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Impact of brain tissue filtering on neurostimulation fields: A modeling study ☆

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ABSTRACT

Electrical neurostimulation techniques, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), are increasingly used in the neurosciences, e.g., for studying brain function, and for neurotherapeutics, e.g., for treating depression, epilepsy, and Parkinson's disease. The characterization of electrical properties of brain tissue has guided our fundamental understanding and application of these methods, from electrophysiologic theory to clinical dosing-metrics. Nonetheless, prior computational models have primarily relied on ex-vivo impedance measurements. We recorded the in-vivo impedances of brain tissues during neurosurgical procedures and used these results to construct MRI guided computational models of TMS and DBS neurostimulatory fields and conductance-based models of neurons exposed to stimulation. We demonstrated that tissues carry neurostimulation currents through frequency dependent resistive and capacitive properties not typically accounted for by past neurostimulation modeling work. We show that these fundamental brain tissue properties can have significant effects on the neurostimulatory-fields (capacitive and resistive current composition and spatial/temporal dynamics) and neural responses (stimulation threshold, ionic currents, and membrane dynamics). These findings highlight the importance of tissue impedance properties on neurostimulation and impact our understanding of the biological mechanisms and technological potential of neurostimulatory methods.

Introduction

Exogenous brain stimulation techniques, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), have been successfully used to study essential properties of the nervous system and to treat numerous neurological disorders, such as Parkinson's disease with DBS and depression with TMS (Kuncel and Grill, 2004; Wagner et al., 2007). Underlying all of these techniques is the necessity to understand how stimulatory electromagnetic fields interact and pass through tissue(s) to effectively influence targeted neural circuits at a distance from the stimulation source (Butson and McIntyre, 2005; Tehovnik, 1996; Wagner et al., 2007).

In biological tissues, electric fields drive currents with ohmic (resistive) and displacement (capacitive) components. Ohmic currents are generated by the movement of free charges, such as unbound extracellular sodium and potassium ions. Electrical conductivity is a

Abbreviations: CSF, Cerebral Spinal Fluid; DBS, Deep Brain Stimulation; FEM, Finite Element Model; HP, Hewlett Packard; IACUC, Institutional Animal Care and Use Committee; MRI, Magnetic Resonance Imaging; RMS, Root Mean Squared; TMS, Transcranial Magnetic Stimulation; VOA, Volumes of Activation.

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measure of how easily these free charges move through the medium. Displacement currents are generated by the polarization of paired charges, such as ionic double-layers that surround cellular membranes and/or macromolecules embedded in cellular membranes (for a further discussion of mechanisms see (Foster and Schwan, 1989, 1996; Pethig and Kell, 1987; Schwan, 1963)). Electrical permittivity is a measure related to how easily these paired charges are polarized. Most biophysical theories of brain stimulation, from those guiding our understanding of essential biological mechanisms to those guiding clinical safety and dosing criteria, assume that stimulating currents are entirely ohmic and consider displacement currents to have essentially no role in the stimulation of neural tissue. This assumption is largely based on ex-vivo tissue impedance measurements, in which measured permittivities predict displacement currents to be orders of magnitude smaller than their ohmic counterparts in the spectral frequency band of the applied stimulatory fields (Heller and Hulsteyn, 1992; Plonsey and Heppner, 1967; Wagner et al., 2004, 2007).

However, experimental work and theoretical studies from the material sciences suggest that within the electromagnetic field frequency band used for brain stimulation, the displacement currents may in fact be significant enough to impact the stimulatory fields ((IFAP), 2007; Butson and McIntyre, 2005; Foster and Schwan, 1989, 1996; Pethig and Kell, 1987; Wagner et al., 2004) — please note that IFAP stands for the Institute for Applied Physics (http://niremf.ifac.cnr.it/tissprop/). Schwan was the first to demonstrate this elevated tissue permittivity with decreased frequency, thought to result from relaxation of counterions tangential to the cell membranes in tissues (i.e., alpha dispersion) (Foster and Schwan, 1989, 1996; Pethig and Kell, 1987; Schwan, 1954, 1963). Furthermore, in-vivo recordings of the electromagnetic fields generated in brain tissues by TMS (Tay, 1992; Tay et al., 1989) and DBS (Miocinovic et al., 2009) both suggest that the stimulatory fields are influenced by both tissue capacitance and resistance. This indicates that past theories of brain stimulation may not fully account for fundamental biophysical processes occurring in neural tissue; which, could impact the predicted network response and the safety/dosing profiles that guide the clinical use of brain stimulation (Wagner et al., 2007). Furthermore, coupled displacement and ohmic mechanisms in neural tissue could lead to frequency dependent filtering of the applied stimulatory fields, or endogenously generated fields (Bedard et al., 2004; Bossetti et al., 2008; De Geeter et al., 2012; Foster and Schwan, 1996; Grant and Lowery, 2010; Tracey and Williams, 2011; Wagner et al., 2004). Such filtering effects could alter a predicted stimulatory waveform's size and shape, impacting the expected neural response and electrochemical interactions taking place in the brain. In this study, we recorded in-vivo head and brain tissue impedance properties throughout the neurostimulation frequency range and assessed their impact on the mechanisms of neural stimulation and metrics guiding its use.

