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Spherical statistics for characterizing the spatial distribution of deep brain stimulation effects on neuronal activity

YiZi Xiao¹ and Matthew D. Johnson^{1,2,†}

¹Department of Biomedical Engineering, University of Minnesota, Minneapolis, USA

²Institute for Translational Neuroscience, University of Minnesota, Minneapolis, USA

Abstract

Background—Computational models of deep brain stimulation (DBS) have played a key role in understanding its physiological mechanisms. By estimating a volume of tissue directly modulated by DBS, one can relate the neuronal pathways within those volumes to the therapeutic efficacy of a particular DBS setting.

New Method—A spherical statistical framework is described to quantify and determine salient features of such morphologies using visualization techniques, empirical shape analysis, and formal hypothesis testing. This framework is shown using a 3D model of thalamocortical neurons surrounding a radially-segmented DBS array.

Results—We show that neuronal population volumes modulated by various DBS electrode configurations can be characterized by parametric distribution models, such as Kent and Watson girdle models. Distribution parameters were found to change with stimulus settings, including amplitude and radial distance from the DBS array. Increasing stimulation amplitude through a single electrode resulted in more diffuse neuronal activation and increased rotational symmetry about the mean direction of the activated population. When stimulation amplitude was held constant, the activated neuronal population distribution was more concentrated with distance from the DBS array and was also more rotationally asymmetric. We also show how data representation (e.g. stimulus-entrained cell body vs. axon node) can significantly alter model distribution shape.

Comparison to Existing Methods—This statistical framework provides a quantitative method to analyze the spatial morphologies of DBS-induced effects on neuronal activity.

Conclusions—The application of spherical statistics to assess spatial distributions of neuronal activity has potential usefulness for numerous other recording, labeling, and stimulation modalities.

Graphical abstract

[†]Address correspondence to: Matthew D. Johnson, Department of Biomedical Engineering, University of Minnesota, 7-105 NHH, 312 Church Street SE, Minneapolis, MN, 55455, ph: (612)-626-6492, fax: (612)-626-6583, john5101@umn.edu.

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Keywords

deep brain stimulation; DBS; spherical statistics; computational modeling; electrode array; current steering

1. Introduction

Electrical stimulation within the brain is known to modulate the rate and pattern of neuronal spike activity around an active electrode [1-5]. Such effects are thought to stem from directly modulating a range of afferent and efferent neuronal processes as well as directly modulating nearby axonal fibers of passage [6-8], which together create a sparsely activated volume that is highly dependent on electrode placement [9, 10]. Characterizing the spatial distribution of modulation around an active electrode has importance for better understanding the neurophysiological mechanisms of electrical stimulation [11, 12] and has clinical relevance in the design of patient-specific strategies to improve the selectivity of targeting individual pathways within the brain [13-15]. In particular, assessing the spatial distribution of modulation is important for field-shaping capabilities of high-density electrode arrays for application in deep brain stimulation (DBS) [16-18] as well as characterizing the spatial precision of modulation for visual [19, 20] and auditory [21] neuroprostheses.

Currently, there does not exist a systematic and widely accepted method to quantify the spatial distribution of stimulus-induced changes in neuronal activity around an active electrode, be it from computational modeling [18] or experimental recordings using electrophysiological [10] or imaging-based [22] techniques. Commonly used metrics include: population center of mass (COM), total volume enclosing the population, or maximal radial extent of activation [23]. These metrics while useful do not provide a consistent way to account for important information about the underlying distribution of the activated neuronal populations. As is the case with any data, it is important to use statistical approaches to analyze them and describe their distributions with parametric models.

Spherical statistics [24] provides a framework to analyze the directional distribution of data in space. This branch of statistics focuses on the analysis of orientation of lines/vectors in space and has applications in diverse disciplines, including the Earth sciences [25], remote sensing [26], and auditory psychophysics [27]. Three-dimensional data can be characterized

into different distributions based solely on their directional components relative to a pre-specified origin. The radial component of the data generally does not play an important role and is normalized to the same value (e.g. unit radius). In cases in which radial distance needs to be taken into account, spherical statistics can then be applied to concentric shells of data, delineated by their radial distance from a pre-specified origin.

In this study, we develop a framework for applying spherical statistics to analyze the spatial distribution of neuronal spike activity around one or more active electrodes. The method is motivated by a computational model of deep brain stimulation using a population of thalamocortical neurons distributed around a DBS lead with four columns of elliptical electrodes arranged around the circumference of the lead. We show the process for making hypotheses on the shapes of neuronal data distributions, testing the data for hypothesized shapes, examining the importance of analytical perspective on interpretation of the results, and analyzing the effects of stimulus amplitude and electrode-neuron distance on the distribution of neuronal modulation.

2. Materials and Methods

2.1. Directionally-segmented DBS lead

A directionally-segmented DBS lead¹ with 8 rows of 4 elliptical electrodes (semi-major axis: 0.265 mm; semi-minor axis: 0.14 mm) embedded on a 0.5×40 mm shaft (diameter $\times$ height) was generated in a finite element model (FEM) (COMSOL Multiphysics, v4.3b) (Fig. 1A,B). The angular distance between adjacent contacts in the same row was 45° and the distance between two rows of contacts was 0.75 mm. The lead was positioned such that the horizontal midline of the bottom row of electrodes was defined as the origin.

2.2. Tissue conductance model

A simplified inhomogeneous tissue conductance model was developed to simulate the tissue potential distribution resulting from current-controlled stimulation through one or more electrodes on the DBS array. For the purposes of this theoretical example, a 0.1×40 mm (thickness $\times$ height), 0.18 S/m homogeneous encapsulation layer and a 100×100 mm (diameter $\times$ height), 0.3 S/m cylinder of homogeneous bulk tissue surrounds the lead [28, 29] (Fig. 1B). The lead electrodes and insulation were assigned conductance values of 10^6 S/m and 10^{-12} S/m, respectively. The electrode surfaces were designated as boundary current sources with uniform normal current density (A/m^2). The walls of the bulk tissue cylinder were set to ground. The finite element model mesh contained 1116911 tetrahedral elements with finer mesh resolution near each electrode. The voltage distributions resulting from electrical stimulation through the electrodes were calculated via the finite element method (Fig. 1C) by solving Poisson's equation using the electrostatic solver.

2.3. Multi-compartment neuron models

Multi-compartment thalamocortical (TC) relay neurons ($n=5000$) [7] were uniformly distributed within a 10 mm diameter sphere giving a spatial population density of

¹This model is based on a research device used in our for *in-vivo* electrophysiology experiments in non-human primates.

approximately 10 neurons/mm³ around the DBS lead. Model neuron axonal efferents were oriented vertically (parallel to lead shaft) (Fig. 1B,C). Current-controlled stimulation was applied using a waveform (130Hz, 90μs cathodic phase, 400 μs interphase delay, 3ms anodic phase) scaled from a constant-current pulse generator [30]. The FEM solution was scaled with the waveform, and the resulting time-varying voltage distribution was used to estimate activation, defined as the stimulus pulse train eliciting action potential(s) 3 ms after each stimulus pulse for at least 8 of 10 stimulus pulses.

