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SEGMENTATION OF MULTIVARIATE MEDICAL IMAGES VIA UNSUPERVISED CLUSTERING WITH "ADAPTIVE RESOLUTION"

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Abstract—The need for quantitative information is becoming increasingly important in the clinical field. In this paper we present an interactive X11 based system, devoted to segmentation of multivariate medical images, including an unsupervised neural network approach to clustering. The following steps are considered in the analysis sequence: feature extraction, reduction of dimensionality, unsupervised data clustering, voxel classification, interactive post-processing refinement. The environment turns out to be extremely interactive, thus making the user able to display and modify data during processing, to set parameters, to choose different methods and different tools for each step, and to define online the whole analysis sequence. Copyright © 1996 Elsevier Science Ltd.

Key Words: Segmentation, Multimodal images, Neural networks, Principal component analysis, Unsupervised clustering, Interactive tools, Brain, MRI

INTRODUCTION

A number of different diagnostic methodologies are provided, at present, by medical imaging technology. From X-ray tomography (CT), magnetic resonance imaging (MRI), single photon emission tomography (SPECT) and positron emission tomography (PET) complementary information (both structural and functional) on biological tissues can be obtained.

Multi-modal volumes can be built, from these data, for fully correlating information about the same patient, by a very accurate registration, i.e. a geometric transformation performing a spatial correlation between voxels in volumes (1, 2). Moreover, considerations about multi-modal volumes can be easily extended to more generally defined multi-feature or multi-variate volumes, eventually produced during a post processing phase.

An efficient analysis of multi-variate medical imaging volumes is an inherently complex task in which each component of the data structure, that is the spatial distribution of the values of a single feature, must be considered together with all the other components. For these reasons, due to the complexity of data, a fully quantitative analysis of multi-variate medical imaging volumes is unfeasible by manual methods and exploiting the multi-dimensional nature of the data requires, at least partially, automation of the analysis process (3, 4). Conversely, the fully automated analysis of these volumes does not appear to be an attainable goal, at least currently, because of the absence of gold standards against which automated results may be compared and because of the general knowledge that the expert is able to insert in the data analysis. Moreover, intra- and inter-slice intensity variations due to data acquisition uncertainty require an on-line tuning of analysis parameters. For these reasons, more realistically, users must be provided, as support to their task, with integrated computer environments implementing not only various processing tools with very high performances but also powerful capabilities of interaction with different representations of the data structure.

In this paper we present an X11-based system devoted to the segmentation of multivariate medical images. In this context, our choice has been a neural network approach which combines the unsupervised paradigm for clustering and classification together with interactive postprocessing tools for introducing general knowledge.

OUR APPROACH TO ANALYSIS OF MEDICAL IMAGES

Possible applications of this methodological approach in the clinical environment are:

1. to support in delineating volumes to be treated in radiotherapy and surgery to quantify the response

assessment (in terms of tumor mass or detection of metastases) after oncological treatments
2. to improve the accuracy of the volumetric measurements of different compartments in morphometric studies
3. to define software phantoms based on real patient data to be used in simulated experiments

All these applications involve the extraction of objects or other entities of interest from the imaging data, usually by defining sets of voxels with similar features within the entire multi-variate volume. This task is actually a possible definition of image segmentation and is usually accomplished, either, by methods of boundary detection, as gradient operators, and by methods of similarity detection, as thresholding and region growing techniques. Unfortunately, volumes of interest in medical imaging are not strictly bounded and the application of similarity methods to multi-variate data is not as obvious as desirable and often is very time-consuming with complex geometries.

Let us consider a multi-variate volume resulting from the spatial registration of a set of s different imaging volumes. We may notice that its voxels result associated to an array of s values, each one representing the intensity of a single feature in that voxel. In other words, the s different intensity values related to each voxel in such multi-variate volumes can be viewed as the coordinates of the voxel within an s-dimensional feature space where multi-variate analysis can be made.

