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Gaussian Mixture Models for Brain Activation Detection from fMRI Data

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Abstract. Gaussian Mixture Model (GMM) based clustering has been successfully used in various types of medical and image data analysis, because of its robustness and stability under high noise levels. GMMs are employed in this work to extract the activation patterns from functional Magnetic Resonance Imaging (fMRI) data. The highly correlated time-series obtained with a given stimulus has been used to find the voxels contributing to the Blood Oxygenation Level Dependent (BOLD) activation regions. GMM clustering has been used for modeling of various activation patterns considering the strength, delay and duration of the epochs. A synthetic dataset and a real dataset provided by the Wellcome Trust Centre for Neuroimaging, University College London, UK are used to demonstrate the superiority of this approach in automating the process of identifying activated brain regions.

Keywords: fMRI, Clustering, Gaussian Mixture Models, BIC

1. Introduction

Clustering methods are most popular among the available feature extraction techniques, where, finite mixture model based methods have proved to be powerful unsupervised learning based data analysis tool. These methods have been found suitable in various social, healthcare and image data processing domains. The clustering of time series fMRI data has also been suggested as useful to obtain the brain regions which are responsible for the given activity. Due to their increasing applicability in scientific analysis, many model selection criteria are introduced to reduce the uncertainty in the decision making about number of classes available in the data and hence, these were found as a potential tool in partitioning the data into optimal number of clusters. [Fonseca, 2009; Garg et al., 2009; Dimitriadou et al., 2004; McLachlan and Peel, 2000].

Different types of classification techniques are suggested to extract significant features from fMRI data and to characterize activation patterns of the energy metabolism of the brain [Buxton et al., 1998]. However, the unpredictable noise levels in the fMRI environment severely deteriorate the signals and make it difficult to detect regions of significant activation accurately. For this reason, parametric methods such as general linear model implemented in SPM have been employed [Friston et al., 1995]. Even though these methods were found useful in many of the cases, they have the limitation of their dependency on the prior assumption about the characteristics of the activity related responses where, in case of the brain it is impossible to be certain about the prior assumptions, and hence dependability of these methods can be problematic. On the other hand, data driven methods such as GMMs are free from any type of prior assumption about the characteristics of data (e.g. region of activation) thus using the exploratory data analysis seems more meaningful approach [Goutte et al., 1999; Goutte et al., 2001; Davoudi et al., 2009]. A data driven approach allows more control on the data analysis related to systemic background noises in the fMRI environment. These noises reduce the quality of the data to such an extent that it becomes difficult to analyze with common methods. Therefore, we propose a data-driven method using Gaussian Mixture Model (GMM) based clustering; this algorithm is used to find the activation patterns from the noisy fMRI dataset.

Clustering algorithms search for some patterns of signal strength based on the similarity in the statistical characteristics of the group of fMRI voxel values and its distance from the other patterns in the data. Many algorithms have been proposed, broadly classified as Crisp (CLARA, k-means, neural gas etc), Fuzzy based and hierarchical Clustering methods for synthetic and hybrid data [Dimitriadou et al., 2004]. Among these K-Means has been shown to be superior. The main limitation of many of these methods is that the prior inference about number of clusters is essential. Many types of model selection criterion are suggested to overcome this problem, namely Akaike's Information criterion and Schwarz's Bayesian information criterion (BIC) and their variants such as Consistent AIC, AIC_2, AIC_3,

