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

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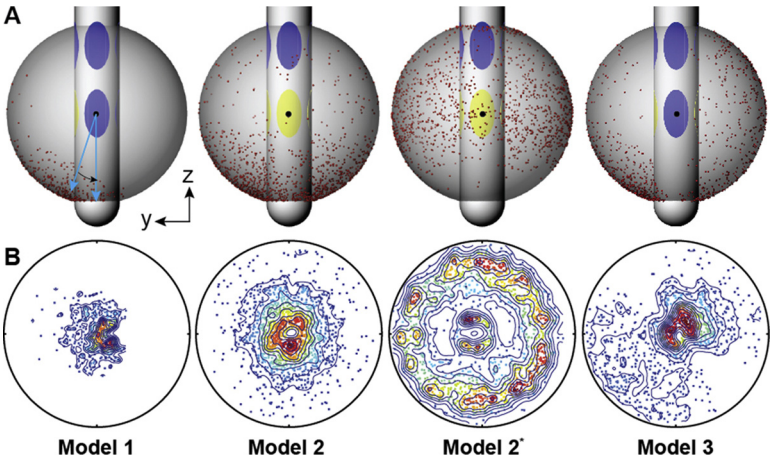
HIGHLIGHTS

- 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.

GRAPHICAL ABSTRACT



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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

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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.

1. Introduction

Electrical stimulation within the brain is known to modulate the rate and pattern of neuronal spike activity around an active electrode (Bar-Gad et al., 2004; Boraud et al., 1996; Dostrovsky et al., 2000; Filali et al., 2004; Meissner et al., 2005). 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 (Johnson and McIntyre, 2008; McIntyre et al., 2004; Miocinovic et al., 2006), which together create a sparsely activated volume that is highly dependent on electrode placement (Tolias et al., 2005; Histed et al., 2009). Characterizing the spatial distribution of modulation around an active electrode has importance for better understanding the neurophysiological mechanisms of electrical stimulation (Johnson et al., 2008; Tehovnik et al., 2006) and has clinical relevance in the design of patient-specific strategies to improve the selectivity of targeting individual pathways within the brain (McIntyre et al., 2009, 2011; Frankemolle et al., 2010). 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) (Butson and McIntyre, 2008; Martens et al., 2011; Keane et al., 2012) as well as characterizing the spatial precision of modulation for visual (Matteucci et al., 2013; Jepson et al., 2014) and auditory (Bonham and Litvak, 2008) 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 (Keane et al., 2012) or experimental recordings using electrophysiological (Histed et al., 2009) or imaging-based (Lim et al., 2012) techniques. Commonly used metrics include: population center of mass (COM), total volume enclosing the population, or maximal radial extent of activation (Toader et al., 2010). 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 (Fisher, 1993) 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 (Borradaile and Henry, 1997), remote sensing (Allen and Kupfer, 2000), and auditory psychophysics (Leong and Carlile, 1998). 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 lead[1] 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 x height) was generated in a finite element model (FEM) (COMSOL Multiphysics, v4.3b) (Fig. 1A and 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 × height), 0.18 S/m homogeneous encapsulation layer and a 100 × 100 mm (diameter × height), 0.3 S/m cylinder of homogeneous bulk tissue surrounds the lead (Ranck, 1963; Grill and Mortimer, 1994) (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 1116,911 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 ($n = 5000$) (McIntyre et al., 2004) were uniformly distributed within a 10 mm diameter sphere giving a spatial population density of approximately 10 neurons/mm^3 around the DBS lead. Model neuron axonal efferents were oriented vertically (parallel to lead

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