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Parkinson's Disease Diagnosis and Prognosis Using Diffusion Tensor Medical Imaging Features Fusion

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1. Introduction

Despite important advances in medical imaging, cognitive testing methods are still used almost exclusively nowadays for Parkinson's Disease (PD) diagnosis. These tests are evaluated and scored using predefined scales representing the disease severity like UPDRS (Unified Parkinson's Disease Rating Scale) or H&Y (Hoehn and Yahr) scale. Using the same scales, our objective is to include information extracted and fused from different medical imaging modalities, in order to obtain a quantification of the disease evolution, for diagnosis and prognosis purposes.

The dopamine, one of the main neurotransmitters, is lost when PD is installed. By the time the disease can be identified, 80-90% of the dopamine is no longer produced (Today, 2009). Medical studies concluded that the Substantia Nigra, a small anatomical region situated in the midbrain, is the producer of dopamine (Chan et al., 2007). The same anatomical region contains the motor fibres and the effect of the dopamine lost affects these fibers, as the patients lose their motor functions and start trembling once the disease starts manifesting. The importance of the motor fibers for the evolution and the early detection of the disease, represent a major medical motivation to set up a method able to extract and quantify abnormalities in the strationigral tract.

As recently a match between the dopamine level in the Substantia Nigra(SN) and the Parkinson's disease evolution has been detected (Chan et al., 2007), we are using this information further as we are studying the area where the Substantia Nigra(SN) produces the dopamine. David Vaillancourt, assistant professor at University of Illinois at Chicago has leaded a study using a scanned the part of the brain called Substantia Nigra on Parkinson's patients using DTI images and has discovered that the number of dopaminergic neurons in certain areas of this region is 50% less (Vaillancourt, 2009). His study includes 28 subjects from which half have symptoms of early Parkinson's disease and another half do not have these symptoms. This area is not well defined anatomically as there the contours are

unclear. In this case, we detect the midbrain, being certain that it contains the SN. This segmented area is then studied to determine the correlation between the PD patients and the dopamine level, measured by the fractional anisotropy (Teodorescu et al., 2009b). Using a statistical evaluation, the correlation is revealed. For diagnoses purposes, we need also a value quantifying this correlation.
Another study performed to show the relationship between cerebral morphology and the expression of dopamine receptors, conducted on 45 healthy patients, reveals that on grey matter, there is a direct correlation at the SN level. This study (Woodward et al., 2009) uses T_1 weighted structural MRI images. Using Voxel-based morphometry (VBM), the authors create grey matter volumes and density images and correlate these images with Biological Parametric toolbox. Voxel-wise normalization also revealed that the grey matter volume and SN are correlated.
In order to quantify the impact of PD on the patients at the motor level, we study the motor tract to determine if there is a direct link to the loss of dopamine and the degeneration of the neural fibers of this tract. A statistical analysis of the number of fibers and their density is able to reveal if together with the loss of dopamine, the motor fibers that are inactive have a relationship with the PD severity.

1.1 Problems that we aim to solve

The main purpose of our approach is to detect PD based exclusively on the image features. We desire, based on the metrics developed at the image level, to detect PD on early stages and deduct the installation of PD - most likely cases to develop the disease. Working with medical image features, we include medical knowledge when extracting the features, based on the previous studies. The fact that the producer of dopamine is the SN area, makes it an essential volume of interest in our approach. Because this anatomical region is not well defined, we aim on extracting the midbrain, region that contains the SN.
The medical knowledge determines the area of study and the methods extracting the features required by the medical knowledge from the image level. The neural fibers affected by PD, represent the motor tract that we detect using the volume of interest. For an accurate detection, as we are using the midbrain area, where there are many neural tracts passing through, we need another volume of interest, able to select among the neural fibers starting at the midbrain level, just the motor ones. We choose the second volume as the Putamen, anatomical region where the motor tract passes also through.
These volumes of interest are detected using segmentation methods applied on medical images. The fibers are revealed using a deterministic global tractography method with the two-segmented anatomical regions as volumes of interest. The detected fibers must be evaluated and further used as a metric for PD in the diagnosis and prognosis processes. The main purpose of our work, the image based diagnosis/prognosis, determines image processing aims, as well as image analysis ones: **volumes of interest detection** achieved trough medical image segmentation, respectively **exclusive detection of the motor tract** determined by tractography.
There are other aspects that must be taken into account as well, aspects that do not derive from the medical knowledge. The **inter-patient variability** is one of these aspects and it is determined by the demographic parameters: age, sex and race of the patient. These characteristics influence the performance of the algorithms at every level. The brain structures volumes vary depending on the sex of the patient, the shape of the head differs depending on the race, and age determines brain atrophy, inducing a variation of the anatomical structures.

All these manifestations are linked to demographic parameters.
There are special limitations regarding the medical **images resolution** and specificity for the image processing algorithms. One of the main tasks is to find the appropriate slice in which to look for the volume of interest. Each slice contains different information and we rely on volumetric information when choosing the slice of interest for each of the segmentation algorithms. The **position of each patient in the image** is different, as is the size and shape of the head. This aspect determines the location of the volumes of interest of the brain (starting from the nose level or from the eyes level) or for the same number of slices, the whole brain or only a part of it (for smaller skulls the whole brain can be scanned, whereas for bigger ones, only a percentage of it, even if the scanning starts at the same level). This aspect determines an evaluation of the volume content in the image stack provided. We can place our analysis parameters, based on the center of mass of the brain.
Another aspect regarding **intra-patient variability** is the difference between the two hemispheres of the brain for the same patient. The Putamen is not symmetrically placed on the left and right side of the middle axis that separates the hemispheres, neither at the same relative position with regard to the center of mass of the brain. This is one of the challenges, together with the fact that the right side Putamen can have a different shape and size from the left side and be placed higher or lower than the other one. Tough finding the limit between the two hemispheres of the brain is another bid as it must be determined. The two hemispheres are not perfectly symmetrical and the line is not necessarily perpendicular on the horizontal axis of the image- **the intra-patient specificity**. The need to determine this axis with no connection to the specificity of the patient, determines also a need for an automatic overall detection approach.

1.2 General presentation of the methods

Using the provided images, we obtain different features from different DTI (Diffusion Tensor Imaging) modalities. By fusing the image information and using it to attach a value to the severity degree from the disease scale, we propose a new approach altogether with image processing (specific anatomical segmentation) and analysis methods. With a geometry-based automatic registration, we fuse information from different DTI image methods: FA (Fractional Anisotropy) and EPI (Echo-Planar Imaging). The specificity of the EPI resides in the tensor information, but it lacks anatomical detail, as it has a low resolution. At this point, the FA completes the informational data, as it contains the anisotropy representing the dopamine flow. As at the midbrain level, there are many fiber tracts, this area does not provide just the motor tract. The fibers from this tract cross also the Putamen. Determining the fibers that cross the two anatomical areas - midbrain and Putamen - at the same time, provides a more accurate selection using a global deterministic tractography. The midbrain can be detected and segmented on the image that contains the tensors, the EPI, but the Putamen is not detectable even on the high-resolution images like T_1 or T_2. The FA image, due to the dopamine flow, has the boundaries of the Putamen and an accurate segmentation is possible on this image.
The registration is needed as the segmented area is used for the tractography on the EPI image volume and not on the FA, where it is detected. The dopamine flow revealing the Putamen represents one type of information at the image level, different from the tensor information with anatomical detail, present on the EPI image. This is the reason for an information fusion from the two image modalities, achieved by registering the extracted Putamen map on the EPI.

