INT3007: Practical 5 – Neurons in Action

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This practical is based on:
'Doing Physics with Matlab'
Hodgkin-Huxley model: Membrane Current
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Content

In this practical, you will be familiarized with a Matlab implementation of the Hodgkin-Huxley model (part 1) and will work with the Allen Brain Atlas (part 2)
You will learn how to

- Modify critical parameters of the Hodgkin-Huxley model
- Interpret output of the Hodgkin-Huxley model
- Examine a research question using the Allen Brain Atlas

In between steps there are questions related to the methodology or biological interpretation. The aim of these questions is to make you really think about the analysis you are performing and the produced results.

Software

You will need Matlab to execute Part I of this practical. You can either:

- Work from your own laptop. Make sure to install Matlab before the start of the practical (see https://library.maastrichtuniversity.nl/news/matlab-license/ for instructions).
- Work on the UM computers, where Matlab should be installed.

Part II of this practical can be done from your own laptop or the UM computer without the need for specific software required.

Set up

- Work in pairs and follow the instructions step-by-step. Answer the questions in the questions document to keep notes and make screenshots.
- If you have a question, check the discussion board where we will note common questions and mistakes. If your question is not yet posted, feel free to post it or ask an instructor.
- Answers to the questions along with screenshots of the output will be posted early next week.

PART I. The Hodgkin-Huxley single neuron model

The core mathematical framework for modern biophysically based neural modelling was developed around 1950 by Alan Hodgkin and Andrew Huxley. They carried out a series of elegant electrophysiological experiments on the squid giant ion which has an extraordinarily large diameter ~ 0.5 mm.

Hodgkin and Huxley systematically demonstrated how the macroscopic ionic currents in the squid giant axon could be understood in terms of changes in Na^+ and K^+ conductances in the axon membrane. Based on a series of voltage-clamp experiments, they developed a detailed mathematical model of the voltage-dependent and time-dependent properties of the Na^+ and K^+ conductances. Their model accurately reproduces the key biophysical properties of the action potential. For this outstanding achievement, Hodgkin and Huxley were awarded the 1963 Nobel Prize in Physiology and Medicine.

In part I of this skills training, you will explore the Hodgkin-Huxley model using Matlab

Assignment 1 – Simulate the response to a single current pulse

In this assignment, you will use a Hodgkin-Huxley single neuron model implemented in Matlab to simulate the response of a neuron to a current pulse.

Preparatory steps:

- Download 'Scripts_Practical5.zip'
- Copy-paste the zip file to a path that you can find back later
- Unzip the file
- Open Matlab
- Browse to your unzipped Scripts_Practical5 folder (see (1) in Fig. 2 below)
- Click 'Open file' (see (2) in Fig. 2 below)
- Open the file 'bp_neuron_01.m'

