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Short Paper

Visualization for Understanding Uncertainty in Activation Volumes for Deep Brain Stimulation

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Abstract

We have created the Neurostimulation Uncertainty Viewer (nuView or νView) tool for exploring data arising from deep brain stimulation (DBS). Simulated volume of tissue activated (VTA), using clinical electrode placements, are recorded along with patient outcomes in the Unified Parkinson's disease rating scale (UPDRS). The data is volumetric and sparse, with multi-value patient results for each activated voxel in the simulation. νView provides a collection of visual methods to explore the activated tissue to enhance understanding of electrode usage for improved therapy with DBS.

Categories and Subject Descriptors (according to ACM CCS): J.3 [Computer Applications]: Life and Medical Sciences—Health

1. Introduction

Deep brain stimulation (DBS) is an established therapy for the treatment of Parkinson's disease (PD) and shows great promise for the treatment of several other disorders. However, while the clinical analysis of DBS has received great attention, a relative paucity of quantitative techniques exists to define the optimal surgical target and most effective stimulation protocol for a given disorder.

There is broad agreement that the effects of DBS for PD patients are critically dependent on stimulation location, and there has been growing recognition that analysis of previously implanted patients can be used to predict outcomes for future patients if three important factors are taken into account [BCH*11]. First, DBS parameters and electrode location(s) act synergistically in each patient and together they define the spread of stimulation to surrounding neural structures. Second, there is evidence to suggest that the optimal stimulation target of DBS may not be the subthalamic nucleus (STN) itself, but rather nearby structures. Third, there is substantial variability among PD patients with regard to the anatomical regions that are affected during DBS.

We are currently developing the Neurostimulation Uncertainty Viewer (nuView or νView) tool for visualizing the results of the computational volume tissue activated (VTA) with regard to patient outcome. In the context of DBS, the VTA is defined as the threshold of voltage in brain tissue causing an axonal activation [BCHM07]. The goal of νView is to both directly explore the simulation results, helping scientists design and troubleshoot experiments, and to help understand the relationship of electrode placement and settings in the context of DBS clinical efficacy. The challenges to this goal stem mainly from the complexity of the data; we are given multiple patient scores for each voxel. The structure of the data is inherently difficult; the spatial domain of the data is 3D, so simply displaying the data causes occlusion and clutter. Indicating further attributes within the 3D context is a formidable challenge. To address this issue, we have created νView to experiment with the collection of visualization techniques, including three-dimensional spatial displays, as well as the incorporation of information visualization approaches, to find meaningful visual representations.

The broader goal of this work is to develop visualization techniques that can concisely express the nature of the uncertainty within this type of complex data for domain scientists and health care professionals alike. The main contributions of this work stem from the use of multiple visualization approaches to get a sense of the uncertainty in the data. Due to the complexity of the data and the domain, multiple views are employed to allow the user to explore different characteristics of the data. Each visual interface is designed to highlight specific aspects of the uncertainty within the data display, and interactions within a specific display are linked, as appropriate, to the other views. While each specific view is limited in its novelty for displaying this type of uncertainty information, the strength of our technique lies in the combination of our selected views to extract aspects of the uncertainty that is complimentary to the other views and appropriate visualization of uncertainty in DBS for the specific needs of our domain scientists. We feel that this approach contributes knowledge to the field by demonstrating a collection of visualization techniques appropriate for uncertainty information within a 3D spatial domain that addresses the needs of scientists working with this specific type of complex data.

2. Background

2.1. Probabilistic Analysis of Activation Volumes in Deep Brain Stimulation

A patient-specific computer model of DBS is a tool that can be used to implicate regions of the brain that are related to benefits and side effects of this surgical approach. A patient-specific model allows for visualization of the effects of DBS by using a reconstruction of an individual DBS lead on a neuro-anatomically correct morphed atlas and MRI scan, thereby allowing for direct quantification of lead location, neuro-anatomical regions of interest, and VTA.

