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Relationship between Neural Activation and Electric Field Distribution during Deep Brain Stimulation

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Abstract— Models and simulations are commonly used to study deep brain stimulation (DBS). Simulated stimulation fields are often defined and visualized by electric field isolevels or volumes of tissue activated (VTA). The aim of the present study was to evaluate the relationship between stimulation field strength as defined by the electric potential, V , the electric field, E , and the divergence of the electric field $\nabla^2 V$, and neural activation. Axon cable models were developed and coupled to finite element DBS models in 3D. Field thresholds (V_T , E_T , and $\nabla^2 V_T$) were derived at the location of activation for various stimulation amplitudes (1 to 5 V), pulse widths (30 to 120 μ s), and axon diameters (2.0 to 7.5 μ m). Results showed that thresholds for V_T and $\nabla^2 V_T$ were highly dependent on the stimulation amplitude while E_T were approximately independent of the amplitude for large axons. The activation field strength thresholds presented in this study may be used in future studies to approximate the VTA during model-based investigations of DBS without the need of computational axon models.

Index Terms— axon cable model, deep brain stimulation (DBS), finite element method (FEM), simulation, field visualization

I. INTRODUCTION

DEEP brain stimulation (DBS) is an effective treatment for movement disorders such as Parkinson's disease, essential tremor and dystonia [1, 2]. DBS leads are implanted with stereotactic neurosurgical techniques in the deep regions of the brain [3]. Chronic electrical stimulation is delivered to the leads from battery-operated pulse generators that are implanted below the clavicle. The clinical benefit of DBS is largely dependent on the spatial distribution of the stimulation field in relation to brain anatomy [4-8].

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To maximize therapeutic benefits while avoiding unwanted side-effects, precise control over the stimulation field is essential.

Finite element models and simulations of DBS are commonly used to calculate and display the distribution of the stimulation field. Stimulation fields may be represented and visualized by different electrical quantities such as the electric potential [6, 9, 10], the electric field [11-13], the second difference of the electric potential, [4, 14, 15], as well as with a volume of tissue activated (VTA) derived from neuron models coupled to finite element simulations [6, 8, 16, 17]. During modelling and simulation of DBS a challenge is to display a stimulation field that is relevant to the stimulation-induced therapeutic effects as well as side-effects. In order to visualize an electric entity that is relevant for the therapeutic outcome of DBS it should ideally be related to what is responsible for the clinical effects. However, the mechanisms of DBS are not fully known. It is hypothesized that jamming of the pathological activity is likely to play a prominent role [18]. It is further hypothesized that activation of axons may to a large part be responsible for the jamming but also for inducing stimulation-induced side-effects [19].

Activation of axons during extracellular stimulation is, however, rather complex. First of all, the threshold for activation is widely ranging for different sizes of axons [20], and it is not known what sizes of axons are responsible for therapeutic effects and side-effects during DBS. In addition, polarization at a particular axon node (voltage sensitive ion channel) is dependent on the potential differences at the adjacent nodes on either side of the particular node [21]. Thus, it is not possible to derive the amount of polarization at a specific node without considering the field distribution in the vicinity of that location i.e. the curvature of the stimulation field. In addition, as presented in Weiss' equation [22] the width of the stimulation pulse affects the polarization of neurons in a non-linear fashion.

Activation of neurons of a specific type, size and orientation in relation to the stimulation field may be investigated by the coupling of neuron compartment models to finite element simulations [4, 14, 17, 23, 24]. Simulations with coupled neuron models are, however, limited by their complexity, and the extensive execution time, as well as the obvious reason that it is not known what neurons are responsible for certain effects and side-effects. The complexity of implementing and solving axon models may be a major hurdle for many research groups that would like to perform model-based investigations

of DBS. Computational time is also a major issue for software tools that are to be used in clinical practice. In the present study we sought to identify activation threshold levels related to the simulated stimulation field that can be used to define the VTA. Specifically, the aim was to derive activation threshold levels for the electric potential, the electric field, and the second derivative of the electric potential (activating function) and investigate if these can be used to define the VTA during model-based investigations of DBS, without the need for computational axon models.