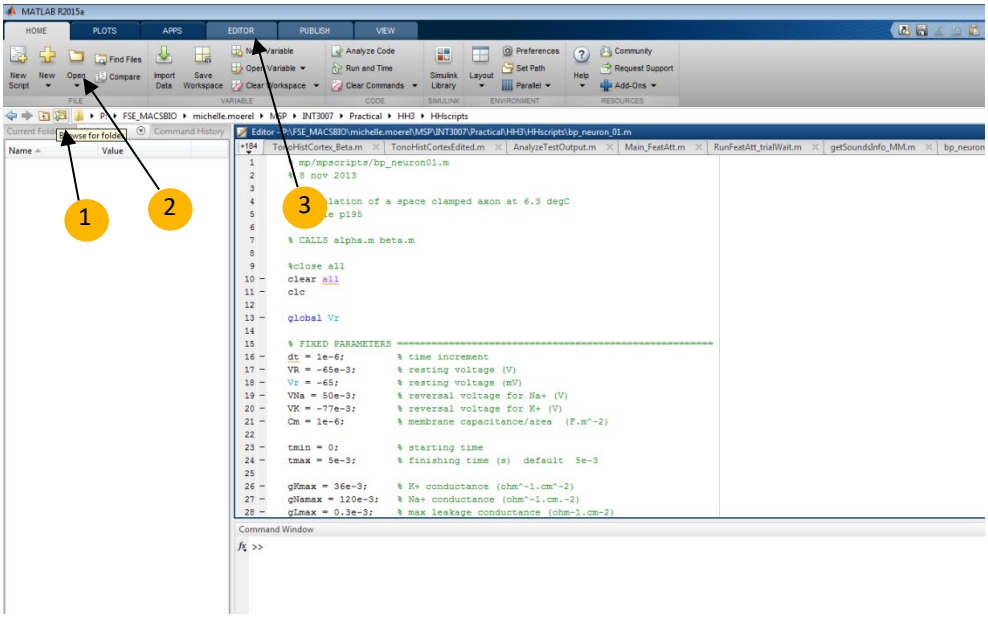


Fig.2. Preparatory steps. (1) click here to browse to your unzipped folder Scripts_Practical5. (2) click here to open file 'bp_neuron_01.m'. (3) click here to go to the editor tab.

Run the script:

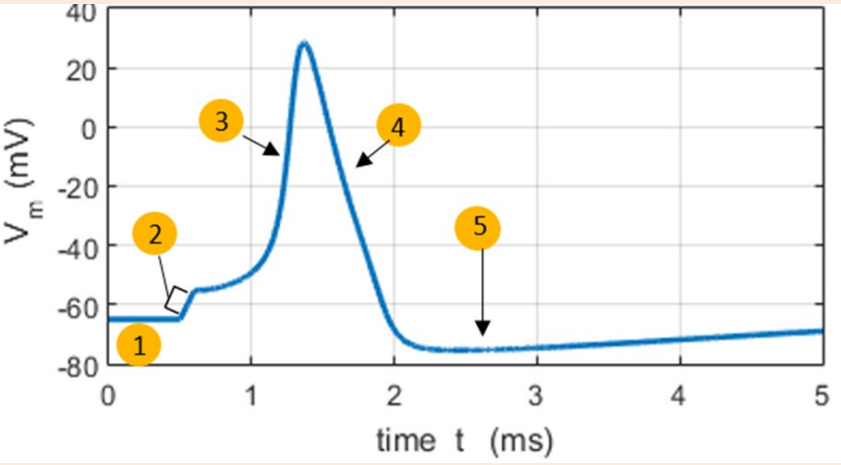
- Go to the editor tab (see (3) in Fig. 2 above)
- Click on the green arrow 'RUN'

Interpret the output:

- A figure with three subpanels should be generated
- Use Appendix I (at the end of this manual) to answer the questions below

Questions for Assignment 1:

a) What does the top panel reflect?
b) What does the middle panel reflect?
c) What does the bottom panel reflect?
d) Label the stages visible in the bottom panel:



1: .....

2: .....

3: .....

4: .....

5: .....

Assignment 2 – Explore the effect of modified pulse intensity

Next, explore what happens to the action potential when the intensity of the current pulse is modified.

Modify the script:

- Find the variable that controls the intensity of the current pulse. This variable is called: Jext_max
- The default value of Jext_max = 1e-4 (which is 0.0001 $A.cm^{-2}$ or 0.1 $mA.cm^{-2}$). Increase or decrease this value, and click on the green arrow to run the script
- This should generate figures with the same information as in Assignment 1. Use them to answer the questions below.

Questions for Assignment 2:

a) What intensity no longer produces an action potential?
b) What is the effect of increased pulse intensity on the action potential?
c) How can you model inhibitory input?