These models can be utilized to determine how much an individual effect is due to direct stimulation of a target region or due to overlap with other regions. When prescribing DBS there are two major variables that must be decided on an individual patient basis: 1) the electrode location, which is planned prior to surgery; 2) the stimulation protocol, which consists of the voltage, pulse width, frequency and configuration of anodes and cathodes. As our body of knowledge about DBS grows, we are identifying not only different stimulation targets for PD (STN versus GPi) but also subregions near each anatomical target that are correlated with specific motor or neuro-psychological outcomes.

We have recently created a novel computational framework that integrates magnetic resonance imaging data, finite element electric field models, and predictions on the VTA generated by DBS on a patient-specific basis. The purposes of this framework are to: 1) predict the effects of DBS on an individual patient basis; 2) express VTAs from a multi-patient cohort in the context of an atlas brain; and 3) construct a PSA that incorporates clinical outcomes. A summary of this approach from a recently-published prospective study [BCH*11]. Using this method we identified subregions around the STN where stimulation-induced activation was correlated with motor improvement on a per-symptom basis.

2.2. Uncertainty Visualization

Interest in uncertainty visualization has increased during the past few years [GS06, JS03, MRH*05, PWL97], and the topic has been identified as a top research problem [Joh04]. Related to this work are techniques aimed at incorporating uncertainty information into volume rendering and isosurfaces, using linked multiple windows, the visual representation of probability distribution functions (PDFs), and displaying the results of parameter-space explorations.

Volume rendering and isosurfacing are techniques designed to convey spatial characteristics of volumetric scalar data. Approaches to add uncertainty information include pseudo-coloring, overlay, transparency, glyphs and animation [DKLP02, JLRP98, LLPY07, RLB*03]. Fout and Ma [FM12]propose a computational model that computes a posteriori bounds on uncertainty propagated through the entire volume rendering algorithm and developed an interactive tool to inspect the resulting uncertainty.

Rather than using isosurfaces to directly convey uncertainty in data, they can be used to show shape and extent of clusters [Luc06]. Probabilistic formulations of marching cubes [PWH11] and isocontours [SZD*10] allow for the display of positional uncertainty of isosurfaces colored by their distance from a mean [PH11].

While these three-dimensional representations are quite useful for conveying geometric structure and providing context, the complexity of the data often requires multiple presentation types to enable full understanding. For this reason multi-window linked-view systems are popular for addressing uncertainty [FKLTI10, HMH08, PWB*09, SZD*10].

Another way to look at uncertainty is to consider the multiple values as PDFs and to use statistical methods for characterizing them. Initial work in the area began by extending existing techniques to work with PDFs [LKP03]. Clustering [BKS04] and slice planes [KLDP02] can be used to reduce the dimensionality of the data for visualization, while colormaps, glyphs, and deformations have been used to express summaries and clusters [KDP01, KVUS*05].

Finally, the type of data we are looking at here can be thought of in terms of parameter-space exploration in which the effect of perturbations of input parameters is related visually to outcomes through techniques such as parallel coordinates [BPFG11] and preattentive highlighting [FKL*10]. Similar work was presented in Rosen et al. [RBPJ13] with a viewer for myocardial ischemia. However, their approach used primarily cross-sectional analysis and isosurface extraction. Such analysis was applicable to their application and did not utilize uncertain volumetric rendering.

3. Visualization System

νView is an interactive n-way linked view system, where the main view contains a 3D visualization of the data, see Fig. 1. A statistical panel contains information on a user selected voxel (via picking) showing histogram patient data. Additionally, a parallel coordinates view of overall outcome per patient is also provided.

