Rough Set Rules Help to Optimize Parameters of Deep Brain Stimulation in Parkinson's Patients

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Abstract. Deep brain stimulation (DBS) is a well established method used as treatment in patients with advanced Parkinson's disease (PD). Our main purpose is to increase precision of DBS method by determining which parts of cortex are stimulated in different set-ups. In this paper we have analyzed MRIs that are performed as a standard procedure before and after the DBS surgery. We have used 3D Slicer for registration of MRIs with anatomical brain atlas. In addition, we have generated trajectories of neural tracts (tractography) connecting STN with cortex using data colected by DTI (Diffusion Tensor Imaging). In the following step we have used Rougt Set Theory to compare MRI data with neurological findings acquired by neurologists. We have tested prediction of DBS electrode contact's position and stimulating parameters in individual patients on improvements of particular neurological symptoms. Our results may give a basis to set optimal parameters of stimulation and electrode's position in order to obtain the most effective PD treatment.

Keywords: Deep Brain Stimulation, Parkinson's disease, 3D image analysis, RSES, MRI, DTI.

1 Introduction

The treatment of PD by the DBS is now used worldwide as a method that improves patients' health when pharmacological treatments become ineffective. The first experiments were performed on monkeys treated with MPTP that caused Parkinson-like state [1]. In fact, the first tests of the compound MPTP were performed by a drug-dealer who synthetized meperidine analog that caused that young cocaine addicts after taking it, could not move anymore [2]. In the 1980's a French neurosurgeon at the UJL Hospital in Grenoble, Alim-Louis Benabid was routinely performing lessoning of the thalamus in the brains of severely affected patients with Parkinson'. On the animal experiments basis, Benabid, also a professor of biophysics, in 1987 performed the first stimulation of the thalamus and later in the 90's has changed the target to the Subthalamic nucleus (STN) [3]. Nowadays, the major targeted structures are: STN [4]

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and Globus Pallidus Interna (GPi) [3]. As the most surgeries are still aiming STN that is a small nucleus 3x5x9 mm localized in the midbrain, mostly invisible in MRI, there is a problem with finding the exact stereotactic coordinated of its borders. An approximate STN localization, from other MRI visible neighboring structures, is normally verified by the electrophysiological data obtained during the DBS surgery. Pattern recognition of the STN spike train characteristic is not an easy task. It needs experienced team of neurosurgeon – neurologist and/or an intelligent on-line software analysis [5]. There are also additional complications as different parts of the STN are taking parts in different pathways related to the following loops: somatic motor, oculomotor, prefrontal and limbic.

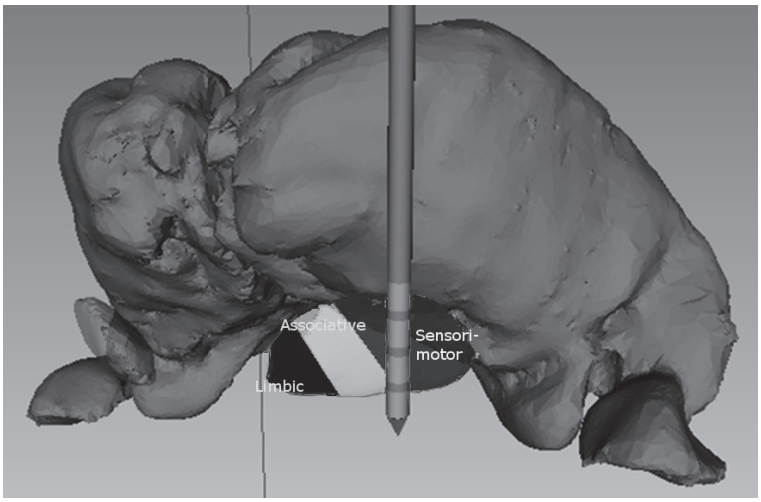


Fig. 1. The image of the thalamus with the STN (a small nucleus below the thalamus). A realistic model of the electrode with stimulating contacts was added as illustration of the DBS. Three parts of the STN were marked: sensorimotor, associative and limbic [6, 7]. Notice four contacts of the stimulating electrode that are near the STN.

