Simulating the Therapeutic Effects of Deep Brain Stimulation in Rodents Using a Cortico-basal Ganglia Network and Volume Conductor Model

Christian Schmidt and Eleanor Dunn and Madeleine Lowery and Ursula van Rienen

Abstract—Models of the cortico-basal ganglia network and volume conductor models of the brain can help to gain insight into the mechanisms of action of deep brain stimulation (DBS). In this study, the coupling of a network model under Parkinsonian conditions to the extracellular field distribution obtained from a 3D finite element model of a rodent’s brain during DBS is presented. This coupled model is used to investigate the influence of variations in the electrical properties and thickness of the encapsulation tissue, which is formed around the electrode body after implantation, on the suppression of oscillatory neural activity during DBS. First results suggest that variation in the properties of the encapsulation tissue, within the range examined, have a limited influence on the suppression of pathological oscillatory activity during DBS in rodents.

I. INTRODUCTION

Deep brain stimulation (DBS) is a neurosurgical therapy used to treat symptoms of neurodegenerative disorders such as Parkinson’s disease (PD). Despite its approval for the treatment of PD and its widely acknowledged success, the mechanisms of action of DBS remain uncertain. Current studies provide evidence that PD causes an excessively synchronized oscillatory neural activity in the cortico-basal ganglia network [1] accompanied by an increased power in the beta band (15 - 30 Hz) frequency range [2]. For almost two decades now, computational models of DBS have been established to investigate its mechanisms of action. Among these models, biological neural networks of the cortico-basal ganglia network based on the excitatory and inhibitory connections between the different deep brain nuclei are used to investigate the effect of common, square-wave DBS signals on the dynamical behaviour of the network [3], [4]. In these network models, the DBS pulses are applied as an internal current to the neurons of the target nuclei, typically the subthalamic nucleus (STN) or globus pallidus interna (GPI) for PD DBS [2]. This modeling approach does not consider the effect of the extracellular field distribution along the neurons, which depends on the electrode geometry, the electrode-tissue interface, and the heterogeneity of the brain tissue as well as its electrical properties. Computational studies based on volume conductor models of the brain have shown that neural activation in the proximity of the stimulation electrode depends strongly on the field distribution caused by the DBS signal and, therefore, on the mentioned factors [5], [6], [7]. In addition, further simulation results suggest that the uncertainty in the electrical properties of brain tissue has a substantial influence on the field distribution and required stimulation amplitude to activate the target nuclei [8]. The aim of this study is to investigate the mechanisms of action of DBS in a computational model by combining a cortico-basal ganglia network model and a volume conductor model of a rodent’s brain. The network model is based on a cortico-basal ganglia network model, which was used in previous studies to investigate the relative effects of antistromic and orthodromic activation of cortico-STN afferents [10]. The nodes of the cortico-STN afferent axons are first identified to ensure proper coupling of the field distribution in the rodent’s brain and the network model. The coupled model is then used to investigate the influence of the electrical properties of the encapsulation tissue, which results from the reaction of the body to the implant, on the suppression of beta band oscillatory activity in the network.

II. METHODS

A. Cortico-basal ganglia network model

The network model is based on a previous cortico-basal ganglia model in which the stimulus to cortico-STN afferent axons was applied using an analytical, purely resistive point source to model the field distribution during DBS [10]. In this network model, the neurons in the STN, and globus pallidus external (GPe) are modeled as single compartment, conductance based Hodgkin-Huxley-models with threshold crossing models representing the interneurons. The cortical neuron consists of a soma, an axon initial segment, a myelinated main axon, comprising five nodes of Ranvier and four internodes, and an axon collateral. Each nucleus and neuron type consisted of a population of 30 neurons. The nuclei were connected by excitatory (glutamergic) and inhibitory (GABA) synapses (Fig. 1). The STN neurons received inhibitory input from the GPe and excitatory input from three randomly chosen cortical neurons. The PD state of the network was simulated by increasing the synaptic gains within the network as described in [9], leading to oscillatory bursting of the STN neurons within the beta frequency range. The network model was implemented in NEURON 7.1 [11]. A time step of 1µs was used and the random seed was

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reused to ensure same connections between the nuclei for each computation. To ensure a stable PD state, the model was initialized for 1500 ms. Afterwards, DBS was modeled by applying the extracellular potential for 500 ms to both the axon collateral and the main axon of the cortical neurons. One run of the network model lasted approximately 30 min on a common workstation (4 × 3.6 Ghz).

B. Extracellular field distribution in the rodent’s brain

The volume conductor model of the rodent’s brain is based on a three-dimensional digital atlas database of the adult C57BL/6J mouse brain. The segmented brain atlas data comprises an average from magnetic resonance microimages of 10 adult males and has an isotropic resolution of 47 μm [12]. The brain surface was parametrized using non-uniform rational B-splines with the software Geomagic Studio® (http://www.geomagic.com). The finite element model of the rodent’s brain was generated using Comsol Multiphysics™ (http://www.comsol.com) by importing the parametrized brain surface model and a model of a DBS microelectrode (diameter: 125 μm, electrode contact height: 320 μm [13]), as illustrated in Fig. 2. The microelectrode was positioned in the STN area ventral and lateral to the thalamus by comparing the image data with the Allen Brain Atlas of the mouse brain (http://atlas.brain-map.org). The electrical ground of the model was set to the area of the cerebellum to model the placement of the ground electrode in the neck of the mouse. A common current-controlled DBS signal with a frequency of 130 Hz and a pulse duration of 60 μs was applied to the electrode contact via a Dirichlet boundary condition [14]. The time-dependent field distribution was computed using the Fourier Finite Element Method [5] by solving the Laplace equation

