Estimation of dispersive properties of encapsulation tissue surrounding deep brain stimulation electrodes in the rat

Author List: Karthik Sridhar, Judith Evers, Diego Pereira Botelho and Madeleine M. Lowery

4	
5	Corresponding Author: Madeleine Lowery
6	School of Electrical and Electronic Engineering,
7	University College Dublin, Belfield, Dublin 4, Ireland
8	madeleine.lowery@ucd.ie
9	Affiliations: J Sridhar, J Evers, D Pereira Botelho and M. M. Lowery are with the School of
10	Electrical and Electronic Engineering, University College Dublin, Ireland.
11	Link to Published Manuscript, DOI: <u>10.1109/EMBC.2019.8857062</u>
12	Details of Funding: Research supported by Science Foundation Ireland (SFI), the European
13	Regional Development Fund (Grant Number: 13/RC/2073) and the European Research Council
14	(Grant Number: ERC-2014-CoG-646923- DBSModel).
15	© 2019 IEEE. Personal use of this material is permitted. Permission from IEEE must be
16	obtained for all other uses, in any current or future media, including reprinting/republishing this
17	material for advertising or promotional purposes, creating new collective works, for resale or
18	redistribution to servers or lists, or reuse of any copyrighted component of this work in other
19	works.

20 Abstract

21 The aim of this study was to estimate the electrical properties of the encapsulation tissue 22 surrounding chronically implanted electrodes for deep brain stimulation in the rat. The 23 impedance spectrum of a concentric bipolar microelectrode implanted in the rat brain was 24 measured immediately following surgery and after 8 weeks of implantation. The experimental 25 impedance data were used in combination with a finite element model of the rat brain using a 26 parametric sweep method to estimate the electrical properties of the tissue surrounding the 27 electrode in acute and chronic conditions. In the acute case, the conductivity and relative 28 permittivity of the peri-electrode space were frequency independent with an estimated 29 conductivity of 0.38 S/m and relative permittivity of 123. The electrical properties of the 30 encapsulation tissue in the chronic condition were fitted to a dispersive Cole-Cole model. The 31 estimated conductivity and relative permittivity in the chronic condition at 1 kHz were 0.028 32 S/m and 2×10^5 , respectively. The estimated tissue properties can be used in combination with 33 computational modeling as a basis for optimization of chronically implanted electrodes to 34 increase the efficacy of long-term neural recording and stimulation.

35 Introduction

36 Over the past twenty years, deep brain stimulation (DBS) has been established as an effective 37 clinical intervention to restore motor function in patients with Parkinson's disease. However, 38 the mechanisms by which it works are not yet fully understood. To better understand the 39 mechanisms of DBS it is necessary to establish the distribution of the electric field induced in 40 the surrounding tissues and the effect that it has on activity in the target neurons. Mathematical 41 modelling has been widely used to investigate the electric field distribution and consequent 42 volume of neural tissue activated [1], [2], [16]. Using this approach, bioelectric field modelling 43 of the brain has been extensively used for surgical planning, and to investigate variations in 44 electrode configuration and simulation parameters system [1], [19]. Accurate modelling of the 45 electric field requires knowledge of the distinctive properties of the electrode-tissue interface 46 which includes the electrical double layer formed at the electrode-tissue interface and the 47 electrical and geometrical properties of the encapsulation tissue formed around the electrodes. 48 The electrical properties of the encapsulation layer are poorly understood and vary widely in the 49 reported values used in the literature. Since the accuracy of computational models of DBS in 50 predicting realistic electric fields directly depends on electrical properties and representation of 51 anatomical structures of the tissues in the brain, identification of these properties is a critical 52 issue. The encapsulation tissue formed at the electrode-tissue interface can have a substantial 53 effect on the region of tissue which is stimulated. During voltage controlled stimulation, the

- 54 electric field in the surrounding tissues reduces significantly due to an increase of the impedance
- 55 at the electrode-tissue interface resulting from the formation of a glial scar. In the chronic
- 56 condition, the impedance of the encapsulation tissue increases for several weeks after
- 57 implantation and remains while the implant is in the body. It is also reported that both
- 58 encapsulation tissue properties and the thickness of the layer may change over time [3]. In the
- 59 context of computational modelling of DBS, incorporation of the electrical double layer at the
- 60 electrode tissue interface is well-established [4]. However, models to date have considered the
- 61 encapsulation tissue to be purely resistive and frequency independent [5], [2], [17]. It has been
- 62 established that capacitive and dispersive properties of the surrounding brain tissue can
- 63 influence the volume of tissue activated during deep brain stimulation [2], [7]. However, it is
- 64 not clear whether the encapsulation tissue exhibits similar capacitive or dispersive. The aim of
- 65 the present study was, therefore, to estimate the electrical double layer and electrical properties
- of encapsulation tissue surrounding a DBS electrode chronically implanted in the rat brain,
- 67 across a range of frequencies. The estimated electrode-tissue properties were incorporated in a
- 68 computational finite element model of the electrode and surrounding brain tissue.

