CONSTRAINED NONLINEAR ESTIMATION OF FMRI HEMODYNAMIC RESPONSE PARAMETERS

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ABSTRACT

We present a constrained nonlinear optimization approach to the estimation of hemodynamic response (HR) shape from fMRI images. The controlled random search (CRS) based strategy limits the HR parameters within a physically/physiologically plausible phase space, and thus may produce more meaningful results than the traditional unconstrained methods. Block-design and event-related fMRI experiments have been conducted to examine the validity of the framework.

Index Terms— hemodynamic response, controlled random search, optimization

1. INTRODUCTION

There is an increasing interest in understanding the time course of the hemodynamic response and its modulation with respect to different experimental conditions. A common approach is based on *a priori* temporal knowledge of the event sequence, such as a parametric model, and such knowledge is fully used to detect the specific brain regions whose hemodynamic evolution can be evaluated by mean of various statistical approach [1, 2]. However, there are potential problems raising from those statistical testing approaches. While a high statistic confidence tells us that the model comes very close to the data points, that does not necessarily mean that the fit is actually *good* in other ways. This is because there is no guarantee that the best-fit values of the parameters obtained by the statistic test will be meaningful in physics and/or physiology, or simply because there is no intersection between a poor experiment dataset, a poor model, or both [3].

To overcome these possible drawbacks, we argue that statistical inference about underlying patterns should be made in a physically/physiologically plausible phase space, that is, estimated parameters should possess maximum probability within the domain of meaningful physical constraints. In particular, the HR parameter estimation can be converted into a constrained optimization problem, in which physical constraints need to be enforced when one searches for the minimum of a specified objective function. Furthermore, since the hemodynamic response function (hrf) typically possesses strong nonlinear characteristics, in which the effects of model parameters on the output strongly interweave together, the relevant optimization should be able to deal with nonlinear multi-modal objective function.

Conventionally, direct, random search techniques have been applied to multi-modal optimization problems by discretizing the phase space. It is easy to show that the search accuracy highly depends on the fineness of discretization and convergence could be slow for satisfying results. The controlled random search algorithms [4, 5] combine the random search and mode-seeking routines into a single, continuous process, and thereby provide a reasonable compromise between search accuracy and convergence speed. Furthermore, since only very limited measures are recorded for each fMRI trial, it is difficult to estimate complex models with many parameters for conventional strategies. CRS algorithms have shown overwhelming superiority in such situations [5].

As an initial effort to explore constrained nonlinear estimation strategy of fMRI hemodynamic response parameters, we have applied the controlled random search algorithm to Gaussian HR models for block-design and event-related fMRI experiments, in the hope that the estimates can offer *the best goodness of fit* and are *interpretable in terms of physiological variables*. With studies of more sophisticated HR models underway, we believe that such methodology, which results in compact, concise, and meaningful parametrizations of the HR shapes, may give a better understanding for inter-trial, inter-region and inter-individual differences in fMRI experiments.

2. METHODOLOGY

2.1. Gaussian Function Model

The BOLD responses, induced by experimental stimuli, have been modeled by various HR functions which attempt to characterize some features in the temporal aspects of the fMRI-measured HR and provide an approximate to the time course

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of the fMRI signal. Some of the better known heuristic functions for the hemodynamic response modeling include the Poisson function, the Gamma function, the Gaussian function, and the balloon model which is a more comprehensive biomechanical model of hemodynamic modulation [6, 7].

In the context of this paper, as an initial attempt, we concentrate on the Gaussian function for its relative simplicity:

$$h(t, \boldsymbol{\beta}) = \beta_0 \exp(-\frac{(t-\beta_2)^2}{2{\beta_1}^2}) + \beta_3 \quad (1)$$

with $\boldsymbol{\beta} = (\beta_0, \cdots, \beta_3)$. β_0, being interpreted as the gain in the hrf, is the height of the HR; β_1, as the dispersion of the hrf, is proportional to the duration of the HR; β_2, the delay, is the time from stimulation onset to the HR peak; and β_3 is the baseline of the hrf.

The Gaussian hrf can offer the best goodness of fit to HR [7], and its model parameters are interpretable in terms of physiological variables. However, the shape of the Gaussain kernel, which is symmetrical around its peak, is not confirmed by experimental inspection of hrf. Furthermore, it also neglects initial dip and the post-stimulus undershoot.

