

Suppression of Artefactual Time Courses in phMRI through Iterative Wavelet Cluster Analysis

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Abstract.

Wavelet-based cluster analysis (WCA) is a technique that can be used to separate fMRI and phMRI data into different clusters, where no model of the neural response is known *a priori*, based on the similarity of decomposed time courses at certain temporal scales. Here we extend this iteratively as an interactive step in a data-driven analysis. It works by removing voxels from further analysis by examining how they are clustered at temporal scales which may be different to that of any neural response under investigation. This is in contrast to existing techniques that suppress artefactual effects through excessive smoothing which may also suppress localised drug responses in phMRI. The method is demonstrated here on an auditory fMRI experiment. We conclude that it will be a useful step in the preprocessing and further analysis of phMRI data.

1 Introduction

A wide variety of analysis techniques are applied to functional magnetic resonance imaging (fMRI) data. The most popular of these uses the general linear model to identify voxels whose time course correlates with the *a priori* experimental procedure, implemented as statistical parametric mapping (SPM) [1]. Recently, pharmacological MRI (phMRI) has emerged as a development of fMRI. In conventional fMRI the experimental procedure is generally a well-defined activation task (word generation, finger tapping etc). In phMRI the experimental procedure is the administration of a drug; consequently the analysis procedure must look to identify voxel time courses correlating with the expected neural response to the drug. This can be problematic if the expected neural response is not well established or could be expected to have a number of differing spatial and temporal modes [2]. There is correspondingly greater potential for data-driven methods in phMRI than in conventional fMRI.

One way to attempt to discover this neural response is to find what components make up the time courses in the data. Techniques such as principal component analysis (PCA) and independent component analysis (ICA) find mutually uncorrelated components through maximizing variance and minimizing Gaussianity respectively. A correlation analysis may subsequently be performed to discover the spatial positions of those voxels which contribute to particular components. Other techniques attempt to group voxels which exhibit similar behaviour. In wavelet-based cluster analysis (WCA), coefficients from wavelet decompositions are grouped so that intra-group variance is minimized [3]. It has been applied to several phMRI experiments on the rat brain with success and promises to be a useful data-driven method in human phMRI.

However, any data-driven method will detect many effects which are not caused by the neural response of the drug under investigation, such as cardiac and respiratory signal, scanner drift, mutual partial voluming, and residual motion artefacts which may remain (or even be introduced) after motion correction. The original WCA processing pipeline attempts to suppress outlier and artefactual time courses through a smoothing operation [4]. Although it is generally necessary to do some form of spatial smoothing to increase the signal-to-noise ratio of the data, too large a filter kernel may suppress a very localised neural response, which may be present in some phMRI experiments. In an exploratory analysis, it may be beneficial to perform a very low level of smoothing, while fully suppressing only artefactual time courses.

In this paper we extend WCA iteratively to become a preprocessing step in exploratory data-driven analysis by repeatedly performing WCA and completely removing those clusters which appear to the expert user to be artefactual (based on their position or average time course). In particular, it is not necessary for the temporal scale used in the discovery of artefactual clusters to be that of any expected response of interest. Since the aim of a data-driven analysis is often not the testing of hypotheses but the creation of new ones, the method introduced here is based on allowing researchers to quickly explore the data and refine it using their expert knowledge. This is enabled since each iteration takes only seconds. For straightforward fMRI experiments it may also be used to do a full analysis and an example is presented here.

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2 Methodology

Once a 4D (3D + time) dataset has been preprocessed to realign each point so that it may be confidently compared to itself over time, it may be represented as a matrix of voxels

$$\mathbf{X} = \begin{pmatrix} v_{1,1} & v_{1,2} & v_{1,3} & \cdots & v_{1,t} \\ v_{2,1} & v_{2,2} & v_{2,3} & \cdots & v_{2,t} \\ v_{3,1} & v_{2,3} & v_{2,3} & \cdots & v_{3,t} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ v_{x \times y \times z, 1} & v_{x \times y \times z, 2} & v_{x \times y \times z, 3} & \cdots & v_{x \times y \times z, t} \end{pmatrix} \quad (1)$$

where each column represents a full 3D brain volume at one point in time and each row represents the temporal changes of one voxel. x , y and z are the spatial dimensions of one brain volume, while t is the number of volumes in the session. The methods discussed here do not use any knowledge of the spatial position of any voxels until the data is reassembled for visualisation.