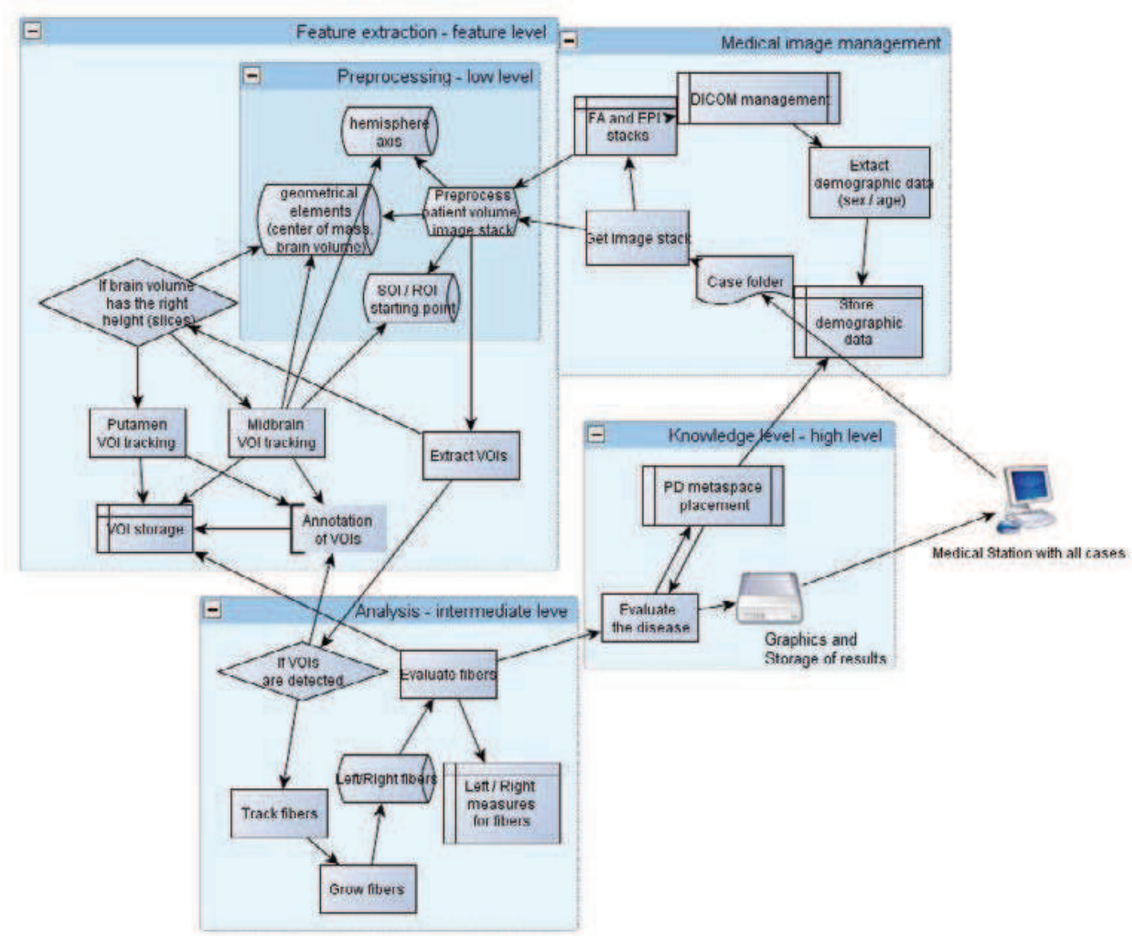


Fig. 1. PDFibAtl@s prototype integrating our methods

Once the fibers are detected, they are evaluated introducing specific metrics for the fiber density. Using a statistical method, correlation between the PD severity and the fiber values is detected. The specific fibers evaluated are analyzed. The diagnosis based on these values makes the difference between the control cases and the PD. Usually prognosis functions determine the evolution in time of a patient, but for that purpose we need a follow-up on the patients. In other cases, the prognosis function decides on the severity of a disease. For us, the prognosis is able to detect the disease severity for the PD patients.
As shown in figure 1,there are several levels where the information is manipulated:

– Image level
– Feature level
– Knowledge Level

Our prototype - PDFibAtl@s - implements the image processing and analysis methods taking the images from the medical station in DICOM format and extracting the significant features. The first level of information, the *image level*, deals with the medical image standard files and extracts the primary information from it, making the difference between the image and the protocol elements. At the *feature level*, a preprocessing step is applied to the image. The

information retrieved by feature extraction, encapsulates medical knowledge as well. The analysis part uses the tractography to determine the motor fibers. Having as input the value obtained by measuring the fibers, we develop at the *knowledge level*, the algorithms performing diagnosis and prognosis assistance.
From the clinical point of view, translational researches are necessary by next to go from the Proof of Concept (POC) to the Proof of Value (POV).
The structure of this chapter contains in the next section similar methods with the ones developed in our work and the systems that include these methods (subsec. 1.3). After presenting the protocols and characteristics of the medical images (sec. 2), we present the image processing methods (sec. 3) with the tractography approach, and the diagnosis and prognosis module performing the data analysis. These methods make the transition of information from the rough image level to the knowledge level as presented in section 4. The final conclusions together with future works and perspectives are presented in section 5.

1.3 Methods used in other approaches

We have tested several methods before designing our approach. We used our database for these tests, in order to detected the problems at the image level and define the requirements for the pre-processing stage. Different methods, provided by dedicated systems, offered a background view as well as a comparison method for evaluating our own methods.

1.3.1 Matlab based systems (SPM and VBM)

Statistical Parametric Mapping (SPM)- is a plug - in software that extends statistical processes dedicated to the functional imaging data. The software package performs analysis of brain imaging data sequences[1]. This plug-in software is designed for the Matlab environment. The SPM5 version accepts DTI images for processing and provides alignment and preprocessing using the fMRI (Functional MRI) dedicated module. Testing Statistical Parametric Mapping algorithms (Maltlab SPM toolbox), we obtain results only on the entire brain analysis and due to the image quality, the skull extraction cannot be properly performed and thus, we have interferences with the results on the anisotropy. A specific atlas, containing automatically detected anatomical volumes, represents a tool that can be applied to any type of patient.
Voxel Based Morphometry (VBM)[2] represents another module that can be integrated in Matlab with SPM, as a plug-in in SPM5. This module is able to make segmentation in WM (white matter) and GM (grey matter) based on voxel-wise comparison.
The segmentations provided by the SPM and VBM - depending on the tissue type - are not enough for our purpose, as we need specific anatomical regions as SN and the Putamen. SPM uses the atlas approach (Guillaume, 2008) for this purpose and categorizes the brain images on the race of the patients. This approach is not applicable for us, as we have a heterogeneous database. By using the atlas approach, the inter-patient variability is not considered. When performing the registration using VBM, the resulted images are "folded" and not usable for tracking.

[1]SPM site - http://www.fil.ion.ucl.ac.uk/spm/ - last accessed on May 2010
[2]Voxel based morphometry (VBM) - http://en.wikipedia.org/wiki/Voxel-based_morphometry - last accessed on May 2010

1.3.2 DTI dedicated systems

MedINRIA[3] system is designed for DTI management providing different modules for image processing and analysis procedures. In this case, the segmentation is a manual one, offering the necessary accuracy. The Fusion module of this system provides several registration methods that we are testing: the manual approach, the automatic affine registration and the diffeomorphic registration. The fact that the registration does not perform with the accuracy needed on our images to generate the correct fibers, represents the major drawback. Beside, the fact that we cannot limit, using two volumes of interest, the chosen fibers, makes us regard another option altogether for the tractography method. Even though, because of technical reasons, manual registration would be optimal for our case, we cannot use the DTI track module for the global tractography, using Log-Euclidian metrics on a deterministic approach, because it would mean choosing only one volume of interest, which cannot separate only the bundle of interest. This module provides only a local method for tractography.

Slicer 3D is another system tested with our database on the registration and tractography. The same manual segmentation approach is offered by the Slicer 3D system[4], but in this case, at the registration level, the system provides just the manual method as a valid one for our images. The tractography overcharges the memory of the computer when applying a probabilistic global approach. In some of the cases, even the registration cannot be completed by the system.

TracVis provides a probabilistic global method for tractography. This probabilistic global approach implemented in Diffusion Toolkit[5] performs the best for our database. The approach offers several methods for computing the propagation of the diffusion: FACT, second order Runge Kutta, Interpolated Streamline and Tensorline. We are testing the second order Runge Kutta, as it is the closest to our approach. Using a previous mask for the volumes of interest does not perform well on our data, but the possibility of limiting the computed fibers using a manual segmented volume of interest (VOI), or even two VOIs, provides the specific motor tract representing the bundle of interest. The drawback is the fact that this approach needs to compute all the fibers and limit them afterwards. We do not need all the fibers and this time-consuming process can be avoided with the mask volume. This possibility exists in the Diffusion Toolkit, but our mask volumes could not be read either by the Diffusion Toolkit or the TrackVis module. This aspect constrained us to perform the manual segmentation. However, even with the manually detected VOIs, the results on the fibers were either null or noisy.

1.3.3 Diagnosis and prognosis methodologies

Once the segmentation of the volumes of interest is achieved and the tractography performed, the extracted values for the fibers are analyzed for diagnosis and prognosis. We need to estimate the PD severity using the same scale as the one in the cognitive testing for estimation and comparison purpose. For the database, we are working with the provided H&Y values as a ground truth.

We have tested several classical clustering methods like KNN (K Nearest Neighbor) and KMeans but, due to the dispersions and uncertainty existent in our data, the results were not satisfactory. When deciding the way to analyze the extracted fiber values, we take into account several prognosis approaches. We need a decision-based method to analyze the features and

[3]MedINRIA - http://www-sop.inria.fr/asclepios/software/MedINRIA/ - last accessed on May 2010
[4]Slicer - http://www.slicer.org/ - last accessed on May 2010
[5]Diffuion toolkit -dtk - http://www.trackvis.org/dtk/

give an exact placement of the case on the PD scale. We can take into account rule-based systems, as they include predicates with medical knowledge. Considering fuzzy logic, we can capture the behavior of the system. Statistical methods include all possibilities for the features, but the selection of a decision threshold is very challenging and subject to sensitivity.
Working with non-probabilistic uncertainties, fuzzy sets, determines an approach based on fuzzy models. A fuzzy inference system, or fuzzy model, can adapt itself using numerical data. A fuzzy inference system has learning capability and using this aspect, the link between the fuzzy controllers and the methodologies for neural networks is possible using the Adaptive Network-Based Fuzzy Inference Systems (ANFIS). These networks have the overall input-output behavior influenced by a set of parameters. These parameters define functions that determine adaptive nodes at the network level. Applying the learning techniques from the neural networks to the fuzzy sets, allows us to determine an ANFIS structure. For us, the fuzzy sets represent the values extracted at the tractography level. These sets are defined in intervals and determine the If-Then rules. Together with these rules, the database (fuzzy sets) and a reasoning mechanism, determine a fuzzy inference system. At the reasoning part, we have to take into account the inference model (Jang & Sun, 1995).
Following an ANFIS (Bonissone, 1997), we can combine the fuzzy control offered by the medical background and statistical analysis with neural networks. The fuzzy features represent the a priori knowledge as a set of constraints - rules. One of the applications of ANFIS is presented as a mode to explain past data and predict behavior. In our approach, we use as Fuzzy Control (FC) a fuzzy set. For the FC technology we use rule inference where we make the difference between the disease stages. We adapted this approach, but as the neural networks separately did not perform well, we use adaptive interpolation functions.

