

Modeling Multiple Sclerosis & Epilepsy

Computer Exercises using the NEURON Simulator

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These exercises make use of the NEURON simulator (www.neuron.yale.edu).
Prewritten code and Graphical User Interface is available for all exercises.

Code files:

MultipleSclerosis_BNNI2017.hoc
EpilepsyI_DentateGyrus_BNNI_2017.zip
EpilepsyII_GranuleCell_BNNI_2017.zip

1. Multiple sclerosis tutorial: Demyelination & action potential propagation

Note: The tutorial is adapted from: Neurons in Action (NIA), by John W. Moore and Ann E. Stuart, <http://neuronsinaction.com/tutorials/partial>
Important steps are in **bold**. Please answer the questions.

A. Overview:

Multiple sclerosis is an autoimmune neurological disease leading to demyelination of nerve fibers in the CNS thereby disrupting the conduction of electrical signals along the axons. The purpose of this tutorial is to simulate and analyze action potential propagation through myelinated and demyelinated regions of the axon.

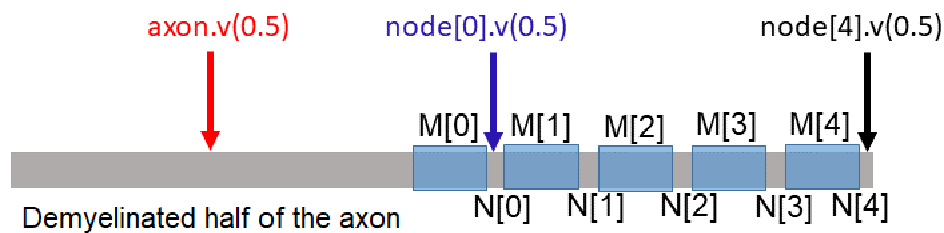
B. Goals of the tutorial

- * To simulate **action potential propagation** from the myelinated region of the axon into the demyelinated (and vice versa)
- * To analyze/understand how changes in the **temperature** affect the invasion of the action potential into the demyelinated portion of the axon
- * To analyze/understand how changes in **ion channel conductances** in the demyelinated axon affect the invasion of the action potential into the demyelinated portion of the axon

B. Opening the tutorial file

To start the tutorial open the **MultipleSclerosis_BNNI2017.hoc** file using NEURON (by double-clicking on its icon). A **Panel & Graph Manager** panel and a **Run Control** panel will appear.

C. Running exercise simulations using NEURON



The axon's length is 10 mm. The **left half** of the axon is **demyelinated**, whereas the **right half** is still **myelinated**. The myelinated half contains **5 nodes N[0-4]** with **5 myelinated internode regions M[0-4]**. Ion channel densities in the nodes are greater than those in the unmyelinated region of the axon.

One **stimulating electrode** (not depicted in the schematic) will be inserted later (see below) into the left end of the axon or into the right end of the axon. **Recording electrodes** are located in the center of the demyelinated half (left part of the axon, red arrow in the above schematic) and in the nodes N[0] (dark blue arrow in the schematic) and N[4] (black arrow in the schematic). Click the "**Voltage vs Time**" button (in the **Panel & Graph Manager** panel) to open a **graph** with color-coded Voltage-vs-Time traces for the three recording sites shown in the schematic above. Click the "**Voltage vs Space**" button (in the **Panel & Graph Manager** panel) to open a **graph** with the Voltage-vs-Space trace.

1. **Stimulating the left end** of the axon (left end of the **demyelinated** region) and studying the **invasion** of the action potential **into the myelinated region**:

Click the "**Stimulus Electrode in Demyelinated Axon**" button in the **Panel & Graph Manager** panel. A **Stimulus Control (Axon)** panel pops up showing a stimulating electrode in the left end of the demyelinated half of the axon. **Run** the simulation by clicking the **Reset & Run button** in the **Run Control** panel. The action potential will be initiated at the stimulation site, i.e. at the left end of the demyelinated region (red trace in the **Voltage-vs-Time** graph). It will spread into the right myelinated region. In the **Voltage-vs-Time** graph, the second (dark blue) and third (black) recorded action potential (recorded at the node[0] & node[4]) are much closer in time than are the first and second recorded action potentials (recorded in the demyelinated area and at the node[0]).

Question 1. What is the reason for this?

If you want to watch the **left-right spread of the voltage** change along the axon, click the "**Reset**" button in the **Run Control** panel and then click the "**Continue For (ms)**" button in the Run Control panel to play and pause the simulation repeatedly. If you focus on a point

where a recording electrode is located (e.g., in the middle of the demyelinated axon), you can compare the **Voltage-vs-Space** trace to the **Voltage-vs-Time** trace.