In this study we are interested in the parallel STN signals processing. These signals are derived from the primary motor cortex (M1) and SMA (supplementary motor area) and related to the somatic motor circuit. Our interest is limited to the somatotopic organization of the connections between M1, SMA and STN (Fig. 1). By finding position of the electrode's contacts in relationship to different STN parts (loops), we can estimate possible motor effects that are related to stimulation of different contacts. In the near future, our method may give instructions to neurosurgeons where precisely should be placed stimulating electrodes in order to improve particular symptoms in each individual patient.

In the present study we have registered the position of the DBS electrode in relationship to the STN localization, and observed different neurological effects when the position electrode-STN and parameters of the stimulation were changed. In order to find how neurological effects are changing, we have used Rough Set Theory to generate rules for different electrode positions in all individual patients. On the basis

anatomical position of the electrodes contact and parameters of stimulation we have proposed rules that can predict related neurological effects. In the next step, we have verified our predictions by comparing them with neurological diagnosis for each individual patient.

2 Methods

In this section we describe how to define relationship between electrode's position and STN. We have determined anatomical positions of important for our project structures by performing registration [8–10] of the individual patient's brain with the brain atlas [11, 12] and use postoperative imaging to locate exact position of implanted DBS electrodes. Then our experimental data are compared with an SPL-PNL atlas by localizing anterior and posterior commissure (AC-PC) line and brain's midline and aligning them with the atlas.

2.1 Data for Processing

In this project, we have processed the following sets of data: preoperative magnetic resonance imaging (pre-OP MRI), postoperative MRI (post-OP MRI), preoperative diffusion weighted imaging (pre-OP DWI), and 2008 SPL-PNL brain atlas. In several cases, in order to find DBS electrode, we have used the postoperative computer tomography (CT) instead of the post-OP MRI. It is important for our project that MRI data has small slice spacing and is performed in the 3D image acquire mode (equal spacing in all directions). We have analyzed data from nine patients with advanced Parkinson disease (PD), and with implanted DBS electrodes. The image processing in this work was performed by means of 3D Slicer, available as an open source-license from www.slicer.org. In the preparation for our analysis, we have performed the following steps as described below and illustrated as a diagram in Fig. 2.

2.2 MRI Registration

We have performed pre-OP versus post-OP images registration in order to mark electrode's contacts positions according to the post-OP MRI. The registration procedure has to be performed separately for each patient. As normally many images are taken from the same subject, only a simple linear registration using Slicer "BRAIN FIT" module had to be applied. Parameters for the registration were as follows: use center of head align, only rigid registration phase, 100 000 samples, and 1500 iterations. A quality of the registration was evaluated by comparing structures' surface coverage of the MRI measurements with the atlas.

After post-OP MRI to pre-OP MRI registration, the output transform was applied to the post-OP MRI images. Thanks to this transformation, DBS electrode became visible in preoperative images. In the next step electrode trajectory was marked with a ruler tool, setting its parameters to 0.5 mm point spacing and 1.5 mm point size.

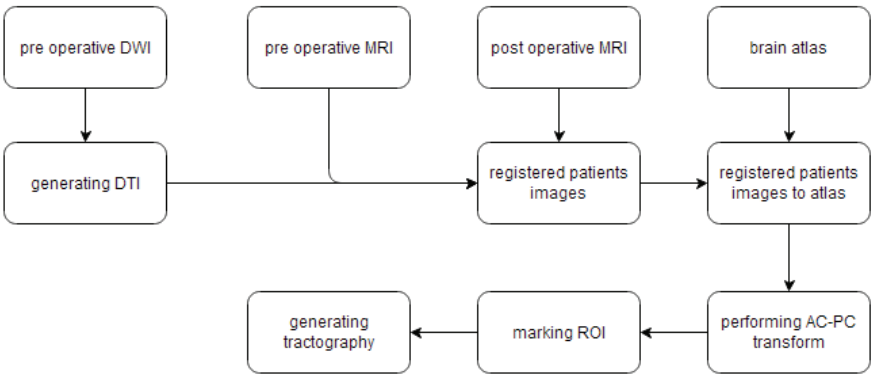


Fig. 2. In our procedures we have used different registration phases. First we have performed a linear registration of pre- to post-operative imaging. Next we apply local nonlinear registration to brain atlas followed with ROI selection and DTI generation.

