Working module title: Neural tissue models

Keywords: neural tissue, electromagnetic (EM) fields, EM-neuron interactions, low-frequency (LF) safety, functionalization, modeling, simulation, optimization

WM topic and description

Numerical simulations are increasingly being used to investigate the impact of external stressors on the human body, providing a complementary approach to traditional experimental studies. Along with the gradual development and adoption of *in silico* tools for biomedical research, significant effort has also been invested in developing and improving computational phantoms, in particular, whole-body phantoms, necessary for such simulations. Over the last 50 years, the quantity, the complexity, and the quality of these anatomical models have increased significantly (reviewed in [1]). Concurrent advances and improvements in these *in silico* tools and software and hardware computational power and sophistication have resulted in a much broader implementation of these models by the research community. The next challenge is to develop physiological models that accurately depict the complexity of specific biological processes, such as neuronal dynamics. The goal of this module is to develop novel *in silico* tools for investigating electromagnetic field (EMF)-based nerve stimulation. The developed tools should allow both the research and the application-oriented communities to push the boundaries of current mechanistic understanding of EM-neuron interactions and to simulate realistic applications where targeted and selective activation of specific nerves or nerve bundles is required. Specific applications include neuro-prosthetics, deep-brain stimulation, or neuromodulation by transcarnial direct-current stimulation and transcutaneous spinal direct current simulation. Furthermore, the developed tools will also be valuable for safety evaluations.

Comprehensive review (state of the art)

Although the body of work summarized in this section is vast, only several exemplary references are provided here. EM simulations have become an established, valuable, and frequently employed tool to assess *in vivo* exposure, and the use of realistic anatomical models as a simulation environment has also become standard. Increasingly, thermal and EM simulations are being used in combination to assess exposure safety; however, coupled EM-neuronal dynamics modeling is still extremely rare.

The beneficial application of external potentials to influence neuronal activity has been modeled mostly in the context of deep brain stimulation (DBS) and transcranial stimulation by electric or magnetic fields (transcranial alternating current stimulation, transcranial direct current stimulation, transcranial magnetic stimulation). Some of the studies performed on DBS (McIntyre, Butson, Grill) and on transcranial stimulation, most notably Datta et al., 2009, Datta et al., 2012, Neuling et al., 2012, Russell et al., 2013, Parazzini et al., 2014, Shahid et al., 2014, Wagner et al., 2014, use realistic head models.

Different models of coupled EM-neuronal dynamics exist (Gerstner and Kistler, 2002, Deco et al., 2008). They are mainly characterized as either a) conductance-based models (e.g., Hodgkin-Huxley) in which the dynamics of different ion channels are modeled to predict transmembrane potential evolution, or b) mass models (Deco et al., 2008), which describe the interactions between different neuron subpopulations

to capture behavior on a larger scale (most common variants: neural mass and mean-field models). Conductance-based models have been used to simulate axons, neurons, multiple neurons, and small neural networks, and their interactions with externally applied fields, and to study DBS (e.g., work by McIntyre, Butson, Sotiropoulos) and transcranial stimulation (Manola et al., 2005). Mass models have mostly been used to simulate cortical activity as the interplay of pyramidal cells, different interneurons, and other subpopulations, and have been applied to investigate transcranial stimulation (Esser et al., 2005, Molaee-Ardekani et al., 2013).

Another beneficial application of EM fields, for which coupled EM-neuronal dynamics simulations have previously been performed, is neuroprosthetics (Raspopovic et al., 2011). Studies have been published on the determination of stimulation selectivity and corresponding indices (Raspopovic et al., 2012). .

Coupled EM-neuron modeling (mostly based on the generic SENN neuron model) has also been performed in the context of low frequency safety standardization (Reilly, 2011).

In summary, different models of coupled EM-neuronal dynamics exist. However, although the modeling of incident fields involving anatomical models is becoming more common, coupled simulations are still extremely rare, and functionalized anatomical models as well as the tools for assessing stimulation selectivity and for optimizing stimulation are generally not available. Models of neuronal dynamics have so far only been constructed for very few beneficial applications of EM fields.

Gaps and challenges

Numerous medtech and communications applications entail human exposure to EMF. To ensure safety and to determine the potential beneficial applications of EMF, the development of accurate simulations for determining the precise effects of EMF on specific biological systems and tissues is a prerequisite. The nervous system is one of the many biological systems that are exposed to EMF, and can potentially benefit from exposure.

Numerous challenges exist in the field of EM-neuron interactions, however. For example, there is no existing framework to couple EM exposure and neuron dynamics models in realistic virtual anatomies, thus jeopardizing the ability to i) identify the precise bio-physical and bio-physiological mechanisms underlying the interactions between EMF and neurons, and thus determine the relevant bio-physical and bio-physiological properties; ii) predict the impact of EMF on neuronal dynamics; and iii) develop optimization methods for the targeted and selective delivery of EMF in this specific field of application.

Furthermore, more advanced methods must be developed to effectively obtain the anatomical features necessary for generating highly detailed anatomical patient-specific models including the relevant neuron models. The absence of safety standards and guidelines that account for the complexity of EMF-neuron interactions, particularly in the low frequency domain, provides additional challenges as well.

