Analysis and Design of Electrodes for Deep Brain Stimulation

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biomedical Engineering in the Graduate School of Duke University

2009
ABSTRACT

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Abstract

Deep brain stimulation (DBS) electrodes are intended to stimulate specific areas of the brain to treat movement disorders including essential tremor, Parkinson’s disease and dystonia. An important goal in the design of next generation DBS electrodes is to minimize the power needed to stimulate specific regions of the brain. A reduction in power consumption will prolong battery life and reduce the size of implanted pulse generator. Electrode geometry is one approach to increase the efficiency of neural stimulation and reduce the power required to produce the level of activation required for clinical efficacy.

We first characterized the impedance of the presently used clinical DBS electrodes in vitro and in vivo. Characterization of the electrode-tissue interface impedance is required to quantify the composition of charge transfer to the brain tissue. The composition of charge transfer was dependent on both the current density and the sinusoidal frequency. The assumption of the DBS electrode being ideally polarizable was not valid under clinical stimulating conditions. This implies that irreversible processes that can cause electrode or tissue damage might occur when high charge injection is required for DBS.

Current density distribution is an important factor in determining patterns of neural excitation, tissue damage and electrode corrosion. We developed a recursive simulation scheme to calculate the current density distribution that incorporates the nonlinear electrode-tissue interface into finite-element based models of electrodes. The
current density distributions on the electrode surface were strongly dependent on the sinusoidal frequency. The primary current density distribution without including the electrode-tissue interface can be used to estimate neural excitation, tissue damage and electrode corrosion with rectangular stimulus pulses as most of the signal power is at frequencies where the secondary current density distribution matches closely the primary current density distribution.

We designed and analyzed novel electrode geometries to decrease stimulation thresholds, thus reducing power consumption of implanted stimulators. Our hypothesis was that high-perimeter electrode geometries that increase the variation of current density on the electrode surface will generate larger activating functions for surrounding neurons and thereby increase stimulation efficiency. We investigated three classes of electrodes: segmented cylindrical electrodes, serpentine-perimeter planar electrodes, and serpentine-perimeter cylindrical electrodes. An approach that combined finite element models of potentials and cable models of axonal excitation was used to quantify the stimulation efficiency of electrodes with various geometries. Increasing the electrode perimeter increased the electrode efficiency by decreasing stimulation threshold. Both segmentation and serpentine edges provided means to increase the efficiency of stimulation. Novel cylindrical electrodes that combined segmentation with serpentine edges decreased power consumption by ~20% for axons parallel to the electrode and by ~35% for axons perpendicular to the electrode. These electrode designs could potentially prolong the average battery life of deep brain stimulator by more than one year.
Dedication

To my parents, Liqian Guo and Xicheng Wei
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Contents

Abstract ........................................................................................................................................ iv

Dedication ................................................................................................................................... vi

Acknowledgements ................................................................................................................ vii

Contents ...................................................................................................................................... iv

List of Tables .......................................................................................................................... x

List of Figures ........................................................................................................................... xi

Chapter 1 : Introduction and Overview ................................................................................ 1
  1.1. Deep Brain Stimulation and Electrode ........................................................................ 1
  1.2. Electrode-Electrolyte/Tissue Interface ...................................................................... 3
       1.2.1. Capacitive charge transfer ................................................................................ 4
       1.2.2. Faradaic charge transfer ................................................................................... 4
       1.2.3. Impedance effects due to diffusion ................................................................. 6
  1.3. Current Density Distribution ....................................................................................... 7
  1.4. Power Consumption of DBS System ......................................................................... 8
  1.5. High-Efficiency Electrode Designs ........................................................................... 10
  1.6. Estimation of Tissue Damage ................................................................................... 13
  1.7. Hypotheses and Objectives ....................................................................................... 17
  1.8. Outline of Chapters ..................................................................................................... 18

Chapter 2 : Impedance Characteristics of Deep Brain Stimulation Electrodes in vitro and in vivo ......................................................................................................................... 21
  2.1. Abstract ......................................................................................................................... 21
3.3.2. Finite element modeling and simulation ......................................................... 52
3.4. Results .................................................................................................................. 55
  3.4.1. Determine interface impedance from in vitro measurements ...................... 56
  3.4.2. Effects of interface on current density and potential distributions .......... 57
3.5. Discussion ............................................................................................................ 60
  3.5.1. Implications for DBS ...................................................................................... 62
  3.5.2. Modeling limitations ....................................................................................... 65
3.6. Conclusions .......................................................................................................... 66

Chapter 4 : Impedance and Field Analysis of Segmented Cylindrical Electrodes ... 67

  4.1. Abstract ............................................................................................................. 67
  4.2. Introduction ........................................................................................................ 68
  4.3. Methods ............................................................................................................ 70
    4.3.1. Calculations of current density distributions ............................................. 70
    4.3.2. Calculation of activation patterns ............................................................... 72
    4.3.3. In vitro measurement of electrode impedance .......................................... 72
  4.4. Results ............................................................................................................... 74
    4.4.1. Current density distributions on segmented electrodes ......................... 75
    4.4.2. Activation patterns generated by segmented electrodes ....................... 77
    4.4.3. Impedance of segmented electrodes ......................................................... 80
      4.4.3.1. Effect of electrode length on impedance .............................................. 81
      4.4.3.2. Effect of number of segments on impedance ...................................... 82
      4.4.3.3. Effect of number of segments at the same electrode length on impedance. ............................................................... 82
4.5. Discussion ............................................................................................................ 83
  4.5.1. Synthesis of results ....................................................................................... 83
  4.5.2. Validation of results ..................................................................................... 88
  4.6. Conclusions ..................................................................................................... 90

Chapter 5 : Analysis of High-Perimeter Planar Electrodes for Efficient Neural Stimulation .................................................................................................................. 92
  5.1. Abstract .......................................................................................................... 92
  5.2. Introduction .................................................................................................... 93
  5.3. Methods ......................................................................................................... 96
  5.3.1. Description of electrode geometry .............................................................. 96
  5.3.2. Prototype high-perimeter planar electrodes .............................................. 97
  5.3.3. In vitro measurement of electrode impedance .......................................... 99
  5.3.4. Finite element models of high-perimeter planar electrodes ................. 100
  5.3.5. Computer simulation of neuronal activation ......................................... 102
  5.4. Results .......................................................................................................... 103
  5.4.1. Load impedance .......................................................................................... 103
  5.4.2. Distributions of current density on the electrode surface ...................... 106
  5.4.3. Input-output curves of activation of model axons .................................... 106
  5.4.4. Distribution of the activating function ...................................................... 109
  5.5. Discussion ..................................................................................................... 110
  5.5.1. Synthesis of results .................................................................................... 111
  5.5.2. Estimation of tissue damage ................................................................. 113
  5.5.3. Model limitations ...................................................................................... 115
Chapter 6: Analysis of High-Perimeter Cylindrical Electrode Designs for Deep Brain Stimulation

6.1. Abstract ................................. 118
6.2. Introduction .............................. 119
6.3. Methods .................................... 121
  6.3.1. Serpentine cylindrical electrode designs ................................. 121
  6.3.2. Computer-based simulation of neuronal stimulation .............. 124
6.4. Results ........................................ 126
  6.4.1. Distributions of current density ............................................ 127
  6.4.2. Input-output curves of activation of 12 μm axons ................... 128
    6.4.2.1. Axons parallel to the electrode ...................................... 128
    6.4.2.2. Axons perpendicular to the electrode ............................. 130
  6.4.3. Input-output curves of activation of 4 μm diameter axons ........ 131
    6.4.3.1. Effect of frequency of sinuous variation on efficiency ........ 134
    6.4.3.2. Effect of amplitude of sinuous variation on efficiency .......... 134
    6.4.3.3. Effect of aspect ratio on efficiency ................................. 136
    6.4.3.4. Effect of segmenting on efficiency ................................. 137
  6.4.4. Distribution of potentials and the activating functions ............. 138
6.5. Discussion ..................................... 141
  6.5.1. Dependence of stimulation efficiency on fiber orientations ....... 142
  6.5.2. Optimal design of high-perimeter electrodes for DBS .............. 146
  6.5.3. Model limitations ....................................................... 149
6.5.4. Estimation of tissue damage ................................................................. 150

Chapter 7: Conclusions and Future Work .................................................... 154

7.1. Summary of Results ................................................................................ 154

7.2. Future Directions ..................................................................................... 157

7.2.1. Refinement of interface and tissue model ............................................. 157

7.2.2. Prototype high-perimeter electrode development and testing .......... 158

7.2.3. Design of optimal high-efficiency electrodes ..................................... 159

References .................................................................................................... 162

Biography ..................................................................................................... 173
List of Tables

Table 3.1: Increases of $k$ values ($\Delta k$) when applying maximum charge density calculated at various sinusoidal frequencies. .......................................................................................... 64

Table 4.1: Total currents and current densities of segmented cylindrical electrodes ...... 77

Table 5.1: Dimensions of prototype planar high-perimeter electrodes.......................... 97

Table 5.2: Geometrical parameters of the axon model.................................................. 103

Table 5.3: Increase of $k$ values ($\Delta k$) when applying maximum charge density instead of average charge density for planar electrodes. .............................................................. 115

Table 6.1: Dimensions of prototype cylindrical high-perimeter electrodes .................. 123

Table 6.2: Increase of $k$ values ($\Delta k$) when applying maximum charge density instead of average charge density for cylindrical electrodes......................................................... 151
List of Figures

Figure 1.1: Deep brain stimulation system and electrode................................. 3
Figure 1.2: The Randles equivalent circuit of the electrode-electrolyte interface........... 7
Figure 1.3: The dependence of tissue damage on stimulation parameters. ............ 16
Figure 2.1: Equivalent circuit representation of the electrode-electrolyte interface........ 23
Figure 2.2: Experimental setup used to measure impedance.................................. 26
Figure 2.3: Impedance spectra of DBS electrode in vitro and in vivo. .................. 31
Figure 2.4: R_f and C_dl as a function of frequency............................................. 32
Figure 2.5: R_f and C_dl as a function of current density................................. 34
Figure 2.6: Voltage responses to symmetrical biphasic square currents................. 35
Figure 2.7: Equivalent circuit elements estimated from voltage transients.............. 36
Figure 2.8: Ratio of capacitive charge transfer to Faradaic charge transfer............. 38
Figure 2.9: Voltage responses to square currents at various amplitudes.................. 44
Figure 3.1: Flowchart of the simulation scheme.............................................. 55
Figure 3.2: Impedance spectra of DBS electrodes.............................................. 56
Figure 3.3: Current density and overpotential profiles along the interface.............. 58
Figure 3.4: Distributions of current densities at various frequencies.................... 59
Figure 3.5: Distributions of potentials at various frequencies.............................. 60
Figure 3.6: Power spectra of three different 1mA neural stimulation pulses............ 63
Figure 4.1: Geometry of a segmented cylindrical electrode model...................... 71
Figure 4.2: Three-electrode technique to measure impedance............................ 73
Figure 4.3: Profiles of current density on segmented electrodes.......................... 76
Figure 4.4: Distributions of extracellular potentials and driving functions. ................. 79
Figure 4.5: Second spatial difference of extracellular potentials.............................. 80
Figure 4.6: Impedance of prototype segmented cylindrical electrodes. ....................... 81
Figure 5.1: High-perimeter planar electrodes. .............................................................. 96
Figure 5.2: Digital micrographs of high-perimeter electrode samples. ......................... 99
Figure 5.3: Geometry of finite element models of planar electrodes. ......................... 101
Figure 5.4: Impedance spectra of the electrode samples #1 and #6............................. 104
Figure 5.5: Tissue resistances and voltage responses to square currents...................... 105
Figure 5.6: Distributions of current density on planar electrodes............................... 106
Figure 5.7: Input-output curves of activation of model axons..................................... 107
Figure 5.8: Reductions in threshold voltage and power consumption......................... 108
Figure 5.9: Second spatial difference of extracellular potentials............................... 109
Figure 5.10: Non-damaging limits of planar electrodes modified for maximum charge
density. ............................................................................................................................ 115
Figure 6.1: High-perimeter cylindrical electrodes. ...................................................... 122
Figure 6.2: Geometry of finite element models of serpentine cylindrical electrodes.... 125
Figure 6.3: Distributions of current density and calculated total currents................. 128
Figure 6.4: Input-output curves of activation of parallel axons................................. 129
Figure 6.5: Input-output curves of activation of perpendicular axons....................... 130
Figure 6.6: Effect of frequency of sinuous variation on efficiency............................ 133
Figure 6.7: Effect of amplitude of sinuous variation on efficiency............................. 135
Figure 6.8: Effect of aspect ratio on efficiency......................................................... 137
Figure 6.9: Effect of segmenting on efficiency. ......................................................... 138
Figure 6.10: Distributions of extracellular potentials and the driving functions......... 141
Figure 6.11: Second spatial difference of extracellular potentials............................... 145
Figure 6.12: Changes in threshold voltage and power consumption............................. 147
Figure 6.13: Non-damaging limits of cylindrical electrodes modified for maximum charge density. ................................................................................................................ 151
Chapter 1 : Introduction and Overview

1.1. Deep Brain Stimulation and Electrode

Deep brain stimulation (DBS) delivers high frequency (typically 100-200 Hz) electrical pulses in one of several anatomical targets in the thalamus or basal ganglia. It has rapidly emerged as an alternative to surgical lesions and has become an effective treatment for movement disorders including essential tremor, Parkinson’s disease and dystonia [1-3]. DBS is also under investigation as a treatment for psychiatric disorders including obsessive compulsive disorder and depression [4, 5]. Since DBS therapy was first approved in Canada, Europe and Australia in 1995 and in the United States in 1997, over 40,000 people worldwide have received DBS for essential tremor, Parkinson’s disease, and dystonia [6]. For Parkinson’s disease alone, it is estimated that 60,000 new cases are diagnosed each year in the United States, joining the 1.5 million Americans who currently have Parkinson’s disease. 10 to 20 percent of people with Parkinson’s disease may be eligible for surgical treatments [7].

DBS is an implantable system which consists of a pulse generator implanted subcutaneously below the clavicle, a cable that travels across the posterior aspect of the neck and skull, and a lead (electrode) implanted in the brain (Figure 1(a)). The currently used DBS system is FDA approved for the treatment of essential tremor, Parkinson’s disease and dystonia, and is manufactured by Medtronic Inc. (Minnesota, USA). Presently used DBS leads (Models 3387, 3389, Medtronic Inc.) have a linear array of 4 cylindrical electrode contacts (Figure 1(b)) that can be individually turned on depending
on the placement of the electrode and the specific area of the brain to be stimulated. Multiple contacts and a variety of combinations of contact polarities (monopolar, bipolar or tripolar stimulations) provide flexible device programming, and a larger effective area for lead placement. Currently, significant effort has been put into finding optimal anatomical targets for DBS [8-10]; however, little effort has been devoted to the design of DBS electrodes [11]. The current clinical DBS electrode design was initially adapted from cardiac pacing technology ~20 years ago without knowledge of several fundamental neurostimulation principles that have only recently been elucidated [11]. An important goal in the design of the next generation deep brain stimulator is to minimize the power needed to stimulate specific regions of the brain. A reduction in power consumption will prolong battery life and reduce the size of implant package. This can be achieved by developing more efficient stimulating electrodes that reduce stimulation threshold to cause neural excitation. To design more efficacious stimulating electrodes, we need first to develop a better understanding of the presently used DBS electrodes.
1.2. Electrode-Electrolyte/Tissue Interface

Stimulation of excitable tissue, including deep brain stimulation, requires the passage of electric charge across the cell membrane between the extracellular and intracellular media. The passage of electric charge causes the cell membrane to depolarize and generate action potentials through the opening of the voltage gated ion channels. This is achieved by passing electric charges from a stimulating electrode to the tissue medium, or in more general electrochemical term, the electrolyte. Charge is carried by electrons in the metal electrodes and ions in the electrolyte. At the electrode-electrolyte/tissue interface, a flow of electrons in the metal electrode is converted into a flow of ions in the electrolyte.

A charge separation, and therefore a potential difference, arises when a metal electrode is inserted in a solution. The potential difference is a result of the balance
between the force that cause the metal to release cations in the solution and the opposing force that causes the metal cations in the solution to transmit their positive charge to the metal. At equilibrium the net flow of electrons (or ions) into or out of the metal is zero and a potential, known as the half-cell potential, is developed at the interface. If a current/charge is passed through the electrode, for example during deep brain stimulation, the interfacial potential is altered from the half-cell potential. The difference between the half-cell potential and when a current is passing is called overpotential and is due to polarization of the electrode. Charge delivery to tissue by net current flow can be through capacitive (non-Faradaic) charge transfer and Faradaic charge transfer.

1.2.1. Capacitive charge transfer

Capacitive charge transfer involves the repulsion and attraction of ions in the tissue medium in response to the electric charge variation on the metal electrode; this is essentially like charging or discharging an electrical capacitor. This capacitor is known as double layer capacitance ($C_{dl}$). Through capacitive charge transfer, no actual charge crosses the electrode-electrolyte interface when a current is applied, as this current is a displacement current that charges/discharges a capacitor. The capacitive method is an ideal mechanism for injecting charge into the tissue, because it is reversible and does not produce any chemical byproducts.

1.2.2. Faradaic charge transfer

Faradaic charge transfer involves the actual transfer of charge across the interface. This means that some chemical species have to be either reduced or oxidized. The
overpotential is the driving force for the redox reactions to generate a net current. The Butler-Volmer equation [12] relates the overpotential to net current density through an electrode interface:

\[
J_{\text{net}} = J_o \left[ \exp \left( -\frac{anF}{RT} \eta \right) - \exp \left( \frac{(1-\alpha)nF}{RT} \eta \right) \right],
\]

where \( J_{\text{net}} \) is the net Faradaic current density, \( J_o \) is the exchange current density, \( \eta \) is overpotential, \( \alpha \) is the transfer coefficient associated with kinetics, \( n \) is the number of moles of electrons per mole of reactant oxidized or reduced, \( F \) is Faraday’s constant ~96,485 C/mole of electrons, \( R \) is the gas constant ~8.314 J/(mol K), and \( T \) is the absolute temperature. This equation relates the net Faradaic current to an exponential function of the overpotential. This indicates that for a sufficiently small overpotential, current flows primarily in the capacitive form, charging the double layer capacitance. As more charge is delivered through an electrode-electrolyte interface, the overpotential increases as the double layer capacitance continues to charge and the Faradaic current (proportional to the exponential of overpotential) begins to be a significant fraction of the total injected current. The Faradaic charge transfer can be modeled as an electrical resistor called Faradaic resistance \( (R_f) \), and in the Butler-Volmer equation, \( R_f \) is the ratio - \( \eta/J_{\text{net}} \) [12], as it has the dimensions of specific resistance \((\Omega \text{ cm}^2)\).

Depending on whether the reduction-oxidation reactions introduce new species into the tissue, the Faradaic charge transfer can be either reversible or irreversible [12, 13]. Reversible Faradaic reactions involve the production of chemical species that remain bonded to the electrode surface and can be recovered upon reversing the direction of current. Irreversible Faradaic charge transfer forms products in solution that cannot be
recovered because the products diffuse away from the electrode. For chronic stimulation applications such as DBS one has to minimize the release of any chemical byproduct into the tissue; therefore the irreversible Faradiac charge transfer should be avoided.

1.2.3. Impedance effects due to diffusion

The Butler-Volmer equation describes the relationship between electrode overpotential and current density in the absence of mass transfer effects. As mentioned previously, Faradaic charge transfer becomes irreversible if the redox products diffuse away from the electrode. In the Butler-Volmer equation, the net Faradaic current density is proportional to the exchange current density, which is a measure of the kinetic rate of the reaction. The degree of reversibility depends on the relative rates of kinetics and mass transfer. In a Faradaic reaction with relatively slow electron transfer kinetics, chemical reactant is able to diffuse to the surface to support the kinetic rate, and product diffuses away quickly relative to the kinetic rate. In this case, mass transfer limitations by diffusion can be modeled as an impedance, known as the Warburg impedance ($Z_w$), which is in series with the Faradaic resistance $R_f$ in the circuit model of the interface. The Warburg impedance becomes gradually less important at high frequencies when the time scale is so short that diffusion does not influence reactions at the interface, or if the concentrations of reactants are high near the interface.

Based on the charge transfer mechanisms and the diffusion effect of the interface, a simplified electrical model, known as the Randles equivalent circuit [14], can be constructed for an electrode-electrolyte interface (Figure 1.2). Characterization of the
DBS electrode-electrolyte/tissue interface impedance is required to quantify the composition of charge transfer to the brain tissue. Further, electrode interface impedance is an important factor that contributes to power consumption of deep brain stimulators (Section 1.4). Presently a complete description of the electrical characteristics of DBS electrode-electrolyte interface is lacking. The first specific objective of this dissertation research was to characterize the impedance of presently used DBS electrodes in vitro and in vivo, and this work is presented in Chapter 2.

![Randles equivalent circuit](image)

**Figure 1.2: The Randles equivalent circuit of the electrode-electrolyte interface.**
The Randles equivalent circuit of the electrode-electrolyte interface comprises double layer capacitance $C_{dl}$, in parallel with the series combination of Faradaic resistance $R_f$ and the Warburg impedance $Z_w$.

### 1.3. Current Density Distribution

The distribution of current density on the electrode surface is an important factor in determining patterns of neural excitation, tissue damage and electrode corrosion. The electrode-electrolyte interface has been largely ignored in previous models of DBS. In the absence of the electrode-electrolyte interface, the current density distribution on the DBS electrode is the primary current density distribution, and is completely controlled by the spreading resistance of the electrolyte solution between the stimulating and return
electrodes [15]. The patterns of neural excitation are determined by the electric field in the tissue media [16]. Current density, which is proportional to the electric field in the tissue, can thus affect the patterns of neural excitation. Neglecting the electrode-electrolyte interface impedance may affect the estimation of the volume of neuronal activation [17, 18], and the propensity for tissue damage [19] and electrode corrosion [20, 21].

Both calculations [22-25] and experimental measurements [26-29] indicate that the current density on a metal disk or rod is non-uniform with very high current density at the edges and much lower current density in the center. This is often called the ‘edge effect’. Previous models of current density distributions on stimulating electrodes considered only the primary current density distribution, when there is negligible interface impedance. The secondary current density distribution arises when charge transfer across the interface occurs, and may be more uniform than the primary current density distribution [15]. The second specific objective of this dissertation research was to determine the secondary current density distribution on the surface of DBS electrodes during electrical stimulation, and this work is presented in Chapters 3.

1.4. Power Consumption of DBS System

Equipped with the knowledge about presently used DBS electrodes, the third specific objective of this dissertation research was to propose alterations of electrode design that decrease the stimulation threshold, thereby reduce power consumption of deep brain stimulators. Deep brain stimulators are powered with primary cell batteries
and require surgical replacement when they are depleted. The advertised battery life for Medtronic implanted pulse generator (IPG) is 4-5 year but can vary markedly. Clinical studies reported that the median life span of the batteries was less than 4 years [30, 31] and in applications requiring high charge injection it may last less than 1 year [32]. IPG end-of-life led to significant worsening of the symptoms of Parkinson’s disease that may cause adverse events to patients [33]. Surgical replacement is expensive and carries substantial risk. For example, the complication rate is three times higher for replacement of cardiac pacemakers than for original device placement [34], and replacement of implanted defibrillators has an 8.1% complication rate [35]. Rechargeable batteries which are often used for devices that require high power for short times have not yet displaced primary cells in deep brain stimulators that require full-time stimulation to function. The battery is a key to determine the size of an implantable medical device and its operating service life. A smaller battery will reduce overall device size, but it will also cause the device to have a shorter service life. Likewise, a bigger battery will allow longer service life, but at the cost of larger implanted devices. To date, efforts to prolong implant lifetime have mostly focused on battery technology. In this research, we propose to reduce power consumption and thus increase implant lifetimes by alterations in the electrode geometry.

Power is consumed by operating the circuitry of the IPG and by delivery of stimulus pulses. Modern IPGs are highly efficient, and stimulation energy ($V*I*pulsewidth$) is a significant determinant of battery life [30, 36, 37]. To have the
desired effect on the tissue requires passage of a critical (threshold) current. The power consumed by the electrode and tissue is:

\[
power = i_t^2 \cdot Z_{load} = i_t^2 \cdot (Z_{e1} + R_s + Z_{e2}) ,
\]

(1.2)

where \( i_t \) is the current flowing through the tissue and should be above a critical current, and \( Z_{load} \) is the load impedance composed of interface impedance of the working electrode \( (Z_{e1}) \), series tissue resistance \( (R_s) \), and interface impedance of the return electrode \( (Z_{e2}) \). Power consumption can be decreased by reducing the interface impedance of the DBS electrode, or by decreasing the threshold current. Because the power consumption is proportional to the square of \( i_t \), decreasing \( i_t \) is expected to be a highly effective means to decrease power consumption.

