# Assimilating knowledge from neuroimages in schizophrenia diagnostics

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**Abstract**

The aim of this article is to propose an integrated framework for classifying and describing patterns of disorders from medical images using a combination of image registration, linear discriminant analysis and region-based ontologies. In a first stage of this endeavour we are going to study and evaluate multivariate statistical methodologies to identify the most discriminating hyperplane separating two populations contained in the input data. This step has, as its major goal, the analysis of all the data simultaneously rather than feature by feature. The second stage of this work includes the development of an ontology whose aim is the assimilation and exploration of the knowledge contained in the results of the previous statistical methods. Automated knowledge discovery from images is the key motivation for the methods to be investigated in this research. We argue that such investigation provides a suitable framework for characterising the high complexity of MR images in schizophrenia.

**keywords:** Multivariate statistical classification, foundational ontologies, neuroimage, schizoprenia.

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## 1 Introduction

Schizophrenia is a mental disorder characterised by symptoms of psychosis (*e.g.*, delusions and hallucinations), apathy and social withdrawal, as well as cognitive impairment [30]. Although the causes of schizophrenia are unknown, both genetic [25] and environmental factors (including biological - *e.g.*, prenatal infection and obstetric complications - and psychosocial factors) appear to play a role in its etiology. However, these factors are obviously not sufficient to the emergence of schizophrenia, probably exerting their effect in a stress-vulnerability model of disease [31].

The established illness has been shown to be associated with structural and functional brain abnormalities, mainly in prefrontal and temporal lobes, findings largely due to recent advances *in vivo* Magnetic Resonance Imaging (MRI) techniques [41]. However, none of the brain abnormalities found in schizophrenia are characteristic of the disease, and no neuroanatomical finding alone has a diagnostic value for schizophrenia. It is conceivable that the abnormality in brain development is not restricted to a determined brain structure, being rather diffuse, affecting the different brain structures simultaneously. In an attempt to overcome these difficulties, in a previous study [21] we studied 12 Computed Tomography (CT) parameters in 30 schizophrenic patients and 30 sex- and age-matched controls, and evaluated the data simultaneously through multidimensional scaling (MDS). MDS offers a graphic representation in which subtle deviations in the different CT parameters can be detected, independently of predetermined criteria for the definition of abnormalities. MDS distinguished 13 patients from the controls as having deviant values in one or more CT parameters. Five of these patients were first-onset schizophrenics. Our results suggest that the use of multidimensional techniques may improve the sensitivity of neuroanatomical data to identify more precisely schizophrenic patients and to provide information of the possible influence of the structural brain abnormalities upon the course and prognosis of the disease.

The purpose of this paper is to investigate multidimensional techniques on neuroanatomical data through the application of multivariate statistical methods to extract the most discriminant features from neuroimages of schizophrenic patients. Further we discuss how these features could be assimilated into a bio-ontology constructed over spatial regions, size constraints and a semantics based on multiple standpoints.

## 2 Related work

The increasing resolution of 3D anatomical and functional images nowadays has allowed the visualisation of neuroanatomical structures of the human brain with impressive detail. For example, the widely used method of MRI gives good soft-tissue contrast with high resolution, that is, commonly less than 1mm [2]. However, depending on the neurodegenerative disorder and its progression, neuroanatomical changes may be subtle, diffuse, or topologically complex to be detected by simple visual inspection [2]. Thus, in the last years, a considerable amount of effort has been devoted to the design of computational methods for morphological analysis of the human brain. Traditionally, such analysis of brain images has been based either on the definition of regions of interest given some a *priori* hypothesis or on voxel-wise measurements with little prior knowledge ([44,3]). In practice, these methodologies have shown yet limitations in their ability to identify previously unexplored relationships between control and patient populations.

In recent years, statistical pattern recognition methods have been proposed to classify and analyse morphological and anatomical structures of MR images between a reference group of images and the population under investigation [23]. Most of these techniques work in high-dimensional spaces of particular features such as shapes or statistical parametric maps and have overcome the difficulty of dealing with the inherent high dimensionality of medical data by analysing segmented structures individually or performing hypothesis tests on each feature separately. As a consequence, changes that are relatively more distributed and involve simultaneously several structures of the pattern of interest might be difficult to detect, despite the possibility of some statistical learning methods [23] of extracting multivariate differences between image samples of patients and controls.

The principal motivation of this multivariate methodology is to analyse all the data simultaneously rather than segmented versions separately or feature-by-feature. This approach has been specially designed for extracting discriminative information from high dimension, low sample size problems. Although the multivariate statistical methods are capable of separating different classes (or models) according to their discriminant components, they are not suitable for addressing the qualitative aspects of these models. To cope with this issue there is a need of an ontology rich enough to describe the evidences shown in MRI images and general enough to allow consistent cross-fertilisation among magnetic resonance images and other methods for assessing the state of a brain with mental disorders (e.g. FMRI, EEG etc). In general, evidences of brain diseases are noted in neuroimages as spatial regions that differ in their spatial extent from the equivalent regions in the control group. This calls for an ontology having spatial regions as the basic entities and that could ac-

commodate a qualitative description of some attributes of the regions. The formalisation of elementary spatial entities and their qualities is the goal of qualitative spatial reasoning (QSR) [46,13].

One of the best known QSR theories, for instance, is the Region Connection Calculus (RCC) [32,12,34], which is a first-order axiomatisation of space based on regions and on the connectivity relation between spatial regions. The most cited subclass of RCC relations (known as RCC-8) contains the following eight jointly-exhausted pairwise-disjoint (JEPD) relations [2] : $DC(x, y)$, which stands for "region $x$ is disconnected from region $y$"; $EQ(x, y)$, for "$x$ is equal to $y$"; $PO(x, y)$, for "$x$ partially overlaps $y$"; $EC(x, y)$, for "$x$ is externally connected with $y$"; $TPP(x, y)$, for "$x$ is a tangential proper part of $y$"; $NTPP(x, y)$, for "$x$ is a non-tangential proper part of $y$"; $TPPi/2$ and $NTPPi/2$ are the inverse relations of $TPP/2$ and $NTPP/2$ respectively. Other representations of spatial knowledge include theories about shape [38,29,11], distance [26,5], position [10] amongst others [13].

Further in this work we describe the Basic Inclusion Theory (BIT) [15], a region-based spatial theory for formalising biomedical ontologies, and discuss how it could be extended to cope with providing a formal description of the neuroanatomical data within neuroimages. It is worth pointing out that one of the purposes of BIT is to clear the spatial structure underlying the elements of two ontologies for human anatomy, the FMA [35] and the GALEN [1].

The next section discusses a general multivariate statistical approach to identify and analyse the most discriminating hyperplane separating two populations.

## 3 Knowledge extraction: multivariate statistics

In the generic discrimination problem, where the training sample consists of the class membership and observations for $N$ patterns, the outcome of interest fall into $g$ classes and we wish to build a rule for predicting the class membership of an observation based on $n$ variables or features. However, statistical discrimination methods are suitable not only for classification but also for characterisation of differences between a reference group of patterns and the population under investigation. For example, in clinical diagnosis we might want to understand underlying causes of medical data by exploring the dis-

[2] I.e., there is no relation between the domain objects that can not be described by a combination of the JEPD set (meaning the set if jointly exhaustive) and no relation in the JEPD set can be defined in terms of the remainder relations (meaning the set is pairwise disjoint).

criminating hyperplane found by a statistical classifier using image samples of patients and controls.

