Deformable Physiological Atlas-Based Programming of Deep Brain Stimulators: A Feasibility Study

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Abstract. The postoperative neurological management of patients with deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson's disease is a complex and dynamic process that involves optimizing the stimulation parameters and decreasing the anti-parkinsonian medication while assessing the interactions of both treatment modalities. Neurologists who manage patients undergoing DBS therapy must have expert knowledge of the electro-anatomy of the subthalamic area and be familiar with the medical treatment of motor and non-motor symptoms. In clinical practice, finding the optimal programming parameters can be a challenging and time-consuming process. We have developed a computerized system to facilitate one of the bottlenecks of DBS therapy: the IPG (Internal Pulse Generator) programming. This system consists of a deformable physiological atlas built on more than 300 intra-operative macro-stimulations acquired from 30 Parkinson's patients and of a non-rigid registration algorithm used to map these data into an atlas. By correlating the position of the quadripolar electrode implanted in the patient with the information contained in our atlas, we can determine which of four contacts has the highest probability to be the most clinically effective. Preliminary results presented in this study suggest that this approach facilitates the programming process by guiding the neurologist to the optimal contact. The system we propose was tested retrospectively on a total of 30 electrodes. In 19 of these cases, this system predicted the contact that was selected as the optimal one by the neurologist.

1 Introduction

Since its first FDA approval in 1998, deep brain stimulation of the subthalamic nucleus (STN-DBS) has been established as an effective therapy for patients suffering from movement disorders [3], [4]. The therapy has significant applications in the treatment of tremor, rigidity, and drug induced side effects in Parkinson's disease (PD). Generally, the neurologist conducts the majority of DBS programming starting ~2 weeks after implantation. This allows the patient to recover from surgery and provides enough time for the transient lesional effects to resolve. Detailed principles

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and methods used to select the optimal programming parameters have been presented by different authors [1], [2].

Briefly, the first step in postoperative programming is the examination of the effectiveness and side effects induced by each individual contact. The electrode contacts are sequentially evaluated in a monopolar configuration in an effort to determine the contact that produces the best compromise. Frequency and pulse width are typically kept at constant settings of 130-180 Hz and 60-120 μs respectively. Amplitude is steadily increased to the tolerance level of the patient or until side effects occur. Repeated motor evaluation is then performed to assess the efficacy of stimulation. Ten to 15 minutes are allowed to pass between trials of separate contacts to allow the effects from previous stimulations to disappear. If a satisfactory result cannot be achieved with monopolar stimulation, more complex arrays consisting of bipole, tripole, or multiple cathodes are tried. The initial programming session, as described above, can take several hours and requires continuous feedback from the patient to ascertain the degree of benefit and to identify any side effects. This can be very taxing, especially when patients are kept off of medication for long periods of time. Furthermore, finding the optimal settings may take several trials over many months, which can be frustrating.

Automated selection of the optimal contact would facilitate the programming process and reduce the length of time required to determine optimum programming and thus be beneficial to the patients. In this paper, we propose a mechanism to do so. It consists of mapping the position of each of the contacts onto a statistical atlas, which assigns to each of the contacts a probability value for the contact to be the optimal one. This method requires several key ingredients: (1) accurate algorithms to register patients to the atlas, and (2) populating the atlas with data that permits the computation of the aforementioned probability. In our current system, the data we use is the response of previously implanted patients to intraoperative stimulations. In the remainder of this paper, we describe the method we have used as well as promising preliminary results.

2 Patients and Methods

Thirty PD patients undergoing DBS therapy have been enrolled in this study. With IRB approval (Vanderbilt University IRB #010809), a set of CT and MRI volumes were acquired pre-operatively for each patient. These were acquired with the patient anesthetized and head secured to the table to minimize motion. Typical CT images are acquired at kvp = 120 V, exposure = 350 mas, 512 x 512 voxels ranging in size from 0.49 to 0.62 mm, and slice thickness from 1 mm to 2 mm; MR images acquired with a 1.5T GE Signa scanner are 3D SPGR volumes, TR: 12.2, TE: 2.4, dimension 256x256x124 voxels, typical voxels dimensions 0.85x0.85x1.3 mm^3.