1.5. **High-Efficiency Electrode Designs**

Besides advances in battery technology, efforts to prolong implant lifetime include the development of new electrode materials that have decreased interface impedance and/or stimulation thresholds. Oxide coatings such as platinized platinum and iridium oxide reduce interface impedance by increasing charge capacity for stimulation [13, 38], but access to this charge is limited by the rate of electron and ion transport within the coating [39]. High surface area porous electrodes reduce interface impedance and pacing thresholds [40], but similarly diffusion limitations prevent accessing the full surface area of porous electrodes during short duration stimulation pulses (~100 µs) [38, 41]. In cardiac pacing, steroid-eluting electrodes reduce the stimulation threshold by suppression of inflammation [42] that increases the impedance of implanted electrodes.
from tissue encapsulation [43, 44]. In the research presented in Chapters 5-7, we seek to increase stimulation efficiency by alterations in the electrode geometry, rather than by developing new materials. This approach will enable use of established materials (e.g., platinum iridium) and will therefore shorten the delay between development of new electrodes and clinical application, as it minimized the requirements for testing to establish material biocompatibility. Even when a new electrode material is established for DBS, this approach could be applied in concert with the new material to minimize the power consumption for effective stimulation.

The proposed approach to increase the efficiency of neural excitation by alterations in the electrode geometry is based on the fundamentals of extracellular neural stimulation. Neural excitation can be qualitatively predicted with the activating function \( f \). The activating function is proportional to the second spatial derivative of the extracellular potential \( V_e \) (i.e., the activating function, \( f \propto \Delta^2 V_e / \Delta x^2 \)) [45]. We propose to increase stimulation efficiency by increasing the electrode perimeter. Increasing the electrode perimeter without changing the electrode area is expected to increase the current density non-uniformity on the electrode surface. The activating function in the \( x \) direction,

\[
f_x \propto \frac{\Delta^2 V_e}{\Delta x^2} = \frac{\Delta(\Delta V_e)}{\Delta x} \approx \frac{\Delta (\frac{\Delta J}{\sigma})}{\Delta x} = \frac{\Delta J}{\sigma \Delta x}
\]

is proportional to the derivative of current density, \( \Delta J / \Delta x \). Therefore, increasing the spatial non-uniformity of the current density increases \( \Delta J / \Delta x \), and is expected to increase the efficiency of neural excitation. To test the hypothesis that increasing the electrode
perimeter increases stimulation efficiency, we investigated three classes of electrode geometries: segmented cylindrical electrodes, high-perimeter planar electrodes and high-perimeter cylindrical electrodes. The investigations of each of these classes of electrodes are presented in Chapters 5-7 of this dissertation, respectively.

The activating function provides a simple index to compare the relative efficiencies of neural excitation by different electrode geometries. However, it is only an estimate of the effect that the potential will have on the neurons, because the activating function describes the source driving membrane polarization rather than the membrane polarization itself [46]. A more accurate prediction can be achieved by placing neurons in the potentials generated by electrodes with different geometries. Therefore, the second approach we used to predict neural excitation was to develop an integrated electrode-neuron model and investigate the recruitment curves of the percentage activation of a population of randomly distributed neurons around electrodes with different geometries as a function of the stimulation intensity (i.e., input-output curves).

As the power consumed by the electrode and tissue is related to both threshold current and load impedance (Eq. 1.2), prototypes of segmented cylindrical electrodes and high-perimeter planar electrodes were fabricated, and their impedances were measured in physiological saline solution. Initially, segmented cylindrical electrodes were designed to decrease the electrode impedance by exploiting the non-uniform distribution of current density. The impedance of the electrode-electrolyte interface, \( Z_e \), is, by Ohm’s law, inversely proportional to the integral of the current density, \( \mathbf{J} \), over the electrode surface, \( S \):
$$Z = \frac{V}{\int_{S} J \cdot dS}.$$  \hspace{1cm} (1.4)

Since current density is highest at the electrode edges, we expected that increasing the amount of edge (perimeter) of the electrode would increase average $J$, and thus reduce electrode impedance. This was found not to be an effective means to reduce power consumption because the interaction of the current density edge effects from neighboring segments limited the current density on the increased perimeter and segmenting decreased the conductive area of the electrodes. However, higher spatial variation of current density on the segmented electrodes resulted in larger magnitudes of activating functions in the tissue as compared to the conventional DBS electrode. Therefore, in the following investigations on high-perimeter planar electrodes and high-perimeter cylindrical electrodes, we focused on decreasing power consumption of DBS electrodes by increasing stimulation efficiency (decreasing threshold current), rather than decreasing the electrode interface impedance.

1.6. \textit{Estimation of Tissue Damage}

Effective stimulation requires that the charge/current injected must exceed some threshold. As the charge per pulse increases, the overpotential of the electrode increases as does the fraction of the current going into Faradaic reactions, which may be damaging to tissue or the electrode. Non-damaging stimulation, however, requires a sufficiently low charge per pulse, thus preventing the electrode from reaching potentials where deleterious Faradaic reactions occur at an intolerable rate. Design of stimulation protocols involves
acceptable compromises between stimulation efficacy and minimum tissue damage. In this study, we seek to increase stimulation efficiency by alterations in the electrode geometry. Damage must also be assessed in designing new electrode geometries, as it can be impacted by changes in current density distributions resulting from increasing the electrode perimeter. It is desirable that new designs that increase the efficiency of generating neural excitation will not increase the propensity of the electrode to cause damage to the tissue. Therefore, we assessed the impacts of the new high-perimeter electrode designs on the propensity to cause tissue damage.

A quantitative model of neural damage was used to analyze the effects of increasing electrode perimeter on the propensity to cause tissue damage. McCreery et al. found that charge per phase and charge density per phase of the stimulus pulse are cofactors in the generation of neural damage, based on their experiment data of tissue damage from cortical stimulation of cat brain with circular disk electrodes [19, 47]. The model of Shannon describes the McCreery data using the equation:

\[
\log \left( \frac{Q}{A} \right) = k - \log (Q) \quad (1.5)
\]

where \( Q \) is the charge per phase, \( A \) is the electrode area, and \( k \) is a constant derived from data to define the boundary between stimulus parameters that produced tissue damage and those that did not [48]. The proposed limit for non-damaging stimulation levels using disk electrodes was given by \( k = 1.5 \). Figure 1.3 summarizes the charge, charge density and tissue damage tested in several studies [19, 47, 49-55], and indicates that \( k = 1.5 \) gives a fairly conservative non-damaging limit.
This value, however, was estimated using geometrical (average) charge density over the electrode surface. As indicated in Section 1.3, the current/charge density distribution is non-uniform across the surface of the electrode with greatest current/charge density at the edges of the electrode. This non-uniform distribution can result in charge densities exceeding the suggested limit over local regions of the electrode. We determined the actual charge (or current) distribution on the surface of the electrodes and estimated the $k$ values for non-damaging stimulation level while accounting for the current/charge density non-uniformity on the surface of conventional DBS electrodes and the proposed high-perimeter electrode designs.
Figure 1.3: The dependence of tissue damage on stimulation parameters.

Combinations of charge density and charge used in several studies are shown. Charge is the product of pulse width and current amplitude. Circles represent non-DBS studies [19, 47, 49, 50, 54, 55]. Solid circles represent combinations that resulted in tissue damage and hollow circles represent no tissue damage. Squares show the charge and charge density combinations reported in deep brain stimulation post-mortem studies to not have produced tissue damage [51-53]. Charge densities that fall on the solid line that ends at the grey box representing the DBS limit of 30 µC/cm² were calculated using the surface area of 0.06 cm² for the DBS contact. Also shown is the solid line representing $k$ value of 1.5 as developed by Shannon. Redrawn from Kuncel and Grill [56] with the permission from the authors.
1.7. **Hypotheses and Objectives**

**Aim 1:** Characterize the impedance of conventional deep brain stimulation electrodes *in vitro* and *in vivo*. The hypothesis was that electrode-tissue impedance is a non-linear function of both current (density) and frequency. Electrochemical impedance spectroscopic (EIS) measurements were performed over a wide range of frequencies and currents. The composition of charge transfer (Faradaic vs. non-Faradaic) was quantified by fitting the impedance spectrograms with a circuit model of the electrode-tissue interface.

**Aim 2:** Determine the effect of the electrode-tissue interface impedance on the current density distributions on the electrode surface. We implemented a finite element model of the currently used clinical DBS electrode that incorporated the distributed impedance of the electrode-tissue interface. The hypothesis was that electrode-tissue interface makes the current distribution more uniform than the primary current distribution, and that the current distribution depends on frequency.

**Aim 3:** Test the hypothesis that increasing the electrode perimeter will increase the efficiency of neural stimulation by decreasing stimulation threshold. We evaluated electrode geometries with increased perimeters, designed to exploit the non-uniform distribution of current density on the electrode surface, as a means to reduce stimulation threshold. The neuronal excitation produced by different electrode geometries were estimated by calculating the second spatial difference of the potentials in the region surrounding the electrode, and by quantifying input-output curves of activation of model
neurons. Segmented cylindrical electrodes, high-perimeter planar electrodes, and high-perimeter cylindrical electrodes were investigated to test the hypothesis.

**Aim 4:** Assess the impacts of the new high-perimeter electrode designs on the propensity to cause tissue damage. The hypothesis was that increasing current density non-uniformity will not significantly increase propensity to cause tissue damage. The likelihood of causing tissue damage was assessed by calculating the magnitude and distribution of the charge and charge density on the electrode, and the $k$ values in the Shannon model that accounted for the non-uniformity of charge density on the electrode.

### 1.8. Outline of Chapters

Chapter 2 describes the impedance characterization of deep brain stimulation electrodes *in vitro* and *in vivo*. In this study we performed electrochemical impedance spectroscopy measurements *in vitro* and *in vivo* over a range of frequencies and currents. Double layer capacitance ($C_{dl}$) and Faradaic resistance ($R_f$) were quantified as a function of both current density and frequency by fitting an equivalent electrical circuit model to the impedance spectrograms. Voltage transient response was also measured and analyzed. Characterizing the electrode impedance enabled differentiation of the different charge injection pathways through the electrode-electrolyte interface.

Chapter 3 describes the effect of the interface impedance on the current density distribution on the electrode surface. In this study the distributed impedance of the DBS electrode-electrolyte interface measured *in vitro* was incorporated into a finite element model (FEM) of the clinical DBS lead. The secondary current density distribution was
determined at various sinusoidal frequencies, as a result of frequency-dependent interface impedance. The results show that the secondary current density was more uniform than the primary current density, and the uniformity depended on the sinusoidal frequency.

Chapter 4 presents our first attempt to increase stimulation efficiency by exploiting the non-uniform distribution of current density with segmented DBS electrode designs. The segmented design was intended to enhance the edge effect on the electrode and thereby increase the stimulating efficiency. The impedance of segmented DBS electrodes was also measured and analyzed, as impedance is a co-factor with threshold current in determining power consumption. The results show that the edge effects played a critical role in determining the current density distributions, neuronal excitation patterns and impedance of cylindrical electrodes, and segmented electrodes provided a means to increase the efficiency of DBS.

Chapter 5 presents our second attempt to increase stimulation efficiency by exploiting the non-uniform distribution of current density with serpentine-perimeter planar electrode designs. The serpentine design was intended to increase the spatial non-uniformity of the current density on the electrode and thereby increase the stimulating efficiency. The impedance of prototype electrodes was measured with impedance spectroscopy and voltage transients. FEM electrical field models were coupled with neuron models to quantify the effects of serpentine perimeter on efficiency to activate a population of axons. The results show that serpentine perimeter provided a means to increase the efficiency of neural stimulation.
Chapter 6 extended the work of the previous two chapters by investigating the efficiency of high-perimeter cylindrical electrodes that combined serpentine perimeters with segmentation. The effects of increasing the perimeter of cylindrical electrodes through different means (increasing amplitude or frequency of sinuous variation of the perimeters, segmentation) on the efficiency to activate a population of axons were quantified. Proper selection of geometrical parameters decreased power consumption by ~20% for axons parallel to the electrode and ~35% for axons perpendicular to the electrode at DBS-relevant fiber diameters and distances.

Chapter 7 summarizes the main findings of this work and discusses the future directions in refining the interface model and in designing and testing high-efficiency electrodes for deep brain stimulation.
Chapter 2: Impedance Characteristics of Deep Brain Stimulation Electrodes \textit{in vitro} and \textit{in vivo}

2.1. Abstract

The objective of this study was to quantify the electrode-tissue interface impedance of electrodes used for deep brain stimulation (DBS). We measured the impedance of DBS electrodes using electrochemical impedance spectroscopy \textit{in vitro} in carbonate and phosphate buffered saline solution and \textit{in vivo} following acute implantation in the brain. The components of the impedance, including the series resistance (\(R_s\)), the Faradaic resistance (\(R_f\)) and the double layer capacitance (\(C_{dl}\)), were estimated using an equivalent electrical circuit. Both \(R_f\) and \(C_{dl}\) decreased as the sinusoidal frequency was increased, but the ratio of capacitive charge transfer to Faradaic charge transfer was relatively insensitive to the change of frequency. \(R_f\) decreased and \(C_{dl}\) increased as the current density was increased, and above a critical current density this relationship was highly nonlinear. Thus the magnitude of the interface impedance was strongly dependent on the intensity (pulse amplitude and duration) of stimulation. The temporal dependence and spatial non-uniformity of \(R_f\) and \(C_{dl}\) suggested that a distributed network, with each element of the network having dynamics tailored to a specific stimulus waveform, is required to describe adequately impedance of the DBS electrode-tissue interface. Voltage transients to biphasic square current pulses were also measured and suggested that the electrode-tissue interface did not operate in a linear range at clinically relevant current
amplitudes, and that the assumption of the DBS electrode being ideally polarizable was not valid under clinical stimulating conditions.

### 2.2. Introduction

Deep brain stimulation (DBS) for treatment of neurological disorders is delivered from a four-contact electrode array implanted in the thalamus or basal ganglia. The efficacy of DBS is dependent on localizing charge delivery to specific populations of neurons, and charge delivery is influenced by the electrode-tissue interface, where a transduction of charge carriers occurs from electrons in the metal electrode to ions in the tissue. Characterizing the impedance of the DBS electrode-tissue interface is required to determine the charge delivery to the brain. For example, the interface capacitance modified the volume of neural activation by deep brain stimulation [57]. Further, the interface impedance contributes to the distribution of current density on the electrode, which may influence neural excitation, tissue damage, and electrode corrosion during DBS. The purpose of this study was to quantify the impedance of the electrode-electrolyte interface of deep brain stimulation electrodes both \textit{in vitro} and \textit{in vivo}.

The impedance of deep brain stimulation electrodes was characterized using electrochemical impedance spectroscopy (EIS) \textit{in vitro} in carbonate and phosphate buffered saline solution and \textit{in vivo} following acute implantation in the brain. From the impedance spectrum, it is possible to deduce an equivalent electrical circuit model and match the circuit components to the physical characteristic of the interface. In a simple case, the interface can be modeled by a Randles circuit [14], composed of a double-layer capacitor...
in parallel with the series combination of a charge-transfer resistance (Faradaic resistance) and a Warburg impedance (Figure 2.1(a)). The Warburg impedance, which accounts for mass transfer limitations by diffusion, is negligible at high frequencies when the time scale is so short that diffusion does not influence reactions at the interface, or if the concentrations of reactants are high. It was determined experimentally that, under the frequencies and concentration used in this study, the Warburg impedance was negligible, and the equivalent model was reduced to the parallel combination of the double layer capacitance \(C_{dl}\) and the Faradaic resistance \(R_f\) (Figure 2.1(b)). Our results indicate that the double layer capacitance and Faradaic resistance both decreased as the sinusoidal frequency was increased, and the double layer capacitance increased and Faradaic resistance decreased as the current density was increased.

\[\text{Figure 2.1: Equivalent circuit representation of the electrode-electrolyte interface.}\]

(a) The Randles equivalent circuit representation of the electrode-electrolyte interface. It is comprised of the double layer capacitance \(C_{dl}\) in parallel with the series combination of a charge transfer Faradaic resistance \(R_f\) and the Warburg impedance \(W\). (b) The simplified equivalent circuit model of the electrode-electrolyte interface, which is valid when the Warburg impedance is negligible.

23
2.3. Methods

The impedance properties of clinical DBS electrodes (Model 3387, Medtronic Inc., Minnesota, USA) were measured in vivo following acute implantation in the cat brain and in vitro in a near-physiological saline electrolyte buffered with carbonate and phosphate at concentrations found in interstitial fluid (137 mM NaCl, 29 mM NaHCO₃, 1.7 mM Na₂HPO₄, and 0.7 mM NaH₂PO₄) infused with a mixture of gas (5% CO₂, 6% O₂, and 89% N₂) to maintain a pH of 7.4 [58]. Impedance was measured with sinusoidal currents at 40 frequencies evenly distributed on a log scale between 1 Hz and 10 kHz, and at five root-mean-square amplitudes of 0.01 mA, 0.02 mA, 0.05 mA, 0.1 mA and 0.2 mA. As well, the voltage transients generated by applying symmetrical biphasic square currents (1ms per phase) were measured at 9 amplitudes from 0.01 mA to 5 mA. The measurements were replicated three times at each amplitude level for each of the four electrode contacts.

2.3.1. In vitro measurements

The three-electrode technique was used to measure impedance in vitro with an impedance analyzer (Model 1287 Electrochemical Interface (ECI) + Model 1252 Frequency Response Analyzer (FRA), Solatron Analytical, Hampshire, England) (Figure 2.2). The electrode was placed vertically in the middle of a 200 ml beaker of buffed saline solution at room temperature (T ≈ 20 °C). Sinusoidal currents were applied between one contact of the DBS electrode (working electrode) and a counter electrode formed of stainless steel wire spiraling around the wall of the beaker. The resulting
potential between the working electrode and a silver/silver chloride reference electrode (Model RE-5B, BAS Inc., West Lafayette, IN) was measured with the 1287 ECI (input impedance 10 GΩ in parallel with 50 pF). The impedance was calculated by dividing the potential by the current and included the electrode-electrolyte interface impedance in addition to the series resistance arising from the solution between the working electrode and the reference electrode. The series resistance was minimized by positioning the reference electrode within 5 mm of the working electrode.

The same 3-electrode cell was also used to measure voltage transients generated by symmetrical biphasic square currents (1 ms per phase) delivered between the working electrode and the counter electrode. Voltage transients were measured between the DBS electrode and the reference electrode with an isolated differential amplifier (input impedance 100 MΩ in parallel with 25 pF, frequency response ±0.5 dB to 1 MHz, Model SR560, Stanford Research Systems, Sunnyvale, CA), captured via a GPIB-equipped oscilloscope at a sampling rate of 1 MHz, and transferred to computer for storage and analysis (Figure 2.2, inside dashed box).
2.3.2. In vivo measurements

Acute experiments were conducted in 3 adult male cats using the same instrumentation and methods used for the in vitro measurements. All animal care and experimental procedures were approved by the Institutional Animal Care and Use Committee of Duke University. Anesthesia was induced with ketamine HCl (Ketaset, 35
mg/kg, IM, supplemented as required during surgical preparation) and maintained with alphachloralose (65 mg/kg IV, supplemented at 15 mg/kg). Anesthesia level was determined by monitoring blood pressure, heart rate, and withdrawal and blink reflexes. Body temperature was maintained between 37° and 39° C with a water-circulating heating pad, and warm 0.9% saline with 8.4 mg/cc sodium bicarbonate and 5% dextrose added was administered intravenously (~15 cc/kg/hr). A 1-2 cm diameter craniotomy was made and the dura was reflected to expose the underlying cortex. The DBS lead was lowered into the neocortex, and the cortex was covered with surgical gauze soaked with physiological saline. The 3-electrode technique was also used to measure impedance in vivo. The reference electrode was positioned within 5 mm of the DBS lead with its porous tip contacting the saline soaked gauze overlying the cortex. The large-area stainless steel surgical retractor was used as the counter electrode. Impedance spectrograms and voltage transients were measured in vivo at the same amplitudes, frequencies, and repetitions as the in vitro measurements, except biphasic current pulse amplitudes were limited to \( \leq 2 \) mA, as larger currents evoked strong motor responses.

### 2.3.3. Impedance characterization

#### 2.3.3.1. Impedance characterization in sinusoidal study

The measured impedance data were used to estimate the element values of a three-element equivalent circuit model including the parallel combination of \( R_f \) and \( C_{dl} \) in series with \( R_s \):
\[
Z(\omega) = R_s + \frac{R_f}{1 + j \omega R_f C_{dl}} = R_s + \frac{R_f}{1 + (\omega R_f C_{dl})^2} - j \frac{\omega R_f^2 C_{dl}}{1 + (\omega R_f C_{dl})^2} = Z'(\omega) + j Z''(\omega), \quad (2.1)
\]

where \( \omega \) is the angular frequency, \( Z' \) is the real part of impedance and \( Z'' \) is the imaginary part of impedance. Since charge transfer through the electrode-electrolyte interface was shunted by the double layer capacitance at very high frequency, solution resistance \( R_s \) was determined as the asymptotic, high frequency impedance

\[
R_s = Z(f \to \infty), \quad (2.2)
\]

Solution resistance \( R_s \) was then subtracted from the real part of impedance, and \( R_f \) and \( C_{dl} \) at each frequency were determined as

\[
R_f(\omega) = \frac{Z'^2 + (Z' - R_s)^2}{Z' - R_s}, \quad (2.3)
\]

\[
C_{dl}(\omega) = -\frac{Z''}{\omega[(Z' - R_s)^2 + Z''^2]}., \quad (2.4)
\]

### 2.3.3.2. Impedance characterization in transient study

In the voltage transient study, the element values of the three-element equivalent circuit model were determined by minimizing the sum of the squares of the residuals of the measured points minus the theoretical values. The theoretical voltage response to the biphasic square current pulses was described with the equations:

\[
V(t) = \begin{cases} 
1 - \exp\left(-\frac{t}{R_f C_{dl}}\right) & I R_f + I R_s, & 0 \leq t \leq PW \\
-1 + \exp\left(-\frac{t}{R_f C_{dl}}\right) & \left(1 + 2 \exp\left(\frac{PW}{R_f C_{dl}}\right)\right) I R_f - I R_s, & PW < t \leq 2 PW, \\
- \exp\left(-\frac{t}{R_f C_{dl}}\right) & \left(1 + \exp\left(\frac{PW}{R_f C_{dl}}\right)\right)^2 I R_f, & t > 2 PW
\end{cases}
\]  

(2.5)
where \( I \) is the amplitude of the current pulses, and \( PW \) is the pulse width of the current pulses (1 ms).

**2.4. Results**

We measured the impedance of deep brain stimulation electrodes with both sinusoidal and square currents \textit{in vitro} in buffed saline solution and \textit{in vivo} following acute implantation in the brain. \( R_f \) and \( C_{di} \) were quantified as functions of current density and frequency from the impedance spectra, and as a function of current density from the voltage transients.

**2.4.1. Impedance characteristics**

**2.4.1.1. Impedance spectra**

Impedance (amplitude and phase) spectra and impedance Nyquist plots measured \textit{in vitro} and \textit{in vivo} for a single DBS electrode contact at 3 current amplitudes are shown in Figure 2.3. The measured impedance is composed of the electrode-electrolyte interface impedance, which dominates at low frequencies, and the series resistance, which dominates at high frequencies [59]. The asymptotic, high-frequency impedance resulting from the series resistance \( R_s \) was 119±7 \( \Omega \) (mean±SD, range=107-141 \( \Omega \), n=60 (4 contacts×5 amplitudes×3 repetitions)) \textit{in vitro} and 473±159 \( \Omega \) (mean±SD, range=260-928 \( \Omega \), n=180 (4 contacts×5 amplitudes×3 repetitions×3 cats)) \textit{in vivo} (Figure 2.3 (a), (d)). The phase of the impedance approached zero at high frequencies indicating the high-frequency impedance was mainly resistive (Figure 2.3 (b), (e)). The value of \( R_s \) can also
be read from the Nyquist plots where the impedance loci intersect the abscissa (Figure 2.3 (c), (f)). The difference between $R_s$ in vitro and $R_s$ in vivo resulted from both the difference in the conductivities of the surrounding medium and the difference in the proximity of the reference electrode to the DBS electrode. The electrode-electrolyte interface impedance varied inversely with frequency – in the $\text{k}\Omega$ range at 1 Hz decreasing to almost zero at 10 kHz. At low frequencies (<100 Hz), the interface impedance also varied inversely with the current amplitude, both in vitro (Figure 2.3(a)) and in vivo (Figure 2.3(d)).
Figure 2.3: Impedance spectra of DBS electrode in vitro and in vivo.
(a)(d) Impedance magnitude spectra of the DBS electrode in vitro (a) and in vivo (d) measured at 40 frequencies evenly distributed on a log scale from 1 Hz to 10 kHz with sinusoidal currents at root-mean-square amplitudes of 0.01 mA, 0.05 mA and 0.2 mA. (b)(e) Impedance phase spectra of the DBS electrode in vitro (b) and in vivo (e) at amplitudes of 0.01 mA, 0.05 mA and 0.2 mA. (c)(f) Nyquist plots of the real and imaginary parts of the DBS electrode impedance in vitro (c) and in vivo (f) at amplitudes of 0.01 mA, 0.05 mA and 0.2 mA.
2.4.1.2. Changes of $R_f$ and $C_{dl}$ with frequency

The Faradaic resistance $R_f$ and double layer capacitance $C_{dl}$ calculated from the impedance spectra *in vitro* and *in vivo* are shown in Figure 2.4. Both $R_f$ and $C_{dl}$ decreased monotonically with increasing frequency from 1 to 10 kHz both *in vitro* and *in vivo*. $R_f$ and $C_{dl}$ were strongly dependent on the current amplitude at low frequencies (<100 Hz), but not at high frequencies (>100 Hz).

