 2 2 1 2 2 2 2 1 1 1 1 2 2 1 2 1 1 1 2 2 1 1 1 2 2 1 2 2 2 1 2 1 2 1 2 2 2 1 2 2 1 2 1 1 1 2 1 2 1 2 1 1 1 2 1 1 2 2 2 1 1 2 2 2 1 2 1 1 2 2 2 2 1 1 1 1 2 1 1 2 1 2 1 1 1 1 2 1 1 2 2 1 1 2 1 2 2 1 1 1 1 1 1 1 1
284	9	1 2 1 1 1 2 1 2 1 1 2 2 2 1 1 1 1 2 2 1 1 2 2 2 1 2 2 2 2 2 1 2 1 1 2 2 2 1 1 1 1 1 2 2 1 2 1 1 2 2 2 2 2 1 1 1 2 2 1 2 1 1 1 1 1 2 1 1 1 2 2 1 1 2 2 2 2 1 1 1 2 2 1 2 1 2 2 2 1 2 2 2 2 2 2 2 2 2 1 1 2 2 1 2 1 2 1 1 2 2 1 1 2 2 1 2 2 1 1 1 2 1 2 2 2 2 2 2 1 2 1 1 2 1 2 2 1 2 1 1 1 1 2 1 2 2 2 1 2 1 2 1 2 1 1 1 1 2 2 1 1 2 2 2 1 1 1 1 1 1 2 2 1 2 1 2 2 2 1 2 2 1 2 1 1 2 2 1 2 2 1 2 1 1 2 1 1 1 2 1 2 1 1 2 2 2 2 2 2 1 1 1 2 2 1 1 2 2 2 2 1 2 1 2 1 2 1 1 1 2 1 2 2 2 2 1 2 1 1 2 1 2 2 1 2 1 1 1 1 1 1 2 1 2 2 2 1 1 2 1 1 2 2 1 1 2 2 1 2 1 2 1 1 2 2 1 1 1 1 1 1 1 1 1

$s_i \in \boldsymbol{s}$, where $\pi = N - 2 - s_{i_1}$. We set the nth element of an fMRI design $\boldsymbol{d}$ to

$$d_n = \begin{cases} 1, & n = 1 \text{ or } (n-2) \in \boldsymbol{s}^{\pi}; \\ 2, & \text{otherwise}, \end{cases} \quad n = 1, \ldots, N. \tag{3.1}$$

Theorem 3. *The design* $\mathbf{d}$ *obtained via* (3.1) *is universally optimal for comparing two HRFs of length* $K \leq G + 1$.

Proof. By replacing 2 by -1 in (3.1), $\boldsymbol{d}$ forms a column of a normalized Paley type I Hadamard matrix, $\boldsymbol{H}$ (see Hedayat, Sloane and Stufken (1999), Horadam (2007)). This remains true when $\boldsymbol{s}^{\pi}$ in (3.1) is replaced by $\boldsymbol{s}^{\pi+g} = \boldsymbol{s} + \pi + g \pmod{N-1}$ for $1 \leq g \leq G$. The $G+1$ designs obtained as $\boldsymbol{s}^{\pi+g}$, $g = 0, \ldots, G$, are cyclically shifted versions of each other, and form distinct columns of $\boldsymbol{H}$ when -1 substitutes 2 in the designs. Following the fact that the elements of the first column (and the first row) of $\boldsymbol{H}$ are 1, and $\boldsymbol{H}\boldsymbol{H}' = N\boldsymbol{I}_N$, the $\boldsymbol{d}$ obtained via (3.1) has $n_1 = n_2 = N/2$ and $n_k^{(11)} + n_k^{(22)} = n_k^{(12)} + n_k^{(21)}$ for $k = 1, \ldots, G$. This implies that $n_k^{(12)} = n_k^{(21)}$ and $n_k^{(11)} = n_k^{(22)}$. The condition (2.3) is thus satisfied.

For each design length N, the value of G can be obtained numerically; see also Buell and Hudson (1984). In the supplementary material, we provide those G-values for $N \leq 600$ for which Paley difference sets are known. The corresponding designs obtained by (3.1) are also provided. For illustrative purposes, designs with selected N are presented in Table 1 along with their G-values. It is noteworthy that, by replacing 2 with 0 in (3.1), the obtained designs satisfy the sufficient conditions in Kao (2013). These designs are thus universally optimal for estimating an HRF of length $K \leq G+1$. Therefore, by modifying the symbols, all the designs presented in Table 1 can be employed in, say, an experiment reported in Miezin et al. (2000) for studying an HRF of length $K = 7$. These designs enlarge the library of high quality fMRI designs for experimenters to choose from.

4. Conclusion and Discussion

Research on fMRI experimental designs that increase the precision of statistical analyses is still underdeveloped. For comparing the HRFs between two stimulus types, we derive a sufficient condition for fMRI designs to be universally optimal, and present some universally optimal designs that are constructed using m-sequences and difference sets.

Universally optimal designs in $\mathfrak{D}_N$ for comparing HRFs of length $K \leq G+1$ can also be obtained by using a $(G+1)$-by-N circulant partial Hadamard matrix with zero row sums. As described in Craigen et al. (2013), for such a matrix, $\boldsymbol{C} = ((c_{g,n}))_{g=1,\ldots,G+1,n=1,\ldots,N}$, we have that the entries $c_{g,n} \in \{-1, 1\}$, $\boldsymbol{C}\boldsymbol{j}_N = \boldsymbol{0}$, $\boldsymbol{C}\boldsymbol{C}' = N\boldsymbol{I}_{G+1}$, and the gth row is obtained by cyclically shifting the $(g-1)$st row one position to the right with $c_{g,1} = c_{g-1,N}$ and $c_{g,n} = c_{g-1,n-1}$ for $g = 2, \ldots, G+1$ and $n = 2, \ldots, N$; here, $\boldsymbol{j}_N$ is the vector of N ones. Clearly, some of these matrices can be obtained by Paley-difference sets, and a universally optimal design can be constructed by replacing -1 with 2 in any row of $\boldsymbol{C}$. Using a computer search, Low et al. (2005) presented some $\boldsymbol{C}$ matrices having the maximum G for $N = 4r \leq 52$. As also presented in Table 1 of Craigen et al. (2013), the maximum values of G are $1, 2, 4, 6, 6, 8, 8, 11, 13, 16, 15, 16$ and 19 for $N = 4, 8, \ldots, 52$, respectively. Thus, for a given G, we can obtain designs with a shorter length than the designs presented in Section 3. However, it is suggested there that finding a $\boldsymbol{C}$ matrix with the maximum G is a challenging problem.

When deriving our results, we assume that (i) the time between time points where a stimulus can possibly occur equals the time between consecutive MRI scans of the same brain voxel, (ii) the last $K-1$ elements of the selected design are also presented in the pre-period before the first valid MRI measurement, and (iii) there is no drift or trend in the fMRI time series and the error terms are uncorrelated. The first assumption can be controlled by the experimenter. In addition, a pre-period allowing the MRI scanner to reach a steady state is typically needed, and the MRI measurements collected during this pre-period are discarded from the subsequent statistical analysis. Thus, (ii) may not be a strong assumption. However, (iii) may sometimes be violated. If so, we can apply a computational method such as the search algorithm of Kao et al. (2009a) to obtain (near-)optimal designs. Deriving insightful analytical results on optimal fMRI designs by relaxing these assumptions is important. Extension of our results to cases with three or more stimulus types is a future research topic of interest.

Supplementary Material

The supplementary document available online includes a list of fMRI designs of length N (≤ 600) that are obtained via (3.1).

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