Mechanism Investigation, Device Development, and Treatment Personalization Using Anatomical Models Functionalized with Electrophysiological Neuron Models
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Abstract

By functionalizing high resolution anatomical models with electrophysiologically and morphologically detailed neuron models in anatomically realistic positions, it becomes possible to investigate the interaction of externally or internally applied electromagnetic fields with neuronal dynamics. This has been successfully applied for mechanistic elucidation, safety assessment, therapeutic device development and optimization, as well as treatment personalization related to the fields of neuroprosthetics, neurostimulation, electroceuticals, and magnetic resonance imaging (MRI). Some of the functionalized anatomical model predictions have already been experimentally validated, but additional measurements and more comprehensive functionalization, e.g., with major peripheral nerves, are required and planned.

1. Introduction

Electromagnetic (EM) stimulation is therapeutically applied in electroceuticals/bioelectromagnetic and neuroprosthetic devices that primarily target the peripheral nervous system, as well as for classical neurostimulation of the central nervous system (brain and spinal cord) by implants (e.g. deep brain stimulators (DBS)) or externally applied fields (e.g. during transcranial electric (TES) or magnetic stimulation (TMS)).

The complex in vivo field distribution due to anatomy and tissue variability, as well as its interplay with the highly non-linear neuron electrophysiology and the sophisticated neural morphology, make it difficult to predict and optimize stimulation regions and treatment effects.

Neuro-functionalized anatomical models offer a valuable means to investigate and determine these regions and effects and are thus valuable for investigating stimulation mechanisms, developing and optimizing (novel) therapies and devices, and personalizing therapies.

2. Materials and Methods

Detailed anatomical computational models, such as the Virtual Population [1] and MIDA models [2], have been functionalized through anatomically realistic integration of electrophysiologically and morphologically realistic cortical pyramidal neuronal models relevant to transcranial stimulation (e.g. L5 neurons) (see Figure 1), selected internal globus pallidus (GPI) and subthalamic nucleus (STN) neurons as well as cortico-spinal fibers involved in deep brain stimulation (using MRI-derived DTI fiber tracking) (see Figure 2), axonal fibers important to spinal cord stimulation (distinguishing dermatomal zones), a vagus nerve (VN) model featuring fascicles, myelinated A- and B-, and unmyelinated C-fibers of importance to VN stimulation with realistic statistical distribution of axon fiber diameters (see Figure 3), and selected peripheral nerves of concern to low-frequency exposure safety.

A novel quasi-static finite element method solver was developed that handles image-based conductivity inhomogeneity and anisotropy information, as well as very thin insulating layers (e.g., perineurium) and is coupled to neuronal dynamics modeling using the NEURON [3] library.

Functionality was developed within the Sim4Life software (ZurichMedTech, Zurich, Switzerland) to determine stimulation thresholds and fiber recruitment curves, spike initiation locations, as well as exposure-related quantities important for stimulation (‘activating function’ along fiber trajectories – predictive of stimulatability; Jacobian Eigenvalue distributions – for worst-case estimation of the region of unintended stimulation).

3. Results and Discussion

The models and their functionality have allowed:

i) a novel concept for non-invasive localized (deep) brain stimulation via temporal interference electric stimulation to be discovered [4];

ii) the impact of transcranial stimulation pulse shape on stimulation selectivity and latency (important for learning and long-term effects) to be studied and innovative setups for highly targeted stimulation to be suggested [5];

iii) a novel method to optimize stimulation selectivity with multi-electrode stimulators based on activating function interference matrices to be developed and demonstrated in spinal cord stimulation;

iv) assumptions underlying current safety standard (ICNIRP, etc.) to be critically assessed, contributing to the ongoing revision of those standards [6];
VN stimulation to be compared with invasive (cuff electrodes), vascular-catheter-based, and external devices with regard to thresholds and recruitment of different fiber types;

new insights into deep brain stimulation mechanisms and sites of interaction to be gained;

da counter-intuitive major impact of anisotropy on the depth of spinal cord stimulation to be discovered and later explained with an equivalent circuit model;

important differences between established axonal dynamics models (SENN, Sweeney, McIntyre, etc.) to be studied;

counterintuitive major impact of anisotropy on the depth of spinal cord stimulation to be discovered and later explained with an equivalent circuit model;

neuro-functionalized anatomi cal models are a valuable tool for mechanism investigation, device development, and treatment personalization.

Verification against reference solution and validation against measurements and literature data on stimulation threshold, localization, and selectivity have been performed.

4. Conclusions

Further application-specific functionalization of anatomical models is required to increase the applicability of coupled EM-neuronal dynamics modeling. At the same time, further research needs to be devoted to investigate limitations/benefits of existing computational models of neurons and fibers for specific neurostimulation applications (i.e. reproducibility of stimulation thresholds for high frequency electric stimulation or conduction blocks, or short pulses, etc) and create new ones considering specific electrophysiological and neuroanatomical intra-subject fiber differences (e.g. axons in the CNS vs PNS) or between different species (i.e. human vs other mammals). Recently begun work on NEUROMAN, a set of high-resolution anatomical human and monkey models extensively functionalized with peripheral nerve models, is expected to be a valuable contribution to the field of neuroprosthetics, electroceuticals, and low-frequency exposure safety.

Figure 1. Example of functionalized human cortex with realistic L5 pyramidal neurons models in anatomical positions and orientation within the gray matter for the investigation of TES and TMS stimulation mechanisms.

Figure 2. a) Example of a functionalized model for DBS investigations featuring STN neurons and different axonal populations; b) Plot of the ‘activation function’ along selected fiber trajectories to predict sites of spike initiation.

Figure 3. a) Functionalized MIDA [2] head model with a 3D VN in close contact with major vasculature for investigation about invasive and non-invasive VNS protocols. B) Simplified VNS model using a cuff electrode array.

6. Acknowledgements

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7. References