Before we can analyse the MR images, we need to map all images into a common atlas coordinate system. This pre-processing step, called spatial normalisation or image registration, is essential because the construction of the multivariate statistical model relies on anatomical correspondences when comparing patterns across subjects. There are a variety of registration techniques that can be used to warp each image to a common reference or template [9,36,40,47]. We have used a standard Statistical Parametric Mapping [19] T1-MRI template [28], based on 152 health subjects from the Montreal Neurological Institute, to spatially normalise the images. This procedure has essentially two goals: (a) to reduce variability due to size, position and orientation of the brain shape [36,49] and (b) to reduce variability due to differences in the brain shape. Each registered image then forms a pattern of interest consisting of $n$ attributes or voxels which is then converted to an n-dimensional feature vector. For this feature representation to make sense in classification problems, we are making implicitly the assumption that two images that look like one another correspond to two close points in the high dimensional image space. I.e., the effectiveness of the extracting information techniques would be determined by how well patterns from different classes can be separated.

The n-dimensional resulting images are then projected from the original vector space to a lower dimensional space using the well-known Principal Component Analysis (PCA) [20]. There are a number of reasons for using PCA to reduce the dimensionality of the original images. PCA is a linear transformation that is not only simple to compute and analytically tractable but also extracts a set of features that is optimal with respect to representing the data back into the original domain. Moreover, using PCA as an intermediate step will reduce dramatically the computational and storage requirements for the subsequent linear discriminant covariance-based method. Since in our application of interest the number of training patterns $N$ (or images) is much smaller than the number of features $n$ (for instance: voxels), it is possible to transform data in a way that patterns occupy as compact regions in a lower dimensional feature space as possible with far fewer degrees of freedom to estimate. Although much of the sample variability can be accounted for by a smaller number of principal components, there is no guarantee that such additional dimensionality reduction will not add artifacts on the images when mapped back into the original image space. Since one of our main concerns here is to map the subsequent classification results back to the image domain for further knowledge assimilation, we must be certain that any modification on the images, such as blurring or subtle differences, is not related to an *incomplete* or perhaps *misleading* feature extraction intermediate procedure [49]. Therefore, in order to reproduce the total variability of the samples, we have composed the PCA transformation matrix by selecting all principal components with non-zero

eigenvalues.

A Maximum uncertainty Linear Discriminant Analysis (MLDA) approach [53] has been applied next to find the best linear discriminant features on that PCA subspace. The primary purpose of LDA is to separate samples of distinct groups by maximising their between-class separability while minimising their within-class variability. It is well known, however, that the performance of the standard LDA can be seriously degraded if there are only a limited number of total training observations $N$ compared to the dimension of the feature space. Since the within-class scatter matrix $S_w$ is a function of $(N - g)$ or less linearly independent vectors, where $g$ is the number of groups, its rank is $(N - g)$ or less. Therefore in the current situation where the number of training patterns is small with respect to the number of features, $S_w$ might be singular or unstable and the standard LDA cannot be used to perform the task of the classification stage.

The main idea of the MLDA approach is to stabilise the within-class scatter matrix $S_w$ with a multiple of the identity matrix. It is based on the maximum entropy covariance selection method that Thomaz and Gillies [48,53] have developed to improve classification performance on limited sample size problems [48]. Since the estimation errors of the non-dominant or small eigenvalues are much greater than those of the dominant or large eigenvalues, the MLDA's algorithm expands the smaller (less informative) eigenvalues of $S_w$ and keeps most of its larger eigenvalues unchanged. It is a straightforward method that overcomes both the singularity and instability of the within-class scatter matrix when LDA is applied in limited sample and high dimensional problems.

We can divide the design of the PCA+MLDA multivariate approach into two main tasks: classification (training and test stages) and visual analysis. In the classification task the principal components and the maximum uncertainty linear discriminant vector are generated. As illustrated in Figure 1, first a training set is selected and the average image vector of all the training images is calculated and subtracted from each pre-processed image vector. Then the training matrix composed of zero mean image vectors is used as input to compute the PCA transformation matrix. The columns of this $N \times m$ transformation matrix are eigenvectors, not necessarily in eigenvalues descending order. Note that we have retained all the PCA eigenvectors with non-zero eigenvalues. The zero mean image vectors are projected on the principal components and reduced to m-dimensional vectors representing the most expressive features of each one of the pre-processed n-dimensional image vector. Afterwards, the $N \times m$ data matrix is used as input to calculate the MLDA discriminant eigenvector. Since we are assuming only two classes to separate, there is only one MLDA discriminant eigenvector. The most discriminant feature of each one of the m-dimensional vectors is obtained by multiplying the $N \times m$ most

expressive feature matrix by the $m \times 1$ MLDA linear discriminant eigenvector. Thus, the initial pre-processed training set consisting of $N$ measurements on $n$ variables, is reduced to a data set consisting of $N$ measurements on only 1 most discriminant feature.

The other main task performed by this two-stage multivariate statistical approach, and used as input to the ontology described in Section 4, is to visually analyse the most discriminant feature found by the maximum uncertainty method. According to Figure 1, more specifically from right to left in its Visual Analysis frame, any point on the most discriminant feature space can be converted to its corresponding n-dimensional image vector by simply: (1) multiplying that particular point by the transpose of the linear discriminant vector previously computed; (2) multiplying its $m$ most expressive features by the transpose of the principal components matrix; and (3) adding the average image calculated in the training stage to the n-dimensional image vector. Therefore, assuming that the clouds of the classes follow a multidimensional Gaussian distribution and applying limits to the variance of each cloud, such as $\pm 3$ standard deviations of each group, we can move along this most discriminant feature and map the result back into the image domain (as shown in Figure 3). This mapping provides a sequence of images based on a statistical interpretation of the classification experiments and might describe results that are often not detectable [50].

### *3.1 Some results on Schizophrenia*

To illustrate the performance of the knowledge extraction approach, we present in this subsection some results on a MRI dataset that contains 44 patients with schizophrenia and 26 healthy controls. All these images were acquired using a 1.5T Philips Gyroscan S15-ACS MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands), including a series of contiguous 1.2mm thick coronal images across the entire brain, using a T1-weighted fast field echo sequence (TE = 9ms, TR = 30ms, flip angle 30o, field of view = 240mm, 256 x 256 matrix). All images were reviewed by a MR neuro-radiologist. Ethical permission for this study was granted by the Ethics Committee of the Clinical Hospital, University of Sao Paulo Medical School, Sao Paulo, Brazil.

As mentioned earlier, the one-dimensional vector found by the multivariate statistical approach corresponds to a hyperplane on the original image space which direction describes statistically the most discriminant differences between the control and patient images used for training. Figure 2 shows the PCA+MLDA most discriminant hyperplane found by the multivariate statistical approach to describe the differences between the schizophrenia and control samples. As can be seen, the schizophrenia and control sample groups