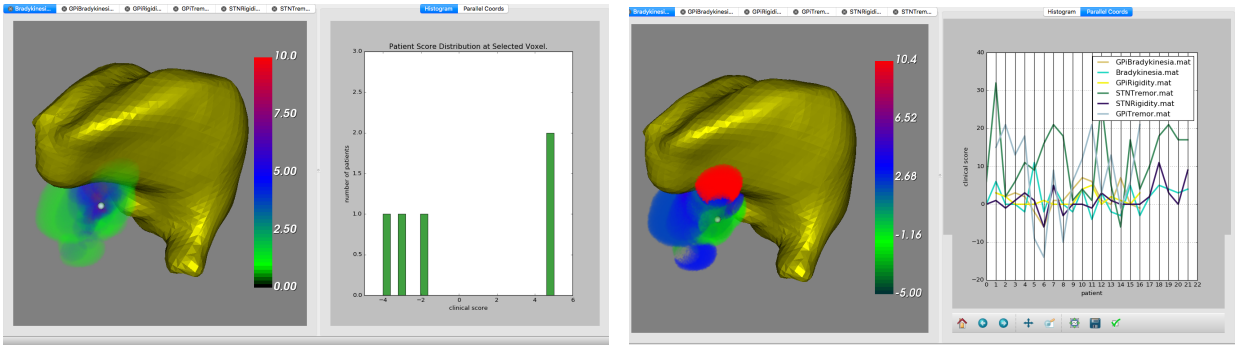
All interfaces are manipulated through mouse interactions and a small menu system. Basic controls for choosing the statistic, setting clipping planes and picking opacity isovalue (i.e., the value of a voxel's opacity which specifies where along the line of site the selected voxel will be selected) are provided in a modeless dialog widget as seen in Fig. 2. Users can select either the mean, variance, minimum value, maximum value, or number of samples (patient outcomes) as the displayed statistic.

The data input into our system consists of a four-dimensional array. The fourth dimension is the number of patient outcomes which varies from seventeen to twenty-four from different data sets (UPDRS scores). The first three dimensions are the spatial extents for the simulation, here 120 x 120 x 120 voxels.

3.1. Visual Interfaces

3D View: We volume render the patient outcome statistics using transfer functions that are initially set by a given statistic. This is explained more thoroughly in section 3.2. Our system allows users to select a subset of the patient group for a data set and to view the statistics related only to that subset. The user may also load relevant brain nuclei for spatial context of the VTA.

Voxel Histogram View: The user can select voxels in real-time, by clipping the volume along one of the major orthogonal axes. The



(a) (b)

Figure 1: *(a) Linked 3D view of number of patient outcomes at each voxel for Bradykinesia efficacy in DBS. Picked voxel and histogram of patient scores are shown in the right panel for the selected voxel at the white spherical glyph. (b) Linked 3D view of mean UPDRS for Bradykinesia with parallel coordinates. The parallel coordinates show patient scores for all loaded data sets. 3D view shows the VTA along with the subthalamic (STN) nucleus. The tool allows for any of the nuclei to be loaded for reference to targeted stimulation areas by clinicians.*

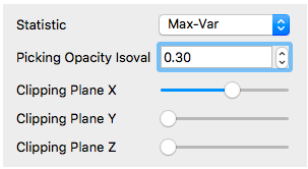


Figure 2: *Modeless dialog allowing user to select statistic to be displayed in the 3D view. The user may also adjust picking opacity, and the location of the x, y, or z aligned clipping planes.*

selected voxel is then shown in the histogram view. This provides a user the ability to drill-down into the data by pinpointing where in the VTA they wish to see the patient results.

Parallel Coordinates View: Parallel coordinates are an alternative way to explore the high-dimensional space of the data. We supply a parallel coordinates interface where each dimension represents a single patient. The values for each patient correspond to their UPDRS outcome and are colored by the dataset / clinical measurement. This allows the user to gain an overview of patient outcomes across the loaded datasets. For example, in Fig. 1 (b), there are six datasets simultaneously loaded and displayed in the parallel coordinates view.

3.2. Transfer Functions for Uncertain Voxels

Because of the complexity of the data, we have adopted a number of transfer functions to color the data, each designed to aid understanding in a unique way.