Actually, the principal steps in segmenting of multi-variate volumes is the definition of clusters within the above described s-dimensional feature space and the classification of all the voxels of the volume in the resulting classes. These two goals can be attained both by supervised and unsupervised methods (5–7). Supervised methods have been largely employed in medical imaging segmentation studies but provide for conditions hardly satisfied in the clinical environment. Firstly, they require the labelling of prototypical samples needed by the generalization process to be applied. Even if the number of clusters is predefined, careful labelling of voxels in the training set, belonging with certainty to the different clusters is not trivial especially when concerning multi-variate data sets. Moreover, bias can be introduced by users due to the large inter-user variability generally observed when manual labelling is performed. Finally, manual labelling itself is a very time-consuming task if large volumes are examined; if not contiguous regions must be defined and a number of features must be considered. However, unsupervised approaches self-organize the implicit structure of data and make clustering of the feature space independent from the user-dependent definition of the training regions (6–8). Moreover, unsupervised methods can iterate training, without further efforts from users, wherever it is required by the inhomogeneity of data as for intra- and inter-slice intensity variations in medical imaging. Finally, the multidimensionality of data is definitely better exploited by self-organizing unsupervised cluster analyses. Nevertheless supervised techniques have been favoured over unsupervised techniques because they can be used interactively, leaving the user in control of the final segmentation. From these considerations, interactive tools supporting an unsupervised clustering method have been our choice for combining the two approaches in order to attain better results.

THE STRUCTURE OF THE SEGMENTATION SYSTEM

Based on these assumptions, the whole system has been structured with a strong attention to modularity, in order to keep the user in control of choices within the course of analysis. This has been accomplished by a deep transparency in the data structure and powerful functions of interactive visualization that allow the user to verify and even modify the results of analysis at different steps. In addition, contemporary views of data (for instance in the image space and in the feature space) are made possible and different methods and tools of analysis can be chosen at each step.

Strictly as regards the functionality of the system, the following set of functions is provided:

1. reduction of dimensionality
2. data clustering
3. voxel classification
4. interactive display and refinement

Within an interactive environment, they can be activated by the user as a complete sequence of complementary tools for the analysis of data. In the following sections the principal modules of the system are described with some considerations about the methods adopted.

Reduction of dimensionality

A number of feature extraction modules may be implemented in order to further explode information contained in the acquisition volumes. Both spatial filters and filters in the Fourier space can also be applied to original images as feature extractors. In

addition, significant correlations among the original volumes may be evidenced by different operators. As a consequence, a larger set of volumes may be derived from the original set, for completely exploiting the latent information. Unfortunately, this may lead to an explosion in data dimensionality that increases the computational complexity of analysis and the reduction of dimensionality both in the feature space and in the image space is often necessary and is anyway very helpful. It may be accomplished, in the feature space, by methods, such as Principal Component Analysis (PCA), and, in the image space, by the definition of volumes of interest (VOI).

Principal component analysis

The principles of PCA may be found in many textbooks on image analysis (10). In short, PCA explains the variance-covariance structure in a multivariate data set through a change of base. This means that the Principal Components are uncorrelated linear combinations of the original variables $X1$, ..., Xs, with the greatest variances sorted by decreasing values. We can notice that, by projecting, in the feature space, the points which define the voxels from the original multi-variate volume on the new axes zi, a new set of images may be reconstructed that describe the data set according to the feature combinations represented by the Principal Components (11).

With some further considerations about mean-centering and variance scaling, the variance concerning each Principal Component may be related to information in that component and the most interesting information about the multi-variate volume results therefore concentrated only in the subspace defined by the first Principal Components. This way, the multi-variate data can be divided in a latent structure and in a noise-related portion and the dimensionality of the feature space can be reduced, by choosing only the first significant Principal Component images, hence simplifying the following clustering process.

Volumes of interest

Volumes of interest can be defined via mouse in the image space and in the feature space, both for reducing the dimensions of the research space during the neural network training for the initial unsupervised clustering, and for delimiting sub-volumes in the multi-variate image, as required by the "zooming" tool available for clustering, in order to refine the segmentation of small details. The definition of volumes of interest is also helpful for pointing out only data actually significant in order to improve the performances of the PCA.

The unsupervised adaptive resolution clustering

In the last decade neural networks have been successfully used in image analysis because of their capability of mapping the data structure by learning in an adaptive way from a limited training set and different unsupervised models have been developed with good results (6, 7, 11–13). But the analysis of multi-variate medical images needs further considerations due to the particularity of their data distribution.