2.4. Stimulation configurations and data representation

Three stimulation configurations were considered in this study using the bottom row of electrodes: one contact monopolar cathodic stimulation (Model 1), four contact monopolar cathodic stimulation (Model 2), and bipolar stimulation using two opposing contacts as cathode and anode (Model 3) (Fig. 1D-F). In Models 1 and 2, each contact delivered 0.25mA of current. In Model 3, each contact delivered ± 1 mA. Current values were chosen to provide canonical distributions for display and analysis. The locations of the somas relative to the center of the bottom row of contacts (FEM origin) in the models were used to represent activated neuronal soma locations in 3D. It is important to note that this is not the only way to represent the data. To demonstrate this, the locations of the axonal nodes of Ranvier that first elicited an action potential following a stimulus pulse were modeled for the stimulus configuration used in Model 2 relative the FEM origin (Model 2*). The details on data representation are listed in Table I.

2.5. Spherical statistical hypothesis testing and parameter estimation

In this study, the spherical statistical framework was used to quantify the directional distribution of neurons activated by each of the four model configurations. This framework followed a simplified version of the analysis put forth by Fisher et al. [24] (Fig. 2). Having identified the data points to use (i.e. soma/node locations), we next made initial hypotheses on the shape of their distributions. We first obtained the polar coordinates of colatitude (θ) and longitude (ϕ) [24] of the data points (Fig. 3) and then projected these points onto the unit sphere. Projection was performed by setting the Euclidean distance between each data point and the origin to 1 while maintaining the orientation (θ, ϕ) of these points. For better visualization, we found the sample mean direction and rotated the data such that this direction pointed to the South Pole (Fig. 4A). In this new coordinate system, we used the Lambert azimuthal equal-area projection (EAP) (Fig. 3B) (1) of each data point (x_i, y_i, z_i) to obtain their projections (X_i, Y_i) in the 2D plane (Fig. 4B). No two data points in 3D will have the same coordinates in 2D when projected in this manner. Data points will project progressively inwards on the 2D circle as their colatitudes vary from the North Pole to the South Pole.

$$(X_i, Y_i) = \left(\sqrt{\frac{2}{1-z_i}}x, \sqrt{\frac{2}{1-z_i}}y \right) \quad (1)$$

The distribution of the projected data can be further visualized in terms of its density. A 200×200 2D histogram was constructed spanning the maximum width and height of the

projected distribution and smoothed [31]. The smoothed density values at data locations were normalized to the maximum density value, assigned indexed colors, and plotted in terms of density contours (Fig. 4B). The normalized eigenvalues (τ_1 , τ_2 , τ_3) of the orientation matrix (2) [32] were computed, and the two-axis logarithmic plot (empirical shape plot or ESP) was constructed by plotting $\log(\tau_2/\tau_1)$ vs. $\log(\tau_3/\tau_2)$ (Fig. 5 G,H).

$$T = \begin{pmatrix} \sum x_i^2 & \sum x_i y_i & \sum x_i z_i \\ \sum x_i y_i & \sum y_i^2 & \sum y_i z_i \\ \sum x_i z_i & \sum y_i z_i & \sum z_i^2 \end{pmatrix} \quad (2)$$

According to Woodcock [32], points on the ESP that plot above, below the $y = x$ line, and near the origin represent cluster, girdle (equatorial/small circle), and uniform types of distributions, respectively. In addition, the mean resultant length $\bar{R}$ ($\bar{R} = R/n$, where R is the length of the resultant vector of all data point vectors on the unit sphere and n is the number of data points) and the relationship between the normalized eigenvalues can serve as further discriminators. Detailed information is listed in Table 2. Typically, uniform distributions tend to have $\tau_1 \approx \tau_2 \approx \tau_3 \approx 1/3$, clusters tend to have $\tau_3 \gg \tau_1, \tau_2$, while girdle distributions tend to have $\tau_1 \ll \tau_2, \tau_3$.

The procedures described above provided the basis for hypotheses on the shape of each model distribution. Based on those results, we performed a series of formal statistical tests on the datasets to determine the fit of their hypothesized models. Data hypothesized to be unimodal in distribution were tested against the null hypothesis of uniformity (H_0 : uniformity, H_A : unimodality) [33]. In the case of bimodal or multimodal distributions, the data were separated into modal groups, and each subpopulation was analyzed and tested separately. Unimodal distributions can be represented by the Kent distribution, which is very versatile because it is able to represent data with or without rotational symmetry about the sample mean direction. The Kent distribution can be characterized by 5 parameters: $\xi_1, \xi_2, \xi_3, \kappa$ and total volume enclosing the population. The first three are unit vectors that represent the mean direction, major axis, and minor axis of the distribution. κ is termed the *concentration parameter*, and it is indicative of the tightness of data distribution about ξ_1 . β is termed the *ovalness parameter*, and it is indicative of the amount of departure in the distribution profile from circular symmetry about ξ_1 [34]. Data that tested significant for the Kent distribution were fitted with the 5 parameters above. Assuming the data were sampled from a larger population, a 95% confidence cone was constructed by calculating the semi-vertical angle [34].

Hypothesized girdle type distributions were tested against the null hypothesis of uniformity (H_0 : uniformity, H_A : girdle) [35]. Two types of girdle distributions can be distinguished based on symmetry properties. The first type is symmetry about the normal vector (polar axis) to the plane of the small circle/equator, which is characterized by the Watson girdle model [35]. The second type is symmetry about the plane of the small circle/equator itself, which is best characterized by the Bingham model [36, 37]. The first type of symmetry implies the second type, but not vice versa [24]. In this study, we focused on fitting girdle type data to the more generalized Watson girdle distribution. We performed both graphical

and formal goodness of fit (GOF) tests [38] on the data fitted for the Watson girdle model to determine the adequacy of their representation. The Watson girdle distribution can be characterized by three parameters, κ , α , and β . (α, β) is the polar coordinate representation of the polar axis. κ is a concentration parameter that is negative in value. The larger the absolute value of κ , the more concentrated the data is about the polar axis. These parameters were determined for data distributions with sufficient symmetry about the polar axis as shown by the graphical and formal GOF tests.

2.6. Application of parametric spherical statistical models to analyze changes in external stimulus parameters

We investigated the effects of stimulation amplitude as well as the distance of the neuronal process from the active electrode on the spatial distribution of the activated neuronal population. We used the FEM of Model 1 and simulated it in two ways: 1) increased the amplitude of stimulation from 0.1 mA to 5 mA in steps of 0.1 mA, and 2) kept the stimulation amplitude constant at 5mA. In the first case, we quantified the distribution of activated neurons at each stimulation amplitude using the appropriate parametric model and analyzed the change in model parameters with increased amplitude. In the second case, we divided the space around the active electrode into concentric spherical shells centered about the FEM origin. Each shell was the difference between two consecutive spheres of radius r_1 and r_2 , where $r = r_2 - r_1 = 0.25$ mm. The distribution of the activated neurons within each shell was quantified using the appropriate parametric model and the change in model parameters with respect to radial distance was analyzed.