II. METHOD

A. Axon model

A computational axon cable model was developed to define axonal activation in response to DBS stimulation. The electrophysiological response of the axon was modelled based on ion channel kinetics and channel densities as described by Wesselink et al. [25] and Richardson et al. [26]. The general equation describing the electrical response of the neuron is given by:

$$C_n \frac{dV_{m,n}}{dt} + \sum_x g_x (V_m - v_x) - g_A \cdot \Delta^2 V_{m,n} = g_A \cdot \Delta^2 V_{e,n} \quad (1)$$

Where the first term on the left-hand side describes the capacitive membrane current proportional to the total membrane capacitance C_n at each position n along the fiber over time; $V_{m,n}$ corresponds to the membrane potential at position n . The second term represents the ionic membrane conductance at each position; fast potassium, slow potassium, fast sodium and leak conductance at nodes of Ranvier and leak conductance at myelinated internodes. The dynamics of the ionic conductance at each node of Ranvier were modelled according to experimental data reported for human fibers [27]. The third term gives the axial current flow which is proportional to the axial conductance g_A between successive fiber segments and the second spatial difference of the membrane potential $\Delta^2 V_{m,n}$. The right-hand part of the equation describes the driving term due to the extracellular electrical potential V_e ; this driving term is often referred to as the activating function (AF). The AF is proportional to the discretized second spatial derivative of V_e along the nodes of the axon, according to:

$$\Delta^2 V_e(n) = V_e(n-1) + V_e(n+1) - 2V_e(n) \quad (2)$$

In addition, the internodal myelinated portion of the fibres was explicitly modelled in order to match empirical data with regards to conduction velocity and strength-duration. The fibre geometry also plays an important part in the axon cable model, since it strongly affects physiological properties such as the action potential conduction velocity and the sensitivity to extra cellular stimuli [21]. In the current model, the fibre geometry was defined by its internodal length L (mm), the outer diameter D (μm), the internodal axon inner diameter d (μm)

Fig. 1. (a) Parameters defining the geometry of the axon cable model where D is the outer diameter, d the inner diameter, d_n the nodal diameter, and L the internodal distance. (b) and (c) DBS lead with simulated electric potential together with red markers displaying the locations of the axon cable model. Here the axon models were located in a plane at the level of the active contact. (d) DBS lead together with red markers displaying the locations of the axon cable model in planes at multiple locations along the lead. The axon cable models were oriented perpendicular to the DBS lead in all cases.

and the nodal axon diameter d_n (μm) (Fig. 1a). The relation between L and d was approximated by a power law according to

$$L = 146 d^{1.12} \quad (3)$$

where

$$d = D * 0.74 (1 - \exp(-D/1.15)) \quad (4)$$

This relationship was derived from morphometric data of mammalian CNS fibers [28-31] and is valid for D in the interval 1.5 to 10 μm .

Definitions of the nodal parameters used in the model are presented in the Appendix, together with plots presenting the relation between d , D and L for the morphometric data used for construction of the axon model. Ionic membrane conductance at nodes of Ranvier were modelled based on data by Schwarz et al. [27] who studied human peripheral nerves (see Appendix). The leak conductance, g_L at nodes of Ranvier and the fiber diameter D are the only parameters that were varied in order to match the fiber model to available data for clinical DBS data. All the other parameters were obtained from experimental literature. In order to optimize g_L , computed chronaxies were matched to strength-duration data for stimulation in ventral intermedius nucleus of thalamus and the internal segment of the globus pallidus (GPi) [32, 33]. Relevant fiber-diameter range for clinical DBS was estimated by matching simulation results to threshold-distance data for thalamic DBS [34].

Axon cable models with 21 nodes were constructed for a range of different axon diameters (2.0 to 7.5 μm) corresponding to a range in internodal length of 0.182 to 0.994 mm [31, 35]. The axon models were implemented in MatLab (The MathWorks, USA), and the solver 'ode15' was used to integrate the differential equations describing each axon cable model.

B. DBS model

A model of the DBS lead as well as surrounding tissue was set up and used for simulation of the stimulation field. The DBS lead was modelled with a diameter of 1.27 mm, 4 electrode contacts with a height of 1.5 mm separated by 0.5 mm in order to mimic Medtronic lead model 3389, (Medtronic Inc., USA). The surrounding tissue was modelled as a sphere with a radius of 30 cm placed as the outer boundary from the active electrode contact. Homogeneous brain tissue was assumed for the sphere and the layer of distributed resistance, and was modelled with a conductivity $\sigma = 0.1$ S/m. Simulations were carried out during single contact monopolar settings where contact 1 was active and the outer boundary of the tissue was set to ground. Non active contacts were set to floating [36]. The total impedance of the model during single contact monopolar settings was 1 k Ω . Simulations were carried out with COMSOL Multiphysics 4.4 (COMSOL AB, Stockholm, Sweden) and consisted of approximately 500,000 tetrahedral mesh elements. The mesh density was defined by the built in physics-controlled mesh generator, where the smallest elements were located by the electrode contacts in order to capture the strong electric field gradients by the edges. The distribution of the electric potential, V_e , in the tissue was simulated for various DBS amplitudes (V_{DBS}) by solving the Laplace equation for steady currents [37]:

$$\nabla \cdot \vec{J} = -\nabla \cdot [\sigma \nabla V_e] = 0 \quad (5)$$

For each amplitude, the distribution of the electric potential was sampled in a region of interest and exported to MatLab. The sampled region of interest was defined as a plane at the level of the active contact, perpendicular to the lead (XY-plane) with a radial extension of 0 to 7 mm in X, and -20 to 20 mm in Y.

C. Simulations

By combining the constructed axon cable models, the exported field distributions, and a function that defined the stimulation waveform over one stimulation cycle, the axonal responses to extracellular stimulation were computed. The function defining the stimulation waveform was based on output from the Medtronic Irel II device [38], and consisted of a cathodic-first biphasic charge-balanced waveform with a 0.4 ms interphase gap. The width of the cathodic pulse was related to the pulse width, while the anodic counter-pulse width was set to 10 times that of the cathodic pulse with an amplitude 0.1 times the cathodic pulse amplitude. The cathodic pulse amplitude was defined as the cathodic-peak to anodic-peak voltage of the DBS waveform.

Axon models were positioned perpendicular to the lead within the sampled region of interest at a radial distance of 0.7 to 7 mm, in steps of 0.1 mm from the center of the DBS lead (Fig. 1b and Fig. 1c). For each stimulation configuration the maximum radial distance for which the axon was activated was stored. At this location of activation the field strength was measured. The field strength was measured in three different entities; the electric potential (V_T), the magnitude of the

Fig. 2. Normalized simulated activation field thresholds, V_T , E_T , $\nabla^2 V_T$, for nine stimulation amplitudes ($V_{DBS} = 1.0$ to 5 V, in steps of 0.5 V), four pulse widths ($T = 30, 60, 90$ and $120 \mu s$), and a fiber diameter, D , of $2.5 \mu m$.

gradient of the electric potential (∇V_T) commonly referred to as the electric field strength (E_T), and the divergence of the electric field ($\nabla^2 V_T$) which is a generalization of the second derivative of the electric potential in three dimensions. In total, 288 simulations were carried out for the fiber diameters, D , (2.0 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, and $7.5 \mu m$), pulse widths, T , (30, 60, 90, and $120 \mu s$), and stimulation amplitudes, V_{DBS} , (1.0 to 5.0 V; in steps of 0.5 V). In order to further investigate the relationship between axonal activation and V_T , E_T , and $\nabla^2 V_T$ additional simulations were carried out for axon diameters of 2.5, 5.0, and $7.5 \mu m$, during stimulation with V_{DBS} of 3 V, and a pulse width set to $60 \mu s$. Axons were then located in the vicinity of the DBS lead similar to the previously explain simulation set up, but in multiple planes separated by 0.1 mm to cover the full field along the lead (Fig. 1d). The result was visualized with stimulation fields for each entity (V_T , E_T , and $\nabla^2 V_T$) as derived at the level of the active contact, together with red markers at the locations where the axons were activated.

Fig. 3. Normalized simulated activation field thresholds, V_T , E_T , $\nabla^2 V_T$, for nine stimulation amplitudes ($V_{DBS} = 1.0$ to 5 V, in steps of 0.5 V), four pulse widths ($T = 30, 60, 90$ and $120 \mu s$), and a fiber diameter, D , of $5.0 \mu m$.

Fig. 4. Normalized simulated activation field thresholds, V_T , E_T , $\nabla^2 V_T$, for nine stimulation amplitudes ($V_{DBS} = 1.0$ to 5 V, in steps of 0.5 V), four pulse widths ($T = 30, 60, 90$ and 120 μ s), and a fiber diameter, D , of 7.5 μ m.

D. Data analysis

Activation field thresholds (V_T , E_T and $\nabla^2 V_T$) at the location of activation were derived for all stimulation configurations. Median field thresholds (*median*) and range (*min-max*) were calculated for each axon diameter and pulse width. In order to compare the activation field thresholds for each entity (V_T , E_T , and $\nabla^2 V_T$) they were normalized with the activation field strength derived during the lowest stimulation amplitude setting i.e. $V_{DBS} = 1.0$ V.

