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Modelling details for electric field simulations of deep brain stimulation

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Abstract. Deep brain stimulation is a well-established technique for symptomatic treatment of e.g. Parkinson's disease and essential tremor. Computer simulations using the finite element method (FEM) are widely used to estimate the affected area around the DBS electrodes. For the reliability of the simulations, it is important to match used simulation parameters with experimental data. One such parameter is the electric field magnitude threshold EF_t required for axon stimulation. Another is the conductivity of the perielectrode space (PES) around the electrode. At the acute stage after surgery the PES will be characterized by an increased conductivity due to inflammation and edema while the later chronic stage will be characterized by a lower conductivity due to gliosis and minor scar formation. In this study, the EF_t and the electric conductivity of the PES have been estimated by comparing FEM simulations with clinical studies of activation distance, pulse length and electrode impedance. The resulting estimates are an EF_t of 0.2 V/mm at the common pulse width of 60 μ s and a chronaxie of 62 μ s. Estimated electric conductivities for the PES are 0.14 S/m in the acute stage and 0.05 S/m in the chronic stage, assuming a PES width of 250 μ m. These values are thus experimentally justified to use in FEM simulations of DBS.

Keywords: Deep brain stimulation (DBS), Finite Element Method (FEM), Electric field (EF).

1 Introduction

Deep brain stimulation (DBS) is an established technique for the disruption of pathologic neural overactivity in e.g. Parkinson's disease, essential tremor and dystonia. The exact mechanism of DBS is not known but it has been found to have similar clinical effects as lesioning techniques in the same targets for these disorders when a sufficiently high pulse frequency is used [1-4]. This is possibly due to depletion of neurotransmitters from the synapses of axons triggered with high frequency [5, 6] or more complex network effects from the interaction between different brain structures [7].

Typical parameters that can be changed in DBS are amplitude (voltage or current), pulse width and pulse frequency. Increasing the pulse width decreases the required amplitude for both therapeutic and side effects according to the chronaxie in the Weiss-Lapicque model [8]. Pulse frequency has a more complicated effect where sufficiently

high frequency as mentioned has a similar effect as lesioning while lower frequencies require a higher voltage for the effect [9] and sufficiently low frequency stimulation of e.g. 4 - 20 Hz on the contrary can worsen the pathological effect in overactive areas [9-11].

One way to estimate the tissue affected in the immediate vicinity of the active DBS contacts is to use finite element method (FEM) simulations to calculate the electric field around them [12]. The electric field magnitude (EF) of 0.2 V/mm at a pulse width of 60 μ s has been used in several studies [13-15] as a threshold value for tissue activation but it has so far not been thoroughly justified.

The insertion of the DBS lead in the brain may cause a small, localized inflammation, which seems to contribute to the effect of DBS and could explain why inserting a DBS lead has clinical effect even when off [16]. Another result is that an edema will form in the immediate vicinity of the lead [17], a vicinity often called the perielectrode space (PES) [18, 19]. The increase in tissue fluid of the edema will cause the electric conductivity of the PES to increase and thus affect the electric field around it. With time, the edema will subside and gliosis will form around the lead instead [20, 21]. However, the electric conductivity for the PES is not known for either the acute edema or the chronic gliosis, making it an unknown parameter for FEM modelling.

The aim of this paper is to calculate realistic values for the electric field magnitude threshold, including its rheobase and chronaxie, and to estimate reasonable conductivities for the perielectrode space during acute postoperative edema and later chronic gliosis formation.

2 Methods and results

2.1 Estimation of activation threshold

Alexis Kuncel et al. [22] have made an estimate of the distance, r (mm), from the electrode contact center to the ventrocaudal nucleus (Vc) of the thalamus at which a certain stimulation amplitude triggers side effects from stimulation of the Vc. A pulse width of 90 μ s and a pulse frequency of 160 Hz had been used in this study. They arrived at a relation of threshold voltage, V_{th} (V), and r as

$$V_{th} = 0.1 + 0.22r^2 \quad (1)$$

and from this an effective activation distance can be calculated as

$$r = \sqrt{\frac{V - 0.1}{0.22}} \quad (2)$$

giving an effective activation radius of 2.0 – 3.9 mm for amplitudes of 1 – 3.5 V. Åström et al. found the average EF at these distances for the different voltages to be 0.165 V/mm [12]. This electric field magnitude threshold, EF_t , can be fitted to the Weiss-Lapicque model according to

$$EF_t = EF_{\text{rheo}} \left(1 + \frac{T_{\text{chr}}}{T} \right) \quad (3)$$

where EF_{rheo} is the rheobase (V/mm), T_{chr} the chronaxie (μs) and T the pulse width (μs). With $T = 90 \mu\text{s}$ and a T_{chr} for axon stimulation assumed to be $62 \mu\text{s}$ after least squares fitting (lsqnonlin, Matlab, Mathworks, USA) to the average result from a clinical study by Mario Rizzone et al. (Table 2) [9], this gives an EF_{rheo} of $0.165/(1+62/90) = 0.098 \text{ V/mm}$. The estimated EF_t at the standard pulse width of $60 \mu\text{s}$ then becomes $0.098 \cdot (1+62/60) = 0.20 \text{ V/mm}$. The corresponding strength-duration curve is presented in Fig 1a.