2.2. Objective Function

Statistical models usually contain two parts: the fixed effects which capture the underline patterns (the hrf here) and the random errors.

Let $\mathbf{S}$ be a set of L fMRI observations to a single experimental trial in discrete time steps $\mathbf{T}$, denote as $\mathbf{S} = \{S(t), t \in \mathbf{T}\}$. We explains the response variable $\mathbf{S}(t)$ in terms of a hrf plus an error term:

$$\mathbf{S}(t) = \mathbf{h}(t, \boldsymbol{\beta}) + \epsilon \quad (2)$$

where $\boldsymbol{\beta}$ denotes a n-dimensional parameter vector, and the errors ϵ are independent and identically distributed normal random variables with zero mean and variance σ^2, written as $\epsilon \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$.

The least squares estimator $\hat{\boldsymbol{\beta}}$ of $\boldsymbol{\beta}$ is the value of $\boldsymbol{\beta}$ that minimizes the sum of squared errors in

$$\underset{\beta}{\operatorname{argmin}} ||\mathbf{S}(t) - \mathbf{h}(t, \boldsymbol{\beta})||_2 \quad (3)$$

This problem corresponds to determine the position, in n-dimensional phase space, of a given objective function, that is, it can be convert into solving an optimization problem. Thus, the objective function can be defined as:

$$f(\boldsymbol{\beta}) = ||\mathbf{S}(t) - \mathbf{h}(t, \boldsymbol{\beta})||_2 \quad (4)$$

where $||.||_2$ denotes the L^2-norm of a vector. It is the L^2-norm of the difference between a measured data point and the model expectant value summed over all points and time steps in a trial. Furthermore, a constraint was imposed to limit the search within the physical/physiological reasonable domain.

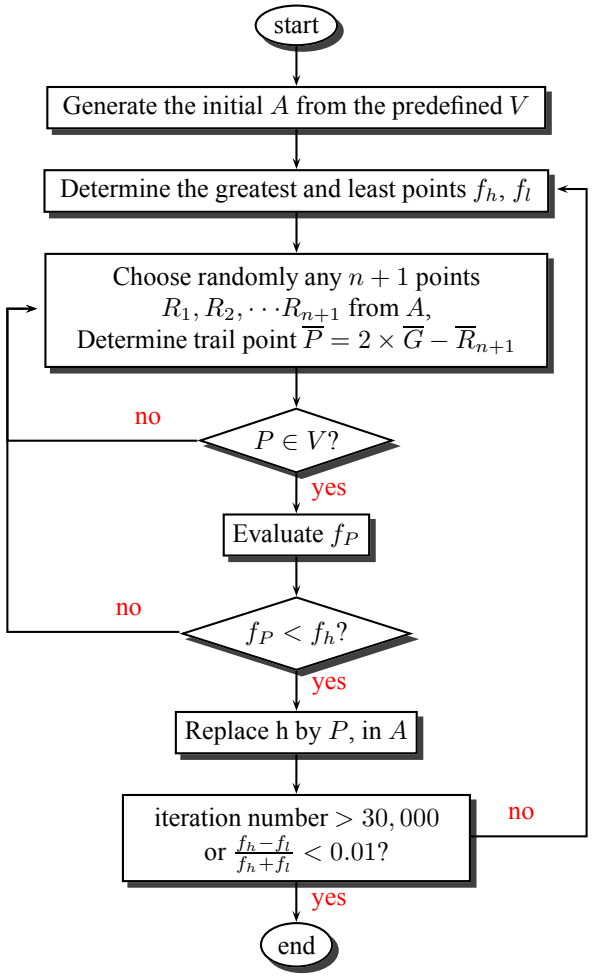


Fig. 1: The flowchart of the Price's CRS algorithm approach.

Hence, a global optimization algorithm, which aims at finding a global minimizer or its close approximation of a function $f : S \subset R^n \rightarrow R$, can be applied. When $\forall\ \boldsymbol{\beta} \in S \bigcap [\{\boldsymbol{\beta} | C(\boldsymbol{\beta})\}]$, where $C(\boldsymbol{\beta})$ is physical constraints, $\exists f = f(\hat{\boldsymbol{\beta}}) \leq f(\boldsymbol{\beta})$, we said point $\hat{\boldsymbol{\beta}}$ is a global minimizer of f.