Suggestions:

- Don't modify the value of Jext_max too much, as you will no longer be able to see the full plot. Interesting values to try are 5e-5 (= 0.05 $mA.cm^{-2}$) and 2e-4 (= 0.2 $mA.cm^{-2}$).
- Use Appendix II (at the end of this manual) to plot action potentials resulting from different pulse intensities in the same figure. This will simplify answering question 2b.

Assignment 3 – Stimulate the modeled neuron with multiple pulses

Next, explore what happens to the action potential when the neuron is stimulated with multiple pulses in a row.

Modify the script:

- Set Jext_max back to 1e-4
- You will want to simulate a longer time period. Find the variable that controls the finishing time and modify it: tmax = 20e-3
- Switch OFF: the part of the code that generates one pulse. This is line 64. You can switch off lines in the code by "commenting" them, which works by putting a "%" at the start of line. See Fig. 3. for instructions on how to comment or uncomment large sections of code.
- Switch ON: the code that generates multiple pulses: uncomment lines 67-78.
- Press the green arrow to run the code

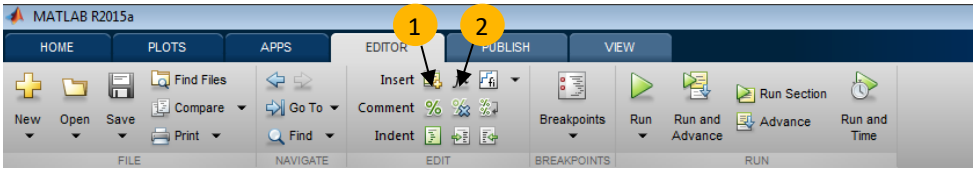


Fig.3. Comment and uncomment large sections of code. Select the text you want to (un)comment, and click (1) to comment or (2) to uncomment.

Questions for Assignment 3:

a) How many pulses are sent? How many action potentials are generated?
b) What do you expect to happen if you send the same pulses in a shorter time interval? Why?
c) How can you generate the same number of pulses in a shorter time interval?

Suggestions:

- To check your answer to question 3b, simulate sending the same number of pulses in a shorter time interval
- You can do this by modifying variable num_d (line 69; default at 0.18 * num). For example, set it to 0.1 * num.
- Press the green error to run the code and observe/explain what happens

Assignment 4 – A single neuron computational model

Next, explore a new script that codes for a single neuron computational model.

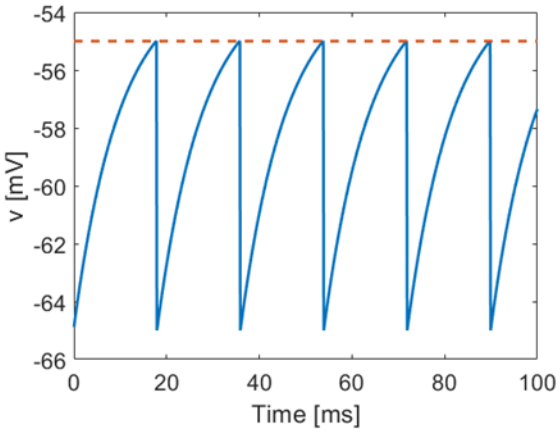
- Open the file 'Assignment4.m'
- Run the script (by clicking on the green arrow 'RUN')

Questions for Assignment 4:

a) What type of computational model is this?
   I. a Hodgkin-Huxley neuron
   II. an integrate-and-fire neuron
   III. a compartmental model

b) Motivate your choice based on the Matlab code (include Matlab line numbers).

c) Explain the figure generated by the code and displayed below. What do the solid blue line and dashed red line show?



Suggestions:

- Slides 40-41 of *Lecture 5: Modeling Neural Coding* can help in answering the questions of Assignment 4.

