IJARCCE

ISSN (Online) 2278-1021
ISSN (Print) 2319 5940

International Journal of Advanced Research in Computer and Communication Engineering
ISO 3297:2007 Certified
Vol. 5, Issue 10, October 2016

Simulative Analysis of Event-Related fMRI Design

Ramandeep Kaur[1], Jyoti Saxena[2] and Sukhjinder Singh[3]

Research Scholar, Dept of Electronics & Communication Engineering, GZSCCET, Bathinda, Punjab, India[1]

Professor, Dept of Electronics & Communication Engineering, GZSCCET, Bathinda, Punjab, India[2]

Assistant Professor, Dept of Electronics & Communication Engineering, GZSCCET, Bathinda, Punjab, India[3]

Abstract: Event-related fMRI allows estimation of the hemodynamic response associated with transient brain activation evoked by various sensory, motor and cognitive events. Choosing a sequence of events that maximizes efficiency of estimating the Hemodynamic Response Function (HRF) is essential for conducting event-related brain imaging experiments. This paper presents a comparative analysis of two different paradigms of event-related fMRI using MATLAB platform. The distinction between random and periodic stimulus trial is used to distinguish between designs that are specified in terms of the occurrence that an event will occur at a series of time points (random) and those in which events always occur after a fixed interval of time or pre-specified time (periodic). These designs can be parameterized using General Linear Model (GLM) in terms of design matrix that embodies constraints and the model of HRF. This analysis shows that statistical efficiency falls off dramatically as the Inter-Stimulus Interval (ISI) gets sufficiently short, if the ISI is kept fixed for all trials. However, if the ISI is properly randomized from trial to trial, the efficiency improves with decreasing mean ISI. The results demonstrate the feasibility of using randomized experimental design for event-related fMRI thereby facilitating imaging modalities.

Keywords: Event-Related fMRI, General Linear Model, Functional Neuro-imaging, Efficiency, Hemodynamic response function.

I. INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is one of the leading brain mapping technologies for studying brain activity in response to mental stimuli. Event-related experimental designs are very popular in fMRI research [1, 3, 6, 10 and 11]. Unlike the traditional blocked designs, where multiple trials of a particular condition are grouped together in blocks, event-related designs allow different trials or stimuli to be presented in arbitrary sequences, thus eliminating potential confounds such as habituation, anticipation, set, or other strategy effects [11, 13]. Most importantly, event-related fMRI is optimal for estimating the parameters of the Hemodynamic Response Function (HRF) associated with individual events [9]. There has been a growing interest in the choice of Stimulus Onset Asynchrony (SOA), i.e., the amount of time between the start of one stimulus and the start of another stimulus that has been focused by the emergence of a dichotomy in event-related fMRI using multiple trial/event types [5]. The distribution of SOAs is a critical factor in experimental design and can be chosen, subject to some constraints, to maximize the efficiency of response estimation. HRF estimation efficiency depends not only on experimental design, but also on the nature of fMRI noise [2].

The estimation efficiency of a given event-related sequence is a mathematical construct that reflects the ability of the sequence to provide an estimate of the HRF, taking into account noise associated with the fMRI signal [2]. Maximization of HRF estimation efficiency is critical for event-related fMRI experimental design, since it minimizes the error in estimating the HRF for a data set of given size, or alternatively, reduces overall scanning time for a criterion signal-to noise level. The aim of this paper is to compare relative efficiencies of random and periodic SOAs of event-related fMRI design.

Rest of the paper is organized as follows: Section II describes theory of general linear model for event-related fMRI, section III presents the experimental step-up, section IV illustrates results and discussion. Conclusion of this work is presented in section V.

II. MODELLING OF EVENT-RELATED FMRI

The most widely used model for the event-related fMRI designs is the General Linear Model (GLM). The following section provides a detailed description of the General Linear Model [8, 14].

General Linear Model

Consider an event-related fMRI experiment where C represents different stimulus conditions to an observer while recording the Blood - Oxygen Dependent level (BOLD) signals evoked in the brain of the subject over a series of T consecutive fMRI measurements i.e., the repetition time (TRs). The stimulus presentation can be represented quantitatively with a $T \times C$, binary Stimulus

IJARCCE

ISSN (Online) 2278-1021
ISSN (Print) 2319 5940

International Journal of Advanced Research in Computer and Communication Engineering
ISO 3297:2007 Certified
Vol. 5, Issue 10, October 2016

