Practical 2: Simulating Synaptic Integration

Physiology PHOL0009
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Part A: Linear and non-linear summation of inputs

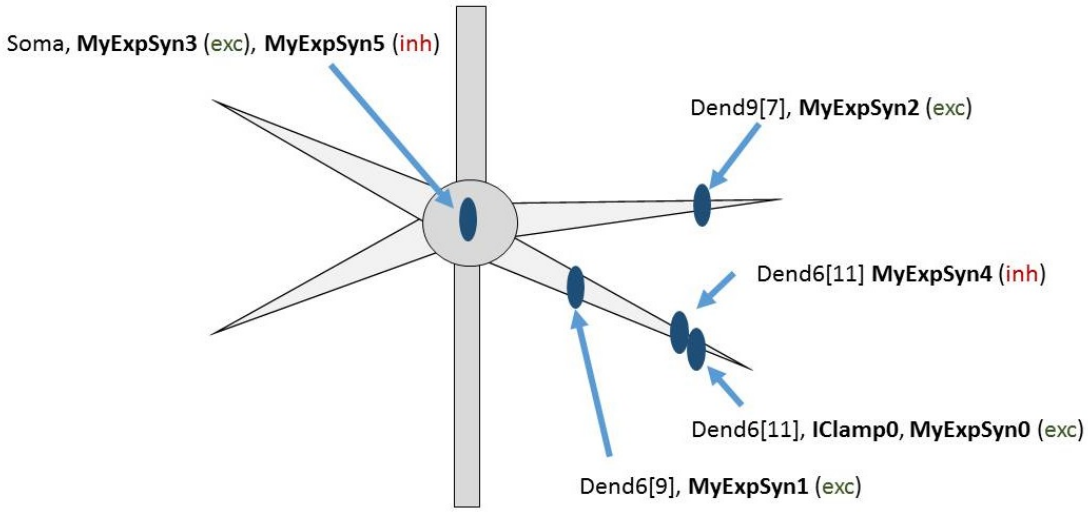
The goal of the first part of this practical is to understand some of the factors influencing linear and non-linear interactions between inputs in a morphologically complex neuron. The practical uses a multi-compartmental model of a cortical layer 5 pyramidal neuron based on a model developed in NEURON by Zach Mainen (Mainen et al. 1995). Some of the exercises look at the passive properties of the cell while others include basic Na^+ and K^+ channels on the dendrites (although it is known that a much wider range of conductances are present on pyramidal cell dendrites).

The procedure for loading these practicals is similar to that outlined in the previous practical summary on Simulating the Action Potential with Hodgkin-Huxley Kinetics. It assumes you have the files extracted into a folder N:\Development\NRN.

Open tutorial2a.hoc. NEURON opens 5 different windows:

- *NEURON Main Menu*
- *Run Control*
- *Cell Parameters (for conductance values of Na, K channels in various parts of the cell)*
- *PointProcessGroupManager (for managing synaptic/current clamp inputs)*
- *Voltage Graph (membrane potential at the soma)*

The NEURON command line window (titled nrniv or sh) is also opened. You may have to reposition the windows if the screen display is not big enough. In NEURON's Main Menu, select Window -> Window Manager, click on *move* and reposition the blue windows. The *PointProcessGroupManager* window shows the morphology of the cell and the location of the different inputs. Click on each of the inputs in the grey column to highlight its cellular location (current injection electrodes are labelled *IClamp* and excitatory and inhibitory synapses are labelled *MyExpSyn*; the name of the neuronal compartment that contains the selected input appears above the cell morphology diagram). Be careful not to click on the 3D morphology itself, as this may move the locations of the synapses! You can zoom by right clicking on the diagram of the cell. Hold down the right mouse button, select *Zoom in/out* and zoom with the left mouse button (move the cell with the middle button), or use the *10% Zoom* function.



