A μm-resolution Heterogeneous Tissue Model for the Magnetic Stimulation of Multifascicular Sciatic Nerve

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***Abstract*— Efficacy of magnetic stimulation of the central or peripheral nervous system depends on the spatial and temporal distribution of the induced electric field generated by the magnetic coil. Therefore, accurate estimation of the induced electric field is crucial to the design and optimization of magnetic coils, particularly as the coil dimensions are reduced. In this work, we developed a numerical model of a multifascicular sciatic nerve to study the effect of tissue heterogeneity on the induced electric field. Using a multi-resolution electric field solver, we can resolve feature sizes as small as $1\mu m$, allowing inclusion of the nerve membrane and the myelination layer. Preliminary results indicate that fascicle distribution and axons' proximity to each other significantly affect the magnitude and distribution of the induced electric field as compared to traditional homogeneous tissue models for field simulation.**

I. Introduction

Neural stimulation of the central and peripheral nervous systems is an emerging stimulation technology for sensory and motor neuroprosthetic devices. Compared to electrical stimulation, which requires direct tissue contact, magnetic stimulation is non-contacting, which may result in improved longevity of the stimulating device. Magnetic stimulation, and particularly extracorporeal magnetic stimulation with large coils, has been found effective in clinical practice. Transcranial magnetic stimulation has been proposed as an alternative technique to electroconvulsive therapy for seizure and depression disorders [1]. Magnetic stimulation is also clinically studied for peripheral nerve stimulation [2] and has been commercialized to reduce neuropathic pain [3].

However, for magnetic stimulation to be effective for neuroprosthetic applications, the area stimulated must be much smaller than that possible with large, extracorporeal coils. Recently, we successfully demonstrated the magnetic stimulation of feline's sciatic nerve via solenoid coils [4], using the ability to generate graded neuronal and muscular action potentials to illustrate its efficacy. Our present research focuses on studying the underlying mechanisms of magnetic stimulation to identify the key coil and stimulator design parameters. There have been multiple studies to investigate the theoretical value of the induced electric field [5], the efficiency of the magnetic stimulation [6], and localization of the excitation [7]. However, these studies have assumed a homogeneous tissue medium to predict the stimulation efficacy [8].

Despite these studies, we recognize that neuronal tissue is heterogeneous. Few studies have been performed to formulate the impact of the surface boundary between differing tissues on the induced electric field distribution. In particular, one study [9] expressed the analytical formulation of the induced field in 3-dimensions for the semi-infinite boundary between air and the tissue. However, the brain and peripheral nerves are finite-dimensional heterogeneous tissues with curved boundaries [10]. Thus, more accurate prediction of the induced electric field calls for an anatomically driven tissue model. Some studies have used finite element (FEM) based numerical models to study the tissue heterogeneity and anisotropy in peripheral nerves [11]. However, voxels with sizes on the order of $1mm^3$ have been used, which limits the complexity of the model to cm-sized tissue structures. To characterize the effect of heterogeneity inside the peripheral nerve, feature sizes of $1\mu m$ need to be resolved. Therefore, the simulation model should include different conductive media such as the axon's membrane, including the impact of myelination and Nodes of Ranvier, the intracellular space, and the extracellular space. To study the effect of the boundary between intracellular and extracellular regions of the axon, a modified cable model for the axon was presented [12]. The modified cable model is limited to simple geometry which has axial symmetry. To study the induced electric field for anatomically correct models [13], the numerical model needs to be created based on the histological data of the nerve.

In this work, we develop a μm-resolution numerical model of a multifascicular sciatic nerve based on a histological cross-section image [13]. The key motive for using this model is to preserve the information of fascicle distribution and to study the effect of the fascicle boundaries on the induced electric fields. We also studied the effect of densely packed, randomly distributed axons on the transmembrane current and induced field (both intracellular and extracellular) for each axon.