E. Comparison with other models

In order to relate our results to existing DBS models our results were compared with voltage-distance data from a widely used axon model developed by McIntyre et al. [4, 39]. Their voltage-distance data was derived during stimulation with a $T = 100$ μ s and $D = 5.7$ μ m. The axon diameter of our model was adjusted in order to align with their results.

In addition, our derived activation threshold levels were compared with two previous studies where neural activation during DBS was investigated [34, 40]. In the study by Kuncel et al. [34] the spatial extent of activation in thalamic DBS during stimulation with a $T = 90$ μ s was investigated. When compared with our results their derived relationship was implemented as:

$$r(U) = \sqrt{\frac{U - U_{offset}}{k}} \quad (6)$$

Where $U_{offset} = 0.1$, and $k = 0.22$.

In addition, comparison were carried out with the results of Madler and Coenen [40] who presented a function that describes the radius of the volume of activated tissue during stimulation with $T = 60$ μ s in the subthalamic nucleus target area:

$$r(\Omega, U) = -\frac{k_4 \Omega - \sqrt{k_4^2 \Omega^2 + 2k_1 k_4 \Omega + k_1^2 + 4k_3 U + k_1}}{2k_3} \quad (7)$$

Where r is the radius of the VTA, Ω the tissue impedance, U the stimulation amplitude in volt, and k_1 , k_3 , and k_4 the derived constants. When compared to our results the following constants were applied:

$$k_1 = -1.0473, k_3 = 0.2786, k_4 = 0.0009856, \text{ and } \Omega = 1000$$

III. RESULTS

A. Activation field thresholds

Activation field thresholds were derived for V_T , E_T , and $\nabla^2 V_T$ for all simulated axon diameters, pulse widths, and V_{DBS} settings. The activation field thresholds were normalized for comparison between the different entities. Normalized results for the axon diameters 2.5 , 5.0 , and 7.5 μ m and the different pulse width are presented in Fig. 2, Fig. 3 and Fig. 4. Activation field thresholds for the electric potential, V_T increased substantially along with an increased V_{DBS} . The influence of the amplitude was most pronounced for the smallest fiber diameter and shortest pulse width (Fig. 2). Activation field thresholds for the electric field, E_T , increased with increased amplitude for the smallest fiber diameter, but remained approximately constant for larger fibers ($D = 5$ μ m and 7.5 μ m) (Fig. 3 to 4). Activation field thresholds for $\nabla^2 V_T$ decreased with increased stimulation amplitude for all fiber diameters and pulse widths. Median and range of the normalized activation field thresholds for V_T , E_T , and $\nabla^2 V_T$ during stimulation with $T = 60$ μ s are presented in Table 1. For large axons (5.0 and 7.5 μ m) the *median* of E_T was close to 1 with a relatively small range (1.00 to 1.19) and (0.97 to 1.06) respectively, while V_T and $\nabla^2 V_T$ showed larger ranges. Absolute activation field thresholds for V_T , E_T , and $\nabla^2 V_T$ are presented in Table 2.

TABLE 1.
NORMALISED ACTIVATION FIELD THRESHOLDS OF THE ELECTRIC POTENTIAL V_T (V), THE ELECTRIC FIELD E_T (V/MM), AND THE DIVERGENCE OF THE ELECTRIC FIELD $\nabla^2 V_T$ (V/MM²) FOR THE THREE DIFFERENT AXON DIAMETERS, D , AT A PULSE WIDTH OF 60 μ s. ACTIVATION FIELD THRESHOLDS WERE DERIVED FOR AMPLITUDES, V_{DBS} , OF 1 TO 5 V. NORMALISATION WAS PERFORMED WITH ACTIVATION FIELD THRESHOLDS FOR THE LOWEST, V_{DBS} , VALUE I.E. 1 V.

	$D = 2.5$ μ m			$D = 5.0$ μ m			$D = 7.5$ μ m		
V_{DBS}	V_T	E_T	$\nabla^2 V_T$	V_T	E_T	$\nabla^2 V_T$	V_T	E_T	$\nabla^2 V_T$
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.5	1.27	1.07	0.94	1.27	1.05	0.90	1.22	0.97	0.82
2	1.55	1.18	0.96	1.47	1.05	0.75	1.43	0.99	0.69
2.5	1.78	1.23	0.92	1.66	1.07	0.71	1.63	1.04	0.70
3	1.97	1.26	0.85	1.86	1.10	0.69	1.79	1.03	0.63
3.5	2.14	1.28	0.80	2.04	1.12	0.63	1.96	1.04	0.59
4	2.36	1.36	0.83	2.20	1.15	0.59	2.11	1.06	0.52
4.5	2.48	1.33	0.76	2.34	1.17	0.61	-	-	-
5	2.68	1.37	0.76	2.50	1.19	0.61	-	-	-
<i>Min</i>	1.00	1.00	0.76	1.00	1.00	0.59	1.00	0.97	0.52
<i>Median</i>	1.97	1.26	0.85	1.86	1.10	0.69	1.63	1.03	0.69
<i>Max</i>	2.68	1.37	1.00	2.50	1.19	1.00	2.11	1.06	1.00