**Figure 2.4: $R_f$ and $C_{dl}$ as a function of frequency.**  
(a)(c) Faradaic resistance ($R_f$) as a function of frequency *in vitro* (a) and *in vivo* (c). (b)(d) Double layer capacitance ($C_{dl}$) as a function of frequency *in vitro* (a) and *in vivo* (c). Note that only the upper errorbar was plotted at 0.2 mA in (c) because the lower errorbar at some frequencies extended beyond the lower range of the log scale.
2.4.1.3. Changes of $R_f$ and $C_{dl}$ with current density

$R_f$ and $C_{dl}$ were dependent on the current density, as well as the frequency [60-63]. To illustrate this dependency, $R_f$ and $C_{dl}$ were plotted versus average current density (RMS current divided by electrode surface area) at different frequencies (Figure 2.5). At each frequency, $R_f$ decreased and $C_{dl}$ increased when current was above 0.02 mA (current density above 0.334 mA/cm^2), and these changes were most prominent in the low-frequency range. Previous studies identified the ‘current density linearity limit’ as the current density at which the values of $R$ or $C$ deviate by 10 per cent from those observed at low current densities [61-63]. $R_f$ and $C_{dl}$ also exhibited a current density linearity limit, which was approximately 0.334 mA/cm^2, corresponding to a stimulus current of 0.02 mA.
2.4.2. Voltage transients in response to biphasic current pulses

The voltage responses to symmetrical biphasic square current pulses with different amplitudes and the corresponding least-square regression fits to the data are summarized in Figure 2.6. The fits matched the measured data well at low current amplitudes, while stronger deviations between the fits and measurements appeared at higher current amplitudes. Increasing deviation at higher currents indicated that the
electrode-electrolyte interface no longer operated in linear range at high currents, and therefore could not be fit as well with a linear circuit. Gas bubbles formed on the surface of the DBS electrode during the \textit{in vitro} measurements at current amplitudes above 1mA, indicating the occurrence of water hydrolysis.

![Figure 2.6: Voltage responses to symmetrical biphasic square currents.](image)

\textit{In vivo} voltage responses (grey) to symmetrical biphasic square currents (1 ms per phase) at different amplitudes between 0.01 mA and 2 mA, and the least-square fitting curves (black) to the voltage responses. The correlation coefficients ($r^2$) are 0.990, 0.994, 0.996, 0.996, 0.996, 0.994 and 0.994 respectively from 0.01 mA to 2 mA. Open circuit potential was $0.34 \pm 0.14$ V (n=36, 4 contacts×9 amplitudes) \textit{in vitro} and $0.38 \pm 0.23$ V (n=96, 4 contacts×8 amplitudes×3 cats) \textit{in vivo}.  

35
The values of $R_s$, $R_f$ and $C_{dl}$ estimated from the voltage transient data are shown in Figure 2.7 as a function of current amplitude. The values of $R_s$ were consistent across current amplitudes both \textit{in vitro} (mean±SD=133±7 \, \Omega, \text{ range}=123-150 \, \Omega, \, n=36) and \textit{in vivo} (mean±SD=533±152 \, \Omega, \text{ range}=335-920 \, \Omega, \, n=96) and were comparable to the $R_s$ values calculated from the impedance spectra. The values of $R_f$ and $C_{dl}$ were consistent at low currents but deviated from these values when the current amplitude increased. These changes, however, cannot be readily compared with the changes of $R_f$ and $C_{dl}$ with current calculated from impedance spectra (Figure 2.5) because fitting the voltage transients with a linear model assumed that $R_f$ and $C_{dl}$ did not change during the time course of the current pulse. This is not a valid assumption because the data from the impedance spectra demonstrated that $R_f$ and $C_{dl}$ changed with frequency (Figure 2.4).

**Figure 2.7:** Equivalent circuit elements estimated from voltage transients. Values of the three elements of the equivalent electrical circuit estimated from the voltage responses to biphasic current pulses \textit{in vitro} and \textit{in vivo}. (a) Series resistance, $R_s$, as a function of current. (b) Faradaic resistance, $R_f$, as a function of current. (c) Double layer capacitance, $C_{dl}$, as a function of current.
2.5. Discussion

The goal of this study was to quantify the impedance of deep brain stimulation electrodes \textit{in vitro} and \textit{in vivo}. Characterizing the electrode impedance enables differentiation of the charge injection pathways through the electrode-electrolyte interface. Charge transfer at the electrode-electrolyte interface can be in the form of capacitive (non-Faradaic) charge transfer, $Q_c$, or resistive (Faradaic) charge transfer, $Q_f$. The ratio of the two forms of charge transfer $Q_c/Q_f$ is an index for evaluating the propensity for stimulation to cause electrode or tissue damage. The charge transfer ratio $Q_c/Q_f$ (Figure 2.8) was calculated from the data in Figure 2.4 as:

$$\frac{Q_c}{Q_f} = \frac{i_c}{i_f} = j \omega R_f C_{dl} = j \cdot 2 \pi f \cdot R_f C_{dl}.$$

If $R_f$ and $C_{dl}$ were independent of frequency, then $Q_c/Q_f$ would increase in proportion to the frequency, and stimulation waveforms with strong high-frequency components (such as short pulse widths, short inter-pulse intervals) could make the electrode highly polarizable by transferring charge mainly in capacitive form. Our results indicate that $R_f$ and $C_{dl}$ both decreased monotonically with increasing frequency (Figure 2.4), and, as a result, the ratio of capacitive charge transfer to Faradaic charge transfer was relatively insensitive to the frequency (Figure 2.8). Also, $Q_c/Q_f$ was ~2-3 times larger \textit{in vitro} than \textit{in vivo} across the frequency range, mostly likely as a result of the different chemical compositions of the \textit{in vitro} and \textit{in vivo} environments [62]. This suggests that the non-Faradaic (capacitive) charge capacity of DBS electrodes is overestimated by \textit{in vitro} measurements.
Figure 2.8: Ratio of capacitive charge transfer to Faradaic charge transfer.
The ratio of capacitive charge transfer to Faradaic charge transfer as a function of frequency in vitro and in vivo.

The interface impedance also influences the distribution of current density on the electrode surface. The edge effect describes that the current density increases toward the perimeter of the electrode [64], and is an important factor that affects the patterns of neural excitation [16, 65] and damage [19]. Our results demonstrate that $R_f$ decreased and $C_{dl}$ increased with increasing current density (Figure 2.5), and this resulted in a decrease of the magnitude of the interface impedance with increasing current density (Figure 2.3(a), (d)). This suggests that the non-uniform distribution of current density will result in a non-uniform interface impedance with the interface impedance decreasing toward the perimeter of the electrode. Further, the decrease of $R_f$ and the increase of $C_{dl}$ with increasing current density occurred when current was above 0.02 mA (section 3.1.2). A typical DBS parameter setting of 2 V, 90 µs pulse width, and 165 Hz yielded peak current of 1.76 mA and RMS current of 0.23 mA measured with the 3-electrode technique in the brain, much higher than the identified current linearity limit of 0.02 mA,
and indicating that the DBS electrode-tissue interface operates in a nonlinear fashion during effective DBS therapy.

A number of mechanisms may underlie the dependence of interface resistance and capacitance on frequency and current density. The monotonic decrease of Faradaic resistance with increasing frequency may reflect that at high frequencies the voltage across the electrode changes its polarity so rapidly that the electrochemical reactants for the reactions to be reversed are more readily available adjacent to the electrode surface (i.e., there is insufficient time for diffusion). The decrease of Faradiac resistance with increasing current density, seen when electrode entered the nonlinear region, is due to the initiation of new reaction mechanisms at the electrode surface, capable of accommodating the increased current beyond the limits of the available reacting species. The frequency dependence of double layer capacitance was suggested to be a result of the relaxation of absorbed water dipoles, which act as a dielectric in the double layer capacitance [66]. The increase of double layer capacitance with increasing current density, seen when electrode entered the nonlinear region, is probably due to the increased fraction of the electrode surface covered by adsorbed chemical species such as halide anions and polar molecules such as water, with a preferential orientation at the interface acting to separate charge.

2.5.1. Equivalent electrical circuit models of the interface impedance

We modeled the interface impedance with the parallel combination of a resistor and capacitor, and this representation has also been used by other investigators [67-69].
However, the interface impedance may also be modeled by the series combination of a resistor and capacitor [59, 62, 63, 70], and the dependence of interface resistance and capacitance on frequency and current density are well documented using this series representation. Both the series resistance and capacitance decreased with increasing frequency for a platinum electrode in 0.9% saline over the frequency range of 0.001-1000 Hz [62], and at 100 Hz the series resistance decreased and the series capacitance increased with increasing current density [70]. Similarly, for a large number of metals the series resistance decreased and the series capacitance increased with increasing current density, but these changes were not pronounced at low current densities [63]. Schwan first defined a ‘limit current of linearity’ as the current at which the values of series resistance and capacitance deviated by 10% from the values observed at low current density [70].

Our results, modeling the interface with the parallel combination of a resistor and a capacitor, revealed similar changes in the parallel resistance and capacitance with frequency and current density as those of the series resistance and capacitance. The changes of parallel components $R_f$ and $C_{dl}$ with frequency and current density have not been previous reported. The impedance of the parallel combination of $R_f$ and $C_{dl}$ is

$$Z_p(\omega) = \frac{R_f}{1+(\omega R_f C_{dl})^2} - \frac{j \omega R_f^2 C_{dl}}{1+(\omega R_f C_{dl})^2}. \quad (2.7)$$

For the series combination of a resistor $R_w$ and capacitor $C_w$, the impedance is

$$Z_s(\omega) = R_w - \frac{j}{\omega C_w}. \quad (2.8)$$
Both models are intended to represent the same physical system and thus \( Z_p(\omega) = Z_s(\omega) \).

This equality yields:

\[
R_f = R_w (1 + \frac{1}{(\omega R_w C_w)^2}), \quad (2.9)
\]

\[
C_{dl} = \frac{C_w}{1 + (\omega R_w C_w)^2}. \quad (2.10)
\]

Warburg stated that at low current densities both \( R_w \) and \( C_w \) vary as the square root of frequency, \( 1/\sqrt{\omega} \) [62, 63]. The consequence of this relationship is that the phase angle, which equals to \( \tan^{-1}(\omega R_w C_w) \) is constant at 45\(^\circ\) at all frequencies. For the special case \( \omega R_w C_w = 1 \), the above relations become:

\[
R_f = 2R_w, \quad (2.11)
\]

\[
C_{dl} = \frac{C_w}{2}. \quad (2.12)
\]

This indicates that parallel and series circuits become equivalent under Warburg’s assumption and that the conversion from one circuit to the other is a simple factor of 2. Hence, the parallel components \( R_f \) and \( C_{dl} \) follow the same trends with the change of frequency and current density as the series components, with exceptions at very low frequencies. The series representation of interface does not allow the passage of direct current; and as \( \omega \) approaches zero, the condition \( \omega R_w C_w = 1 \) breaks down. Thus the parallel model is more appropriate at low frequencies than the series model.
2.5.2. Limitations of experiments

In this study, we measured the impedance of deep brain stimulation electrodes by applying sinusoidal currents \textit{in vitro} in buffered saline solution and \textit{in vivo} following acute implantation in the brain. $R_f$ and $C_{dl}$ were determined as a function of both current density and frequency by fitting an electrical circuit equivalent model to the impedance spectrograms. One limitation of this approach is that the current density was spatially averaged over the geometric area of the electrode when quantifying the changes of $R_f$ and $C_{dl}$ with current density. However, current density varies over the surface of an electrode, and to obtain a relationship between $R_f$ and $C_{dl}$ and the absolute current density requires an electrode with uniformly current density on the electrode surface [25, 71, 72]. Second, spatially-lumped circuit elements were used to describe spatially-distributed interface parameters. However, the lumped circuit model allowed parameterization of the interface impedance using a limited number of circuit elements that have clear physical representations.

2.5.3. Implications for modeling of deep brain stimulation electrodes

The quantitative description of DBS electrode-electrolyte interface impedance from experimental measurement has not been previously documented. Holsheimer \textit{et al.} measured the impedance of DBS electrode \textit{in vitro} in physiological saline with monophasic rectangular voltage pulses [73]. The “impedance” they measured was the “instantaneous” impedance calculated by dividing the amplitude of the rectangular voltage by the instantaneous current. This does not allow characterization of the charge-
transfer processes at the interface through the Faradaic resistance or the double layer capacitance. Using the data from Holsheimer et al., Butson and McIntyre assumed that the DBS electrode was ideally polarizable and included only a capacitance to represent the interface impedance [57]. A highly polarizable (real) electrode can accommodate a large amount of charge on the double layer prior to initiating Faradaic reactions, and thus is highly desirable for stimulation. However, it is necessary to determine whether such a model is representative of the DBS electrode under clinical stimulating conditions.
Figure 2.9: Voltage responses to square currents at various amplitudes.
(a) *In vivo* voltage responses to symmetrical biphasic square current with 1 ms pulse width at amplitudes of 0.02 mA, 0.2 mA and 2 mA (from Figure 2.6) and the voltage response of an ideally polarizable electrode (0.8 μF) in series with tissue resistance (520 Ω) to square current at 2 mA. (b) *In vitro* voltage responses to symmetrical biphasic square current with 0.2 ms pulse width at amplitudes of 0.02 mA, 0.2 mA and 2 mA and the voltage response of an ideally polarizable electrode (1.6 μF) in series with tissue resistance (120 Ω) to square current at 2 mA. The waveform in response to 0.02 mA current was scaled by a factor of 100 and the waveform in response to 0.2 mA current was scaled by a factor of 10 for them to be comparable to the waveform in response to 2 mA current.
Considering the series resistance present in the 3-electrode measurement scheme, the equivalent circuit of an ideally polarizable electrode is a capacitor in series with the solution/tissue resistance. At constant current, the potential across the ideally polarizable electrode changes linearly with time according to

$$V(t) = \frac{1}{C} \int_0^t I(t) \, dt = \frac{I \cdot t}{C},$$  \hspace{1cm} (2.13)$$

if $C$ does not change over time. The voltage responses to 0.02 mA, 0.2 mA and 2 mA biphasic square current pulses were scaled and plotted in Figure 2.9, along with the voltage waveform for an ideally polarizable electrode in series with tissue/solution resistance. The capacitance of the ideally polarizable electrode was chosen to match the initial slope (at $t=0^+$) of the voltage waveforms of the DBS electrode because current was purely capacitive upon pulsing and the instantaneous capacitance at $t=0^+$ is proportional to the inverse of the initial slope. These values, 0.8 $\mu$F in vivo (Figure 2.9(a)) and 1.6 $\mu$F in vitro (Figure 2.9(b)), are also similar to the values fitted with in vivo and in vitro measurements at low currents (Figure 2.7(c)). The voltage response of the real electrode deviated from that of the ideally polarizable electrode and the deviation increased as the current amplitude increased, indicating that a larger fraction of charge was transferred through Faradaic reactions at higher current amplitudes. The deviation was also more pronounced for a long pulse (1 ms) than for a short pulse (0.2 ms) (Figure 2.9). Further, for the ideally polarizable electrode, the electrode potential returned to the open circuit potential after the charge-balanced biphasic pulse because the charge in the first phase was fully recovered during the second phase. For the real electrode, not all of the charge
injected during the first (anodic) phase went into charging of the double layer, and only some fraction of the charge in the second (cathodic) phase was required to discharge the double layer. The “extra” cathodic charge resulted in a post-pulse electrode potential negative of the pre-pulse value (Figure 2.9), and the opposite was observed for cathodic-first biphasic pulses. Thus, the DBS electrode is not ideally polarizable under clinical stimulating conditions.

The results of this study provide parameters required to include accurate representations of the electrode-tissue interface in computational models of DBS. However, the nonlinear dependence of both $R_f$ and $C_{dl}$ on frequency and current density poses a challenge to incorporate readily the interface impedance into models. Because the current density distribution on the electrode is spatially non-uniform, with higher current density at the edges than in the center of the electrode [64], $R_f$ and $C_{dl}$ will vary spatially along the electrode-tissue interface. Further, because the frequency content of the stimulation pulse changes over the time course of the pulse, $R_f$ and $C_{dl}$ also vary temporally during the stimulation. Therefore, the interface impedance is best described by a distributed rather than a lumped parameter network, with each parameter of the network having dynamics tailored to the stimulus waveform.

In summary, this study utilized electrochemical impedance spectroscopy (EIS) and transient pulse responses to characterize deep brain stimulation electrodes in vitro in carbonate and phosphate buffered saline solution and in vivo following acute implantation in the brain. The electrode-tissue interface impedance operated in a nonlinear regime with clinically-relevant current amplitudes, and the nonlinearity complicates incorporation of
the interface impedance into models of DBS. The assumption of the DBS electrode being ideally polarizable is not valid under clinical stimulating conditions, indicating the occurrence of Faradaic charge transfer through the electrode-tissue interface. It awaits further investigation to identify the electrochemical reactions contributing to the Faradaic charge transfer.
Chapter 3: Effect of the Electrode-Tissue Interface on Current Density Distribution on Deep Brain Stimulation Electrodes

3.1. Abstract

The spatial distribution of current density on deep brain stimulation (DBS) electrodes can influence tissue damage, electrode corrosion, and the patterns of excitation generated in the tissue. The current density distribution can be influenced by the impedance of the electrode-electrolyte/tissue interface. The properties of the electrode-electrolyte interface have not been considered in previous models of DBS in determining the current density distribution. The objective of this research was to investigate the effect of the electrode-electrolyte interface on the current density distribution on DBS electrodes.

We implemented a finite element model of a monopolar DBS electrode that incorporated a representation of the electrode–tissue interface by inserting an impedance between the metal electrode and the tissue volume. The interface impedance was measured from electrochemical impedance spectroscopy in 0.9% sodium chloride solution. A distributed interface model was implemented to account for the nonlinearity of impedance with current density, and finite element simulation was performed at fixed frequencies (1 Hz, 10 Hz, 100 Hz, 1 kHz, 10 kHz and 100 kHz) to account for the nonlinearity of the interface impedance with frequency.
The current density distributions on the electrode surface were frequency dependent. At frequencies over 1 kHz, the current density distributions were almost identical to the primary current density distribution obtained from a model without an electrode-tissue interface, and were highly non-uniform. The non-uniformity of the current density decreased as the frequency was decreased until eventually the edge effect was lost at low frequencies below 10 Hz, and the current density was reduced as compared to the primary current density. The primary current density distribution can be used to estimate neuronal activation, tissue damage, and electrode corrosion with rectangular stimulus pulses, as most of the signal power in typical neural stimulation pulses is at frequencies where the secondary current density distribution matches closely the primary current density distribution.

### 3.2. Introduction

Deep brain stimulation (DBS) uses high frequency electrical stimulation from an electrode array implanted in the thalamus or basal ganglia to treat Parkinson’s disease, essential tremor, and other neurological disorders. The implanted stimulator delivers current to the tissue by discharging a capacitor, and thus the impedance of the electrode-tissue interface will affect both the magnitude and time course of the current that flows through the tissue. The effects of electrical stimulation on neurons are mediated by the extracellular electric field and its spatial derivatives [74, 75], which are proportional to the current density in the tissue, and thus the interface impedance can influence patterns and extent of neural excitation. The objective of this study was to quantify the effect of
the electrode-tissue interface impedance on the current density distribution on DBS electrodes and the potential distribution in the tissue.

Both analytical and numerical studies [22-25] as well as experimental measurements [26-29] indicate that the current density on a metal disk or rod is spatially non-uniform with very high current density at the edges and much lower current density in the center. The non-uniform current (or equivalently charge) density distribution may affect the propensity for stimulation to generate either tissue or electrode damage. Electrochemical reactions occur at higher rates at regions of geometrical discontinuity due to the large current density. Gas bubble formation occurred at electrode edges [76], and metal corrosion occurred at the edges of cylindrical electrodes [21] and at the tip of conical microelectrodes [77]. Charge density is a cofactor with charge in determining simulation induced neural damage [19], and the presence of damage was more strongly correlated with the diameter (perimeter) of the electrode than with the electrode area [48]. Therefore, quantifying the distribution of current density on DBS electrodes is important to understanding the stimulation-induced tissue damage and electrode corrosion.

The electrode-electrolyte interface has been largely ignored in previous models of DBS, where the DBS electrode is represented as a perfect voltage source in direct contact with surrounding tissue [78, 79]. When the interface impedance is neglected, the current density distribution is the primary current density distribution, which is completely controlled by the spreading resistance of the electrolyte solution between the stimulating and counter electrodes. The secondary current distribution arises when charge transfer across the interface is taken into account, and may be more uniform than the primary
distribution [15]. Neglecting the electrode-electrolyte interface impedance may affect the estimation of the volume of neuronal activation, and the propensity for tissue damage and electrode corrosion.

In this study, we first measured the electrode-electrolyte interface impedance over a range of current magnitudes in vitro in 0.9% sodium chloride solution. The impedance data were used to define the electrical properties of the electrode-electrolyte interface in a finite element model, and the current density distribution was calculated accounting for both the resistance of the electrolyte solution and the nonlinear distributed interface impedance. The current density distributions on the electrode surface were frequency dependent. At frequencies higher than 1 kHz, the current density distributions were highly non-uniform and almost identical to the primary current density distribution obtained from a model without an electrode-tissue interface. The non-uniformity of the current density decreased as the frequency was decreased until eventually the edge effect was lost at low frequencies below 10 Hz, and the average current density was reduced as compared to the primary current density.

3.3. Methods

3.3.1. In vitro impedance measurements

The impedance of clinical DBS electrodes (Model 3387, Medtronic Inc., Minnesota, USA) was measured at room temperature (\(T \approx 20^\circ C\)) in 0.9% sodium chloride solution using the three-electrode technique. The electrode was placed vertically in the middle of a 200 ml beaker of saline solution. Sinusoidal currents were generated
with an impedance analyzer (Model 1287 Electrochemical Interface (ECI) + Model 1252 Frequency Response Analyzer (FRA), Solatron Analytical, Hampshire, England) and applied between one contact of the DBS electrode (working electrode) and a counter electrode formed of stainless steel wire spiraling around the wall of the beaker. The potential between the working electrode and a silver/silver chloride reference electrode (Model RE-5B, BAS Inc., West Lafayette, IN) was measured with the 1287 ECI (input impedance 10 GΩ in parallel with 50 pF) and output back to the 1252 FRA, where the impedance was calculated by dividing the potential by the current. The measured impedance was the electrode-electrolyte interface impedance in addition to the solution series resistance, which was minimized by positioning the reference electrode within 5 mm of the working electrode. Impedance spectrograms were measured with sinusoidal currents at 6 frequencies between 1 Hz and 100 kHz at root-mean-square amplitudes from 0.01 mA to 2 mA. The measurements were repeated three times at each amplitude for each of the four DBS contacts.

3.3.2. Finite element modeling and simulation

Axisymmetrical finite element models (FEM) were built based on the geometry of Medtronic’s Model 3387 DBS lead, which includes a linear array of 4 cylindrical electrode contacts (conductivity σ = 10^7 S/m; 1.5 mm length, 1.27 mm diameter) separated by insulating rings (conductivity σ = 10^10 S/m; 1.5 mm length). The electrode was positioned in a linear volume conductor with intermediate conductivity (σ = 0.2 S/m) representing brain tissue that had no capacitance as the reactive component of the
conductivity of brain tissue is small relative to the real component [80, 81]. The volume conductor was 30 mm in height and 30 mm in diameter, and the boundary was far enough from the central region of the model that it did not influence the potentials in the regions of interest. The boundary conditions were set to be 1 V on contact 1, and ground on the exterior boundary (i.e., Dirichlet boundary conditions).

Finite element simulations were performed using the conductive media mode of COMSOL Multiphysics 3.4, which solves the sinusoidal steady-state problem by using complex conductivity provided induction effects can be neglected [82, 83]. The complex conductivity of the electrode-tissue interface was represented as $\sigma + j\omega \varepsilon$, where $\omega$ is the radian frequency, $\sigma$ is the resistive conductivity, and $\varepsilon$ is the dielectric permittivity. $\sigma$ and $\varepsilon$ are nonlinear functions of current density and frequency. Simulations were performed at fixed frequencies (1 Hz to 100 kHz), and at each frequency, $\sigma$ and $\varepsilon$ were determined by the appropriate current density. The electrode-tissue interface was modeled as a 10 nm thin film [15] and discretized into mesh elements. At each discrete location, the complex conductivity of the interface was calculated with the current density at this discrete location by fitting the piece-wise linear polynomial curves of measured impedance as a function of current density (current/electrode area).

