SOM and MCODE Methods of Defining Functional Clusters in MRI of the Brain*

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Abstract— **Recent advances in analysis of fMRI have established the existence of functional sub-networks in the human brain that are active during the performance of visual, motor, language, and other tasks. We describe two computational methods of delineating functional sub-networks that are active when an individual performs an approach-avoidance paradigm. The paradigm consisted of presentation of images of pleasant and unpleasant faces that were shown to nine volunteers for 10 seconds after a preceding rest period of 50 seconds during which a green computer screen was displayed. The subjects were instructed to squeeze a ball with their right hand if they judged the face to be unpleasant, in which case the unpleasant face would disappear. An fMRI BOLD activation was created and used as input for two different kinds of clustering method: The MCODE algorithm based on graph-theoretical analysis and a Conscious Self-Organizing Map (CSOM). Clustering obtained with both methods was based on the temporal variations of the fMRI BOLD signal activity. Both methods identified distinct regions in the brain which were separated by long-range connections. The MCODE algorithm was supplied with time-courses for activated voxels when performing the paradigm, while the CSOM clustering used all voxels in the brain. Both yielded similar clusters for activated voxels. The combination of MCODE and CSOM presents a new approach in identifying functional subunits in the human brain and warrants further investigation into the subject.**

I. BACKGROUND

Functional magnetic resonance imaging (fMRI), which makes use of the blood-oxygenation-level-dependent (BOLD) signal, is an accepted method to indirectly infer neural activation. Activation maps of the brain can be constructed displaying the level of engagement of brain regions during a goal-directed task or in response to a stimulus.

Research in recent years has focused on revealing the organization and interrelationship of spatially distinct brain regions, *i.e.,* their functional connectivity, by a variety of computational methods including statistical, neural, and graph-based approaches. Clustering, in particular, has emerged as a viable analytical method.

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We compare two clustering techniques. One, MCODE, is based on theoretical graph-network analysis [1], the other involves Conscious Self-Organizing Maps (CSOMs) [2] to extract functional sub-networks or clusters based on the temporal evolution of the BOLD signal intensity of voxels in the brain of subjects when executing the above approach-avoidance paradigm. Both are semi-automated methods and are entirely data driven, *i.e.,* no a-priori assumptions are made about the data statistics prior to the analysis. Identified subnetworks are projected back into the anatomical space of the subject to help identify their function based on their anatomical location. MCODE has been used to identify clusters in protein-protein interaction networks [3]. A variety of SOMs have been widely applied for clustering problems. Previous work on fMRI has been reported with Kohonen SOMs [4], [5], [6], [7], [8], [9], [10], [11], but we do not know of fMRI clustering with CSOM.

II. DATA ANALYSIS APPROACH

A. The Experimental Paradigm

The paradigm used in this work to study the two computational methods consisted of presentation of images of pleasant and unpleasant faces (5 each) that were shown to nine subjects for 10 seconds after a preceding rest period of 50 seconds during which time a green computer screen was displayed. The subjects were instructed to squeeze a ball with their right hand if they judged the face to be unpleasant, in which case the unpleasant face would disappear. The visual stimulus and the clenching of the subject's right hand evoked prominent increases in the BOLD signal bilaterally in the visual cortex and in the left sensory – motor cortex as well as in the frontal lobes, Wernickes area, cingulate cortex, insula, basal ganglia and thalamus. The resulting time variations of the BOLD activation, recorded in fMRI data cubes, are the target of our analyses.