1.4 Detected requirements from the tested systems

In our prototype, we use a specialized library that provides elementary image processing functions and algorithms: medical image reading and writing, basic filters and plug-ins, enables us to use algorithms already implemented and to begin our processing at a higher level of data management. Indeed *imageJ*[6] is a useful open source Java based library conceived for medical image processing and analysis that offers the possibility to develop a Java application that can be used for testing further in this library as a plug-in.
The systems that we are testing have different approach on the segmentation algorithms. MedINRIA provides a way of manually defining the regions of interest, as this is the most accurate way of segmentation.
The TrackVis module provides also the same accuracy as using the manual approach. 3D Slicer and SPM provide atlas-based approaches, but 3D Slicer does not manage to finish the computation for our images and the SPM results are blurry and not accurate. Analyzing the results obtained with these methods, we decide to adopt a geometrical-based registration with volumetric landmarks. For the segmentation method, the geometrical landmarks are used to guide specific adaptive region growing algorithms.
In our approach, we follow the ANFIS layers, from the input fiber data extracted, to the PD results, adapting the system to our needs. The ground truth is represented by the Hoehn & Yahr (H&Y) grade provided by the medical experts.

[6]ImageJ website -http://rsb.info.nih.gov/ij/ - last accessed on June 2010

2. Database characteristics

A number of 68 patients diagnosed clinically with PD and 75 control cases underwent DTI imaging (TR/TE 4300/90; 12 directions; 4 averages; 4/0 mm sections; 1.2 x 1.2 mm in-plane resolution) after giving informed consent. This represents, as far as we know, one of the biggest cohort of PD patients implicated in this type of study. The heterogeneity of the patients - Asians, Eurasians and Europeans - can also be used to characterize a general trend for PD prognosis. For this type of DTI images, we have 351 images that represent slices of 4 mm of brain structures taken in 13 directions at each step. In this case, we have 27 images (axial slices) that constitute a 3D brain image. The DTI images that we are using were taken with a Siemens Avanto 1.5T(B=800, 12 diffusion directions).
All the images are in DICOM format. This format is specific to the medical images, containing the header file and the image encapsulated in the "dcm" (DICOM) file.

2.1 DTI images used in our approach

From the DTI images, the **Echo Planar Images (EPI)** are among the ones with the lowest resolution. The advantage of this type of DTI is that they contain the tensor information as matrixes, giving the actual orientation of the water flow defining the brain fibers. The diffusion directions have each, as result, one volume of images.
This type of image is not appropriate for the anatomy extraction and analysis, but the tensor and anisotropy values stored represent the bottom line of fiber reconstruction, as well as the source for other images. We perform the entire image preprocessing on the EPIs, as they provide the tensor for the fibers as well. A preprocessing step for these images represents a contrast enhancement of 0.5% for a better detection of the skull and the volumes of interest.
Fractional anisotropy images result from the computation of the anisotropy level for each voxel on the EPI images. They contain not only the anisotropy values, but also the color code for it. This type of image represents the diffusion direction inside the fibers. Accordingly, the Putamen area is well defined as the motor tract reaches it and stands out as contour with high anatomical detail; therefore we use it in the automatic detection of this volume of interest.
After a registration of the volume of interest extracted from this image, we can use it together with the tensors from the EPI, in order to limit the fibers that we take into account. At this point, there is an exchange of information from one image type to another, by information fusion.

2.2 Preparing the image for processing

Due to the complex structure of the medical image-encoding manner of the DICOM format, we need to extract the useful information from the header file. During the processing and analysis steps, we only make use of the image itself, without additional information. This is the reason why we transform the image from the DICOM format to Analyze and store it as stacks of images, representing an entire brain volume for each patient and each modality.
For the axial plane, the images that we have in our database are taken in AC/PC plane - Anterior Commissure/Posterior Commissure. This axis is significant from the anatomical point of view and the radiologist uses it, because distinguishable in all the MRI images.

3. System and method presentation

Testing several systems dealing with specific treatment of DTI images, we construct our approach based on the clinical needs, as well as on the results obtained from other systems.

First, by testing other systems with our own images (subsection 1.3), we evaluate the possibilities that we have of using our images and the data flows that these images can provide.
From figure 1, we define the main processes that our information undergoes from the image level to the knowledge level. We start using EPI images, where we extract the midbrain area first. The FA images are used for automatic Putamen detection and, registering these images on the EPI, place the detected volumes at the right position on the EPI images. Once these volumes of interest are placed, the algorithm for fiber growth is applied on the EPIs and the fibers extracted are analyzed, together with the detected volumes of interest. Another part is represented by the diagnosis step followed by prognosis.

3.1 Image initialization and pre-processing

The preprocessing part has to overcome the **low resolution** of the EPI, as well as the **demographic characteristics** of the patients (age, race and sex differences). In our study, we surmount the sex differences by computing the volume of each brain, as there is a difference between female and male volume of the brain, based on smaller skull usually recorded for women.
In order to detect the elements related to the volume of interest, we consider the relative position of anatomical elements to a fixed point. We have chosen this point to be the center of mass of the brain (X_c, Y_c, Z_c). In order to determine this point, we need to consider the brain, without the skull. Another problem that we have to surmount is the intra-patient variability in the segmentation algorithms. The segmentation algorithm methods perform the detection inside the axial slices. In order to start the algorithms at the right place on the right slice, the position of this slice must be determined first. This position represents the placement of the axial plane (O_x and O_y axis inside the volume) relative to the coronal (O_x and O_z axis of the volume) and the sagittal (O_y and O_z axis of the volume) planes, on the O_z axis of the brain volume. This aspect provided us with the right placement of the algorithm at the slice level - the **placement at the volume level**. We need to find the anatomical region inside the axial image for which we need the volume definition - **placement inside the slice**, with identification of the right place for the volume detection.
From the segmentation point of view, solutions like the one proposed by SPM that performs the entire head segmentation are not applicable, as we need only our volume of interest, not a certain type of tissue. Due to the **patient variability**, we need robust VOI segmentation algorithms.
As one of the volumes is detected using an image stack (FA stack) different from the stack where we later use it (EPI stack), registration is needed. The problems with registration reside at the **landmark level** and influence the accuracy of this process. With no interference from the user, we perform a geometry based intra-patient registration with the geometrical landmarks automatically detected at the preprocessing level.
For the **bundle of interest** choice we use the two VOIs to limit the tracking starting from the midbrain area by selecting just those that reach the Putamen : deterministic global tractography. At this point, we compute measures based on the density of the fibers in the entire volume of the brain or in the volume of interest.

$$FD = \frac{F_{Nr}}{Vol_{Brain}};\ FD_{rel} = \frac{F_{Nr}}{Vol_{VOI}} \tag{1}$$

where FD represents the fiber density computed as the number of fibers - F_{Nr} - in the volume of the entire brain - Vol_{Brain} and FD_{rel} represents the fiber density relative to the volume of

interest- Vol_{VOI}. We try to overcome the age difference as well, by taking the mean age on the testing batch, as close as possible between the PD patients and the control cases. Computing the fiber volume and the brain volume, an analysis is possible to detect the geriatric effects on the brain and on the neural fibers al well.

$$FV = F_{Nr} * V_{height} * V_{width} * V_{depth} * F_{leng} \quad (2)$$

where FV represents the fiber volume computed as the product of fiber number (F_{Nr}), fiber length (F_{leng}) - constant as the fibers must pass through both regions of interest and the voxel dimensions: $V_{width}, V_{height}, V_{depth}$. According to the medical manifestation of the disease, the fiber density and volume should be diminished for the PD patients, compared with the control cases. The degradation of the fibers should also be correlated with the severity of the disease, specified by the H&Y scale.
For our system, we need several elements of image preprocessing for a good image quality, before processing. This is prevailed with morphological operators, together with segmentation algorithms and de-noises filters. Our main concerns are linked to the movement artifacts from our images that must be eliminated for a proper analysis. Due to early study and analysis, the bone tissue constituting the skull needs to be eliminated for a better further processing. At the processing level, another important matter that must be solved is preparing the parameters for our own algorithms, so that the processing algorithms can accomplish the optimal detection of the VOIs: slice detection at the volume level and adaptive anatomical detection at the image level.