and ICL-BIC etc [Fonseca, 2009]. These methods assess the model complexity by the number of parameters and size of the data, where the model would be constrained to make decision with optimal number of clusters. Bayesian information criterion (BIC) has been suggested to be the most reliable among others. BIC has outperformed other algorithms for selecting the optimal number of clusters in almost all the cases [Fonseca, 2009]. For this reason we have employed BIC in the present work. We have also conducted a comparative analysis with the K-Means algorithm which was shown to be superior to many others discussed in previous study by Dimitriadou et. al.[Dimitriadou et al., 2004]. As it is not feasible to present quantitative analysis of real fMRI data where true activation regions are not known, we compared efficiency of our results with those estimated by statistical parametric mapping (SPM) toolbox and we found our results comparable to those obtained from SPM toolbox. The data used for the analysis and verification was of similar characteristics as discussed in many other studies [Dimitriadou et al., 2004] [Davoudi et al., 2009]; [Backfrieder and Baumgartner, 1996]. In general, the merit of our more robust GMM distribution approach incorporating paradigm time-series correlation based analysis over other work [Davoudi et al., 2009] is that our approach is the reduction in the complexity in time series analysis of fMRI data.

The organization of this paper is as; In Section 2, Formation of simulated data and the properties of real dataset is discussed, then the GMM distribution is formulated, also the steps required for the proposed method are given. In the end of this section the performance evaluation criteria is described. In section 3, superiority of the proposed method is discussed while comparing the results with the other traditional methods. Then finally a conclusion is made in section 4.

2. BOLD signals modelled by GMM

The BOLD signals of a brain represented by voxels in an fMRI image can be assumed as a result of interaction of a large number of neuronal activities in the brain [Buxton et al., 1998]. Therefore, an fMRI voxel value can be represented as a weighted sum of the individual effect of each of these activities. According to the central limit theorem the weighted sum of a large number of independent random variables follows Gaussian distribution. However, for better characterizing BOLD signals in different brain regions, these can be considered as a result of contribution of different sets of neuronal activities. A GMM is a weighted sum of a number of Gaussian distributed components (clusters). As GMMs comprise of characteristics of multiple Gaussian components [Garg et al., 2009; McLachlan and Peel, 2000], these can realistically model fMRI images.

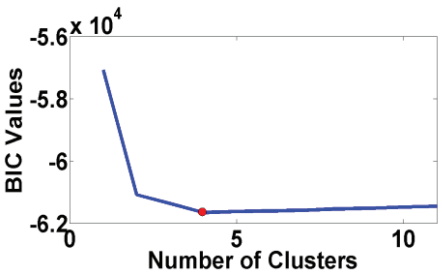


Figure 1. *BIC plot for the correlation coefficients matrix of the real fMRI data. A red mark at 4th number cluster is showing the achieved minimum BIC value.*

Assuming that an fMRI image is modeled by an N component GMM, with Gaussian mixture variable x = $(x_1, x_2 \ldots\ldots x_N)$ generated from N stochastic processes, where a stochastic process n has a probability density function (PDF) $g_n\left(x/\theta_n\right)$, then the PDF for the mixture model would be:

$$g(x|\Theta) = \sum_{n=1}^{N}\left(p_n g_n\left(x/\theta_n\right)\right) \tag{1}$$

Where, $g_n\left(x/\theta_n\right) = \left(\frac{1}{\sqrt{2\pi\sigma_n^2}}\exp\left(-\frac{\left(x-\mu_n\right)^2}{2\sigma_n^2}\right)\right)$ and p_n is the proportion of the n^{th} process in the given mixture, such that $p_n \geq 0$ and $\sum_{n=1}^{N} p_n = 1$, and $\Theta = \bigcup_{n=1}^{N}\theta_n$ is the set of parameters.

The likelihood function for the given mixture model can be defined as:

$$l(x|\Theta) = \prod_{j=1}^{K}\sum_{n=1}^{N}\left(p_n g_n\left(x_j/\theta_n\right)\right) \tag{2}$$

Here, K is the total number of observations and x_j is the j^{th} observation. We would take the logarithm of the likelihood function to make it easier to calculate.

$$L(x|\Theta) = \sum_{j=1}^{K}\left(\ln\sum_{n=1}^{N}\left(p_n g_n\left(x_j/\theta_n\right)\right)\right) \tag{3}$$