Value-based Coloring: Each statistic's range of values is mapped automatically by the tool, such that the minimum value is assigned to blue, the mean value to green, and the maximum value to red. For transfer functions that are intended to allow the user to find given ranges of values in a particular statistic, opacity is initially set to fully opaque. The user can adjust any points in the transfer function. The transfer functions use piecewise-hermite functions to allow interpolation between points set by either the user or the tool itself.

Value-based Opacity: For the mean, maximum, minimum, and number of patients, we also provide opacity mapping via the tool. An example of this can be seen in Fig. 3. We normalize the opacities of each voxel based as a fraction of each voxel's own variance divided by the maximum variance from the data set. The variance is taken from the UPDRS scores. The lesser the variance in UPDRS score, the greater the applied opacity of the voxel is.

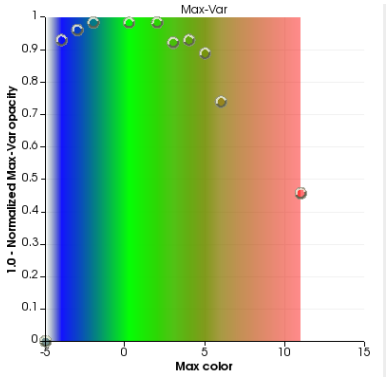


Figure 3: *A transfer function for the maximum value statistic whose opacity is scaled based on the variance of the UPDRS scores at each voxel.*

4. Preliminary Results

Our results were obtained from code written in Python and Pvtkpython [Wil12]. We used data from computational models to analyze 39 PD patients who received unilateral DBS, 22 in globus

pallidus interna (GPi) and 17 in STN. This study used a previously-published method to create patient-specific computational models of DBS [BCHM07]. The VTA was determined for each patient, and from the VTAs a probabilistic stimulation atlas of outcomes was constructed. All patients had a pre-operative MRI which was fused to a post-operative CT. All patients were implanted with a mono-lateral Medtronic 3387 DBS lead. The probabilistic stimulation atlas was created using 4-month UPDRS outcomes. In order to make comparisons, all patient specific models were mapped into a common coordinate space via a non-linear, diffeomorphic atlas building method.

Our initial experiments have been performed primarily on six UPDRS outcomes for categories of electrode placement and parameters across a patient cohort. Our software takes a few moments to load data (10-20 seconds) with a patient cohort size of approximately twenty. During loading, we calculate the moments of the patient outcome distributions, which causes this operation to be the most time intensive among the other operators. Overall, the software is interactive.

We developed this tool as part of a team of visualization and biomedical researchers to better understand the physiology of DBS and patient outcome. νView is being actively developed simultaneously with the development of the probabilistic atlas model and VTA simluation studies, allowing results from the simulation to be explored within νView, and the insights gleaned from νView to be incorporated back into the DBS model. While our results to date are still in the experimental phase, we have already had some success within this collaboration.

5. Future Work

This work is an initial exploration of uncertainty data obtained from DBS, thus we still have much work yet to do. Prior to the development of νView, the biomedical researchers used simple glyphs scaled spatially to represent each voxel in the VTA. We believe our close collaboration with the simulation scientists will greatly guide the choices we make regarding visualization, particularly in light of our discovery of regions of high variance in patient outcome where those regions had the most overlap in stimulation between patients. Prior studies of DBS in this area suggest correlation between patient outcomes. Such a discovery also encourages the question of the computation of the brain atlas, which we plan to further investigate through techniques to allow users to see variation in electrode placement along with individual patient VTA.

Additionally, from a scientific point of view, these studies can also give us a better understanding of the relationship of VTA uncertainty to both brain atlas computation and VTA simulation. In the future, we aim to provide information about simulation parameters and electrode visualization. It may be that for some problems, the level of uncertainty will not greatly effect the results, while for other applications, the uncertainty will invalidate an approach. It may also indicate that uncertainty levels in the VTA should prohibit electrode parameters for a desired efficacy. This could then spark research into generating better electrode parameters and simulation of more specific VTA. Both clinical problems and scientific exploration provide opportunities for improvement in uncertainty visualization techniques, and we look forward to extending νView to have greater research and clinical impact.

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