3. Results

3.1. Graphical interpretation of data distributions

All four models (using stimulation parameters described in Section 2.4) generated different distributions of activated neuronal processes (Fig. 4A). The colatitudes of most data points in Model 1 were concentrated in the $[\pi/2, \pi]$ range, while the longitudes were centered about $\pi/2$, which is the direction of the active electrode (positive y direction). Model 2 showed rather uniform distribution in the longitude of the data points, while the colatitudes were mostly concentrated in the in the $[\pi/2, \pi]$ range. In the case of Model 3, the colatitudes of most data points were centered about the $\pi/2$ and $3\pi/2$, or the axis of the active pair of electrodes. The longitudes of the data points in the hemisphere facing the cathode (positive y direction) were concentrated in the $[\pi/2, \pi]$ range, while those for data points in the direction of the anode were distributed more uniformly in the range $[0, \pi]$. The observations on these three models were consistent with our expectations. In all three models, the data points were represented by the locations of somas, and the origin of the spherical system was the FEM origin. Since the neurons were oriented parallel to the lead with their somas at the bottom, the fact that most activated neurons had their somas located below and not above the plane of the active electrodes suggests that it was their axonal compartments that were activated directly. Model 2* can be used to validate this observation because the locations of the first nodes of Ranvier to be activated by stimulation were used as data points. As expected, the data points in Model 2* were concentrated around the equator of the sphere, indicating that

the points of initiation for action potentials in neurons around the lead were located near the level of the plane of the active electrodes.

The EAP plots (Fig. 4B) further assisted us in identifying the salient features in the data distributions. Both Models 1 and 2 showed up as clusters on their EAP plots. The cluster was larger in Model 2, and there was a distinct mode of high concentration near the South Pole. For Model 2*, the projected data formed a ring centered about a circle with a radius roughly half of the full 2D circle. This is the expected projection location for data points around the equator. In Model 3, the data was distinctly distributed in two groups, most likely representing neurons activated by either the cathode or the anode. We observed 2 modes of concentrated data points, albeit not completely separated. When compared to the spherical projection (Fig. 4A), we determined that the cathode (positive y direction) activated a population of neurons mostly concentrated below the plane of bottom row of electrodes. This was evident on the EAP plot as data points concentrated near the larger mode in the center. In contrast, the anode activated neurons in a more diffuse manner, as reflected by the uniformity in colatitudes. These data points appeared on the EAP plot in a large fan shape spanning half of the 2D circle. The data distribution from Model 3 suggested that the cathode most likely activated axon segments near the plane of the active electrode, while the anodal activation worked through a more distributed mechanism that may involve virtual cathodes.

As described previously, the ESP can provide empirical guidelines on the shape of data distributions (Fig. 5G). Models 1, 2 and 3 all plotted above the line $y = x$ (Fig. 5H), which suggests that they are cluster type data distributions. Model 2* was situated below the line $y = x$, which indicates that it represents a girdle type distribution. Model 3 lied near the line $y = x$, which suggests that it is in a transition zone between cluster and girdle type distributions. The normalized eigenvalues had the relationship of $\tau_3 \gg \tau_1, \tau_2, \tau_1 - \tau_2$ and $R \gg 1$, which implies that the distribution could be bimodal, consistent with previous observation (Fig. 4). Taken together, the evidence from spherical projections, EAP plots, ESPs, normalized eigenvalues, and mean resultant lengths allowed us to make the following hypotheses on the shapes of the model distributions: Model 1 – unimodal, Model 2 – unimodal, Model 2* – girdle and Model 3 – bimodal (also listed in Table I).

3.2. Spherical statistical testing

Models 1, 2, and 2* all tested significant for their respective alternative distributions to the uniform distribution ($p < 0.05$) (Table III). Model 1 had a smaller test statistic compared to models 2, which suggests a more diffuse distribution. In the case of Model 3, we dissected the data into two groups: data points in the hemisphere with positive y coordinates (facing cathode) were grouped into the +y cluster, while those with negative y coordinates (facing anode) were grouped into the -y cluster (Fig. 6A). The ESP (Fig. 6B) and EAP (Fig. 6C) of the +y cluster suggested a unimodal distribution, and this hypothesis was confirmed through formal statistical testing against the null hypothesis of uniform distribution ($p < 0.05$) (Table III). The ESP (Fig. 6B) for the -y cluster suggested a girdle type distribution; however, the EAP (Fig. 6D) showed a small concentrated core of data points near the South Pole while the other data points were spread over the entire hemisphere. The eigenvalues ($\tau_1 = 0.1905$,

$\tau_2 = 0.3325$, $\tau_3 = 0.4770$) and mean resultant length ($R = 0.5922$) further indicated that the data was indicative of a non-symmetric girdle distribution. Statistical testing for the Watson girdle model failed to achieve significance ($\alpha = 0.05$), indicating that there isn't strong symmetry of the data about its polar axis. This is a logical conclusion considering the -y cluster only consists of data from one hemisphere. Further analysis beyond the scope of this study is needed to determine if the Bingham distribution would be a more appropriate fit for the data.

3.3. Fitting activation data to parametric models

Models 1 and 2 both tested significant for the unimodal distribution, which can be well represented by the Kent distribution. The concentration and ovalness parameters κ and β are listed in Table IV. Model 1 was roughly 2.6 times more tightly concentrated about its mean direction compared to Model 2. Model 2 on the other hand was much more rotationally symmetrical about its mean direction, as indicated by the ovalness parameter β . These statistics were consistent with the fact that cathodic stimulation through one contact confined activation to a smaller group of neurons compared to stimulation through four contacts. We have also illustrated that we can estimate 95% confidence cones [34] for these datasets, supposing that they represent samples from a larger, true population (Fig. 7).

Model 2* tested significant for the Watson girdle distribution. We performed both graphical and formal GOF tests to assess the adequacy of using this parametric model. The graphical GOF test consists of the colatitude and longitude plots. The data was first arranged such that the polar axis was pointed to the North Pole and the corresponding colatitude and longitudes (θ_i, ϕ_i) were found. One can imagine that an ideal small circle/equatorial distribution should have the colatitudes of its data points concentrated in a narrow band centered about the plane of the small circle/equator, with few outliers outside of that range. The longitudes should be uniformly distributed in the range $[0, 2\pi]$. In the colatitude plot, the ordered values of $\cos^2 \theta_i$ were plotted against the Chi-squared quantile, and a good fit was signified by an approximately linear line passing through the origin. In the longitude plot, the ordered values of $\phi_i/2\pi$ were plotted against the uniform quantile, and a good fit was signified by a line that was approximately linear, passing through the origin, with a slope of 45° . For the data in model 2*, the longitude plot (Fig. 8A) showed an approximately linear line passing through the origin, the slope of which is 1.0131. This result indicated that longitudes of the data points are uniformly distributed in the range $[0, 2\pi]$. The colatitude plot (Fig. 8B), on the other hand, revealed some deviation from a linear line, especially towards higher $\cos^2 \theta_i$ values. This was due to the presence of data points scattered away from the equator, especially those near the North Pole (Fig. 8C). The colatitude plot therefore illustrated the limitations of the Watson girdle model to accommodate the larger spread in the colatitude of the data. The formal GOF test consisted of both the colatitude test and the longitude test, and it further confirmed the interpretation of the graphical method. The colatitude test was not significant ($\alpha = 0.05$) to indicate a good fit for the Watson girdle model, while the longitude test did reach significance ($p < 0.05$). We calculated the concentration parameter κ to be -2.3161 [35]. A best fit small circle was calculated [39] and it showed a slight tilt from the plane of the equator, which was most likely due to chance activation of axon nodes at lower colatitudes (Fig. 8C).