These parameters were used in order to estimate exact positions of Medtronic (type 3389) electrode's contacts. As different Medtronic stimulating electrodes have different parameters, and DBS contacts are not visible in MRI, we used the following electrode's parameters: distance from the tip to the first contact – 1.5 mm, contact spacing - 0.5 mm, and length of each contact -1.5 mm. The key point was to find out and to mark the distal tip of the electrode at the beginning of the visible in MRI electrode trajectory (see below Fig. 5). The 0.1 mm slice step was used to achieve sufficient accuracy when marking the starting point. The end of the trajectory was marked toward the dorsal part of brain, as close as possible to the skull. Having marked the electrode trajectory, the contacts positions could be marked using the fiducial points on the ruler according to the electrode's specification.

2.3 Generation of the Tractography

In the following step, a tractography separately for each contact was generated on the basis of DTI data from the pre-OP DWI. The DWI to diffuse tensor-imaging (DTI) data was estimated by the least squares approximation.

Following the DTI estimation, it was possible to generate tracts specific for a given contact. At this step it was necessary to use the "Tractography Interactive Seeding" module (3D Slicer). Previously created fiducial points were used with the following module parameters: linear measure start point: 0.3, minimum path length: 20 mm, maximum path length: 800 mm, stopping criteria: fractional anisotropy, stopping track curvature: 0.7 and integration step length: 0.5. According to the generated tractography for a given contact, the seed spacing was increased and the stopping value was decreased until it was possible to record connections to the dorsal parts of brain.

The next step, after acquiring tractography for a given contact, was to normalize the brain's position. For this purpose anterior (AC) and posterior (PC) commissures had to be marked by patient's MRI registration to so-called AC-PC transform. In all

procedures, we have used the SPL PNL brain atlas from 2008 [11]. In the registration procedure, we have performed a local registration of the brain's region of interest, to minimize errors that may occur when the whole brain registration is used. At this step, the appropriate brain parts were selected and cropped using relevant modules in 3DSlicer. The same procedure was applied in all cases, paying attention to select a similar region of interest as in the brain atlas. After the registration process the resulting linear transform was applied to AC-PC models and marked with fiducial points, one point per each structure.

Afterwards, brain's midline was marked with at least three fiducial points. Preferred method for this procedure was to use axial planes of MRIs where the midline is visible. When both the AC-PC and the midline annotation structures were selected, the AC-PC transform module (3DSlicer) was used to generate relevant linear transform that was applied to the whole brain MRI.

When brain images were aligned to AC-PC line we have marked regions of interest (ROI) by tracing tractography from the given electrode's contacts. In this paper, we have focused on three somatotopic areas representing lip, foot and hand in each hemisphere [13, 14]. These areas have variable positions in different patients, but there are some anatomical structures that help their identifications: anterior-posterior commiserates when projected to the cortex determine area of interest - AC position separates pre-SMA from SMA, as well as Cingulate, central and precentral sulci (Fig. 5). After registering we have estimated how many tracts are leading in proximity of each ROI.

2.4 Rough Set Approach

Our experimental data have been analyzed with the Rough Set Exploration System (RSES) version 2.2 [14] based on rough set theory proposed by Pawlak[15].

The structure of data is an important point of our analysis. It is represented in the form of information system or a decision table. We define after Pawlak [15] an information system as $S = (U, A)$, where U, A are nonempty finite sets called the *universe of objects* and the *set of attributes*, respectively. If $a \in A$ *and* $u \in U$, the value $a(u)$ is a unique element of V (where V is a value set). The *indiscernibility relation* of any subset B of A or $I(B)$, is defined [15] as follows:

$$I(B) = \{(x, y) \in A \cup B \mid \forall a \in B, a(x) = a(y)\} \tag{1}$$

Having in discernibility relation we define the notion of reduct $B \subset A$ is a reduct of information system if $IND(B) = IND(A)$ and no proper subset of B has this property. In case of decision tables decision reduct is a set $B \subset A$ of attributes such that it cannot be further reduced and IND(B) ⊂ IND(D). All reduct set in the system consists of set of attributes C – conditional attributes, and attribute D – decision attribute. In general if any object in a set satisfies given set of C attributes it returns value of given D attribute, which is the result of classification process.

In our experiment we build attributes type C from neurological data acquired by doctor and visual analysis data acquired during our experiments in Slicer. Basing on this data we can create decision rules.