3.1.1 Skull removal

As the systems considered in subsection 1.3 provided algorithms that performed the skull removal as well, we have tested these algorithms first and then developed our own, as obviously needed. The systems are tested using our own images with the characteristics specified in section 2 and we are using EPIs, as they are the ones providing the elements for the fiber growth.
Our own algorithm was applied on the EPI image and it uses KMeans classification to detect the bone tissue. This algorithm is already implemented in java and was available as a plug-in in imageJ[7]. Actually, the FA image containing the anisotropy provides the intensity for the skull voxels similar to the one representing the GM. This is the reason for the noise at the FA computation. For our purpose, we use a four-class evaluation to distinguish between the bone tissue and the GM, WM and CSF. The algorithm was not sensitive to the exterior noise, as we have applied a noise removal filter provided by the same library. In this way, all the elements outside the skull perimeter was considered as noise and eliminated.
At his point, the brain tissue represents the only information in the image. Estimation, analysis and processing on these images offer correct results on the brain tissue state.

3.1.2 Retrieving the geometrical elements

Having only the brain as information in the whole volume representation, offers us the possibility to set landmarks based on the whole volume estimation so that we can eliminate at least a part of the patient variability. This is the reason why we retrieve, using an imageJ

[7]KMeans in imageJ: http://ij-plugins.sourceforge.net/plugins/clustering /index.html - last accessed on June 2010

plug-in algorithm -object counter[8], the brain center of mass at the volume level and we are able to perform the same feature extraction at the slice level. This landmark is able to offer us an alignment for all the patients based on their volume, a central axis placement through the aligned volume. Next, we need a manner in which to find the limit the left and right side of the brain and in thus have another landmark for the patient alignment.

3.1.3 Hemisphere detection

This detection is further needed for patient alignment at the volume level to provide, together with the center of mass, a plan that passes through the center of the brain, making the distinction between the two hemispheres. For this detection, we determine the outer boundary of the brain. We analyze this boundary as a variation function determining the maximum inflexion point on the function corresponding to the occipital sinuses at the base of the occipital lobes junction.
This point, together with the center of mass of the brain, determines a sagittal plane between the two hemispheres. The same point, indicating the occipital sinuses and making the distinction between the two brain hemispheres, represents on an axial plane, together with the center of mass, an axis indicating the directionality of the head inside the image. The axis and the determined points will be used for segmentation and registration.

3.1.4 Volume management and slice detection

At the volume level, for the slice detection, we use the determined center of mass with the imageJ plug-in by Fabrice Cordelires and Jonathan Jackson called *Object Counter* [9]. This plug-in detects the 3D objects from image stacks and provides their volume, surface, the center of mass and the center of intensity. We use the volume provided for demographic parameter elimination and the center of mass for an inter-patient alignment.
Detecting the slice of interest starting from the center of mass of the brain is done by taking into account the placement of the anatomical regions that we consider as volumes of interest. For the cases with smaller brain volume, the slices could contain the entire brain, the others cannot. In order to establish the position and the content of the brain volume, we select the first and the last slice and extract the volume of the objects from these slices. We establish levels for defining the position of the midbrain relative to the determined center of mass of the brain.

$$P_{slice} = \frac{Vol_{Zslice}}{Vol_{Fslice}} * \frac{100}{ST} \tag{3}$$

where Vol_{Zslice} and Vol_{Fslice} represent the volumes of the objects in the slice with the determined center of mass, respectively the first slice on the stack; ST is the slice thickness (4 mm) and the values place the midbrain with relative to the determined center of mass with:

- Slice 0 if $P_{slice} < 60$
- Slice 1 if $60 < P_{slice} < 70$
- Slice 2 if $70 < P_{slice} < 85$
- Slice 3 if $85 < P_{slice} < 100$

[8] imageJ plug-in Object Counter: http://rsbweb.nih.gov/ij/plugins/track /objects.html - last accessed on June 2010

[9] Object Counter - http://rsbweb.nih.gov/ij/plugins/track/objects.html - last accessed on June 2010

These threshold values represent the statistical established studies with regard to the midbrain position and its placement relative to the percentage determined value. If the stack is not correct - if it does not contain the minimum slices for the midbrain and the Putamen detection - we transmit an error value for the slice of interest (-1). Once this position is determined, the Putamen algorithm starts with two slices above the midbrain-detected slice - one slice is with the midbrain, and the second one has to contain the AC/PC line. We adjust the Putamen slice if the detected volume is too small (20 pixels) or if it is placed too near to the midline. If this is the case, it means that the brain is bigger than estimated by the relative parameters and we find the Putamen one slice above the one we have placed the algorithm.

3.1.5 Finding the starting point for anatomical segmentation

Once we have the slice of interest detected for each of the volumes used on the tractography, we need algorithms that determine the placement in the image slice of the anatomical region that we are segmenting. Knowing the location of the regions based on the brain physiology, we design specific algorithms for each volume, in order to determine the stating point for the active detection algorithm.

The extraction of the volumes of interest is possible only on the images that provide a clear boundary for the anatomical regions that represent our volumes of interest. The algorithms for extraction must be placed on the right anatomical area inside the 3D image volume, for this detection to be as accurate as possible. The automatic detection is possible only after the starting point for the active volume is set. The difficulty in this case lies in finding, in the slice of interest, the right region for the active volume growth.

Detection for the starting point of the volume of interest in the **midbrain area** is done similar to the detection of the slice of interest and it is combined with the division in hemispheres of the brain. We need the hemispheres separately on account of the study of Dr. Chan (Chan et al., 2007) which states that there are different stages of development of PD in the left side and the right side of the brain. The inter-hemispherical axis detected is used when we detect the volumes of interest, as we want the algorithm to consider only the needed hemisphere. The algorithm for finding the midbrain starts from the center of mass of the volume inside the slice of interest and following the inter-hemispherical axis searches for a gray matter region placed next to this point or above it.

Detecting the starting point for the **Putamen detection algorithm** is different from the one used for the midbrain, as the Putamen is not placed on the inter-hemispherical axis and does not have a geometrically detectable point or standard distance -patient variability. We are working on the FA image as it contains the anisotropy that follows the dopamine flow and makes the Putamen more distinguishable than on the other type of images. Our algorithm is also based on the placement of the two areas relatively to the center of mass of the image as well. As this is a more complex matter there are several steps performed for achieving an adequate positioning inside the image and eliminating the inter-patient variability:

- Classification of images based on the head shape
- Segmentation on tissue type based on the voxel intensity
- Validation of the Putamen region based on the placement with reference to the center of mass

The first step represents a rough categorization of the head based on the sex variance, as well as on the subject provenance (e.g the shape of Eurasians is different of those of Europeans and Afro-Americans). We detect three main classes based on the position of the center of mass with

regard to the middle of the image. The second step is meant to distinguish the anatomical areas and make easier the search for the Putamen. This segmentation is performed using the KMeans[10] plug-in based on (Jain & Dubles, 1988). We establish the number of clusters based on the tissue types the image now contains and the tolerance is left at the default value together with the randomization seed. The image containing all these clusters represents the map for the algorithm that established the volume of interest. Based on this image and the medical knowledge, our algorithm starts at the center of mass and follows the hemisphere axis. Depending on the category established at the first step, the algorithm chooses the proper level for hemisphere exploration on the left and the right side. Passing two tissue types and reaching the CSF area we then reach the Putamen. At this point, the volume-tracking algorithm can be applied.

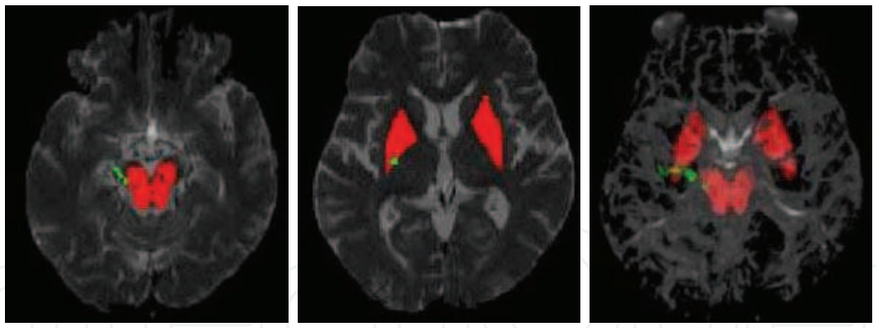
3.2 Volume segmentation algorithms - active volume segmentation

The process of active volume determination is placed at the slice level and the stack level at the same time. At the slice level, after determining the starting point for the active tracking algorithm on the slice of interest (SOI), we move on to the growing step for the volume determination. We are thus performing a segmentation using the active contour algorithm and setting the threshold for it as voxels belonging to the other classes rather than the one we are exploring. At this point, the algorithms differ much depending on the anatomical region we want to extract, as well as on the hemisphere we are exploring. Nevertheless, after this exploration is finished, we apply this approach on the next slice and in this way, we extract volumes by making a stack of the extracted ROIs.
Regions are typically identified based on their internal homogeneity. However, the size of the shape is important when defining the homogeneity. Fractal features can provide additional information from this perspective. The region segmentation can be contour-based or region-based, depending on the restrictions applied for ending the detection process: exterior limits, respectively entropy values (Sonka & Fitzpatrick, 2009). We are using the image representing the KMeans-generated clusters as pixel intensities for the four types of classes. For the midbrain active contour, we perform a region-based detection, whereas for the Putamen, we perform a contour-based detection.
Considering a generalization on the active volume-tracking algorithm, there are several main steps to be followed:

- Seed placement inside the ROI
- Considering new points for the ROI extension
- Comparison with the voxels in the ROI and threshold elements
- Validation of the considered voxel as part of the ROI