3.4. Effect of stimulation amplitude on data distributions

We studied the effects of stimulation amplitude on the distribution of activated neurons using the one contact monopolar cathodic stimulation model, by increasing the amplitude of stimulation from 0 to 5 mA in steps of 0.1 mA (Fig. 9C-D). The data points were represented using the locations of cell bodies of the activated neurons relative to the FEM origin. The number of activated neurons increased in a nonlinear fashion with stimulation amplitude until 1.6 mA, after which a step-like pattern of increase was observed (Fig. 9E). As shown with Model 1, the Kent distribution was adequate to model the neuronal cell population activated under this stimulation scheme. We observed that both κ and β decreased nonlinearly and eventually leveled off at higher stimulation amplitudes (Fig. 9F).

3.5. Model distribution along the radial direction

We modeled monopolar cathodic stimulation through one contact at 5 mA and analyzed the activated neuronal populations within spherical shells separated by 0.25 mm (Fig. 10A). The total number of cell bodies within each shell plateaued after the 6th shell (1.25 – 1.5 mm). The number of activated neurons within each shell reached a maximum of 257 in the 6th shell and then steadily decreased to 92 in the last shell (4.75mm – 5mm). The percent activation within each cell decreased from 100% in the first three shells to 30.26% in the last shell (Fig. 10C). EAP plots of activated populations within each shell suggested that the shape of the activated neuronal population tended to be more erratic in the first few shells close to the lead, which had fewer cells, and then gradually became more concentrated and rotationally symmetric (Fig. 10B). This was confirmed through analysis of the changes in mean colatitude and longitude along the radial dimension (Fig. 10D). The mean longitude remained relatively stable about $\pi/2$, which is the direction of the active contact (Fig. 10A). Fluctuations in mean longitude were observed (shells 2, 3, 10, 11) and these could be attributed to sampling issues (i.e. more model neurons would yield smoother curves). The mean colatitude steadily increased from $\pi/2$ to π within the first 10 shells and remained at approximately that value in shells further away (Fig. 10D). This suggested that as distance away from the lead increased, the majority of the cell bodies of activated neurons were below the plane of the active contact. Finally, we fitted the Kent distribution to the activated neuronal populations within each shell and estimated the parameters κ and β . Both parameters fluctuated initially near the lead, but then steadily increased along the radial dimension, suggesting more focal and symmetrical activation profiles further from the lead despite a reduced probability of activation.

4. Discussion

In this study, we present a spherical statistics framework for quantifying the spatial distribution of modulated neuronal processes around a DBS lead. The framework included visualization techniques, empirical shape analysis, hypothesis testing, and data parameterization. We have demonstrated that the directional distribution of neurons activated by stimulation can be characterized by parametric models, and the model selection and parameterization can depend on the data representation (e.g. soma vs. axon node as the modulated process). In addition, we analyzed the change in model parameters with respect

to external parameters, such as stimulation amplitude and radial distance away from the FEM origin.

4.1. Utility in quantifying the spatial distribution of neuronal activation around a DBS lead

There is a clinical need for DBS electrode arrays with the capability to provide directional stimulation via steering and shifting of the output electric field [40], [16]. Such capability is important in cases of off-target DBS implants [18], [41] and in avoiding inducing adverse side-effects for the patient [42], [43], [44]. Consequently, much research has gone into the development [45], [46], modeling [18], [47], [48] and evaluation [49], [50] of high-density DBS arrays with circumferentially-segmented electrodes and independent current controlled stimulators [51]. A challenge when studying the effects of directional stimulation is to develop quantitative metrics for assessing the spatial distribution of neuronal activation around a DBS lead. Currently, the most widely used metric is the volume of tissue activated (VTA) [52], which is the volume enclosed by activated neurons or axons. Parameters such as the center of mass, total volume and maximal vertical/radial extent of activation can then be used to further characterize the VTA [53]. However, these measures only provide a fragmented picture of the data distribution making it difficult to generalize to compare different DBS settings. The advantage of spherical statistics lies in its ability to enable the user to understand the fundamental characteristics of the shape of a spatial distribution (e.g. unimodal, bimodal, girdle, etc.). In the case of DBS, it provides a number of parametric models that can be used to quantitatively describe the spatial distribution of modulated neuronal processes around a DBS lead. For example, in a recent study [54], researchers were able to use engineering optimization principles to design electrodes that preferentially activated neuronal elements in one orientation versus those in another. Stimulating the same neuronal population using two different electrodes would give different activation profiles (subject to certain definition of origin and data representation, e.g. first axon node that was activated) in space, which could potentially be represented by parametric spherical statistical models. Consider a scenario in which the Kent distribution was adequate to characterize the distribution of axon nodes that were first activated by stimulation in a neuronal population. Examining the differences in model parameters ξ_1 , ξ_2 , ξ_3 , κ and β can provide the directions of most and least data density, the mean direction of activated nodes, as well as degree of symmetry about the sample mean direction. This information is much richer than simply knowing a percent activation level for each electrode. It can potentially give insight into inhomogeneities and anisotropies in tissue conductance (if modeled) as well as directional distributions of the second spatial derivative of the extracellular voltage field. Researchers can also apply these parametric models to electrophysiological or optical recording data and study the spatial activation profiles of neurons under DBS in a quantitative manner. The results can then be used to inform new DBS electrode array designs as well as programming algorithms. The results from such studies can also benefit clinicians by providing 1) quantitative data on the feasibility of directing stimulation radially, 2) quantitative comparisons of neuronal activation profiles between different target brain structures, and 3) statistical description of their intuitions on shaping of the electric field.

4.2. Types of spatial distributions

We have demonstrated that spherical statistics is robust in quantifying spatial distributions of neurons activated by different stimulation configurations. Data representation (e.g. soma vs. axon node processes) is an important consideration and can significantly alter the shape of the resulting distribution. For instance, cathodic stimulation in all four directions (Model 2*) activated axon nodes in a ring-like formation concentrated about the equator of the unit sphere (Fig. 4), which can be characterized by the Watson girdle model. However, the distribution of cell bodies of activated neurons in the same model (Model 2) displayed a unimodal formation centered about the South Pole (Fig. 4) and could be characterized by the Kent model. This discrepancy is explained by the fact that action potentials are thought to initiate first in the axons and propagate antidromically towards the soma [7] with DBS waveforms. Since the cells are oriented such that their somas are located beneath their axons in this example, it is logical that most activated cells would have their somas in the southern hemisphere of the unit sphere, below the level of the active contacts. Cathodic stimulation in one direction (Model 1) also resulted in a unimodal distribution of activated cell bodies. Compared with stimulation in all four directions (Model 2), stimulation in one direction resulted in activation that was more focused in direction (larger κ) and more oval (less rotationally symmetric) in shape (larger β). In the case of bipolar stimulation (Model 3), a bimodal distribution emerged from the cell bodies of the activated neurons. In the projected view (Fig. 6A), data in the hemisphere facing cathodic stimulation (+ y cluster) was mostly concentrated near the South Pole, indicating that action potential initiation in these neurons most likely occurred near the level of the cathode. On the other hand, the soma locations of activated neurons in the hemisphere facing anodic stimulation (– y cluster) displayed much more variation in colatitude (Fig. 6D). There was a small concentration of data points with high colatitude values near the South Pole, while the rest were diffusely distributed over the entire range. This could be explained by anodic stimulation creating virtual depolarization [55] at locations along the axon that were further away from the plane of the anode. Together, the modeling results shown in this study (albeit using idealized model geometries) demonstrated that: 1) cathodic stimulation confined activation of axon nodes of Ranvier within a band centered about the plane of the active electrodes, which is suitable for focal activation; 2) anodic stimulation achieved broader activation in terms of direction and would be suitable for broadening activation of a given target; and 3) axonal projection morphologies play a critical role in determining the shape profile of the somatic population directly affected by the stimulation.