69 Methods

- 70 In this study, experimentally recorded impedance data were used in combination with a three-
- 71 dimensional heterogeneous finite element (FE) model of the rat brain to estimate dispersive
- 72 properties of the encapsulation tissue surrounding an implanted DBS electrode. Tissue
- 73 properties were estimated in both acute and chronic conditions, on the day of surgery and eight
- 74 weeks after surgery, respectively, in the frequency range of 100 Hz to 30 kHz.

75 A. Impedance measurement in vivo

- 76 Electrochemical Impedance Spectroscopy (EIS) was performed on the microelectrode in both
- 77 physiological saline and then in the brain of one male adult Wistar rat in vivo, using Keysight
- 78 E4980 AL precision LCR (inductance (L), capacitance (C), and resistance (R)) meter and
- 79 Keysight data acquisition software (Keysight Technologies, CA, USA). Impedance was
- 80 measured between the frequency range of 20 Hz to 300 kHz by applying a single sinusoidal
- signal of 20 μ A in amplitude. The SNEX-100 concentric bipolar electrode (Microprobes,
- 82 Gaithersburg, USA) was used with active Platinum/Iridium electrode contact with a diameter of
- $100 \,\mu\text{m}$ and stainless steel ground contact with a diameter of $310 \,\mu\text{m}$. The experiments were
- 84 approved by the UCD Animal Ethics Committee and licensed by the Health Products
- 85 Regulatory Authority of Ireland.

86 B. Impedance data analysis

- 87 To estimate the equivalent circuit electrical double layer (EDL) parameters, a circuit model
- 88 similar to that proposed by McAdams and Richardot[8] was used to fit the impedance spectrum
- 89 of the electrode in saline, using the simplex optimization technique in MATLAB (The
- 90 MathWorks, Natick, USA). The equivalent impedance of a 1 nm thick electrical double layer
- 91 was represented as a parallel combination of the constant phase angle element (Z_{cpa}) and the
- 92 over potential independent form of the charge transfer resistance (R_{ct}):

$$Z_{cpa} = K(i\omega)^{-\beta} \tag{1}$$

$$R_{ct} = \frac{RT}{nFI_0} \tag{2}$$

93

94 where K and β are constants denoting the magnitude of Z_{cpa} and inhomogeneities in the surface 95 respectively, R is the universal gas constant, F Faradays constant, T temperature, n the number 96 of electrons per molecule, and I_0 the exchange current density.

98 *C. Model geometry*

- 99 A heterogeneous rat model with geometrical structures comprising cerebrospinal fluid (CSF),
- skull, grey and white matter tissue of the brain was created using image segmentation of T2
- 101 MRI dataset of the rat brain [10]. The segmented masks of brain tissues were converted to a
- 102 geometric model using Simpleware ScanIP software (Synopsys, CA 94043, USA). Before
- 103 segmentation, the MRI dataset was coregistered to Waxholm Space Atlas of the Sprague
- 104 Dawley Rat Brain (WSSD) atlas[10]. Subsequently, the microelectrode was positioned on the
- subthalamic nucleus with the aid of WSSD atlas as shown in Fig. 1. Finally, a surrounding layer
- 106 of tissue of 25 μ m and 60 μ m thickness was created in the geometry to represent the
- 107 encapsulation layer for acute and chronic, respectively.

108 D. Mathematical framework

- 109 To simulate the electrode impedance at different frequencies, the electro-quasistatic equation
- 110 was used, where magnetic and wave propagation effects were neglected [11], [2], [6]:
- 111

$$\nabla . [(\boldsymbol{\sigma}(\boldsymbol{\omega}) + i\boldsymbol{\omega}\boldsymbol{\varepsilon}_r(\boldsymbol{\omega})\boldsymbol{\varepsilon}_0)]\nabla\boldsymbol{\phi} \tag{3}$$

112 where, σ (S/m) and ϵ_r are electrical conductivity and relative permittivity, ω - angular frequency,

113 ε_0 permittivity of free space (F/m), and φ (Volts) scalar potential. Maxwell's equation in this

114 form takes into account the frequency dependent conductivity and permittivity, where both

115 conductivity and permittivity were described using the Cole-Cole model representation [15].