These steps are further adapted and refined to fit our image resolution and the anatomical shapes at the same time.
In the algorithm for **detecting the volume of interest in the midbrain area**, we have two steps for detection: the definition and detection of the region of interest and the volume detection. For the region of interest, we use a snake-based algorithm applied on a segmented image with KMeans in imageJ. We segment the EPI stack in imageJ for which we intent to make the difference between the Cerebrospinal Fluid(CSF) surrounding the midbrain and the area we

[10]IJ Plugins: Clustering http://ij-plugins.sourceforge.net/plugins/clustering /index.html - last accessed on June 2010

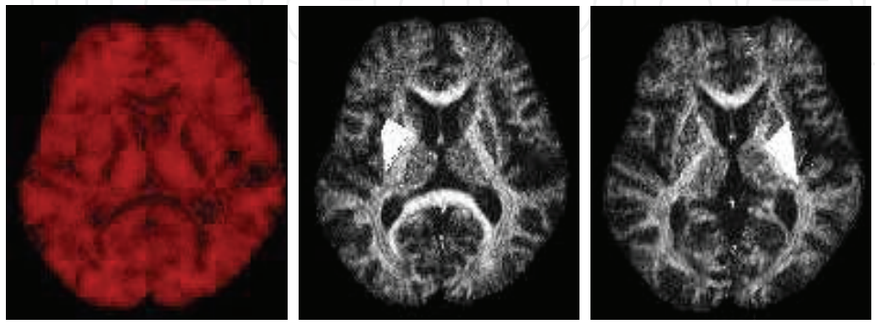


(a) (b) (c)

Fig. 2. EPI with detected VOIs: image 2(a) the midbrain on both hemispheres; image 2(b) the Putamen and image 2(c) with 3D fibers on an example

want to detect. On the gray matter class so obtained, we perform the snake-based algorithm that has the starting point determined in the preprocessing part. This exploration step ends when there is a difference between the new pixel and the previous one or we step on the midline of the brain. After finishing the algorithm on one slice we explore the slice above in similar manner. As we know from the study presented in (Starr & Mandybur, 2009), almost 80% of the SN is found in one slice (4 mm) thus, we want to make sure that in our volume of interest this anatomical region is contained and for this purpose, we take the two slices that most probably contain the midbrain.

For the Putamen volume detection, we take into account the shape of this specific anatomical region and we construct a totally different algorithm, that must overcome several obstacles: the placement of the Putamen that is not necessarily at the same level in both sides, the size of it differs very much from one hemisphere to the other, as well as its shape - intra-patient variability. In the preprocessing stage, we overcome this problem with the automatic Putamen region detection. The Putamen shape on the slice of interest - the slice above the one containing the AC/PC line- is triangular, whereas on the slice above this one is a quadrilateral shape approximation. This is the reason why, if we want a high accuracy, we have two kinds of algorithms for the Putamen tracing. One of these algorithms starts from a triangle placed at the seed place. This triangle moves its vertices only on the class of voxels belonging to the ones from the seed. It stops when reaching another class (3-5 consecutive voxels different from the ones constituting the VOI). The same manner of operating is applied for the other



(a) (b) (c)

Fig. 3. FA image with Putamen detected (Sabau et al., 2010) starting from the KMeans clustered voxels from image 3(a) on the left side in figure 3(b), respectively the right side 3(c)

approach, except the fact that it starts from a quadrilateral shape, moving at each step four vertices. We adjust the obtained shape by comparing the left and right limits and the level of the VOIs on the two hemispheres.
As shown in the flowchart from figure 4, after the positioning at the volume level in the slice of interest, the algorithm has to determine the relative position of the head inside the image in the pre-processing stage. Depending on that position, we choose the starting point for the active volume detection and move on the active volume determination. Once the starting point positioned, we choose the suitable algorithm for the shape extraction. We apply the triangular shape growing for the right side and the quadrilateral shape for the left side and the upper slices in the volume detection. These algorithms divide the starting point into three respectively four points (fig. 3). The three-point algorithm follows the triangular shape of the Putamen, which is more obvious on the slice with the AC/PC line. The choice was made by statistically determining the difference between the two algorithms and the manually segmented images that represents the ideal segmentation shape.
Both approaches consider the extension of the region of interest by taking each pixel next to the ones that represent the initial points in the clustering area. If the pixel appertains to the cluster of the initial points, it becomes one of the shape defining points - the edge of the triangle for the three points segmentation algorithm, or the edge of the quadrilateral shape for the four points segmentation algorithm. The active volume determination finishes when other clusters are encountered.
The determined area is placed with respect to the one determined on the other hemisphere. When the positioning of the two determined area is finished, the algorithm is repeated for the upper slice for the volume determination. The regions thus determined are transformed in mask images that are further transformed according to the parameters determined in the registration algorithms.

3.3 Automatic geometry-based registration

When talking about registration, we refer to matching or bringing the modalities to spatial alignment by finding the optimal geometrical transformation between corresponding image data (Teodorescu, 2010). Our approach is completely automatic as it is based on the determined geometrical landmarks used for the segmentation. These landmarks are independent of the inter-patient variability and on the imaging modality. The challenges for performing the registration reside in finding the best landmarks in both image types, finding a suitable spatial transformation and, for our type of images, preserving the tensor direction. In our case, we perform intra-subject registration, as we match images appertaining to the same subject. Our registration is a rigid one, as it contains only translations and rotations, affine transformation. As we are using homologous features, based on geometrical distances, our registration is a geometrical-based one.
For the midbrain area, we use the EPI B0 image, the one without diffusion, as it is clear enough for this purpose, even if the resolution for this type of image is poor. For the Putamen area, the contours of this anatomical region are not well detected by the algorithms on the same image modality. In this case, we use the FA image and take advantage of the anisotropy difference, represented in this type of image as a different color intensity corresponding to the dopamine flow going in different directions. This makes possible detection of the Putamen area on the FA image. However, when we use the detected Putamen, we want to do that on the EPI image and we need to know that the extracted volume is on the right place.

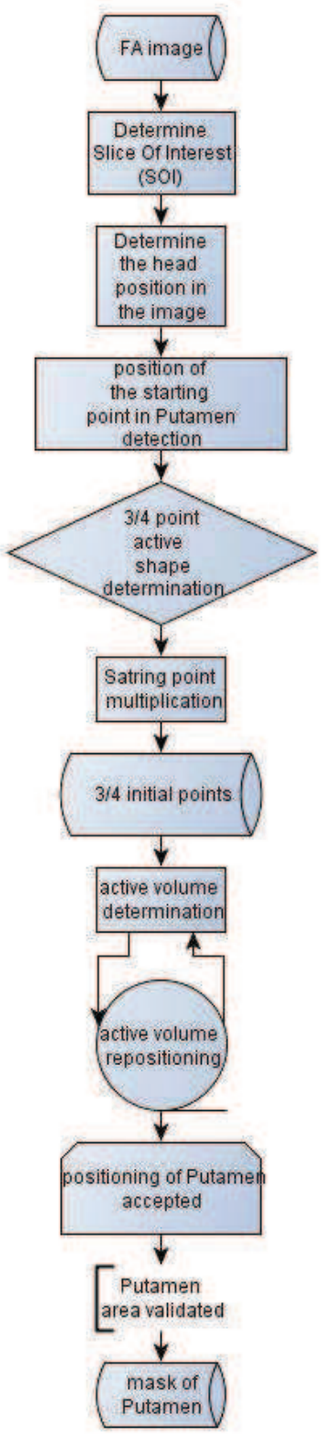


Fig. 4. Putamen detection on the FA image

3.3.1 Transformation parameters

We verify the placement of the volume of interest relative to the center of mass of the brain, as well as the external limits of this volume, relative to the same point. In order to determine the directionality of the image, we use the symmetry axis and its orientation. It gives us the angle with the horizontal and vertical image axes for the rotation and the displacement parameters. All the transformations are performed on the mask image extracted from the FA stack trough segmentation, representing the moving image in the registration process and keeping the EPI as model, representing the still image.

Analyzing the proposed technique, we can say that we perform an iconic registration (Cachier & et al., 2003) because we use on one hand the geometrical relations, as placement of the center of mass and the external limits, but on the other hand, we use the anisotropy values for defining the registered volume. As we are not using that information directly for the transformation of the image, our registration is a geometrical one (Gholinpour et al., 2007) (Maintz & Viergever, 2000). The checkpoints are the same used in our approach for the segmentation: the center of mass of the brain in both image stacks (EPI and FA) and the inter-hemispherical axis that provides the angulation parameters for the transformation. The parameters for this process are presented in 4.

$$\begin{bmatrix} x' & y' & z' & 1 \end{bmatrix} = \begin{bmatrix} cos\theta_x & sin\theta_x & 0 & d_x \\ -sin\theta_y & cos\theta_y & 0 & d_y \\ 0 & 0 & 1 & d_z \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \\ 1 \end{bmatrix} \tag{4}$$

Representing the transformation applied on the FA image in equation 4, we define the parameters for rotation, translation and skewness. The rotation angle for the transformation is computed by taking into account the symmetry axis determined for delimitation of the two brain hemispheres. The θ_x value is the angle between the axis and the O_x axis of the image and the θ_y is the angle between the same axis and the O_y of the image. We compute this angle for each image type and the difference between these angles represents the values for the transformation.

$$sin\alpha_x = \frac{SP_y}{I_1SP} \tag{5}$$

$$sin\alpha_y = \frac{SP_x}{I_2SP} \tag{6}$$

where SP is the starting point of the hemisphere axis, given by the inflexion point (occipital sinuses at the base of the Occipital Bone of the skull) placed on the lower part of the brain (posterior area of the brain) and the SP_x and SP_y are the projections of the SP point on the O_x respectively O_y axis; I_1 is the intersection between the axis and O_x; I_2 is the intersection between the axis and O_y.