2.1 Wavelet-based cluster analysis

WCA was introduced in [3] and expanded upon to include multiple subjects in [4]. We present here a brief overview of the method. If the data does not contain a power of 2 number of timepoints it must first be temporally resampled or some timepoints discarded. The discrete wavelet transform (DWT) is performed independently on each row of \mathbf{X} , decomposing each time course into coefficients, c , which retain temporal information. This is achieved using the Haar wavelet equation, $c_i = \frac{s_{i+1} - s_i}{2}$ (with s_{i+1} and s_i being voxel values, 1 timepoint apart), which acts as a high pass filter revealing the high frequency components of the original time course. The Haar wavelet scaling function, $a_i = \frac{s_{i+1} + s_i}{2}$, acts as a low pass filter, producing a smoothed version, a , of the original time course for use as the input for the next level of wavelet decomposition. At the first temporal scale the coefficients will be the difference between the original time course and a smoothed version of itself. This is continued down the temporal scales, so that the result from an experiment with only 8 timepoints would be 3 scales of wavelet coefficients, λ_1 , λ_2 and λ_3 , having 4 values, 2 values and 1 value respectively. The DWT is in this case an orthogonal transform. Using some knowledge of the likely timescales involved in the experiment, several wavelet scales may be discarded, in practice usually the highest and lowest ones, leaving behind scales which are thought likely to contain signals of interest. K -means clustering is carried out, whereby the now reduced data (represented by a particular scale of coefficients, λ_i) is grouped into a specified number of clusters so that the variance inside each cluster is minimized according to

$$V = \sum_{i=1}^K \sum_{n \in S_i} |x_n - \mu_i|^2 \quad (2)$$

where there are K clusters, x_n is a vector representing wavelet coefficients in this case, and μ_i is the mean of all the points $n \in S_i$. Following Whicher *et al.*, K is chosen by the user so that there are enough clusters to allow time courses with a potential response of interest to be grouped into their own cluster, while not so many that they would be split up into too many clusters [3]. In the case of a single subject between 3 and 6 clusters appears to be a useful guide.

2.2 Iterative WCA

We build upon the method in [3] by repeatedly allowing the removal of whole clusters. The clustered data for the chosen temporal scale is reassembled into a file and shown to the user as an interactive volume rendering, with voxels belonging to the same cluster being assigned the same colour. The average time course for each cluster is also displayed, along with their variances and a measure of their autocorrelation. At this point, using the expert knowledge of the operator, those clusters showing clear temporal or spatial artefacts may be suppressed and the data reclustered. At each iteration any temporal scale may be chosen so that those voxels which show artefactual time courses at one scale may be completely removed from further processing, so that clustering at another scale may better pick out responses of interest. It should be noted that in this case it is every temporal scale of a voxel that is removed, and not just the components that were used in its clustering. This acts to form a mask for the data which we may use in any subsequent processing (Fig. 1). In this way it is possible to suppress artefactual voxel time courses without having to oversmooth the data, preserving those time courses that may be of interest but are spatially very localised.

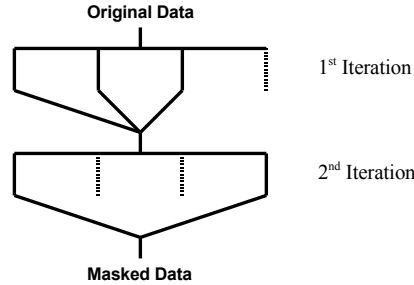


Figure 1. The Iterative WCA (IWCA) process. Dotted lines represent discarded clusters. The same voxel may be in different clusters after each iteration.

As opposed to original WCA, we perform clustering on the data at scales which would usually be ignored. This will prevent issues such as a mutual partial voluming artefact which appears artefactual at one temporal scale being aliased into an apparent signal of interest at a different temporal scale. The data may then be analysed using further WCA or another data-driven approach, where the most powerful components are now more likely to have been caused by a response of interest, whereas without the preprocessing of IWCA some of the most powerful components may have been artefactual. Since the method is quite fast and interactive it could also be used as a sanity check on data before more time consuming processing, or, in the case of a straightforward fMRI experiment, used to perform full processing with those clusters showing no clear spatial or temporal pattern being removed along with artefactual clusters at each iteration.

We have found that the order in which the scales are examined does not have a large effect on the results. In practice, several scales are examined before one is chosen for removal of one or more of its clusters.

3 Experimental Results

The *in vivo* dataset, used here with permission from the Wellcome Trust Centre for Neuroimaging, is from an auditory stimulation experiment carried out on a modified 2T Siemens MAGNETOM Vision system, with the BOLD/EPI volumes consisting of 64 contiguous slices, giving a spatial resolution of 64 x 64 x 64 cubic voxels of side 3mm (acquisition time 6.05s, repetition time 7s). The audio stimulation was bi-syllabic words presented once every second during each of the 42s stimulation blocks, with rest blocks in between.