2.3. Controlled Random Search Alogrithm

Controlled random search (CRS) algorithm was proposed as an improvement to simple random search method [4, 5]. It is an optimization algorithm suitable for searching of global minimizers of objective function which does not require the function to be differentiable or the variables to be continuous, and is applicable in the presence of constraints.

The basic CRS idea for minimization can briefly be described as follows

1. Generate the initial population A of N random points

in predefined phase space V: $A = \{x_1, ..., x_N\}$. Compute the function values of these points. Store these points and corresponding function values in a array of dimension $N \times (n+1)$. Determine the greatest and least values of the N points in store, and corresponding the worst point h and the best point l. If a stopping criterion is already satisfied then stop.

2. Generate a trial point p for replacing some $x \in V$.
3. If $P \notin V$, go to step 2.
4. Evaluate $f_p = f(p)$. If $f_p > f_h$ go to step 2.
5. Update the set A by replacing the current worst point by the trial point. Determine the greatest and least function values f_h, f_l, and corresponding the worst point h and the best point l in new A.
6. If the stopping criterion is satisfied stop; else go to step 2.

The main difference between various CRS versions is the generation of trial point P in step 2, and we have adopted the simplex search scheme [4]. The trial point generation in step 2 is carried out as follows: chose randomly $n+1$ distinct points from the current population A, $R_1, \cdots, R_{n+1}$ (forming a simplex in $\mathbb{R}^n$). The point R_{n+1} is arbitrarily taken as the pole of the simplex, and the new trial point P is defined as the reflection of the pole with respect to the centroid G of the the remaining n points:

$$\overline{P} = 2 \times \overline{G} - \overline{R}_{n+1} \tag{5}$$

In this scheme, the appropriate choice of N is $N = 25n$, and the convergence criterion is the total number of iteration exceeds $50,000$ or $(f_h - f_l)/(f_h + f_l) < 0.01$. The essential features of the algorithm shown as the flowchart in Fig. 1.

3. EXPERIMENTS

We have used two group fMRI data, one each for block-design and event-related, to validate the effectiveness of the method.

Block-design: Totally 72 acquisitions were made (RT=7s), in blocks of 6, giving 12 42-second blocks. The condition for successive blocks alternated between rest and auditory stimulation, starting with rest. Auditory stimulation was bi-syllabic words presented binaurally at a rate of 60 per minute.

Event-related: 2 distinct texture photograph were presented in 2s for touch perception followed by a 14s rest, starting with stimulus. Same 96 volumes were obtained (RT=2s), in periods of 16s, giving 12 16-second circles.

We chose the largest activation blob as region of interest, using the routine fMRI analysis of SPM2, and defined seed cluster based on faces and edges, but not corners, so this voxel had 18 neighbors. The final seed time series (show as blue bar in Fig. 2) were extracted by averaging the time series of the 19 voxels.

Since parameters β_1 and β_2 are the dispersion and the delay time of the HR model, they should be constrained to be positive and within the length of a trial period. Furthermore, β_0 is the *height* of the HR, and should be less than the maximum difference between measured signal. β_3 is the baseline of HR, and thus should be less than the mean signal intensity. In particular, combining all these requirements together, inspection of fMRI time series reveals that the optimization problems for block-design and event-related experiments can be formulated as following:

Find a set of optimal model parameters $\boldsymbol{\beta}$ such that

$$\begin{array}{lll} \min\limits_{\boldsymbol{\beta}} & \mathrm{f} & \\ \text{subject to} & 0 \le \beta_0 < 500; & 0 \le \beta_0 < 500; \\ & 0 \le \beta_1 < 50; & 0 \le \beta_1 < 40; \\ & 0 \le \beta_2 < 50; & 0 \le \beta_2 < 40; \\ & 2400 \le \beta_3 \le 3400; & 1450 \le \beta_3 < 1650; \\ & \text{(block-design)} & \text{(event-related)} \end{array}$$