PART II. The Allen Brain Atlas

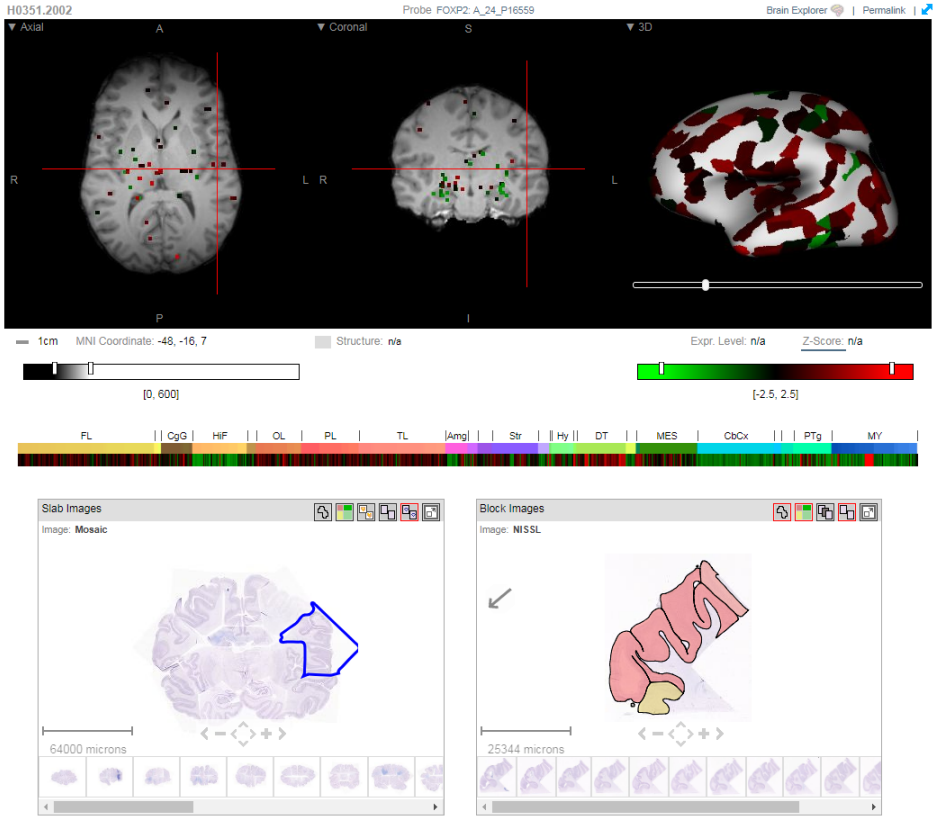
The Allen Human Brain Atlas is a unique multi-modal atlas that maps gene expression across the adult human brain. The atlas integrates anatomic and genomic information, data modalities include magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), histology, and gene expression data derived from both microarray and in situ hybridization (ISH) approaches. Key features include an "all genes, all structures" microarray survey spatially mapped to the MRI, ISH cellular resolution image data for selected genes in specific brain regions, and an annotated human brain atlas guide.

In part II of this skills training, you will use the microarray data available in the Allen Brain Atlas to answer two research questions

Open the human dataset within the Allen Brain Atlas:

- Go to http://human.brain-map.org/
- Perform a gene search on the gene of your choice by entering a gene name or symbol in the search window and clicking 'search'
- Explore the output

Planar view, useful to visualize gene expression across brain regions:



Assignment 5 – Use the Allen Brain Atlas to answer two research questions

Questions for Assignment 5

a) Where in the brain are genes that code for dopamine receptors expressed? Why are they expressed in this region?

b) Which genes show higher expression in the hippocampal formation than in the rest of the brain? What is the function of these genes?

