Maximin and Maximin Efficient

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Designs for fMRI Experiments

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1. Background

• *Functional Magnetic Resonance Imaging* (fMRI) is brain mapping technology for studying brain activity in response to mental tasks or stimuli (e.g. pictures or sounds).

• In an *fMRI experiment*, each subject lies in an MRI scanner. A pre-determined fMRI experimental design is presented to the subject while the scanner repeatedly scans

2. Motivation

• Existing studies in fMRI designs primarily focus on popular general linear models, e.g.

$$\mathbf{y} = \sum_{q=1}^{Q} \mathbf{X}_q \mathbf{h}^* \theta_q + \mathbf{S}\gamma + \mathbf{e}$$

☞ **y**: a vector for fMRI time series obtained from a voxel
☞ $\mathbf{X_q}$: 0-1 design matrix for the qth stimulus type
☞ $\mathbf{h}^*$: an assumed shape of the HRF
☞ θ_q: unknown HRF amplitude of the qth stimulus type.
☞ **S**: given matrix for drift/trend of the time series
☞ γ: unknown parameter vector for drift/trend
☞ **e**: noise

3.2 Information matrix and design criterion

• The information matrix of $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_Q)'$ can be approximated as:

$$M(d;\boldsymbol{\theta},\boldsymbol{p}) = \boldsymbol{E}_d(\boldsymbol{p})'[\boldsymbol{I}_T - w\{\boldsymbol{L}_d(\boldsymbol{\theta},\boldsymbol{p})\}]\boldsymbol{E}_d(\boldsymbol{p}),$$
$$\boldsymbol{E}_d(\boldsymbol{p}) = [\boldsymbol{I}_T - w\{\boldsymbol{V}\boldsymbol{S}\}]\boldsymbol{V}\boldsymbol{X}_d[\boldsymbol{I}_Q \otimes \boldsymbol{h}(\boldsymbol{p})],$$
$$\boldsymbol{L}_d(\boldsymbol{\theta},\boldsymbol{p}) = [\boldsymbol{L}_1, \boldsymbol{L}_6],\ \boldsymbol{L}_i = [\boldsymbol{I}_T - w\{\boldsymbol{V}\boldsymbol{S}\}]\boldsymbol{V}\boldsymbol{X}_d\Big[\boldsymbol{I}_Q \otimes \frac{\partial \boldsymbol{h}(\boldsymbol{p})}{\partial p_i}\Big]\boldsymbol{\theta}$$

☞ ω(**A**): orthogonal projection onto the column space of **A**

☞ **V**: assumed whitening matrix s.t. cov(**Ve) =** σ^2**I**

☞ ⊗: the Kronecker product

• Proposed Strategy:

Strategy. (1) Identify a Θ_0 and $\mathcal{G}$. (2) Over a subclass Ξ_0 of designs, obtain a design d_{Mm,Θ_0,Ξ_0} maximizing $\min_{\Theta_0\times\mathcal{P}} \Phi_A(d;\boldsymbol{\theta},\boldsymbol{p})$; or a design d_{MmE,Θ_0,Ξ_0} maximizing $\min_{\{\{\boldsymbol{0}\}\bigcup\Theta_0\}\times\mathcal{P}} RE(d;\boldsymbol{\theta},\boldsymbol{p})$.

☞ We include all the Q×Q permutation matrices in $\mathcal{G}$
☞ Θ_0 is as in Lemmas 3 and 5, and can be selected to contain 1/(2Q!) of the surface of a unit (Q-1)-sphere
☞ Ξ_0 is selected s.t. the Φ_A-values of the designs in Ξ_0 are (nearly) invariant to the permutation of the coordinates of $\boldsymbol{\theta}$
☞ Our experience suggest that the obtained designs are highly efficient in terms of the maximin and maximin efficient criteria

the subject's brain to collect a bunch of fMRI time series; each time series is from one of the, say, 64×64×30 brain voxels (3-D imaging units).

- An *fMRI experimental design* considered here is a sequence of brief mental stimuli of one or more types, which can be written as a sequence of finite numbers, e.g.,:

$$d = \{1, 1, 0, 2, 0, 2, \ldots, 2\}.$$

- The same shape $\mathbf{h}^*$ is assumed for every voxel. However, some studies showed that the HRF can vary across brain voxels. This assumption may thus be invalid in practice.

- Some statistical analysis methods, such as the use of nonlinear models, were proposed to accommodate the uncertainty in the HRF shape. Addressing this issue at the design stage is also crucially important.