116 E. Boundary conditions and material properties

117 For bipolar stimulation in the computational model, the Platinum-iridium (Pt/Ir) contact of the 118 microelectrode was assigned as the active terminal and the stainless-steel contact as a ground. 119 Neumann boundary conditions were applied to the insulating parts of the electrode and outer 120 surface of the skull [2]. The estimated electrical double layer was implemented using the thin 121 layer approximation for voltage controlled stimulation and the equivalent double layer circuit 122 model coupled to the active terminal of the electrode for current controlled stimulation [4]. The 123 electrical double layer properties were estimated from the in vitro impedance data of the 124 electrode in physiological saline and the skull, grey and white matter tissue properties were 125 obtained from [15].

126 F. Estimation of encapsulation tissue properties

127 A parametric sweep method was used where the Cole-Cole parameters of the encapsulation 128 tissue were swept between grey matter and CSF for the acute condition, and for the chronic

- 129 condition between the white matter and 175% of the white matter properties [15]. Solving the
- 130 FE model for each set of parameters, the parameters for which the deviation between the
- 131 experimentally recorded and simulated impedance data, across the frequency range from 500 -
- 132 27.5 kHz, was minimized were identified. Assuming linearity at the electrical double layer
- 133 interface [9], [13], the impedance of the electrode can be calculated using Ohms law:

$$Z = \frac{V}{I} \tag{4}$$

- where, Z is the magnitude of the impedance of the electrode, V electric potential(Volts)
 calculated from the Laplace equation, and I applied current (Amperes).
- 137 G. Implementation detail

138 The head with DBS electrode model was meshed using the Simpleware software, generated

139 model consists of 1.8 million tetrahedral elements. A quadratic interpolation function was used

140 on each tetrahedral element creating 2.5 million degrees of freedom to approximate the scalar

- 141 potential. Finally, the discretized finite element model was solved using COMSOL Multiphysics
- 142 (COMSOL, Stockholm, Sweden) using the GMRES iterative solver with a geometric multigrid
- 143 preconditioner.

144 **Results**

134

145 *A. Estimation of electrical properties of the double layer*

146 The estimated impedance of the microelectrode in the 0.9 % saline was presented in Fig. 2. The

147 estimated parameters of the constant phase angle element of equation (1) normalized with

148 respect to the active microelectrode surface area were K = 0.96 Ω m 2 s $-\beta$, β = 0.78. The

- 149 estimated charge transfer resistance Rct was 350 k Ω . The impedance due to the electrical
- 150 double layer was dominant in the low frequency range up to 10 kHz.

151 B. Estimation of peri-electrode space electrical properties in acute phase

152 The estimated electrical conductivity and relative permittivity of the 25 µm thick encapsulation

- 153 layer in the acute condition were 0.38 S/m and 123, respectively at 1 kHz. The estimated
- 154 dispersive properties of the encapsulation tissue were found to be constant across the frequency
- 155 range examined. The estimated peri-electrode space electrical properties yielded an impedance
- 156 of the electrode comparable to the experimental data as shown in Fig. 3.

158 *C. Estimation of encapsulation tissue properties in the chronic phase*

- 159 The estimated electrical conductivity and relative permittivity of the 60 µm thick encapsulation
- 160 layer in chronic phase were approximately 0.028 S/m and 2.5×10^5 respectively at 1 kHz. The
- 161 estimated conductivity increased from 0.025 S/m to 0.081 S/m across the frequency range of
- 162 600 Hz to 27.5 kHz, whereas relative permittivity decreased from 3.5×10^5 to 5.7×10^4 . The
- 163 estimated dispersive properties were in close agreement with the experimental results as shown
- 164 in Fig. 4.

165 **Discussion**

166 In this study, the dispersive electrical properties of the encapsulation tissue surrounding an 167 implanted microelectrode in the rat brain were estimated using a 3D finite element model. 168 Encapsulation tissue properties were estimated for both acute and chronic conditions. Before 169 estimating the encapsulation tissue properties, the electrical double layer impedance was first 170 estimated in vitro. The electrical double layer was then incorporated in the FE models to 171 estimate the encapsulation tissue properties in both the acute and chronic conditions. In both 172 conditions, the electrical double layer impedance was dominant in the low frequency range(see 173 Fig. 3 and Fig. 4), and was consistent with values estimated previously for DBS electrodes in a 174 non-human primate [14].