B. Conscience SOM for Clustering fMRI Time Courses

SOMs are competitive unsupervised neural map architectures which, in general, simultaneously accomplish two things by learning. a) Adaptive vector quantization (VQ) of an n-dimensional data manifold $M \subset \mathcal{R}^n$ to approximate the data distribution as well as possible, with a given number of N n-dimensional VQ prototypes $\mathbf{w}_i, i = 1, \cdots N$. The VQ prototype vectors are the weight vectors of the SOM neurons assigned to locations in a rigid grid, the SOM lattice. b) The other aspect is a topological ordering (indexing) of the VQ prototypes $\mathbf{w}_i$ by their similarities on the SOM lattice. This ordering of the prototypes produces an expression of

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the topology of the data manifold M on the SOM lattice (which is usually 2-dimensional). The ordered VQ prototype vectors thus express both the statistical distribution and the topology of the data manifold. The learning procedure that achieves this was proposed by Kohonen in the early 80's and is found in standard texts, *e.g.,* [12]. We use a subsequently developed version, the CSOM [2] because of its ability to enforce equiprobabilistic (maximum entropy) mapping of the data points $\mathbf{x} \in M$ to the VQ prototypes. This facilitates optimal information transfer about the data distribution (with the given N prototypes). For brevity, we give the CSOM learning algorithm and indicate where it differs from the Kohonen SOM.

After initialization of the prototypes $\mathbf{w}_i$, learning consists of many cycles (indexed by t) through the following steps. *Competition*: For a random $\mathbf{x} \in M$ find the closest (winner) prototype $\mathbf{w}_c$:

$$c(\mathbf{x}) = argmin_i(||\mathbf{x} - \mathbf{w}_i|| - bias_i), \;\; i = 1, \cdots, N \quad (1)$$

where the scalar quantity $bias_i$ is computed from the winning frequency F_i of $\mathbf{w}_i$ as $bias_i = \gamma(1/N - F_i)$, and the winning frequencies of all prototypes are updated after winner selection (see details in [2]). (γ is a user-controlled parameter.) The $bias_i$ is the *conscience*, inducing infrequent winners to win more, frequent winners to win less data points. $\gamma = 0$ reduces eq. (1) to the winner selection of the Kohonen SOM. *Weight adaptation*: the winner $\mathbf{w}_c$ and its neighbors in the SOM lattice are moved closer to $\mathbf{x}$.

$$\mathbf{w}_i(t+1) = \mathbf{w}_i(t) + \alpha(t)h_{c,i}(t)(\mathbf{x} - \mathbf{w}_i) \quad (2)$$

The SOM lattice region influenced by the update is defined by the (typically) radially decreasing neighborhood function $h_{c,i}(t)$ centered over the winner. For the Kohonen SOM, it is often a Gaussian, and initially must cover most of the SOM lattice. Both $h_{c,i}(t)$ and the learning rate $\alpha(t)$ must decrease with time t in order to achieve topologically correct ordering of the prototypes in the SOM grid (or, equivalently, topology preserving mapping of the data points). The CSOM has another advantage: it only needs to update the immediate neighbors in eq. (2) because cooperation across the lattice is ensured by the conscience mechanism. This leads to substantial savings in computation. The CSOM's equiprobabilistic behavior was shown in [2] only for 1-dimensional data. For higher-dimensional data [13], [14] provided experimental verification.

Our use of SOMs, in general, differs from most fMRI applications in several ways: We use relatively large SOM lattices, which allows proper representation of many clusters with widely varying sizes, shapes, densities, proximities. Small SOM lattices, especially those where the number of prototypes is very close to the extracted clusters, cannot delineate clusters with irregular properties. We can afford to apply larger lattices because the CSOM mitigates the computational impact of a larger SOM lattice by performing well with small neighborhood. We have developed tools to determine if a learned SOM has topology violations that interfere with correct cluster extraction [13]. While SOMs most likely will have topology violations for fMRI data as pointed out by [9], after sufficient and correct learning most violations are inconsequential for clustering [13] or (the usually small number of severe violations) can be understood and the affected areas excluded from cluster extraction or "hand-repaired". Identification of clusters from a learned SOM is done by identifying groups of similar prototypes in contiguous lattice areas (a.k.a. "clustering the SOM"). This is still mostly achieved by visual inspection of relatively small SOMs in published fMRI analyses. Good examples to the contrary are, *e.g.,* the "node merging" by [15] or [11]. To cluster the SOM prototypes we use interactive visualizations that provide, based on various metrics of the data-space distances of the SOM prototypes, sharper delineation of cluster boundaries than more customarily used visualizations. In this work we relied on the modified U-matrix (mU-matrix) [16] for its easy interpretation and low computational cost. The mU-matrix improves on the popular U-matrix [17] when the number of data points is much larger than the number of SOM prototypes, as in the case of fMRI data. However, its simplicity forces conservative cluster extraction, leaving prototypes unlabeled at boundaries and consequently a number of data points unclustered. To remedy this we will also apply our more advanced tools [13] following this proof of concept study.