Let us now consider in detail the data structure of multi-variate medical images. We notice that anatomical or functional structures can be described, in the feature space, both by small clusters with high probability density and by large clusters with low probability density. This is to say that, in the image space, strictly defined regions as well as very noisy regions can emerge. In the feature space, again, it means that structures can appear at different levels of resolution. An effective cluster analysis of multivariate medical images should therefore fit accurately such different resolutions in the distribution of density. Our original approach consisted of a self-organizing neural network which is able to learn data clustering in an adaptive way taking into account, within certain limits, the local density characteristics of the point-distribution. We call this property adaptive resolution clustering. The network combines standard competitive self-organization of the weight-vectors (14, 15) with a new non-linear mechanism of adaptive local modulation of the Receptive Field (RF) of each neuron called "Capture-Effect" (16–18). The final equilibrium of the network, after training, is characterized by two facts:

1. the distribution of the weight-vectors (prototypes) in the feature-space approaches the optimal vector quantization scheme of the distribution of input data, i.e. approximates its probability density function;
2. the radial size of the RF of each neuron reaches an equilibrium which is strongly related to the spatial density of input data locally around the center of the RF itself, i.e. the weight-vector of the neuron.

The information carried either by the distribution of the centers of the RFs and the distribution of the sizes of the RFs themselves are combined in an unsupervised clustering algorithm which follows the training phase. Each group is thus considered as the

detector and the encoder of a particular input data cluster.

In summary our "Capture Effect" model holds the two following properties:

1. the number of clusters the network has to partition data is not a parameter for the network. During the learning phase the network self-organizes in such a way that a certain number of clusters are autonomously discovered.
2. the partition of data which come out from the learning phase takes into account the natural scale of spatial density the clusters emerge within the distribution of data. This is accomplished by the adaptive local modulation of receptive fields centered on neurons.

Unsupervised coding algorithms

Starting from the definition of clusters in the feature space, a further step is required to generalize results of clustering to the whole volume. With regard to this generalization, two kinds of information are made explicit by the Capture Effect model: the first relates to the distribution of neurons, and the second relates to the distribution of radii of the receptive fields. They can be combined through non-supervised algorithms of coding, to be used just after the clustering phase, in order to attain a completely unsupervised segmentation map.

Different distances in the feature space from voxels not yet assigned to clusters, both to each neuron in each cluster and, alternatively, to the centroid position of all neurons in each cluster are considered. Moreover, the distances between these different points in the feature space can be normalized in relation to the radii of the receptive fields of the neuron actually considered or to the radius of the average receptive field of the cluster whose centroid is considered. Generalization is then performed by simple unsupervised coding algorithms that use the above-mentioned definitions of distance.

Post-processing interactive modules

The characteristics of the model lead to a segmentation map, fully unsupervised, that often can be already considered a satisfactory final result. Otherwise, if the domain knowledge of the human expert is needed in order to obtain satisfactory results, just the information made explicit by the model allows one to refine the segmentation map itself. With this aim, interactive tools for refining clustering both in the feature space and in the image space have been added as components of an interactive environment in order to improve the performances of the system (19). On one hand, interactive correction of clusters identification can be performed, after the unsupervised training, in the feature space. After the generalization of training by coding algorithms, a further interactive correction of voxel classification can be made both in the so-defined image space and in the feature space. That is, clusters can be suppressed and merged or even modified (automatically or manually) by adding or removing voxels in clusters. Users can iterate the procedure in order to obtain the final segmented volumes. As a consequence, this combination of preliminary unsupervised segmentation and interactive post-processing lets the user be in control of the final results, avoiding, on the other hand, the necessity of very time-consuming manual procedures and the introduction of unmotivated bias.

A number of segmentation maps may be produced by different sequences of analysis or by multivariate volumes produced at different times. As a post-processing tool, an interactive module for the quantitative comparison of a set of segmentation maps is available for the user to localize differences in clusters and to establish relationships among points classified in different classes. Corrections can be made, successively, based on this quantitation.

Finally, as pointed out in a previous paragraph, several localized training sets for clustering can be defined within an image by drawing small volumes of interest. This way, a number of segmented sub-maps can be obtained that are able to describe details in segmentation. As a final step, these sub-maps can be superimposed and merged by a further interactive module in order to display the whole segmentation map composed with complementary sub-maps produced at different clustering resolutions.

SEGMENTATION OF MRI BRAIN IMAGES

The segmentation of white matter, gray matter, cerebrospinal fluid and skull has been performed using MRI data of the head (6, 8, 12, 20). The specific goal was to discriminate voxels from different tissues for defining a software-based phantom of the head to be used for the simulation of PET and SPECT images (21, 22). In fact, starting from the segmented images, simulated functional images may be calculated to be used for quantitative evaluation of the imaging artifacts in PET (22), as well as for the validation of reconstruction iterative algorithms (23) and constrained deconvolution algorithms (24) for SPECT images.

The segmentation system has been implemented on a Silicon Graphics Indy R4600 workstation in a

standard X11 Unix environment by using standard Motif libraries. A mixed model approach has been chosen for combining both the low-level interactive functions of the basic X-Windows level and the powerful high-level functions of the SGI Graphics Libraries.