This problem is characterized by a very wide range of distance scales as the electrode diameter (1.27 mm) is more than five orders of magnitude larger in dimension than the thickness of the electrical double layer (10 nm). Consequently, the wide range of scales makes the problem very difficult to solve by finite element techniques. Accordingly, some adjustments were made to preserve the essential features while
making the problem solvable with reasonable computational cost. As current flow in the
double layer is predominantly normal to the electrode surface, the double layer thickness
was increased to 1 μm, and accordingly both the conductivity $\sigma$ and the dielectric
permittivity $\varepsilon$ were increased proportionally to keep the same specific resistance ($\Omega\cdot cm^2$)
and specific capacitance ($\mu F/cm^2$). This approach has previously been used to model the
cell-electrode interface to study the microelectrode impedance change due to cell growth
[82].

The simultaneous dependencies of the current density distribution on the interface
impedance and the interface impedance on the current density required an iterative
approach to calculate the secondary current density. The primary current density,
calculated in the absence of the electrode-electrolyte interface, was used as the initial
current density distribution to determine the initial current density-dependent interface
properties. The modified current density was then calculated, and the process was
continued until the current density distribution converged (less than 3% difference from
the previous loop, $n=1$-8 iterations) (Figure 3.1).
3.4. Results

The goal of this study was to quantify the effect of the electrode-electrolyte interface impedance on the distribution of current density over the surface of a DBS electrode. We first measured impedance spectra of DBS electrodes with sinusoidal currents at different amplitudes, and then simulated the current density distributions using finite element models that incorporated the interface impedance.
3.4.1. Determine interface impedance from *in vitro* measurements

**Figure 3.2: Impedance spectra of DBS electrodes.**

a) Impedance spectra of DBS electrodes at various frequencies (50 points evenly distributed on a log scale from 1 Hz to 100 kHz) at RMS current amplitudes of 0.01 mA, 0.1 mA and 1 mA. b) Impedance loci (Nyquist plots) in the complex plane at fixed current amplitudes of 0.01 mA, 0.1 mA and 1 mA. c) Impedance loci at fixed frequency of 1 Hz.

Figure 3.2 shows the impedance spectra (Figure 3.2(a)), impedance loci at fixed currents (Figure 3.2(b)), and at a fixed frequency (Figure 3.2(c)) of DBS electrode
contacts. The impedance magnitude at low frequencies increased with decreasing current (Figure 3.2(a)), and this was reflected by the increases in both the real and the imaginary parts of the impedance with decreasing current (Figure 3.2(b)(c)).

The measured impedance includes the electrode-electrolyte interface impedance, which dominates at low frequencies, in series with the resistance of the surrounding solution, which dominates at high frequencies [59]. The asymptotic, high-frequency impedance resulting from the solution series resistance $R_s$ was $119 \pm 7 \Omega$ (mean±s.d., range=107-141 Ω, n=60). The series resistance was subtracted from the measured impedance to obtain the electrode-electrolyte interface impedance as a function of the current amplitude at fixed frequencies of 1, 10, 100, 1k, 10k and 100k Hz. Figure 3.2(c) shows the relationship between the interface impedance and the current amplitude at the frequency of 1 Hz. By dividing the current by the electrode surface area (5.98 mm²), a relationship between the interface impedance and the current density at each frequency was obtained and used to determine the distributed complex conductivity for the simulation scheme described by Figure 3.1.

### 3.4.2. Effects of interface on current density and potential distributions

Figure 3.3(a) illustrates current density profiles along the electrode surface at different frequencies. At frequencies over 1 kHz, the current density distributions were highly non-uniform and almost identical to the primary current density distribution. The non-uniformity of the current density decreased as the frequency was decreased until eventually the edge effect was lost at frequencies below 10 Hz, and the average current
density was reduced as compared to the primary current density. Current density distributions at different frequencies generated by application of 1 V RMS amplitude at contact 1 are shown in Figures 3.4. The current density distributions on the electrode surface were strongly frequency dependent. The spatial spread of current density was similar at high frequencies (f>1 kHz), but was much more local at low frequencies (f<100 Hz).

![Figure 3.3: Current density and overpotential profiles along the interface.](image)

(a) Current density profiles along the electrode-electrolyte interface at different frequencies. The current density profiles for frequencies of 1 kHz, 10 kHz and 100 kHz overlap with the primary current density profile. b) Overpotential profiles along the electrode-electrolyte interface at various frequencies. The overpotential profiles for frequencies of 10 kHz and 100 kHz overlap in the figure.
Figure 3.4: Distributions of current densities at various frequencies.

Distributions of current densities at different frequencies generated by application of 1V RMS amplitude at contact 1.

The voltage across the interface (overpotential) was calculated as the voltage difference between the DBS electrode and the adjacent tissue medium, and the profiles (Figure 3.3(b)) indicate that the overpotential increased progressively from virtually zero at a frequency of 100 kHz to approximately 0.7 V at a frequency of 1 Hz. The distributions of potential at different frequencies generated by application of 1 V RMS at contact 1 are shown in Figures 3.5. The potential distributions were also frequency dependent. The potential distributions were similar at high frequencies (f>1 kHz) and the potential progressively decreased from the electrode contact to the tissue. However, at
low frequencies (f<$10$ Hz), there was a large potential drop across the interface. At $1$ Hz, the potential dropped from $1$ V on the electrode to $\sim 0.3$ V in the tissue adjacent to it.

Figure 3.5: Distributions of potentials at various frequencies
Distributions of potentials at different frequencies generated by application of $1$V RMS amplitude at contact 1.

3.5. Discussion

The goal of this study was to quantify the effect of the electrode-electrolyte interface impedance on the spatial distribution of current density over the surface of a DBS electrode. This has important implications for patterns of neural excitation, stimulation induced tissue damage, and metal corrosion. The current density distribution was strongly frequency dependent, and resembled the highly non-uniform primary current density distribution only at high frequencies. As the frequency was decreased, the
current density decreased in amplitude and progressed from a non-uniform to a uniform distribution.

Similar observations have previously been described in the literature. Newman derived an analytical solution of the current density distribution on a disk electrode embedded in an infinite insulating plane with the counter electrode at infinity, by solving Laplace’s equation subject to various boundary conditions on the electrode-electrolyte interface representing Faradaic or capacitive charge transfer. He demonstrated that a highly non-uniform primary current density was created on the surface of a disk electrode when there was negligible surface overpotential, and that a much more uniform secondary current density distribution was created when the interfacial resistance was relatively large compared to the solution resistance [64, 84]. Next, by incorporating double layer capacitance at the interface and considering an a.c. driving potential, he determined the frequency dependence of the secondary current density distribution that progressed from a non-uniform to a much more uniform distribution as the frequency was decreased [85]. Similar observations were also found in analytical solution of current density distribution on a cylindrical electrode [86], and in numerical solution using finite element analysis on a cone-shaped microelectrode [87]. The electrical properties of the interface in these studies were described by a lumped Faradaic resistance or double layer capacitance, or by an empirical impedance formulation. In contrast, we incorporated distributed current-dependent interface impedance measured directly from electrochemical impedance spectroscopy of DBS electrodes.
Experimental measurements of current density distributions supported the conclusion that the distribution is frequency dependent and that the secondary current density distribution is more uniform than the primary distribution. Suesserman et al. calculated current density distributions generated by a disk electrode in saline solution by measuring potentials using a microelectrode, and observed a reduction in the uniformity of current density as the frequency was decreased from 5 kHz to 100 Hz [88]. Maus et al., using electrogenerated chemiluminescence to image the current density distribution at the surface of a microdisk electrode and a conical microelectrode, also observed that the non-uniformity of current density increased as the frequency was increased [28]. Further, consistent with the results of our numerical model, Maus et al. observed greater non-uniformity of current density when the surface overpotential was small.

### 3.5.1. Implications for DBS

The current density distribution approaches the primary distribution at high frequencies. Because electrical stimulation of the nervous system is generally in the form of rectangular pulses, the primary current density distribution accurately represents that occurring at the instant the electric pulse is first delivered (t=0). At t>0, the charge transfer processes occurring at the interface leads to a time-dependent variation in the interfacial impedance, and thereby variation in the current density distribution dependent on the frequency components of the pulse. The power spectra of three typical 1mA neural stimulation pulses revealed that the bulk of signal power (monophasic pulse: 80%; symmetrical biphasic pulse: 99%; asymmetrical biphasic pulse: 80%) is at frequencies
over 1 kHz (Figure 3.6) where the current density distribution is well approximated by the primary current density distribution (Figure 3.3(a)). Therefore, employing the primary current density distribution to estimate neuronal activation, tissue damage and electrode corrosion during clinically effective stimulus pulses is appropriate.

**Figure 3.6: Power spectra of three different 1mA neural stimulation pulses.**
MP=100 μs duration monophasic rectangular pulse; SBP=100 μs per phase symmetrical charge-balanced biphasic rectangular pulses; ABP=asymmetrical charge balanced biphasic rectangular pulses composed of a 100 μs primary phase followed by a 1 ms secondary phase.

Charge per phase and charge density per phase are co-factors in the generation of neural damage [19, 47], and this relationship is described by the equation (Shannon’s model):

\[
\log \left( \frac{Q}{A} \right) = k \log(Q),
\]

(3.1)

where \( Q \) is the charge per phase, \( A \) is the electrode area, and \( k \) is a constant derived from data to define the boundary between stimulus parameters that produced tissue damage.
and those that did not [48]. The proposed limit for non-damaging stimulation levels using disk electrodes was $k=1.5$, but this value was estimated using the geometric (average) charge density over the electrode surface. The limit of non-damaging stimulation was linearly related to electrode diameter, not electrode area, suggesting that higher charge (current) densities around the perimeter of the electrode was more predictive of neural damage than geometric charge density [48].

<table>
<thead>
<tr>
<th>Table 3.1: Increases of $k$ values ($\Delta k$) when applying maximum charge density calculated at various sinusoidal frequencies.</th>
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<tbody>
<tr>
<td>(Q/A)$_{max}$</td>
</tr>
<tr>
<td>Primary f=1 Hz f=10 Hz f=100 Hz f=1 kHz f=10 kHz f=100 kHz</td>
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<td>3.17</td>
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We calculated the average current density ($J_{avg}$) and maximum current density ($J_{max}$, average over the 1% of the electrode area with the highest current density) for the profiles in Figure 3.3(a). The ratio $J_{max}/J_{avg}$ is the same as the ratio of maximum charge density $(Q/A)_{max}$ to average charge density $(Q/A)_{avg}$. The changes in $k$ ($\Delta k$) were calculated when $(Q/A)_{max}$, instead of $(Q/A)_{avg}$, was considered (Table 3.1). If we replace $(Q/A)_{avg}$ with $(Q/A)_{max}$ in Shannon’s model, then $k$ increases by 0.5 when considering the primary current density distribution. While previous studies have established non-damaging limits for electrical stimulation of the brain, it is not possible to extend these values to other electrodes because the charge (current) density is not uniform on the
electrode surface. By adopting \((Q/A)_{\text{max}}\) instead of \((Q/A)_{\text{avg}}\) in Shannon’s model, the limit established for one electrode can be extrapolated to electrodes of different geometries, if the electrode material and the tissue medium are the same.

### 3.5.2. Modeling limitations

The models utilized in this study have several limitations. First, the tissue media was modeled as homogenous volume conductor with only resistive conductivity \(\sigma\). Capacitive effects increase with frequency and may be ignored if \(j\omega\varepsilon << \sigma\). To assume the tissue medium as purely resistive across the entire frequency range allowed us to focus on the effects of the electrode-electrolyte interface on the current density distributions. Further, the exact solution for the potential can be approximated by quasi-static simplifications for commonly used stimulus pulse parameters [83].

Second, the current density was spatially averaged over the entire electrode surface when calculating the relationship between complex conductivity and current density at various frequencies from the relationship between interface impedance and current (Figure 3.2(c)). To obtain a relationship between complex conductivity with the absolute current density, an electrode with uniformly distributed current density is necessary, which can only be achieved on sphere/hemisphere or some other novel shapes [25, 71, 72].

Third, the double layer capacitance of the electrode-tissue interface has a time-varying transient response when it is being charged or discharged. However, finite element simulations were performed using the complex conductivity for the electrode-
tissue interface to calculate the a.c. steady state solutions to time-harmonic problems. As a periodic square wave can be represented by the linear combination of its Fourier series, the current density distribution responding to a voltage pulse can thus be calculated by the linear combination of the current density distribution at the harmonic components of the square wave. In this work, only current density distributions at sinusoidal steady state of various frequencies were simulated.

3.6. Conclusions

We quantified the effects of the electrode-electrolyte interface impedance on the current density distribution on DBS electrodes. The current density distribution on the electrode surface was strongly frequency dependent. The current density distributions resembled the highly non-uniform primary current density distribution at high frequencies, but as the frequency was decreased, the current density decreased in amplitude and become more uniform. The primary current density distribution can be used to estimate neuronal activation, tissue damage, and electrode corrosion with rectangular stimulus pulses, as most of the signal power in typical neural stimulation pulses is at frequencies where the secondary current density distribution matches closely the primary current density distribution.
Chapter 4: Impedance and Field Analysis of Segmented Cylindrical Electrodes

4.1. Abstract

Deep brain stimulation (DBS) electrodes are designed to stimulate specific areas of the brain. The most widely used DBS electrode has a linear array of 4 cylindrical contacts that can be selectively turned on depending on the placement of the electrode and the specific area of the brain to be stimulated. The efficacy of DBS therapy can be improved by localizing the current delivery into specific populations of neurons and by increasing the power efficiency through a suitable choice of electrode geometrical characteristics. We investigated segmented electrode designs created by sectioning each cylindrical contact into multiple rings. Prototypes of these designs, made with different materials and larger dimensions than those of clinical DBS electrodes, were evaluated in vitro and in simulation. A finite element model was developed to study the effects of varying the electrode characteristics on the current density and field distributions in an idealized electrolytic medium and in vitro experiments were conducted to measure the electrode impedance. The current density profile over the electrode surface increased towards the edges of the electrode, and multiple edges increased the non-uniformity of the current density profile. The edge effects were more pronounced over the end segments than over the central segments. Segmented electrodes generated larger magnitudes of the second spatial difference of the extracellular potentials, and thus required lower stimulation intensities to achieve the same level of neuronal activation as
solid electrodes. For a fixed electrode conductive area, increasing the number of segments (edges) decreased the impedance compared to a single solid electrode, because the average current density over the segments increased. Edge effects played a critical role in determining the current density distributions, neuronal excitation patterns and impedance of cylindrical electrodes, and segmented electrodes provide a means to increase the efficiency of DBS.

4.2. Introduction

Electrical stimulation of the nervous system is a technique to restore function to individuals with neurological impairment [89]. Deep brain stimulation (DBS) uses high-frequency electrical stimulation of the thalamus or basal ganglia (subthalamic nucleus (STN), external segment of the globus pallidus) to treat movement disorders, and has rapidly emerged as an alternative to surgical lesions [1-3]. Although the mechanisms of the action of DBS are still unclear, the efficacy of DBS therapy requires localizing the current delivery to specific populations of neurons. While significant effort has been put into finding optimal anatomical targets for DBS [8-10], very little effort has been devoted to design of DBS electrodes. The objective of the present analysis was to characterize the current density distributions, field distributions, and impedances of segmented cylindrical electrodes.

The design of the electrodes is important for selective and controlled activation of populations of neurons in three ways. First, the electrode geometry can affect the spatial distribution of current density over the electrode surface, a cofactor with charge in
stimulation induced neural damage [19]. Second, the electrode geometry can affect the pattern of neural excitation by determining the electric field generated in the tissue medium [16]. Third, the electrode design can affect electrode impedance, a concern in designing electrodes as it impacts power consumption. These elements are linked in that current density ($J$) and electric field ($E$) are related by Ohm’s law,

$$J = \sigma \cdot E \quad (4.1)$$

and the impedance ($Z$) depends on the current density distribution over the electrode surface,

$$Z = \frac{V}{\int_{S} J \cdot dS} \quad (4.2)$$

where $V$ is the potential drop across the electrode-electrolyte interface and $S$ is the electrode surface area.

We investigated a segmented electrode design created by sectioning each contact of a cylindrical electrode into multiple rings which were electrically connected together to form a single multi-segment electrode. Presently used DBS leads (Models 3387, 3389, Medtronic Inc., Minnesota, USA) have a linear array of 4 cylindrical electrode contacts that can be individually turned on depending on the placement of the electrode and the specific area of the brain to be stimulated. The segmented design was intended to enhance the “edge effect” of the electrode, and thereby reduce the electrode impedance. The edge effect describes that the current density at the electrode surface increases toward the perimeter of the electrode [64], and a more pronounced edge effect was expected to reduce the electrode impedance [23]. The segmented design is different from
the multi-channel banded electrode arrays used in DBS and in cochlear implants [90] where each band forms a single channel because the segments are electrically connected together and form a single channel. The goal of this study was to characterize the current density distributions, field distributions, and impedances produced by segmented cylindrical electrodes. We investigated the effects of the number of segments, aspect ratio (diameter/length) of each segment, total surface area and surface coverage (percentage of conductive surface area) of the electrode on the current density distributions, field distributions and electrode impedance.

4.3. Methods

4.3.1. Calculations of current density distributions

Three dimensional (3D) numerical models, implemented using the finite element method, were used to quantify the current density profiles on the surface of segmented electrodes. Five electrode models with the same total length of 7 cm and diameter of 1 cm but different combinations of conductive and insulating segments were developed to examine the effects of electrode geometry on current density distributions. Figure 4.1(a) shows the geometry of a 4-segment electrode model. The electrode included conductive contacts ($\sigma = 10^8$ S/m) separated by insulating rings ($\sigma = 10^{-10}$ S/m) (Figure 4.1(b)) and was positioned in a homogeneous volume conductor representative of CNS tissue ($\sigma = 0.2$ S/m). The tissue surrounding the electrode was modeled as a cylinder with a radius of 15 cm and a height of 15 cm with the outer boundary set to 0 V. The electrode contacts were set to 10 V, which is approximately three times larger than the average voltage used
clinically, but the model was linear and both the current density and electric field intensity scale with the applied voltage. The 3D model was partitioned into mesh elements by a finite element software package FEMLAB (Comsol Inc., Stockholm, Sweden).

Figure 4.1: Geometry of a segmented cylindrical electrode model. Finite element models were used to quantify the current density profiles on the surface of segmented cylindrical electrodes. (a) Model geometry of a segmented cylindrical electrode and surrounding tissue. The electrode was positioned in a homogeneous volume conductor representative of CNS tissue. The surrounding tissue was modeled as a cylinder with a radius of 15 cm and a length of 15 cm. (b) Close view of a typical segmented cylindrical electrode. Four conductive rings (dark gray) with the length of 1 cm were separated by 1 cm insulating rings (light gray). The length of the electrode was 7 cm with a diameter of 1 cm.

The nodal voltages ($\Phi$) were calculated by solving Laplace’s equation

$$\nabla^2 \Phi = 0 \quad (4.3)$$
Laplace’s equation describes the potential variation in the electrolytic solution or tissue where the concentrations are uniform [64]. The element current densities were derived from the nodal voltages with Ohm’s law:

\[ J = -\sigma \cdot \nabla \Phi \]  

The mesh size was set such that further refinement of the mesh resulted in < 3% change in the total current delivered by the electrode. The total current delivered by the electrode was calculated by integration of the current density along the electrode surface.

**4.3.2. Calculation of activation patterns**

The second spatial difference of the extracellular potentials (the activating function, \( f_i \propto \frac{\Delta^2 V_e}{\Delta x^2} \)) drives neuronal polarization by generating transmembrane currents in neurons [45, 46], and \( \Delta^2 V_e/\Delta x^2 \) can provide qualitative predictions on the activation patterns of neurons by extracellular sources. Distributions of \( \Delta^2 V_e/\Delta x^2 \) (for neurons perpendicular to the electrode) and \( \Delta^2 V_e/\Delta y^2 \) (for neurons parallel to the electrode) were calculated in the tissue medium from the nodal potentials of the finite element models where the mesh spacing (from ~100 µm close to electrode to ~2 cm near the outer boundary) was used as the space step, \( \Delta x \) or \( \Delta y \).

**4.3.3. In vitro measurement of electrode impedance**

The three-electrode technique was used to measure the impedance of prototype segmented electrodes in a cylindrical (10 cm in diameter and 12 cm in height) saline-filled tank (0.154 M NaCl (0.9%) solution) (Figure 4.2). Charge-balanced sinusoidal
currents were passed between the test (working) electrode and a distant counter electrode formed of stainless steel wire spiraling around the wall of the tank. The resulting potential was measured between the working electrode and a reference electrode formed of silver-silver-chloride wire and positioned within 0.5 cm of the test electrode to minimize the series resistance. The test electrodes were made of stainless steel rod insulated with acetate rings, and ranged in size from 1 cm to 7 cm in length and from 0.55 cm to 0.95 cm in diameter. Although substantially larger than clinical DBS electrodes, the larger prototypes enabled simple fabrication with accurate dimensions. The test electrode was placed vertically in the middle of the tank, and the measurements were conducted at room temperature (T ≈ 20 °C).

![Three-electrode technique to measure impedance.](image)

**Figure 4.2: Three-electrode technique to measure impedance.**

The three-electrode technique was used to measure *in vitro* the impedance of segmented cylindrical electrodes. Sinusoidal currents were applied between the working electrode and the counter electrode, and the voltage was measured between the working electrode and the reference electrode.
Regulated sinusoidal currents with a root-mean-square amplitude of 100 mA and frequencies at 10 Hz, 50 Hz, 100 Hz, 500 Hz, 1 kHz, 5 kHz were applied to the three-electrode cell using the waveform generating function of a lock-in amplifier (SR830 DSP, Stanford Research Systems, Sunnyvale, California) and a linear voltage-to-current converter (BSI-1 biphasic stimulus isolator, BAK Electronics Inc., Germantown, Maryland). The amplitude of the test current was an order of magnitude larger than currents employed clinically, but was used to increase the signal to noise ratio of measurements on large electrodes with comparatively low impedances. The voltage was measured with the lock-in amplifier which had an input impedance of 10 MΩ in parallel with 25 pF and a bandwidth of 1 mHz -102 kHz. The measured voltage was the voltage drop resulting from the electrode-electrolyte interface impedance in addition to the saline resistance between the working electrode and the reference electrode. This combined impedance was calculated as the voltage drop divided by the current flowing in the electrolyte cell and was measured over three repetitions at each frequency for each electrode.