These rules are created based on training set and are later evaluated to classify test subset of data. By using only such rules we would end having a lot of redundant data for all of the patients with similar results. In order to limit number of rules we reduce them to reducts. It can be accomplished by different techniques for example by using discretization function on data, creating ranges of values for given decision class for given attribute. There are different algorithms available for creating those, among them LEM2 algorithms, covering algorithms, genetic algorithms and exhaustive algorithms. In this stage of project with yet limited data for analysis best results were acquired using exhaustive algorithm.

Since not all data was complete for patients analyzed during this research some objects appeared with *MISSING* values. In RSES we have possibility to choose how to approach such data, we can:

- fill empty values with most common value for given attribute
- fill empty values with most common value for given decision class
- analyze data without taking into account empty values
- treating missing values as information

3 Results

As described in the Methods section registered and processed MRI/DTI data were put as objects with their attributes in the decision table (see below). Fig. 3 illustrates the DTI tractography generated for whole STN after registration patient's imaging data to the brain atlas. There are placed registered thalamus and electrode on MRI patient's data (Fig. 3). There are many neuronal tracts in this figure showing connections of different cortical areas with STN, but normally DBS electrode activates only a small number of these connections. Which connections are activated it depends on the exact position of the electrode in relationship to the STN. In Fig. 4 is shown an example of the electrode's contact position in STN. The electrode trajectory and electrode's contacts served as points of interest for generating target tracts. Using this approach we were able to determine number of tracts leading to given ROI and use this data in decision table described later in this section. In this project, we have studied effects of the selected contact on both neurological effects and results of our analysis from 3DSlicer. In order to do this we have prepared different data sets as input for RSES and performed different experiments changing sets of parameters in order to determine the most efficient and accurate method.

At the first step, we have selected a single electrode's contact for each patient's scan. In the next step, we have marked characteristic brain structures and areas, which we have used for counting tracts generated with particular stimulation amplitude. It gave us a quantitative relationship between the stimulation amplitude to stimulated region. When this data was gathered we applied RSES to a set of objects organized into decision table, based mainly on neurological and Slicer data (Tab. 1).

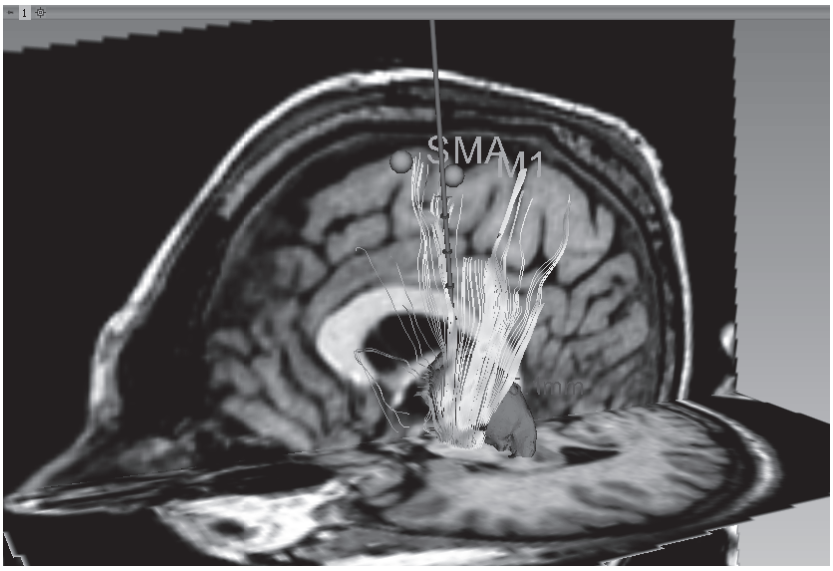


Fig. 3. An example of the tractography that was generated from the whole STN. The thalamus and electrode are marked in dark gray in the sagittal view of the brain. There are put together sagittal (vertical in this figure) and coronal (horizontal) views of the right brain MRIs.