In particular, three volumetric data sets representing T1-, T2- and proton density-weighted MRI data of a healthy volunteer have been used. No corrections have been made to reduce the inter-slice variability of image intensity. The fusion of data sets produces a three-variate volume that defines a three-dimensional feature space as previously described. That is, each triplet of voxel intensity in the volume is represented by a point in a 3D feature space, whose coordinates represent the intensity values in that voxel of each volume belonging to the multi-variate volume. Our aim is to detect clusters in such a space and to use them for segmenting the input images.

Let us point out a further aspect of segmenting these multidimensional data sets. Two different spaces have to be considered for a more complete description of the segmentation problem: an image space (usually 3D) defined by the spatial coordinates of the data set, and a multidimensional feature space as described before. The interplay between these two spaces plays a very important role in understanding the data structure. Therefore, during the whole sequence of analysis, not only a true multidimensional approach is strongly recommended, but also powerful tools, able to correlate the representation of data in the two spaces, should be implemented for really exploiting information.

As a consequence, tools for the visualization of data both in the image space and in the feature space have been developed in order to make the user able to examine data from different points of view. On one hand, images may be displayed on orthogonal planes (transversal, coronal, sagittal) with spatially correlated views, and anatomical tags may be set in order to help the user in locating structures (Fig. 1). On the other hand, bidimensional orthogonal projections of the feature space, name scatter plots, may be examined (Fig. 2) in order to have a look at the probability distribution of data in the feature space. Each point in the scatter plots describes a specific combination of intensities from two different images and the gray level of points is related to the number

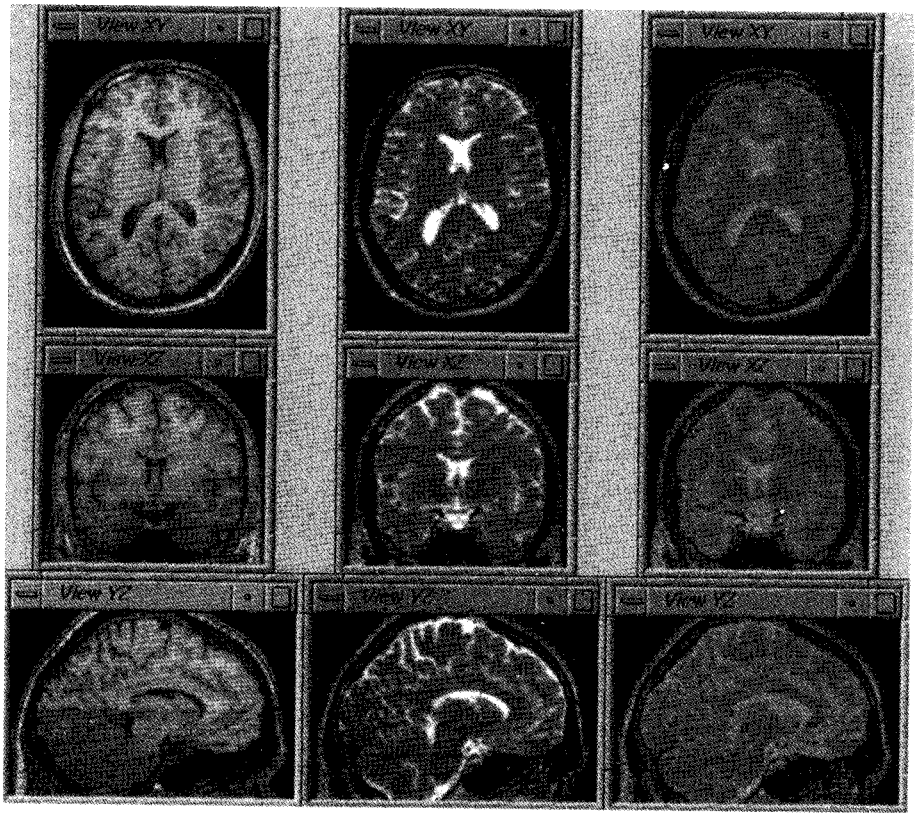

Fig. 1. Transversal, coronal and sagittal views of T1-, T2- and proton density-weighted MR volumes (courtesy of the Montreal Neurological Institute at McGill University).