II. Magnetic Neural Stimulation

Magnetic stimulation uses the induction principle to induce current at the stimulation site (Figure 1 (a)). Based on electromagnetic theory, the dependence of the induced electric field $\vec{E}$ on the time varying magnetic field $\vec{B}$ can be represented by Equation 1. The induced electric field can be solved in terms of the magnetic vector potential $\vec{A}$ using

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Equation 2.

$$\vec{\nabla} \times \vec{E} = -\frac{\partial \vec{B}}{\partial t} = -\frac{\vec{\nabla} \times \vec{A}}{\partial t} \quad (1)$$

$$\vec{E}(r,t) = -\frac{\partial \vec{A}(r,t)}{\partial t} - \vec{\nabla} V(r,t) \quad (2)$$

where $\vec{\nabla} V(r,t)$ represents the electric field generated by the surface charge due to the tissue heterogeneity. For a homogeneous medium, $\vec{\nabla} V(r,t) = 0$ and analytical formulations have been presented to calculate the electric field in the homogeneous media (tissue) due to the magnetic coil [8]. However, in response to the change in tissue conductivity in the direction of the induced electric field, significant surface charge can be generated at the heterogeneous interface [9]. Therefore, for a heterogeneous structure such as the multifascicular sciatic nerve, the electric field can be greatly affected by the surface charge density. In the following section, we developed an impedance network based numerical model to include the effect of interfaces between different tissues. To generate the time-varying current in the magnetic coil, a pulse discharge circuit is commonly used [5], [8]. Traditionally, magnetic stimulation requires a high current pulse (~0.5-4 kA) for very short time (100 μs to 2 ms) [4], [5]. The magnitude and shape of the current pulse can be controlled by the coil inductance L, the discharge capacitor C, and the coil resistance R (Figure 1(b)). The temporal distribution of the induced electric field is directly proportional to the time derivative of the current in the coil.

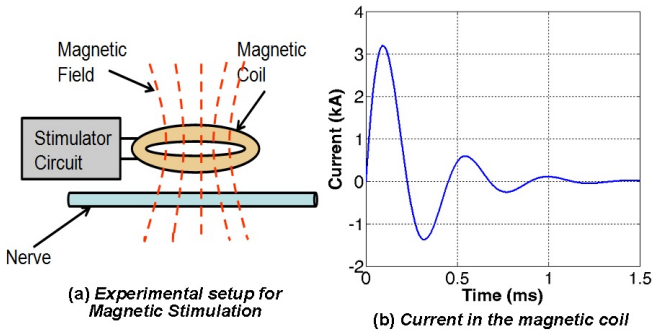

Fig. 1. (a) Block diagram of the experimental magnetic stimulator system. (b) Generated time varying current in the magnetic coil for L_{coil} = 10.32μH, C = 450 μF, R = 80 $m\Omega$, and charging voltage = 700 V.

III. Impedance Method for Field Simulation

The impedance method is a frequency domain solver of the induced electric field $\vec{E}$ by solving Faraday's induction law (results from Equation 1). It discretizes the simulation domain into cuboid voxels (Figure 2) [14]. Each voxel is created using a network of lumped impedances and the value of each impedance is derived from the material properties (e.g. conductivity, permittivity), and the voxel's dimensions. For the fixed frequency and coil current, an analytical expression is used to calculate the 3-dimensional magnetic field generated by the magnetic coil. For the voxel index (i,j,k), in response to the applied time-varying magnetic field intensity

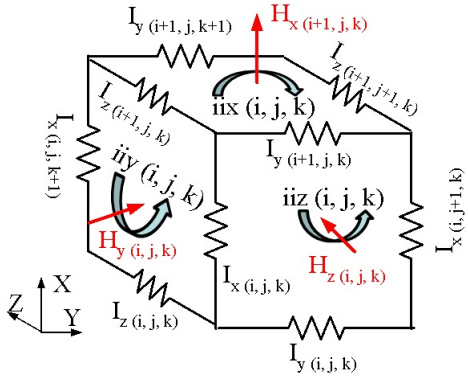

Fig. 2. 3-dimensional voxel used for the impedance method. Loop current is calculated at each face of the cuboid in response to the time-varying magnetic field.

($H_x(i,j,k)$, $H_y(i,j,k)$ or $H_z(i,j,k)$) at the voxel's face, loop currents iix(i,j,k), iiy(i,j,k), and iiz(i,j,k) are calculated by the Kirchhoff voltage law. Branch currents (e.g. I_x(i,j,k), I_y(i,j,k), I_z(i,j,k)) are calculated from the loop currents and the electric field for each voxel is calculated from the branch current, dimensions, and conductivities of each voxel.