Materials and methods

We first measured the conductivity, σ, and permittivity, ε, values of tissues, in the frequency range from 10 to 50,000 Hz, in anesthetized animals. We then constructed MRI guided finite element models (FEMs) of the electromagnetic fields generated during TMS and DBS based on the individual tissue impedance properties we recorded and, for comparison, with impedance values used in past modeling studies, primarily developed from ex-vivo measurements. We then evaluated how these tissue properties affect the TMS and DBS stimulatory fields. Finally, we explored the effects of the tissues and resulting field responses on stimulation thresholds and response dynamics of a conductance based model of the human motor neuron (see Supplementary methods, Supplementary Fig. 1 (i.e., Supplementary Fig. 1)).

Tissue recordings

Two adult cats were obtained from licensed cat breeders (Liberty Laboratories, Waverly, NY). Neurosurgical/craniotomy procedures, detailed in Rushmore et al. (2006), and approved by the Boston University School of Medicine IACUC committee, were conducted. Anesthetized (4% isoflurane in 30% oxygen and 70% nitrous oxide) animals' head/brain tissues were exposed and a specialized impedance probe, fabricated from a modified forceps, was applied.

At low electromagnetic field frequencies, typical of brain stimulation sources, the characterization of tissue impedances is complicated by the potential for large electrode polarization artifacts, even in four-terminal measurements (see, e.g., (Pethig and Kell, 1987; Schwan, 1963)), which can be further complicated by nonlinear electrode materials (Schwan, 1966, 1968), needle microelectrode effects (Schwan, 1966, 1968), and measurement electronics (Pethig and Kell, 1987; Schwan, 1963; Schwan and Ferris, 1968). For our measurements, we followed the method detailed in Gabriel et al. (1996b) to account for polarization artifacts in the probe. We also used a material well characterized in our recording band for our impedance probe interface (i.e., platinum) (Schwan, 1966, 1968, 1992), used modified forceps without the pronounced geometrical constraints of needle microelectrodes (Schwan, 1966, 1968), and implemented a recording system (Hewlett Packard HP4192A) capable of resolving impedance in the spectrum analyzed, all detailed below.

First, the tissue impedance probe was produced by modifying a self-closing forceps mechanism (Dumont N5) for use as a controllable, two plate sputtered platinum probe to limit polarization effects (Schwan, 1992). Probe tips were created by cutting the tips off of the stainless steel forceps and coating the inside faces using electron beam evaporation. The tips were coated under high vacuum conditions (5×10^{-7} Torr) with 10 nm titanium (99.99% Alfa Aesar) as an adhesion layer and then 50 nm of platinum (99.99% Alfa Aesar). The tips were then re-attached to the closing mechanism using two plastic adapter plates, providing electrical insulation from proximal instruments and tissues. The self-closing handle mechanism was also modified using two fine-threaded screws to allow for precise and repeatable control of the inter-electrode separation distance. Further control was achieved by fixing the impedance probe to a micropositioner (Kopf, Tujunga, CA). Overall, soft tissue sample volume was maintained constant at 50 μm × 200 μm × 400 μm (+/− 10 μm on the largerdimensions). Prior to the animal recordings, the probe's transfer function was characterized from 0.01 to 50 kHz in saline solutions from 0.0 (deionized) to 0.09 M NaCl, to account for electrode polarization effects (Schwan, 1992), via the substitution/subtraction technique methods directly outlined in Gabriel et al. (1996b).

The probe was used as a surgical instrument to systematically grasp and isolate the tissues, where they were investigated with an HP4192A impedance analyzer (Hewlett Packard, Palo Alto) to determine the tissue impedances (conductivity and permittivity) of the skin, skull, gray matter, and white matter following methods similar to Gabriel et al. (1996b). Tissue measurements were primarily taken along the radial axis for the skin and bone and approximately tangential to the tissue boundary for gray matter and white matter. Tissue anisotropy was not explored in this current study, to minimize proximal tissue disturbance with our probe, and was left for future studies. Recordings were taken from 10 to 50,000 Hz to span the typical brain stimulation power spectrum, at 75 logarithmically spaced points on the frequency log scale (20 points per decade). Approximately 8 separate sweeps per cat and tissue were performed across the frequency band. Average values of the conductivity and permittivity were then calculated for each frequency. Saline measurements were repeated throughout the experiment, and the probe was examined for integrity under a surgical microscope between measurements (approximately every 8 recordings). For each tissue, an additional 3–4 sweeps were made at 5 Hz steps (30,000–40,000 additional points), throughout