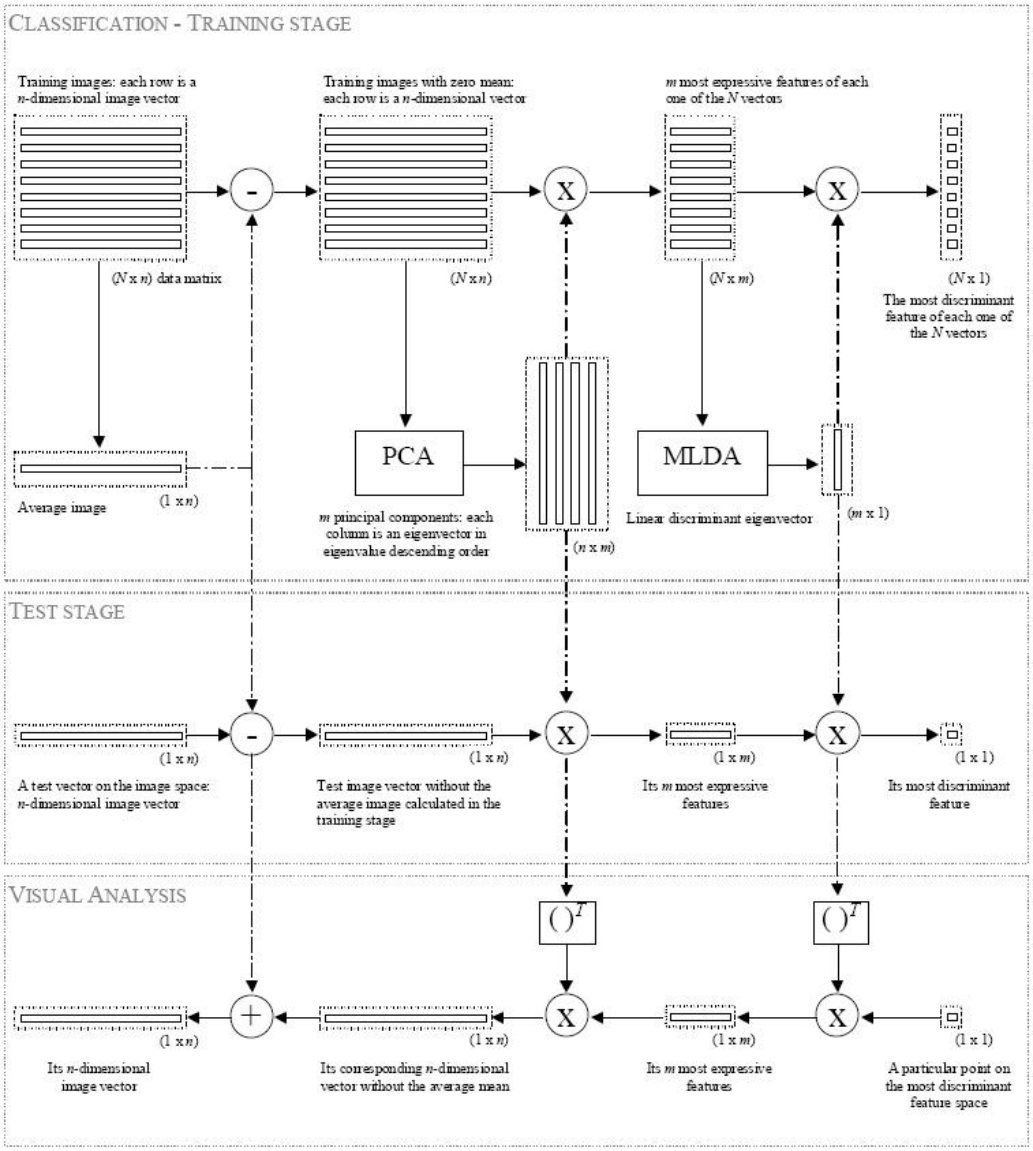



Fig. 1. Design of the multivariate linear approach [49].

could be fairly approximated by Gaussian distributions and, applying limits of $\pm 3$ standard deviations ($sd$) to the variance of each sample group, we can move along this PCA+MLDA most discriminant feature and map the result back into the image domain. The PCA+MLDA classification boundary (assuming equal prior probabilities and misclassification costs for both groups) is illustrated by a continuous vertical line, and the mean of the schizophrenia and control clouds as well as their limits of variation ($\pm 3sd$ whenever sensible) are displayed as asterisks on the most discriminant vector. In the scatter plot, schizophrenia samples are coded with a cross whereas control samples are coded with a circle. The vertical axis of the scatter plot is illustrative only and represents the corresponding index of each sample in the data set.

The statistical differences between the control and schizophrenia MRI sam-

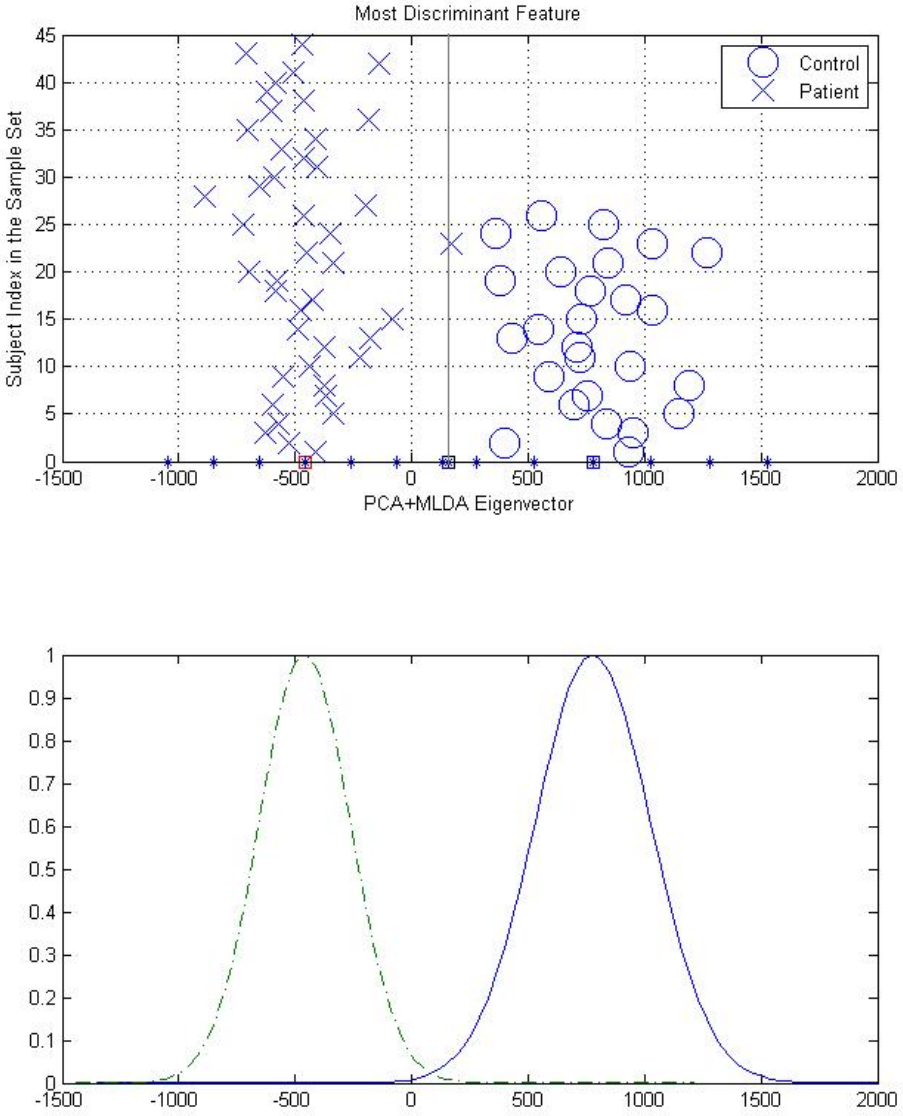



Fig. 2. PCA+MLDA most discriminant hyperplane found by the multivariate statistical approach to describe the differences between the schizophrenia and control samples. In the scatter plot, schizophrenia samples are coded with a cross whereas control samples are coded with a circle. The vertical axis of the scatter plot is illustrative only and represents the corresponding index of each sample in the data set.

ples captured by the PCA+MLDA hyperplane are illustrated in Figure 3. It shows the differences between the patient (on the top left) and control (on the right bottom) images captured by the multivariate statistical classifier using MR intensity features as inputs and all the spatially normalised samples for