C. Clustering fMRI Time Courses With MCODE

To identify functional sub-networks, the Molecular Complex Detection (MCODE) algorithm as implemented in the Cytoscape ClusterViz plugin was employed (http://code.google.com/p/clusterviz-cytoscape/). This algorithm identifies locally dense regions in a network graph with a node-weighting scheme. The algorithm uses the concept of k-cores of the network graphs, which are parts of the graph where every node is connected to other nodes by at least k edges. From this definition, it is apparent that the highest k-core is the most densely connected region of a graph. MCODE consists of three stages:

1) *Network Weighting*
   The highest k-core for a node is identified for all its neighbors. For this k-core, its density is calculated as the number of edges divided by the number of possible edges. A score for this node is then calculated as the product of k times the density.
2) *Complex Detection*
   Starting with the node with the highest score (seed node), the algorithm moves outward including connected nodes until a threshold score (as percentage of score of the seed node) is reached.
3) *Optional Post-processing*
   Optionally, 2-core nodes can be removed or additional nodes can be included in the cluster if their neighborhood density is larger than a certain ("fluff") parameter. None of these post-processing options were used.

The MCODE algorithm was chosen to identify functional brain sub-networks because compared to other clustering techniques only nodes with a high connectivity (*i.e.,* high

synchronicity) are segmented into clusters and nodes with low connectivity (*i.e.,* low synchronicity) are discarded. Another advantage is the unique allocation of certain voxels to a certain brain sub-network. The clusters obtained with MCODE can therefore be considered to each consist of the most highly synchronized voxels thereby emphasizing the separation of the fMRI activation into functionally distinct units.

III. RESULTS

We applied CSOM clustering in a pilot study using data from a single subject who was shown only three unpleasant faces. Clustering in all nine subjects was studied with MCODE. With CSOM clustering we used all available voxels from the entire brain (*i.e.,* we did not pre-select voxels with activation levels that exceeded some threshold). For the image data available for our subject, this yielded approximately 133,000 time courses to process, in 82 brain slices. The time courses are the n-dimensional input vectors for clustering, where n = 62. We subjected the fMRI data cube to preprocessing consisting of several customary steps that proved beneficial for these data: geometric rectification, motion correction, and temporal smoothing. The effects of these procedures versus some others not included in the preprocessing were experimentally determined and described by [18]. As an important aspect, the original voxel size of 3.3 x 3.3 x 5.0 mm^3 was transformed to 2 x 2 x 2 mm^3 voxels by the geometric rectification. The time courses that are input to the CSOM come from these transformed voxels.

Since SOM learning is a summarizing and noise mitigating process, it is not limited by the number of data points (time courses) as severely as, for example, graph-based algorithms which operate on matrices of pair-wise distances of points. The ability of SOMs' to explore all data points for similarity groups holds the potential of discovering previously unknown activation / deactivation patterns. We used a 40 x 40 SOM, a size sufficient for expressing the relevant properties of the 50 or so clusters we found [18]. It provided an approximately 100-fold volume reduction for this data set while preserving the noise-reduced representation of the time-courses in the VQ prototypes. As a next step, the average time courses of the identified clusters may be further analyzed to study correlations between functional areas of the brain.

A representative image showing several SOM clusters that cover known functional areas, is displayed in Fig. 1. Only a few selected clusters are shown here in order to facilitate comparison with the MCODE results. AFNI [19] was used to display the clustering results superimposed on the anatomical background.