Suggestions:

- Use the 'Gene Search' option to answer Question 5a, and the 'Differential Search' option to answer Question 5b
- To answer Question 5a, you can simply ask for a 'dopamine receptor' (knowing the name of a specific gene is not required)

Appendix I. Physical Quantities: Symbols, Units, Typical values

t	~ ms	time
a	$5x10^{-6}$ m	Radius of axon
b	$6x10^{-9}$ m	Membrane thickness
Ri	Ω	Longitudinal resistance of axon
rin	$6.4x10^{9}$ Ω.m^{-1}	Longitudinal resistance / length axoplasm resistance / length
V(*t*,x) *V*m(t,x)	~ - 70 mV to + 40 mV	instantaneous potential difference across membrane (membrane potential)
*V*in(t,*x*)	~ - 70 mV to + 40 mV	potential inside cell Vin = V (membrane potential)
Vout	0	potential outside cell: consider as ground potential
VR	-65mV	Resting membrane potential
C	F	membrane capacitance
cm	$1.0x10^{-6}$ F/cm^{2}	Capacitance / area
Q(*t*,*x*)	C	instantaneous charge on capacitor plates
IC(*t*,*x*)	A	instantaneous capacitive current
Iion(*t*,*x*) = *Im*(*t*,*x*)	A	ion current or membrane current
INa(*t*,*x*)	A	Na+ current
IK(*t*,*x*)	A	K+ current
IL(*t*,*x*)	A	leakage current – small, mainly Cl^{-}
Iin(*t*,*x*)	A	Longitudinal current – current along inside of axon
Jext(*t*,*x*)	A.cm^{-2}	Instantaneous external stimulus current density
Jion(*t*,*x*) = *Jm*(*t*,*x*)	A.cm^{-2}	ion current or membrane current density
JNa(*t*,*x*)	A.cm^{-2}	Na+ current density
JK(*t*,*x*)	A.cm^{-2}	K+ current density
JL(*t*,*x*)	A.cm^{-2}	leakage current density – small, mainly Cl-
Jext(*t*,*x*)	A.cm^{-2}	external stimulus current density
GNa(*t*,*x*)	$Ω^{-1}$	Na+ conductance

GK(*t*,*x*)	Ω^{-1}	K+ conductance
GL(*t*,*x*)	Ω^{-1}	leakage conductance
gNa(*t*,*x*)	$\bar{g}_{Na}$ = 120x10^{-3} Ω^{-1}.cm^{-2}	Na+ conductance / area maximum value
gK(*t*,*x*)	$\bar{g}_{K}$ = 36x10^{-3} Ω^{-1}.cm^{-2}	K+ conductance / area maximum value
gL(*t*,*x*)	$\bar{g}_{L}$ = 0.3x10^{-3} Ω^{-1}.cm^{-2}	leakage conductance / area maximum value
ENa	+ 50 mV	reversal potential for Na+
EK	- 77 mV	reversal potential for K+
EL	- 75.6 mV	reversal potential for leakage
k	1.38x10^{-23} J.K^{-1}	Boltzmann's constant
e	1.60x10^{-19} C	Charge on an electron
z		Valency of an ion
T	K or ^{o}C	Temperature

Appendix II. Plot overlapping lines

Run the code below in Matlab:

- Create an empty Matlab script (via the button that says: "+ New" in the Matlab Editor tab)
- Copy-paste the text below in the empty file: this is a new matlab script
- Save the new matlab script (via the "Save" button in the Matlab Editor tab)
- Set 'bp_neuron_01.m' to the current intensity that you want to try and run that script
- Run the new matlab script
- Repeat the previous two steps for different current intensities

```
figure(2)                    %plot in figure 2
x = t.*sf;    y = V.*sf;     %x = time, y = voltage
plot(x,y,'linewidth',2);     %plot membrane voltage over time
xlabel('time  t   (ms)'); ylabel(' V_m (mV)');  %label axes
grid on                      %switch on background grid
hold on                      %overlay next plot on top of current plot

LegendVar = Jext_max;        %choose which variable to display in legend
hLegend = findobj(gcf, 'Type', 'Legend');       %check existing legend
if ~isempty(hLegend)
    hLegend.String(end) = {num2str(LegendVar)};
else
    Legend_this{1} = num2str(LegendVar);
end
legend(Legend_this);                            %add legend to plot
```