As expected it was found that the activation field thresholds for all electrical entities were lower for larger fiber diameters and for longer pulse widths. In order to cover the range of clinically relevant axon diameters in DBS targets, additional simulations were carried out for axons in the range 2.0 to 5.0 μm in steps of 0.5 μm (Tab. 3).

Comparisons between V_T , E_T , and $\nabla^2 V_T$ and axonal activation were also carried out at different depths along the lead for axon diameters of 2.5, 5.0, and 7.5 μm . The results was visualized with stimulation field isolevels for each entity (V_T , E_T , and $\nabla^2 V_T$) at thresholds derived at the level of the active contact. Red markers displays the locations where action potentials was initiated (Fig. 5). It was found that all the electrical entities roughly fitted the volume of axonal activation, although none of the electrical entities aligned perfectly with the VTA.

B. Comparison with other models

The results from our axon model were compared with voltage-distance data from McIntyre's axon model (Fig. 6a). In order to align the results a pulse width of 100 μs and an axon diameter of 3.5 μm were used for our axon model, contrary to what was used in McIntyre's study 5.7 μm and 100 μs . The difference in axon diameter was to a large part related to how the two models calculated the diameter based internodal length. After this adjustment both models showed similar results. In Fig. 6b two activation field thresholds for the electric field (0.165 V/mm and 0.190 V/mm) were used for comparison with the results of Kuncel et al. and Madler and Coenen. The electric field matched well with both studies.

TABLE 2.

ABSOLUTE ACTIVATION FIELD THRESHOLDS OF THE ELECTRIC POTENTIAL V_T (V), THE ELECTRIC FIELD E_T (V/MM), AND THE DIVERGENCE OF THE ELECTRIC FIELD $\nabla^2 V_T$ (V/MM²) FOR THREE DIFFERENT AXON DIAMETERS D (μm), AT A STIMULATION PULSE WIDTH T OF 60 μs . ACTIVATION FIELD THRESHOLDS WERE DERIVED FOR DIFFERENT AMPLITUDES V_{DBS} (V).

	$D = 2.5 \mu\text{m}$			$D = 5.0 \mu\text{m}$			$D = 7.5 \mu\text{m}$		
V_{DBS}	V_T	E_T	$\nabla^2 V_T$	V_T	E_T	$\nabla^2 V_T$	V_T	E_T	$\nabla^2 V_T$
1	0.428	0.255	0.362	0.271	0.100	0.921	0.216	0.062	0.448
1.5	0.544	0.274	0.342	0.344	0.105	0.831	0.264	0.061	0.369
2	0.662	0.301	0.349	0.398	0.106	0.692	0.309	0.062	0.307
2.5	0.761	0.315	0.332	0.450	0.107	0.656	0.351	0.065	0.314
3	0.844	0.323	0.309	0.504	0.110	0.634	0.386	0.064	0.281
3.5	0.914	0.326	0.290	0.553	0.112	0.578	0.423	0.065	0.266
4	1.009	0.346	0.301	0.595	0.115	0.544	0.455	0.066	0.232
4.5	1.063	0.338	0.277	0.632	0.117	0.565	-	-	-
5	1.146	0.351	0.277	0.677	0.119	0.559	-	-	-
Min	0.428	0.255	0.277	0.271	0.100	0.544	0.216	0.061	0.232
Median	0.844	0.323	0.309	0.504	0.110	0.634	0.351	0.064	0.307
Max	1.146	0.351	0.362	0.677	0.119	0.921	0.455	0.066	0.448

IV. DISCUSSION

Finite element DBS models were coupled to a novel axon model in order to investigate the relationship between neural activation and the stimulation field strength at the location of activation. The results showed that the VTA can be approximated by a constant stimulation field threshold (V_T , E_T , or $\nabla^2 V_T$) presented in this study without the need to couple axon models to the finite element solution. The simulations were carried out for clinically relevant amplitudes and pulse widths typically used for treatment of Parkinson's disease [1].