4.4. Results

Three elements were used to characterize prototype segmented cylindrical stimulating electrodes: the current density distribution over the electrode surface, the second spatial difference of the potentials in the surrounding tissue, and the electrode impedance.
4.4.1. Current density distributions on segmented electrodes

Three dimensional finite element models were developed to quantify the current density distributions on segmented electrodes with variable numbers of segments, aspect ratios of each segment, total surface area, and surface coverage. The current density profiles over the surface of various electrodes are shown in Figure 4.3. The current density over a segment was non-uniform and increased toward the perimeter of the segment. The current density profiles varied across the different segments in the segmented electrodes, and the average current density over the central segments was lower than over the side segments. Table 4.1 shows: at the same segment length, the total current delivered by the electrode at a fixed potential increased as coverage (number of segments) increased; at the same coverage, the total current increased as segment length decreased (number of segments increased); and at the same overall conductive length, the solid electrode delivered the most current.
Figure 4.3: Profiles of current density on segmented electrodes.
Profiles of the current density on the electrode surface calculated using finite element models of segmented cylindrical electrodes. Five different electrode configurations, labeled as electrodes a, b, c, d and e, represent electrodes E-Rod, E-2, E-4, E-4t and E-8, respectively, in Table 4.1. All five electrodes had a total electrode length of 7 cm, and the number of segments and segment length for each electrode are shown in Table 4.1.
Table 4.1: Total currents and current densities of segmented cylindrical electrodes

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Number of segments</th>
<th>Conductive segment length (cm)</th>
<th>Coverage (%)</th>
<th>Total delivered current ($10^{-1}$ A)</th>
<th>Average current density over segments ($10^{-2}$ A/cm²)</th>
<th>Proportion of conductive area above average current density (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Rod</td>
<td>1</td>
<td>7</td>
<td>100</td>
<td>4.26</td>
<td>1.94</td>
<td>24.4</td>
</tr>
<tr>
<td>E-2</td>
<td>2</td>
<td>2</td>
<td>57.1</td>
<td>3.46</td>
<td>2.76</td>
<td>24.0</td>
</tr>
<tr>
<td>E-4</td>
<td>4</td>
<td>1</td>
<td>57.1</td>
<td>3.71</td>
<td>2.95</td>
<td>27.0</td>
</tr>
<tr>
<td>E-4t</td>
<td>4</td>
<td>0.5</td>
<td>28.6</td>
<td>3.00</td>
<td>4.77</td>
<td>21.0</td>
</tr>
<tr>
<td>E-8</td>
<td>8</td>
<td>0.5</td>
<td>57.1</td>
<td>3.79</td>
<td>3.02</td>
<td>24.8</td>
</tr>
</tbody>
</table>

4.4.2. Activation patterns generated by segmented electrodes

The distribution of potentials, $V_\text{c}$, generated in the tissue medium by the 4-segment electrode (E-4 in Table 4.1) is shown in Figure 4.4(a), and the second spatial differences of the potentials, $\Delta^2 V_\text{c}/\Delta x^2$ and $\Delta^2 V_\text{c}/\Delta y^2$, generated by the single-segment (solid) and 4-segment electrodes are shown in Figure 4.4(b)-(e). $\Delta^2 V_\text{c}/\Delta x^2$ and $\Delta^2 V_\text{c}/\Delta y^2$ have both positive components resulting in depolarization and negative components resulting in hyperpolarization of neurons surrounding the electrode [45]. The spatial distributions of the activating function for neurons perpendicular to the electrode ($\Delta^2 V_\text{c}/\Delta x^2$) are quite similar for the solid and segmented electrode, while the activating function for neurons parallel to the electrode ($\Delta^2 V_\text{c}/\Delta y^2$) generated with segmented electrode has a larger spatial extent than with the solid electrode.
The spatial profiles of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$ along a specific line (illustrated in Figure 4.4(a)) generated by each of the segmented electrodes are shown in Figure 4.5. Different electrodes generated similarly shaped profiles of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$, and the profiles created by each of the segmented electrodes were highly correlated with the profiles created by the solid electrode ($r>0.95$). However, with the same stimulation intensity (electrode voltage), segmented electrodes generated larger magnitudes of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$ surrounding the conductive contact and thus required lower stimulation intensity than the solid electrode to achieve the same level of neural activation. The electrode with 4 thin segments (E-4t) generated larger magnitudes of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$ than the electrode with 4 “thick” segments (E-4). For different segmented electrode configurations with same segment length (E-4t and E-8), the electrode with the larger insulative gap (E-4t) resulted in a larger magnitude of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$ surrounding the conductive contact.
Figure 4.4: Distributions of extracellular potentials and driving functions.
Distributions of extracellular potentials ($V_e$) and the second spatial difference of the extracellular potentials ($\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$). (a) Slice view of $V_e$ generated by the 4-segmented electrode (E-4) in 3-dimensional space. The vertical line in the Z-direction indicates the position over which the profiles of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$ in Figure 4.5 were calculated. (b) $\Delta^2 V_e/\Delta y^2$ in the axial (Y) direction (i.e., neurons parallel to the long axis of the electrode) in the $Z=0$ plane for the solid electrode (E-Rod). (c) $\Delta^2 V_e/\Delta x^2$ in the radial (X) direction (i.e., neurons perpendicular to the long axis of the electrode) in the $Z=0$ plane for the solid electrode (E-Rod). (d) $\Delta^2 V_e/\Delta y^2$ in the axial (Y) direction in the $Z=0$ plane for the 4-segmented electrode (E-4). (e) $\Delta^2 V_e/\Delta x^2$ in the radial (X) direction in the $Z=0$ plane for the 4-segmented electrode (E-4).
Second spatial difference of the extracellular potentials \( \Delta^2 V_e / \Delta x^2 \) and \( \Delta^2 V_e / \Delta y^2 \) generated by each of the five segmented electrodes along a line radial to the electrode (illustrated in Figure 4.4(a)) on the \( Y=3.25 \text{cm} \) plane (i.e., axial center of the most distal segment of E-4t and E-8). (a) \( \Delta^2 V_e / \Delta x^2 \) (in the radial (X) direction, i.e., neurons perpendicular to the long axis of the electrode) as a function of the distance along Z from the electrode array. (b) \( \Delta^2 V_e / \Delta y^2 \) (in the axial (Y) direction, i.e., neurons perpendicular to the long axis of the electrode) as a function of the distance along Z from the electrode array.

### 4.4.3. Impedance of segmented electrodes

To evaluate the effect of the geometrical characteristics of segmented electrodes on electrode impedance, we conducted a series of measurements and changed only one parameter at a time with the other parameters fixed. The impedance of all electrodes decreased as the frequency increased as a result of the double layer capacitance of the electrode-electrolyte interface (Figure 4.6).
Figure 4.6: Impedance of prototype segmented cylindrical electrodes.
Impedance of prototype segmented cylindrical electrodes at various frequencies measured in vitro using the three-electrode technique. (a) Impedance of electrodes with one segment and the same diameter (0.95 cm), but different lengths. (b) Impedance of electrodes with same total conductive length (4 cm), the same diameter (0.95 cm), but different numbers of segments and different segment lengths. (c) Impedance of electrodes with same total electrode length (6 cm), the same diameter (0.55 cm), but different numbers of segments and different segment lengths.

4.4.3.1. Effect of electrode length on impedance.

The impedances of electrodes with a single segment and a fixed diameter (0.95 cm) but with four different lengths (1 cm, 2 cm, 3 cm and 4 cm) were measured to determine the effect of electrode area on the impedance (Figure 4.6(a)). The impedance was inversely related to the electrode area as well as the sinusoidal frequency, and ANOVA indicated that both electrode length and frequency had significant effects on electrode impedance (p<0.001). Post-hoc pairwise comparisons using Tukey’s test showed that there were significant differences between impedances for each pair of electrodes (p<0.001).
4.4.3.2. Effect of number of segments on impedance.

The impedances of electrodes with equal area (diameter = 0.95 cm, total conductive length = 4 cm) but with 1, 2 or 4 segments were measured to investigate the effect of electrode perimeter (number of edges) on the impedance (Figure 4.6(b)). For the electrodes with multiple segments, the insulating rings had the same length as the conductive rings. The electrode impedance was inversely related to the number of segments, and ANOVA indicated that both number of segments and frequency had significant effects on electrode impedance (p<0.001). Post-hoc pairwise comparisons using Tukey’s test showed that there were significant differences between the impedances of the electrode with a single 4 cm segment and the electrode with two 2 cm segments (p<0.001), and between the impedances of the electrode with two 2 cm segments and the electrode with four 1 cm segments (p=0.007).

4.4.3.3. Effect of number of segments at the same electrode length on impedance.

Subsequently, three electrodes with the same overall length (6 cm) and diameter (0.55 cm) but with different numbers of conductive segments (1, 2 and 3), and therefore different amounts of both surface area and perimeter were studied (Figure 4.6(c)). The first electrode was a single 6 cm conducting contact, the second electrode had two 2 cm conductive segments separated by a 2 cm insulating segment, and the third electrode had three 1.2 cm conductive segments separated by two 1.2 cm insulating segments. ANOVA indicated that both number of segments and frequency had significant effects on electrode impedance (p<0.001). Post-hoc pairwise comparisons using Tukey’s test showed that
there was no significant difference between the impedances of the first electrode and the second electrode \((p=0.145)\), but there were significant differences between the impedances of the first electrode and the third electrode \((p<0.001)\) and between the impedances of the second electrode and the third electrode \((p=0.002)\).

4.5. Discussion

The current density distributions, neural activating functions, and impedances of prototype segmented cylindrical electrodes were investigated in this study. A finite element model was used to quantify the effects of geometry on the distributions of current density on the electrode surface and potentials in the surrounding medium, and \textit{in vitro} measurements were used to quantify electrode impedance.

4.5.1. Synthesis of results

The electrode geometrical characteristics we investigated included aspect ratio (defined as the ratio of the segment length to the segment radius [24]), number of segments, surface coverage (defined as the percentage of the surface area of the conductive elements over the total surface area of the electrode [24]) and surface area.

According to Ohm’s law, at a fixed voltage electrode impedance is reversely related to total current delivered by the electrode, which equals the surface area of the electrode times the average current density over the electrode surface. Thus, electrode impedance can be decreased either by increasing the surface area or by increasing the average current density over the electrode surface. Our experimental measurements
demonstrated that the impedance was inversely related to the electrode area (Figure 4.6(a)), and our numerical study corroborated this by indicating that the total current increased as the electrode area increased (Table 4.1). Aspect ratio, number of segments and surface coverage impact electrode impedance by influencing the edge effects of the current density profile. Edge effects represent the tendency for the current density to increase toward the perimeter of the electrode, and the presence of the edges can increase the average current density over electrode surface. This result was demonstrated in our numerical study where increasing the number of edges increased the average current density (Table 4.1). The increase in average current density can lower the electrode impedance, and our experimental results demonstrate that electrode impedance was decreased by increasing the number of electrode edges (Figure 4.6(b)).

If the total length of the electrode was fixed while the number of segments and the segment lengths were varied, then electrode impedance was determined by the tradeoff between electrode conducting area and the number of edges, which were competing factors in that more edges came from adding insulating segments between the conducting segments, but this decreased the conducting area. Table 4.1 shows that decreasing the segment length (aspect ratio) resulted in higher average current density. However, higher average current density did not necessarily result in more total current delivered, because of competing reductions in electrode conductive area. The solid electrode, although it had the lowest average current density (table 4.1) and the smallest number of edges, had the lowest impedance (Figure 4.6(c)) and delivered the most total current (table 4.1). The larger conductive area compensated for the low average current density and made the
impedance of the single solid electrode lower than the impedance of any segmented electrode with the same total length.

The current density profiles of different electrode configurations provide an explanation for the differences in impedance across electrode geometries. The current density profiles differed over each segment within an electrode with multiple segments (Figure 4.3). The average current density over the central segments was lower than over the side segments, and the difference between the current density over the segments became more pronounced as the number of segments was increased (Figures 4.3(d),(e)). As the number of segments was increased at the same segment length and electrode overall length, the insulating gap between conducting segments was decreased, and there were stronger interactions between currents delivered by neighboring segments. In the limit, as the number of segments continues to increase, the conducting segments would fuse and form a solid electrode rod. At this point the adjacent edges are lost, no edge effect contributes to the central segments, and the average current density over central portion of the electrode becomes the lowest [91].

In addition to impacting electrode impedance, the distribution of current density across the electrode surface is also an important consideration for tissue damage arising from electrical stimulation. Charge density (the product of current density and pulse duration) is a cofactor with charge per phase in determining stimulation induced neural damage [19], and the effects of electrode geometry on the non-uniformity of current density distribution over electrode surface may therefore impact the propensity for tissue damage. The proportion of conductive area carrying above average current density was
calculated as an index of current density non-uniformity, and the results are summarized in Table 4.1. Although increasing the number of edges appeared to increase the non-uniformity of current density, the percentages of conductive area carrying above average current density (21 – 27%) were similar for different electrode geometries, and thus segmenting an electrode into multiple rings is expected to have little effect on tissue damage when compared to a solid electrode.

The relative efficiencies of neural excitation by different electrode geometries were compared by calculating the second spatial difference of the potentials $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$ (the activating function) [45]. The activating function describes the sources driving membrane polarization (i.e., the right hand side of the cable equation) rather than the response (i.e., the solution to the cable equation), and thus is only an estimate of the effect that the potentials will have on the neuron [46]. However, the magnitude of the activating function is correlated with the threshold to stimulate neurons with cylindrical DBS electrodes [17], and the activating function has also been used to quantify the stimulatory effects of spinal cord stimulation [92].

Electrodes that exhibited less uniform distributions of current density on their surfaces generated patterns of potential in the tissue that exhibited greater spatial variation, and therefore generated larger magnitudes of $\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta y^2$. Segmented electrodes generated larger magnitudes of the activating function in both the axial and radial directions (Figure 4.5) implying that segmentation will increase functional stimulation coverage in both the axial and radial directions. The changes in the spatial distribution of the activating function may influence the selectivity of stimulation.
both for different neural elements (local cells vs. axons of passage) and for neurons lying at different distances from the electrode. Segmented electrodes generated patterns of electric field with greater spatial variation than did a large solid electrode, and it is reasonable to expect that more selective activation to targeted neural elements could be achieved by electrode arrays with greater numbers of more densely spaced, smaller contacts, preferably combined with multiple stimulation channels.

The prototype electrodes that we analyzed differed from present clinical (Medtronic) DBS leads in both their dimensions and material. The larger size of the prototype electrodes made possible accurate segmenting of the electrodes, while with the clinical electrodes it would be quite challenging to perform segmentation with high precision. The aspect ratios of the prototype electrodes investigated \textit{in vitro} (contact diameter/contact length = 0.95 cm/1 cm = 0.95) and in the model (contact diameter/contact length = 1 cm/1 cm = 1.0) were similar to the aspect ratio of the clinical electrodes (contact diameter/contact length = 1.27 mm/1.5 mm = 0.85). The effects of segmentation on the current density distributions, neural activation functions, and impedance apply qualitatively to any cylindrical lead, and thus the impact of the geometric changes investigated with the prototype electrodes are expected to scale and apply to the clinical electrodes. Secondly, the use of stainless steel, as opposed to platinum-iridium (Pt-Ir), dramatically reduced the cost of materials. Although the clinically used DBS electrode is made of Pt-Ir, the impedance properties of stainless steel and Pt-Ir are similar because both metals passivate to form oxides on their surface [93].
4.5.2. Validation of results

Current density and potential distributions were quantified numerically but not experimentally in this study. It is difficult to measure current density distributions experimentally within an aqueous environment because of the divergence of current as it leaves the electrode surface. Suesserman et al. proposed a modified method that determined the potential difference by subtracting spatially separated single-wire measurements of the potential. However, the measurement required highly precise spatial control over placement of the measuring microelectrode, and the presence of the measuring microelectrode in the tank induced distortion of the potential distribution [88]. Thus numerical solution using the finite element method provided a simple alternative approach to study the current density distributions on segmented electrodes.

Electrode impedance was quantified experimentally but not numerically in this study. Laplace’s equation describes the potential variation in electrolytic solutions with uniform concentrations. To apply Laplace’s equation to the entire medium, the concentration gradient at the electrolyte side of the electrode-electrolyte interface and the electrode surface overpotential were neglected in the numerical model. This implies that the potential in the solution adjacent to the electrode was the same as the potential on the electrode surface, while in reality there is a potential drop across the interface. Thus the electrode interface impedance could not be calculated numerically in the modeling study. In the case of negligible concentration overpotential and surface overpotential, the current distribution is the so-called primary current distribution [94]. The primary current distribution results when the electrode double layer approaches a short circuit, which
occurs at frequencies high enough to shunt a majority of the current through the double-layer capacitance. Hence the numerically calculated current density distribution represents the electrical properties of the interface at high frequencies. The total current delivered from the electrode can thus be used as an index of the electrode impedance at high frequencies. Although the electrode impedance could not be quantified in modeling study as the model did not include a representation of the electrode-tissue interface impedance, a relative comparison can be made between the electrode impedance measured \textit{in vitro} and the total current delivered by the electrode calculated from the model. At low frequencies, reactive component cannot be neglected and reaction kinetics takes effect in the electrode-electrolyte interface. In the limiting case, when electrochemical reaction and diffusion kinetics dominate charge transfer across the electrode surface, secondary current distribution results [94], and this distribution was not taken into account in our numerical models.

Although there was clear qualitative agreement between the experimental and numerical results, there were several differences between the studies that limit quantitative comparison. Firstly, current density profiles, but not electrode impedances, were calculated numerically because the electrode-electrolyte interface was not included in the finite element model. The numerically calculated current density profile resulted from the primary current distribution, which could only be used to explain the experimental results of electrode impedance at high frequencies when the electrode double layer behaved as a short circuit. Secondly, different boundary conditions were employed in the experimental and numerical studies. Charge-balanced regulated
sinusoidal currents were applied to the experimental samples, and the high conductivity of the metal ensured that the samples were equipotential over their surfaces. To replicate this in the model required using a constant voltage boundary condition, which ensured equipotentiality and allowed for non-uniform current density over the electrode contacts. To employ a current boundary condition in the model would have required specification a priori of the distribution of current density. Thirdly, an AC source over a range of frequencies was used in the experimental study, while in the simulation study a DC voltage source was applied to the electrodes. Using a DC voltage source ensured that the current density distribution over electrode surface did not change in time and was determined only by the electrode geometry. Even with these differences, the effects of electrode geometry on impedance in the experimental study followed the same trends as the effects of electrode geometry on current density profiles in the numerical study. Further, the current density profiles available in the numerical study, but not the experimental study, enabled explanation of the effects of geometrical changes on electrode impedance.

4.6. Conclusions

The geometrical characteristics of segmented electrodes changed electrode impedance by altering the distribution of current density over the electrode surface. Edge effects, reflected as an increase in current density at the perimeter of the electrodes, played a critical role in determining the current density distributions and thus the impedance of the electrodes. For segmented electrode designs, conductive segments that
occupied the central portions of the electrode had less pronounced edge effects as compared to segments at the ends of the electrode due to the interaction of currents delivered by the adjacent segments. The impedance measurements indicated that for a fixed electrode area, increasing the number of segments (edges) resulted in a decrease in impedance over a single solid electrode, but for electrodes with a fixed length, the impedance of the single solid electrode was lowest. Segmented electrodes generated larger magnitudes of the second spatial difference of the extracellular potentials, and thus required lower stimulation intensities to achieve the same level of neuronal activation as solid electrodes.
Chapter 5: Analysis of High-Perimeter Planar Electrodes for Efficient Neural Stimulation

5.1. Abstract

Planar electrodes are used in epidural spinal cord stimulation for treatment of pain and in epidural cortical stimulation for experimental treatment of epilepsy, pain, and movement disorders. Electrode geometry is one approach to increase the efficiency of neural stimulation and reduce the power required to produce the level of activation required for clinical efficiency. Reduced power consumption will extend the battery life of implantable pulse generators, and thus reduce both cost and risk associated with generator replacement surgeries. Our hypothesis was that electrode geometries that increased the variation of current density on the electrode surface would increase stimulation efficiency. High perimeter planar disk electrodes were designed with sinuous (serpentine) variation in the perimeter. Prototypes were fabricated that had equal surface areas but perimeters equal to 2, 3 or 4 times the perimeter of a conventional circular disk electrode. The interface impedance of high-perimeter prototype electrodes measured in vitro did not differ significantly from the impedance of the circular electrode measured over a wide range of sinusoidal frequencies, but the interface impedance of the high-perimeter prototypes calculated from transient pulse responses increased by up to 50% as compared to that of the circular electrode. Finite element models of the electrodes and the surrounding volume conductor indicated that the variation of current density on the electrode surface was significantly higher on the high-perimeter electrodes. We
quantified activation of 100 model axons randomly positioned around the electrodes with 100 μs cathodic stimuli. Input-output curves of the percentage of axons activated as a function of stimulation intensity indicated that the stimulation efficiency was dependent on the distance of the axons from the electrode. The high-perimeter planar electrodes were more efficient at activating axons a certain distance away from the electrode surface. These results demonstrate the feasibility of increasing stimulation efficiency through the design of novel electrode geometries.

5.2. Introduction

Most implanted pulse generators (IPGs) used for neural stimulation are powered with primary cell batteries, and the IPG requires surgical replacement when the battery is depleted. Electrode design is one means to reduce the power requirements and extend the lifetime of existing IPGs, thus reducing both cost and risk associated with repeated IPG replacement surgeries. As well, reduced power demands could enable the use of smaller batteries, thereby reducing the size of the IPGs. Previous efforts to increase the efficiency of stimulating electrodes focused on new materials that decreased electrode impedance and/or stimulation thresholds. Oxide coatings including platinized platinum and iridium oxide reduce interface impedance and increase charge capacity for stimulation [13, 38], but charge capacity during rapid pulsing is limited by the rate of electron and ion transport [58]. Similarly, high surface area porous electrodes reduce interface impedance and pacing thresholds [40], but diffusion limitations prevent accessing the full surface area during short duration stimulation pulses [38, 41]. Steroid-eluting electrodes reduce
stimulation thresholds by suppression of inflammation [42] that increases the impedance of implanted electrodes from tissue encapsulation [43, 44]. We propose to increase the efficiency of stimulation by alterations of the electrode geometry. The potential advantages of this approach are that novel electrode designs can be implemented with existing manufacturing techniques and will not require the exhaustive biocompatibility testing required for new materials. Further, this approach could be applied in concert with new materials to maximize the efficiency of stimulation.

The proposed approach to increase the efficiency of neural excitation by alterations in the electrode geometry is based on the fundamentals of extracellular neural stimulation. Neural excitation by extracellular sources can be qualitatively predicted with the activating function \( f \), which is proportional to the second spatial derivative of the extracellular potential \( V_e \) (i.e., \( f \propto \Delta^2 V_e/\Delta x^2 \)) [45]. The activating function can be re-written in terms of the current density \( J \) and tissue bulk conductivity \( \sigma \) as:

\[
 f_x \propto \frac{\Delta^2 V_e}{\Delta x^2} = \frac{\Delta (\Delta V_e/\Delta x)}{\Delta x} \approx \frac{\Delta (J_x/\sigma)}{\Delta x} = \frac{\Delta J_x}{-\sigma \Delta x}. 
\]  

(5.1)

The activating function in \( x \) direction is proportional to the derivative of current density, \( \Delta J_x/\Delta x \). Therefore, increasing the spatial non-uniformity of the current density increases \( \Delta J_x/\Delta x \), increases \( f_x \), and is expected to increase the efficiency of neural excitation. Our design ideas were motivated by geometries that generate higher variation of current density in the tissue than conventional electrodes.

We propose to increase stimulation efficiency by increasing the electrode perimeter. Increasing the electrode perimeter without changing the electrode area is
expected to increase the non-uniformity of current density on the electrode surface. Increasing the electrode perimeter by segmenting of cylindrical electrodes increased stimulation efficiency [65]. To test further the hypothesis that increasing the electrode perimeter increases stimulation efficiency, we investigated high-perimeter planar disk electrodes with sinuous (serpentine) variation in the electrode perimeter. Planar electrodes offer a simple, low cost test bed to quantify the effects of increased perimeter on stimulating efficiency, and are of interest for applications including epidural spinal cord stimulation for treatment of pain [95, 96] and epidural cortical stimulation for experimental treatment of epilepsy, pain, and movement disorders [97-101].

The power consumed by the electrode and tissue is equal to $i_t^2 \cdot Z_{\text{load}}$, where $i_t$ is the current flowing through the tissue and should be above the threshold current, and $Z_{\text{load}}$ is the load impedance composed of the series combination of the tissue resistance, the interface impedance of the working electrode, and the interface impedance of the return electrode. It is important to determine how both $i_t$ and $Z_{\text{load}}$ are affected by electrode design to determine efficiency. First, the impedances of prototype serpentine-perimeter electrodes were measured in vitro to quantify the effects of increased perimeter on the interface impedance. Second, finite element models were coupled with cable models of a population of neurons to test the hypothesis that increasing the perimeter increases stimulation efficiency by increasing the activating function.
5.3. Methods

5.3.1. Description of electrode geometry

The planar electrode designs included a series of circular disks with radii \((r_0)\) of \(~5\) mm, and serpentine perimeters with different variations in the amplitude \((h)\) and frequency \((n)\) of sinuous variation (i.e., the number of periods around the perimeter) (Figure 5.1(a)). The radius as a function of the angle, \(\theta\), is defined by:

\[
r(\theta) = r_0 + h \sin(n\theta).
\]  

(5.2)

When \(h\) is zero, the electrode has a circular perimeter with a diameter of \(~1\) cm.

Figure 5.1: High-perimeter planar electrodes.
(a) Planar geometry with serpentine perimeter. (b) Test structure (top and side views) with machined metal sample embedded in epoxy. (c) Test sample geometries with same area (78.5 mm\(^2\)) but different perimeters (\(P_o=31.4\) mm, \(2P_o, 3P_o\) and \(4P_o\)).

The surface area of the electrode can be calculated by polar integration:

\[
\text{Area} = \frac{1}{2} \int_0^{2\pi} r(\theta)^2 \, d\theta \\
= \pi r_0^2 + \frac{\pi h^2}{2}
\]  

(5.3)

For each period of the sinusoid, the length of the curve can be calculated by:
The electrode perimeter can be calculated as \( n \) periods of the sinusoid around the perimeter:

\[
\text{Perimeter} = n \times \text{Arclength}. \quad (5.5)
\]

### 5.3.2. Prototype high-perimeter planar electrodes

**Table 5.1: Dimensions of prototype planar high-perimeter electrodes.**

- \( r_0 \): radius of the circular perimeter;
- \( h \): amplitude of sinuous variation;
- \( n \): frequency of sinuous variation (the number of periods around the perimeter);
- Perimeter ratio: ratio of the perimeter of the test sample to the perimeter of the control (sample #6).

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>( r_0 ) (mm)</th>
<th>( h ) (mm)</th>
<th>( n )</th>
<th>Area (mm(^2)) (Actual area)</th>
<th>Perimeter (mm) (Actual Perimeter)</th>
<th>Perimeter ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>4.886</td>
<td>1.500</td>
<td>20</td>
<td>78.5 (77.8)</td>
<td>125.6 (117.6)</td>
<td>400%</td>
</tr>
<tr>
<td>#2</td>
<td>4.893</td>
<td>1.453</td>
<td>15</td>
<td>78.5 (77.4)</td>
<td>94.5 (97.1)</td>
<td>300%</td>
</tr>
<tr>
<td>#3</td>
<td>4.960</td>
<td>0.9077</td>
<td>24</td>
<td>78.5 (76.7)</td>
<td>94.4 (91.4)</td>
<td>300%</td>
</tr>
<tr>
<td>#4</td>
<td>4.914</td>
<td>1.307</td>
<td>10</td>
<td>78.5 (75.7)</td>
<td>62.8 (66.1)</td>
<td>200%</td>
</tr>
<tr>
<td>#5</td>
<td>4.960</td>
<td>0.8730</td>
<td>15</td>
<td>78.5 (75.0)</td>
<td>62.9 (65.5)</td>
<td>200%</td>
</tr>
<tr>
<td>#6</td>
<td>5.000</td>
<td>0</td>
<td>--</td>
<td>78.5 (75.7)</td>
<td>31.4 (32.9)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Design parameters for the prototype electrodes (Table 5.1) were selected such that the effects of perimeter on impedance and stimulation efficiency could be isolated by
including multiple samples with the same area but with different perimeters (Figure 5.1(c)). Further, the same perimeters were achieved through different variations in the amplitude and frequency of the sinuous variation, and thus the effects on impedance and stimulation efficiency of increasing perimeter through different means could be assessed.