So the complete log-likelihood function for GMM can be given as

$$L(x\,|\,\Theta) \;=\; \sum_{j=1}^{K}\left(\ln\left(\sum_{n=1}^{N} p_n\left(\frac{1}{\sqrt{2\pi\sigma_n^2}}\exp\left(-\frac{\left(x_j-\mu_n\right)^2}{2\sigma_n^2}\right)\right)\right)\right) \tag{4}$$

The Bayesian Information criterion (BIC) [Garg et al., 2009; McLachlan and Peel, 2000] is then:

$$\mathrm{BIC} = 2\mathrm{L}(\mathrm{x}|\Theta) + C\,\ln(K) \tag{5}$$

Here, K is the number of samples in data and C is the degrees of freedom for the number of free parameters. Each of the distributed mixture have 3 characteristic parameters, so the degrees of freedom for N distributed components (stochastic processes) is $C = 3N\text{-}1$ [McLachlan and Peel, 2000].

This Gaussian mixture model based clustering with Bayesian Information Criterion is used to find the most stable distribution of the mixture components in the brain volume.

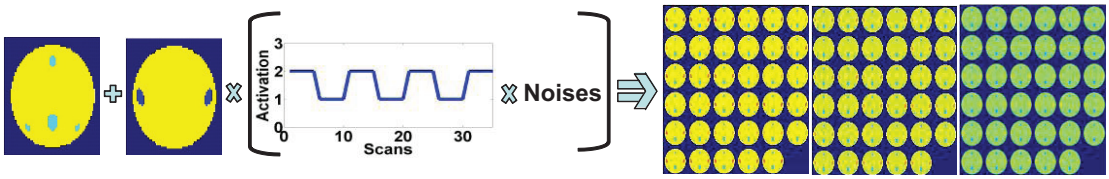
BIC criterion was used to find the optimal number of clusters. We applied the GMM algorithm to obtain the BIC values for many number of clusters to use it as a stopping criterion. Fig.1. shows a BIC value plot for real fMRI data. Here, when the algorithm achieves the minimum BIC value for four clusters and does not get any further lower value, then according to BIC these four clusters should be the optimal clusters.

3. Materials and Methods

3.1 Datasets

We developed two artificial datasets to test the performance of the proposed method. The method used to develop these datasets (cf., Fig. 2.) is similar to the method suggested in [Backfrieder and Baumgartner, 1996]. The datasets were generated by using 35 artificial phantom images, in which we have placed some patches (Fig. 2(b).) to define activation regions. These patches were correlated to the paradigm time-series sequence of '5 off' and '5 on', therefore totaling 35 repetitions of these respective sequences for four and three times in an interleaved manner (Fig.2(c)). We created two types of noise masks. As suggested in [Backfrieder and Baumgartner, 1996], one (Fig.2(f)) used 1% and 3% standard deviations for thermal and random noise respectively and the other dataset (Fig.2(g)) was used to check the performance in heavy noise case by introducing 10 times higher noise (standard deviations of 10% for thermal and 30% for random noise).

We further test our approach using a real dataset (not shown in above figures) provided by the Wellcome Trust Centre for Neuroimaging at University College London (UCL), which is available for download at the SPM tool's website http://www.fil.ion.ucl.ac.uk/spm/data/auditory/. This dataset contains 96 scans of the human brain in 3D (64x64x64 voxels) where repetition time (TR) was 7 seconds. The data was recorded for a paradigm of binaural audio stimuli. The ON and OFF sequence of auditory stimuli was 42 seconds each, meaning that 12 scans represent one complete cycle of stimuli.



(a) (b) (c) (d) (e) (f) (g)

Figure 2. *(a) 35 Noisless head phantoms, (b) Activation Mask and (c) Activation paradigm (d) Thermal and Random Noise; and synthetic or simulated datasets (e) without noise, (f) with 1% thermal and 3% random noise and (g) with 10% thermal and 30% random noise respectively.*

3.2 Proposed approach

The first step is the preprocessing of real fMRI dataset. This step includes removal of the fMRI environment caused background noise, human caused artifacts and any linear trend from the data. There is no preprocessing required for simulated data sets. In the second step, we applied the GMM clustering on both the simulated and the preprocessed real datasets. This step is important to reduce the noise caused variations from the data. After the initial run of the clustering algorithm, we generated the matrix of correlation coefficients [Edwards, 1984] for the given paradigm for each of the datasets. In the last step, the same GMM clustering algorithm was applied again to separate the clusters associated with various regions of activation in brain from the previously obtained correlation coefficients.