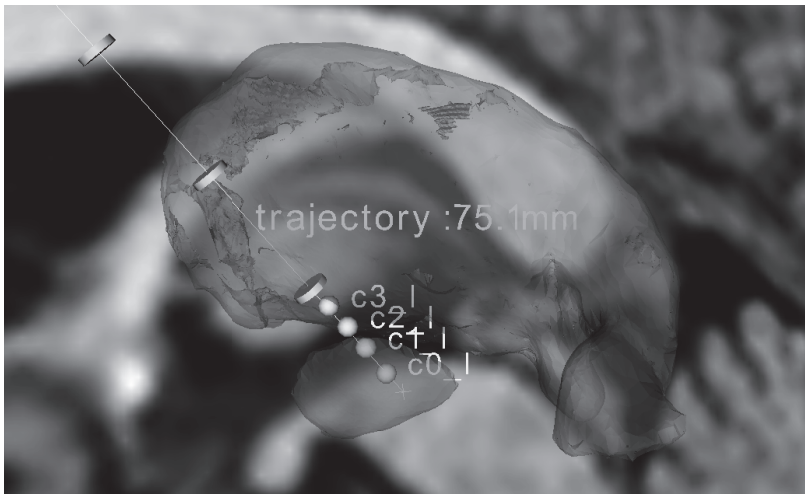


Fig. 4. A sagittal view of MRI registered to anatomical atlas. Two structures are visible in this picture: thalamus as a large structure and under it smaller STN. Electrode's contacts are labeled as c0_l,…, c3_I. The thin line represents trajectory of implanted electrode. In this example, two lower contacts are in STN, and the upper contact is in the thalamus.

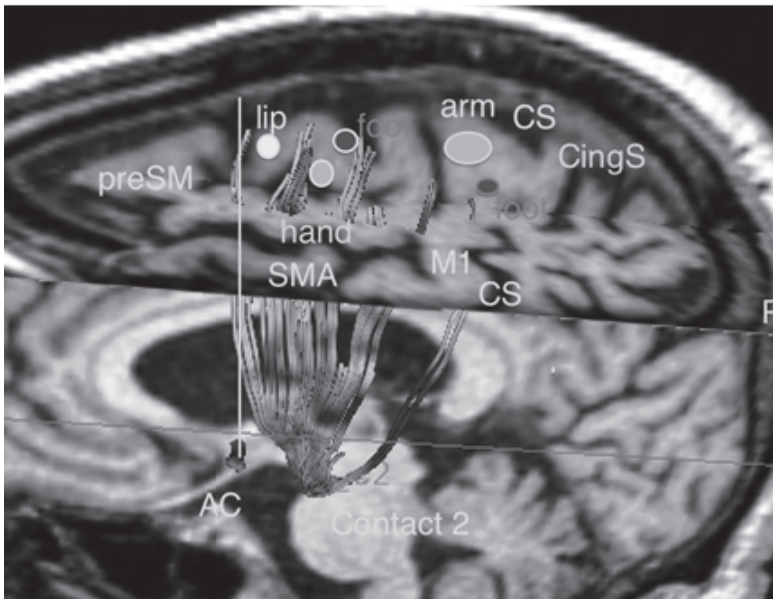
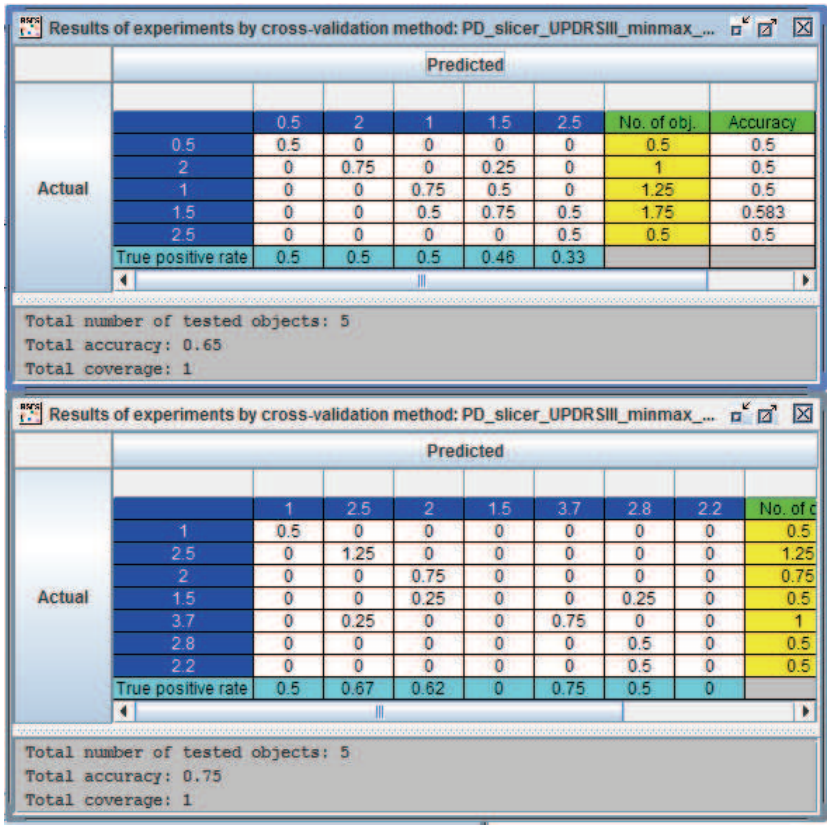