- We would like a design maximizing:

$$\Phi_A(d; \theta, \mathbf{p}) = 1/\mathrm{tr}[\mathbf{M}^{-1}(d; \theta, \mathbf{p})]$$

- With uncertain θ and $\mathbf{p}$, we consider the following maximin and maximin efficient design criteria:

$$\min_{(\boldsymbol{\theta},\boldsymbol{p})\in\Theta\times\mathcal{P}} \Phi_A(d;\boldsymbol{\theta},\boldsymbol{p})$$

$$\min_{(\boldsymbol{\theta},\boldsymbol{p})\in\Theta\times\mathcal{P}} RE(d;\boldsymbol{\theta},\boldsymbol{p}) = \min_{(\boldsymbol{\theta},\boldsymbol{p})\in\Theta\times\mathcal{P}} \frac{\Phi_A(d;\boldsymbol{\theta},\boldsymbol{p})}{\Phi_A(d^{\dagger}_{\boldsymbol{\theta},\boldsymbol{p}};\boldsymbol{\theta},\boldsymbol{p})}$$

☞ **$\Theta \times P$:** parameter space; $P = \{p_1 \in [6,9],\ p_6 \in [0,2]\}$

☞ $d^{+}_{\theta, \mathbf{p}}$: a locally optimal design for given $(\theta, \mathbf{p})$

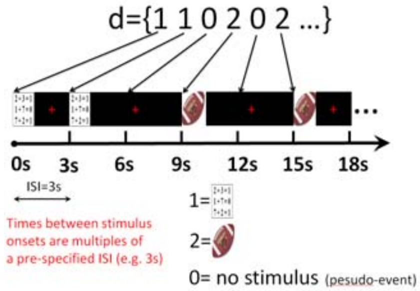
4. Case studies

- Performance of the proposed strategy:

Designs	maximum value min-Φ_A	maximum value min-RE	mean value (std) min-Φ_A	mean value (std) min-RE	mean CPU time (min.)
			$Q=1$		
d_{Mm,Θ_0}	75.67	0.657	75.34 (0.26)	0.652 (0.004)	0.85
d_{MmE,Θ_0}	63.71	0.835	63.33 (0.27)	0.830 (0.004)	0.88
			$Q=2$		
d_{Mm,Θ_0,Ξ_0}	25.64	0.713	25.54 (0.11)	0.702 (0.010)	4.16
d_{Mm}	25.60	0.721	25.48 (0.09)	0.708 (0.006)	20.75
d_{MmE,Θ_0,Ξ_0}	22.82	0.829	22.58 (0.21)	0.820 (0.006)	5.88*
d_{MmE}	22.67	0.822	22.45 (0.20)	0.816 (0.006)	24.44*
			$Q=3$		
d_{Mm,Θ_0,Ξ_0}	14.41	0.757	14.29 (0.08)	0.736 (0.012)	56.54
d_{Mm}	14.23	0.741	14.15 (0.06)	0.729 (0.011)	965.27
d_{MmE,Θ_0,Ξ_0}	13.13	0.829	12.87 (0.16)	0.823 (0.004)	52.04*
d_{MmE}	12.75	0.820	12.64 (0.06)	0.815 (0.003)	978.77*

☞*: obtaining the needed locally optimal designs required 4 hours for Q=2, and 46 hours for Q=3.

◊ Example:



☞ Number of stimulus (picture) types: Q = 2

☞ Each picture lasts 1 second after its onset; times between stimulus onsets are multiples of ISI (= 3 seconds)

☞ The subject fixates on a cross when no picture is presented

3. Methodology

3.1 Statistical Model

• Taking uncertain HRF shape into account, we consider the following model:

$$\mathbf{y} = \sum_{q=1}^{Q} \mathbf{X}_q \mathbf{h}(\mathbf{p})\theta_q + \mathbf{S}\gamma + \mathbf{e}.$$

☞ **h(p)**: a discretized parametric function for the HRF shape

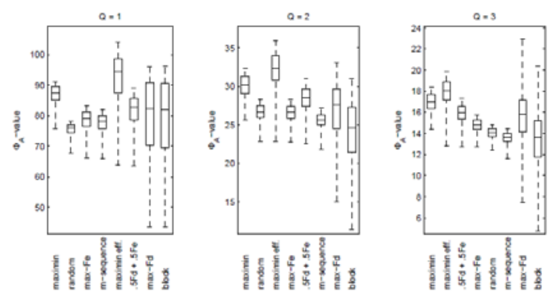
☞ **p**: unknown parameter vector to be estimated for each voxel; different voxels may have different estimates.

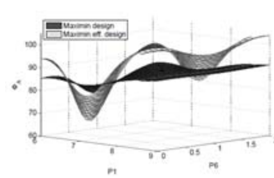
3.3 Maximin & maximin efficient approach

• We adapt a recently proposed genetic algorithm to search for good designs, and develop some results to help to reduce the computational burden.