$$\nabla \kappa(r) \nabla \varphi(r) = 0$$

with the electrical conductivity $\kappa$ and the electrical potential $\varphi$. The electrical conductivity of brain tissue was set to the conductivity of white matter $\kappa_{wm} = 0.064 \text{Sm}^{-1}$ based on literature data [15] determined at a frequency of 2 kHz, which constitutes a good approximation of the dispersive nature of the electrical properties in volume conductor models of the brain [7]. Due to reactions of the body to the implant, scar tissue forms an encapsulation layer around the electrode. The electrical properties and thickness of this highly resistive layer vary considerably within the literature [6], [16]. To capture this variation, its electrical properties and thickness were set to $\kappa_e = (0.0064 \text{Sm}^{-1}, 0.032 \text{Sm}^{-1}, 0.064 \text{Sm}^{-1})$ and $d_e = (10 \mu m, 20 \mu m, 30 \mu m)$, respectively, to investigate the influence of the encapsulation tissue properties on the beta band suppression during DBS.

The collaterals of the cortical neurons branching to the STN were placed randomly and equally spaced in the proximity of the stimulation electrode within a distance of 500 μm to the center of the electrode contact (Fig. 2). The axons of the cortical neurons were orientated perpendicular to the collateral and parallel to the electrode. To ensure a sufficient resolution of the finite element mesh with regards to the size of the collaterals and the axons, manual mesh refinement was applied by setting a maximum mesh size of 25 μm in the area of the collaterals, 50 μm in the area of the axons, and 10 μm at the electrode contact surface. The final mesh consisted of approximately 1.2 million elements resulting in approximately 1.7 million degrees of freedom using quadratic basis functions. The linear system was solved using generalized minimal residual method with a relative tolerance of $1 \cdot 10^{-6}$. The solution time was approximately 4 min on a common workstation (4 × 3.6 Ghz).
A B

C

Average Beta Suppression

PD State (DBS Off)

STN Neuron Activity

Table I

<table>
<thead>
<tr>
<th>Thickness $d_e$</th>
<th>Conductivity $\kappa_e$ [Sm$^{-1}$]</th>
<th>0.032</th>
<th>0.064</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 $\mu$m</td>
<td>$-18.02$ dB</td>
<td>$-17.73$ dB</td>
<td>$-18.20$ dB</td>
</tr>
<tr>
<td>20 $\mu$m</td>
<td>$-18.00$ dB</td>
<td>$-15.83$ dB</td>
<td>$-17.18$ dB</td>
</tr>
<tr>
<td>30 $\mu$m</td>
<td>$-19.12$ dB</td>
<td>$-19.72$ dB</td>
<td>$-19.44$ dB</td>
</tr>
</tbody>
</table>

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The stimulus was chosen based on initial results to stimulate some, but not all, cortical neurons within the target area.

IV. DISCUSSION

The coupling of a cortico-basal ganglia network with the extracellular field distribution in the target area of DBS allows for an investigation of the mechanisms of action of DBS in a simulation model, that captures both volume conductor and network effects. Analytic models of the extracellular field distribution add the spatial location of the neurons to the network model, but are unable to consider effects of the geometry of the electrode, of the brain anatomy and the electrode-tissue-interface. Therefore, in this study a 3D model of a mouse brain was coupled to a network model to investigate the influence of changes in the encapsulation layer parameters on the beta band suppression in the network model during DBS.

Based on the assumption that orthodromic as well as antidromic stimulation of afferent STN neurons contribute to the therapeutic effects of DBS [10], the results suggest that in coupling a network and volume conductor model, the application of the extracellular potential along only the collaterals of the cortical neurons may overestimate the predicted stimulation amplitude required to suppress beta band STN activity (Fig. 4). Furthermore, the magnitude of the beta band oscillatory activity within the network was already substantially reduced at stimulation amplitudes at which not all STN neurons were entrained to the DBS (Fig. 3). This result suggests that DBS models that use the method of the “volume of tissue activated” [5], [6], [8] to predict neural activation during DBS may also overestimate the required stimulus amplitude to obtain therapeutic effects of DBS.

The results of the study suggest that the variations in the conductivity and thickness of the encapsulation tissue within the range examined have only a minor influence on the suppression of beta band activity in the network model. Considering the influence on the extracellular field distribution, a deviation between its minimal and maximal obtained values of approximately 7% and 1.5% for a collateral and axon located at the boundary of the encapsulation tissue and the brain tissue, was determined. These deviations decreased with the distance to the encapsulation layer to 1.4% and 0.9% (distance: 250 µm). The small deviations in the field distribution, especially for neurons further away from the electrode contact could be a result of the small dimensions of the mouse brain and may explain for the minor effect of encapsulation tissue properties on the beta band suppression found in this study. Therefore, a precise knowledge of the encapsulation layer properties in the post-operative state may not be crucial for modeling the mechanisms of action of DBS in the rodent’s brain.

Nevertheless, the development of realistic volume conductor models coupled to network models of the basal ganglia move towards the prediction of required stimulation amplitudes to obtain therapeutic effects of DBS, based on realistic brain anatomy and electrical properties as well as the electrode-tissue-interface and neural dynamics. In this study, the extracellular potential was coupled to the collaterals and axons of cortical neurons, based on the assumption that antidromic as well as orthodromic stimulation of afferent STN neurons contributes to the therapeutic effect of DBS. The results in this study support this hypothesis, but for future studies a more complex coupling to other nuclei and neurons of the network will be incorporated. This will require a more detailed description of the STN neuron geometry and dynamics in the network model. In addition, the volume conductor model should be made more realistic including heterogeneous tissue properties as well as anisotropy, in particular along white matter fibre tracks within the mouse brain.

REFERENCES