Model Based Spatial and Temporal Similarity Measures between Series of Functional Magnetic Resonance Images

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Abstract. We present a method that provides relevant distances or similarity measures between temporal series of brain functional images. The method allows to perform a multivariate comparison between data sets of several subjects in the time or in the space domain. These analyses are important to assess globally the inter subject variability before averaging subjects to draw some conclusions at the population level. We adapt the *RV-coefficient* to measure meaningful spatial or temporal similarities and use multidimensional scaling for visualisation.

1 Introduction

Functional brain imaging has been an extremely active field of research during the last fifteen years, first with Positron Emission Tomography and more recently with the advent of functional Magnetic Resonance Imaging (fMRI) because of their potential for the understanding of the human brain functions organisation.

An fMRI experiment consists for one subject, in the acquisition of a large number (100 to 1500) of 3D volumes (64x64x32) measuring a parameter related to the brain neural activity in each voxel. The subject is submitted to a experimental paradigm consisting in different conditions designed to study a particular brain system (e.g. memory, language, vision ...). A entire study consists in the acquisition of data for approximately 10 to 30 subjects.

The most challenging problem of the neuro-imaging field is to extract the relevant information in this vast amount of data. It is especially important to be able to draw some conclusions from the study across subjects, therefore at the *population* level. This is complex because of the anatomical and functional differences between subjects. A standard way to analyse multi-subjects data is to summarise the relevant information per subject in one brain volume (for instance the average difference between condition A and B) and use the inter subject variance to infer results at the population level (the so-called random effect group analyses) [8].

T. Dohi and R. Kikinis (Eds.): MICCAI 2002, LNCS 2489, pp. 509–516, 2002.

These multi-subjects analyses are based on the assumption that subjects are drawn from a single population, and therefore assumes some homogeneity between subjects. Clearly, this assumption may not be verified. Subjects are not necessarily homogeneous in the spatial domain (different brain regions are activated) or in the time domain (the time courses of the brain responses are different for a common experimental paradigm for different subjects). This non homogeneity can be due to many factors, including different strategies across subjects, or acquisition differences that cannot be controlled. If the group studied is not homogeneous this may lead at best to less efficient analyses and at worst to erroneous results and interpretations [8].

Although this topic is clearly of major importance for the analysis of fMRI data, it has so far received little attention. This is probably due to both the complexity and the amount of data to be analysed that depend on the experimental paradigm and the noise characteristics.

In this paper, we introduce a general technique to derive relevant distances between series of 3D fMRI brain images in order to assess their similarity in the time or spatial domain. The technique is based on the *RV-coefficient* adapted for this purpose and the use of the multi-dimensional scaling to visualize the group structure. It is flexible, and allows to compare data sets (e.g. subjects) in a the light of a specific question relating to the experimental paradigm in a reasonable computational time.

In the following, we first briefly review possible distances or similarity measures and discuss their pros and cons in relation with their application to neuroimaging data. In the section 2.2 we introduce the selected distance based on the RV-coefficient. In section 2.4 we present the experimental data set and some results on the differences in the spatial and temporal domains between subject for this fMRI study.

2 Methods

2.1 Candidate Similarity Measures or Distances Given the Data and Problem Specificities

In this section, we briefly present an overview of measures or distances that could be used for comparing series of images. We first review some characteristics of our data and some desirable features for the distance measures.

Data and Problem Specificities.

(C_1) The data originating from different subjects may have different number of voxels. Conversely, if images are put in a common spatial reference (realigned to an atlas) the number of scans (time dimension) may not be the same across subjects.

(C_2) When addressing the temporal (resp. spatial) aspect of the data, the mean image (data averaged across time, resp. the mean time course) does not convey any meaningful information.

(C_3) Time series at different position in the brain may have different variance due to physiological reasons. The distance looked for should be insensitive to a voxel per voxel variance scaling and to the overall data variance.

(C_4) Estimated covariance structure in the time domain can be inverted (although this may not be advised given the estimation noise). This inversion is not possible in the spatial domain.

(C_5) Data may have non Gaussian components.

(C_6) Similarity measure computations have to be fast enough to be used by clinicians or brain scientists. This is a challenge given the size of the data.

(C_7) The measure should be able to include information from the experimental paradigm and from the known noise characteristics of the data. This is mainly addressed in section 2.3 through the modeling of the experimental variance due to the paradigm.