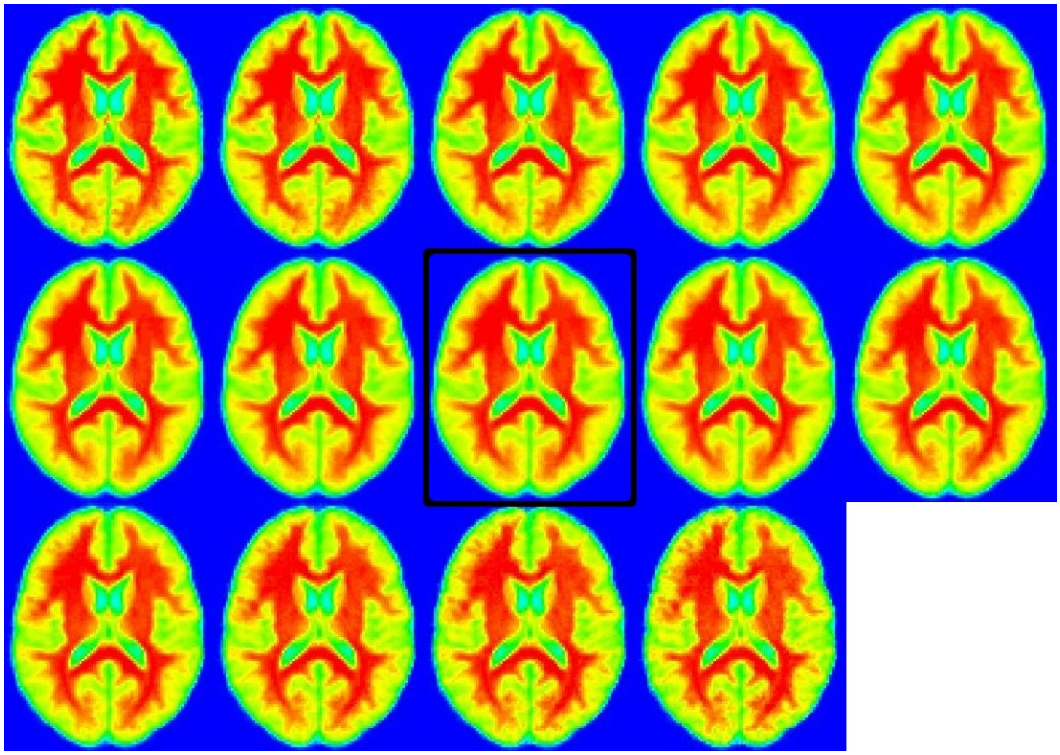


Fig. 3. Statistical differences between the schizophrenia (on top left) and control patient (on bottom right) images captured by the multivariate knowledge extraction approach.

training. These 14 images (from top left to bottom right) correspond to the 14 asterisks (from left to right) shown on Figure 2 projected back into the image domain. We can interpret this mapping procedure as a way of defining intensity changes that come from "definitely schizophrenia" and "definitely control" samples captured by the knowledge extraction approach [49].

However, the output of the PCA + MLDA process are images to be interpreted by a specialist. In the next section, we discuss some issues concerning the development of an ontology for interpreting some qualitative aspects of such images.

## 4 Knowledge assimilation

The multivariate statistical methods described in the previous section are very powerful tools for discovering the most important discriminating features between two sets of input images, however they are incapable of providing a qualitative description of what these features represent within a certain context. For instance, in [52,49], MLDA discovered a set of contraction and expansion regions that best classified neuroimages of preterm from control

groups of babies. However, a paediatrician was needed to point out which of these findings were actual differentiating features between these two groups and which were possibly originated from other sources (image artifacts for instance). In this section we discuss ongoing research on how the specialist knowledge could be formalised in an ontology whose purpose is to assimilate facts from neuroimages.

In this work, the *pre-existing domain* of the ontology is the medical expert knowledge connected to neuroimages of schizophrenia and its *formalisation* should support the interpretation of brain images. In fact, this is the goal of research on decision-support systems.

There are a number of decision support systems for schizophrenia reported in the literature [45,6,18] all of them were based on formalising the symptomatology of the disease [33]. The challenge here is to develop a knowledge representation and reasoning system that incorporates (as elementary entities) spatial regions in neuroimages that are known to be affected by mental disorders. There are several reasons for pursuing a knowledge representation and reasoning avenue in this research. First, we want to formalise the basic concepts for an automated process of image interpretation that would facilitate the medical assessment of the information contained in neuroimages. Second, it is largely believed in the medical communities that the pathogenesis of schizophrenia may rely on a myriad of factors, ranging from neuroanatomical and neurochemical abnormalities to genetic predisposition [27]. Defining a common ontology underlying the research on the possible causes of this disease is essential in order to develop computer systems that process findings from distinct fields.

The next section discusses some key ideas in the construction of as ontology based on the spatial information contained in neuroimages.

### *4.1 A biomedical ontology for neuroimage*

The images resulting from the multivariate statistical method (Figure 3) show some of the most commonly found anatomical abnormalities in schizophrenic patients, which include the following: an enlarged lateral and third ventricles, a reduction in the volume of the cortex of the medial temporal lobe and in the anterior portion of the hippocampus [27] (see [24] for a critical review of the schizophrenia's neuropathology).

In this section we describe the Basic Inclusion Theory (BIT) [15], a spatial theory for formalising biomedical ontologies, and discuss how it could be extended to cope with providing a formal description of the neuroanatomical abnormalities commonly found in MRI from schizophrenic individuals.

The main reason for assuming BIT is the distinction that it makes from mereological and location relations. Mereological relations are properties defined in terms of parts and their respective wholes [8]. For instance, in a mereology we could express formally that the fourth ventricle is *part of* the ventricular system, but it would be a mistake to say that it is also part of the hindbrain, although it is *located within* it. This is the reason why we need both, mereological and location relations, as briefly described below.

*Mereology*

In the mereological part of BIT variables range on individuals of the domain (in the present case, on distinct neuroanatomical structures).

Let $P$ be a parthood relation, Axioms (1), (2) and (3) (representing, respectively, the reflexivity, antisymmetry and transitivity of $P$) constrain the meaning of $P$.

$$P(x, x) \tag{1}$$
$$P(x, y) \wedge P(y, x) \rightarrow x = y \tag{2}$$
$$P(x, y) \wedge P(y, z) \rightarrow P(x, z) \tag{3}$$

Formula (1) states that every individual $x$ is proper part of itself; Formula (2) states that if $x$ is part of $y$, and vice-versa, then $x$ and $y$ are the same individual. Finally, Formula (3) represents the fact that if $x$ is part of $y$ and $y$ is part of $z$, then $x$ is part of $z$.

With the parthood relation two important relations can be defined: the proper part relation $PP$ (Formula (4)) and the overlap relation $O$ (Formula (5)).

$$PP(x, y) \equiv P(x, y) \wedge x \neq y \tag{4}$$
$$O(x, y) \equiv \exists z(P(z, x) \wedge P(z, y)) \tag{5}$$

In other words, $x$ is proper part of $y$ if and only if $x$ is part of $y$ and $x$ and $y$ are distinct individuals (cf. Formula (5)); similarly, $x$ overlaps with $y$ if there is at least one $z$ that is part of both $x$ and $y$.