Of the 96 scans we discarded the first 9 due to T1 effects, leaving 87 which were then realigned and spatially normalised (to a spatial resolution of 53 x 63 x 46) using the SPM5 software package. Axial slices 14 to 28 of the first 64 of the remaining scans were used here. Those voxels outside the brain were masked using simple thresholding. Each voxel time series was reexpressed as the percentage differences from their own mean, with those voxels showing very high variance being masked. Each was then corrected at every timepoint according to the global mean value of all non-thresholded voxels in each scan. The DWT was applied to each non-masked voxel time series, producing wavelet scales λ_1 to λ_6 of coefficients at each voxel.

Wavelet scale λ_1 , containing 32 coefficients for each voxel, was chosen for examination and K -means clustering (for 4 clusters), with each cluster being assigned a colour (red, blue, green or yellow)¹. The average time course for each of the clusters was then presented graphically, along with a 3D reconstruction displayed using an interactive volume renderer developed by the first author [5], showing the spatial positions of every clustered voxel in their original context as seen in Fig. 2. From examination of the average time course plot it was seen that those clusters coloured green and yellow had much larger variance than the red and blue clusters. From the interactive volume rendering, shown in Fig. 2 (row 1), it was seen that the green and yellow voxels were found almost exclusively at the interior and posterior brain parenchyma edges. It was decided using this knowledge of position and signal that these voxels were artefactual, and so should be removed before any further analysis. It should be noted that the green and yellow clusters removed at this point have no relationship to any later green or yellow clusters since the colours are chosen randomly at each iteration. Wavelet scale λ_3 , shown in Fig. 2 (row 2), was then examined and the blue clusters removed, before moving onto λ_2 , shown in Fig. 2 (row 3), where the red, blue and yellow clusters appeared not to show any sensible signal.

¹More figures of this process may be viewed in full colour at <http://www.cs.bris.ac.uk/home/mcgonigle/IWCA/>.