4.3. Empirical analysis and statistical testing

Empirical analysis and statistical testing are complementary approaches that serve different functions. The ESP is able to provide a general outline of the data distribution and put it into perspective in a continuum of changing morphologies. Other empirical information listed in Table 2 allows for fast categorization of the shape of the data distribution and narrows the direction of further data analysis. However, formal statistical testing is needed to provide the confidence in confirming or rejecting a hypothesized shape. Ambiguities may arise in this process, when the shape of a distribution falls in a transition zone between two different categories (e.g. bimodal vs. girdle). In such a case, fitting the data to different parametric models and assessing the goodness of fit in each case becomes important. Discordancy tests

are available to identify the outliers in the data that negatively affect the fit to a particular parametric model. These outliers can then be removed to achieve a better fit of the data. Once parametric models have been established for different stimulation settings, they can serve as quantitative metrics to describe and compare the spatial distributions of activated neuronal populations under these different settings.

4.4. Effect of stimulation settings on the parametric model parameters

The parameters of parametric models reflect the characteristics of the underlying distribution and can be used for quantitative analysis of the effects of directional stimulation. For example, the concentration parameter κ of the Kent distribution, when analyzed in the context of neuronal activation profile, is reflective of the degree of focus in stimulation. A higher κ value indicates that in directional terms, neuronal activation is more confined about a certain mean direction, which in turn reflects a more focused effect in stimulation. Similarly, the ovalness parameter β is a reflection of the uniformity of stimulation. A lower β value is associated with more rotational symmetry of the distribution and vice versa for higher β values. The differences in the amount of rotational symmetry can be further indicative of either asymmetry in the distribution of the underlying neuronal population or a difference in the mechanism of activation (e.g. cathodic vs. anodic stimulation).

Unidirectional cathodic stimulation at increasing amplitudes resulted in unimodal distributions of activated neurons (soma) that were well characterized by the Kent model (Fig. 9). The model parameters of κ and β decreased in a nonlinear fashion and eventually flattened out at higher amplitudes of stimulation. The implication is that at lower stimulation amplitudes, the activated neuronal population is more concentrated about its mean direction while less rotationally symmetric in shape. At higher stimulation amplitudes, a larger population was activated, which was more diffusely distributed about the mean direction but more rotationally symmetric in shape (Fig. 9C,D). The decrease in κ and β largely happened within 1 mA of stimulation, suggesting that the shape profile of the activated population became mostly stable above this threshold. This reinforced the observation that the mean colatitudes and longitudes of the activated populations also became relatively stable after 1 mA.

This approach of using the Kent distribution to model the activation profile of monopolar stimulation can be used to assess the viability of directional stimulation in a region of interest. As shown previously, nodal activation directionality may not reflect somatic activation directionality. It is expected that effective current steering via monopolar stimulation through one electrode would yield an activated cell body population that forms a Kent distribution, with mean direction close to the direction of stimulation. Distributions not described by the Kent model or have mean directions that largely deviate from the direction of stimulation would suggest that axonal projections are such that they render directional stimulation ineffective.

4.5. Limitations and considerations

In this study, we constructed a simplified and idealized computational model to demonstrate the application of spherical statistics. Additions of inhomogeneous and anisotropic tissue

conductivities, non-uniformity current density distributions across the electrode surface as well as voltage drop and capacitance at the electrode-electrolyte interface would make for a more realistic model and likely affect the model fits [56]. FEM mesh density is also an important consideration to ensure convergence of action potential thresholds [57], and while our mesh density was relatively high compared with the feature sizes of our DBS array and tissue model, there may be slight differences in the modeling results in the case of an even finer mesh. The axonal projection patterns and uniform distribution of neurons around the DBS lead that were modeled in this study were grossly idealized scenarios. Diffusion tensor imaging with probabilistic tractography methods [58], [59] as well as neuroanatomical tracing studies [60] could be used to construct realistic fiber tract morphologies, and the same analysis techniques and processes demonstrated in this study would apply.

Data representation in spherical statistical analysis can impact results and their interpretation. In this regard, the selection of coordinate systems is an important consideration and will vary depending on the particular application. Another consideration in data representation is the potential for different spatial profiles in the distributions as one extends in space from the DBS array. In this study, we analyzed the shape profile of activated neurons within concentric spherical shells. However, this approach could be modified by adopting amorphous shells that conform to layered structures such as the layers of the cortex or segments within deep brain structures.

There are many other useful methods within the field of spherical statistics not described here, such as analyzing properties of rotational symmetry about an axis [61] or testing for common mean direction between two distributions [62]. Additionally, there are other parametric models including the Wood distribution (for bimodal distributions with two modes of equal strength) [63], the Bingham distribution (for symmetric/asymmetric girdle or bipolar distributions) [36] [37], as well as the multipurpose General Fisher-Bingham distribution [64]. In these cases, there is a trade-off between the complexity of a model and its range of applicability, which should be weighed by the user. In cases of multimodal distributions, as one would expect with neuronal populations activated by multipolar stimulation, clustering the data (e.g. using k-means clustering) into smaller unimodal or bimodal groups and analyzing them individually may be the most suitable and informative approach [24].

4.6. Applications to other neurophysiological recording modalities

Advances in two-photon imaging have enabled *in-vivo* real-time imaging of large neuronal populations (with single-cell resolution) [65] [66] as well as simultaneous monitoring of different brain regions [67]. The spherical statistical approach used in the context of DBS has potential to be of value in quantifying network dynamics of neurons and constructing spatiotemporal maps of their activities. Studies have shown that spiking activities in rat neocortex are heterogeneous over time, generated by a continually changing subpopulation of active neurons [66]. Furthermore, microstimulation of the cat cortex has shown that neuronal populations are sparsely activated by stimulation, and patterns of activation are highly dependent on electrode location and likely arise from direct activation of axons in the vicinity [68]. Similar to what we have described in this paper, spherical statistics can be

applied in these studies by introducing a reference origin via the stereotactic reference system. The origin of the reference system may be placed at a point on the cortical surface, in which case all imaged cells would reside in the hemisphere below the cortex. This framework could provide a unified view of the distribution of neuronal dynamics in all cortical layers. Alternatively, the origin may be placed at a point in a particular cortical layer in the middle of the imaged volume (e.g. layer III, which contains projections to other cortical layers [69]), and neuronal activity would be analyzed from the perspective of this locus. Spherical statistics can also be useful in assessing whether two cortical regions are correlated by determining the correlation coefficient between two random vectors [70]. These vectors could represent time ordered population mean directions from two cortical areas. Correlation could be established if shifting the mean direction of neuronal activity in one region through stimulation induced a shift in the other region as well.