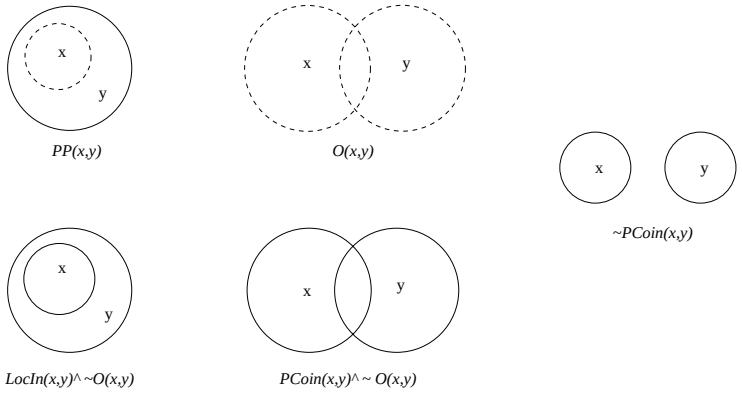



Fig. 4. Basic Inclusion Theory relations.

*Location*

The distinction between mereological and location relations is accomplished by defining location relations whose arguments are spatial regions that are unique mappings from neuroanatomical structures to the distinct spatial regions they occupy. Therefore, location relations can be defined from the mereological relations using a region function $r$ that maps each individual to its occupancy region.

There are two basic location relations in BIT: the $LocIn$, standing for "object $x$ is **located in** object $y$" which holds if and only if the occupancy region of $x$ is part of the occupancy region of $y$" (cf. Formula (6)) and $PCoin$ which states that "objects $x$ and $y$ **partially coincide**", which holds if and only if their occupancy regions overlap (cf. Formula (7)).

$$LocIn(x, y) \equiv P(r(x), r(y)) \tag{6}$$
$$PCoin(x, y) \equiv O(r(x), r(y)) \tag{7}$$

The qualitative distinctions that the basic part of BIT makes (Axioms (1) – (7)) are shown in Figure 4.

For the purposes of an example, we can express formally the facts below.

Let $VS$ be the ventricular system, and V be the set: {lateral ventricles, third ventricle, fourth ventricle, intraventricular foramina, cerebral acqueduct}, then we can state that

$$\forall pv \in V, PP(pv, VS),$$

and the following facts:

- the lateral ventricles $LV$ are *located within* the cereberum $C$: $LocIn(LV, C)$;
- the third ventricle $TV$ is *located within* the diencefalon $D$: $LocIn(TV, D)$;
- the fourth ventricle $FV$ is *located within* the hindbrain $HB$: $LocIn(FV, HB)$

The BIT axioms imply a number of theorems that can be used to infer a large amount of facts about biomedical ontologies [15]. Assertions about classes of individuals, rather than about particular instances, are also feasible in an extension of BIT that includes an *instantiation* relation linking a class to its individual instances. Therefore, in this extended version of BIT, it is possible to express (for instance) the spatial relation between the classes Ventricular System and Cerebrospinal Fluid, as well as the spatial relation between the individuals's right and left lateral ventricles.

Therefore, BIT is a language expressive enough to describe neuroanatomical facts, allowing automated reasoning about the part-whole relations between structures in the brain. However, the full development of an ontology about neuroanatomy warrants a paper in itself.

Although BIT is rich enough to express part-whole relations between anatomical structures, the relative locations between distinct structures and the relative relations with respect to classes of individuals, it is not sufficiently expressive to represent the kinds of information needed to characterise MRI data from schizophrenic patients. Take for instance the most evident findings described at the beginning of this section:

- an enlarged lateral and third ventricles;
- a reduction in the volume of the cortex of the medial temporal lobe;
- a reduction in the volume of the anterior portion of the hippocampus.

These findings are related to changes in size of neuroanatomical structures, which is an issue outside the expressibility capability of BIT. Therefore, the underlying ontology has to be extended with a set of axioms representing the size of spatial regions. The next section overviews some novel approaches to combine part-whole relations with size constraints.

*Combining size and mereo(topo)logy*

Combining size with part-whole, as well as topological, relations has been the interest of recent research [5,39,22], due to the potential applications of spatial calculi capable of dealing with multiple modalities of spatial information. In particular [39] combines the Region Connection Calculus (RCC) [32] with a qualitative size relation to define the notions of spatial granularity (i.e. the

definition of elementary spatial entities according to a context) and local spatial context (meaning the portion of space under consideration in a reasoning process). Similarly, [5] formalises qualitative distance relations (such as *close-to*, *near-to*, *away-from* etc) from a mereological basis extended with a linear order relation holding on the exact size of regions.

The work reported in [22] is an extensive study on the complexity of reasoning with combinations of mereotopological and size information. Taking into account the integration of four classes of qualitative and metric size constrains with the region connection calculus, [22] presents tractable subclasses of RCC combined with size constraints. Although assuming both qualitative and metric size information, for the purposes of the present article, we present below a brief description of the metric size information investigated in that paper.

Let $x$ and $y$ be two spatial regions. Let also $size(x)$ denote the exact size of region $x$, $\omega$ be a positive real number and $I$ an interval of real numbers (which can be open, closed or semi-open). The following three size constraints are considered in [22]:

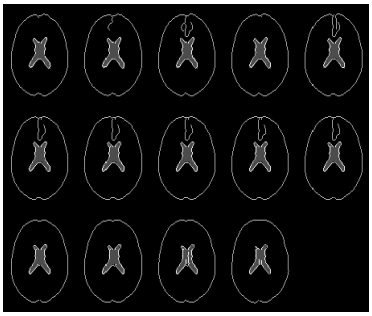
- *Metric size constraints (MS)*: $size(x)\ \ R\ \ \omega \times size(y)$, where $R \in \{<, \leq, = , \neq, \geq, >\}$
- *Size difference constraint (SD)*: $size(y) - size(x) \in I$
- *Domain size constraints (DS)*: $size(x) \in I$

The consistency of scenarios described using a combination of these constraints with RCC is tractable for a subclass of RCC-8 that do not include the relation *partially overlap* (PO). A proof for whether or not this result can be extended to the combination of BIT with size constraints is is a task for future research. The main interest here is on the expressibility of BIT+size constraints to describe the spatial extent of neuroimage data from schizophrenic patients. The next section discusses how the results from the multivariate statistical methods presented in Section 3 can be described with the formalism described above.

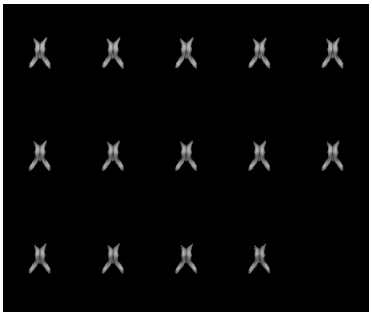
*Some results on schizophrenia: lateral ventricles*

Using the lateral ventricle as a case study, we now illustrate how the ontology could be used to describe qualitatively the differences between the control and schizophrenic patients, given the output of the multivariate statistical methods discussed in Section 3.

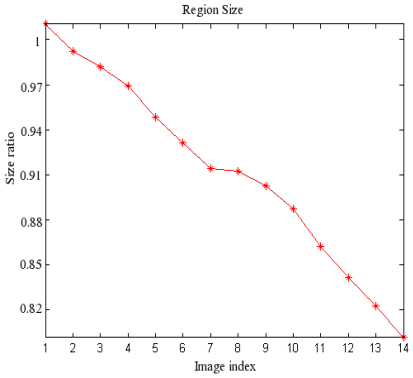
From the neuroimages output by the multivariate statistical classifier (whose axial cut is shown in Figure 3) we used a Canny edge detector algorithm [7] allied with a background-foreground filter to extract the boundaries of



(a) FIGURE 5A



(b) FIGURE 5B




(c) FIGURE 5C

Fig. 5. Results of the image segmentation of the lateral ventricle from the axial cut.