Matrix, D, whose entries indicate the onset of each stimulus condition (columns) at each point in time (rows). Now assume that the model of how a voxel is activated by a single, very short stimulus is accurate model. This activation model is called hemodynamic response function (HRF), h, for the voxel. It can be estimated from the measured BOLD signals. Assume that the voxel is also activated to an equal degree to all stimuli. In this scenario the BOLD signal evoked can be represented over the entire experiment with another $T \times C$ matrix X called the Design Matrix that is the convolution of the stimulus matrix D with the voxel's HRF, h [12].

$$X = D * h$$

A simple way to model tuning to the stimulus conditions in an experiment is to multiply each column of the design matrix by a weight that modulates the BOLD signal according to the presence of the corresponding stimulus condition. The selectivity of V individual voxels can be modelled simultaneously through a $C \times V$ Selectivity Matrix, β. Each entry in β is the amount that the v^{th} voxel (columns) is tuned to the c^{th} stimulus condition (rows). Given the design matrix and the selectivity matrix, the BOLD signals y of selectively-tuned voxels can be predicted with a simple matrix multiplication:

$$y = X\beta$$

The noise in a voxel is often modeled as a random variable ϵ. A common choice for the noise model is a zero-mean Normal/Gaussian distribution with some variance σ^2

$$\epsilon \sim N(0, \sigma^2)$$

Though the variance of the noise model may not be known prior, there are methods for estimating it from data.
Combining all of these to compose a comprehensive quantitative model of BOLD signals measured from a set of voxels during an experiment:

$$y = X\beta + \epsilon$$
$$y = (D * h)\beta + \epsilon$$

This is referred to as the General Linear Model (GLM) [14].

Estimation
In a typical fMRI experiment the researcher controls the stimulus presentation, D, and measures the evoked BOLD responses y from a set of voxels. The problem then is to estimate the selectivities of the voxels based on these measurements. Specifically, the parameters $\hat{\beta}$ that best explain the measured BOLD signals during the experiment are to be estimated. The most common way to do this is a method known as Ordinary Least Squares (OLS) Regression. Using OLS, the idea is to adjust the values of $\hat{\beta}$ such that the predicted model BOLD signals are as similar to the measured signals as possible. In other words, the goal is to infer the selectivity each voxel would have to exhibit in order to produce the measured BOLD signals. The optimal OLS solution for the selectivities $\hat{\beta}$ is given by:

$$\hat{\beta} = (X^T X)^{-1} X^T y$$

Therefore, given a design matrix X and a set of voxel responses y associated with the design matrix, the selectivities of voxels to the stimulus conditions represented by the columns of the design matrix can be calculated.

Basis Function
The basic assumption made in order to use the GLM is that the model of the Hemodynamic Response Function (HRF) for the voxel is an accurate model. A common practice is to use a canonical HRF model established from previous empirical studies of fMRI time-series. However, voxels throughout the brain and across subjects exhibit a variety of shapes, so the canonical model is often incorrect. Therefore it becomes necessary to estimate the shape of the HRF for each voxel [7].

There are a number of ways that have been developed for estimating HRF's, most of them are based on temporal basis function models [15]. There are a number of basis function sets available and Finite Impulse Response is one such basis function. The HRF is modelled using a flexible basis set composed of a set of delayed impulses called Finite Impulse Response basis.

In order to estimate the HRF of each voxel to each of the C stimulus conditions using an FIR basis function model, a design matrix composed of successive sets of delayed impulses is created, where each set of impulses begins at the onset of each stimulus condition. For the $T \times C$-sized stimulus onset matrix D, calculate an $[T \times HC]$ FIR design matrix, X_{FIR}, where H is the assumed length of the HRF which is to be estimated.

For each voxel, the weight on each column of X_{FIR} that will best explain the BOLD signals, y, measured from each voxel is to be determined. Now this problem can be formed in terms of a General Linear Model:

$$y = X_{FIR}\,\beta_{FIR}$$

where, β_{FIR} are the weights on each column of the FIR design matrix. The values of β_{FIR} are set such as to minimize the sum of the squared errors (SSE) between the model above and the measured actual responses

$$SSE = \textstyle\sum_i^N (y^{(i)} - X_{FIR}^{(i)})^2,$$

Then the Ordinary Least Squares (OLS) solution can be used to solve the problem for β_{FIR} [4]. Specifically, the weights are solved as:

$$\widehat{\beta_{FIR}} = (X_{FIR}^T X_{FIR})^{-1} X_{FIR}\, y$$

Once determined, the resulting $CH \times V$ matrix of weights $\widehat{\beta_{FIR}}$ has the HRF of each of the V different voxels to each stimulus condition along its columns.