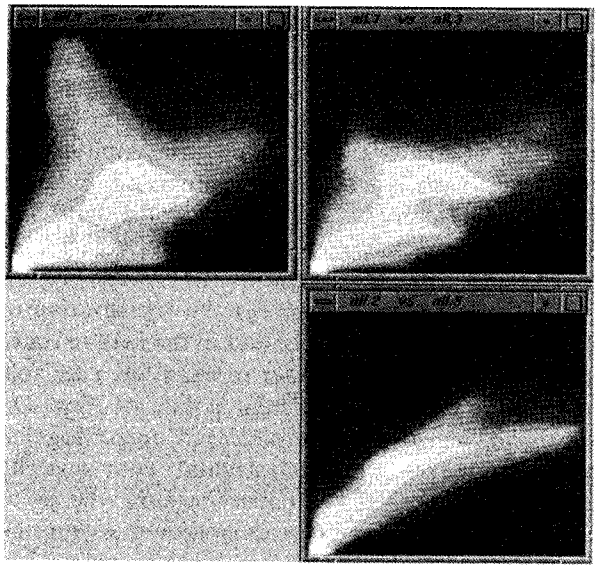

Fig. 2. Orthogonal projections of the feature space relative to the multimodal volume.

of voxels that are represented in each point. This means, for example, that light points describe voxels with a high probability density and dark points describe voxels with combinations of scarcely present values. This may help the user to choose different strategies of analysis (filters, PCA).

Initially, a Principal Component Analysis has been performed in a delimited volume of interest and principal component images have been produced. The eigenvectors of the Principal Components, i.e. the new axes produced as uncorrelated linear combinations of the original axes, superimposed to orthogonal projections of the original feature space, are calculated. The images reconstructed from the projections of data points in the feature space on the new coordinates are shown in Fig. 3. We may notice that most of the information has been condensed in the first two components, while the third presents a heavily noisy aspect. Due to this reconfiguration of data, only the first two components may be selected as images constituting the two-variate 3D volume to be used in the following steps of analysis (Fig. 4) This reduction of dimensionality (three to two) obviously simplifies the task of defining clusters in the feature space by reducing the uncertainty in the points classification. As a consequence, this speeds up the performances of the system and contributes to the stability of results. Moreover, as in this case, PCA may be useful to reduce spatial inhomogeneity and artifacts in images.

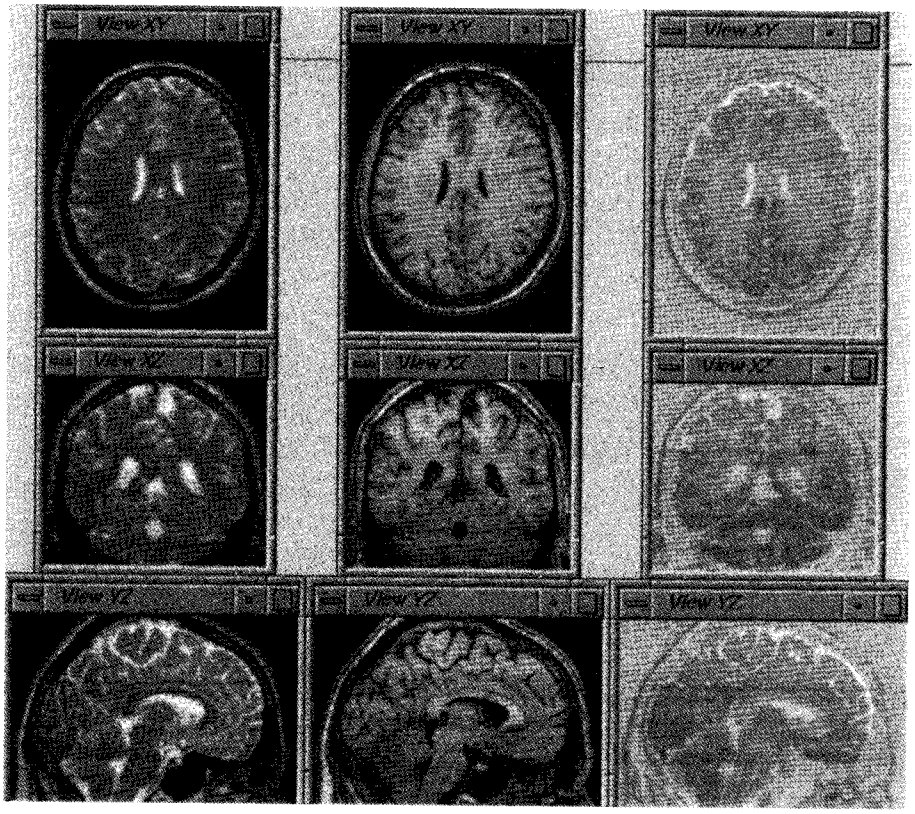

Fig. 3. Principal components with decreasing eigenvalues.