2. **Stimulating the right end** of the axon (right end of the **myelinated** region) and studying the **invasion** of the action potential **into the demyelinated region**:

To remove the stimulating electrode from the left end of the axon, close the "**Stimulus Electrode in Demyelinated Axon**" panel. Click the "**Stimulation Electrode in Node [4]**" button in the **Panel & Graph Manager** panel. A **Stimulus Control (Axon)** panel pops up showing a stimulating electrode in the right end of the myelinated half of the axon. **Run** the simulation by clicking the **Reset & Run button** in the **Run Control** panel. The action potential will be initiated at the stimulation site, i.e. at the right end of the myelinated region (**black trace** in the **Voltage-vs-Time** graph).

Question 2. Will the action potential reach the demyelinated region? (red trace in the **Voltage-vs-Time** graph)

If you want to watch the **right-to-left spread of the voltage** change or its failure, click the "**Reset**" button in the **Run Control** panel and then click the "**Continue For (ms)**" button in the Run Control panel to play and pause the simulation repeatedly. Compare the **Voltage-vs-Time** traces (for 3 recording sites) with the **Voltage-vs-Space** recording.

Question 3. Describe and explain what happens to the action potential at the border between the myelinated and demyelinated portion of the axon.

3. Simulating the effects of **temperature** changes on the **invasion** of the action potential **into the demyelinated portion** of the axon

Decrease/increase the **temperature** in the **Run Control** panel. Run the simulation by pressing the **Reset** button and by repetitive clicking the **Continue for (ms)** button.

Question 4. Does decrease or increase in temperature improve the action potential propagation in multiple sclerosis patients? What is the smallest change in temperature needed to restore the invasion of the action potential into the demyelinated axon? What is the effect of cooling/warming up on the duration of the action potential? What change in temperature is allowing the action potential to supply more charge to the demyelinated region and thereby increasing the probability of action potential invasion? Cooling or warming up?

4. Simulating the effects of changes in **ion channel conductances** on the **invasion** of action potentials into the demyelinated region.

Make sure that the temperature has been reset to its default value of 25.2 °C.

Open the **Demyelinated Axon Parameters** panel in the **Panel & Graph manager**.

Increase or decrease the **density of K channels**.

Question 5. What change is improving the invasion of the action potentials into the demyelinated region?

Increase or decrease the **density of Na channels**.

Question 6. What change is improving the invasion of the action potentials into the demyelinated region?

5. Simulating the effects of parameter changes in **myelinated** part of the axon on the **invasion** of action potentials into the demyelinated region.

Open a panel with parameters of the myelinated axon by clicking the "**Internode Parameters**" button.

Question 6. Try to explore the effects of the following changes:

a) the **length** of the myelinated internode M[0] (myelin [0])

b) **capacitance/degree of myelination** (= capacitance $1 \mu\text{F}/\text{cm}^2$ divided by the number of myelin wraps)

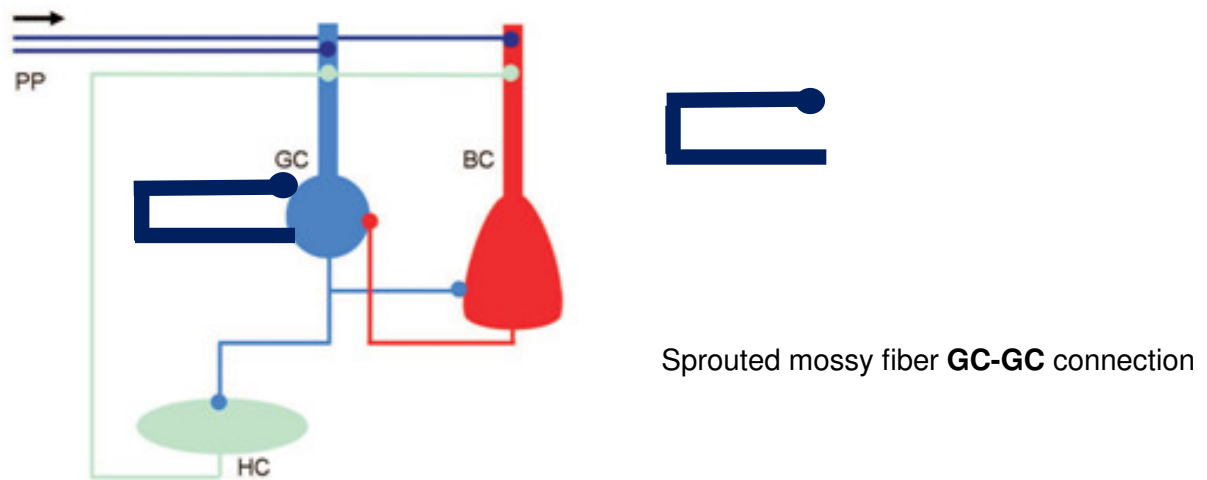
c) the **diameter** of the axon (without its myelin wrapping).