We followed the similar steps replacing GMM with the K-Means to make a comparison with the proposed method. The accuracy and precision indices were calculated for our proposed GMM based

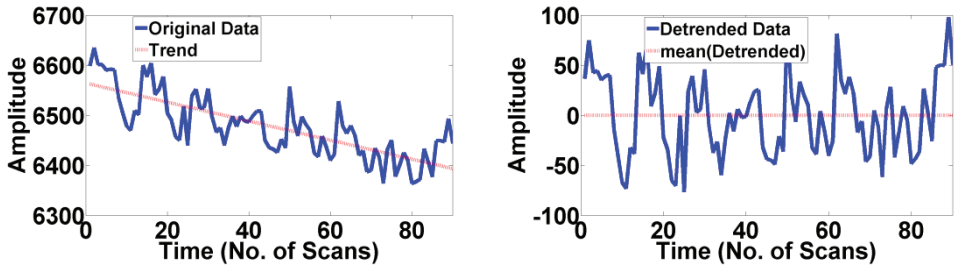
and the K-Means based clustering methods. These indices are similar to the Jaccard's Coefficients with minor modifications to make these equally restricted for truly inactive and truly active regions. MATLAB® software from Mathworks Inc. has been used for all element of this study.

3.3 Preprocessing

We followed the SPM toolbox to preprocess the real fMRI data. This involved realigning, smoothening and warping of the given brain scans. These steps gave us a 3D brain matrix of 53x63x46 for 90 brain scans where initial 6 scans were discarded for the fMRI stabilization error. The preprocessing is a very important step to remove the artifacts caused due to head movement in the electromagnetic environment inside the fMRI scanner.

We also did detrending prior to apply GMM because the detrending can bring the data to baseline. Detrending is basically a process to find the linear trend in data and removing any bias because of this trend. Although, detrending the data can remove the information about the strength of activation as the mean is required to be subtracted from the data however then it helps providing better correlation with the given auditory stimuli [Davoudi et al., 2009]. The plots in Fig. 3. illustrate its advantage, where the trend has been calculated from the time-series for 90 scans of real data at the voxel (47, 28, 23), and then subtracted from the data to detrend it [Edwards, 1984].

Artificial datasets do not require any type of preprocessing because they do not contain any type of misalignment and background noise outside the synthetic brain phantom image.



(a) (b)

Figure 3. *Linear trends from right superior temporal lobe voxel at (47, 28, 23): (a) Before detrending, (b) After detrending*

3.4 Correlation Coefficients

Correlation coefficients are best known for the weights of cross-correlation function, where they represent the ratio and phase for the similarity between two or more sequence of some data or time-series. Positive correlation coefficients denote the similarity in the phase while negative coefficient values indicate opposition in phase [Edwards, 1984]. These coefficients are required to be calculated for the similarity between activated regions and paradigm time-series. The correlation coefficient matrix, as shown in Fig. 4, was first scaled to bring all the values in positive range then the GMM method was applied to classify the activated regions.

For the purpose of comparison, we applied a similar procedure to the other popular clustering algorithm, namely K-Means for the same number of clusters as obtained for GMM classification.