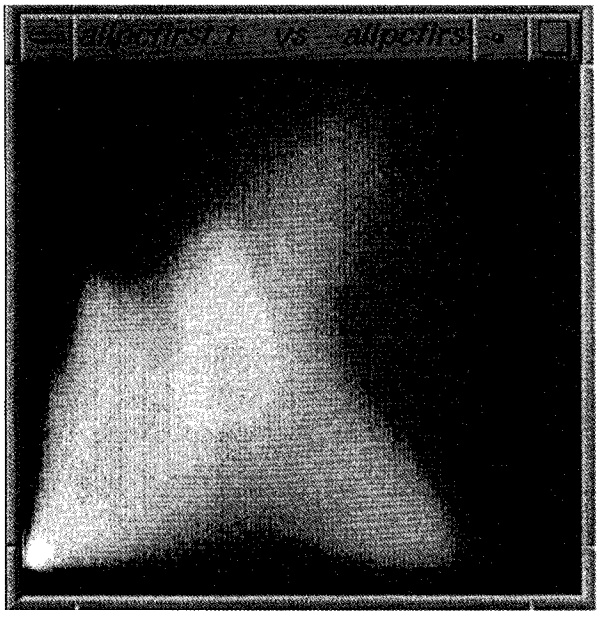

Fig. 4. Feature space relative to the first two principal components.

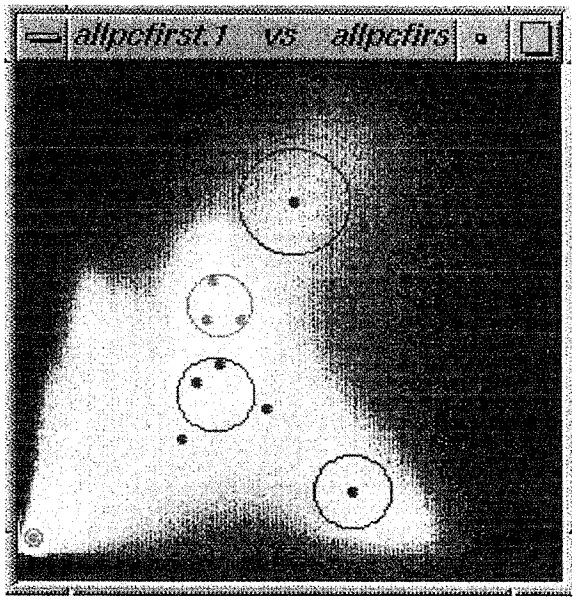

Fig. 5. Results of the unsupervised clustering in the feature space. Each cluster is described by the centroid and the mean radius of the related neurons.

The Capture Effect network has been applied to the bidimensional point distribution in this reduced feature space in order to obtain a totally unsupervised clustering. A scatter plot that describes the cluster distribution in the feature space may be examined at this point (Fig. 5). In general, clusters described by their centroids in the feature space and by the radii of their Receptive Fields, could be selected and modified (joined and split), via mouse, allowing the user to introduce his/her own knowledge in clustering, starting from unsupervised preliminary results. Anyway, in the example considered no modifications have been made on clusters.

Accurately segmented images are then derived by coding algorithms able to exploit the information extracted during the learning phase, concerning both the distribution of 'neurons' and the distribution of radii of the receptive fields. Results of an unsupervised segmentation both in the image space and in the feature space are shown in Fig. 6. The whole sequence of clustering and coding is completely unsupervised and, up to here, no intervention from the user has been required.

For a three-variate (T1, T2, PD) volume with dimensions $171 \times 220 \times 143$, a totally unsupervised segmentation is performed, at present, in about 10 min. With the same dimensions, for a two-variate (first two principal components) volume, the calculation time is reduced to about 3 min. The loss of accuracy that we may notice in the lower regions of the coronal and sagittal views is strictly related to the inhomogeneity of the original data set and does not affect the overall performances of the method. However, the stability and the reproducibility of the unsupervised segmentation seem to be very good (results of several different repetitions appear indistinguishable) and suggest a possible reduction of the number of training patterns. By reducing the number of training patterns on the whole volume and by optimizing the code of clustering and coding, improvements in speed performances are planned. With such modifications a totally unsupervised segmentation is supposed to be obtained, on the same machine and with the same dimensions, in less than 5 min for a three-variate volume, and in less than 2 min for a two-variate volume.