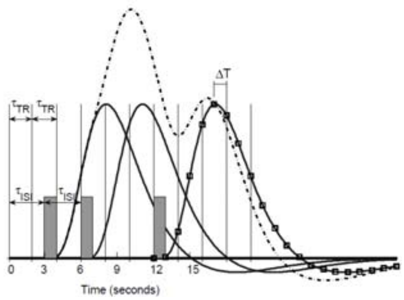
• Instead of directly searching for maximin and maximin designs, we propose to obtain highly efficient designs over a restricted design space on a reduced parameter space.

• Design comparisons:





• At an active voxel, a stimulus changes the strengths of local magnetic field, leading to a fluctuation in MR signals; this fluctuation is described by a function of time called *hemodynamic response function (HRF)*.



• **h(p)** may be set to the popular double-gamma function with two (most influential) free parameters; i.e.,

$$((\mathbf{h}(\mathbf{p})))_j = g_0((j-1)\triangle T;\mathbf{p})/\max_s g_0(s;\mathbf{p})$$

$$g_0(t;\mathbf{p}) = \frac{(t-p_6)^{p_1-1}e^{-(t-p_6)}}{\Gamma(p_1)} - \frac{1}{6}\frac{(t-p_6)^{15}e^{-(t-p_6)}}{\Gamma(16)}$$

☞ p_1: time-to-peak; p_6: time-to-onset
☞ $\Gamma(.)$: the gamma function
☞ $\triangle T$: discretization interval
☞ Other functions may also be considered

• Some developed tools:

Lemma 1. $\boldsymbol{M}^{-1}(d;\mathbf{0},\boldsymbol{p}) \le \boldsymbol{M}^{-1}(d;\boldsymbol{\theta},\boldsymbol{p})$ in Löwner ordering for any $\boldsymbol{\theta}$, $\boldsymbol{p}$, and a design d that ensures the existence of $\boldsymbol{M}^{-1}(d;\boldsymbol{\theta},\boldsymbol{p})$.

Lemma 2. $\boldsymbol{M}(d;c\boldsymbol{\theta},\boldsymbol{p}) = \boldsymbol{M}(d;\boldsymbol{\theta},\boldsymbol{p})$ for any scalar $c \neq 0$.

Lemma 3. Let $\mathcal{G} = \{\boldsymbol{G}_1,\ldots,\boldsymbol{G}_G\}$ be a set of $Q \times Q$ permutation matrices. Suppose $\Theta_0 \subset \Theta$ is such that $\Theta = \bigcup_{g=0}^{G}\Theta_g$, where $\Theta_g = \{\boldsymbol{G}_g\boldsymbol{\theta} \mid \boldsymbol{\theta} \in \Theta_0\}$ and $\boldsymbol{G}_0 \equiv \boldsymbol{I}_Q$. If d_{Mm,Θ_0} is a maximin design for $\Theta_0 \times \mathcal{P}$ and $\min_{\Theta_0\times\mathcal{P}} \Phi_A(d_{Mm,\Theta_0};\boldsymbol{\theta},\boldsymbol{p}) = \min_{\Theta_g\times\mathcal{P}} \Phi_A(d_{Mm,\Theta_0};\boldsymbol{\theta},\boldsymbol{p})$ for any g, then d_{Mm,Θ_0} is also a maximin design for $\Theta \times \mathcal{P}$.

Lemma 4. A locally optimum design $d^{\dagger}_{\boldsymbol{\theta},\boldsymbol{p}}$ for $(\boldsymbol{\theta},\boldsymbol{p})$ is also a locally optimum design for $(c\boldsymbol{\theta},\boldsymbol{p})$ for any $c \neq 0$.

Corollary 1. $RE(d;\boldsymbol{\theta},\boldsymbol{p}) = RE(d;c\boldsymbol{\theta},\boldsymbol{p})$ for any design d and $c \neq 0$.

Lemma 5. A maximin efficient design d_{MmE,Θ_0} for $\{\{\mathbf{0}\}\bigcup\Theta_0\}\times\mathcal{P}$ is also a maximin efficient design for $\Theta \times \mathcal{P}$ if, for any g,

$$\min_{\{\{\mathbf{0}\}\bigcup\Theta_0\}\times\mathcal{P}} RE(d_{MmE,\Theta_0};\boldsymbol{\theta},\boldsymbol{p}) = \min_{\{\{\mathbf{0}\}\bigcup\Theta_g\}\times\mathcal{P}} RE(d_{MmE,\Theta_0};\boldsymbol{\theta},\boldsymbol{p}).$$

5. Conclusion:

• We propose efficient approaches for obtaining maximin and maximin efficient designs for fMRI, while consdering uncertain HRF shape. Our obtained designs outperform widely used designs.

• We focus on A-optimality, but our proposed methods can be applied to criteria that are invariant under simultaneous permutations of rows and columns of the information matrix.