TABLE 3.

MEDIAN AND RANGE (MIN-MAX) OF THE ELECTRIC FIELD, E_T , (V/MM) ACTIVATION THRESHOLDS FOR VARIOUS PULSE WIDTHS T (μs) AND AXON DIAMETERS D (μm) IN STEPS OF 0.5 μm . SIMULATIONS WERE CARRIED OUT FOR AMPLITUDES OF 1 TO 5 V IN STEPS OF 0.5 V (N = 9).

	<i>Pulse width, $T \mu\text{s}$</i>			
$D \mu\text{m}$	30	60	90	120
	0.765	0.457	0.376	0.323
2.0	(0.556-0.833)	(0.371-0.538)	(0.288-0.433)	(0.255-0.351)
	0.504	0.323	0.240	0.210
2.5	(0.421-0.538)	(0.255-0.351)	(0.205-0.279)	(0.167-0.237)
	0.376	0.240	0.185	0.157
3.0	(0.322-0.401)	(0.205-0.264)	(0.150-0.202)	(0.126-0.167)
	0.300	0.185	0.142	0.121
3.5	(0.255-0.316)	(0.161-0.202)	(0.126-0.154)	(0.108-0.135)
	0.240	0.150	0.115	0.096
4.0	(0.226-0.264)	(0.137-0.160)	(0.100-0.130)	(0.087-0.111)
	0.225	0.142	0.107	0.090
4.5	(0.205-0.237)	(0.126-0.149)	(0.093-0.119)	(0.080-0.100)
	0.177	0.110	0.087	0.074
5.0	(0.161-0.192)	(0.100-0.119)	(0.075-0.094)	(0.066-0.078)

A. Activation field thresholds

Activation threshold levels for the electric potential, the electric field, and the divergence of the electric field, were derived at the location of activation during one contact monopolar stimulation. Simulations showed that the derived field thresholds were dependent upon stimulation amplitude, pulse width, and axon diameter. The electric field, E_T , showed the least sensitivity to stimulation amplitude, and were approximately independent of the amplitude for large axons (Fig. 2, Fig. 3, Fig. 4 and Table 1). This suggests that the VTA for large axons can be approximated by a constant electric field threshold independent of the stimulation amplitude, while for smaller axons the stimulation amplitude should be considered when using the electric field as an approximation of the VTA. The electric potential field thresholds, V_T , increased substantially with increased stimulation amplitude and showed a non-linear appearance. This has also been shown by Chaturverdi et al., [10]. The activation thresholds for the divergence of the electric field, $\nabla^2 V_T$, decreased with increased stimulation amplitude. Similarly McIntyre et al. [4, 14] showed a non-linear decrease of the activation field strength by increased distance to axon for the second derivate of the electric potential.

Since the mechanisms of DBS are not well understood, it is not know which neurons are primarily responsible for the therapeutic effects and side effects. It is likely that certain side-effects are related to stimulation of large axons such as

Fig. 5. Axonal activation in 3D for the electric potential V_T the electric field E_T and the second derivative of the electric potential $\nabla^2 V_T$. The simulations were carried out for a stimulation amplitude V_{DBS} of 3.0 V, and pulse width T of 60 μs , and axon diameters D of 2.5 μm , 5.0 μm , and 7.5 μm . The red markers represents the location where the axon cable models were activated.

capsular fibers, while other effects may be related to stimulation of smaller axons when nuclei are targeted such as the STN or the GPi. Measurements of axon diameters inside the STN and GPi have shown axon diameters ranging from 0.1 to 2.5 μm [41]. In a model-based study axons in the STN were modelled with a diameter of 2 μm , while axons in the fields of Forel H2, substantia nigra, and zona incerta were modelled with a diameter of 3 μm [24]. In order to cover this range of axon diameters additional simulations were also carried out and electric field thresholds were derived and presented in Table 3.

B. Visualization

Several previous studies have used an electric field isolevel of 0.2 V/mm for defining the stimulation field [12, 13, 42]. In our study this isolevel correspond to a fiber diameter between 3 and 3.5 μm for a pulse width of 60 μs (Table 3). When comparing the simulations with the results of Kuncel et al., and Madler and Coenen the 0.165 V/mm and 0.190 V/mm isolevels (Fig. 6b) would correspond to axon diameters between 3 and 4 μm . Multiple electric field isolevels have also been used to define and display the stimulation field [43, 44]. Such multilevel presentations might be useful in order to visualize tentative activation of different axons. Independent of the threshold chosen for visualization, the electric field has the advantage of making relative comparisons possible between patients and studies, since the results are not limited to a specific axon model.