Fig. 5. Above image present ROI classification of patient's brain with marked major brain structures that helped in determining ROI used in our experiments, AC- anterior commiserate, CS – central sulcus, CingS – cingulate sulcus, M1 – primary motor cortex, SMA – suplamentary motor area, preSMA – pre SMA. Notice neural pathways connecting contact #2 with lip, hand, foot areas of SMA, and foot area of M1.

Table 1. A part of the input table. DBS: 0/1 - DBS on/off; BMT: 0/1 – L-DOPA medication was on/off; UPDRS <code> - UPDRS III/for particular movement; L/R selected - contact L/R; L/R amplitude of contact - selecte contact amplitude for left/right side; SlicerMAX / SlicerMIn L/R fiducial region size – Slicer tractography radius in mm for selected electrode contact; SlicerMAX / SlicerMIn L/R tracts lip – number of tractc reaching proximity of lip ROI.

Patient #	20	10	10	25	25
DBS	0	0	1	0	1
BMT	1	1	1	0	1
UPDRS III	7	13		16	
UPDRS 30 - Postural Stability	3	3		1	
L - selected contact	2	1	1	1.5	1.5
L - amplitude of contact	2.5	2	2	1.5	1.5
R - selected contact	2	1	1	1.5	1.5
R - amplitude of contact	2.5	3.2	3.2	1.5	1.5
SlicerMAX L - fiducial region size	5.5	6	6	8	8
SlicerMAX L - tracts lip	2	20	20	22	22
SlicerMAX R - fiducial region size	5	5	5	8.5	8.5
SlicerMAX R – tracts lip	4	15	15	35	35

Table 2. We have compared statistics for choosing selected contact (the upper table) and selected amplitude(the lower table) for the right side for UPDRS III with all data from slicer. Notice that prediction for selecting proper amplitude was more accurate.



Results of experiments by cross-validation method: PD_slicer_UPDRSIII_minmax_...

Actual \ Predicted	0.5	2	1	1.5	2.5	No. of obj.	Accuracy
0.5	0.5	0	0	0	0	0.5	0.5
2	0	0.75	0	0.25	0	1	0.5
1	0	0	0.75	0.5	0	1.25	0.5
1.5	0	0	0.5	0.75	0.5	1.75	0.583
2.5	0	0	0	0	0.5	0.5	0.5
True positive rate	0.5	0.5	0.5	0.46	0.33		

Total number of tested objects: 5
Total accuracy: 0.65
Total coverage: 1

Results of experiments by cross-validation method: PD_slicer_UPDRSIII_minmax_...

Actual \ Predicted	1	2.5	2	1.5	3.7	2.8	2.2	No. of o
1	0.5	0	0	0	0	0	0	0.5
2.5	0	1.25	0	0	0	0	0	1.25
2	0	0	0.75	0	0	0	0	0.75
1.5	0	0	0.25	0	0	0.25	0	0.5
3.7	0	0.25	0	0	0.75	0	0	1
2.8	0	0	0	0	0	0.5	0	0.5
2.2	0	0	0	0	0	0.5	0	0.5
True positive rate	0.5	0.67	0.62	0	0.75	0.5	0	

Total number of tested objects: 5
Total accuracy: 0.75
Total coverage: 1

In order to get decision rules rows and columns of Table 1 must be exchanged so that measurements of different objects (patients) are in rows and their attributes (measurements results) are in columns. Then we can get equivalent rule to each row, for example the first raw gives:

('Pat#'=20)&('DBS'=0)&('BMT'=1)&('UPDRS_III'=2)&('UPDRS_30'=3)&...
&('SlicerMAX_region_size_L'=5.5)&('SlicerMAX_lip_tracts_L'=2)&('SlicerMAX_region_size_R'=5.5)&('SlicerMAX_lip_tracts_R'=2)=>'selected_contact'= 2 (2)

In all experiments we used neurological data based on Unified Parkinson Disease Rating Scale (UPDRS). In an early stage of this research we reduced the number of attributes to UPDRS III, which refers to the Motor Examination [16]. For each patient neurological data consists of few series of measurements, containing data set with and without medications or before and after DBS procedure. From interactive DTI label

seeding in Slicer we have added parameters for generating tracts for given patient, namely region size, stopping value, number of tracts in proximity of each ROI – lip, foot and hand. In Slicer for each patient we have collected two measurements, first using parameters that allowed us to show only few tracts leading into the ROI, described with tag MIN in our data set and second where number of tracts to the ROI's is close to 30-40, this measurement was tagged as MAX.