IJARCCE

ISSN (Online) 2278-1021
ISSN (Print) 2319 5940

International Journal of Advanced Research in Computer and Communication Engineering
ISO 3297:2007 Certified
Vol. 5, Issue 10, October 2016

Efficiency
Since fMRI data are a continuous time series, the underlying noise ϵ is generally correlated in time. This noise can be modeled as a Gaussian process with zero mean and a constant multivariate covariance, C_ϵ. In general, the values that comprise C_ϵ are unknown and have to be estimated from the fMRI data themselves.
For a known or estimated noise covariance, the Maximum Likelihood Estimator (MLE) for the model parameters $\hat{\beta}$ is:

$$\hat{\beta} = (X^T C_\epsilon^{-1} X) X^T C_\epsilon^{-1} y$$

Because the ML estimator of the HRF is a linear combination of the design matrix X and a set of corresponding responses, which are both random variables, the estimator is itself a random variable. It thus follows that the estimate for the HRF also has a variance.
A formal metric for efficiency of a least-squares estimator is directly related to the variance of the estimator. The efficiency is defined to be the inverse of the sum of the estimator variances. An estimator that has a large sum of variances will have a low efficiency, and vice versa. The variances can be recovered from the diagonal elements of the estimator covariance matrix $C_{\hat{\beta}}$, giving the following expression for the efficiency, E [16]

$$E = 1/trace(C_{\hat{\beta}})$$

The covariance matrix $C_{\hat{\beta}}$ for the GLS estimator with a given noise covariance C_ϵ is:

$$C_{\hat{\beta}} = (X^T . C_\epsilon^{-1} . X)^{-1}$$

Thus the efficiency for the HRF estimator is

$$E = 1/trace((X^T . C_\epsilon^{-1} . X)^{-1})$$

Since the HRF is estimated using the FIR basis set, thus the model design matrix is X_{FIR}. This gives the estimate efficiency for the simulation experiments:

$$E = 1/trace(X_{FIR}^T X_{FIR})$$

The above mentioned GLM model has been used to create the experimental setup for the analysis purpose. The simulations implicated are described in the next section.

III. EXPERIMENTAL SETUP

This work analyses the experimental design for event-related fMRI using different inter-stimulus interval (ISI), i.e., the interval between the offset of one stimulus to the onset of another stimulus. The following steps are implemented in the simulations and an analysis is carried out comparing random and periodic SOAs based on the efficiency and selectivity profile. The simulations were carried out on MATLAB platform.

Step 1: Construct a stimulus matrix D, in which columns indicate onset of each stimulus condition and rows indicate corresponding time at each point.
Step 2: Generate input sequence.
Step 3: Create a Design Matrix X, which is the convolution of stimulus matrix and hemodynamic response function.
Step4: Make a selectivity matrix predicting BOLD signals.
Step 5: Define General Linear Model.
Step 6: Estimate parameters.
Step 7: Result.

Simulations:
Two simulations of event related fMRI are used to analyse the event-related fMRI design. The first paradigm is randomly presented stimulus onset which is the event-related fMRI in which the input stimulus are presented randomly. The second paradigm is periodically presented stimulus onset which is the event-related fMRI in which the input stimulus are presented periodically with fixed interval sequence or inter-stimulus interval (ISI). The efficiency of 20 event sequence at each combination of ISI and jitter is estimated. The ISI ranged from 2s to 30s. The TR is kept fixed at 1 sec. A noise signal was added to estimate HRF. These parameters are used for both simulations.

Simulation 1:
This simulation demonstrates event trials. The stimulus train is presented randomly. In simulation 1, a sequence of stimulus is generated using the pseudo random number generator function available in MATLAB. An input sequence of randomly presented stimulus onset is generated from the stimulus matrix. For this simulation, a BOLD signal is presented which is evoked by 20 stimulus onsets that occur at random times over the course of the 80 second run duration.

Simulation 2:
This simulation demonstrates events trials over a fixed interval of time. In simulation 2, a sequence of periodically presented stimulus is generated from the stimulus matrix. For this simulation, a stimulus is presented periodically 20 times, once every 4 seconds, for a run of 80 seconds in duration.
The results of the simulations are discussed in the following segment.

IV. RESULTS AND DISCUSSION

Accurate estimates of the HRFs from different event types can be obtained using event-related fMRI with very rapid presentation, as long as the inter-stimulus interval is randomized. The following section provides detailed discussion of the results.