Some Candidate Similarity Measures. In this section, we only address the comparison in the time domain and mention the comparison in the space domain when dimensions can not be simply swapped. The presentation follows an "incremental" line of thought. Distance measures successively address different (more complex) aspects of the data.

Let Y_i be the sample data for the ith subject represented as a matrix with n_i rows (voxels dimension) and t_i columns (scans or time dimension) with $n_i \gg t_i$. The corresponding (time x time) sample covariance matrices are denoted Σ_i for the ith subject. Σ_{i+j} denotes the pooled covariance matrix between the ith and the jth subjects.

• *Mahalanobis distance* D^2. This widely used distance is most meaningful when data are multi-normal and measures the weighted distance between data sets means [1]. It relies on the inversion of the (common) covariance matrix of the data and is computed with $D^2 = (\overline{Y}_i - \overline{Y}_j)^t \Sigma_{i+j}^{-1} (\overline{Y}_i - \overline{Y}_j)$. It can be tested for the null hypothesis that the two groups have the same mean through an F-test. Clearly, this distance can only be computed in the time dimension (cf (C4)) and can not reflect complex links.

• *Covariance equality test and distance.* Once the data means have been compared, a likelihood ratio statistic such as the *Box'M* can be conducted to test the hypothesis that covariance matrices are equals [1]. The issuing B coefficient ($B = e^{\frac{-M}{df}}$) can be used as a distance measure between covariance matrices. Two data sets have similar density volumes if B is close to one. This test is meaningful with multi-normal data but is not robust otherwise (cf (C5)).

• *Canonical Correlation Analysis (CCA).* CCA is used to identify linear relations between two data sets [1] found to have an overall link with the covariance distance. CCA finds successive sets of pair of linear combinations (one canonical eigenvector per data set) that explain best this relation and the corresponding canonical roots inform about the relation strength. It is therefore more general than the Mahalanobis distance since the search of the linear link is done in a greater space. However, it relies on the computation of the inverse covariance

matrix of the data in the time and space domains, while the latter is not tractable (cf (C4)).

• *Krzanowski's method :* One problem with CCA is that it explicitly searches for linear links between two data sets corrected for their covariance structures. This might not be the most relevant comparison between fMRI data series. An alternative to this can be found in the seminal work of Krzanowski [4], who suggests to compare data sets based on the computation and comparison of the eigen-components of their covariance matrices. Comparison is performed by computing angles between sub-spaces spanned by their first principal components. The drawbacks of these methods are those of PCA analysis, they are not scale invariant and highly depend on the pre-processing steps (centering, normalisation,...), (cf (C3)).

• *Distribution distance :* While the previous methods hold in general under multi normal assumptions and linear links, it is easy to define distances that are more general through the data sampled distributions. Several authors [5,7] have proposed such measures, related to mutual information, the expression of which is simplified if the data are normal. For example Matusita derives a separability measure between densities [7]. The difficulty lies in the efficient computation of probability densities (C7). Nethertheless, we plan to investigate these similarity measures in the future.

2.2 The *RV-coefficient* as a Similarity Measure.

The *RV-coefficient* was first described by Robert [9] for evaluating multidimensional linear association between several data sets. For each data sets, the matrix: $S_i = Y_i^t Y_i$ (a time by time $t_i \times t_i$) can be considered as a point in $R^{{t_i}^2}$. The comparison of two data sets i, j in this space can be made by computing the *RV-coefficient* as follow

$$RV_{i,j} = \frac{trace(S_i {S_j}^t)}{\sqrt{trace(S_i {S_i}^t)}\sqrt{trace(S_i {S_i}^t)}} \tag{1}$$

Escouffier [9] considers each S_i as an operator and derives an inner product (and a distance metric) based on the Hilbert-Schmidt norm: $|A|_2 = \sqrt{trace(A^t A)}$, for a given matrix A. In this context, the *RV-coefficient* is seen as the cosine of the angle between S_i and S_j. The *RV-coefficient* can also be considered as a multivariate extension of the classical Pearson correlation coefficient. Lavit showed that if $RV_{i,j}$ is one, then one can derive eigen-components of data set i from data set j through an homothetic transformation [6].