The shape of each sample was machined into the last 5 mm of a 5 cm length of 316L stainless steel (SS) rod using electrical discharge machining (EDM). Although clinically used electrodes are more often made of 90% platinum / 10% iridium (Pt/Ir), the use of SS results in a substantial cost savings during this phase of the project. Further, the impedance properties of SS and Pt/Ir are similar because they both passivate to form oxides on their surface [93, 102]. The rod was centered in a plastic sleeve and encapsulated with epoxy filled flush to the shaped end of the rod (Figure 5.1(b)). The shaped face of the rod was cut perpendicular to the length of the rod and ground flush and polished according to ASTM 03-01, Standard Practice for Preparation of Metallographic Specimens [103]. The other end of the rod was tapped for mechanical and electrical connection. Digital micrographs of the faces of the samples are shown in Figure 5.2. The electrode boundaries were traced, and the areas and perimeters of actual samples were calculated using the image processing toolbox of Matlab.
Figure 5.2: Digital micrographs of high-perimeter electrode samples.
Digital micrographs of the face of each sample (samples #1-#6) illustrated in Figure 5.1(c).

5.3.3. *In vitro* measurement of electrode impedance

The three-electrode technique was used to measure electrode impedance *in vitro* with an impedance analyzer (Model 1287 Electrochemical Interface + Model 1252 Frequency Response Analyzer, Solartron Analytical, Hampshire, England). The electrode was placed with its planar surface parallel to the ground in the middle of a 1000 ml beaker of physiological saline (0.9% sodium chloride) at room temperature (T ≈ 20 °C). Regulated sinusoidal currents with a r.m.s. amplitude of 0.1 mA were applied between the test (working) electrode and a return (counter) electrode formed of stainless steel wire spiraling around the wall of the tank at 41 frequencies at equal logarithmic steps between
1 Hz–10 kHz. The potential between the working electrode and a Ag-AgCl reference electrode (Model RE-5B, BAS Inc., West Lafayette, Indiana, USA) was measured with the 1252/1287 system which has an input impedance of $> 10 \, \text{G}\Omega$ in parallel with 50 pF, an amplitude accuracy of 0.2%, and a phase accuracy of 0.2°. The measurement was repeated 6 times for each electrode sample.

For measurement of voltage transients, electrodes were pulsed with regulated current symmetrical biphasic pulses with amplitude of 1 mA and pulse width of 200 µs, delivered between the working electrode and the counter electrode. Voltage transients were measured between the working electrode and the reference electrode with an isolated differential amplifier (Stanford Research SR560: input impedance $> 100 \, \text{M}\Omega$ in parallel with 25 pF, frequency response $\pm 0.5 \, \text{dB}$ to 1 MHz), captured with a digital oscilloscope (1M sample/sec), and transferred to a computer for storage and analysis.

### 5.3.4. Finite element models of high-perimeter planar electrodes

We developed three-dimensional finite element models of planar electrodes adjacent to a semi-infinite homogenous tissue medium (Figure 5.3). The model included an electrode surface with a potential of 1 V, an insulating surface around the electrode, and a homogenous volume conductor representing CNS tissue ($\sigma = 0.2 \, \text{S/m}$ [80]). The tissue adjacent to the electrode was modeled as a cylinder with a diameter of 20 cm and a height of 20 cm and the outer boundaries set to ground ($V = 0$) except for the boundary on the electrode side. The 3D models were implemented in COMSOL Multiphysics (version 3.4, Stockholm, Sweden), and were partitioned into between 32,743 and 34,589
tetrahedral elements. The sizes of the tissue volume and element mesh were set such that doubling the volume of the tissue or reducing the mesh size resulted in < 3% change in both the potentials near the electrode surface and the total current delivered by the electrode, calculated by integrating of the current density over the electrode surface. The conjugate gradient method with preconditioning (algebraic multigrid) was used to solve the model.

Figure 5.3: Geometry of finite element models of planar electrodes. Geometry of the finite element model of a planar electrode (grey) adjacent to a semi-infinite homogenous volume conductor. The tissue medium was modeled as a cylinder 20 cm in diameter and 20 cm in height with a conductivity of 0.2 S/m. The dashed box represents the cross section (range: y: -10–10 mm, z: 0–20 mm) through which the population of 100 model axons passed, oriented in the x direction.
5.3.5. Computer simulation of neuronal activation

We quantified the stimulation efficiency of different electrode geometries using a population of modeled mammalian myelinated axons. The geometrical parameters of the axon model are summarized in Table 5.2 and all electrical parameters were as in [104]. The models were implemented in NEURON version 6.1 [105] and solved using backward Euler implicit integration with a time step of 0.001 ms. The threshold voltages were calculated with a binary search algorithm with a tolerance of 1 µV. We distributed 100 axons parallel to the surface of planar electrodes (oriented in the $x$ direction) randomly positioned inside a 20 mm by 20 mm box (dashed box in Figure 5.3). The extracellular potential at each node of Ranvier was determined by quadratic spline interpolation from the potentials solved by the finite element models. Input-output (recruitment) curves of the percentage of activated axons as a function of stimulus amplitude were generated by applying a monophasic cathodic voltage pulse with a pulse width of 100 µs to the planar electrode. Input-output curves of the percentage of activated axons as a function of the power consumption were also generated by multiplying the threshold voltage by the delivered current at the threshold voltage. The second spatial difference of the extracellular voltages ($\nabla^2 f(x)$) was calculated in the region around the electrode using the inter-nodal length of the myelinated model axons as the space step, $\Delta x$ (= 1.2 mm, as in Table 5.2) to assist in interpretation of the results.
Table 5.2: Geometrical parameters of the axon model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axon diameter</td>
<td>12 μm</td>
</tr>
<tr>
<td>Inter-nodal length</td>
<td>1.2 mm</td>
</tr>
<tr>
<td>Node length</td>
<td>1.5 μm</td>
</tr>
<tr>
<td>Node diameter</td>
<td>7.2 μm</td>
</tr>
<tr>
<td>Number of nodes</td>
<td>32</td>
</tr>
</tbody>
</table>

5.4. Results

We quantified both electrode impedance and stimulation threshold to determine the efficiency of high-perimeter planar electrodes. We measured the interface impedance of the electrode prototypes in vitro, calculated the tissue resistance using finite element models, and compared threshold voltage and power consumption by calculating input-output curves of activation of a population of model neurons. We primarily illustrate the results of electrode samples #1 and #6, as sample #1 represents the extreme case of high perimeter among the samples and sample #6 acts as the control.

5.4.1. Load impedance

The load impedance is composed of the series combination of the interface impedance of the stimulating (working) electrode and the tissue resistance between the electrode and the return (the ground at infinity). The impedance spectra (amplitude and phase) of electrode samples #1 and #6 are shown in Figure 5.4. The series access resistance $R_s$ between the working electrode and the reference electrode, determined from
the asymptotic high-frequency impedance, was 34.8 Ω for sample #1, and 37.6 Ω for sample #6. The interface impedance was calculated by subtracting $R_s$ from the measured impedance. Two-way ANOVA indicated that both electrode and frequency had significant effects on interface impedance ($p < 0.001$). However, post-hoc paired comparisons using Fisher’s PLSD method showed there were no significant differences ($p > 0.05$) between the impedances of sample #1 and sample #6 at most (30 out of 41) of the measured frequencies. Similarly, no significant differences were found between the impedances of sample #1 and samples #2-#5 at most (33 to 41 out of 41) of the measured frequencies.

![Figure 5.4: Impedance spectra of the electrode samples #1 and #6.](image)

(a) Magnitude spectra. (b) Phase spectra. The impedance spectra were measured in vitro in saline solution with sinusoidal currents with a r.m.s. amplitude of 0.1 mA at 41 frequencies evenly distributed on a log scale from 1 Hz to 10 kHz.

The spreading tissue resistance between the electrode and the ground was calculated with the finite element model by dividing the electrode voltage (1 V) by the total current delivered by each electrode (Figure 5.5(a)). The spreading tissue resistance decreased with increasing perimeter of the planar electrodes, and at the same perimeter
(#2 and #3, #4 and #5) the electrodes with large amplitude of the sinuous variation exhibited lower tissue resistance than the electrodes with more periods around the perimeter (Figure 5.5(a)).

The voltage responses to symmetrical biphasic square current pulses with amplitudes of 1 mA and pulse widths of 200 μs for electrode sample #1 and #6 are shown in Figure 5.5(b). The series access resistance $R_s$ caused the instantaneous voltage increase upon the onset of the pulse and was $\sim$30 Ω. The instantaneous interface impedance ($Z_e$) at the end of 200 μs pulse was $\sim$10 Ω for sample #1, $\sim$15 Ω for sample #6, and $\sim$12-15 Ω for samples #2-#5, over one order of magnitude smaller than the spreading tissue resistances (> 200 Ω), indicating that most of the voltage drop and power consumption occurred in the tissue and not across the electrode-tissue interface under clinically-relevant pulsing conditions.

**Figure 5.5: Tissue resistances and voltage responses to square currents.**
(a) The spreading tissue resistances between the electrode prototypes and the ground. (b) Voltage responses to symmetrical biphasic square currents with amplitudes of 1 mA and pulse widths of 200 μs for electrode samples #1 and #6.
5.4.2. Distributions of current density on the electrode surface

The current density distributions on the surface of electrodes #1 and #6 when a constant voltage of 1V was applied are shown in Figure 5.6. Current density increased towards the perimeter of the electrodes. For electrode #1, current density was highly non-uniform along the serpentine perimeter, and was highest at the crests and lowest in the troughs. For electrode #6, current density was uniform along the circular perimeter.

![Figure 5.6: Distributions of current density on planar electrodes.](image)

Distributions of current density on the surface of electrode #1 (a) and #6 (b) when a constant voltage of 1V was applied. The white dashed line in (a) indicates the location beneath which the activating function profiles in Figure 5.9 were calculated.

5.4.3. Input-output curves of activation of model axons

A population of 100 model axons parallel to the surface of the planar electrodes and randomly distributed within 20 mm of the electrode surface was used to calculate input-output curves of the percentages of activated axons as a function of stimulus amplitude (Figure 5.7(a)) or stimulus power (Figure 5.7(b)). Electrode #1 decreased the average threshold voltage ($V_t$) by 10.1 ± 0.6% ($n = 5$ differently randomized populations...
of model axons), and decreased the average power consumption by 9.5 ± 1.2% (n = 5), as compared to electrode #6. Electrode #6 activated the first 25 ± 4 (n = 5) axons with lower thresholds, while electrode #1 activated the rest 75 ± 4 (n = 5) axons with lower thresholds (Figure 5.7(a) inset), suggesting that the serpentine perimeter resulted in more efficient stimulation of axons positioned further from the electrode.

![Figure 5.7: Input-output curves of activation of model axons.](image)

(a) Percent of activated axons as a function of stimulus voltage for electrode #1 and electrode #6. Electrode #1 decreased the average threshold voltage by 10.1% as compared to electrode #6. The inset shows the axons that were activated by electrode #1 with lower thresholds (grey circles) and those activated by electrode #6 with lower thresholds (black circles). (b) Percent of activated axons as a function of power consumption for electrode #1 and electrode #6. Electrode #1 decreased the average power consumption by 9.5% as compared to electrode #6. The inset shows the axons that were activated by electrode #1 with lower power requirement (grey circles) and those activated by electrode #6 with lower power requirement (black circles).

The decreases in average threshold voltage and average power consumption of the serpentine-perimeter designs (samples #2-#5) as compared to the circular-perimeter electrode (#6) are summarized in Figure 5.8. Increasing the electrode perimeter reduced threshold voltage as compared to the circular-perimeter electrode. However, increasing the electrode perimeter also increased the total current delivered to the tissue at the same
electrode voltage, and the decrease in power consumption as compared to the circular-perimeter electrode did not increase with increasing the electrode perimeter. Between the electrodes with the same perimeter (#2 and #3, #4 and #5), the electrodes with more periods but smaller amplitude of sinuous variation exhibited larger reductions in power consumption.

**Figure 5.8: Reductions in threshold voltage and power consumption.**
Reductions in threshold voltage and power consumption with the serpentine-perimeter electrodes (#1-#5) as compared to the circular-perimeter electrode (#6). The means and standard deviations were calculated across 5 randomized populations of model axons. * indicates significant difference (p < 0.05) as compared to electrode #1. # indicates significant difference (p < 0.05) between electrodes with the same perimeter. The p-values were calculated with ANOVA post-hoc paired comparisons using Fisher’s PLSD test.
5.4.4. Distribution of the activating function

Figure 5.9: Second spatial difference of extracellular potentials.
Second spatial difference of extracellular potential ($\Delta^2 V_e/\Delta x^2$) was calculated on a line parallel to the electrode surface at various electrode-to-axon distances (0.1 mm (a), 1 mm (b), 10 mm (c) and 20 mm (d)) generated by electrodes #1 and #6. The second difference of potential was calculated using a spatial step equal to the inter-nodal length of the model axons ($\Delta x = 1.2$ mm). The projection of the line along which the above profiles were calculated is illustrated by the white dashed line in Figure 5.6(a).

Profiles of $\Delta^2 V_e/\Delta x^2$ were plotted along a line parallel to the electrode surface at four electrode-to-axon distances (Figure 5.9). The circular-perimeter electrode (#6) generated higher maximum activating functions at electrode-to-axon distances of 0.1 mm (Figure 5.9(a)) and 1 mm (Figure 5.9(b)), while the serpentine-perimeter electrode (#1)
generated higher maximum activating functions at electrode-to-axon distances of 10 mm (Figure 5.9(c)) and 20 mm (Figure 5.9(d)). This corroborates the results suggested by the input-output curves that the serpentine perimeter resulted in more efficient stimulation of axons positioned further from the electrode.

5.5. Discussion

The objective of this study was to increase the stimulation efficiency of planar disk electrodes through novel high-perimeter designs. Increases in stimulation efficiency will reduce the power requirements of IPGs, thereby increasing device lifetime. We fabricated prototypes of high-perimeter planar electrodes that had the same surface area, but had perimeters 2, 3, or 4 times larger than a planar electrode with a circular perimeter. The interface impedance of the prototypes was measured in vitro, and indicated that the high-perimeter electrode impedance did not differ significantly from the impedance of the circular electrode across a wide range of sinusoidal frequencies, but the interface impedance of the high-perimeter prototypes calculated with transient pulse responses increased by up to 50% as compared to that of the circular electrode. Finite element models were used to calculate the potentials in a modeled tissue medium, and the potentials were coupled with a population of model axons to quantify stimulating efficiency. The planar electrodes with serpentine perimeters were more efficient in activating neurons further away from the electrode surface and reduced power consumption by ~10%.
5.5.1. Synthesis of results

The input-output curves of activation of axons as a function of stimulation intensity indicated that the stimulation efficiency was dependent on the distance of the axons from the electrode. The serpentine perimeter resulted in more efficient stimulation of axons positioned further from the electrode. The average power reduction of ~10% was based on our choice of the region for the randomized distribution of axons and would increase if the axons were positioned further from the electrode. As illustrated in Figure 5.7, the input-output curves of activation of axons as a function of stimulus voltage for electrodes #1 and #6 crossed at ~25% activation, and the input-output curves of activation of axons as a function of power consumption for electrodes #1 and #6 crossed at ~50% activation. This suggests that the serpentine perimeter resulted in smaller threshold current for axons positioned even further from the electrode. Indeed, when the activation of axons was plotted as a function of stimulus current, the crossing of the curves for electrodes #1 and #6 occurred at ~80% activation.

According to Ohm’s law, the calculation of power consumption using $V_t \times i_t$ is equivalent to $i_t^2 \times Z_{load}$. The interface impedance ($Z_e$) of the electrode was not included in the model, thus $Z_{load}$ only included the spreading tissue resistance ($R_{tissue}$) from the electrode surface to infinity (the theoretic ground). This is a fair approximation because $R_{tissue}$ was over one order of magnitude larger than $Z_e$ during clinically-relevant stimulus pulses (Figure 5.5). Current follows the path of least resistance, and in a homogeneous medium the path of least resistance is the shortest path. This resulted in different spreading resistance of tissue for various electrode geometries. The serpentine perimeter
resulted in smaller spreading tissue resistance, and this contributed to the power reduction of the serpentine-perimeter electrode, regardless of the electrode-to-axon distance.

The dependence of power reduction on electrode-to-axon distance was a result of the dependence of the change of the threshold current/voltage on the electrode-to-axon distance. Our hypothesis was that serpentine perimeter would increase the variation of current density on the electrode surface and generate larger activating functions for surrounding neurons, thereby increasing stimulation efficiency. Consistent with the input-output curves, the profiles of activating function along parallel axons ($\Delta^2 V_e / \Delta x^2$) indicated that the serpentine-perimeter electrode generated higher maximum activating functions only for axons positioned further from the electrode (Figure 5.8). This can be explained by the fact that the current flow out of the electrode surface is in the normal direction ($z$ direction). For parallel axons (in $x$ direction), the non-uniformity of current density on the electrode surface created by the serpentine perimeter can only be translated into the higher variation of current density along the direction of the axons further from the electrode surface where the current has diverged with a stronger parallel component.

The prototype electrodes that we analyzed were larger than present clinical planar electrodes for epidural spinal cord stimulation for treatment of pain. For example, the circular planar electrodes designed by Medtronic Inc. (Models 3587A, 3986A, and 3987A) have a diameter of 4.1 mm, thus are ~6 times smaller in area than the prototypes. The larger size of the prototype electrodes enabled fabrication of serpentine perimeter with high precision. The effects of serpentine perimeter on the current density distributions and activating functions apply qualitatively to planar electrodes of different
sizes, and thus the impact of the geometric changes analyzed with the prototype electrodes are expected to scale and apply to the clinical electrodes. However, a smaller electrode has a higher interface impedance. If the interface is modeled as double layer capacitance and Faradaic resistance in parallel, the interface impedance is inversely proportional to the electrode area. The spreading resistance of a circular disk electrode adjacent to a semiconductor is inversely proportional to the diameter of the circular disk (i.e., the square root of electrode area) [106, 107]. Therefore, the interface impedance will increase at a higher rate with the decrease of electrode size than the spreading tissue resistance. This will result in higher proportion of the power consumed by the electrode-tissue interface, and the increase of interface impedance of the serpentine electrode as compared to the circular electrode (Figure 5.5(b)) may become critical in determining the power efficiency of stimulation.

5.5.2. Estimation of tissue damage

The serpentine perimeter increased the current density on the electrode surface, and this may increase the propensity for tissue damage. A quantitative model of neural damage was used to analyze the effects of increasing electrode perimeter on tissue damage. Charge per phase and charge density per phase are cofactors in the generation of neural damage [19, 47], and this relationship is described by:

\[
\log \left( \frac{Q}{A} \right) = k - \log (Q),
\]

where \(Q\) is the charge per phase, \(A\) is the electrode area, and \(k\) is a constant derived from data to define the boundary between stimulus parameters that produced tissue damage.
and those that did not (Figure 5.10) [48]. The proposed limit for non-damaging stimulation levels using circular disk electrodes was $k = 1.5$, but this value was estimated using geometrical (average) charge density over the electrode surface [48].

As current density was higher around the perimeter of the electrode, and this non-uniformity was more pronounced for electrodes with serpentine edge, we calculated the average current density ($J_{avg}$) and maximum current density ($J_{max}$, average over the 1% of the electrode area with the highest current density) on the surface of electrodes #1 and #6. The ratio $J_{max}/J_{avg}$ is the same as the ratio of maximum charge density ($Q/A)_max$ to average charge densities ($Q/A)_avg$. The increases in $k$ ($\Delta k$) were calculated when ($Q/A)_max$, instead of ($Q/A)_avg$, was considered (Table 5.3). Replacing ($Q/A)_avg$ with ($Q/A)_max$ in Eq. 5.6 for a circular disk electrode will give an adjusted $k$ value ($k'$ in Figure 5.10) that is transferable to other electrode geometries when maximum charge density is considered. Assuming that $k$ is 1.5 estimated with the average charge density of the circular disk electrode (#6), Table 5.3 suggests that the adjusted $k$ ($k'$) is 1.85 when the maximum charge density is considered. Calculated from $k'$, $k$ for electrode #1 is 1.05 when the average charge density is considered, resulting in a smaller region of non-damaging stimulus parameters (Figure 5.10). This suggests that at the same stimulus parameters, the planar electrode with serpentine perimeter has a higher propensity of inducing local tissue damage than the planar electrode with circular perimeter.
Table 5.3: Increase of $k$ values ($\Delta k$) when applying maximum charge density instead of average charge density for planar electrodes.

<table>
<thead>
<tr>
<th>Electrode</th>
<th>$J_{avg}$ (A/m²)</th>
<th>$J_{max}$ (A/m²)</th>
<th>$\frac{(Q/A)<em>{max}}{(Q/A)</em>{avg}}$</th>
<th>$\Delta k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>61.6</td>
<td>388</td>
<td>6.29</td>
<td>0.80</td>
</tr>
<tr>
<td>#6</td>
<td>53.5</td>
<td>119</td>
<td>2.23</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Figure 5.10: Non-damaging limits of planar electrodes modified for maximum charge density.

Relationship between charge per phase ($Q$), charge density per phase ($Q/A$), and stimulation induced tissue damage. The $k$ value defines the boundary between stimulus parameters that produce tissue damage and those that do not, and $k = 1.5$ was estimated using geometrical charge density of circular disk (planar) electrodes. In the modified model where the ordinate represents maximum charge density, the new $k$ value ($k'$) was 1.85. Applying $k'$ to the serpentine-perimeter planar electrode (#1) yielded $k$ equal to 1.05 when geometrical charge density was considered.

5.5.3. Model limitations

Finite element models of electrodes and the surrounding volume conductor were coupled with compartmental cable models of a population of neurons to study the effects
of increasing the perimeter of planar electrodes on stimulation efficiency. The electrical potentials were calculated based on the assumption that the tissue medium was homogenous and isotropic. Although the true biological volume conductor is inhomogeneous and anisotropic, a recent study of deep brain stimulation indicated that a homogenous isotropic model provided predictions of voltage distributions remarkably similar to a more detailed inhomogenous and anisotropic model [108]. Further, the current study did not focus on the absolute stimulation efficiency of an electrode, but rather the comparative stimulation efficiency between electrodes with various geometries, and therefore the simplified model was appropriate.

The population of model neurons had specific orientations (parallel to the electrodes) and did not include cell bodies, dendrites, or synaptic inputs. Although both experimental studies [109, 110] and computational models [74] indicate that during extracellular stimulation, action potential initiation occurs in the axon, the impact of changes in geometry on the efficiency of activating other neural elements may differ from those for axons. Investigations of high-perimeter electrode designs for specific applications, such as epidural spinal cord stimulation or epidural cortical stimulation, should consider using compartment cable models with more specified orientations, more detailed membrane dynamics, and more accurate morphology representative of the target neurons.
5.5.4. Summary

The objective of this study was to increase the stimulation efficiency of planar disk electrode through novel high-perimeter designs. The combined finite element model of potentials and cable models of axonal excitation permitted quantitative estimations of the stimulation efficiency of various high-perimeter planar electrodes. The proposed high-perimeter planar electrodes reduced power consumption by ~ 10%, and the amount of power saving was dependent on the orientation of the axons and the distance of the axons from the electrode. These results demonstrate the feasibility of increasing stimulation efficiency through the design of novel electrode geometries. This approach will enable the use of established materials to reduce power requirement of implantable neural stimulators, and can also be applied in concert with the development of new materials for more efficient neural stimulation.
Chapter 6: Analysis of High-Perimeter Cylindrical Electrode Designs for Deep Brain Stimulation

6.1. Abstract

Deep brain stimulators are powered with primary cell batteries and require surgical replacement when they are depleted. We sought to decrease power consumption, and thereby increase device lifetime by increasing neuronal stimulating efficiency with novel electrode designs. Our hypothesis was that high-perimeter electrodes that increase the variation of current density on their surface will generate larger activating functions for surrounding neurons, hence increasing stimulation efficiency. We implemented finite element models of a cylindrical DBS electrode with conventional circular perimeters and cylindrical electrodes with segmented contacts and serpentine perimeters 2, 4 or 8 times as large as that of the conventional electrode. The high-perimeter electrodes significantly increased the variation of current density on the electrode surface. We randomly positioned a population of 100 model axons around the electrodes and quantified neural activation with 100 μs cathodic stimuli. Input-output curves of percentage axons activated as a function of stimulation intensity indicate that reductions in stimulation thresholds with high-perimeter designs were dependent on the orientation of the fibers, the diameter of the fibers, and the distance of fibers from the electrode. High-perimeter electrodes reduced stimulation thresholds more for axons perpendicular to the electrode than for axons parallel to the electrode. With proper selection of geometrical parameters, the novel segmented cylindrical electrode with serpentine perimeters decreased power
consumption by ~20% for axons parallel to the electrode and ~35% for axons perpendicular to the electrode at DBS relevant fiber diameters and distances. Reduced power consumption achieved with these designs will reduce the costs and risks associated with surgeries to replace depleted stimulators.