Schematic of cell with positions of synaptic and current clamp inputs

Exercises

A1. Linear addition of input currents. What is the effect of different input currents on the voltage response in the soma? What does linear mean? Inject different currents into one of the basal dendrites (*IClamp[0]* at *dend6[11]*; vary the amplitude of injected current e.g. between 0.5 and 5 nA). You will have to readjust the axes because the somatic voltage responses are fairly small (in the *Voltage Graph* window, hold down the right mouse button and select *View... -> View = plot*). To overlay and compare different voltage responses, select (again after right mouse click) *Keep Lines* (note that there is also an *Erase* option and that you can change the colour of the traces with *Color/Brush*). You can read out the peak voltages by left clicking on the curves (a crosshair appears and the values are shown in the title bar). Are the voltage responses linear?

A2. Neighbouring excitatory synapses. Set the current injection amplitude back to zero. Apply excitatory synaptic input to AMPA receptors at a single location (*MyExpSyn[0]* at *dend6[11]*). To stimulate a single synapse at this location, set the *gmax* field of *MyExpSyn[0]* to 0.001 μS. Rescale the voltage axis to –71 - -66 mV (the somatic voltage response to a single synaptic input is very small). Simulate the simultaneous activation of 10, 20 and more synapses (by changing *gmax* to 0.01 μS, 0.02 μS etc.) and compare the voltage responses. Why is the summation of responses at the soma to synaptic input different from that of responses to injected current?

A3. Spatially separated excitatory synapses. Compare the response to gmax = 0.02 μS at one dendritic location (*MyExpSyn[0]* at *dend6[11]*) with the summed response to gmax = 0.01 μS at two separate dendritic locations (*MyExpSyn[0]* at *dend6[11*] and *MyExpSyn[2]* at *dend9[7]*). What is happening and why?

A4. Attenuation of voltage responses. Compare the somatic response when a synapse is activated at a location 218 μm from the soma (*MyExpSyn[0]* at *dend6[11]*, set *gmax* to e.g. 0.01 μS when this is activated) to the response to one at 106 μm from the soma (*MyExpSyn[1]* at *dend6[9]*, set *gmax* to the same value when this is activated). In addition to plotting the membrane potential at the soma (what has been plotted until

now) plot the local voltage responses. You can add a trace to the voltage graph by holding down the right mouse button, selecting *Plot What* and entering the specific variable, i.e. *dend6[9].v* and *dend6[11].v*. If these are not in the list, select a similar one and edit it in the text box to the correct variable name. You might want to change the colour of the traces, see above. What is the peak depolarisation at each the three locations when a) only the distal synapse (*MyExpSyn[0]*) is activated and b) only the more proximal (*MyExpSyn[1]*) is activated? How does the time course of the voltage responses in the three locations differ? Why is this?

A5. Amplification of dendritic input by Na channels. Compare the responses from above in the presence and absence of dendritic Na channels. Add fast Na channels to the model by setting the value of *gna* to e.g. 100 pS/μm^2 (in all 4 *gna* fields in the *Cell Parameters* window). How are the attenuation and temporal profile of voltage responses affected? What happens when K channels are added (also 100 pS/μm^2) in addition to the Na channels?

A6. Global inhibition and local shunting. Remove the active channels as used in the previous question. Compare the somatic voltage responses to AMPA receptor activation at the three locations from above (*MyExpSyn[0-2]*) when inhibitory input is added to the model. Add inhibition by setting the maximum conductance of the dendritic inhibitory synapse *MyExpSyn[4]* (next to one of the excitatory synapses) to 0.01 μS, and compare this to the effect of setting the conductance of the somatic inhibitory synapse *MyExpSyn[5]* to 0.01 and 0.1 μS. What is the effect of inhibitory input, and how does it depend on the location of the inhibition? Why do we need larger inhibitory conductances for effective somatic inhibition?