For comparing fMRI data sets, it has several advantages. It reflects the linear link between data sets covariance but is normalised for the absolute amount of variance in the data (C3). Second, it can be used in both the spatial and the temporal domain (C1) and (C2). Third, it is fast to compute (C6). Fourth, it does not necessarily require the inversion a covariance structure, although such normalisation can be included when possible (C4). Lastly, it should be robust with non gaussian data (C5), and is easily adaptable to compare data

sets considering a specific question (that can be put in the framework of standard fMRI analysis (C7)). This is the subject of the next section.

2.3 Model Based *RV-coefficient* in fMRI Analysis

Adapting the *RV-coefficient*. The analysis of fMRI data generally relies on the specification of an *a priori* model describing the expected time courses derived from the experimental paradigm. The model consists in a time by parameter matrix X $(t \times p)$, assumed to explain all deterministic temporal variations of the data. A fMRI analysis consists in linearly regressing the model at each and every voxel, and in testing a contrast of the parameters reflecting the neuroscience question under study. So called statistical parametric maps are constructed with the test statistic attributed at each voxel. The model X, used to analyse the data, can be introduced in the similarity measure. Rather than considering for each subject the covariance matrix estimated from the raw data, it is generally more meaningful to consider the covariance matrix between the data and the model (C7). This allow to compare subjects data sets depending on *how well the model X predicts the data*. This is obtained through the modified *RV-coefficient* computed with $S_i = Y_i^t X X^t Y_i$, a $(p \times p)$ matrix.

More often than not, only a sub-space G of the model X is of interest (for instance the subspace representing the difference between experimental conditions). In such a case, both model and data can be projected onto this subspace. The model X becomes X_G and the data Y becomes Y_G, leading to a *RV-coefficient* tuned for the specific question represented by G.

The *RV-coefficient* allows the introduction of two metrics, M and N, respectively for the column (temporal) and row (voxels) spaces, defined respectively by:

$$M^{-\frac{1}{2}} = (X_G^t V X_G)^{-1/2} \tag{2}$$

$$N^{-\frac{1}{2}} = \mathrm{diag}\{\hat{\sigma}_1^{-1}, \hat{\sigma}_2^{-1}, \cdots \hat{\sigma}_n^{-1}\} \tag{3}$$

The metric M corrects for the scaling differences in the model regressors and takes into account the temporal correlation represented by the (estimated or assumed) time by time matrix V. The diagonal elements of the metric N are the inverse of the square-root of the residual variances estimated for each voxel. This leads to compute S_i with : $Y_i = M^{-\frac{1}{2}} X_G^t Y_G N^{-\frac{1}{2}}$.

Spatial and Temporal Similarity Measures. We have so far constructed the S_i matrices as a time by time cross-product matrix. If all Y_i have identical number of rows, the same computation can be made in the voxel space considering $S_i = Y_i {Y_i}^t$, a $n_i \times n_i$ matrix. This leads to the same formulation of the *RV-coefficient*, and provides a similarity measure in the space domain.

Computational Cost. The method based on *RV-coefficient* involves the computation of the trace of matrices. Due to the large amount of data in an fMRI

experiment computation and data storage can be very cumbersome. Our implementation is designed to avoid direct computation of the products between the matrices (using the Hadamard product). Only one pass through the data simultaneously for all the subjects is needed. Whenever possible, computations are performed in the model parameter space which reduces considerably computational cost. For the set of data presented in the following, computation time was of the order of a few minutes on a Sun workstation (.8Ghz, 512M RAM).

Results Visualization. The two by two similarity measures $R_{i,j}$ are first transformed into a distance measure with with $d_{i,j} = \sqrt{2(1 - R_{i,j})}$. A symmetric distance matrix $(d_{i,j})$ with $k(k-1)$ distinct values is constructed and processed through Multidimensional Scaling (MDS) [2] to get the best *Euclidean representation* of these distances.

2.4 Experimental Paradigm and Data

Data are obtained from nine subjects who underwent a calculation task and a control task [10]. During the fMRI scanning, six blocks of 26s each alternating computation and control tasks were presented. Each subject performed two such sequences. A total of 186 scans (64x64x28 voxels per scan) were acquired per subject.

The (linear) model used for analysing the data consisted in 3 regressors per condition (computation and control) derived from a standard hemodynamic response. Within this model a sub-space of interest was formed to highlight activations induced by the calculation task relatively to the control task.