The surgical procedure as well as pre- and post-operative evaluations were identi-cal for all 30 patients. Seventeen of these were followed for a period of at least 6 months after DBS implantation and had optimal programming parameters determined by their neurologist or neurosurgeon. At the time of writing, the remaining 13 patients have not had long enough follow-up to achieve stable programming.

Surgical planning as well as the operative procedure performed at our institution has been described in detail in our previous work [6]. Briefly, pre-operative target

identification is performed automatically using an atlas-based method; automatically predicted targets are then checked by the functional neurosurgeon. This location is then refined intra-operatively based on the surgical team's interpretation of electrophysiological recordings and responses to stimulations; this team includes a neurosurgeon, a neurophysiologist, and a neurologist.

At our institution the procedure is performed with a miniature stereotactic frame, the StarFix microTargeting Platform® (501(K), Number K003776, Feb. 23, 2001, FHC, INC; Bowdoinham, ME) instead of a standard stereotactic frame. During surgery, a micropositioning drive (microTargeting® drive system, FHC Inc., Bowdoinham, ME) is mounted on the platform. Recording and stimulating leads are then inserted through the guiding tubes. The StarFix platform is designed based on the CT images (geometric distortions that affect the markers in MR images reduce platform accuracy when this modality is used) and its design is such that the pre-operative target is located on the central track. Details on the platform, including a study of its accuracy that shows it to be at least as accurate as standard frames can be found in [7]. The depth of the electrode is read from the micropositioning device and converted into x, y, and z CT coordinates. The x, y, and z position of each contact is computed using the geometry of the lead and the final intraoperative position of the center of the implant in CT coordinates. The implants used for these patients are the Medtronic 3389 implants, where the size of each contact is 0.5 mm and the gaps between the contacts are 0.5 mm.

2.1 Rigid and Non-rigid Registration Algorithms

A key component of the method we propose is our ability to map information acquired from a population of patients onto one reference image volume, which we call the atlas. Two types of registrations algorithms are needed to achieve this goal: rigid and non-rigid. The rigid registration algorithm is required to register MR and CT volumes of the same patient. This is necessary because, as mentioned above, the intra-operative positions of the electrode contacts provided by the micropositioning drive are in CT coordinates. The algorithm we have used to register MR and CT images of the same patient is an independent implementation of a standard Mutual Information-based algorithm [6]. Non-rigid registration is required to register patient data to the atlas and vice-versa. In this study, non-rigid registration is always performed on MR image volumes using an algorithm we have proposed recently [5]. Briefly, this algorithm computes a deformation field that is modeled as a linear combination of radial basis functions with finite support. The similarity measure we use is the Mutual Information between the images. We also compute simultaneously two transformations (one from the atlas to the subject and the other from the subject to the atlas) that are constrained to be inverses of each other.

While validation of non-rigid registration algorithms is an open-ended problem, in [6] we demonstrate our ability to register accurately MR volumes for STN-DBS implantation tasks. This, in turn, indicates that we are able to register accurately the patient volumes to the atlas.