Fig. 1. (a) Strength-duration curves with chronaxies fitted to Rizzone’s experimental [9] and Åström’s simulated [12] data, assuming an EF_t of 0.2 V/mm at a pulse width of $60 \mu\text{s}$. **(b)** Three-dimensional bipolar model for estimation of PES conductivity. The green isosurface corresponds to $EF = 0.2 \text{ V/mm}$.

2.2 Estimation of the conductivity of the perielectrode space

A study by Codrin Lungu et al. [23] was used to estimate the electric conductivity of the perielectrode space under the assumption that it has a characteristic thickness of $250 \mu\text{m}$ [18, 19]. The electric conductivity was set between 0.01 and 0.2 S/m in a parametric sweep in steps of 0.01 S/m with a surrounding tissue domain assumed to be a mixture of gray and white matter with a conductivity of 0.09 S/m . Bipolar stimulation at a voltage, U , of 3 V between contacts 0 and 1 of a 3389 lead (Medtronic Inc., USA) was simulated for the parametric sweep. Modelling and simulation (Fig 1b) was done in Comsol Multiphysics 5.2a (COMSOL, Sweden). For details, see [18]. The impedance, R (Ω), was calculated according to Ohm’s law with the current calculated as the integration of the current density, $\mathbf{J}$ (A/m^3), normal to the surface of contact 0.

$$R = U / \left| \int \mathbf{n} \cdot \mathbf{J} dS \right| \quad (4)$$

In the Lungu study, the average measured impedance in the first week after implantation was 1530Ω and after 3 weeks it had risen to 2530Ω [23]. The parametric sweep gave corresponding closest impedances of 1551Ω for a PES conductivity of 0.14 S/m

and 2619 Ω for a PES conductivity of 0.05 S/m. The PES conductivities of 0.14 and 0.05 S/m are thus suitable values to use for the acute and chronic phases respectively.

3 Discussion

In this study, suitable rheobase and chronaxie to describe the electric field magnitude threshold, EF_t , as well as suitable conductivities of the perielectrode space have been estimated from experimental studies [22, 23].

Hemm et al [24] had associated the 0.1 V/mm isolevel from 1.5 V stimulation to the lateral extent of the GPi in a dystonia patient. However, they had used a very long pulse width of 450 μ s. Putting that pulse width in equation (3) with $EF_{rheo} = 0.098$ V/mm and $T_{chr} = 62$ μ s gives an EF_t of 0.11 V/mm, in good agreement with the 0.2 V/mm level for 60 μ s in this study. Åström et al [12] have studied the impact of the pulse width on EF_t with neuron model simulations. Least squares fitting to their results (Table 3 [12]) gives a T_{chr} of 100 μ s (Fig 1a), which would give an EF_{rheo} of $0.165/(1+100/90) = 0.078$ V/mm and thus an EF_t of $0.078 \cdot (1+100/60) = 0.21$ V/mm at $T = 60$ μ s when comparing to Kuncel's study [22].

Comparing the EF_t of 0.2 V/mm at 60 μ s with simulations of activation of axons with different fiber diameters [12] indicate that the typical diameter of axons stimulated by DBS should be around 3.5 μ m, which is among the larger axons in the deep brain structures although still smaller than the value of 5.7 μ m used in many DBS simulation studies [25]. Median axon diameters for different nuclei and white matter tracts have been found to be around 0.5 μ m in human (range: 0.16 – 9 μ m) and rhesus monkey brains [26, 27].

The 250 μ m thickness of the PES may vary between patients. A larger distance would result in a lower increase in the electric conductivity due to the inflammation/edema and a lower decrease due to the gliosis when estimating the conductivity from measured impedance.

It is interesting to note that the most energy-efficient stimulation occurs at pulse widths equal to the chronaxie [8]. The optimal pulse width to maintain a long battery lifetime is thus the default 60 μ s when the chronaxie of the triggered tissue is the same as in Rizzone's study [9].

In conclusion, based on the experimental studies used, suitable rheobase and chronaxie for axon activation seem to be 0.98 V/mm and 62 μ s respectively, giving a threshold electric field of 0.20 V/mm for the default pulse width of 60 μ s. Suitable values for a 250 μ m PES are 0.14 S/m for the acute edema phase and 0.05 S/m for the chronic gliosis phase. More experimental studies similar to those of Kuncel [22] and Lungu [23] would be desirable in order to further increase the reliability of these estimates and to see if there are differences in them between different parts of the brain.

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