We compute the α angle for the FA image and the β angle for the EPI image. The θ angle is the difference between α and β and we use it for the rotation. The translation valued from the transformation matrix from equation 4 (d_x, d_y and d_z) represents the difference between the centers of mass in the two types of images.

Another aspect of the transformation is represented by the axis orientation. The difference between the orientations of the axis determines us to flip the transformed image. This orientation is determined by the placement of the starting point (SP) and the center of mass

on the image axes. Different orientation of the axis determines a flipping of the image in horizontal and/or vertical plane.
Because the FA images are generated on the AC/PC plane as well as the EPIs, there could not be any skewness problems or resizing aspects, thus we are concentrating our registration efforts on the translation and the rotation aspects. As the FA images have different orientations, we need to be sure that the volume of interest is correctly placed on the model image.

3.3.2 The feature fusion aspect

Another aspect when registering the two images information is represented by the nature of the information and the significance of the process itself. Fusing two images refers to the process of morphing them or warping them, at the image level. Both these techniques represent registration methods used and alter one of the images by incorporating the information from the other image. In this case, we are talking about fusion from another point of view, as we do not want to change the image, we put together information extracted from images with different meaning.
Putting together information from different sources enhances common characteristics and adds specific (usually complementary) elements from each source. In our case, we fuse them by putting together the displacement of the molecules and the anatomical regions, with the space displacement from the EPI respectively the FA images. The information is fused by taking the detected mask for the Putamen from the FA image and placing it with the tensor information in the EPI. We take the needed information from one image and inserting it into the other one by using registration (Maintz & Viergever, 2000)(Wirijadi, 2001). In this manner, after the images are segmented, the information from the FA image is registered to the EPI and used further for analysis and validation purposes.

3.4 Tractography

The initial method introduced by Basser (Basser et al., 2000) takes into account the diffusivity directions and the values of the tensors and Le Bihan (Le Bihan et al., 2001) takes into account the anisotropy characteristics at the tissue level for a better detection of the fibers. We choose this approach because it represents a classical approach of fiber tracking, which we can further develop and modify according to out needs. Our approach is a **global deterministic tractography** as it uses the neighbor voxels in tracking the fibers, providing the seeds as the volume of interest and using the thresholds of 0.1 for the FA value, and 0.6 for the angulation. It is a local method as it determines just a specific set of fibers, by using for selection the two-segmented volumes of interest as source and destination for the bundle of interest.
Using this approach, we are determining the fibers passing trough the midbrain area, the first volume of interest, and arriving to the Putamen volume on both sides of the brain hemispheres.
In the Basser approach, the algorithm is based on the Fernet equation for the description of the evolution of a fiber tract. This approach is specific to white matter, as the axons are the white matter. The midbrain area is gray matter. Growing fibers from the gray matter is a challenge since the number of axons in this area is much less than in the white matter and the fibers are not as well aligned as the ones in the white matter. We apply this algorithm in order to see if there are relevant fibers that we can grow between the two VOIs. Fibers too small, with anisotropy higher than 0.1, or those that do not go towards the Putamen area, whit angulation that exceeds 0.6 degrees, are not validated. The threshold values are the same as used in

(Basser et al., 2000)(Le Bihan et al., 2001)(Karagulle Kenedi et al., 2007). In this manner, with the second region of interest, taking a global tractography approach, we have an element that validates the grown fibers, without needing the SN clearly defined. The values estimated for the fibers represent the input for the diagnosis and prognosis module.

3.5 Diagnosis and prognosis

We define at this point the fiber density at 3D level on each side as presented in equation 7 where Nr_F represents the number of fibers detected on the hemisphere that we are analyzing; V represents the voxel size and Vol_{Brain} is the brain volume of the patient.

$$FD_{3D} = \frac{Nr_F * V}{Vol_{Brain}} \tag{7}$$

Once we defined, computed and then normalized the features, the learning stage for the clustering includes intervals of variation on each feature. These intervals are defined using fuzzy classes. We thus have in this case the five severity stages, the control cases class, 0 value. As we have patients for training only for PD stages 2 and 3, the other levels of PD are defined using the variation functions from the prognosis definition. After the interval definition, the rules supporting the intervals on each feature are implemented, including the medical knowledge.

We decide to use the rule-based approach, as the medical knowledge can be included, it can take into account different features at different stages of analysis and we can refine it. As presented in (Teodorescu et al., 2009a), there is a clear relation between the measured fiber values, extracted on the left hemisphere of the brain, and the severity of the disease. There are cases that do not register the fibers due to the image quality or the tracking method. In such cases, we consider the midbrain detected and the right side fibers, if detected. This approach is used also when a case can be placed in more than one class - for tangent clusters.

3.5.1 Diagnosis approach

The definition of the rules for diagnosis includes not only medical knowledge, but overcomes inter-patient variability. It takes into account the hemisphere of the brain, the density of the fibers, the volume of interest where the dopamine flow starts and the 3D density of the fibers. As presented in equation 8, after defining the clusters using the fiber density- HY_{FD}- and based on the midbrain volume- $HY_{VOI_{Vol}}$ - we evaluate the threshold and place a new case depending on these features. When conflicts appear and a decision between clusters is not obvious, an additional feature is used for diagnosis. If we do not have a positive positioning of the case on the feature axis, the VOI is not correctly determined due to image quality or insufficient slices on the volume. These conflicts generate the set of rules that we use for the expert system that determines a classification of the cases, depending on the disease severity. The fiber density (FD) values are classified on the H&Y scale. These classified FD values from the table are used next to define the rules in equation 8. When the left side fiber density does not provide a reliable value for diagnosis, the right side bundle of fibers is taken into account. If the fibers are not determined, the volumes of interest are taken as measures for diagnosis. By testing the rules in equation 8 we obtain the variation function of the FD according to the severity of PD.

$$
\begin{aligned}
&If(HY_{FD} = HY_{VOI_{Vol}} \wedge HY_{FD} \neq -1)\ then\ HY = HY_{FD}\\
&If(HY_{FD} = -1 \wedge HY_{VOI_{Vol}} \neq -1)\ then\ HY = HY_{VOI_{Vol}}\\
&If(HY_{FD} \neq -1 \wedge HY_{VOI_{Vol}} = -1)\ then\ HY = HY_{FD}\\
&If(HY_{FD} \neq -1 \wedge HY_{VOI_{Vol}} \neq -1) \wedge (HY_{FD} \neq HY_{VOI_{Vol}}))\ then\\
&If(FD_{3D} \neq 0)\ then\ HY = 2\\
&else\ HY = 0\\
&If(HY_{FD} = -1 \wedge HY_{VOI_{Vol}} = -1) then\ \ The\ image\ is\ invalid!
\end{aligned}
\tag{8}
$$

For the moment, at this level, only the difference between the control and the PD cases is possible using this rule-based algorithm. At the PD level, only cases rated stage 2 and 3 can be classified, as these are the cases used for training. For new cases, as well as for variation study on the features, we consider the clusters and determine their variation.
In ANFIS architecture, the next step is represented by the rule strengths definition. We define a set of rules based on the detected clusters and include the medical knowledge as well.
Based on the intervals determined on the H&Y scale, each variable has a set of data, part of a rule: the FD variable determines the first rule from equation 8 and delivers the HY_{FD} scale value. The $FD_{3D}L$ metric determines the $HY_{3D}L$ from the set of rules. For determining the $HY_{VOI_{Vol}}$ value we are using values from $R1_{vol}$. The volume obtained for the midbrain, expressed as Vol_{avg} is correlated with H&Y as well and is used on the set of rule equations.
From diagnosis to prognosis, there is apparently only one step. While the diagnosis based on the rules is matching the patients into the classes that it was trained to recognize, the prognosis can place patients at levels that are not learned by the system. The diagnosis makes a classification of the patient by placing it in one of the disease stages or the control case. The prognosis offers the value of the correlation between the disease and the affected features and by extrapolation is able to find the evolution stage of the features for early cases of the disease.