175 In the acute condition, the estimated electrical properties of the peri-electrode space were 176 frequency independent, and the influence of permittivity on the electrode impedance was 177 negligible, as shown in Fig. 3. A single conductivity value for the encapsulation produced a 178 comparable impedance spectrum to the in vivo impedance data (see Fig. 3). The surrounding 179 tissue conductivity of 0.38 S/m estimated on the day of surgery was found to be substantially 180 lower than the values for CSF (1.7-2 S/m) which are frequency independent used as the basis 181 for simulation of peri-electrode space properties in the acute phase [2], [5], [18]. The difference 182 in the electrical conductivity in the peri-electrode space from that of CSF may be due to the 183 presence of other cells resulting from insertion of the microelectrode. The conductivity 184 estimated here lies above the effective conductivity of 0.1-0.27 S/m for a suspension of cell 185 bodies within CSF reported in [12].

186 In the chronic condition, the estimated electrical properties of the encapsulation tissue were

187 frequency dependent, and the permittivity had a substantial influence on the impedance for the

188 measured frequency range. The impedance simulated assuming a single value of conductivity

- and relative permittivity for the encapsulation tissue was not able match the *in vivo* impedance
- 190 data (see Fig. 4). The estimated conductivity of the encapsulation tissue of 0.038 S/m at 1 kHz

191 is higher than that reported previously for subcutaneously implanted epoxy and silicone rubber 192 electrode arrays in the cat [17]. Variations in the impedance values observed across the studies 193 are likely due to differences in the tissue in which the electrodes were implanted, variations in 194 materials and in electrode geometry. A number of study limitations should be considered when 195 interpreting the data. The preliminary data presented were recorded in a single rat. A group 196 study is ongoing to quantify the variability across animals. The electrical properties of the 197 double layer were estimated *in vitro* and may change slightly *in vivo* and over time. Finally, the 198 encapsulation tissue was assumed to be a homogenous isotropic conductor of simplified 199 geometrical structure. The estimated electrical properties thus represent macroscopic bulk tissue 200 properties. The detailed structure of glial scar and variations in tissue with distance from the 201 electrode may influence the distribution of the electrode field in the region immediately 202 surrounding the electrode in computational volume conductor models.

203 Conclusions

204 A detailed model of the rat brain was used in combination with experimentally recorded

205 impedance data to estimate the electrical properties of the peri-electrode space and

206 encapsulation tissue surrounding an implanted DBS electrode in the rat. The results confirm the

207 increase in electrode impedance in the weeks following implantation observed in previous

animal and human studies, and provide an estimate of the change in corresponding electrical

209 properties of the tissue immediately surrounding the electrode. The estimated tissue properties

210 can be used in combination with computational modeling as a basis for optimization of

211 chronically implanted electrodes to increase the efficacy of long-term neural recording and

stimulation.

213 **References**

- 214 [1] C. R. Butson, C. B. Maks, C. C. McIntyre, S. E. Cooper, J. M. Henderson, and C. C.
- 215 McIntyre, "Patient-specific analysis of the volume of tissue activated during deep brain
- 216 stimulation," Clin. Neurophysiol., vol. 117, no. 2, pp. 661670, 2007.
- 217 [2] P. F. Grant and M. M. Lowery, "Effect of dispersive conductivity and permittivity in volume
- 218 conductor models of deep brain stimulation," IEEE Trans. Biomed. Eng., vol. 57, no. 10 PART
- 219 1, pp. 23862393, 2010.
- 220 [3] S. F. Lempka, S. Miocinovic, M. D. Johnson, J. L. Vitek, and C. C. McIntyre, "In vivo
- impedance spectroscopy of deep brain stimulation electrodes," J. Neural Eng., vol. 6, no. 4,2009.
- [4] D. R. Cantrell, S. Inayat, A. Taflove, R. S. Ruoff, and J. B. Troy, "Incorporation of the
- 224 electrode-electrolyte interface into finite-element models of metal microelectrodes," J. Neural
- 225 Eng., vol. 5, no. 1, pp. 5467, 2008.
- [5] N. Yousif and X. Liu, "Modeling the current distribution across the depth electrodebrain
 interface in deep brain stimulation," Expert Rev. Med. Devices, vol. 4, no. 5, pp. 623631, Sep.
 2007.
- [6] B. Tracey and M. Williams, "Computationally efficient bioelectric field modeling and
 effects of frequency-dependent tissue capacitance," J. Neural Eng., vol. 8, no. 3, 2011.
- 231 [7] C. A. Bossetti, M. J. Birdno, and W. M. Grill, "Analysis of the quasistatic approximation for
- calculating potentials generated by neural stimulation," J. Neural Eng., vol. 5, no. 1, pp. 4453,
 2008.
- [8] A. Richardot and E. T. McAdams, "Harmonic analysis of lowfrequency bioelectrode
- 235 behavior," IEEE Trans. Med. Imaging, vol. 21, no. 6, pp. 604612, 2002.
- 236 [9] E. T. McAdams and J. Jossinet, "A physical interpretation of Schwans limit current of
- 237 linearity," Ann. Biomed. Eng., vol. 20, no. 3, pp. 307319, 1992.
- 238 [10] E. A. Papp, T. B. Leergaard, E. Calabrese, G. A. Johnson, and J. G. Bjaalie, "Waxholm
- 239 Space atlas of the Sprague Dawley rat brain," Neuroimage, vol. 97, pp. 374386, 2014.
- 240 [11] N. S. Stoykov, M. M. Lowery, A. Taflove, and T. A. Kuiken, "Frequency- and time-
- 241 domain FEM models of EMG: Capacitive effects and aspects of dispersion," IEEE Trans.
- 242 Biomed. Eng., vol. 49, no. 8, pp. 763772, 2002.