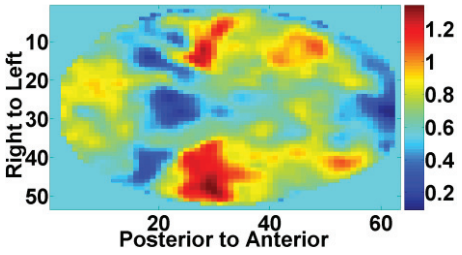


Figure 4. *A 63x53 matrix of corr-coeffs. for the real fMRI data at slice no. 24.*

Table 1. *Simulated datasets*

(a) *Simulated dataset 1*
(1% Thermal Shift And 3% Random Noise)

Algorithm	$J_{Accuracy}$	$J_{Precision}$
K-Means	*99%*	*99%*
GMM	*100%*	*100%*

(b) Simulated dataset 2
(10%Thermal Shift And 30% Random Noise)

Algorithm	$J_{Accuracy}$	$J_{Precision}$
K-Means	*80%*	*72%*
GMM	*86%*	*99%*

3.5 Performance Evaluation

Many of the clustering performance calculation methods have used the Jaccard's coefficient [Dimitriadou et al., 2004; Goutte et al., 1999] as an index of measurement and validation of the calculated results with respect to the known reference template, where the regions of true activity are already known. In this work the aim is to create an algorithm that is capable of finding the true activations and at the same time not misidentifying the regions of activation.

The modified coefficient of accuracy are calculated as the ratio of the sum of true positives (TPs) and True Negatives (TNs) and the sum of true positives (TPs), false positives (FPs), True Negatives (TNs) and false negatives (FNs)[Demirci et al., 2008].

We have estimated the reliability and robustness of the proposed algorithm for those cases where the variation between active and inactive regions is less and thus difficult to identify the each locations of the boundaries. For this we considered the precision index calculation by removing the criterion for true negatives and false negatives. This focuses on the performance that an algorithm can achieve by ideally avoids False Positives (FPs) and does not suggest any region which is not truly active [Dettori and Semler, 2007].

$$J_{accuracy} = \frac{TPs + TNs}{TPs + FPs + TNs + FNs}$$

$$J_{precision} = \frac{TPs}{TPs + FPs}$$

4. Result and Discussion

The results from the simulated and real datasets are presented by using the accuracy and precision indices from modified Jaccard's Coefficients [Dimitriadou et al., 2004; Goutte et al., 1999]. The performance has been calculated for the two artificial datasets with respect to K-Means and for the real dataset with respect to the SPM's results which is considered as a standard and accurate technique used for activation detection.

The two brain images (Fig. 5(a). and 5(b).) and the accuracy and precision results (Table. 1.) are presented for each pair of Simulated1 and Simulated2 datasets. For the low noise dataset, the BIC criterion gave minima for 9 and 3 clusters for the first and the second run of GMM respectively. Similarly, for the high noise dataset algorithm converged for 5 and 2 clusters for respective runs. It can be inferred from the Table. 1., that the GMM method can achieve promising performance even in unusually high noise conditions. The precision index is also very high (99%) which means that these results are reliable. It can be clearly depicted from the figure (Fig. 5.) as well that in both cases GMM outperformed than other method in terms of higher accuracy and reliability in precision values, which is a very significant advantage of the proposed algorithm. By looking into the tables, it is clear that we can satisfactorily estimate the truly activated regions in both the datasets when using GMM, but on the other hand K-Means provides much less accuracy and precision particularly for the high noise case of simulated data-2.

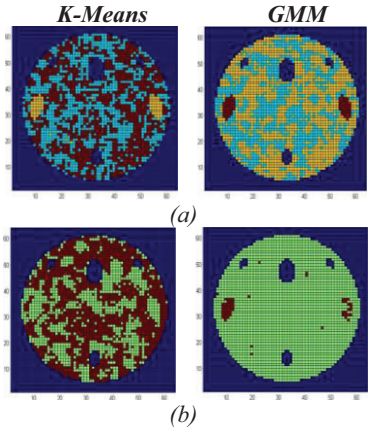


Figure 5. *Activation detected from the K-Means and GMM based clustering for (a) the Simulated data 1 for low noise and (b) the Simulated data 2 for heavy noise.*