Having defined the data set we have performed following case scenarios. In first scenario we used exhaustive algorithm, and split of 60% to 40% of learning to testing part of data set (Tab 2). In the rest of scenarios we used 4 fold cross validation method (Tab 2 and 4).

First we tried to analyze full data set consisting of 53 attributes and 20 objects. For this data set we have conducted studies to choose as decision attribute for each experiment: left contact, left contact amplitude, right contact and right contact amplitude. In cases where there were two contacts involved we use notation 1.5 to mark that both contact 1 and 2 were used in a given case.

Table 3. This are an example results generated for choosing the left contact from data set containing all attributes related to motoric functions of patients. As we can see with this set up we were able to achieve 62.5% of accuracy with full result set coverage.

Results of experiments by train&test method: PD_slicer_UPDRSIII_minmax...

		Predicted					
		0	2	1	No. of obj.	Accuracy	Coverage
Actual	0	0	0	0	0	0	0
	2	0	2	1	3	0.667	1
	1	2	0	3	5	0.6	1
	True positive ...	0	1	0.75			

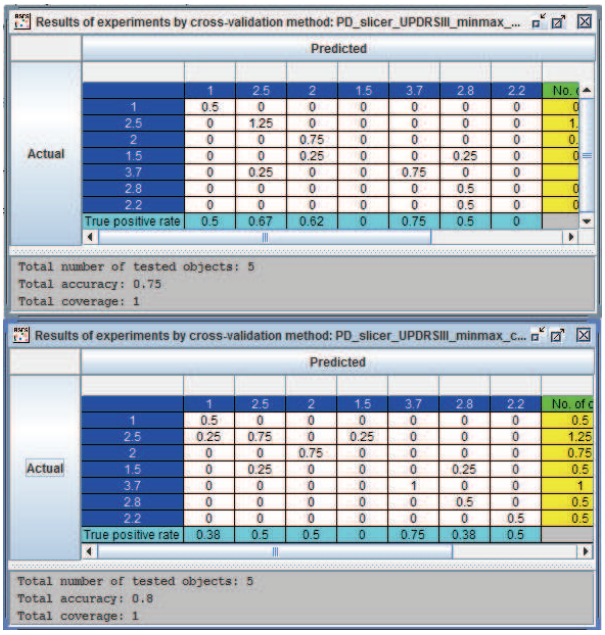
Total number of tested objects: 8
Total accuracy: 0.625
Total coverage: 1

Other test cases included ability to predict both selected contacts and amplitude chosen for given case based on reduced data set. It included testing for:

- selecting left electrode contact giving only neurological data for right side described by UPDRS like rigidity of right lower extremities, right hand tremor, etc.
- selecting left electrode contact for giving UPDRS III .

Both data sets included as well as previous experiments 20 objects and respectively 32 and 15 attributes. Our preliminary results demonstrated that accuracy of prediction of selected contact is greater in case when we have used UPDRS III with data acquired from Slicer. Moreover it can be further seen that we were able to better predict amplitude for given contact that selecting one.

Table 4. In the upper part are results of predicting selection of left side contact amplitude based on attributes from UPDRS III, and the lower part we have used the only right side specific UPDRS for given disorder to determine the same contact amplitude. Notice an increase in accuracy when attributes and decision parameters were for specific UPDRS.



4 Conclusions

We have analyzed MRI data of patients who underwent the DBS surgery in order to determine if data mining may help to increase precision of this method. We have applied rough set theory to standard data recorded before and after surgery in order to determine whether we were able to optimize selection of proper stimulating parameters in an individual patient. Our results showed that this approach is more accurate in prediction of used stimulating amplitude for given electrodes than in selecting a contact. We are planning to apply our method to larger population of patients in order to introduce it in the clinical practice.

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