- 243 [12] C. Gabriel, A. Peyman, and E. H. Grant, "Electrical conductivity of tissue at frequencies
- 244 below 1 MHz," Phys. Med. Biol., vol. 54, no. 16, pp. 48634878, 2009.
- [13] B. Onaral and H. P. Schwan, "Linear and nonlinear properties of platinum electrode
- 246 polarisation. Part 1: frequency dependence at very low frequencies," Med. Biol. Eng. Comput.,
- 247 vol. 20, no. 3, pp. 299306, 1982.
- 248 [14] S. F. Lempka, S. Miocinovic, M. D. Johnson, J. L. Vitek, and C. C. McIntyre, "In vivo
- impedance spectroscopy of deep brain stimulation electrodes," J. Neural Eng., vol. 6, no. 4,2009.
- 251 [15] S. Gabriel, R. W. Lau, and C. Gabriel, "Physics in Medicine Biology. The dielectric
- 252 properties of biological tissues: III. Parametric models for the dielectric spectrum of tissues,"
- 253 Phys. Med. Biol. Phys. Med. Biol, vol. 41, no. 41, pp. 22512269, 1996.
- 254 [16] M. Astrom, E. Diczfalusy, H. Martens, and K. W" ardell, "Relationship" between neural
- activation and electric field distribution during deep brain stimulation," IEEE Trans. Biomed.
- 256 Eng., vol. 62, no. 2, pp. 664672, 2015.
- 257 [17] W. M. Grill and J. Thomas Mortimer, "Electrical properties of implant encapsulation
- 258 tissue," Ann. Biomed. Eng., vol. 22, no. 1, pp. 2333, 1994.
- [18] A. R. Kent and W. M. Grill1, "Analysis of deep brain stimulation electrode characteristics
 for neural recording,"vol. 71, no. 11, pp. 38313840, 2014.
- 261 [19] C. R. Butson, J. Vorwerk, A. D. Dorval, D. N. Anderson, and B. Osting, "Optimized
- 262 programming algorithm for cylindrical and directional deep brain stimulation electrodes," J.
- 263 Neural Eng., vol. 15, no. 2, p. 026005, 2017.
- 264

265 Figures



267 Fig. 1. Cross sectional view of model of rat brain with micro electrode, where 1-Grey matter, 2-

268 micro-electrode, 3-encapsulation tissue, 4-white matter



Fig. 2. Comparison of experimentally measured electrode impedance and electrode impedance

estimated for the FE model in 0.9% saline.



278

Fig. 3. Comparison of experimentally measured electrode impedance and electrode impedance estimated for the FE model in the acute condition. Data are also shown for the FE model where the electrical double layer (EDL) was included but the peri-electrode space was omitted from the model.



284

Fig. 4. Comparison of experimentally measured electrode impedance and electrode impedance

estimated for the FE model in the chronic condition. Data are also shown for the FE modelwhere the electrical double layer (EDL) was included but the encapsulation tissue was removed

from the model and for conductivity and relative permittivity values estimated at a single

289 frequency.