Table 2. *Real fMRI dataset*

Comparative results of Proposed Algorithm with SPM

$SPM\ (P_{values})$	$J_{accuracy}$	$J_{precision}$
0.05	*94.4%*	*97.9%*
0.03	*95.2%*	*97.7%*
0.02	*95.5%*	*97.6%*
0.008	*95.3%*	*97.4%*
0.005	*98.1%*	*97.5%*

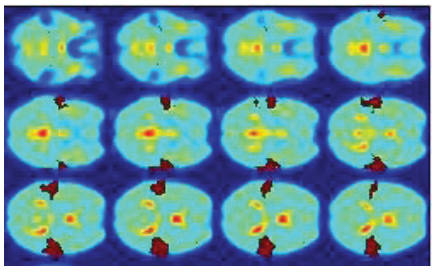
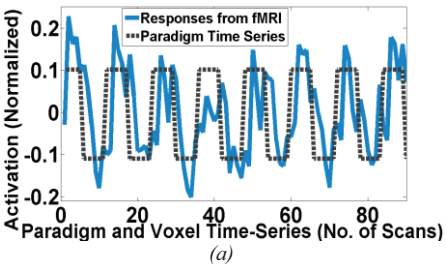


Figure 6. *Few slices (from 12 to 23) masked with activation map (in brown colour).*

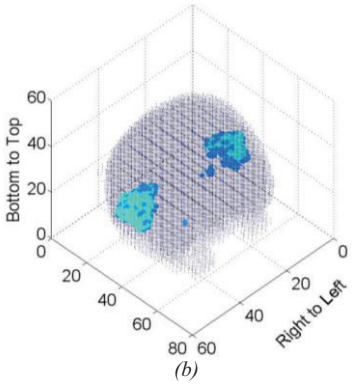
SPM is the most popular tool for fMRI analysis so we have used SPM to analyze the real fMRI data and compared the results with the proposed method (Table. 2.). We applied the standard SPM method as given in its user manual and obtained the positive tailed t-contrast images. Then, the accuracy and precision have been compared (See Table. 2.) with the activation maps generated by the GMM and the SPM toolbox for the given error probability (P value) to validate the results. SPM provides a statistical indication of the regions of activation. BIC gave 40 and 4 clusters for the first and second run respectively. The GMM method has shown a maximum of 98% similarity for a low error probability ($p = 0.005$). In addition the precision was quite high (97.5% approx.) which should be considered as reliable.

An averaged time-series has also been plotted (See Fig. 7(a)) for those clusters which were falling in the activation regions. This time series also shows a good correlation with the paradigm tasks. As the auditory activity has been suggested to be related to the temporal lobe, we can see this in Fig. 6 and

Fig. 7(b), where the activation regions were plotted in 3D. To determine which approach performs the best or identifies the active regions correctly it is necessary to have clinicians mark the datasets for the real human subjects, which has not been done here for either SPM or for the proposed method. However, the consistency and similarity in the performance of the results demonstrate that the proposed GMM approach has potential for activation detection given that the SPM toolbox was considered as a reference for a state-of-the-art method.



(a)



(b)

Figure. 7. *(a) Average of the time-series for the activated voxels, and (b) 3D view of the activated regions (blue) for Auditory fMRI data.*

5. Conclusion

This study illustrates a simple but reliable method based on GMM clustering to analyze fMRI data. We have shown that some of the common methods such as correlation coefficients and detrending along with the GMM clustering method can be used for reliable estimation of activation regions from fMRI data. At the same time, this method was found to provide comparatively higher accuracy as well as precision to other standard methods. These results also show a high affinity with the stimulus time-series which is another advantage of clustering of the whole dataset once before doing any correlation analysis as proposed in this work. The proposed method has been successfully used in various image processing applications; however, its potential as an effective clustering tool in the field of neuroimaging is still unexplored. The main limitation of the proposed method is its applicability for stimulus dependent analysis only. Therefore, as part of future work, our focus will be on the stimulus dependence issues and identifying activation patterns in resting state fMRI data.

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