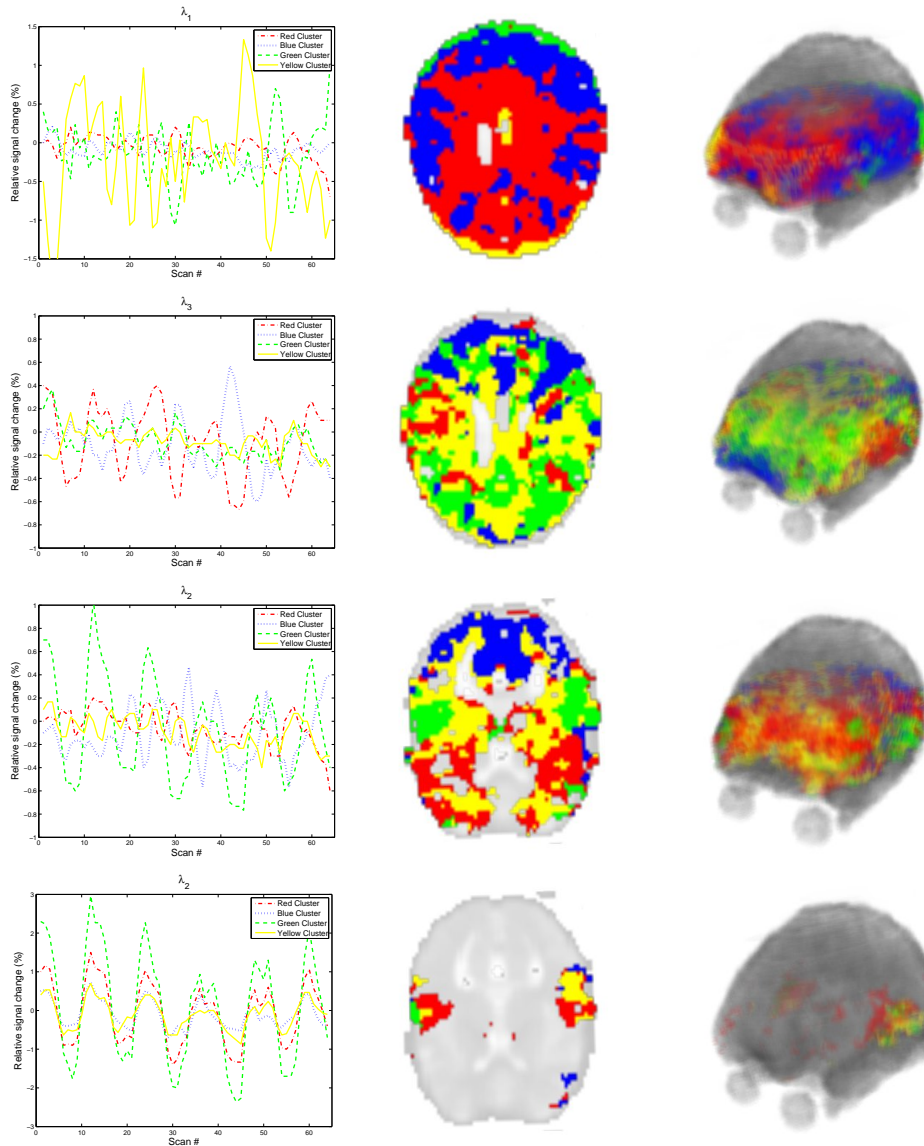


Figure 2. The average time courses of the clusters at scales λ_1 (where the green and yellow clusters were subsequently removed), λ_3 (where the blue cluster was removed) and λ_2 (where the red, blue, and yellow clusters were removed), along with a representative slice and a volume rendering for each. The plotted colours correspond to the rendered colours. The colour assigned to a particular cluster is random, and bears no relationship to the same colour at a different scale or iteration.

Scales above λ_3 were not used due to having too few points to be useful (since most drift had been corrected for earlier). With further iterations producing similar signal in all clusters, it was decided that all remaining voxels contained the same signal of interest, so their time courses were averaged, and their positions shown in Fig. 3. These results are in agreement with what would be expected from this experimental design, namely bilateral activation in the primary auditory cortex which is correlated with the activation task.

4 Discussion and Future Work

The technique presented here should *not* be seen as an excuse to use bad scans or sessions that would normally be discarded, but as a method which allows a multivariate and data-driven analysis without suppressing the very response of the drug under examination. In practice this approach is quite similar to the dendrogram sharpening clustering method of [6], as well as the segmentation of [7] and similar in concept to iterative temporal clustering analysis [8]. Since it is of interactive speed and presents the clusters in a natural way through volume visualisation it shows promise as a method to quickly sanity check data before further, more time consuming analysis since clear artefacts, either spatial or temporal will be presented to the user and a decision on whether to continue further made.

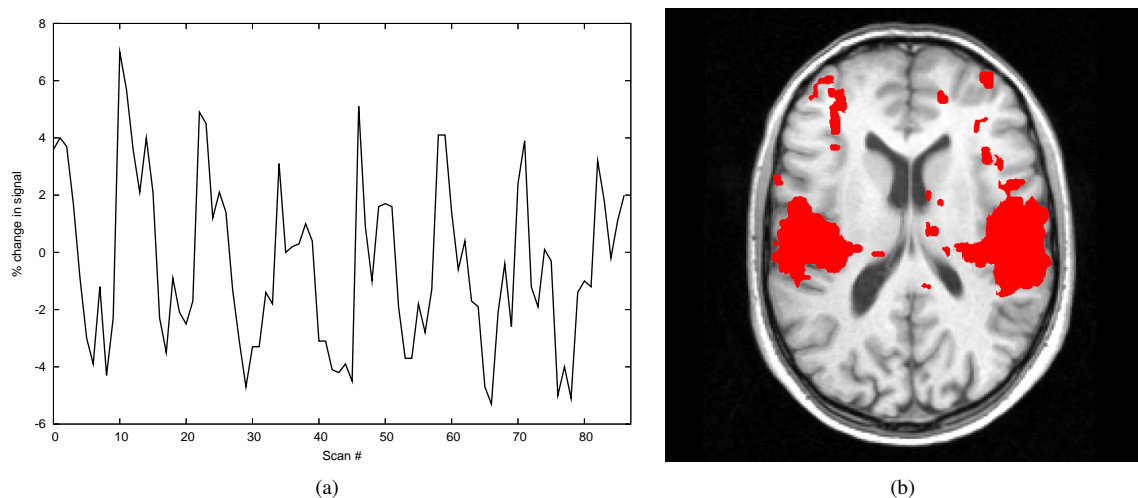


Figure 3. The average time course of all remaining voxels for the full length of the experiment (a), along with their spatial location shown as a maximum intensity projection of slices 14 to 28 superimposed on a representative structural slice (b).

It is designed as a research technique, and as such would be used in the initial stages of an exploratory analysis, where the emphasis is on the possibility of discovering an unexpected effect, which could later be tested using more traditional approaches. The process is not currently completely automated since it is necessary for decisions to be made which use the experience of the expert user. Artefactual time courses are often strongly autocorrelated in the same way we would expect a signal of interest to be, while conversely, what appears to be a cluster of noise at a particular scale may contain many voxels of a signal of interest which appears at a different scale.

A quantitative comparative analysis is ongoing into the improvement in sensitivity compared to other data-driven approaches when applied to particular classes of phMRI experimental data. We are also investigating the weighting of the temporal clusters based on the spatial position of their constituent voxels so that localised responses may more easily be detected.

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