6.2. Introduction

Deep brain stimulation (DBS) is an FDA-approved, clinically effective treatment for symptoms of essential tremor, Parkinson’s disease and dystonia, and shows promise in the treatment of other disorders including epilepsy, obsessive-compulsive disorder and depression. Little effort has been devoted to the design of DBS electrodes, and the original electrode geometry remains unchanged since DBS was first approved by FDA for the treatment of essential tremor in 1995. Electrode design is one means to reduce the power requirements of implantable neural stimulators. Deep brain stimulators are powered with primary cell batteries and require surgical replacement when they are depleted. The median life span of the batteries was less than 4 years [30, 31] and in applications requiring high charge injection it may last less than 1 year [32]. IPG end-of-life led to significant worsening of the symptoms of Parkinson’s disease that may cause adverse events to patients [33]. Surgical replacement is expensive and carries substantial risk. For example, the complication rate is three times higher for replacement of cardiac pacemakers than for original device placement [34], and replacement of implanted defibrillators has an 8.1% complication rate [35]. Rechargeable batteries, which are often used for devices that require high power for short times, have not yet displaced primary
cells in deep brain stimulators that require full-time stimulation to function. A reduction in power consumption will prolong battery life and/or reduce the size of implant package. To date, efforts to prolong implant lifetime have primarily focused on battery technology. We propose to reduce power consumption and thus increase implant lifetimes by alterations in the electrode geometry.

The proposed approach to increase the efficiency of neural excitation by alterations in the electrode geometry is based on the fundamentals of extracellular neural stimulation. Neural excitation by extracellular sources can be qualitatively predicted with the activating function \((f)\), which is proportional to the second spatial derivative of the extracellular potential \((V_e)\) (i.e., the activating function, \(f_x \propto \Delta^2 V_e / \Delta x^2\)) \([45]\). Our design ideas were motivated by geometries that generate larger activating function in the tissue than conventional DBS electrodes. The activating function can be re-written in terms of the current density \(J\) and tissue bulk conductivity \(\sigma\) as:

\[
f_x \propto \frac{\Delta^2 V_e}{\Delta x^2} = \frac{\Delta (\frac{\Delta V_e}{\Delta x})}{\Delta x} \approx \frac{\Delta (\frac{J_x}{\sigma})}{\Delta x} = \frac{\Delta J_x}{\sigma \Delta x} . \quad (6.1)
\]

This indicates that the activating function in the \(x\) direction is proportional to the derivative of current density, \(\Delta J_x / \Delta x\). Our hypothesis is that electrode geometries that increase the variation of current density over the electrode surface will generate larger activating function for surrounding neurons, thereby decreasing thresholds and increasing neuronal stimulating efficiency. The objective of this project was to design novel high-perimeter cylindrical electrodes intended to increase the efficiency of deep brain stimulation.
Based on our previous work, which demonstrated that increasing electrode perimeter by segmenting increased the magnitude of the activating function [65], we designed prototype cylindrical electrodes with high-perimeters achieved by using a serpentine edge and segmentation. Electrical finite element models were combined with cable models of a population of neurons to test the hypothesis that increasing the electrode perimeter increased stimulation efficiency. Our proposed high-perimeter electrode decreased power consumption by ~20% for axons parallel to the electrode and ~35% for axons perpendicular to the electrode at DBS-relevant fiber diameters and distances.

6.3. Methods

6.3.1. Serpentine cylindrical electrode designs

The prototypes included an electrode with circular perimeter \( h = 0 \); electrode #1) and 6 electrodes with serpentine perimeters (electrodes #2-#7) with different amplitudes \( h \) and frequencies \( n \) of sinuous variation (i.e., the number of periods around the perimeter), as well as different numbers of segments (Figure 6.1). The distance between the center and edge of the electrode, as a function of the angle, \( \theta \) is defined by

\[
L(\theta) = L_0 + h \sin(n\theta),
\]

(6.2)

where \( 2L_0 \) is the contact length, \( 2h \) is the peak-to-peak amplitude of the sinuous variation, and \( n \) is the number of complete periods around the perimeter (Figure 6.1(a)). All electrodes had a diameter \( 2R_0 \) of 1.27 mm, consistent with current clinical electrodes used for DBS.
Figure 6.1: High-perimeter cylindrical electrodes.
(a) “Side” views showing the geometries of cylindrical electrodes with circular (top) and serpentine (bottom) edges. $2L_0$ is the contact length, $2R_0$ is the electrode diameter, and $2h$ is the peak-to-peak amplitude of the sinusoidal edge. (b) Prototype electrode geometries with same electrode diameter ($2R_0=1.27\text{mm}$), but different number of segments (1 or 2) and different perimeters (Table 6.1). All electrodes have the same total length ($2L_0=1.5\text{mm}$), except for electrode #7, which had a tip-to-tip length of 1.5mm.

The area of the serpentine cylindrical electrodes is

$$\text{Area} = 4\pi R_0 L_0, \quad (6.3)$$

and is dependent on the diameter ($2R_0$) and length ($2L_0$) of the electrode contact, but not on either the amplitude ($h$) of the sinuous variation or the number of periods around the perimeter ($n$). The perimeter for a single-segmented electrode can be calculated from

$$\text{Perimeter} = 2n \int_0^{\frac{2\pi R_0}{n}} \sqrt{1 + \left(\frac{dL(\theta)}{d\theta}\right)^2} \, d\theta$$

$$= 2n \int_0^{\frac{2\pi R_0}{n}} \sqrt{1 + n^2 h^2 \cos^2(n\theta)} \, d\theta. \quad (6.4)$$
The parameters for the prototypes (Table 6.1) were selected to study the effects of perimeter on stimulation efficiency could be distinguished by including multiple designs with the same area but with different perimeters (Figure 6.1(b)). Further, the same perimeters were achieved through different variations of the amplitude of sinuous variation, the frequency of sinuous variation, or segmentation and thus the effects on stimulation efficiency of increasing perimeter through different means could be assessed.

**Table 6.1: Dimensions of prototype cylindrical high-perimeter electrodes.**
h: amplitude of sinuous variation; n: frequency of sinuous variation (the number of periods around the perimeter); Area ratio: ratio of the area of the prototype to the area of the control (prototype #1); Perimeter ratio: ratio of the perimeter of the prototype to the perimeter of the control (prototype #1).

<table>
<thead>
<tr>
<th>Prototype ID</th>
<th>Number of segments</th>
<th>Segment length (mm)</th>
<th>h (mm)</th>
<th>n</th>
<th>Area (mm²)</th>
<th>Area ratio</th>
<th>Perimeter (mm)</th>
<th>Perimeter ratio</th>
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<td>--</td>
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<td>100%</td>
<td>7.980</td>
<td>100%</td>
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<tr>
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<td>0.3303</td>
<td>5</td>
<td>5.985</td>
<td>100%</td>
<td>15.96</td>
<td>200%</td>
</tr>
<tr>
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<td>1.5</td>
<td>0.1651</td>
<td>10</td>
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<td>100%</td>
<td>15.96</td>
<td>200%</td>
</tr>
<tr>
<td>#4</td>
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<td>1.5</td>
<td>0.7590</td>
<td>5</td>
<td>5.985</td>
<td>100%</td>
<td>31.92</td>
<td>400%</td>
</tr>
<tr>
<td>#5</td>
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<td>1.5</td>
<td>0.3795</td>
<td>10</td>
<td>5.985</td>
<td>100%</td>
<td>31.92</td>
<td>400%</td>
</tr>
<tr>
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<td>63.84</td>
<td>800%</td>
</tr>
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<td>0.3795</td>
<td>10</td>
<td>2.957</td>
<td>49.4%</td>
<td>31.92</td>
<td>400%</td>
</tr>
</tbody>
</table>
6.3.2. Computer-based simulation of neuronal stimulation

We used computational models to quantify the efficiency of neural excitation of prototype high-perimeter cylindrical electrodes. The potentials generated in a modeled tissue medium were calculated using the finite element method. The potentials were coupled to a population of model myelinated nerve fibers to calculate input-output curves of the proportion of nerve fibers activated as a function of the stimulation magnitude and stimulation power. Three dimensional finite element models of cylindrical electrodes positioned in a homogenous isotropic tissue medium were implemented in COMSOL Multiphysics (version 3.4, Stockholm, Sweden) (Figure 6.2(a)). The model included an electrode surface with a potential of 1 V (Dirichlet boundary condition), surfaces of the insulating shafts on both sides of the electrode (Neumann boundary condition), and a homogenous volume conductor representative of CNS tissue (σ = 0.2 S/m [80]). The tissue medium was modeled as a box with the side length of 30 cm and all the outer boundaries set to ground (V = 0). The sizes of the tissue volume and element mesh were set such that doubling the volume of the tissue or reducing the mesh size resulted in <3% change in the total current delivered by the electrode. The total current delivered by the electrode at 1 V was calculated by integrating of the current density along the electrode surface.

The 3D surface of the electrode (hollow inside) was constructed of 90 thin rectangles (Figure 6.2(b)). The number of rectangles chosen to represent the surface of the serpentine cylindrical electrode was a tradeoff between the accuracy of the representation and computational cost. Large number of rectangles yielded smoother and
more accurate representations of the exact geometry, but the larger number of faces resulted in more dense meshes, particularly around the electrode-insulator junction, which significantly increased the memory requirement and computation time. The 3D models were partitioned into tetrahedral elements between 398,232 and 1,722,879 in quantities. The conjugate gradient method with preconditioning (incomplete Cholesky factorization) was used to solve the models. The simulations calculated the distributions of current density and of potentials ($V_e$) in the modeled region for each electrode configuration.

Figure 6.2: Geometry of finite element models of serpentine cylindrical electrodes. (a) Geometry of the finite element model of a cylindrical electrode positioned in a homogenous isotropic volume of modeled tissue, with the boundary conditions of 1 V on the electrode (dark grey), and 0 V at the outer boundary. Tissue medium was modeled as a 30cm-by-30cm box with a conductivity of 0.2 S/m. (b) Geometry of serpentine cylindrical electrode. The 3D surface of the electrode consisted of 90 thin rectangles.
Populations of 100 myelinated nerve fibers were randomly positioned either parallel or perpendicular to the cylindrical electrode. The model nerve fibers had mammalian membrane dynamics [104] and were either 4 µm or 12 µm in diameter. The models were implemented in NEURON version 6.1 [105] and solved using backward Euler implicit integration with a time step of 0.001 ms. The threshold voltages were calculated with binary search algorithm with a tolerance of 1 µV. The extracellular potential at each node of Ranvier was determined by spline interpolation from the potentials solved by the finite element models. Input-output (recruitment) curves of percentage of activated nerve fibers as a function of stimulation magnitude were generated by applying a monophasic cathodic voltage pulse with pulse width of 100 µs to the electrode. Input-output curves of the percentage of activated axons as a function of the stimulation power were also generated by multiplying the threshold voltage by the delivered current at the threshold voltage, which was the scaled version of the current at unit voltage because the model was linear.

6.4. Results

We used finite element models to calculate current density distribution on the surface of serpentine- and circular-perimeter cylindrical electrodes, as well as the potentials generated in a modeled tissue volume around the electrodes. Subsequently, we used populations of model myelinated nerve fibers to calculate input-output curves of nerve fiber activation as a function of stimulation magnitude and stimulation power. We first considered electrode #5 as an example of a serpentine-perimeter electrode and
compare it to a circular-perimeter electrode (electrode #1). Then we determined the effects of the amplitude and frequency of sinuous variation of serpentine perimeter, designs with larger aspect ratios (diameter/length ratio), and designs with segmentation. We investigated two populations of model axons: 12 µm diameter axons randomly distributed within a 15 mm box surrounding the electrode, and 4 µm diameter axons randomly distributed within a 6 mm box surrounding the electrode. The fibers were oriented either parallel to the electrode surface or perpendicular to the electrode surface.

6.4.1. Distributions of current density

The current density distributions on the surface of electrodes #1 and #5 when a constant voltage of 1V was applied are shown in Figure 6.3(a). The current density increased towards the perimeter of the electrodes. The current density was uniform along the circular perimeter, while the current density was highly non-uniform along the serpentine perimeter, and was highest at the crests and lowest in the troughs of the sinusoid. The total current delivered to the tissue was 1.640 mA with the circular perimeter (electrode #1) and 1.681 mA with the serpentine perimeter (electrode #5). The total currents delivered by all 7 prototypes when a constant voltage of 1V was applied are summarized in Figure 6.3(b).
Figure 6.3: Distributions of current density and calculated total currents.
(a) Distributions of current density on the surface of electrodes #1 and #5. The blank color at the crests of serpentine edges means the current density in these regions was beyond the upper limit of the color bar. The arrows on scale indicate the average current densities. (b) Total currents delivered by all 7 test samples when constant voltage of 1V was applied.

6.4.2. Input-output curves of activation of 12 µm axons

We quantified activation of a population of 12 µm diameter axons randomly positioned in a 15 mm box around the electrode. This diameter is representative of myelinated axons in peripheral nerve bundles; for example, the diameter range of in α-motor neuron axons is 9-20 µm [111].

6.4.2.1. Axons parallel to the electrode

100 axons were randomly positioned parallel to the electrode within a 15 mm box centered at the electrode (Figure 6.4(a)). Input-output curves indicate that electrode #5 decreased the average threshold voltage by 12% (Figure 6.4(b)), and decreased the average power consumption by 21% (Figure 6.4(c)), as compared to electrode #1.
Comparing the activating functions of all 100 axons, we found that the serpentine-perimeter electrode (#5) generated larger maximum activating functions than the circular-perimeter electrode (#1) in 88 out of 100 axons.

Figure 6.4: Input-output curves of activation of parallel axons.
Input-output curves of the percentage of activated axons as a function of the stimulation amplitude and stimulation power. (a) 100 axons with 12 µm diameter were positioned parallel to the electrode surface within a 15 mm box centered at the electrode. (b) Percent of activated axons as a function of stimulus voltage for electrode #1 and electrode #5. Electrode #5 decreased the average threshold voltage by 12% as compared to electrode #1. The inset shows the axons that were activated by electrode #1 with lower thresholds (dark circle) and that activated by electrode #5 with lower thresholds (grey circle). (c) Percent of activated axons as a function of stimulation power for electrode #1 and electrode #5. Electrode #5 decreased the average power consumption by 21% as compared to electrode #1.
**6.4.2.2. Axons perpendicular to the electrode**

Figure 6.5: Input-output curves of activation of perpendicular axons.

Input-output curves of the percentage of activated axons as a function of the stimulation amplitude and stimulation power. (a) 100 axons with 12 µm diameter were positioned perpendicular to the electrode surface within a 15 mm box centered at the electrode. (b) Percent of activated axons as a function of stimulus voltage for electrode #1 and electrode #5. Electrode #5 decreased the average threshold voltage by 13% as compared to electrode #1. The inset shows the axons that were activated by electrode #1 with lower thresholds (dark circle) and that activated by electrode #5 with lower thresholds (grey circle). (c) Percent of activated axons as a function of stimulation power for electrode #1 and electrode #5. Electrode #5 decreased the average power consumption by 22% as compared to electrode #1.

100 axons were positioned perpendicular to the electrode surface within a 15 mm box centered at the electrode (Figure 6.5(a)). Input-output curves indicate that electrode #5 decreased the average threshold voltage by 13% (Figure 6.5(b)), and decreased the average power consumption by 22% (Figure 6.5(c)), as compared to electrode #1. The
serpentine-perimeter electrode (#5) generated larger maximum activating functions than the circular-perimeter electrode (#1) in 99 out of 100 axons.

6.4.3. Input-output curves of activation of 4 µm diameter axons

Next, we quantified activation of a population of model myelinated fibers with diameter of 4 µm randomly positioned in a 6 mm box centered at the electrode (within ~2.5 mm of the electrode). This diameter is representative of axons in the CNS, for example axons in the STN (subthalamic nucleus) have diameters of 1-2 µm, and axons in the internal capsule have diameters of 4-6 µm [112]. The spatial extent of activation in thalamic deep brain stimulation was predicted to have a radius of 2.0–3.9 mm for stimulation amplitudes of 1–3.5 V [113].

With 100 axons positioned parallel to the electrode, the average threshold voltage with the serpentine-perimeter electrode (#5) was 2.2% lower (Figure 6.6(d)) and the average power consumption was 7.7% lower (Figure 6.6(e)) than with the circular-perimeter electrode (#1). The serpentine-perimeter electrode generated a larger maximum activating function than the circular-perimeter electrode in only 34 out of 100 axons. The input-output curves as a function of stimulus voltage for the two electrodes crossed at approximately 60% activation, indicating that the serpentine-perimeter electrode recruited the last (farther) ~40 axons at lower thresholds than the circular-perimeter electrode, but not the first (closer) ~60 axons (Figure 6.6(b)).

With 100 axons positioned perpendicular to the electrode, the serpentine-perimeter electrode (#5) decreased the average threshold voltage by 15% (Figure 6.6(f))
and decreased the average power consumption by 26% (Figure 6.6(g)), as compared to the circular-perimeter electrode (#1). The serpentine-perimeter electrode generated a larger maximum activating function than the circular-perimeter electrode in 88 out of 100 axons. The input-output curves as a function of stimulus voltage for the two electrodes crossed at 7% activation, indicating that the serpentine-perimeter electrode recruited the last (farther) ~93 axons at lower thresholds than the circular-perimeter electrode, but not the first (closer) ~7 axons (Figure 6.6(c)).
Figure 6.6: Effect of frequency of sinuous variation on efficiency.
Input-output curves of the percentage of activated axons as a function of the stimulation amplitude and stimulation power for electrodes #1, #4 and #5. (a) Geometries of electrodes #1, #4 and #5. (b)(c) Axons that were activated by electrode #1 with lower thresholds (dark circle) and that activated by electrode #5 with lower thresholds (grey circle) when 100 axons were positioned parallel to the electrode (b) and perpendicular to
the electrode (c). (d)(e) Percent of activated axons as a function of stimulation voltage (d) and stimulation power (e) when 100 axons were positioned parallel to the electrode. Electrode #5 decreased the average threshold voltage by 2.2% and electrode #4 increased the average threshold voltage by 1.7%, as compared to electrode #1. Electrode #5 decreased the average power consumption by 7.7% and electrode #4 increased the average power consumption by 7.9%, as compared to electrode #1. (f)(g) Percent of activated axons as a function of stimulation voltage (f) and stimulation power (g) when 100 axons were positioned perpendicular to the electrode. Electrode #5 decreased the average threshold voltage by 15% and electrode #4 decreased the average threshold voltage by 26%, as compared to electrode #1. Electrode #5 decreased the average power consumption by 26% and electrode #4 decreased the average power consumption by 35%, as compared to electrode #1.

6.4.3.1. Effect of frequency of sinuous variation on efficiency

The same perimeters can be achieved through different variations in the amplitude (h) and frequency of the sinuous perimeter, i.e., the number of complete periods around the perimeter (n). For example, electrode #4 had the same perimeter as electrode #5 (4 times perimeter of electrode #1) using half the number of complete periods around the perimeter and twice the amplitude of sinuous variation of electrode #5 (Table 6.1). Electrode #4 was less efficient in activating parallel fibers (power increased by 7.9%) than electrode #5 (power decreased by 7.7%), but more efficient in activating perpendicular fibers (power decreased by 35%) than electrode #5 (power decreased by 26%) (Figure 6.6(d)-(g)).

6.4.3.2. Effect of amplitude of sinuous variation on efficiency

The effect of the amplitude of the sinuous perimeter on efficiency was accessed by changing the amplitude of sinuous variation while maintaining the same frequency. Electrode #3 had the same frequency of sinuous variation as electrode #5 (n=10) but only half the perimeter of electrode #5 because of the smaller amplitude of the sinuous
variation (Table 6.1). Electrode #3 was less efficient in activating both parallel fibers (power decreased by 2.6%) than electrode #5 (power decreased by 7.7%), and perpendicular fibers (power decreased by 8.2%) than electrode #5 (power decreased by 26%) (Figure 6.7).

**Figure 6.7: Effect of amplitude of sinuous variation on efficiency.**
Input-output curves of the percentage of activated axons as a function of the stimulation amplitude and stimulation power for electrodes #1, #3 and #5. (a)(b) Percent of activated axons as a function of stimulation voltage (a) and stimulation power (b) when 100 axons were positioned parallel to the electrode. Electrode #3 decreased the average threshold voltage by 1.2% and decreased the average power consumption by 2.6% as compared to electrode #1. (c)(d) Percent of activated axons as a function of stimulation voltage (c) and stimulation power (d) when 100 axons were positioned perpendicular to the electrode. Electrode #3 decreased the average threshold voltage by 4.8% and decreased the average power consumption by 8.2% as compared to electrode #1.
6.4.3.3. Effect of aspect ratio on efficiency

The aspect ratio, defined as the diameter/length ratio, was 1.27mm/1.5mm for electrodes #1-#5 (Figure 6.1(b)), and may affect the stimulation efficiency. Although these electrodes (#1-#5) have the same contact “length”, the tip-to-tip length, which equals 2Lo+2h, increased as the amplitude of sinuous variation was increased. We designed a new electrode (#7) with the same frequency and amplitude of sinuous variation as electrode #5, but with a tip-to-tip length (1.5mm) equal to the length of a DBS electrode contact. Electrode #7 had a smaller contact length (0.741mm), and its surface area was about half (49.4%) of the area of electrodes #1-#5 (Table 6.1). Electrode #7 required larger average threshold voltage to activate both parallel fibers (increased by 6.9%) and perpendicular fibers (increased by 14%) than electrode #1 (Figure 6.8(a), (c)). However, because electrode #7 delivered less current than electrode #1 at the same applied voltage (Figure 6.3(b)), it required less power to activate both parallel fibers (decreased by 16%) and perpendicular fibers (decreased by 7.0%) than electrode #1 (Figure 6.8(b), (d)). Electrode #7 was more efficient in activating parallel fibers (power decreased by 16%) than electrode #5 (power decreased by 7.7%), but less efficient in activating perpendicular fibers (power decreased by 7.0%) than electrode #5 (power decreased by 26%).
6.4.3.4. Effect of segmenting on efficiency

The serpentine perimeter increased stimulation efficiency, and our previous results suggested that segmentation may also increase stimulation efficiency [65]. We designed an electrode (#6) that combined segmentation and a serpentine perimeter. Electrode #6 required smaller average threshold voltage to activate fibers in either orientation (Figure 6.9(a), (c)). Electrode #6 was also highly efficient in activating both
parallel fibers (power decreased by 20%) and perpendicular fibers (power decreased by 35%) (Figure 6.9(b), (d)), making it the most efficient electrode among the 7 electrode samples in activating fibers in both orientations.

Figure 6.9: Effect of segmenting on efficiency.

Input-output curves of the percentage of activated axons as a function of the stimulation amplitude and stimulation power for electrodes #1, #5 and #6. (a)(b) Percent of activated axons as a function of stimulation voltage (a) and stimulation power (b) when 100 axons were positioned parallel to the electrode. Electrode #6 decreased the average threshold voltage by 1.3% and decreased the average power consumption by 20% as compared to electrode #1. (c)(d) Percent of activated axons as a function of stimulation voltage (c) and stimulation power (d) when 100 axons were positioned perpendicular to the electrode. Electrode #6 decreased the average threshold voltage by 14% and decreased the average power consumption by 35% as compared to electrode #1.

6.4.4. Distribution of potentials and the activating functions

The distribution of potentials ($V_c$) and the second spatial derivatives of the potentials ($\propto$ the activating functions), $\Delta^2V_c/\Delta x^2$ and $\Delta^2V_c/\Delta z^2$, generated in the tissue
medium by the circular-perimeter electrode #1, the serpentine-perimeter electrode #5, and the segmented serpentine-perimeter electrode #6 are shown in Figure 6.10. \( \Delta^2 V_e / \Delta x^2 \) and \( \Delta^2 V_e / \Delta z^2 \) have both positive components resulting in depolarization and negative components resulting in hyperpolarization of neurons surrounding the electrode [45]. The spatial distributions of the activating function for neurons perpendicular to the electrode (\( \Delta^2 V_e / \Delta x^2 \)) generated with the serpentine-perimeter electrode #5 (figure 6.10 (e),(k)) and the segmented serpentine-perimeter electrode #6 (figure 6.10 (f),(l)) had a larger spatial extent than with the circular-perimeter electrode (figure 6.10 (d),(j)), while this change was not obvious for neurons parallel to the electrode (\( \Delta^2 V_e / \Delta z^2 \)) (electrode #1: figure 6.10 (g),(m), electrode #5: figure 6.10 (h),(n), and electrode #6: figure 6.10 (i),(o)). This corroborated the results suggested by the input-output curves that the serpentine-perimeter electrode resulted in more efficiency stimulation of axons perpendicular to the electrode than of axons parallel to the electrode (figure 6.6).
Figure 6.10: Distributions of extracellular potentials and the driving functions. Distributions of extracellular potentials ($V_e$) and the second spatial difference of the extracellular potentials ($\Delta^2 V_e/\Delta x^2$ and $\Delta^2 V_e/\Delta z^2$) generated in the tissue medium by the circular-perimeter electrode #1, the serpentine-perimeter electrode #5, and the segmented serpentine-perimeter electrode #6. (a)-(c) Distributions of extracellular potentials generated by the 3 electrodes respectively. (d)-(f) Distributions of the second spatial difference of the extracellular potentials $\Delta^2 V_e/\Delta x^2$, proportional to the activating function for neurons perpendicular to the electrode, generated by the 3 electrodes respectively. (g)-(i) Distributions of the second spatial difference of the extracellular potentials $\Delta^2 V_e/\Delta z^2$, proportional to the activating function for neurons parallel to the electrode, generated by the 3 electrodes respectively. (j)-(l) Distributions of $\Delta^2 V_e/\Delta x^2$, proportional to the activating function for neurons perpendicular to the electrode, generated by the 3 electrodes respectively displayed with a smaller scale. (m)-(o) Distributions of $\Delta^2 V_e/\Delta z^2$, proportional to the activating function for neurons parallel to the electrode, generated by the 3 electrodes respectively displayed with a smaller scale. The blank color in (j)-(o) means the values in this region was beyond the range of the color bar.