5. Conclusions

In this study, we demonstrated the use of spherical statistics to analyze computational neuron models of DBS. We have described a complete set of methods to visualize data, hypothesize on the shape of their distributions, perform statistical tests on the hypothesized shape, and finally fit the data to parametric models and access the goodness of the fit. In addition, we used parametric models to analyze the change in the distribution of activated neuronal populations with increased stimulation amplitude as well as radial distance from the active contact. Characterizing neuronal population activity using spherical statistical models allowed us to quantitatively analyze the behavior of such changes. The advent of segmented high density electrode arrays with current steering capabilities for DBS applications [50], [71] brings with it necessities of validation. Various methods can be used to study the effects of current steering on neuronal tissue, including electrophysiology [5], [72], histology [73], optical imaging [65], [10], and computational modeling [47], [18]. The methods of spherical statistics described in this study can provide a unified and rigorous framework to analyze directional data from such studies.

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References

1. Bar-Gad I, et al. Complex locking rather than complete cessation of neuronal activity in the globus pallidus of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primate in response to pallidal microstimulation. *J Neurosci*. 2004; 24(33):7410–9. [PubMed: 15317866]
2. Boraud T, et al. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. *Neurosci Lett*. 1996; 215(1):17–20. [PubMed: 8880743]
3. Dostrovsky JO, et al. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *J Neurophysiol*. 2000; 84(1):570–4. [PubMed: 10899228]
4. Filali M, et al. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. *Exp Brain Res*. 2004; 156(3):274–81. [PubMed: 14745464]
5. Meissner W, et al. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain*. 2005; 128(Pt 10):2372–82. [PubMed: 16123144]

6. Johnson MD, McIntyre CC. Quantifying the neural elements activated and inhibited by globus pallidus deep brain stimulation. *J Neurophysiol.* 2008; 100(5):2549–63. [PubMed: 18768645]
7. McIntyre CC, et al. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. *J Neurophysiol.* 2004; 91(4):1457–69. [PubMed: 14668299]
8. Miocinovic S, et al. Computational analysis of subthalamic nucleus and lenticular fasciculus activation during therapeutic deep brain stimulation. *J Neurophysiol.* 2006; 96(3):1569–80. [PubMed: 16738214]
9. Tolias AS, et al. Mapping cortical activity elicited with electrical microstimulation using FMRI in the macaque. *Neuron.* 2005; 48(6):901–11. [PubMed: 16364895]
10. Histed MH, Bonin V, Reid RC. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron.* 2009; 63(4):508–22. [PubMed: 19709632]
11. Johnson MD, et al. Mechanisms and targets of deep brain stimulation in movement disorders. *Neurotherapeutics.* 2008; 5(2):294–308. [PubMed: 18394571]
12. Tehovnik EJ, et al. Direct and indirect activation of cortical neurons by electrical microstimulation. *J Neurophysiol.* 2006; 96(2):512–21. [PubMed: 16835359]
13. McIntyre, CC., et al. Customizing deep brain stimulation to the patient using computational models; Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE; IEEE; 2009.
14. McIntyre, CC., et al. Improving postural stability via computational modeling approach to deep brain stimulation programming; Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE; IEEE; 2011.
15. Frankemolle AM, et al. Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. *Brain.* 2010; 133(Pt 3):746–61. [PubMed: 20061324]
16. Butson CR, McIntyre CC. Current steering to control the volume of tissue activated during deep brain stimulation. *Brain Stimul.* 2008; 1(1):7–15. [PubMed: 19142235]
17. Martens HC, et al. Spatial steering of deep brain stimulation volumes using a novel lead design. *Clin Neurophysiol.* 2011; 122(3):558–66. [PubMed: 20729143]
18. Keane M, et al. Improved spatial targeting with directionally segmented deep brain stimulation leads for treating essential tremor. *J Neural Eng.* 2012; 9(4):046005. [PubMed: 22732947]
19. Matteucci PB, et al. Current steering in retinal stimulation via a quasimonopolar stimulation paradigm. *Invest Ophthalmol Vis Sci.* 2013; 54(6):4307–20. [PubMed: 23661370]
20. Jepson LH, et al. Spatially patterned electrical stimulation to enhance resolution of retinal prostheses. *J Neurosci.* 2014; 34(14):4871–81. [PubMed: 24695706]
21. Bonham BH, Litvak LM. Current focusing and steering: modeling, physiology, and psychophysics. *Hear Res.* 2008; 242(1-2):141–53. [PubMed: 18501539]
22. Lim DH, et al. In vivo Large-Scale Cortical Mapping Using Channelrhodopsin-2 Stimulation in Transgenic Mice Reveals Asymmetric and Reciprocal Relationships between Cortical Areas. *Front Neural Circuits.* 2012; 6:11. [PubMed: 22435052]
23. Toader E, Decre MM, Martens HC. Steering deep brain stimulation fields using a high resolution electrode array. *Conf Proc IEEE Eng Med Biol Soc.* 2010; 2010:2061–4. [PubMed: 21096152]
24. Fisher, NI. Statistical analysis of spherical data. Cambridge University Press; 1993.
25. Borradaile GJ, Henry B. Tectonic applications of magnetic susceptibility and its anisotropy. *Earth-Science Reviews.* 1997; 42(1-2):49–93.
26. Allen TR, Kupfer JA. Application of spherical statistics to change vector analysis of Landsat data: Southern Appalachian spruce-fir forests. *Remote Sensing of Environment.* 2000; 74(3):482–493.
27. Leong P, Carlile S. Methods for spherical data analysis and visualization. *J Neurosci Methods.* 1998; 80(2):191–200. [PubMed: 9667392]
28. Ranck JB Jr. Analysis of specific impedance of rabbit cerebral cortex. *Exp Neurol.* 1963; 7:153–74. [PubMed: 13990733]
29. Grill WM, Mortimer JT. Electrical properties of implant encapsulation tissue. *Ann Biomed Eng.* 1994; 22(1):23–33. [PubMed: 8060024]