3.5.2 From diagnosis to prognosis

Prognosis systems learn from the formerly acquired data and by analyzing and studying it, a pattern is revealed and used for new cases. Prediction systems using artificial intelligence can be based on neural networks, on fuzzy logic, on genetic algorithms or on expert systems. The interference among different PD levels at the feature level does not provide a clear boundary for classification using neural networks. We tested the KMeans and KNN approaches and they did not offer satisfactory results on our data. The interference among different feature groups at the class level represents a fuzzy dispersion on the features space. The rule-based expert system, using the fuzzy feature classes identifies the known stages of PD, but it does not offer the possibility for prognosis.
At this stage, the learning and classes are already defined and we intend to find a function by using interpolation among the existing points, representing the patient features on the disease severity. The ANFIS architecture at this stage has already defined the functions for determining the consequence parameters that provide the final decisional value. In our case we define the interpolation functions for this purpose. The intervals with their limitations can be considered as weights in defining the interpolation functions for the ANFIS approach. Like the RBFN (Radial Basis Function Network) model, in this case the weights represent the medical constraints, encapsulated in the intervals, and the variation functions are in our case the interpolation functions. The function found in this manner should be used for extrapolation onto disease areas that are not detectable at this moment. The function describes

the disease variation based on features and for any new patient, a correct placing of the case on the PD scale.
The interpolation methods are based on the shape of the mesh function, which can be: linear, polynomial or spline. Analyzing our data set, a linear approach is not possible due to the dispersed points on the plot. A polynomial approach is challenging at the parameter level and at the degree level as well. The cubic spline interpolation method has weights attached to each flat surface to guide the bending of the variation function, but the challenge at this point is to find the correct variations among the weights.
Looking at the polynomial approach, the Lagrange function that determines the parameters and can be adapted easily is a good choice for our data. This is a good choice also because each time we have a new input, the basis polynomials are recalculated and thus we improve our prediction each step of the way. With the help of weights we can improve the polynomial functions and define the spline as Lagrange functions. For a definition of a polynomial using the Lagrange approach we need the coefficients determined using equation 9. In this function, the points (x_i,y_j) represent the features extracted at the image level.

$$L(x) = \sum_{i=0}^{n} y_i * \prod_{j=0, j\neq i}^{n} \frac{x - x_j}{x_i - x_j} \tag{9}$$

Using the data from the training set we determine a forty degree polynomial that computes the coefficients using equation 9. This kind of function is hard to handle, as it becomes very complicated and in the case of new points in the data evaluation takes a lot of time and is not accurate. At this point, we divide the feature points in the H&Y space into sets and define a variation function for each set of points. A two point set definition determines a linear function and we already know that the variation is nonlinear; therefore we start from three set points. A five-degree polynomial function becomes too complicated so the highest degree of polynomial representation on an interval is a four-degree polynomial function.

3.5.2.1 Specific prognosis adaptive methods

When we provide a new case for analysis, we extract the fiber features and we try to place it on an interval, determining the left and right closest values. Defining the interval where the new value needs to be placed, we determine the H&Y values corresponding to the interval and the middle value of the same interval. The three H&Y values provide the data for the rule-based diagnosis system. This system provides the final value for the new case.
When a new point is to be evaluated and its H&Y value determined, we have several steps to perform. We perform this estimation using the "ideal" set of points. The position of the new point (X) among the others is determined by finding the next point higher (X_M) and lower (X_m) - figure 5 - and recurrently determining polynomial functions(LF) for evaluating the new value(X).
This algorithm describes an Independent Adaptive Polynomial Evaluation (IAPE) method as it is applied both on PD and controls determining the most likely polynomial that can be applied on these data. This method is a hybrid ANFIS approach as it uses as back-propagation the difference between polynomials at each stage but it works like the RBF using the Lagrange polynomials.
An extension of this approach, adapted for PD cases, is called PD Adaptive Polynomial Evaluation method (PD-APE). The estimation function is used basically for the PD patients, adding the condition that if HY_1 or HY_2 have as result 0, the other value is taken as result. This condition does not affect the results of the overall performance. The variation function

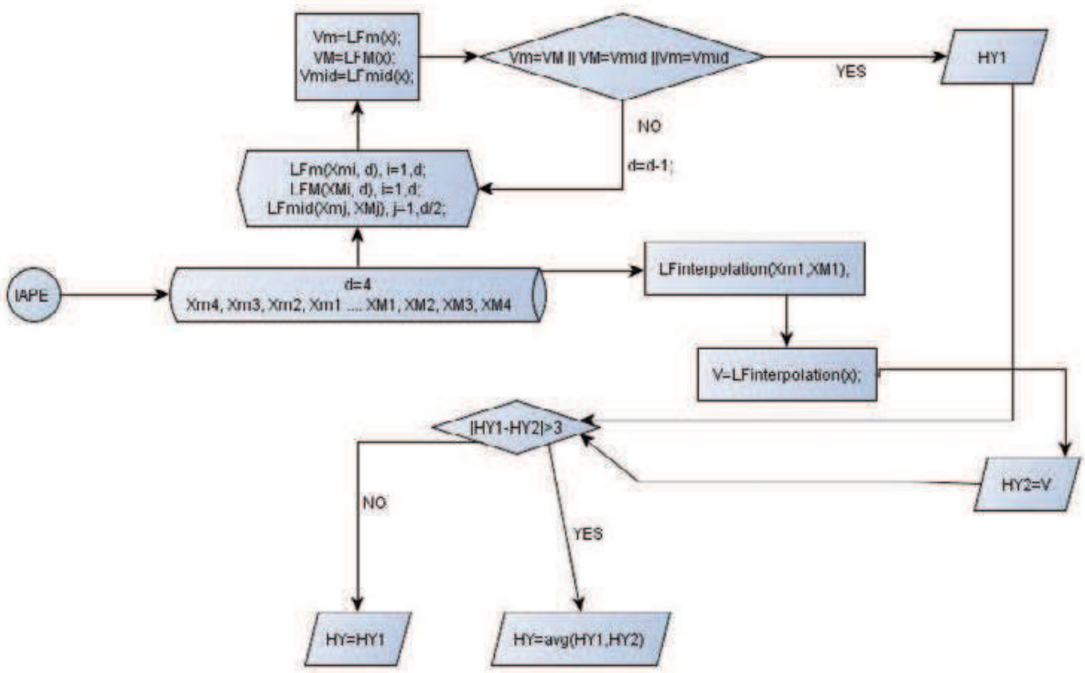


Fig. 5. Independent Adaptive Polynomial Evaluation (IAPE)- When evaluating a new feature X, starting from fort degree polynomials (d=5) computed for neighbor values, we obtain HY1, a first evaluation of the PD severity. A second evaluation using an interpolation on the two closest values is determined as well: HY2. Using these estimations, the final HY value representing the severity is determined.

with this condition performs the best on the accuracy level. From the ANFIS point of view this method takes into the second layer the firing strength given by the PD appurtenance. Determining the control and the PD cases first and then applying the function that provides the best interpolation for the set of points represents a fuzzy adaptive method for prognosis. This variation function uses for the control cases the second-degree polynomial method and for the patient cases the PD adaptive polynomial evaluation method.

4. Testing and results

There are several stages of evaluation in our system. At the image processing level, the preprocessing stage provides the automatic landmarks for the segmentation and the registration methods. At the image processing level, the neurologist validates the midbrain detection. The Putamen segmentation is evaluated against the manual one, performed by a specialist. By comparing the detected fibers obtained after the tractography with the ones determined using the manual detected Putamen directly on the EPI, we evaluate the registration. The registration method is a fully automatic geometric registration. This method was visually validated as well, in collaboration with the radiologists.

4.1 Test sets and requirements

Testing procedures must assure that they are sensitive to our parameters, and robust to other exterior factors. Thus, we construct several testing batches by varying parameters that we

need our system to be robust to. We apply this procedure for the demographical parameters. The whole database contains 66 patients and 66 control cases that managed successfully to generate the segmented areas. We dispose of 68 patients and 75 control cases, but due to the image stacks unable to provide the entire volume between the midbrain and the Putamen, several were eliminated from the test, as they did not have valid images. We use this database to evaluate the methods developed using a test batch (42 patients: 21 PD cases and 21 controls - on which we have the manual Putamen segmented) .
At the image processing level, we have as input data the images and we test the automatic detection against the manual one. At the feature level, we have as input data the extracted values for the neural fibers on the left and the right side, the detected volumes on both sides and/or the new computed parameters: FD, FD_{3D}, FD_{rel}, FV.
For the diagnosis and prognosis, the ground truth is represented by the H&Y value given by the medical doctors using the cognitive tests. The neurologist also performs the validation of the fibers, so that we can be sure of detecting the right bundle of fibers for further study.

4.2 Evaluation of the segmentation algorithms

There are several characteristics when analyzing the result of a region-based segmentation. Comparing an image segmentation result to ground truth segmentation - the manual detected one from the specialist- represents one way of evaluating the automatic segmentation. Another way would be to estimate the overlap between the ground truth image and the segmented one. There can be over-segmentation or under-segmentation when the two images overlap, but one of them is bigger than the other one. When there is a ground truth region that the segmentation does not contain, we are dealing with a missed region. A noise region manifests as a region identified in the segmented image, but not contained in the noise region.
Midbrain automatic detection is preformed on the EPI stack with no diffusion direction. The algorithm providing the segmentation presented is applied on the test set and our specialist studies the results. Validating the algorithm actually means verifying if it managed to segment the whole midbrain and just this part, without taking part of the surrounding tissue or the CSF (see fig. 2(a)). This is the criterion followed by the neurologist in validating the algorithm.
For the **Putamen detection** the evaluation is performed by comparing the manually segmented images with the automatically detected ones. Performing a logical AND operation at the image level between the two Putamen slices at the pixel level, we are using the imageJ Image Calculator on the segmented volumes. The error rate estimated the difference area on our segmentation algorithm compared with the manual one.
Also, a validation done by the neurologist is necessary for this step. For the registration performed on the detected volume, we use medical knowledge for validation and visual evaluation.
When using just the triangular segmentation of the Putamen, we detect an error rate of 34.66% on the left side and 35.75% on the right side of the brain. When evaluating the alignment algorithm based on the center of mass, the relative error rate is 37.16% on the left side and 39.6% on the right side.
The results show a smaller error rate for the left Putamen area, which has more clear boundaries than the right Putamen area. This is consistent with the medical approach as PD patients usually are more affected on the left side of the brain by this disease.
As the Putamen correct placement determines the validation for the strationigral fibers, its placement together with the correct detection of the volume, determine the number of fibers and directly affect the analysis results.