6.5. Discussion

Deep brain stimulators are powered with primary cell batteries with a medium lifetime of less than 4 years. When batteries are depleted, stimulator must be surgically replaced. Surgical replacement is expensive and carries significant risk. The objective of this study was to increase the stimulation efficiency of DBS electrode through novel high-perimeter designs. Increases in stimulation efficiency will reduce the power requirements of implantable neural stimulators, thereby increasing device lifetime.

We constructed 3D finite element models of a series of electrodes including a conventional DBS electrode with circular perimeter and 6 other electrodes with serpentine perimeters of different amplitudes and frequencies of sinuous variation. The potentials calculated with the FEM models were coupled with cable models of myelinated nerve fibers to calculate neuronal stimulation thresholds. Input-output curves of activation of a population of randomly distributed nerve fibers with electrodes of
different geometries were compared to quantify stimulation efficiency. Stimulating efficiency was increased by increasing the perimeter of the electrode. The effects of increasing electrode perimeter on stimulating efficiency were dependent not only on the electrode geometry (amplitude of sinuous variation, frequency of sinuous variation, and segmentation), but also on the orientation of the fibers and the distance of the fibers from the electrode. Thus, novel electrode geometries provide a means to reduce power consumption by implantable pulse generators, and may provide a means to enhance the threshold differences between differently oriented fibers (i.e., selectivity).

6.5.1. Dependence of stimulation efficiency on fiber orientations

The relative efficiency of stimulation with different electrode designs was dependent on the orientation of the fibers and the distance of the fibers from the electrode. For axons parallel to the electrode, the input-output curve generated by the serpentine-perimeter electrodes often crossed with the input-output curve generated by the circular-perimeter electrode, indicating that the circular-perimeter electrode activated axons close to the electrode at lower thresholds while serpentine-perimeter electrodes activated mode distant axons at lower thresholds. When the curves crossed at small percentages of activation, the serpentine-perimeter electrodes significantly increased the stimulating efficiency of parallel axons. For example, in the case of 12 µm axons positioned within ~7 mm of the electrode (in a 15 mm box), the input-output curves of electrodes #1 and #5 crossed at 3% activation, and the serpentine-perimeter electrode (#5) decreased the average threshold voltage by 12% (Figure 6.4(b)). However, the
reduction of average threshold may not be significant or may even be reversed when the curves cross at large percentages of activation. For example, in the case of 4 µm axons positioned within ~2.5 mm of the electrode (in a 6 mm box), the input-output curves of electrodes #1 and #5 crossed at 59% activation and the serpentine-perimeter electrode (#5) reduced the average threshold voltage by only 2.2% (Figure 6.6(d)); serpentine electrode #4 increased average threshold voltage by 1.7% (Figure 6.6(d)). On the other hand, for axons perpendicular to the electrode, the input-output curves generated by serpentine-perimeter electrodes were always to the left of the input-output curves generated by the circular-perimeter electrode (Figures 6.5-6.9), indicating that the serpentine-perimeter electrodes activated perpendicular axons with lower thresholds regardless of the distance of the fibers to the electrode.

The increased efficiency of stimulating parallel axons with the serpentine-perimeter electrode was strongly dependent on the distance of the fibers from the electrode. This can be explained by the fact that the current flow out of the electrode surface is in the normal direction (x-y plane). For parallel axons (in z direction), the non-uniformity of current density on the electrode surface created by the serpentine perimeter (Figure 6.3(a)) cannot be translated into the higher variation of current density along the direction of the axons in a region around the electrode surface where the current density is still predominately perpendicular to the axon fibers. This is further corroborated by comparing the activating functions generated by the serpentine-perimeter electrode #1 and circular-perimeter electrode #5 (Figure 6.11). The activating function, calculated as the second difference of the extracellular potential at the nodes of Ranvier, describes the
source driving changes on transmembrane potential [46]. Using nodal lengths of 1.2 mm and 0.4 mm (100 times of the fiber diameter), the maximum second difference of potential generated by the serpentine-perimeter electrode #5 was larger than that generated by circular-perimeter electrode #1 when axons were running parallel close to the electrode (Figure 6.11(c)-(f)), but was smaller when parallel axons were further away from the electrode (Figure 6.11(i), (j)).
Figure 6.11: Second spatial difference of extracellular potentials.
Second difference of extracellular potential ($\Delta^2 V_e/\Delta z^2$) on a line parallel to the electrode surface at various distances (on the surface, 0.1 mm, 1 mm, 3 mm and 5 mm) generated by electrodes #1 and #5 with constant voltage of 1V. The second difference of potential was calculated using a spatial step the same as the internodal length of 12 µm or 4 µm axons (i.e., $\Delta z = 1.2$ mm or 0.4 mm). The projection of the line was aligned to meet the crest and trough of the sinuous variation on the surface of serpentine electrode #5.
6.5.2. Optimal design of high-perimeter electrodes for DBS

Because the effects of increasing electrode perimeter on stimulating efficiency were dependent on the fiber orientation relative to the axis of the electrode, it is important to consider the orientation of the fibers targeted during deep brain stimulation. The stereotactic position of the DBS electrode has an inclination of 30° with respect to the coronal plane [114]. Both subthalamic nucleus (STN) projection neurons and globus pallidus internus (GPI) fibers of passage represent possible therapeutic targets of DBS in the treatment of Parkinson’s disease [115, 116]. Internal capsule (IC) fibers of passage also pass in close proximity to STN DBS electrode, and are often related to the side effects of DBS. There is large anatomical variability among the orientations of different groups of fibers. Axonal tracing experiments [117] have revealed that STN projection neurons course either dorsally along the ventral border of the thalamus or ventrally along the lateral border of the STN on their way to the globus pallidus, which results in a more perpendicular orientation to the electrode. The direction of GPI fibers turns to run along the border of the STN [116, 118, 119], thus GPI fibers have portions both in parallel orientation and in perpendicular orientation to the electrode. The IC fibers define the lateral border of the STN and course ventrally at a ~20° anterior-to-posterior angle [118], which is approximately parallel to the electrode. Therefore, to account for this anatomical variability of fiber orientations and the therapeutic or side effects caused by stimulating different fiber groups, it seems more desirable that our novel electrode designs increase stimulating efficiency of perpendicular axon fibers than that of parallel axon fibers.
Figure 6.12: Changes in threshold voltage and power consumption.

Changes in threshold voltage and power consumption with the serpentine-perimeter electrodes (#2-#7) as compared to the circular-perimeter electrode (#1) when 100 axons were positioned parallel to the electrode (a) and perpendicular to the electrode (b).

Changes in threshold voltage and power consumption with the serpentine-perimeter electrodes (#2-#7) as compared to the circular-perimeter electrode (#1) are summarized in Figure 6.12 for axons parallel to the electrode (Figure 6.12(a)) and for
axon perpendicular to the electrode (Figure 6.12(b)). The model study indicates consistent increase of stimulation efficiency of perpendicular axons across various serpentine electrode geometries. The input-output curves of a population of model axons indicate that: increasing perimeter by means of increasing the amplitude of sinuous variation was more efficiency in activating perpendicular axons than by means of increasing the frequency of sinuous variation (Figure 6.6(f), (g)), which suggests promising designs to increase selectivity for neurons oriented in different directions; serpentine electrode with multiple segments was highly power-efficient in activating parallel axons as well as perpendicular axons (Figure 6.9). Optimal design of high-perimeter electrode for DBS should be based on the anatomic demand of selective activation of fiber groups. If the dominant orientations of fibers representing therapeutic targets of DBS are indeed more perpendicular than parallel to the electrode, then increasing perimeter by means of increasing the amplitude of sinuous variation would be the design direction. If the anatomy demands bulk stimulation of all passing fibers, then electrodes with multiple segments and with larger number of complete sinusoidal periods along the perimeter would be the design direction.

Although FEM-neuron coupled model in conjunction with activating function provide us ideas about what geometrical parameters of electrode design affects stimulating efficiency of fibers, optimizing these geometrical characteristics is challenging and has not been studied in this research. Many independent variables (degrees of freedom) need to be considered in finding optimal high-perimeter design, including number and frequency of sinuous variation, number of segments, aspect ratio of
each segment, and surface coverage (percentage of conductive surface area). The existence of a large number of degrees of freedom, on one hand, complicates the optimization of the geometrical characteristics for electrode design, on the other hand, suggests that by optimizing these geometrical characteristics there may still have big room for improvement in power saving, as compared to the current best of increasing efficiency by \( \sim 20\% \) for parallel axons and \( \sim 35\% \) for perpendicular axons (electrode #6) based on a handful of designs that were investigated in this study.

### 6.5.3. Model limitations

Finite element models of electrodes and the surrounding volume conductor were coupled with compartmental cable models of a population of neurons to study the effects of increasing perimeter of the DBS electrode on stimulation efficiency. The electrical potentials were calculated using the FEM based on the assumption that the tissue medium was homogenous and isotropic. Although the true biological volume conductor is inhomogeneous and anisotropic, a recent study of deep brain stimulation indicated that a homogenous isotropic model provided predictions of voltage distributions remarkably similar to a more detailed inhomogenous and anisotropic model for the expected region of stimulation around the electrode [108]. Further, the current study did not focus on the absolute stimulation efficiency of an electrode, but rather the comparative stimulation efficiency between electrodes with various geometries.

The population of model neurons did not include cell bodies, dendrites, or synaptic inputs. Although both experiment studies [109, 110] and computational models
[74] indicate that during extracellular stimulation action potential initiation occurs in the axon, the impact of changes in geometry on the efficiency of activating other neural elements may differ from those for axons.

6.5.4. Estimation of tissue damage

The serpentine perimeter increased the local current density on the electrode surface, and this may increase the propensity for tissue damage. A quantitative model of neural damage was used to analyze the effects of increasing electrode perimeter on tissue damage. Charge per phase and charge density per phase are cofactors in the generation of neural damage [19, 47], and this relationship is described by the equation (Shannon’s model):

\[
\log \left( \frac{Q}{A} \right) = k - \log (Q), \quad (6.5)
\]

where \( Q \) is the charge per phase, \( A \) is the electrode area, and \( k \) is a constant derived from data to define the boundary between stimulus parameters that produced tissue damage and those that did not [48]. The proposed limit for non-damaging stimulation levels using disk electrodes was \( k = 1.5 \), but this value was estimated using geometrical (average) charge density over the electrode surface [48].
Table 6.2: Increase of $k$ values ($\Delta k$) when applying maximum charge density instead of average charge density for cylindrical electrodes.

<table>
<thead>
<tr>
<th></th>
<th>$J_{avg}$ (A/m²)</th>
<th>$J_{max}$ (A/m²)</th>
<th>$\frac{(Q/A)<em>{\max}}{(Q/A)</em>{avg}}$</th>
<th>$\Delta k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>electrode #1</td>
<td>274</td>
<td>563</td>
<td>2.05</td>
<td>0.31</td>
</tr>
<tr>
<td>electrode #5</td>
<td>281</td>
<td>932</td>
<td>3.32</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Figure 6.13: Non-damaging limits of cylindrical electrodes modified for maximum charge density.

Relationship between charge per phase ($Q$), charge density per phase ($Q/A$), and stimulation induced tissue damage. The $k$ value defines the boundary between stimulus parameters that produce tissue damage and those that do not, and $k = 1.5$ was estimated using geometrical charge density of circular disk (planar) electrodes. In the modified model where the ordinate represents maximum charge density, the new $k$ value ($k'$) was 1.85. Applying $k'$ to the circular-perimeter cylindrical electrode (#1) yielded $k$ equal to 1.54, and to the serpentine-perimeter cylindrical electrode (#5) yielded $k$ equal to 1.33 when geometrical charge density was considered. Squares show the charge and charge density combinations reported in deep brain stimulation post-mortem studies to not have produced tissue damage [51-53].
As the current density was higher around the perimeter of the electrode, and this non-uniformity was more pronounced for electrodes with serpentine edge, we calculated the average current density ($J_{avg}$) and maximum current density ($J_{max}$, average over the 1% of the electrode area with the highest current density) on the surface of the circular-perimeter electrode #1 and the serpentine-perimeter electrode #5 when a constant voltage of 1V was applied (Figure 6.3). The ratio $J_{max}/J_{avg}$ is the same as the ratio of maximum charge density ($Q/A)_{max}$ to average charge densities ($Q/A)_{avg}$. The increases in $k$ ($\Delta k$) were calculated when ($Q/A)_{max}$, instead of ($Q/A)_{avg}$, was considered (Table 6.2). Replacing ($Q/A)_{avg}$ with ($Q/A)_{max}$ in Shannon’s model (Eq. 6.5) for a circular disk electrode will give an adjusted $k$ value ($k’$ in Figure 5.10 and Figure 6.13) that is transferable to other electrode geometries when maximum charge density is considered. Assuming that $k$ is 1.5 estimated with the average charge density of the circular disk electrode, the adjusted $k$ ($k’$) is 1.85 when the maximum charge density is considered. Calculated from $k’$ and $\Delta k$ in Table 6.2, $k$ is 1.54 for the circular-perimeter cylindrical electrode (#1) and 1.33 for the serpentine-perimeter cylindrical electrode (#5) when the average charge density is considered, resulting in a slightly smaller region of non-damaging stimulus parameters (Figure 6.13). This suggests that at the same stimulus parameters, the cylindrical electrode with serpentine perimeter has a slightly higher propensity of inducing local tissue damage than the cylindrical electrode with circular perimeter. However, post-mortem studies reported that typical charge and charge density settings used for deep brain stimulation did not produce tissue damage [51-53], and these charge and charge
density combinations were well below the non-damaging limits for both the conventional circular-perimeter electrode and the serpentine-perimeter electrode (Figure 6.13).
Chapter 7 : Conclusions and Future Work

7.1. Summary of Results

The purpose of this dissertation work was to answer three fundamental questions related to the electrode system used for deep brain stimulation. 1) What is the composition of charge transfer across the electrode-electrolyte/tissue interface during electrical stimulation? 2) What is the current density distribution on the surface of electrode that can be used to estimate neuronal activation and damage? 3) Can we increase the stimulating efficiency and thereby reduce power consumption of implanted stimulators by modifying the electrode geometry?

The results of this study were generated using three general methods: 1) impedance measurements of the electrode-electrolyte interface; 2) finite element models of electrodes and volume conductors; and 3) compartmental cable models of neurons. The outcomes of the study were: 1) quantification of the components of charge transfer by characterizing the impedance of DBS electrode; 2) a modeling framework that incorporates the electrode-tissue interface into finite-element based models of electrodes; and 3) high-efficiency electrode designs that reduce power consumption and thereby prolong battery life of implanted stimulators.

There are three major conclusions from this work representing answers to the three questions addressed above. First in relation to the question: What is the composition of charge transfer across the electrode-electrolyte/tissue interface during electrical stimulation? We answered this question by quantifying the impedance of deep brain
stimulation electrodes *in vitro* and *in vivo*. The results show that: 1) both Faradaic resistance ($R_f$) and double layer capacitance ($C_{dl}$) decreased as the sinusoidal frequency was increased, but the ratio of capacitive charge transfer to Faradaic charge transfer was insensitive to the change of frequency; and 2) $R_f$ decreased and $C_{dl}$ increased as the current density was increased, and this resulted in an increase of both the Faradaic charge transfer and the capacitive charge transfer with increasing current density towards the perimeter of the electrode. The assumption of the DBS electrode being ideally polarizable was not valid under clinical stimulating conditions. This implies that irreversible processes that cause electrode or tissue damage might occur when high charge injection is required for DBS. High charge-injection capacitive materials, such as titanium nitride, tantalum/Ta$_2$O$_5$, carbon nanotubes, and high charge-injection Faradaic materials that employ reversible redox reactions, such as iridium oxide, are alternatives to platinum alloy as materials for future DBS electrodes.

In relation to the second question: What is the current density distribution on the surface of electrode that can be used to estimate neuronal activation and damage? We developed a recursive simulation scheme to calculate current density distribution that incorporates the nonlinear electrode-tissue interface into finite-element based models of electrodes. The current density distributions on the electrode surface were frequency dependent. At frequencies over 1 kHz, the current density distributions were almost identical to the primary current density distribution obtained from a model without an electrode-tissue interface, and were highly non-uniform. The non-uniformity of the current density decreased as the frequency was decreased until eventually the edge effect
was lost at frequencies below 10 Hz, and the average current density was reduced as compared to the primary current density. Power spectra of clinically-relevant stimulus pulses revealed that the bulk of signal power was at frequencies over 1 kHz where the current density distribution was well approximated by the primary current density distribution. Therefore, employing the primary current density distribution to estimate neuronal activation, tissue damage and electrode corrosion during clinically-relevant stimulus pulses is appropriate.

And finally in relation to the third question: Can we increase the stimulating efficiency and thereby reduce power consumption of implanted stimulators by modifying the electrode geometry? To answer this question, we investigated three classes of electrodes: 1) segmented cylindrical electrodes; 2) serpentine-perimeter planar electrodes; and 3) serpentine-perimeter cylindrical electrodes. Coupling the finite element models of electrodes and volume conductors with compartmental cable models of neurons permitted determination of how changes in electrode geometry affected the efficiency of stimulating a population of neurons. The results supported the hypothesis that increasing the electrode perimeter increased the electrode efficiency by decreasing stimulation threshold, and showed that both segmentation and serpentine edges provided means to increase the efficiency of DBS. With proper selection of geometrical parameters, our novel cylindrical electrode that combined segmentation with serpentine perimeter decreased power consumption by ~20% for axons parallel to the electrode and ~35% for axons perpendicular to the electrode at DBS-relevant fiber diameters and distances, and
thus could prolong the average battery life of deep brain stimulators by more than one year.

7.2. Future Directions

7.2.1. Refinement of interface and tissue model

In Chapter 2, Faradaic resistance $R_f$ and double layer capacitance $C_{dl}$ were determined as a function of both current density and frequency by fitting an electrical circuit equivalent model to the impedance spectrograms. The electrical circuit equivalent model was a simplified Randles circuit model that neglected the Warburg impedance. Warburg impedance, which accounts for mass transfer limitations by diffusion, was experimentally determined to be negligible over the frequency range (1 Hz–10 kHz) used for the measurements. The remaining two circuit component, $R_f$ and $C_{dl}$, each represents a clearly identifiable electrochemical process. However, this circuit equivalent model was spatially lumped, which is applicable only to electrodes where the entire interface is equally accessible to the current (i.e., uniform current density distribution). Smooth spherical electrodes, or electrodes with some novel shapes [25, 71, 72], provide such a surface.

For cylindrical DBS electrodes whose interface is not equally accessible to the current, there are two possible ways to describe more accurately the characteristics of the interface impedance with changing current density and frequency. First, as the interface is not equally accessible to the current, the interface can be divided into a lot of micro-regions above which current density is approximately uniform. Each micro-region of the
interface will have a unique capacitance, charge transfer resistance, and resistive path through the bulk electrolyte [60, 120]. The interface needs to be modeled as a spatially-distributed array of RC circuits all connected in parallel where each individual RC element represents the interface of one micro-region. The problem with implementing such a circuit representation is that parameterization of a large number of interface parameters may not be possible using impedance spectroscopy. Alternatively, a smooth spherical/ hemisphere electrode can be manufactured using the same material and with the same surface area as the DBS electrode. \( R_f \) and \( C_{dl} \) as a function of current density and frequency can be determined for this “lumped” electrode and applied to the “distributed” DBS electrode based on the current density at each local region.

Electrodes implanted in the body become encapsulated with tissue over time. The electrical properties of encapsulation tissue are different from those of normal brain tissue [43]. Growth of encapsulation tissue around implanted electrodes may change the load impedance, modify the shape and magnitude of the electric field, and thus alter the recruitment properties of chronically implanted electrodes. Previous study has shown that encapsulation around the electrode lead had a strong effect on impedance [121] and on the fraction of axons activated during DBS [119]. These changes will need to be quantified and accounted for in our electrode model.

**7.2.2. Prototype high-perimeter electrode development and testing**

The work described in Chapter 6 analyzed novel serpentine-perimeter cylindrical electrode designs that increased the efficiency of activating a population of modeled
axons. The important next step is experimental testing in animal models, to address both stimulating efficiency and the propensity to cause tissue damage. Ideally the experiment testing of stimulating efficiency should be conducted with electrodes positioned in the basal ganglia region of the animal brain. However, it is difficult to quantify the efficiency of stimulating the nerve fibers in the central nervous system in an acute experiment because of the complex orientations and projections of the nerve fibers. It is much more feasible to test the efficiency of prototype electrodes for stimulating peripheral nerves. The cat sciatic nerve is the model of choice for testing the efficiency of various electrode designs. Both the cat sciatic nerve and the muscle groups it innervates, such as the tibialis anterior and the gastrocnemius muscles, are relatively easy to identify and access during surgery [122]. Electromyograms (EMGs) of these muscles provide a quantitative indictor of the percentage of axons being activated during the stimulation [123, 124]. Tissue damage induced by different electrodes was estimated using Shannon’s empirical model in this research. Histological evaluation of the brain tissue adjacent to the electrode sites, following in vivo continuous pulsing of electrodes using regulated current, would permit direct estimation of tissue damage induced by the high-perimeter electrodes as compared to conventional electrodes.

### 7.2.3. Design of optimal high-efficiency electrodes

An important goal of this research was to design DBS electrodes that decrease the power consumption of implantable stimulators. To achieve this goal, finite element models of electrodes and the surrounding volume conductor were coupled with
compartmental cable models of neurons to study the effects of varying geometrical characteristics of the electrode on the efficiency of activating a population of myelinated nerve fibers. The volume conductor was homogenous and isotropic, and the population of axons had specific orientations (parallel or perpendicular to electrodes) and did not include cell body, dendrites, or synaptic inputs.

To improve the fidelity of the model prediction, the following two steps will be taken. The first step is to use a geometrically realistic finite element electrical model incorporating anisotropic and inhomogenous conductivities around the DBS electrode. However, previous model study suggests that when evaluating DBS voltage distributions within a few millimeters of an active electrode contact, an homogenous isotropic model provides similar overall predictions to a more detailed inhomogenous and anisotropic model [108]. The second step is to use multi-compartment biophysical models of STN projection neurons, GPi fibers of passage, and internal capsule fibers of passage with geometry and orientation consistent with anatomical features of the brain regions of interest.

The above two steps will permit an exploration of what geometrical characteristics of electrode design influence the efficiency of activating fibers in the context of STN DBS. However, optimizing these geometrical characteristics remains a challenge because of the large number of independent variables (degrees of freedom) that need to be considered, including number and frequency of sinuous variation, number of segments, aspect ratio of each segment, and percentage of conductive surface. In addition to the characteristics considered in this study, other characteristics are available to
optimize the high-efficiency electrodes design. For instance, both the length of each segment and the gap between adjacent segments can be varied along the electrode length; the radius of the electrode can be varied along its length; the perimeter can be increased using other shapes including triangle waves or rectangular waves. Apart from high-perimeter design idea, as motivated by the results that segmented electrodes generated patterns of electric field with greater spatial variation than did a large solid electrode, it is reasonable to expect that more efficient and selective activation could be achieved by electrode arrays with greater numbers of more densely spaced, smaller contacts, preferable combined with multiple stimulation channels. For instance, the electrode can be designed as many small conductive patches on a cylindrical insulative mandrel. These characteristics may change the efficiency of neural excitation by modifying the spatial non-uniformity of the current density profile on the electrode surface and the distribution and magnitude of the activating function in the tissue.

The effects of increasing the perimeter of the electrode on the efficiency of neural excitation were studied only in the case of monopolar and monophasic stimulation. The optimal high-efficiency electrode designs may also depend on the stimulation waveforms and the electrode configuration. The effects of electrode geometrical characteristics on stimulation efficiency with different waveforms (different pulse widths, anodic vs. cathodic, mono- vs. biphasic, non-symmetrical vs. symmetrical, etc.) and with different electrode configurations (monopolar, bipolar and tripolar) also needs to be studied in the future.
References


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Publications and Patents


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