IV. Modeling of Multifascicular Sciatic Nerve

The sciatic nerve is a heterogeneous tissue which consists of multiple fascicles [10]. To create a numerical model of the nerve bundle, the fascicle boundaries and their distribution inside the nerve are extracted from the anatomical cross-sectional image of the sciatic nerve [13]. A 3-dimensional model of the nerve bundle is created by extruding the cross sectional image along the nerve and is shown in Figure 3 (a). The distributions and boundaries of different fascicles are shown in the cross sectional view (Y-Z plane) of the nerve model (Figure 3(b)). The nerve is placed along the x-axis and Table I shows the conductivities of different tissue types in different directions [10]. Individual fascicles can be populated using randomly distributed axons as shown Figure 3(c). Moreover, an impedance network model of each axon can be created to include the intracellular, extracellular and axonal membrane (myelination layer) regions (Figure 3(d)).

V. Simulation Model and Induced Electric Field

To correlate our simulation with our in-vivo experimental data [4], a numerical model of the solenoid coil under the same operating conditions was created (Figure 4 (a)). A 30-turn, 22-mm outer diameter solenoid coil was placed adjacent to the nerve. The midpoint between the inner and outer diameters of one side of the coil was centered over the nerve.

TABLE I

Tissue Property

Tissue Type	Conductivity ($\sigma_x, \sigma_y, \sigma_z$) (S/m) [10]
Surrounding tissue	(0.5, 0.5, 0.5)
Nerve membrane	(0.02, 0.02, 0.02)
Epineurium	(0.1, 0.1, 0.1)
Perineurium	(0.01, 0.01, 0.01)
Intracellular space	(0.91, 0.91, 0.91)
Extracellular space	(0.33, 0.33, 0.33)

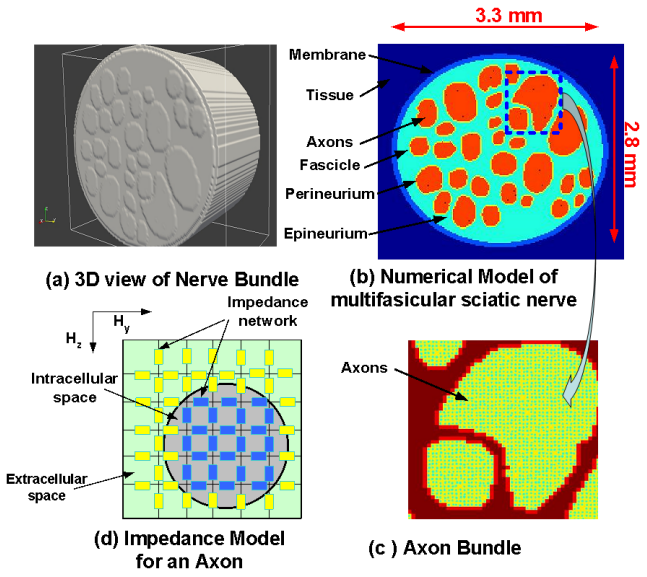

Fig. 3. (a) 3-dimensional model of the multifascicular sciatic nerve (b) cross-section view of the nerve consists of different tissue interfaces (c) distribution of the axons inside the fascicle (d) network model of the individual axon consisting of intracellular and extracellular space.

The distance between the coil and the nerve was 1.5 mm (measured at the point of smallest separation). The modeled nerve was 80-mm long and had an elliptical cross section of 3.3 mm by 2.8 mm. The nerve was embedded in conductive surrounding tissue (e.g. muscle). To simulate the feature size down to $1\mu m$, a multi-resolution impedance method was developed. To include the effect of surrounding tissue for the cm-size magnetic coil, coarse simulation was performed with a resolution of 1 mm over the simulation space of 100 mm (x-dir) x 80 mm (y-dir) x 40 mm (z-dir). To simulate the low resolution region, a multistep field simulation was performed that reduces the resolution of each simulation (e.g. 1 mm $\rightarrow$ 200 μm $\rightarrow$ 40 μm $\rightarrow$ 20 μm $\rightarrow$ 1 μm) and reduces the region of interest similarly. Figure 3(b) shows the cross-section view of the model at a resolution of 20 μm (in Y-Z directions) that includes the fascicle distribution and their boundaries. Along the nerves long axis (x-dir), a coarse resolution (1 mm) was used based on the average distance between nodes of Ranvier for large myelinated axons.