Fig. 6. (a) Comparison of our axon cable model with the axon cable model of McIntyre et al., 2004 [4]. In order to align the results a diameter of 3.5 μm was used for our axon cable model. (b) Comparison between electric field strength and the results of Kuncel, and Madler and Coenen. [34, 40]. Electric field isolevels at 0.165 and 0.190 V/mm correlated very well with the results of those studies.

C. The axon model

As the axon geometry and in particular the internodal length, L , has a substantial impact on the activation threshold, efforts were put to model L based on detailed morphometric data previously reported in the literature [28-31]. From this data a power law (equation 3) was derived to calculate L based on D . Resulting internodal lengths deviate slightly from the commonly approximated relationship of 100:1 [21]. The fit of the power law to the morphometric data is shown in Appendix Fig. 7.

Our axon model is valid for smaller fiber diameters (range 1.5 to 10 μm , see Appendix) than what is commonly used during model-based studies on DBS. This fiber diameter range should be compared to the neuron model presented by McIntyre et al., [39] which is valid for D in the interval 5.7 to 16 μm , and commonly used in the model-based DBS community [14, 17, 23, 24]. When comparing our axon model with this axon model it was clear that there was a difference with regards to axon diameters and corresponding internodal lengths (Fig. 6a). In McIntyre's model a D of 5.7 μm

corresponds to an L of 0.5 mm, while in our model the same axon diameter corresponds to an L of 0.726 mm. Due to the substantial impact of the internodal length on the activation threshold it may be considered in the future to define modelled axons by their internodal length instead of their axon diameter.

D. The DBS model

Model-based studies are in general full of assumptions and simplifications [45, 46]. Thus, model-based investigations should always be considered on a rough level. Nevertheless, models and simulations can be valuable for providing knowledge on a general level, or when relative differences are studied. In the present study, homogeneous tissue was used in order to produce general results. Thus, no heterogeneity such as encapsulation tissue, tissue in-homogeneities, or anisotropic tissue properties were implemented although such properties will influence the results in the patient-specific case.

One contact cathodic monopolar stimulation settings was used together with a model of Medtronic lead model 3389. Thus, the results of this study are only valid for this case and it is not evident that the results can be generalized for other configurations and DBS leads. The underlying reason is that activation of axons is dependent upon the curvature of the stimulation field, and different configurations and DBS leads may generate fields with different field curvatures.

The curvature of the stimulation field may also be affected by the location of the grounded reference electrode as shown by Walckiers et al. 2010, [47] and the inclusion of a whole-head model [48]. Field thresholds for the electric field, E_T , showed the smallest influence of field curvatures with only a threshold range of 9% for the largest axon diameter (7.5 μm) during stimulation with 1 to 5 V (Table 1). In order to minimize the influence of the curvature of the stimulation field, the electric field thresholds, E_T , may be preferred when approximating the VTA with a constant stimulation field threshold. Future studies may investigate how these activation thresholds are related to other modes of stimulation, such as double monopolar, bipolar, and tripolar stimulation, or stimulation with other DBS leads. In addition, patient specific tissue models with axons positioned in a patient-specific manner in the vicinity of the DBS lead have been used extensively in the past [7, 14, 17, 23]. Similar studies could be carried out to investigate the impact of tissue heterogeneity [13] and anisotropy [44] on the stimulation field thresholds.

V. CONCLUSION

A neuron model valid for small axon diameters has been introduced and used together with finite element models of DBS for calculation of activation field thresholds. Results showed that the electric potential, the electric field as well as the second derivative of the electric potential can be used to approximate the VTA without the need to couple axon models to the finite element solution. Electric field thresholds showed the least sensitivity to stimulation amplitude, and were approximately independent of the amplitude for large axons. The activation field strength thresholds presented in this study may be used in future studies to approximately define the VTA during model-based investigations of DBS.

APPENDIX

A. Axon model

Ionic membrane conductance at nodes of Ranvier were modelled following data by [27] on human peripheral nerves. Nodal width was assumed 1 μm independent of fiber diameter. Original data at 20°C have been corrected for 37°C using appropriate Q_{10} factors [25]. For clarity, units are given in behind the equations.