The MCODE clustering algorithm succeeded in identifying functional subnetworks within the fMRI BOLD activation map in all nine subjects. A typical example is shown in Fig. 2. Two different kinds of subnetworks could be distinguished, focal subunits, which were limited to specific anatomical regions, in this case, visual cortex–(red and bright green) and motor cortex–(orange) and distributed subunits

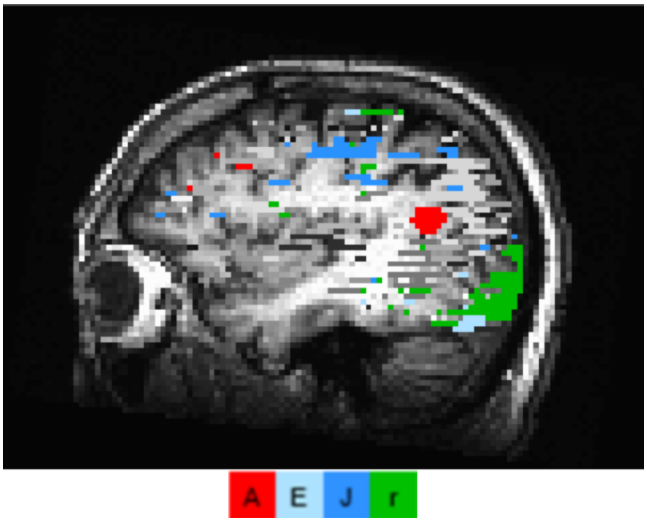

Fig. 1. Selected SOM clusters in sagittal slice 31: Clusters are superimposed on the anatomical gray-scale background, and shown in AFNI. The striping noise, present in this data set, has been suppressed for clarity. The clusters, keyed by the color wedge, coincide with functional areas as follows. A: Wernickes area J: pre- and postcentral gyri E, r: visual cortex

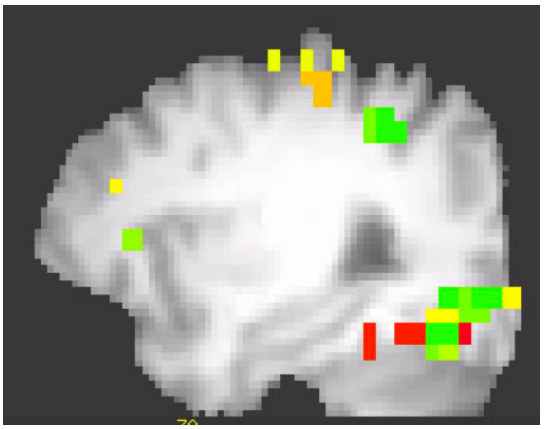

Fig. 2. Clusters identified by the MCODE method in another subject (lateral sagittal slice). Focal subnetworks: visual cortex (red and bright green) and motor cortex (orange). Distributed subnetworks spanning several anatomical regions (yellow and dark green).

(yellow and dark green) which spanned several anatomical regions. These findings are in agreement with the small world behavior postulated for the functional connectivity of the human brain, *i.e.,* highly connected focal regions that communicate with each other via long range connections.

Computation time for graph models, including MCODE, are more dependent on the number of data vectors than vector quantization processes (such as the SOM). The size of the initial graph, which is segmented to obtain clusters, scales quadratically with the number of fMRI time courses, and can create challenges for memory use and computing time.

To probe the interaction of brain regions when performing the paradigm introduced above, MCODE analysis was limited to activated voxels (resized to 5 x 5 x 5 mm^3) identified by a Student t-test group analysis of the fMRI BOLD activation maps from the nine subjects after transformation into a standard space (Talairach atlas).

Both SOM and MCODE identified synchronized regions in the brain based on the time course of the BOLD signal intensity. While the CSOM analyzed voxel signal intensities of the entire brain, MCODE as applied here focused on voxels which were activated when performing the paradigm of interest. For activated voxels both approaches appear to have found very similar functional units. These two independent complementary methods may provide a valuable tool set to study brain activation in fMRI data.

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