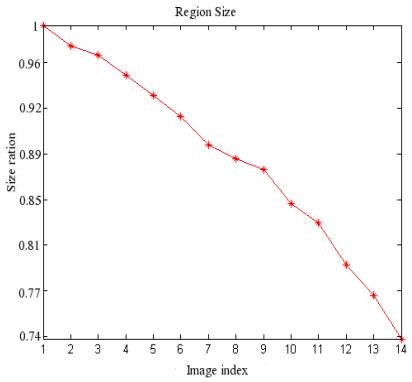
the regions relative to the lateral ventricles (as shown in Figure 5(a)). This segmentation provided the mask with which it was possible to retrieve the ventricle area (using an inverse pixel selection method, Figure 5(b)), that was measured by counting the number of inversed pixels in the selected area. Figure 5(c) shows a graph representing the results of such measurements, where the horizontal axis represents the image ordering as output by the multivariate statistical methods [3], and the vertical axis represents the ratio of change in area, taking the greatest area (that of the "definitely patient") as a reference. Figures 6(c) and 7(c) depict, respectively, the ventricle areas of the coronal and sagittal cuts relative to the same data items.

The graphs in Figures 5(c), 6(c) and 7(c) show a linear decreasing in the size of the lateral ventricles when they are ordered as output by the multivariate knowledge extraction approach (cf. Figure 3). We can now use these results to make a statement in the ontology characterising, thus, the control and schizophrenia cases according to the ratios in the vertical axes of the graphs, the hyperplane separating both groups (shown in Figure 2) and the idea of metric size constraints (presented above).

[3] I.e. index 1 corresponds to the top-left most image shown in Figure 3 ("definitely patient") following, in order, to the index 14, that corresponds to the bottom-right most image ("definitely control").

(a) FIGURE 6A

(b) FIGURE 6B




(c) FIGURE 6C

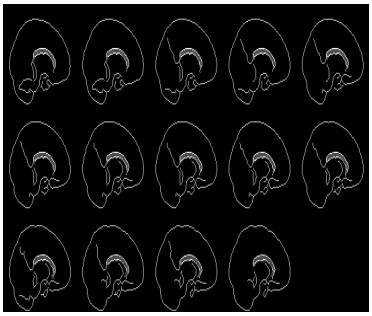
Fig. 6. Results of the image segmentation of the lateral ventricle from the coronal cut.

Let $S$ be a region representing a lateral ventricle and $R$ a constant representing the size of the largest ventricle in the dataset. In the results presented in Section 3 $R$ is the area of the ventricle in the top-left most brain picture in Figure 3 (or the leftmost asterisk in Figure 2). Let's also use the image corresponding to the hyperplane separating schizophrenic patients from individuals in the control group (in Figure 2) as a reference that provides a threshold on the ventricle areas between these groups. This reference image is shown inside a black box in Figure 3 and has ventricle areas indexed by the number 8 in the horizontal axes in Figures 5(c), 6(c) and 7(c), and whose size ratios are, respectively, $w_1 = 0.92$, $w_2 = 0.89$ and $w_3 = 0.88$.

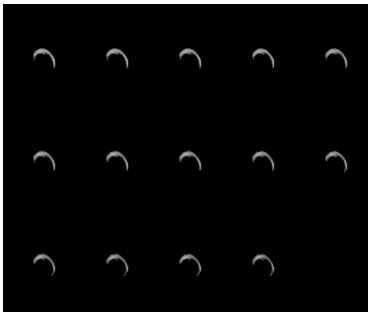
We can now use the metric size constraint to assimilate these results in the ontology by characterising the lateral ventricles $S$ of a schizophrenic patient as having

(1) $size\_axial\_cut(S)/R \geq w_1$;
(2) $size\_coronal\_cut(S)/R \geq w_2$;
(3) $size\_sagittal\_cut(S)/R \geq w_3$;

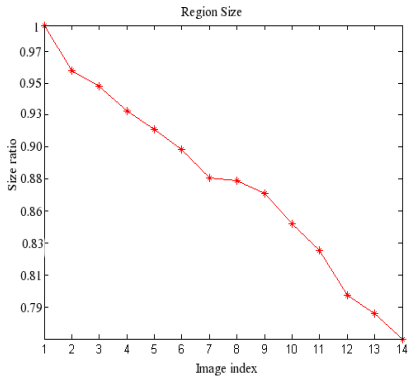
where $size\_axial\_cut(S)$, $size\_coronal\_cut(S)$ and $size\_sagittal\_cut(S)$ are functions that map a particular ventricle $S$ to the area occupied by its axial, coronal



(a) FIGURE 7A



(b) FIGURE 7B




(c) FIGURE 7C

Fig. 7. Results of the image segmentation of the lateral ventricle from the sagittal cut.

and sagittal cuts, respectively.

The lateral ventricle $S$ belonging to the control group could then be characterised by

(1) $size\_axial\_cut(S)/R < w_1$:
(2) $size\_coronal\_cut(S)/R < w_2$:
(3) $size\_sagittal\_cut(S)/R < w_3$:

The constants $w_1$, $w_2$ and $w_3$ are context-dependent thresholds as they are defined for the particular data set assumed in this work and the hypotheses of equal prior probabilities and misclassification costs for the schizophrenia and control groups (as mentioned in Section 3). Moreover, in the exercise of medicine the practitioner may want to tweak the hyperplane (generating a new set of thresholds) depending on his diagnosis standpoint.

In fact, distinct sets of values for the thresholds may result in distinct (sometimes incompatible) definitions of these groups. It is desirable to view such variations as *standpoints* on the vagueness inherent in classifying patients and non-patients. The supervaluation semantics [17] may be used to provide a formal treatment for standpoints on the ontology.

Supervaluation semantics views a vague language as a set of distinct precise versions of itself. Each of these versions is called a *precisification* of the language. Formally, each precisification $p$ is identified with a particular interpretation $I_p$ of the language. A *supervaluation model* is defined as a set of precisifications. Therefore, given a supervaluation model $\Upsilon$ we can talk about propositions that are unequivocally true (i.e. are true in *every* interpretation $I_p \in \Upsilon$) and propositions that are *in some sense* true (i.e. are true in *some* interpretation $I_p \in \Upsilon$). For instance, it is *unequivocally true* that the lateral ventricles are part of the ventricular system but it is *in some sense true* that the thresholds $w_1$, $w_2$ and $w_3$ characterise the distinction between patient and control groups. Therefore, various distinct classifications discriminating control and patients may coexist as distinct precisifications of the same concept. In fact, the apparatus of supervaluation semantics allows for logical relationships between vague concepts to be represented by quantifying over the (possibly infinite) space of precisifications [4,37], as well as providing the machinery to make *reliable inferences* involving vague concepts. This ability to derive the reliable consequences of vague knowledge is the main advantage of supervaluation semantics over fuzzy logic [16].

In this section we have presented and illustrated the main elements of an ontology to assimilate knowledge from neuroimages. The full accomplishment of this project, however, is our long-term goal.

## 5 Discussion

This work proposes an integrated framework for classifying and interpreting patterns of the schizophrenia disorder from 3D MR images using a combination of knowledge extraction and assimilation methods. In the following paragraphs, we discuss some points that have emerged from this study which might be relevant in other similar investigations.