Transient Na^+ current:

$$i_{\text{Na}} = m^3 h p_{\text{Na}} F^2 \frac{V_m}{RT} \frac{[\text{Na}_{\text{in}}] - [\text{Na}_{\text{out}}] e^{-(FV_m/RT)}}{1 - e^{-(FV_m/RT)}} \text{ (A/m}^2\text{)}$$

$$dm/dt = \alpha_m(1 - m) - \beta_m m \text{ (Hz)}$$

$$dh/dt = \alpha_h(1 - h) - \alpha_h h \text{ (Hz)}$$

$$\alpha_m = 6.81 \times 10^6 \times (V_m + 0.0184) / (1 - e^{(-0.0184 - V_m)/0.0103}) \text{ (Hz)}$$

$$\beta_m = 3.15 \times 10^5 \times (-0.0227 - V_m) / (1 - e^{(V_m + 0.0227)/0.00916}) \text{ (Hz)}$$

$$\alpha_h = 2.17 \times 10^5 \times (-0.111 - V_m) / (1 - e^{(V_m + 0.111)/0.0110}) \text{ (Hz)}$$

$$\beta_h = 1.48 \times 10^4 / (1 + \exp^{(-0.0288 - V_m)/0.0134}) \text{ (Hz)}$$

Fast K^+ current:

$$i_{\text{Kf}} = g_{\text{Kf}} n^4 (V_m - E_K) \text{ (A/m}^2\text{)}$$

$$dn/dt = \alpha_n(1 - n) - \beta_n n \text{ (Hz)}$$

$$\alpha_n = 5.46 \times 10^4 \times (V_m + 0.0932) / (1 - e^{(-0.0932 - V_m)/0.00110}) \text{ (Hz)}$$

$$\beta_n = 9.71 \times 10^4 \times (-0.0760 - V_m) / (1 - e^{(V_m + 0.0760)/0.0105}) \text{ (Hz)}$$

Slow K^+ current:

$$i_{\text{Ks}} = g_{\text{Ks}} s (V_m - E_K) \text{ (A/m}^2\text{)}$$

$$ds/dt = \alpha_s(1 - s) - \beta_s s \text{ (Hz)}$$

$$\alpha_s = 8.34 \times 10^3 \times (V_m + 0.0125) / (1 - e^{(-0.0125 - V_m)/0.0236}) \text{ (Hz)}$$

$$\beta_s = 5.05 \times 10^3 \times (-0.0801 - V_m) / (1 - e^{(V_m + 0.0801)/0.0218}) \text{ (Hz)}$$

Leak current:

$$i_L = g_L (V_m - E_L) \text{ (A/m}^2\text{)}$$

The nodal membrane parameters used in our model are listed in Table 4.

TABLE 4.
PARAMETER VALUES USED FOR NODES OF RANVIER IN THE AXON MODEL.

Parameter	Value	Unit	Reference
c_{node}	0.028	F/m ²	[25]
p_{Na}	$7.04 \cdot 10^{-5}$	m/s	[27]
$[\text{Na}_{\text{in}}]$	20	mM	
$[\text{Na}_{\text{out}}]$	154	mM	
E_K	-0.084	V	
g_{Kf}	300	S/m ²	
g_{Ks}	600	S/m ²	
E_L	-0.084	V	This study
g_L	400	S/m ²	

The myelin conductance and capacitance are inversely related to the number of myelin lamella $n_l = D(1 - g)/2d_l$ where each lamella is $d_l = 24$ nm thick:

$$G_{\text{my}} = \pi DL \frac{1+g}{2n_l} g_{\text{lam}} \quad (\text{S})$$

$$C_{\text{my}} = \pi DL \frac{1+g}{2n_l} c_{\text{lam}} \quad (\text{F})$$

The axial conductance g_A between adjacent model segments is given by

$$g_A = \frac{\pi d^2}{2L\rho_a} \quad (\text{S})$$

The electrical parameters describing the myelinated fiber portions are summarized in Table 5.

TABLE 5.
PARAMETERS VALUES USED FOR AXIAL AND MYELINATED SEGMENTS OF THE AXON.

Parameter	Value	Unit	Reference
g_{lam}	5	S/m ²	[49]
c_{lam}	0.0005	F/m ²	
ρ_A	0.40	$\Omega \cdot \text{m}$	[50]
V_{rest}	-0.084	V	[27]

The relation between d , L and D for the morphometric data used for construction of the axon fiber model are presented in Fig. 7.

Fig. 7. Morphometric data used for construction of the fiber model. (a) Experimental relation between axon inner diameter, d , and internodal length (L). (b) Dependence of normalized nodal diameter on axon inner diameter. (c) Variation of the ratio between d and D with fiber outer diameter. Drawn lines in the plots correspond to empirical fits to the data as described in equation 3 and 4.

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