Ultrastructural Neuronal Modeling of Calcium Dynamics under Transcranial Magnetic Stimulation

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1 Introduction

An important question in the study of calcium (Ca^{2+}) signaling is how this ion regulates a wide spectrum of cellular processes, which include: fertilization, proliferation, learning, and cell death, all of which are the result of synaptic strengthening/weakening. Part of the answer lies in the spatial-temporal interactions of Ca^{2+} at the extracellular and intracellular levels of a neuron [SU14]. There is a complex concert of Ca^{2+} ion exchange and transport mechanisms that are activated (or inactivated) by external stimuli and it remains to be studied the role of these interactions at the ultrastructural scale.

One mode of external stimulation is by Transcranial Magnetic Stimulation (TMS) and repetitive TMS (rTMS). TMS is a noninvasive brain stimulation method to modulate human brain activity by generating a strong magnetic field near the cranium [BJF85]. The magnetic field traverses the skull to induce an electric field which may depolarize neurons [Hal07]; therefore, TMS is used in clinical applications to treat neuropsychiatric and neurological disorders [LAOA$^+$14]. However, it is not well known the affects of TMS on intracellular Ca^{2+} interactions; therefore, we endeavor to determine the types of calcium interactions that occur when a neuron experiences TMS.

We also determine how intracellular calcium mechanisms are affected by TMS stimuli. In particular, the cellular regulators of calcium are given by: the internal Ca^{2+} store ("calcium bank") of a neuron called the endoplasmic reticulum (ER) with spine apparatus (SA), the voltage dependent calcium channels (VDCCs), and calcium influx at synaptic spines. Ultimately, the ER is responsible for synaptic plasticity [BQ18] and from here we determine under what conditions does TMS cause intracellular calcium to induce synaptic plasticity.

2 Statement of Research

Research Objectives For this project I endeavor to formulate a spatio-temporal calcium methodology which will predict when a calcium wave is initiated by ion exchanges due to:

the intracellular mechanisms SA and ER, PM transport mechanisms (including VDCCs), and extracellular effects i.e. electric fields and post synaptic calcium influx. The methodology takes into account the aforementioned physiological phenomena, and will determine geometric properties of the PM, ER, SA, and electric field under which a calcium wave is propagated through the dendrite.

This project requires detailed simulations of surface and volumetric geometries. The degrees of freedom (DoFs) of the geometries can range from $10^6 - 10^9$ depending on the scope of the geometry i.e. spine-dendrite simulations to full cell simulations. The simulation times can range from 30 ms to 3 seconds; in particular, 30 ms simulations are used to determine the physiological parameters of the SA for which calcium enters the dendritic region of the neuron. Longer simulations in the 1-3 second range are used to determine the stability of the calcium wave(s) that are propagated.

Some of the physiological parameters studied in the project are ryandoine-receptor (RyR) density, initial Ca^{2+} concentration, IP3R density, post synaptic calcium influx, and ER calcium concentration. For the simulations I will run parameter sweeps of each of the physiological values i.e. run a simulation where the RyR density is incremented by 0.01. Geometric parameters are also taken into account such as SA volume, synapse area, spine surface area and volume, electric field orientation, electric field intensity; all of which are used to determine correlations of the physiological parameters. The model equations are simulated on three types of spine geometries: neck, mushroom, and stubby spines. To summarize, my objective is to establish novel methodologies for strengthening neuron calcium signaling under given physiological conditions by determining

a) empirical laws that predict a release of calcium into the dendrite volume region,

b) minimal ER/SA geometric properties and TMS/rTMS induced electrical field properties that allow stable calcium wave propagation.

3 Computational and Mathematical Tools

Numerical Methods For numerical simulations, the calcium dynamic equations are discretized in space using finite volumes [LeV02]. The equations governing the TMS electric field are solved numerically using finite element methods (FEM) as described in [OTZ05]. The differential equations governing the transport mechanisms on the plasma membrane and ER/SA membrane are nonlinear and require precise calibration of the time step size for achieving numerical accuracy. The calcium simulations are discretized with respect to a highly non-uniform domain i.e. the ER/SA volume and surface geometry. Therefore, this research will determine the best numerical scheme and spatial discretization for achieving numerical accuracy.

Mathematical Software For this research, I am working with collaborators to generate the TMS potential waveforms using software developed from the Department of Biomedical Engineering, University of Minnesota, Opitz Lab and I am working with collaborators from the Department of Neuroanatomy, Institute of Anatomy and Cell Biology, Faculty of Medicine, University of Freiburg, to obtain realistic spine dendrite geometries.

UG4 Simulation Framework UG4 is an open source simulation framework for the numerical solution of systems of partial differential equations [VRR+13] using Finite Element and Finite Volume methods on hybrid, adaptive, and unstructured multigrid hierarchies. UG4 allows for the simulation of complex real world models (physical, biological etc.) on massively parallel computer architectures.

NeuroBox All model components will be implemented in a NeuroBox project [SBHQ19, BSG+16]. NeuroBox is a neuroscientific toolbox that combines 1D, 2D and 3D modeling and simulation of electrical and biochemical signaling in a visual workflow environment.

High Performance Computing Services This research includes calculations carried out on Temple HPC resources supported in part by the National Science Foundation through major research instrumentation grant number 1625061 and by the US Army Research Laboratory under contract number W911NF-16-2-0189. This research also uses compute resources from the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1548562.

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