It is important to remark that the construction of the multivariate statistical model (PCA+MLDA) for knowledge extraction relies on the quality of the inter-subject correspondences calculated by either affine or non-rigid registration algorithms. In other words, when we use PCA as a feature extraction technique we must have in mind that PCA outputs projection directions that maximise the total scatter composed of all images of all classes. As a consequence, when we retain all the PCA eigenvectors and choose such projection without any previous alignment of the images, PCA might describe unwanted variations inherent to any image acquisition process, such as differences in rotation, translation, scaling, and shape [49]. Therefore, in order to minimise those variations that are not necessarily related to anatomical differences between the images, and transform data in a way that the images belonging to

distinct classes occupy as compact and disjoint regions in a lower dimensional feature space as possible, the spatial normalisation of the images provided by the image registration algorithms is a fundamental pre-processing stage for the success of the multivariate statistical model [49].

We seek the assimilation results from the multivariate statistical methods in order to serve two purposes: on one hand to provide a precise conceptual description of the domain; and on the other hand, to serve as a *lingua franca* for automatically combining different sources of data from the same individual. In a broader sense, these are the goals of the modern investigation on ontology, particularly on biomedical ontologies [43,42]. Assuming an ontology based on spatial regions and size constraints, Section 4 shows how to formally express, not only neuroanatomical facts, but also the changes in sizes of particular neuroanatomical structures that were picked out by the knowledge extraction process discussed in Section 3. Changes in size were obtained applying image segmentation methods that allowed the individualisation of the region to be described. However, the results obtained are not absolute as they depend, for instance, on the image segmentation methods used and on the initial hypotheses about the probability distribution of the data items (which changes the position of the hyperplane, cf. Section 3). We see this context dependency of the results as distinct standpoints about the same dataset. Distinct standpoints are modelled in this work as distinct precisifications of the ontology. Therefore, the formalism proposed is capable of handling multiple versions of the object domain. This characteristics allows for the combination of various sources of data about schizophrenia, providing a complete picture of the disease, which may be crucial for the complete understanding of its causes.

*Future research directions*

The first part of this article (Section 3) extended a general multivariate linear framework [49] to extract statistical differences of 3D MR brain images of adult subjects suffering from schizophrenia compared to a healthy control group. Although the multivariate linear approach has been demonstrated in two-class problems, it is extensible to several classes. Since the brain changes found in schizophrenia are not exclusively characteristic of this disease, a multi-class analysis involving a number of brain disorders and controls could provide a comprehensive understanding of abnormalities in brain development.

The second part of this article (Section 4) delineated some aspects in the development of a bio-ontology about neuroimages. Subject of our current investigations are the complete description of neuroanatomy using BIT and the further assimilation of other findings about schizophrenia from neuroimages, such as the change in size of the hippocampus, amongst others [24]. Likewise,

the change in standpoint (ruled by the supervaluation semantics) shall lead also to fruitful results when reasoning about multiple (distinct) datasets and classification premises.

Subject of future work is also the investigation of theories capable of representing the shapes of brain regions and what changes they may suffer under psychiatric diseases such as schizophrenia. A rigorous treatment of shapes, however, is one of the most elusive issues in Qualitative Spatial Reasoning [13] and Computer Vision [14], and has not yet started in a bio-ontology context. The concept of continuity between distinct brain structures is also a notion still to be introduced in the ontological framework presented in this article.

## 6 Concluding remarks

This article discussed our current research on methods for knowledge extraction and assimilation applied to the problem of finding discriminative features and rules that characterise schizophrenia from neuroimages.

In the present work, we discussed the main issues involving the construction of a novel integrated framework for classifying and analysing patterns of disorders from medical images using a combination of image registration, multivariate statistics, and knowledge-based formalisms. Our first goal is to analyse all the data simultaneously rather than assuming *a priory* regions of interest. In a first stage, multivariate statistical methodologies (here materialised as a joint PCA+MLDA approach) are proposed to identify the most discriminating hyperplane separating two populations contained in the input data. We discussed some previous results indicating the capability of this methodology for the classification of neuroimages ([51,52,49]). In a second stage, this work is inspired by novel results on the development of bio-ontologies ([15]) and proposes, as a challenge to this field, the automatic extraction of qualitative descriptions of the outputs from the multivariate statistical approach in order to provide a clear, high-level, description of the classes discriminated by this approach.

## References

[1] J. E. Rogers A. L. Rector and P. A. Pole. The galen high level ontology. In *Proc of MIE 96*, pages 174–178. IOS Press, 1996.

[2] J. Ashburner, J. G. Csernansky, C. Davatzikos, N. C. Fox, G. B. Frisoni, and P. M. Thompson. Computer-assisted imaging to assess brain structure

in healthy and diseased brains. *Neurology*, 2(79-88), 2003.

[3] J. Ashburner and K. J. Friston. Voxel-based morphometry - the methods. *NeuroImage*, 11(6):805–821, 2000.

[4] B. Bennett. Application of supervaluation semantics to vaguely defined spatial concepts. In D.R. Montello, editor, *Spatial Information Theory: Foundations of Geographic Information Science; Proceedings of COSIT'01*, volume 2205 of *LNCS*, pages 108–123, Morro Bay, 2001. Springer.

[5] T. Bittner and M. Donnelly. A formal theory of qualitative size and distance relations between regions. In *Proc. of the 21st Annual Workshop on Qualitative Reasoning (QR07)*, 2007.

[6] J.D. Bronzino, R. A. Morelli, and J.W. Goethe. Overseer: a prototype expert system for monitoring drug treatmentin the psychiatric clinic. *IEEE Transactions on Biomedical Engineering*, 36(5):533–540, 1989.

[7] J. Canny. A computational approach to edge detection. *IEEE Trans. Pattern Analysis and Machine Intelligence*, 8:679–714, 1986.

[8] R. Casati and A. C. Varzi. *Parts and Places: the structures of spatial representation*. MIT Press, 1999.

[9] G. E. Christensen and H. J. Johnson. Consistent image registration. *IEEE Trans. Med. Imag.*, 20:568–582, 2001.

[10] E. Clementini, P. di Felice, and D. Hernández. Qualitative representation of positional information. *Artificial Intelligence*, 95(2):317–356, 1997.

[11] E. Clementini and P. Di Felice. A global framework for qualitative shape description. *GeoInformatica*, 1(1):11–27, 1997.

[12] A. G. Cohn, B. Bennett, J. Gooday, and N.M. Gotts. Representing and reasoning with qualitative spatial relations about regions. In Oliviero Stock, editor, *Spatial and Temporal Reasoning*, pages 97 – 134. Kluwer Academic Publishers, 1997.

[13] A. G. Cohn and S. M. Hazarika. Qualitative spatial representation and reasoning: An overview. *Fundamenta Informaticae*, 46(1-2):1–29, 2001.

[14] L.F. Costa and R. M. Cesar. *Shape analysis and classification: theory and practice*. CRC Press, 2006.

[15] M. Donnelly, T. Bittner, and C. Rosse. A formal theory for spatial representation and reasoning in biomedical ontologies. *Artificial Intelligence in Medicine*, 36(1):1–27, 2006.

[16] C. Elkan. The paradoxical success of fuzzy logic. In *Proceedings of the National Conference on Artificial Intelligence (AAAI-93)*, pages 698–703, 1993.

[17] K. Fine. Vagueness, truth and logic. *Synthése*, 30:263–300, 1975.

[18] M.B. First, L.A. Opler, R.M. Hamilton, J. Linder, L.S. Linfield, and J.M. Silver et al. Evaluation in a inpatient setting of dtree, a computer-assisted diagnostic assessment procedure. *Compr Psychiatry*, 1993.