3 Results and Conclusion

This section presents the results of the temporal and spatial comparisons for the nine subjects data sets using the adapted *RV-coefficient* to investigate inter-subject distances with respect to the comparison between activation and control. For this purpose, we use equation (1) and formulas in section 2.3 with a subspace G that spanned the expected activation space.

Temporal Distances. Figure 1 shows a 2D MDS representation of the temporal distance between subjects. In this case, we observe that although subjects can not be easily divided into more than one group, subjects 3 and 4 lie far apart from the group center of mass. This indicates a different temporal behaviour such that these subjects should probably be considered as outliers.

These temporal differences between subjects are observed in figure 2. This figure shows first components of the output of a Multivariate Linear Model (MLM) analysis described in [11]. Components summarise the temporal behaviour and are clearly seen to be similar for two subjects (8,9) close on figure 1. Conversely, those patterns are clearly different from subject 4 component, a subject that is also found far from subject 8 and 9 on figure 1. This result is in accordance with

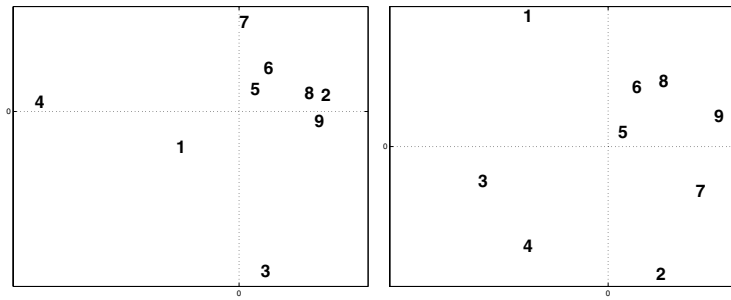

Fig. 1. Inter-subject variability in terms of temporal (left panel) and spatial (right panel) distances.

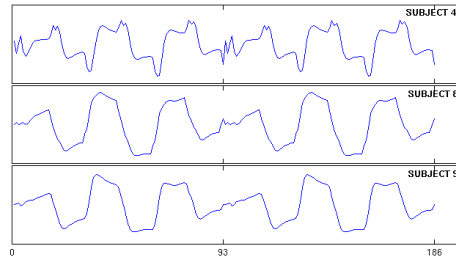

Fig. 2. Illustration of the temporal variability observed in figure 1 (left) with the first temporal MLM eigencomponents.

an other study [3] that showed the particular temporal behaviour of those two subjects data.

Spatial Distances. Figure 1 (right panel) shows a 2D MDS representation of the spatial distance between subjects. In this plot, part of the inhomogeneity found in the temporal domain is observed again. In particular, subjects number 1, 3, and 4 are found to be the farthest from the group center. This spatial distance is illustrated on a statistical parametric map showing the activation effect in figure 3 (one axial slice for each subject). Distances between the subject 4 and subjects 8 and 9 are mainly reflected by a greater activity in the left parietal lobe for subjects 8 and 9.

4 Conclusion

We have developed an easy to use, fast and flexible method to analyse the similarity of different subjects fMRI time series in the temporal or spatial domain, taking into account the specificities of these complex data. The method has the potential to detect outliers in the time or spatial before performing any kind of group analysis (resp. in the time or space domain), or to detect any particular

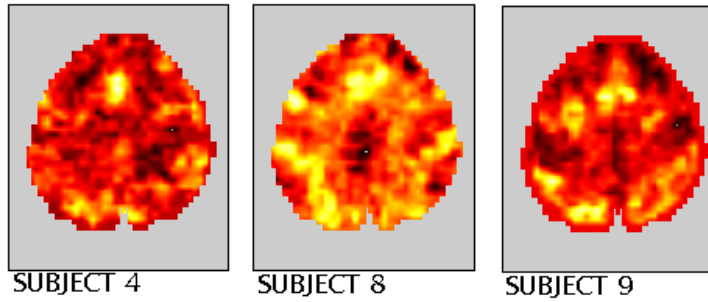

Fig. 3. Illustration of the spatial variability observed in figure 1 (right) on an axial slice.

grouping in the data that would invalidate such group analyses. In the future, the method will be coupled with clustering and outliers detection tests. The method is likely to find a number of application in clinical (e.g. helping for the diagnosis psychiatric diseases) or neuroscience context (e.g. relating the distances with genetic or phenotypic information).

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