2. Epilepsy tutorial I: Simulating the effects of axonal (mossy fiber) sprouting

A. Overview:

This tutorial focuses on simulating hyperexcitability in the dentate gyrus, which represents the "gate" protecting the hippocampus from the invasion of seizures (Krook-Magnuson et al. J Physiol 2015). We will use a realistic network model of the dentate gyrus (see the schematic above) comprised of multicompartmental neurons representing **4 excitatory and inhibitory cell types** (Santhakumar et al. J Neurophysiol 2005): 500 excitatory granule cells (GC), 15 excitatory mossy cells (MC – not depicted in the schematic), 6 inhibitory basket cells (BCs) and 6 inhibitory hilar cells (HCs). GCs, BCs and some MCs receive excitatory perforant

path input. Each cell type model is equipped with detailed ion channel mechanisms (defined by parameters for kinetics, densities, and distributions). In epileptic animals, sprouting of GC axons (i.e. mossy fibers) and establishment of pathological GC-GC connections has been observed.



B. Goals of the tutorial

* To study the effects of mossy fiber sprouting on the excitability of dentate circuitry.

C. Running exercise simulations using NEURON

Download EpilepsyI_DentateGyrus_BNNI2017.zip

Note: Before running the simulations, it is necessary to compile the mechanisms in mod files. Initiating synaptic connections takes several minutes, then network simulation starts running.

To run a simulation of a healthy (control) network, open the **HealthyDentateGyrus.hoc** file using NEURON (by double-clicking the file). To run a simulation of an epileptic network with mossy fiber sprouting, open the **Sprouting.hoc** file using NEURON (by double-clicking the file). To test whether increased conductance of BC-GC synapses (perisomatic inhibition) is able to prevent seizure activity in a network with mossy fiber sprouting, open the **Sprouting&strongInhibition.hoc** file using NEURON (by double-clicking on the icon).

Question 7. Observe the differences in spike rasters and voltage trace and explain your observations.

3. Epilepsy tutorial II: Simulating the effects of ion channel changes in dentate granule cells during epilepsy

A. Overview:

Experimental data show that temporal lobe epilepsy is accompanied by altered expression of ion channels in the principal neurons of the hippocampus including CA1 pyramidal and dentate granule cells (Wolfart & Laker, Front Physiol 2015).

B. Goals of the tutorial

* This tutorial focuses on the effects of enhanced Kir channel expression (Young et al., J Physiol 2009) on the excitability of dentate granule cells. Kir channel is an inwardly rectifying potassium channel passing more current in the inward direction than the outward direction.

C. Running exercise simulations using NEURON

Download EpilepsyII_GranuleCell_BNNI_2017.zip

Note: Before running the simulations, it is necessary to compile the mechanisms in mod files.

Open the **mosinit.hoc** file by double-clicking. In the Load Morphologies panel click the **Load only single morphology** button and the **Beining rat GC** button. This will load a reconstructed rat granule cell morphology (from Beining, Jungnitz et al., Brain Structure & Function 2017) and call up **Load biophysics** panel. In this panel, click the **mature rat GC** button to load biophysical mechanisms, which include a set of ion channels including the **Kir channel**. To see the morphology and parameters of the granule cell model, you can click the **Tools** button in the **NEURON Main Menu** panel and open the **Model View** panel. In the **Load experiments** panel, click the **Current injection** button. Start the simulation by clicking the **Init & Run** button in the **RunControl** panel. Explore the input-output properties of the cell (number of spikes induced by a given current injection) by injecting currents of different amplitudes. The amplitude of the injected current can be changed in the **Current injection** panel. Increase the expression of the Kir channel in the soma by typing **forsec "soma" gkbar_Kir21*=4** in the Neuron prompt interface. Determine the input-output properties and compare them to the previous simulations.

Question 8. How does the increased expression of the Kir channel affect the excitability of the granule cell? What implications will it have for temporal lobe epilepsy?