To evoke neuronal activity, traditional magnetic simulators utilize a pulse current in the magnetic coil. The dominant frequency components of the pulse are in the range of 500 Hz to 20 kHz. The induced electric field is directly proportional to the current and the frequency of the current in the coil. Therefore, the impedance method based field solution, at a single frequency and current, can be used to calculate the induced electric field at all frequency components of the current pulse. For our simulations, we use a sinusoidal current of amplitude 600 A at 2 kHz (fundamental frequency component of the current pulse in Figure 1(b)). For the 20 μm resolution heterogeneous model, Figure 4(b), (c) and (e) show the simulated value of electric field in x-, y-, and z- directions, respectively. As shown in Figure 4(b), due to the tissue homogeneity in the x-direction, fascicle

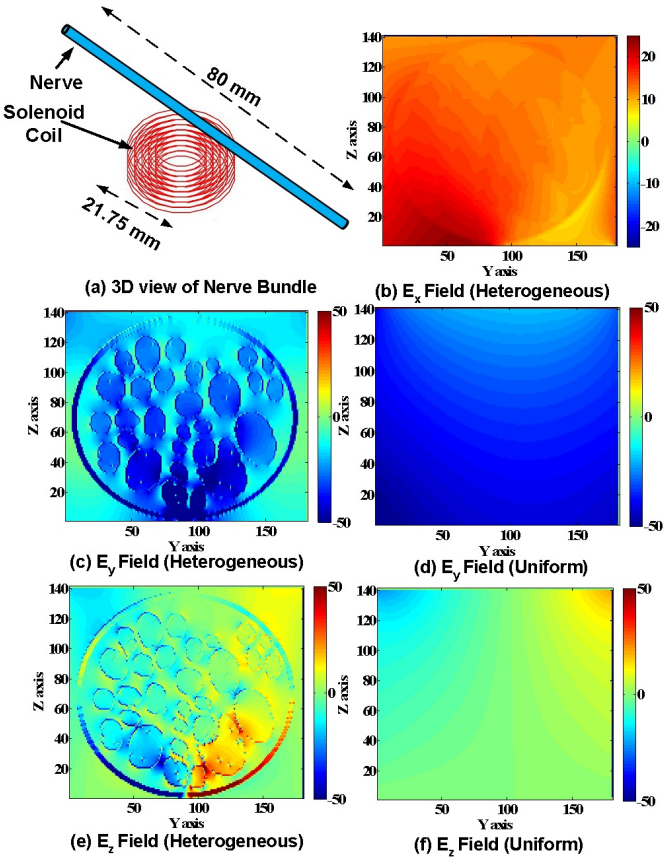

Fig. 4. (a) Orientation and position of the solenoid magnetic coil with respect to nerve bundle. Induced electric field in direction of (b) x- (c) y- and (e) z- directions in effect of fascicle distribution. Induced electric field in (d) y- and (f) z-directions for uniform tissue model. All fields are in V/m. Y-axis and Z-axis are the voxel count in y- and z- direction, respectively (resolution $20\mu m$).

boundaries do not effect E_x significantly. To study the impact of heterogeneity, the induced electric field was compared with the field generated in the uniform tissue model under the same operating conditions. As shown for the uniform model, the induced electric field in y- (E_y, Figure 4(d)) and z- (E_z, Figure 4(f)) directions are homogeneous. However, the induced electric fields for the heterogeneous model in y- (E_y, Figure 4(c)) and z- (E_z, Figure 4(e)) directions demonstrate the field distributions featuring the effect of tissue boundaries.

