Functionalizing MIDA

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Abstract

The Multimodal Imaging-based Detailed Anatomical (MIDA) model of the human head and neck is a static, macroscopic model. It is currently one of the most detailed computational models in the scientific community, with 153 structures and a resolution of 0.5 mm. Functionalizing the MIDA model by inserting biologically realistic neural networks would allow for a comprehensive analysis of the effects of electromagnetic fields on the brain. This would lead to a better understanding of the mechanisms of brain stimulation devices in treating neurodegenerative and neuropsychiatric diseases. A preliminary network consisting of four neurons has been inserted into the neostriatum, the thalamus and the Globus Pallidus externus structures of the deep brain. The electromagnetic properties of the functionalized structures will be assessed and analyzed as a proof of concept.

Introduction

The absence of a functionalized computational brain model has been a challenge to neuroscientists in their attempt to study how different brain stimulation technologies impact neural activity, especially in the remote regions of the brain, like the deep brain nuclei. Currently, neurosurgeons often must perform risky and invasive procedures without any prior simulations because of the lack of appropriate technologies or dynamic models of the human brain. A model of the brain that provides electrophysiologically accurate neuronal networks would significantly advance and expedite research in the fields of neuroscience and medicine.

One of the most recent advancements in computational neuroscience is the Multi-modal Imaging-based Detailed Anatomical (MIDA) model of the human head and neck (Iacono et al., 2015). MIDA is a high-resolution (0.5 mm), macroscopic computational model that was developed by an international alliance of scientists, including those at the FDA, and is currently available as voxel- and surface- based versions. It accurately models structures in the head and neck, including bones, muscle tissues, vasculature, eyes, and ears. It also provides anisotropic properties of the axonal white matter that were acquired through MRI, MRA, and DTI modalities. MIDA has been proven to be effective in testing the performance of numerous medical devices, but it still lacks the rich repertoire of microscopic neuronal activity that might provide insight on current issues with the mechanisms of action for medical device designs to re-calibrate neuronal function that's gone awry. These microscopic properties are vital for neurosurgeons and researchers because they would allow for in silico testing, which could lead to a new gold standard of truth, and the elimination of risky clinical trials.

This research takes interest in understanding the mechanisms in which various electroceuticals function, including Deep Brain Stimulation (DBS), Transcranial Magnetic Stimulation (TMS),

Vagus Nerve Stimulation (VNS), and Transcranial Alternating Current Stimulation (tACS). DBS devices use a neurostimulator to send electrical pulses to deep brain structures for the purpose of alleviating symptoms of various neurological disorders by altering neuronal properties. TMS is a non-invasive stimulation technology used to stimulate nerve cells to alleviate depression. The magnetic fields from TMS target brain regions that are involved in mood regulation and depression, such as the left prefrontal cortex, the parietal cortex and the cerebellum (Schutter & Honk, 2005). VNS sends electrical pulses to the vagus nerve in order to treat epilepsy and depression. It is currently being studied to assess whether it could be used to treat multiple sclerosis, Alzheimer's, and migraines. tACS is a non-invasive technique to modulate brain oscillations, which have been linked to basic motor and sensory processes as well as cognitive functions such as perception and decision making (Herrmann et al., 2013). These devices can be improved through having more precise knowledge about how their function and dysfunction is calibrated. This could be achieved through neuromodulation simulations where the effects of the electromagnetic fields from these devices are assessed.

To simulate these neuronal stimulations, a variety of softwares are required. For instance, Joucla et al. (2014) utilized NEURON in conjunction with COMSOL Multiphysics in order to model neuronal stimulation. NEURON is a neuronal modeling and testing environment, and COMSOL is a multiphysics solver that allows for further testing of neurons and visualization of resulting EM fields. Joucla's testing was performed through two stages: the first was to compute the electrical field created by the stimulation, and the second was to calculate the response of passive and active neurons to the field. In order to compute the electrical field resulting from the stimulation, the Finite Element Method (FEM) was built into the COMSOL Multiphysics software, in which membrane potential and the extracellular environment were computed simultaneously. The second stage of modelling was achieved through NEURON. A source electrode was used to induce an electrical field in an electrically uniform and homogenous environment. Joucla was able to build the hybrid model using 2-D circular cells and assuming an infinite electrically conductive environment.