Interactive graphics tools may be successively used in order to perform corrections and refinements in the feature space and in the image space via simple mouse operations. This post-processing utilities fully correlate the display of data in the image and in the feature space in order to keep the user in control of the consequences of his/her interventions in both the spaces. That is, corrections of points classification made on the scatter plots describing the feature space produce modifications of voxels coding that are automatically displayed in the related segmented image. Symmetrically, in consequence of interactive corrections on voxel coding in the image space, the feature space classification results modified and may

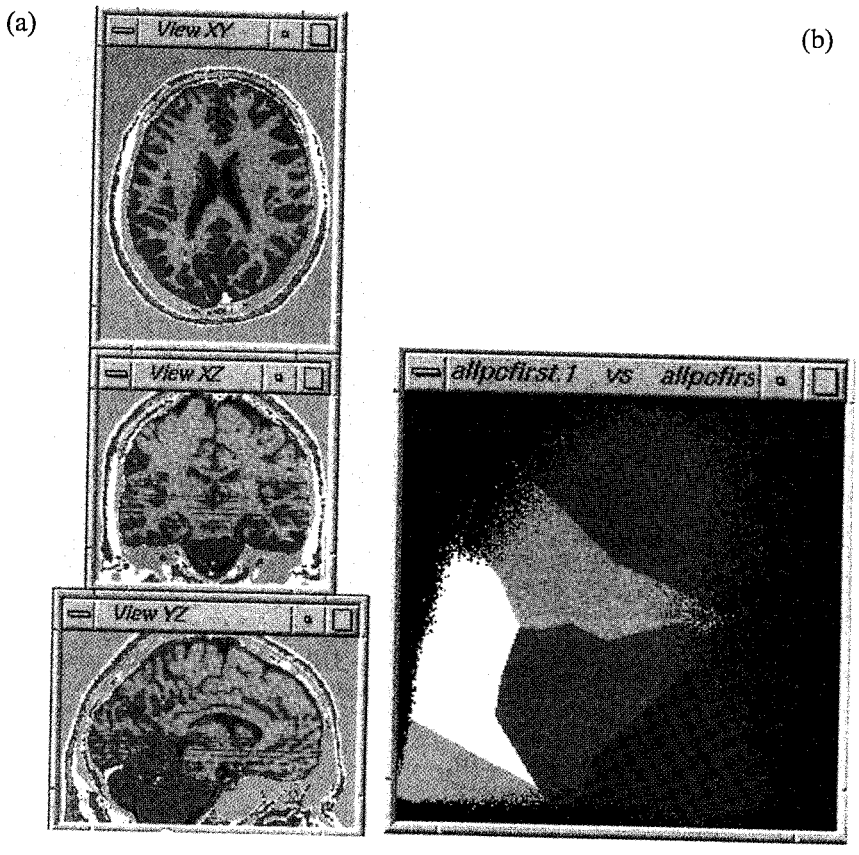

Fig. 6. Results of the fully unsupervised segmentation. (a) Orthogonal views of the segmented volume. (b) Voxel classification in the feature space.

be displayed and even further modified on appropriate scatter plots.

In Fig. 7 the final segmented image together with the final points classification in the feature space are displayed and the relationship emerges between editing operations and results in the feature space and in the image space. On one hand, as we note, the shifting of the edges between clusters in the feature space produces the correction of some misclassifications in the image. On the other hand, further interactive corrections in the image space produce changes in the voxel classification in the feature space.

DISCUSSION

The following steps have been considered in the analysis sequence: reduction of dimensionality, unsupervised data clustering, voxel classification, interactive post-processing refinement.

At first, the reduction of dimensionality of the data structure is made possible by a module performing, at present, a linear Principal Component Analysis with helpful display tools. Improvements, such as the implementation of a neural network-based, non-linear Principal Component Analysis, will be considered in the near future.

Successively, a completely unsupervised approach to clustering and classification produces a preliminary segmented image where structures of interest are precisely defined by a neural network model based on a standard competitive self-organization. Unsupervised analysis of data clusters which naturally appear at different scales of density in different regions of the feature-space is made possible thanks to the fact that the captured neurons have their receptive field locally tuned, in a completely adaptive way, to the density of data around their corresponding weight-vectors. This property is called "adaptive resolution clustering", and a suitable clustering algorithm has been developed based on this property.