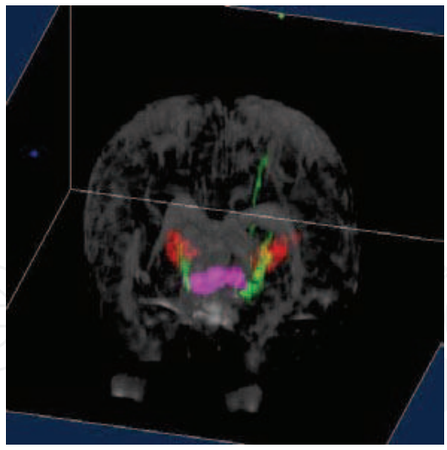


Fig. 6. 3D View of the grown fibers from PDFibAtl@s: the detected midbrain in pink; the two Putamen volumes on each side in red and the fibres in green.

4.3 Evaluation of the registration method

In our approach, the registration process with the acquired parameters determined is fully automatic. It uses the EPI stack with no diffusion and the FA one. The results can be visually verified as we are applying the transformation on the Putamen mask and we transpose the image on the EPI. Thus, we verify the correct anatomical position.
For fiber evaluation, the number of fibers identified for each patient represents the measure of a correct or incorrect segmentation. The tracking algorithm does not change, but it is sensitive to the Putamen area. This is the reason why values above 20 fibers, represent a misplacement of the Putamen area or an incorrect detection - this happens when our algorithm detects more than just the strationigral tract. Based on these elements, we define the metrics for the sensitivity, specificity and accuracy.
With these classes, the overall performance of the algorithms on the existing data, corresponds to 63% of specificity, 81% of sensitivity and 78.5% of accuracy.

4.4 Tractography evaluation

The motor tract is automatically detected in our case by growing the fibers between the two volumes of interest: midbrain area and the Putamen. This is consistent with a global tractography method. After computing the FD and FV on each side of the brain, we study the effects of PD in each bundle of interest. For this purpose, we perform the T-Test making the correlation between FD/FV and H&Y scale. As the FD is dependent on the FV, the two parameters have the same variation. For the medical relevance on correlating the H&Y parameter with the fibers, we test the obtained values using WinSPC (Statistical Process control Software).
We first evaluate the PD-APE prognosis function on a test batch, representing the manually processed Putamen detection (37 PD patients and 52 control cases that provided valid features after the fiber extraction). Together with the manual Putamen data, in the training function, we include five PD patients from the initial valid 42. With an accuracy rate of 32.43% on the patients and 46.15% on the control data, the overall system provides an accuracy of 40.44% .
When updating the Putamen detection, we perform a reevaluation of the diagnosis and prognosis module on the entire automatic methods applied on the database (68 patients and 66 controls).

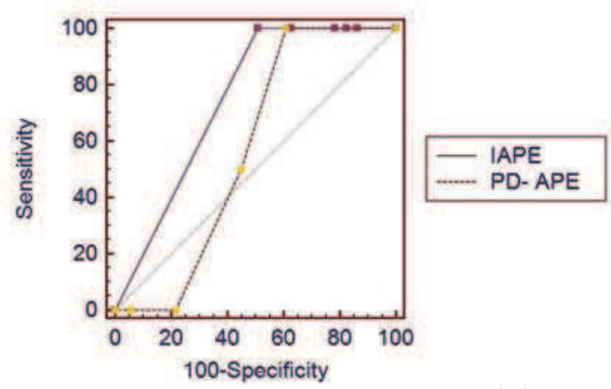


Fig. 7. The two ROC curves for IAPE and PD-APE methods applied on the database (143 cases: 68 patients and 75 controls). The AUC values for IAPE and PD-APE are 0.745, respectively 0.569. By evaluating the ROC difference between the two tested methods, the AUC indicates a difference of 0.176.

The patients are characterized by the value of the sensitivity - maximum value for the Independent Adaptive Polynomial Evaluation (IAPE) approach with 62.16%. On the control cases, the specificity represents the evaluation value that characterizes it - maximal value for the second degree polynomial approach is 43.9%. The accuracy represents the overall performance of the algorithms that performs the best on PD Adaptive Polynomial Evaluation (PD-APE) method, generating a value of 44.87%.
The overall performance of the prognosis module is provided by the ROC curve. We compute this metric using the SPSS 17.0 (Statistical Package for the Social Sciences) for the patient estimation. By evaluating the IAPE method for this case, we obtain an area under the curve (AUC) of 0.705, whereas for the PD-APE, we obtain 0.959. This indicates a much better performance on the patients' data for the second method.
We evaluate the prognosis performances on the control and patients' data, to estimate the overall capacity of the proposed methods at this level. We compare the ROC curves for different methods and for this purpose, we use the MedCalc[11] software. This software provides two approaches for the ROC curve estimation: De Long and Hanley & McNiel. Using the database results on IAPE, the AUC values for these two ROC estimation approaches were the same. We further use the De Long approach when evaluating the ROC, as the error rate provided on the same test is slightly lower compared with the McNiel approach (0.1%). For the PD-APE method of prognosis, we obtain a value of 0.569 for AUC and for IAPE, the same metric has a value of 0.745. Comparing the two curves, the difference between the areas is 0.176 - figure 7.

4.5 Computational speed and requirements

We use Java for all the systems with imageJ toolbox and bio-medical imaging plug-ins [12]. The initialization of the preprocessing part is done by enhancing the contrast for the EPI images and by removing the noise. For the 3D visualization, we are using the Volume Viewer from imageJ [13].

[11] MedCalc 11.3.3.0 - www.medcalc.be
[12] Bio-medical image - http://webscreen.ophth.uiowa.edu/bij/ - last accessed on May 2010
[13] Volume Viewer 3D - http://rsbweb.nih.gov/ij/plugins/volume-viewer.html - last accessed on March 2010

The algorithm is tested on Intel core Quad CPU Q660 (2.4GHz; 4.0G RAM) and the average time for each patient is 4.68 min with the automatic detection and the fiber growth algorithm. If with DTI tracker from MedINRIA took us 3 min just to have the fibers, without segmentation or other preliminary preparation, but with our prototype it takes us an average of 2 min. A similar time (1.2 min) is provided using a probabilistic global method with the Diffusion Tracking module (TrackVis) for image selection and the tractography, without segmentation and computation for the fiber metrics.

5. Conclusion and Future work

Proposing a fully automatic way for estimating the severity of the PD, based on the information provided by the image, represents altogether a new demarche. The prognosis represents another scientific act, based on measurable functionality and specific features, to determine at a higher scale, the diseases severity, even on early cases. These scientific aims are reached by studying the images and the possibility to extract and use the information specific to the disease from these images. This research corresponds to the learning and understanding part on the image modality study and specific elements. The methods developed for preparing the images and volume-based analysis are created for sustaining the more complex systems corresponding to the volume segmentation algorithms. The tractography method, using the extracted volumes of interest, offers not only a much better time on processing but also the selectivity needed by the diagnosis and prognosis model.

Our approach is important from the clinical point of view, offering a new method for the neurologists in PD and a mean to verify/confirm their diagnosis and prognosis. From the technical standpoint, the fusion is novel, as it combines the tensor based information and the anatomical details. This system provides data for H&Y estimation and PD prognosis.

Analyzing the results obtained by each new method, we have to take into account the fact that the image quality together with patient variability influences the algorithms.

The main breakthrough initiated by this study is represented by the method able to predict PD by offering a view on the early cases as well, not only on those starting from the second stage of the disease. This evaluation method based on the image attributes, on the anatomical and neurological aspects of the patient, offers a measurable value of the severity of the disease. As the H&Y test is based on the cognitive facet, our method is complementary to the test, but is placed on the same scale.

PDFibAtl@s is a new system, able to automatically detect the volumes of interest for PD diagnosis using the DTI images and a geometrical approach. The algorithms included in this platform are original and are based not only on the brain geometry, but also including medical knowledge by taking into account the position of different anatomical structures at the brain level, hence the atlas dimension. Concerning the fusion contribution of our work, it brings together the FA clarity at the Putamen level with the tensors matrix for the fiber tracking algorithms. Our algorithm automatically detects the elements that until now were obtained by user interaction: detection of the slice of interest, detection of volumes of interest, automatic detection of the registration parameters. Introducing parameters for fiber evaluation and eliminating the demographic factors at the atlas level, as well as at the volume level represents another important contribution.

Our new prototype represents a first attempt to provide not only image-based analysis and features for PD diagnosis, but also an automatic system specialized for this task. There is place for improvements, like in any new system, but the results obtained so far are encouraging.

The accuracy of the system can be augmented, especially at the prognosis level by applying a specially designed function.

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