One current researcher that has followed similar protocols to the aforementioned research is Dr. Cassara of ZMT. Dr. Cassara used Sim4Life's FEM solver, developed by Neufeld et al. (2016), along with NEURON, in order to integrate pyramidal neurons with realistic electrophysiological properties into the cortical structures of the MIDA model. This was done in order to assess the effectiveness of internal and external electrostimulation, since pyramidal neurons are most receptive to electromagnetic fields, as opposed to neurons that belong in the deep brain nuclei. Many of the current papers from Dr. Cassara and others show a heavy reliance on neuronal integration in order to understand the neuronal dynamics in simulations. It is hypothesized by many that the insertion of neurons would expand the understanding of EM fields for specific

brain structures, which would enhance therapeutic procedures that involve the use of electroceuticals such as DBS.

In 2004, another research group, McIntyre et al. conducted a study to uncover the mechanism of deep brain stimulation by analyzing the effects of neural modeling, neurochemistry, and neural recording. Modeling the function of neurons was used specifically to study the generation of action potential as a result of the stimulation. Finite element modeling (FEM) of the electric field generated by a Deep Brain Stimulation (DBS) electrode was used in combination with a compartmental thalamocortical relay neuron. It was concluded that field application on the neural membrane results in regions of hyperpolarization and depolarization, and that activation of afferent input from the stimulus has an effect on local neurons. Modeling results show that afferent input has a low threshold for activation, and that efferent output to local cells is dependent on the neuron position with respect to the electrode and the type of neuron. These results, while not the first of its kind, were some of the first advanced examples of computational modeling for neuroscience. McIntyre's work with DBS electrodes applied extensively to the device for DBS, and his work with neuron modeling has set an example for the neuromodulation testing and stimulation optimization that is needed for deep brain nuclei.

MIDA has been cited by nearly twenty other research papers as a pivotal tool in independent research groups for its contribution as a model of the entire human head and neck. The creation of MIDA has been instrumental in expanding and validating research endeavors in the field. It was stated by the original researchers of MIDA that "the model was created primarily as a tool to simulate the interactions of tissues with electromagnetic fields generated by medical devices as well as for electromagnetic dosimetry" (Iacono et al 2015).

To illustrate the possible applications of the human head and neck model, the creators of MIDA performed case studies with a special focus on how biomedical devices could be improved. In one case study, they assessed the outcomes of tACS that resulted from altering numerical methods, tetrahedral elements to rectilinear voxels discretization approaches, and tissue specific scalar electrical conductivity to DTI-based anisotropic electrical conductivity approaches for tissue property assignment. The Fpz-Cz electrode placement was found to release higher electrical currents throughout the retina and surrounding tissue, and the Cz-(Fz, C3, C4, Pz) placement was found to mostly avoid the retina. When experimenting with resolutions of higher and lower structured and unstructured meshes, simulation results were found to be similar as long as the mesh was fine enough to resolve the skin, skull layers, and dura. In another case study, a simulation was performed to compare the EM fields from scalar, homogenous tissue properties to the EM field emitted from inhomogeneous, anisotropic tissue. In both simulations, image-based properties were used, and similar field distributions were obtained. When the

image-derived anisotropic conductivity was evaluated, they observed that there was less of an inherent effect on current distribution, and the EM field inside the brain was around 25% weaker.

This study expands the ideas of previous researchers by functionalizing the MIDA model with the NEURON software and Sim4Life platform. The insertion of computationally modeled neurons with accurate biological properties are relevant for two reasons: to allow for future research on deep brain structures, and to advance the treatment of neuropsychiatric and neurodegenerative diseases. Through the use of the NEURON software and the Sim4Life platform, this study will work to computationally insert neurons into the MIDA model. Dr. Cassara states that with the integration of "electrophysiologically and morphologically detailed neuron models," the investigation into electromagnetics with neuronal dynamics in a software like Sim4Life will be made possible. Through the use of the platform, model, and software, functional basal ganglia neural networks can be created and embedded into the MIDA model. This will bring researchers closer to mapping all of the neuronal connections within the basal ganglia and the full connectome. The model will be suitable for simulations once DTI imaging is implemented in the future, which would allow for the construction of the axonal fiber tracts in the white matter. Being able to experiment on a model of neural networks will be an extremely useful platform for testing efficacy and safety of medical devices on the human brain, and will inherently reduce the need for testing treatments on humans and animals. This simulation platform would also enable medical specialists to avoid risks by allowing them to account for any negative consequences prior to performing procedures. Using MIDA, researchers can gain a stronger understanding of the human brain and its neuronal and electromagnetic properties.