A. Efficiency
The estimator efficiency is investigated on varying the mean ISI in random and periodic stimulus design. Figure 1 shows the efficiency measure, E, for the maximum likelihood HRF estimate for a event type or condition as a function of mean ISI, for both random stimulus and

IJARCCE
ISSN (Online) 2278-1021
ISSN (Print) 2319 5940
International Journal of Advanced Research in Computer and Communication Engineering
ISO 3297:2007 Certified
Vol. 5, Issue 10, October 2016

periodic similar efficiency measures. For shorter mean ISIs, the efficiency of random stimulus designs increases dramatically, whereas the efficiency stimulus. Relative efficiency of random and periodic ISI experimental designs is shown as a function of mean ISI. For very long mean ISIs (e.g. >20s), random and periodic stimulus designs result in very of periodic stimulus designs decreases.

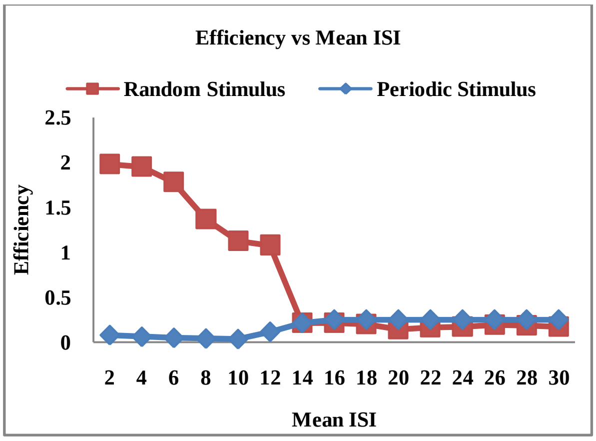

Figure 1 Efficiency of Periodic and Random Stimulus Events

B. Selectivity Profile

Selectivity is a simple characterization of the function of a voxel in terms of its response to each of the different experimental conditions. Usually two to eight conditions are used in most imaging studies and here too, selectivity is varied in this range.

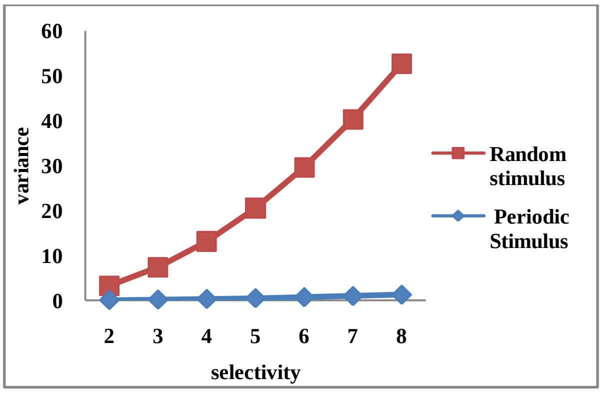

Figure 2 Selectivity vs Variance Plot for Random and Periodic SOAs.

Figure 2 shows plot for varying variance corresponding to shifting selectivity for both random and periodic stimulus design. The variance for randomly presented stimulus increases monotonically with increasing selectivity whereas variance for periodic stimulus barely shows any increase with increasing selectivity.

The results drawn out clearly shows that randomly presented stimulus onset outperforms in comparison to the periodically presented stimulus onset.

Table 1: Results of simulations for Event-Related fMRI Design.

S. No	Parameter	Simulation 1	Simulation 2
1.	Variance	7.40	0.18
2.	Mean	2.9886	3.9061
3.	Standard Error	0.2706	1.5147
4.	Power	717.0001	716.0006

From these results, it is obvious that the random stimulus presentation rate gives rise to more accurate and less variable estimates of the HRF function.

The variance of the underlying signal should be large compared to the noise so that the signal can be detected. The estimated variance of the periodic-based signal is 0.18. In contrast, the signal evoked by the random stimulus presentation schedule varies wildly, reaching maximum amplitude that is roughly 2.5 times as large as the maximum amplitude of the signal evoked by periodic stimuli. The estimated variance of the signal evoked by the random stimuli is 7.4, roughly 40 times the variance of the signal evoked by the periodic stimulus. Since larger the variance lesser the effect of noise on signal and thus more information retained. So the random stimulus provides more information. Another way for efficient design of an experimental design is maximizing the amount of power in the resulting evoked BOLD responses.

The efficiency exhibited by randomly presented stimulus onset is much larger as compared to the periodically presented stimulus onset. Thus, randomly presented stimulus onset for event-related fMRI design gives better results and so, while considering design considerations for fMRI, the stimulus must be presented randomly rather than at fixed interval. The efficiency of random stimulus designs increases with decreasing inter-stimulus interval (ISI). Thus, the simulations presented here clearly demonstrate the advantages of using random stimulus design rather than periodic stimulus design in event-related fMRI experiments.