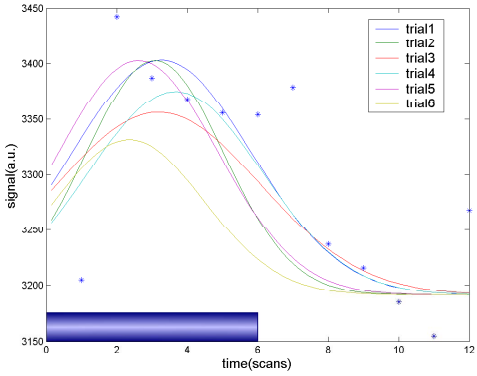
$\forall \boldsymbol{\beta} \in \mathbf{V}$.

4. RESULTS AND DISCUSSION

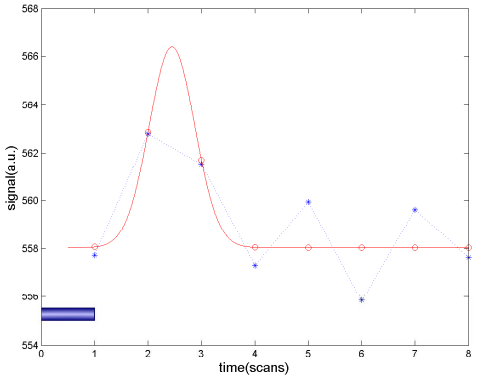
In Fig. 2 (a), we present observable responses obtained from different trials in block-design experiment, the blue star symbol denotes the raw data from the first trial. There are good fit (see the 6th column in Tab. 1., $F < F_{0.95}(7, 10)$ for all trials) between the HR signals (blue) and Gaussian model functions (red). Fig.2 (b) present the representative fMRI time courses obtained from the largest activation blobs and the fitted model waveforms in event-related experiment.

It is a major advantage of using model functions that some physiologically meaningful parameters, that is the temporal properties of a HR to single trial, can be derived. Table 1. shows the HR Gaussian model parameters of different trails from the largest activation area of the block-design data. We do not assign the baseline parameter β_3 since it is regarded as a trial-wise constant. The result shows that the time courses of the evoked HR differed substantially, even within the same subject and session. It may related to subject strategy changes and attention shifts during the experiment [8].

Another advantage is on observation noise. Statistical models usually contain two parts: the model response and the random error. The classical optimization approach simply assumes that the random error is spherically distributed [9]. Or further, autoregressive model was also introduced to model the noise temporal correlation by considering the influence of random error of the preceding time points on that of the current time point. However, the error source may be observation noise, but may also come from structural inaccuracy of the model. The state-dependent noise depends on measured



(a) Block-design



(b) Event-related

Fig. 2: (a) HR from the largest activation blob across different trials in block-design experiment, the blue star symbol denotes the raw data from the first trial. (b) The time course of HR (blue) to the first trial from the largest activation blob and fitted Gaussian model (red) in event-related experiment. Stimulus duration is shown as blue bar.

noise, and it is hard to require it to have a certain probabilistic property such as independence or martingale property. The CRS approach may relax the restrictions made on the noise by constructing distinct objective function (e.g., L^{∞}-norm objective function), though we make spherically distributed assumption on the observation noise in eq. 2.

Moreover, the proposed scheme can be applied to the evaluation of hemodynamic responses at every voxel, it may give a better understanding about intertrial, interregion and interindividual differences in fMRI experiment. Combining with corresponding statistical strategy, it may serve as a valuable tool for activation detection in functional neuroimaging studies. Further studies are needed in more physiological plausible HR model and establishing reasonable statistical strategy to obtain activation detection over global brain.

trial	β_0	$\beta_1[s]$	$\beta_2[s]$	minimizer (f_t)	F test $(10, 11df)^a$
1	211.45	17.86	22.94	185.22	3.77
2	211.17	13.66	21.58	214.73	4.37
3	164.79	20.22	22.31	136.18	3.42
4	183.66	17.19	25.66	186.79	4.49
5	211.18	15.94	18.30	178.89	3.29
6	140.04	14.86	16.49	208.89	6.34

Table 1: Gaussian model parameters for block-design HR to different trail from the largest activation blob in SPM2.

[a] $F_{0.95}(10, 11) = 2.85$.

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