The results of our totally unsupervised 3D segmentation appear extremely stable and seem to be an advanced starting point for clinical applications. A comparison with standard unsupervised methods (k-means, Isodata) is not very significant, in the clinical environment, in consequence of the

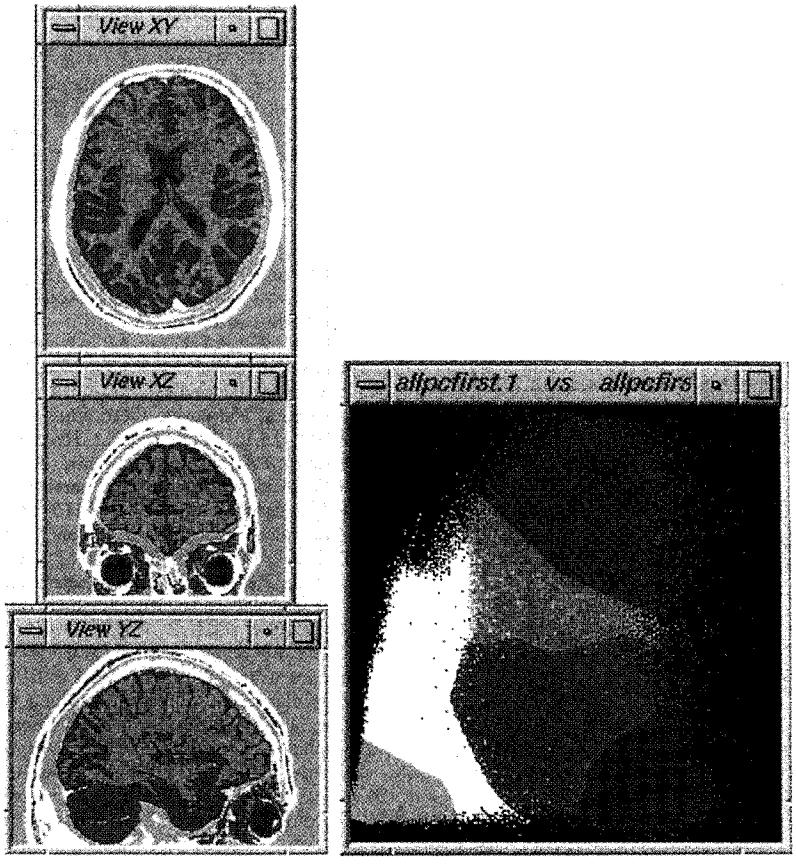

Fig. 7. Final segmentation after interactive refinements both in the image space and in the feature space.

large amount of calculation time needed by such methods for 3D data (some hours for a 3D segmentation of our set of data), due to the fact that they must take into account the whole data set at each step. Anyway a qualitative comparison with the above mentioned standard unsupervised methods on 2D data has been accomplished for one single slice at time and our method seems to be more accurate.

Indeed, the Capture Effect network model has been structured, from the beginning, in view of a fully 3D clustering approach and with the goal of directly fitting the multi-resolution density in the feature space. As a consequence, the redundancy of data is fully exploited and the network may easily adapt its structure to the real data distribution. Moreover, also the classification step is unsupervised, and an accurate, completely unsupervised 3D segmentation of a huge multivariate volume may be performed in a few minutes. With such premises, the performances of our model are presumed to be quite competitive in comparison with other neural or neuro-fuzzy unsupervised methods (6, 7) for a fully 3D image segmentation.

Finally, a subsequent step of interactive refinement of the automatically segmented volume is made possible through a friendly graphical interface in order to allow the user to introduce his/her knowledge both in the image space and in the feature space. The interactive tools for such a task strictly correlate the views of data in both the two spaces, in order to present the multivariate data structure as a whole. The interactive tools are implemented with a really 3D approach, and the refinement of a volume requires a sequence of operations on different orthogonal views of the image space and of the feature space.

To conclude the assessment of the encouraging results shown above, a qualitative and quantitative validation of the clinical significance of our segmentation system is planned through a comparison with manual segmentations actually performed by medical specialists. Variabilities intra- and inter-operator will be obtained both for humans and machine and will be compared in order to quantify the real clinical reliability of the proposed system.

SUMMARY

In this paper we have presented a 3D interactive system developed in a standard X-Windows Unix environment, devoted to segmentation of multivariate medical images through an unsupervised neural network approach to clustering. The following steps may be used in the analysis sequence: reduction of dimensionality, unsupervised data clustering, voxel classification, interactive post-processing refinement. The whole system turns out to be extremely interactive, thus making the user able to display and modify data during processing, to set parameters, to choose different methods and different tools for each step, and to define online the analysis sequence (9).

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