V. CONCLUSIONS

In this paper, the comparative study focuses on the analysis of event-related fMRI design for two paradigms i.e. periodic SOAs and random SOAs. The most widely used model viz. GLM for the fMRI design has been implemented using MATLAB platform and the results corresponding to the simulations are presented in terms of variance, standard error, mean and power. The results clearly distinguish the performance of randomly presented stimulus being better than the periodically presented stimulus. The selectivity profile has been varied for both stimuli and the results depict that the variance for the random stimuli increases monotonically as opposed to the periodic stimuli. Random stimulus provides higher variance than periodic thus resulting in more information

IJARCCE
ISSN (Online) 2278-1021
ISSN (Print) 2319 5940

International Journal of Advanced Research in Computer and Communication Engineering
ISO 3297:2007 Certified
Vol. 5, Issue 10, October 2016

and lesser noise with increase in selectivity. It has been gathered from the simulations that it is difficult to attain optimal efficiency using longer ISI and hence it is suitable to use randomly presented SOA for the event-related fMRI designs.

REFERENCES

[1] Anders M. Dale and Randy L. Buckner, (1997), "Selective Averaging of Rapidly Presented Individual Trials using fMRI", Human Brain Mappng, 5, pp. 329-340.
[2] Anders M. Dale, (1999), "Optimal Experimental Design for Event-Related fMRI", Human Brain Mapping, 8, pp. 109-114.
[3] Bruce R. Rosen, Randy L. Buckner, and Anders M. Dale, (1998), "Event-related functional MRI: Past, present, and future", Neuroimaging of Human Brain Function, 95, pp. 773-780.
[4] Danial Lashkaria, Ed Vulb, Nancy Kanwisherb, and Polina Gollanda, (2010), "Discovering Structure in the Space of fMRI Selectivity Profiles", NeuroImage, 50(3), pp. 1085-1098.
[5] Edson Amaro Jr. and Gareth Jr. Barker, (2006), "Study Design in fMRI: Basic Principles", Brain and Cognition, 60(3), pp. 220-232.
[6] Eric Zarahn, Geoff Aguirre, and Mark D'Esposito, (1997), "A Trial-Based Experimental Design for fMRI", Neuroimage, 6, pp. 122-138.
[7] Friston K. J., Jezzard P. J., and Turner R., (1994), "Analysis of Functional MRI Time-Series", Human Brain Mapping, 1, pp-153-171.
[8] Giedrius T. Buračas and Geoffrey M. Boynton, (2002), "Efficient Design of Event-Related fMRI Experiments using M-Sequences", NeuroImage, 16(3), pp. 801-813.
[9] K. J. Friston, E. Zarahn, O. Josephs, R. N. A. Henson and A. M. Dale, (1999), "Stochastic Designs in Event-related fMRI", NeuroImage, 10, pp. 607-619.
[10] K. J. Friston, P. Fletcher, O. Josephs, A. Holmes, M. D. Rugg, and R. Turner, (1998), "Event-Related fMRI: Characterizing Differential Responses", Neuroimage, 7, pp. 30-40.
[11] Marc A. Burock, Randy L. Buckner, Marty G. Woldorff, Bruce R. Rosen and Anders M. Dale, (1998), "Randomized Event-Related Experimental Designs Allow for Extremely Rapid Presentation Rates using Functional MRI", Neuroreport, 9, pp. 3735–3739.
[12] Martin J. McKeown, Vijay Varadarajan, Scott Huettel and Gregory McCarthy, (2002), "Deterministic and Stochastic Features of fMRI Data: Implications for Analysis of Event-Related Experiments", Journal of Neuroscience Methods, 118, pp. 103-113.
[13] Michael W.L. Chee, Vinod Venkatraman, Christopher Westphal, and Soon Chun Siong,(2003), "Comparison of Block and Event-Related fMRI Designs in Evaluating the Word-Frequency Effect", Human Brain Mapping, 18, pp. 186-193.
[14] Ming-Hung Kao, M'hamed Temkit and Weng Kee Wong, (2014), "Recent Developments in Optimal Experimental Designs for Functional Magnetic Resonance Imaging", World Journal of Radiology, 6(7), pp. 437-445.
[15] Thomas T. Liu, (2012), "The Development of Event-Related fMRI Designs", NeuroImage, 62(2), pp. 1157-1162.
[16] Tor D. Wager and Thomas E. Nichols, (2003), "Optimization of Experimental Design in fMRI: A General Framework using a Genetic Algorithm", NeuroImage, 18, pp. 293-309.