Part B: Spike initiation and backpropagation

Exit the first part of the practical (*File – Quit* from the *Main Menu*) and load the second part by opening *tutorial2b.hoc*. *Tutorial2b.hoc* is a modification of Zach Mainen's original simulation script, which implements a fully active model of a cortical layer 5 pyramidal cell. The model contains fast Na channels and delayed rectifier K channels, all other channels types are assumed to be irrelevant for the behaviour that is studied. Channel kinetics and distributions have been adjusted to reproduce previous electrophysiological experiments (e.g. Stuart & Sakmann 1994).

Opening on *tutorial2b.hoc* opens a similar set of windows as *tutorial2a.hoc*. The distal dendritic branch *dend9[78-81]* has been singled out in the *Cell Parameters* window so that the effect of a localised "hot spot" of elevated Na conductances can be studied. The location of the synapses and current injection sites can again be seen in the *PointProcessGroupManager* window. Two additional tools will be useful that were not needed for part A of the tutorial:

The Space Plot window. The temporal evolution of the voltage along a path through the dendritic tree can be plotted using the *Space Plot* function. From the *NEURON Main Menu*, select *Graph – Shape Plot*, which opens a morphological diagram of the cell. Right click to select *Space Plot* and use the left mouse button to draw a line next to the path through the dendritic tree that is studied (in this case it is useful to draw a vertical line along the length of the whole cell). A space/time plot of voltage will open in another window.

The Shape Plot window. In the previous window, use the right mouse button to select *Shape Plot*. The *Shape Plot* function can be used to display a colour coded 2D diagram of the temporal evolution of the voltage in the whole cell. To use this function you should stop the simulation from the *Run Control* window and step it forward very slowly by clicking on the *Continue For (ms)* button. Pressing Init will reset the simulation time to 0.

Exercises

B1. Where is the site of action potential initiation (the region of the cell where the voltage first spikes) for current injection into the soma (*IClamp[1])* and dendrite (*IClamp[2]* at *dend9[76]*), respectively? Use current injections of about 0.2 nA.

B2. Add a plot of the voltage at *dend9[76]*. Do the spikes invade the dendrites, and if yes, how fast (both for dendritic and somatic current injection)? To calculate the propagation velocity you can display the distance from the soma by typing

oc>soma distance()
oc>dend9[76] print distance(0.5)

on the command line (*sh/nrniv* window).

B3. Compare the amplitude of the voltage responses in the distal dendrites (*dend9[81]*) for somatic and dendritic (*dend9[76])* current injection. Why do they differ? Hint: plot the Na channel inactivation variable *dend9[81].h_na3* using the *Graph – State Axis* function from the NEURON Main Menu.

B4. What happens for dendrites without Na channels? How is the amplitude of the dendritic voltage responses affected?

B5. How can we change the location of spike initiation? Suggestion: increase the Na channel conductance at the selected dendritic location *dend[78-81]* and inject current either into the soma or into the dendrite at *dend9[76]*. Can you think of any other physiological changes/variations that could change the location of spike initiation?

Essay

Which factors influence synaptic integration and action potential initiation in neurons?

Write an **essay** based around the topics posed by all the questions above using the simulation results you have obtained from the practical exercises to illustrate your main points. Note that this should not simply be a set of answers to the exercises. Target is general neuroscientist; assume they have not done practical (i.e. don't say "when I applied a current to dend9[76]..." etc.).

Max length ~5 pages A4 (excluding figures), 2500 words (excluding legends, but keep legends brief & to the point). Figures properly numbered/labelled/with legends/referenced in main text/standalone/descriptive only (look at published papers).

References

Methods in Neuronal Modeling: from Ions to Networks. C. Koch and I. Segev editors, MIT Press (1998).

Computational Neuroscience: Realistic Modeling for Experimentalists. E. De Schutter editor, CRC Press (2000).

Mainen, Z., Joerges, J., Huguenard, J.R. and Sejnowski, T.J. (1995). A model of spike Initiation in neocortical pyramidal neurons. Neuron 15, 1427-1439.

Stuart, G.J. and Sakmann, B. (1994). Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature 367, 69-7