VI. The Effect of Axon Proximity

Most axons in feline sciatic nerve have a diameter below 20 μm which requires finer resolution voxels ($\sim$ 1μm) to represent the intracellular and extracellular space for each individual axon. Traditionally, 1-dimensional models are used to model transmembrane current i_m due to the induced electric field [5]. The steady-state passive model of the axon calculates i_m as a function of intracellular resistance and applied electric field distribution along the nerve ($i_m = -\frac{1}{r_i}\frac{\partial E_x}{\partial x}$, where r_i is the intracellular resistance per unit length). However, these analytical expressions were derived with the assumption that the axon was placed in an infinite homogeneous extracellular region, and thus there

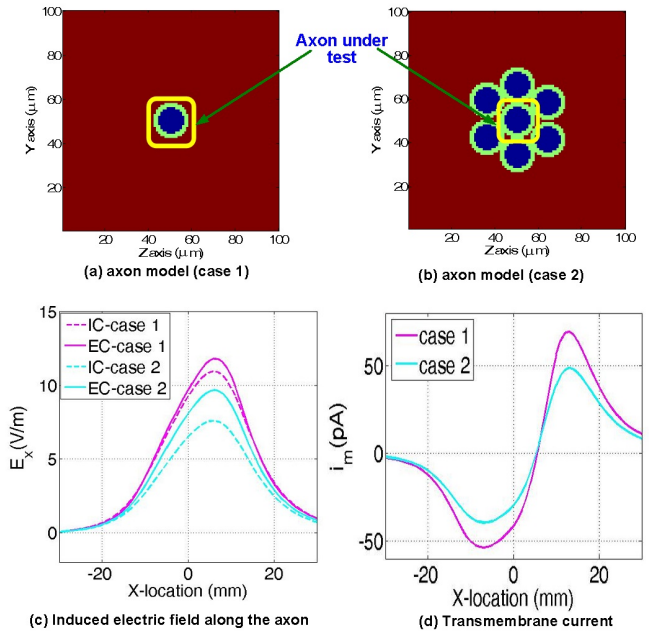

Fig. 5. Cross section view (Y-Z plane) of the numerical model for (a) a single axon model in case 1, and (b) a multi-axon model in case 2. (c) Intracellular (IC) and extracellular (EC) induced electric fields (E_x) for case 1 and case 2. (d) Transmembrane currents (i_m) along the axon for the selected axon in case 1 and case 2. Due to the axon proximity, the intracellular induced electric field for case 2 has $\sim$32% lower electric field.

was no interaction between the axon and its surroundings. To study the impact of axon proximity, two test cases were taken. For the first case, a single axon (diameter 16-μm) was placed in a large homogeneous extracellular medium (Figure 5 (a)). In the second case, the axon was surrounded by the neighboring axons (Figure 5 (b)) to create a high fill factor of $\sim$90%.

For both cases, simulation models of 94 mm x 100 μm x 100 μm were created with the spatial resolution of 1 μm in y and z directions and 1 mm in the x direction. For these simulations, the effective nodal impedance of $\sim$40 MΩ was estimated based on the membrane leakage conductance g_L of 35 mS/cm^2. As shown in Figure 5 (c), the intracellular electric field (E_x) along the central axon in case 1 has a higher magnitude ($\sim$32%) than central axon in case 2. This was due to the close proximity of the other axons to the central axon for case 2. Figure 5 (d) shows the transmembrane current i_m (intracellular to extracellular) along the axon, which reflects the proportionality of the membrane current to the derivative of the induced electric field ($i_m \propto -\frac{\partial E_x}{\partial x}$). In general, fascicles are populated with axons of different radii and can achieve a high fill factor $\sim$90% as shown in case 2. This increases the interaction and coupling between different axons. Therefore, electric field simulation for the homogeneous models cannot provide accurate estimations of the induced electric field and requires numerical simulation as shown in this work.

VII. Conclusion

In this work, we created and simulated a multi-resolution numerical model of a multifascicular sciatic nerve to study the effect of fascicle distributions and axon proximity on the magnetically-induced electric field. It was shown that heterogeneity in the different regions (membrane and axons) of the nerve can significantly alter the electric field. For the densely populated (fill factor $\sim$90%) axons inside a fascicle, the transmembrane current and induced electric field was $\sim$32% lower than the values for the axon placed in the homogeneous extracellular medium. In the future, we intend to increase the complexity of our numerical model by populating the fascicles with different radii axons based on their statistical distribution [10] and use active axon models to estimate the stimulation threshold to make a comparison with the experimental findings. With these models, we can investigate if mm-size magnetic coils can achieve more selective stimulation and provide a more physiologically normal recruitment order. Further, we believe that through these stimulations we can design and optimize magnetic coils and will subsequently compare the simulated neuronal recruitment results.

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