The purpose of this study is to begin the functionalization of MIDA. This entails starting the insertion of neurons into deep brain structures based on the tractography of the axonal white matter. The objectives of this study include: completely understanding the NEURON environment, constructing NEURON models, understanding the integration of NEURON and Sim4Life to commence simulations between the two environments, understanding and beginning the integration of neurons on neuronal pathways, and evaluating the issue of network integration.

Materials

The functionalization of MIDA requires the use of several softwares, files, and programming languages. The software that will be used in this research is Sim4Life, which is a multiphysics solver, particularly for EM properties. NEURON is another software required for the construction, exercising, and managing of models (Hines, Carnevale 2010). NEURON is a computational modeling environment that is used for experimenting with and testing electrical properties using the HOC and Python programming languages.

Numerous neuronal files are required for this project. Databases that are frequently used for this research are ModelDB and Neuromorpho, as well as individual neuronal models from researchers in the field of computational modeling, such as Dr. Cassara. ModelDB is an extensive source for already constructed neurons using NEURON and the HOC programming language, while Neuromorpho contains an inventory of neurons in the form of .dat files. Models from both databases are sourced from peer-reviewed publications. The MIDA model is the most vital file for this research as it contains 153 head and neck structures not yet functionalized, potentially making it the first prototype of a fully functional brain model.

This research uses the most current version of Sim4Life (V 4.2) in conjunction with NEURON 7.4, HOC 3, and Python 2.7.

Research Methodology

Computationally inserting neurons into the basal ganglia of MIDA requires the use of NEURON and Sim4Life. Neuronal modeling is being achieved through two alternative approaches: either acquiring previously modeled neurons from ModelDB or modifying data files from Neuromorpho and then generating the HOC code to correctly model them.

```
1 1 0 0 0 6.36753 -1
2 1 -2.75 -5.73 0 6.36753 1
3 1 2.75 5.73 0 6.36753 1
4 3 0.69 5.24 -0.1 0.675 1
5 3 0.78 6.38 -0.1 0.675 4
6 3 -0.7 9.8 -0.15 0.675 5
7 3 0.58 14.38 -0.63 0.675 6
8 3 0.97 17.02 -0.63 0.675 7
9 3 1.14 23.91 -3.5 0.675 8
10 3 1.44 37.91 -5.44 0.675 9
11 3 1.64 40.49 -5.44 0.675 10
12 3 2.47 41.59 -2.68 0.675 11
13 3 4.26 45.05 -3.81 0.675 12
14 3 6.09 47.59 -7.65 0.675 13
15 3 8.02 50.37 -12.68 0.675 14
16 3 12.62 55.3 -13.88 0.675 15
17 3 15.22 58.23 -10.67 0.675 16
18 3 16.24 61.6 -7.78 0.675 17
19 3 16.37 64.37 -8.21 0.675 18
20 3 14.45 67.83 -8.21 0.675 19
21 3 14.88 70.6 -10.63 0.675 20
22 3 11.95 76.91 -9.35 0.675 21
23 3 7.24 80.8 -15.39 0.675 22
24 3 1.3 84.25 -18.87 0.675 23
25 3 -2.61 84.8 -18.87 0.675 24
```

Image One

For the first approach, the HOC files require little editing as they already hold information about the neuron's morphology and electrical properties. The only thing required for these files is the removal of certain commands that are not compatible with Sim4Life's software. These commands are typically GUI instructions and code to ensure that file paths are listed completely.

For the second approach, neurons are taken from Neuromorpho to be modeled in NEURON. When modeling neurons in NEURON using HOC code, a crucial method responsible for the neuron modeling is pt3dadd(). The Neuromorpho only provides a .swc file that is not compatible with NEURON's pt3dadd() function, as shown in Image One. The format for the parameters of pt3dadd() is (branch-number, child1, child2, diameter, Length, X_1, Y_1, Z_1, X_2, Y_2, Z_2). Each parameter is important for the modeling of a segment, as the starting and ending points need to be explicitly stated in order to create a connection between the two points. Although all of these parameters are necessary for the pt3dadd() method, the .dat files provided by Neuromorpho do not always have every parameter,

nor have the parameters in order. To compensate for this, massive rewriting of the .dat files needs to be accomplished prior to the complete modeling of neurons as shown in Image Two.