30. Lempka SF, et al. Current-controlled deep brain stimulation reduces in vivo voltage fluctuations observed during voltage-controlled stimulation. *Clin Neurophysiol.* 2010; 121(12):2128–33. [PubMed: 20493764]
31. Eilers PHC, Goeman JJ. Enhancing scatterplots with smoothed densities. *Bioinformatics.* 2004; 20(5):623–U82. [PubMed: 15033868]
32. Woodcock NH. Specification of Fabric Shapes Using an Eigenvalue Method. *Geological Society of America Bulletin.* 1977; 88(9):1231–1236.
33. Rayleigh L XXXI. On the problem of random vibrations, and of random flights in one, two, or three dimensions. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science.* 1919; 37(220):321–347.
34. Kent JT. The Fisher-Bingham Distribution on the Sphere. *Journal of the Royal Statistical Society Series B-Methodological.* 1982; 44(1):71–80.
35. Watson G. Equatorial distributions on a sphere. *Biometrika.* 1965:193–201.
36. Bingham, C. Distributions on the sphere and on the projective plane. Yale University; 1964.
37. Bingham C. An antipodally symmetric distribution on the sphere. *The Annals of Statistics.* 1974:1201–1225.
38. Best D, Fisher N. GOODNESS-OF-FIT AND DISCORDANCY TESTS FOR SAMPLES FROM THE WATSON DISTRIBUTION ON THE SPHERE. *Australian Journal of Statistics.* 1986; 28(1):13–31.
39. Mardia K, Gadsden R. A small circle of best fit for spherical data and areas of vulcanism. *Applied Statistics.* 1977:238–245.
40. Johnson MD, et al. Neuromodulation for brain disorders: challenges and opportunities. *IEEE Trans Biomed Eng.* 2013; 60(3):610–24. [PubMed: 23380851]
41. Martens HCF, et al. Spatial steering of deep brain stimulation volumes using a novel lead design. *Clinical Neurophysiology.* 2011; 122(3):558–566. [PubMed: 20729143]
42. Krack P, et al. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. *Mov Disord.* 2002; 17(Suppl 3):S188–97. [PubMed: 11948776]
43. Papavassiliou E, et al. Thalamic deep brain stimulation for essential tremor: Relation of lead location to outcome. *Neurosurgery.* 2004; 54(5):1120–1129. [PubMed: 15113466]
44. Tamma F, et al. Anatomic-clinical correlation of intraoperative stimulation-induced side-effects during HF-DBS of the subthalamic nucleus. *Neurol Sci.* 2002; 23(Suppl 2):S109–10. [PubMed: 12548367]
45. Gijssbers JTM, Gielen FLH, Knuth HM. High resolution brain stimulation lead and method of use. 1998 Google Patents.
46. Hetke JF, et al. Modular multichannel microelectrode array and methods of making same. 2011 Google Patents.
47. Zitella LM, et al. Computational modeling of pedunculopontine nucleus deep brain stimulation. *J Neural Eng.* 2013; 10(4):045005. [PubMed: 23723145]
48. Buhlmann J, et al. Modeling of a segmented electrode for desynchronizing deep brain stimulation. *Front Neuroeng.* 2011; 4:15. [PubMed: 22163220]
49. Pollo C, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain.* 2014; 137(Pt 7):2015–26. [PubMed: 24844728]
50. Contarino MF, et al. Directional steering: A novel approach to deep brain stimulation. *Neurology.* 2014; 83(13):1163–9. [PubMed: 25150285]
51. Lempka SF, et al. Current-controlled deep brain stimulation reduces in vivo voltage fluctuations observed during voltage-controlled stimulation. *Clinical Neurophysiology.* 2010; 121(12):2128–33. [PubMed: 20493764]
52. Butson CR, et al. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. *Neuroimage.* 2007; 34(2):661–70. [PubMed: 17113789]
53. Toader, E.; Decre, MMJ.; Martens, HCF. Steering deep brain stimulation fields using a high resolution electrode array; 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Embc); 2010. p. 2061–2064.

54. Howell B, Huynh B, Grill WM. Design and in vivo evaluation of more efficient and selective deep brain stimulation electrodes. *J Neural Eng.* 2015; 12(4):046030. [PubMed: 26170244]
55. Roth BJ. Mechanisms for electrical stimulation of excitable tissue. *Crit Rev Biomed Eng.* 1994; 22(3-4):253–305. [PubMed: 8598130]
56. Chaturvedi A, et al. Patient-specific models of deep brain stimulation: influence of field model complexity on neural activation predictions. *Brain Stimul.* 2010; 3(2):65–7. [PubMed: 20607090]
57. Howell B, Naik S, Grill WM. Influences of interpolation error, electrode geometry, and the electrode-tissue interface on models of electric fields produced by deep brain stimulation. *IEEE Trans Biomed Eng.* 2014; 61(2):297–307. [PubMed: 24448594]
58. Behrens TEJ, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience.* 2003; 6(7):750–757. [PubMed: 12808459]
59. Johansen-Berg H, et al. Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. *Cereb Cortex.* 2005; 15(1):31–9. [PubMed: 15238447]
60. Hampel S, et al. Drosophila Brainbow: a recombinase-based fluorescence labeling technique to subdivide neural expression patterns. *Nat Methods.* 2011; 8(3):253–9. [PubMed: 21297621]
61. Stephens MA. Edf Statistics for Goodness of Fit and Some Comparisons. *Journal of the American Statistical Association.* 1974; 69(347):730–737.
62. Watson, GS., et al. *Statistics on spheres.* Vol. 6. Wiley New York; 1983.
63. Wood A. A Bimodal Distribution on the Sphere. *Applied Statistics-Journal of the Royal Statistical Society Series C.* 1982; 31(1):52–58.
64. Kent JT. The Fisher-Bingham distribution on the sphere. *Journal of the Royal Statistical Society.* 1982:71–80. Series B (Methodological).
65. Stosiek C, et al. In vivo two-photon calcium imaging of neuronal networks. *Proc Natl Acad Sci U S A.* 2003; 100(12):7319–24. [PubMed: 12777621]
66. Kerr JN, Greenberg D, Helmchen F. Imaging input and output of neocortical networks in vivo. *Proc Natl Acad Sci U S A.* 2005; 102(39):14063–8. [PubMed: 16157876]
67. Lecoq J, et al. Visualizing mammalian brain area interactions by dual-axis two-photon calcium imaging. *Nat Neurosci.* 2014; 17(12):1825–9. [PubMed: 25402858]
68. Histed MH, Bonin V, Reid RC. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron.* 2009; 63(4):508–522. [PubMed: 19709632]
69. Burkhalter A, Bernardo KL. Organization of corticocortical connections in human visual cortex. *Proc Natl Acad Sci U S A.* 1989; 86(3):1071–5. [PubMed: 2464827]
70. Jupp PE, Mardia KV. A General Correlation-Coefficient for Directional-Data and Related Regression Problems. *Biometrika.* 1980; 67(1):163–173.
71. Pollo C, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain.* 2014
72. Schlag J, Villablanca J. A quantitative study of temporal and spatial response patterns in a thalamic cell population electrically stimulated. *Brain Res.* 1968; 8(2):255–270. [PubMed: 5652719]
73. Bullitt E. Expression of C-Fos-Like Protein as a Marker for Neuronal-Activity Following Noxious-Stimulation in the Rat. *Journal of Comparative Neurology.* 1990; 296(4):517–530. [PubMed: 2113539]

Highlights

- Spherical statistics to characterize spatial distributions of neuronal activity.
- Demonstrated visualization, hypothesis testing and parametric modeling techniques.
- Directional distribution of neurons activated by deep brain stimulation.
- Modeled neuronal distributions with changing stimulus amplitude or radial distance.