[19] K. J. Friston, A. P. Holmes, K. J. Worsley, J. P. Poline, C. D. Frith, and R. S. J. Frackowiak. Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, 2:189 – 210, 1995.

[20] K. Fukunaga. *Introduction to Statistical Pattern Recognition*. Boston: Academic Press, second edition, 1990.

[21] W F Gattaz, W Rost, K Kohlmeyer, K Bauer, C Hubner, and T Gasser. Ct scans and neuroleptic response in schizophrenia: a multidimensional approach. *Psychiatry Research*, 26:293–303, 1988.

[22] A. Gerevini and J. Renz. Combining topological and size information for spatial reasoning. *Artificial Intelligence*, 137:1–42, 2002.

[23] P. Golland, W. Grimson, M. Shenton, and R. Kikinis. Detection and analysis of statistical differences in anatomical shape. *Medical Image Analysis*, 9:69–86, 2005.

[24] P. J. Harrison. The neuropathology of schizoprenia: a critical review of the data and their interpretation. *Brain*, 122:593–624, 1999.

[25] P J Harrison and M J Owen. Genes for schizophrenia: recent findings and their pathophysiological implications. *Lancet*, 361:417–19, 2003.

[26] D. Hernández, E. Clementini, and P. di Felice. Qualitative distances. In W. Kuhn and A. Frank, editors, *LNAI*, pages 45–58. Springer-Verlag, 1995.

[27] E. R. Kandel, J. H. Schwartz, and T. M. Jessell. *Principles of Neural Science*. McGraw-Hill Medical, 2000.

[28] John C. Mazziotta, Arthur W. Toga, Alan Evans, Peter Fox, and Jack Lancaster. A probabilistic atlas of the human brain: Theory and rationale for its development : The international consortium for brain mapping (icbm). *NeuroImage*, 2(2, Part 1):89–101, 1995.

[29] R. C. Meathrel and A. P. Galton. A hierarchy of boundary-based shape descriptors. In *Proc. of IJCAI*, pages 1359–1364, 2001.

[30] K T Mueser and S R McGurk. Schizophrenia. *Lancet*, 363(2063-72), 2004.

[31] K H Nuechterlein and M E Dawson. A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin*, 10:300–12, 1984.

[32] D. Randell, Z. Cui, and A. Cohn. A spatial logic based on regions and connection. In *Proc. of KR*, pages 165–176, Cambridge, U.S., 1992.

[33] D. Razzouk. *Construção de uma base de conhecimento de um sistema de apoio à decisão*. PhD thesis, UNIFESP, São Paulo, Brazil, 2001.

[34] J. Reinz and B. Nebel. On the complexity of qualitative spatial reasoning: a maximal tractable fragment of the region connection calculus. *Artificial Intelligence*, 108:69–123, 1999.

[35] C. Rosse and J. Mejino. A reference ontology for biomedical informatics: the foundational model of anatomy. *Journal of Biomedical Informatics*, 36(6):478–500, 2003.

[36] D. Rueckert, L. I. Sonoda, C. Hayes, D. L. G. Hill, M. O. Leach, and D. J. Hawkes. Non-rigid registration using free-form deformations:application to breast mr images. *IEEE Transactions on Medical Imaging*, 18(8):712–721, 1999.

[37] Paulo Santos, Brandon Bennett, and Georgios Sakellariou. Supervaluation semantics for an inland water feature ontology. In Leslie Pack Kaelbling and Allessandro Saffiotti, editors, *Proceedings of the 19th International Joint Conference on Artificial Intelligence (IJCAI-05)*, pages 564–569, Edinburgh, 2005. Professional Book Center.

[38] C. Schlieder. Qualitative shape representation. In P. A. Burrough and A. U. Frank, editors, *Geographic Objects with Indeterminate Boundaries*, pages 123–140. Taylor & Francis Inc., 1996.

[39] H. Schmidtke and W. Woo. A size-based qualitative approach to the representation of granularity. In *Proc. of IJCAI*, pages 563–568, 2007.

[40] D. Shen and C. Davatzikos. Hammer: Hierarchical attribute matching mechanism for elastic registration. *IEEE Trans. Med. Imag.*, 2002.

[41] M E Shenton, C C Dickey, M Frumin, and R W McCarley. A review of mri findings in schizophrenia. *Schizophr Research*, 49(1-2):1–52, 2001.

[42] B. Smith, W. Ceusters, B. Klagges, J. Khler, A. Kumar, J. Lomax, C. Mungall, F. Neuhaus, A. Rector, and C. Rosse. Relations in biomedical ontologies. *Genome Biology*, 6(5), 2005.

[43] B. Smith and C. Rosse. The role of foundational relations in the alignment of biomedical ontologies. In *Proc. of Medinfo*, pages 444–448, 2004.

[44] E. R. Sowell, P. M. Thompson, C. J. Holmes, R. Batth, T. L. Jernigan, and A. W. Toga. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *NeuroImage*, 9:587–597, 1999.

[45] R. L. Spitzer and J. Endicott. Diagno: computerized program for psychiatric diagnosis utilizing the differential diagnostic procedure. *Arch. Gen. Psychiatry*, 18:747–756, 1968.

[46] Oliviero Stock, editor. *Spatial and Temporal Reasoning.* Kluwer Academic Publishers, 1997.

[47] C. Studholme, D. L. G. Hill, and D. J. Hawkes. An overlap invariant entropy measure of 3d medical image alignmen. *Pattern Recognition*, 32(1):71–86, 1999.

[48] C. E. Thomaz. *Maximum Entropy Covariance Estimate for Statistical Pattern Recognition*. PhD thesis, Department of Computing, Imperial College London, 2004.

[49] C. E. Thomaz, J. P. Boardman, S. Counsell, D. L. G. Hill, J. V. Hajnal, A. D. Edwards, M. A. Rutherford, D. F. Gillies, and D. Rueckert. A multivariate statistical analysis of the developing human brain in preterm infants. *Image Vision Comput.*, 25(6):981–994, 2007.

[50] C. E. Thomaz, J. P. Boardman, S. Counsell, D.L.G. Hill, J. V. Hajnal, A. D. Edwards, M. A. Rutherford, D. F. Gillies, and D. Rueckert. A whole brain morphometric analysis of changes associated with preterm birth. In *proceedings of SPIE International Symposium on Medical Imaging, Image Processing*, pages 1903–1910, San Diego, California, USA, 2006.

[51] C. E. Thomaz, J. P. Boardman, D. L. G. Hill, J. V. Hajnal, A. D. Edwards, M. A. Rutherford, D. F. Gillies, and D. Rueckert. Using a maximum uncertainty lda-based approach to classify and analyse mr brain images. In *Proc. of the 7th International Conference on Medical Image Computing and Computer Assisted Intervention MICCAI'04*, LNCS 3216, pages 291–300, Saint-Malo, France, September 2004. Springer-Verlag.

[52] C. E. Thomaz, J. P. Boardman, D. L. G. Hill, J. V. Hajnal, A. D. Edwards, M. A. Rutherford, D. F. Gillies, and D. Rueckert. Whole brain voxel-based analysis using registration and multivariate statistics. In *proceedings of the 8th Medical Image Understanding and Analysis MIUA'04*, pages 73–76, London, UK, September 2004.

[53] C. E. Thomaz and D. F. Gillies. A maximum uncertainty lda-based approach for limited sample size problems - with application to face recognition. In *proceedings of the 18th Brazilian Symposium on Computer Graphics and Image Processing SIBGRAPI'05*, pages 89–96, Natal, Rio Grande do Norte, Brazil, October 2005. IEEE CS Press.