3		0	0	0	0	0.0000000001	0	0	0	0
4		1	-0.16	13.61	1.37	1.165	0	0	0	0
5		2	-0.35	14.19	1.51	1.165	1	-0.16	13.61	1.37
6		3	-0.57	14.9	1.71	1.165	2	-0.35	14.19	1.51
7		4	-0.86	15.84	2.08	1.165	3	-0.57	14.9	1.71
8		5	-1.11	16.66	2.37	1.165	4	-0.86	15.84	2.08
9		6	-1.48	17.82	2.57	1.165	5	-1.11	16.66	2.37
10		7	-1.81	18.86	2.77	1.165	6	-1.48	17.82	2.57

Image Two

Major drawbacks to the two approaches used are that files from ModelDB lack visualization and files from Neuromorpho are generally incomplete for use with HOC. As a result, a mixture of the two is vital for the visualization of the neurons in question and compatibility with HOC.

A third method that is currently being examined is a complete modeling of the neurons using data from current research to create new .dat files to model the neurons. This requires extensive data from neurons, as spatial orientation is vital for understanding the neuronal connections and properties.

After a fully functional neuron is created in NEURON using hoc code, insertion into Sim4Life begins. At this stage, it is important that the NEURON file has its .dll files compiled, because without it, Sim4Life would not recognize the neuron. Once in Sim4Life, multiple neurons can be networked together. Networking the neurons correctly is important for ensuring the integrity of the project when neuron simulations are later run. Neurons have to be networked in the Sim4life platform rather than imported, since an already made network will not be accepted into the software. The project will move towards the creation of a script that could expedite the process of entering the necessary biological information, to ensure that neurons can be modeled correctly in a smooth manner. Additionally, this script will allow for much larger networks to be created.

DTI data for the MIDA model has been completed at the FDA, and attainment of the data will allow for networks to be created correctly. The modeled axonal fiber tracts are used as a guide for the placement of neurons. After the DTI data is inserted, MIDA is imported into Sim4life. With MIDA in Sim4Life, neuron simulations will be run on the previously modeled neurons with Sim4Life's neuron solver. For researchers and clinicians to perform realistic simulations before executing their planned procedure, the neuronal electrophysiological properties need to be accurate. That is why neuron insertion is such an important step. Accurately performing this step will allow researchers and clinicians to ensure that all procedures performed are safe while reducing the need for expensive biological testing.

Results

The insertion of a network consisting of four neurons into basal ganglia structures has been accomplished as shown in Figure 1 and 2. The network consists of two medium spiny neurons, a thalamic neuron, and a Globus Pallidus externus (GPe) neuron. Three of the neurons were modeled using code from Neuromorpho.org and one neuron was modeled using code from the ModelDB database. All neurons were inserted into Sim4Life for visualization purposes as well as future electromagnetic testing. Currently, the neuronal network is placed as accurately as the literature suggests due to the lack of DTI data for the MIDA model. Each neuron has accurate biophysical and electrophysiological properties.

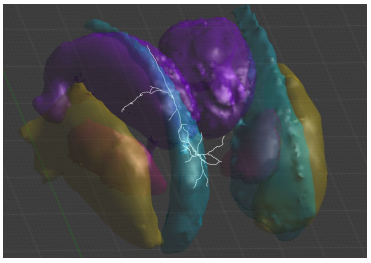

Figure 1: Simulation of the Indirect pathway of the Basal Ganglia in MIDA.

Discussion

The current findings show that accurate biophysical and electrophysiological neurons can be modeled and inserted into the MIDA model. While these are preliminary findings, it is evident that this can be extrapolated for more involved networks of neurons. The current work can be improved drastically with the development of scripts that can easily write files for the Neuromorpho.org .dat files, which can be quite complex for larger neurons, such as those of the thalamus. Additionally, accuracy can be increased with DTI data and mesoscale anatomy of unmyelinated fibers within the basal ganglia. Further work will be conducted on the analysis of the electromagnetic properties of these neurons using the NEURON solver in Sim4life in order to understand the mechanisms of deep brain stimulation devices. This will lead to progress in improving treatment for neurodegenerative diseases that rely on such electroceuticals, such as Parkinson's disease.

Figure 2: Biologically realistic Indirect pathway network.

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