2.2 Intra-operative Efficacy Atlas

Intra-operatively, macro-stimulation is performed to determine the optimal implant position. While targeting the STN, stimulation is applied approximately every 2 mm along the track, starting at the boundary of the STN, which is determined by micro-electrode recordings (MERs) acquired prior to stimulation. At every position, stimulation is typically performed with voltages starting at 0.5 V up to 5 V by 0.5 V increments. The effect of the stimulation on rigidity, muscle tone, bradykinesia, paresthesias, muscle contraction, eye movements and subjective sensations are assessed for every voltage. The optimal voltage is determined at each position and the loss of rigidity expressed in percent is recorded for this voltage. Because we can map the intra-operative coordinates of a patient's electrode onto the atlas, any information acquired intra-operatively can be projected onto the atlas. This, in turn, permits the creation of a number of statistical maps relating spatial coordinates in the atlas to characteristics measured intra-operatively. In [6] we have, for instance, shown that it is possible to create maps of features extracted from MERs. This study showed that maps of the mean spike rate can be used to define the boundary of the STN in the atlas. In this work, we have focused on developing maps that can provide useful information to the neurologist for programming. The key idea is to create an atlas that associates position with the efficacy of each electrode contact. Here, we define efficacy as being (1) proportional to the percent of loss of rigidity; (2) proportional to the therapeutic window, which equals the difference in voltage required to achieve this loss of rigidity (V) and the voltage at which side effects occur (VSE); and (3) inversely proportional to V. A position is good if the percent of loss of rigidity is high, V is low, and the difference between VSE and V is large. To create an atlas that captures this information, we first map the intra-operative stimulation position onto the atlas. At each position, we then center a Gaussian curve defined as follows:

$$F(x,y,z) = Loss\_of\_Rigidity * (V^{SE} - V) * \frac{1}{V} \exp\{-(\frac{x^2 + y^2 + z^2}{2V^2})\}$$

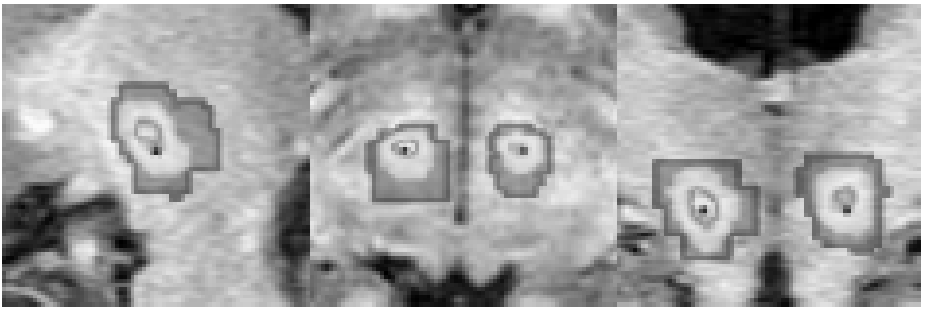

Fig. 1. Physiological stimulation map. White values represent a high likelihood to get good stimulation results, dark gray represents low likelihood to get good stimulation results. The star represents the optimal point in the atlas at which to place the implant when targeting the STN [6].

A point with a small stimulation voltage and a high loss of rigidity (in percent) will thus be associated with a curve with a small standard deviation and large amplitude. We repeat this procedure for every point for which we have intra-operative information and we produce a statistical atlas by averaging all these curves. In this atlas, a point associated with a curve that has a small standard deviation and large amplitude has a large but localized effect on the atlas. A point with a large standard deviation has a smaller impact that extends over a larger region. Fig. 1 illustrates results obtained with this method. In this figure, white means a high probability of obtaining good efficacy while dark gray means low probability of obtaining good efficacy. The black star is the average intra-operative position of the centers of all electrodes mapped onto the atlas for each side.

2.3 Atlas-Based Contact Selection

Once the atlas is created it can be used post-operatively to assist the neurologist in selecting the optimum contact for stimulation. To achieve this, the position of the patient's electrode is first mapped onto the atlas. The contact that falls into the area on the atlas corresponding to the highest probability of good efficacy would be the optimum contact for stimulation.

3 Results and Discussion

Table 1 shows quantitative results we have obtained with the method we've developed. We correlated the efficacy probability from our atlas to each contact in the 17 subjects included in the study. In table 1, the numbers in gray are the contacts selected by the neurologist. Contacts are numbered from C0 (distal contact) to C3 (proximal contact). The column labeled "V" is the amplitude of the therapeutic voltage.

Results show that about 60% of the contacts selected by the neurologist are the contacts with the highest efficacy probability in our atlas. Albeit preliminary, this supports the feasibility of using a statistical atlas to facilitate the programming process. A more detailed analysis of this process also suggests that using predictions from our atlas may shorten the time required to reach stable programming. For example, programming notes from the neurologists for patient P3 show that contact C1 was tried first on the right side before moving to C2 which produced better results. For patient P11 the C0 contacts were first tried on both sides before moving to contacts C2. A similar trend has been observed for the left implant in patient P12. Here, the neurologist moved from contact C3 to C2. For patient P15, contact C1 on the left side was observed to have a better effect on rigidity than contact C2.