Objectives to be achieved

The objective is to provide the scientific community with functionalized computational phantoms and simulation tools for *in silico* research on the beneficial interactions between EMF and nerves. This requires a sound understanding of the bio-physics and bio-physiology of EM exposure and EM-nerve interactions; the modeling of neuronal dynamics in a realistic anatomical environment, i.e., potentially integrating realistic neural tissue models into anatomically detailed computational phantoms; the computational tools for simulating the exposure of these models to EMF; and the tools for optimizing exposure to guarantee safety and efficacy as well as targeting and selectivity. The tools we propose to develop should facilitate the development of applications proposed in other work modules, including:

- the stimulation of the vagus nerve (by enabling selective and targeted nerve stimulation, facilitating model personalization, and contributing to mechanism identification)
- cerebellar and spinal neuromodulation by transcarnial direct-current stimulation and transcutaneous spinal direct current simulation (by contributing to safety guidelines and dosimetry, mechanism identification and parameterization - particularly in terms of pulse shape – and establishing the methodology for selective stimulation)
- non-invasive brain stimulation (by facilitating device design and optimization in addition to other aspects already mentioned)
- research on EM-thermal dosimetry of the human brain and its application to transcranial magnetic stimulation (by enabling nerve activation selectivity assessment, dosimetry, simulating the temperature dependence of conduction velocity, and investigating intended and unintended exposure scenarios)
- microdosimetry (multi-scale neuronal cell models) and general dosimetry.

Proposed research activities

The research activities proposed in this module include:

- the development of the necessary computational tools and routines to facilitate the generation of functionalized models, such as models of the peripheral nervous systems, the retina, the cochlear system, the vagus nerve, and the spinal cord
- the development of the necessary tools for personalizing existing models based on novel image data
- the integration of the NEURON software and the modeling of neuron dynamics
- the coupling of EM simulations and neuronal activity
- the development of optimization routines for handling the complexity of neuron stimulation in complex anatomical environments
- the development of *in silico* tools for enabling and optimizing selective and targeted stimulation
- the design and realization of mechanistic studies to validate the tools and models
- the application of the developed tools and methods for safety evaluations in the low frequency range, which corresponds to the frequency range relevant to many EM-based medical applications, and the identification of safety criteria.

References

Datta A., Bansal V., Diaz J., Patel J., Reato D., and Bikson M., 2009. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using

a ring electrode versus conventional rectangular pad. Brain Stimulation Vol. 2(4), pp. 201-107.

Datta A., Truong D., Minhas P., Parra L.C., and Bikson M., 2012. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. Frontiers in Psychiatry Vol. 3.

Deco G., Jirsa V.K., Robinson P.A., Breakspear M. and Friston, K., 2008. The dynamic brain: from spiking neurons to neural masses and cortical fields. Plos Computational Biology, Vol. 4(8).

Esser S.K., Hill S.L, and Tononi G., 2005. Modeling the effects of transcranial magnetic stimulation on cortical circuits. Journal of Neurophysiology Vol. 94(1), pp. 622-639.

Gerstner W. and Kistler W.M., 2002. Spiking neuron models: single neurons, populations, plasticity. Cambridge University Press.

Manola L., Roelofsen B.H., Hoslheimer J., Marani, E., and Geelen, J., 2005. Modelling motor cortex stimulation fro chronic pain control: electrical portential field, activating functions and responses of simple nerve fibre models. Medical & Biological Engineering & Computing, Vol. 43, pp. 335-343.

Molaee-ARdekani B., Marquez-Ruiz J., Merlet I., Leal-Campanaario R., Gruart A., Sanchez-Campusano R., Birot G., Ruffini G., Delgado-Garia J.M., and Wendling F., 2013. Effects of transcranial Direct Current Stimulation (tDCS) on cortical activity: A computational modeling study. Brain Stimulation Vol. 6, pp. 25-39.

Neuling T., Wagner S., Wolters C.H., Zaehle T., and Hermann C.S., 2012. Finite-element model predicts current density distribution for clinical applications of tDCS and tACS. Frontiers in Psychiatry, Vol. 3.

Parazzini M., Rossi E., Ferrucci R., Liorni I., Priori A., and Ravazzani, P., 2014. Modelling the electric field and the current density generated by cerebellar transcranial DC stimulation in humans. Clinical Nuerophysiology, Vol. 125, pp. 577-584.

Raspopovic S., Capogrosse M., and Micera, S., 2011. A computational model for the stimulation of rat sciatic nerve using a transverse intrafascicular multichannel electrode. IEEE Transactions on Neural Systems and Rehabilitation Engineering Vol. 19(4), pp. 333-344.

Raspopovic S., Capogrosse M., Badia J., Navarro, X., and Micera, S., 2012. Experimental validation of a hybrid computational model for selective stimulation using transverse intrafascicular multichannel electrodes. IEEE Transactions on Neural Systems and Rehabilitation Engineering Vol. 20(4), p. 615.

Reilly J.P., 2011. Electrostimulation. Artech House.