Figure 1. Computational model of neuronal activation by stimulation through a directionally-segmented DBS electrode array

(A) Volume conductor model with the DBS array in the center. (B) The blue spheres represent the cell bodies of 5000 thalamocortical relay neurons that were uniformly distributed about the center of bottom row of electrode contacts, in a sphere 5mm in radius. (C) Close up view of one of the neurons. The axon is oriented vertically and parallel to the shaft of the DBS array. (D)-(F) Cross sectional view of the voltage field in models 1,2 and 3. The dashed line represents the boundary of the encapsulation layer. (G)-(I) Top-down view of the neuronal activation profiles in models 1,2 and 3. The red spheres represent the cell bodies of neurons activated by stimulation.

Figure 2. Spherical statistics workflow

Framework for hypothesis testing and parametric modeling of the spatial distribution of soma or axonal nodes affected by stimulation.

Figure 3. Data representations in 3D and their projections onto 2D

(A) Data were transformed into polar coordinates with colatitude and longitude variables.

(B) Illustration of Lambert azimuthal equal-area projection.

Figure 4. Model data representations in 3D and their projections onto 2D

(A) Multi-compartment, thalamocortical neuron model simulations were conducted in the context of three different stimulation configurations: monopolar cathodic stimulation through one electrode at -0.25mA (left column), monopolar cathodic stimulation through all four electrodes along a single row at -0.25mA/contact (middle two columns), and bipolar stimulation with opposing electrodes on a single row at $\pm 1\text{mA/contact}$ (right column). For neuron models in which stimulation elicited stimulus-locked spike activity, the location of either the cell body (Models 1-3) or the first-activated node of Ranvier (Model 2*) was projected onto a sphere. (B) The mean direction of the distribution was then aligned to the South Pole (as shown in part A, left column) and then projected down to an equal area projection map to provide a basis for estimating the spatial distribution of the neuronal processes modulated by stimulation. Color indicates the density of the modulated neuronal processes.

Figure 5. Canonical distributions and the empirical shape plot

Examples of (A) uniform, (B) unimodal, (C) bimodal, (D) bipolar, (E) symmetrical girdle, and (F) unsymmetrical girdle distributions. (G) Empirical shape plot showing the two-axis logarithmic eigenvalue ratio distributions for cluster, girdle, bimodal, and uniform distributions (adapted from Woodcock [32]). (H) Empirical shape plot for the thalamocortical neuron model data showing geometrical estimates for the distribution of each Model.

Figure 6. Analysis of a bimodal distribution in Model 3

(A) Somas of neurons activated by bipolar stimulation in Model 3 projected onto the unit sphere. The red data points in the positive y hemisphere (facing the cathode) were grouped into the positive y coordinate cluster. The cyan data points in the negative y hemisphere (facing the anode) were grouped into the negative y coordinate cluster. Active electrode contacts are in yellow. (B) Empirical shape plot representation of all activated neurons, neurons in the positive y coordinate cluster and neurons in the negative y coordinate cluster. (C) Equal-area projection of data in the positive y coordinate cluster. (D) Equal-area projection of data in the negative y coordinate cluster.

Figure 7.

Projection of somas of activated neurons in models 1 and 2 onto the unit sphere. The blue line is the population mean direction in each model. The blue circle represents the 95% confidence cone.

Figure 8. Analysis of the goodness of fit of Model 2* to the Watson girdle distribution
 (A) Longitude plot graphically displaying the goodness of fit of Model 2* to the Watson girdle model. A good fit is signified by an approximately linear line, passing through the origin with a slope of approximately 1. (B) Colatitude goodness of fit plot. A good fit is signified by an approximately linear line passing through the origin. (C) Cell bodies of activated neurons in Model 2* projected onto the unit sphere. The cyan ring is the best-fit small circle for the data.

Figure 9. Analysis of activation profiles from single contact monopolar cathodic stimulation using the Kent distribution

(A) Idealized illustration of change in the Kent distribution with increased concentration parameter κ . (B) Idealized illustration of change in the Kent distribution with increased ovalness parameter β . (C) Top-down view of the voltage fields from single contact monopolar cathodic stimulation at eight example amplitudes. (D) Top-down view of the distribution of cell bodies of the corresponding activated neurons. (E) Number of activated neurons vs. stimulation amplitude. Stimulation amplitudes ranged from 0.1 – 5 mA at increments of 0.1 mA. (F) The distributions of activated neurons were characterized using the Kent model. The plot shows the change in Kent model parameters (κ , β) with stimulation amplitude. (G) Change in sample mean colatitude and longitude with stimulation amplitude.

Figure 10. Analysis of activation profiles within concentric spherical shells using the Kent distribution

(A) Illustration of the concentric spherical shells about the center of the bottom row of electrodes. The thickness of each shell is 0.25 mm. The red electrode contact delivered cathodic stimulation at 5 mA. (B) Equal area projection of the cell bodies of activated neurons within each spherical shell. (C) Number of activated neurons vs. radius of spherical shell. (D) Sample mean colatitude and longitude of activated neurons vs. radius of spherical shell. (E) The distribution of activated neurons in each spherical shell was characterized using the Kent model. The plot shows the change in Kent model parameters (κ , β) with radius of spherical shells.

TABLE I

(Model Information Summary)

	Model 1	Model 2	Model 2*	Model 3
<i>Data Type</i>	Soma	Soma	Node of Ranvier	Soma
<i>Origin</i>	Model origin	Model origin	Model origin	Model origin
$\tau_1/\tau_2/\tau_3$	0.09/0.13/0.78	0.19/0.24/0.57	0.18/0.38/0.44	0.16/0.27/0.57
R^-	0.872	0.6679	0.0805	0.4858
Hypothesized model	Unimodal	Unimodal	Girdle	Bimodal

TABLE II

(Categorization of parametric distributions based on normalized eigenvalues of the orientation matrix)

Relative magnitude of normalized eigenvalues			Type of distribution
$\tau_1 = \tau_2 = \tau_3 = 1/3$			<i>Uniform</i>
$\tau_3 \gg \tau_1, \tau_2$	$\tau_1 \approx \tau_2$	$R = 1$	<i>Unimodal</i>
		Otherwise	<i>Bimodal</i>
	$\tau_1 \approx \tau_2$	$R = 1$	<i>Unimodal</i>
		Otherwise	<i>Bipolar</i>
$\tau_1 \ll \tau_2, \tau_3$	$\tau_2 \approx \tau_3$		<i>Girdle</i>
	$\tau_1 \approx \tau_2$		<i>Symmetric Girdle (about polar axis)</i>

TABLE III

(Hypothesis testing on the shape of model distributions)

	Model 1	Model 2	Model 2*	Model 3	
Test against uniformity (H_0 : uniformity)	(H_A : unimodal)	(H_A : unimodal)	(H_A : girdle)	+y cluster (H_A :unimodal)	-y cluster (H_A :girdle)
Test Statistic	1017.3436 *	1985.8278 *	0.1781 *	1042.0512 *	0.1905

* indicates test was significant at $\alpha=0.05$

TABLE IV

(Kent distribution parameters for models 1,2 and 2*)

	Model 1	Model 2	Model 2*	
κ	7.9582	3.0247	-2.3161	
β	0.5408	0.1020	---	