For a few cases, the optimal electrode predicted by our atlas has been tried and rejected. In patient P16, contacts C0 and C1 were tried but not selected because these caused significant side effects. These effects were reduced with contact C3 but this particular patient still has significant rigidity and bradykinesia. For a number of cases, the optimal electrode predicted by our atlas has not been tried or programming records have not been available. Therefore, whether or not the electrode our atlas predicts would have led to better results cannot be determined.

Table 1. Shows, for 17 STN patients, the likelihood of the four contacts to produce good stimulation results. The number in gray shows the contact that was selected as the best one by the neurologist. Contacts are numbered from C0 to C3 (bottom to top contact). V shows the therapeutic voltage that was used.

	Left					Right				
Patient	C0	C1	C2	C3	V	C0	C1	C2	C3	V
P0	0.47	0.77	0.84	0.61	1.1	NI	0.1	0.2	0.3	1.1
P1	0.18	0.53	0.55	0.71	2.2	0.2	0.4	0.6	0.7	2.2
P2	0.53	0.84	0.94	0.61	2.4	0.4	0.7	0.9	1.0	1.7
P3	0.64	0.78	0.69	0.27	1.5	0.2	0.4	0.7	1.0	1.3
P4	0.06	0.07	0.10	0.24	1.5	0.3	0.6	0.7	0.4	1.8
P5	0.01	0.11	0.12	0.30	1.8					
P6	0.74	0.74	0.69	0.47	1.5	0.4	0.7	0.8	0.7	1.5
P7	0.65	0.59	0.47	0.21	1.6	0.7	0.9	1.0	0.9	1.7
P8	0.80	0.47	0.23	0.10	1.4					
P9	0.73	0.98	0.93	0.65	2.3	0.8	0.9	0.8	0.4	2.2
P10	0.72	0.84	0.84	0.59	3.2	0.3	0.6	0.6	0.4	3.2
P11	0.59	0.85	0.90	0.65	1.8	0.2	0.4	0.6	0.9	1.5
P12	0.60	0.49	0.41	0.11	2.1	0.2	0.4	0.6	0.5	2.7
P13						0.9	1.0	0.9	0.8	2.3
P14	0.12	0.47	0.84	0.84	0.8	NI	0.1	0.2	0.4	1.0
P15	0.73	0.91	0.80	0.40	1.5	0.3	0.5	0.7	0.6	1.5
P16	0.85	0.92	0.69	0.50	1.8	0.3	0.6	0.7	0.6	1.8
P17						0.2	0.4	0.7	1.0	3.2

The results presented in this study demonstrate that a computer-assisted method can be developed to facilitate what remains a bottleneck in DBS therapy. A number of improvements on the method presented herein are currently being developed. First, a prospective validation study has been initiated. Rather than verifying that the electrode we propose is the optimal one after programming has been completed, we will propose the optimal contact to the neurologist at the time of initial programming. We have followed this approach when developing and validating our automatic pre-operative target prediction for DBS implantation [6]. Second, at the time of programming, we will provide the neurologist with a 3D display of the position of the electrodes in the efficacy map overlaid on high resolution MR images. This will permit correlation of these positions with anatomy, thereby facilitating spatial orientation and navigation between the contacts. Third, as the number of patients increases, we will create maps of side effects. Currently, we only use a crude definition of efficacy: reduction in rigidity weighted by

the therapeutic voltage window (i.e., the difference between the voltage required to suppress the symptoms and voltage inducing side effects). We will refine this definition to improve the way side effects are taken into consideration. To achieve this, we will create maps of side effects as we have done for our current definition of efficacy. This will permit an automatic multi-parameter optimization procedure that will minimize side effects while maximizing the positive effects of the stimulation.

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