Alzheimer's disease

Computer Exercises using the NEURON Simulator

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Alzheimer's: introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease that usually manifests itself at old age (Burns and Iliffe, 2009). It causes various cognitive impairments, such as dementia, short-term memory loss, disorientation and various others. There have been multiple hypotheses regarding AD causes, focusing on some molecular biomarkers, such as amyloid β (Aβ) deposits, tau protein abnormalities, senile plaque deposits and others (de la Torre, 2011). It has been shown that hippocampus is one of the structures that are heavily affected by AD (Menschik and Finkel, 1998), for example by Aβ proteins, that accumulate extracellularly in AD brain, have various effects on hippocampal pyramidal neurons (Chen, 2005; Abramov et al., 2009).

Our goal in this exercise is, using the newly acquired NEURON simulator knowledge, to better understand how one of the AD correlates, Aβ protein, and suppression of back-propagating actions potentials caused by Aβ, affects a single CA1 pyramidal cell.

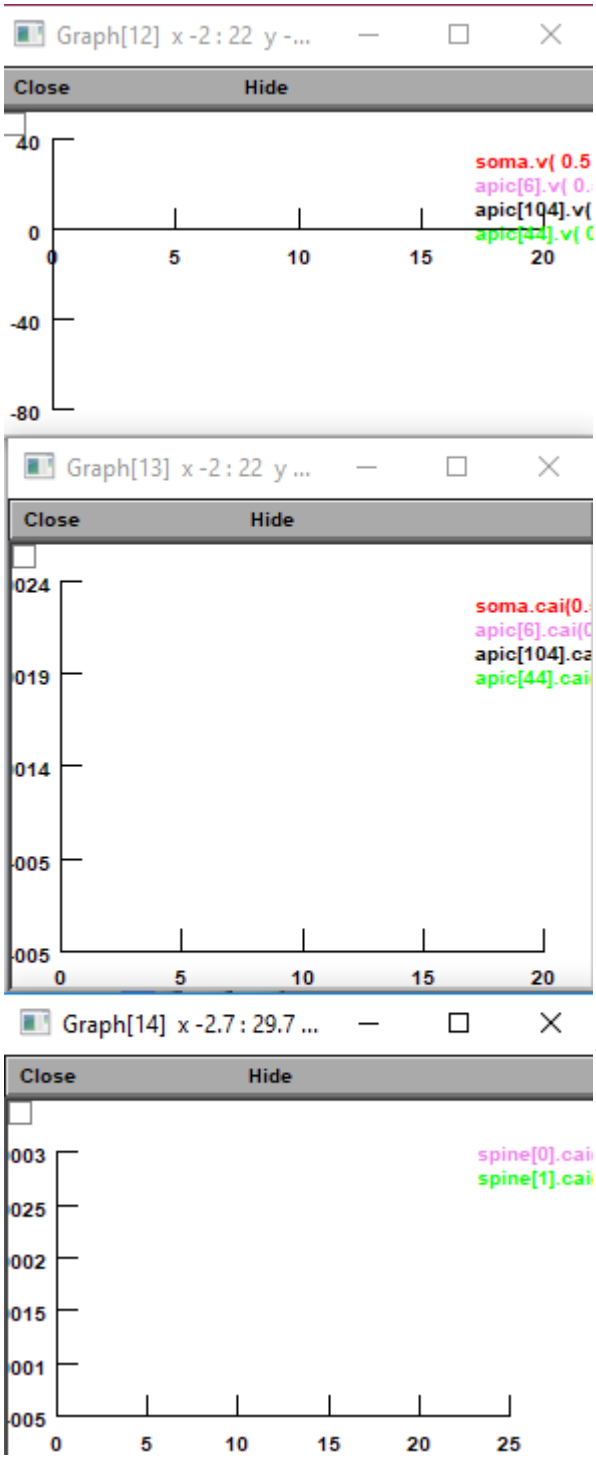
Back propagating action potential spread and Ca^{2+} transient enhancement by Aβ

This exercise focuses on the model developed by Morse et al. (2010). In this study authors, using computatonal modeling, investigated Aβ modulation of a specific K^+ current (I_A). Concretely, the study investigated how Aβ modulation of I_A affects the magnitude of backpropagating action potentials (bAPs) at different locations in the dendritic tree and the associated Ca^{2+} dynamics. I_A has been shown to decrease bAP spread into the dendritic tree (Hoffman et al., 1997; however different studies report slightly different bAP suppresion). Chen (2005) experimentally showed that Aβ downregulates I_A by 31.5% in the soma and by 46.5% in the dendrites, increasing both bAPs and Ca^{2+} influx. The Morse et al. (2010) model can be downloaded from ModelDB (https://senselab.med.yale.edu/modeldb/), accession number 87284.

Instructions

1. **Download Alzheimers_BNNI_2017.zip**
2. Open the model folder and find the file named "mosinit.hoc"
3. Double-click on this file, this will open the NEURON simulator and multiple graphs and tables with various buttons. For now, find the largest table with three collumns, this is our research panel. Also find the three graphs that are shown in a picture to the right. The first one of them shows voltage at various sections of the cell, the other one shows internal Ca^{2+} concentration at those same sections of the cell, the third shows internal Ca^{2+} concentrations in a spine attached to the dendritic trunk (violet) and another spine attached to an oblique dendrite (green). The curves are color coded: red curves represent the soma, violet curves represent the dendritic trunk (135µm from the soma), black curves represent an oblique dendrite (263µm from the soma), green curves represent an apical tuft dendrite (640µm from the soma).

4. Let's familiarize with the research panel. For now, focus on the left-most column of the table, especially "run model", "remove aBeta", "confirm" and buttons and the field just right to "aBeta concentration factor". The first two buttons are self-explanatory, while the third button "confirm" applies the Aβ concentration specified in "aBeta concentration factor" field (in µM) to every section of the cell.



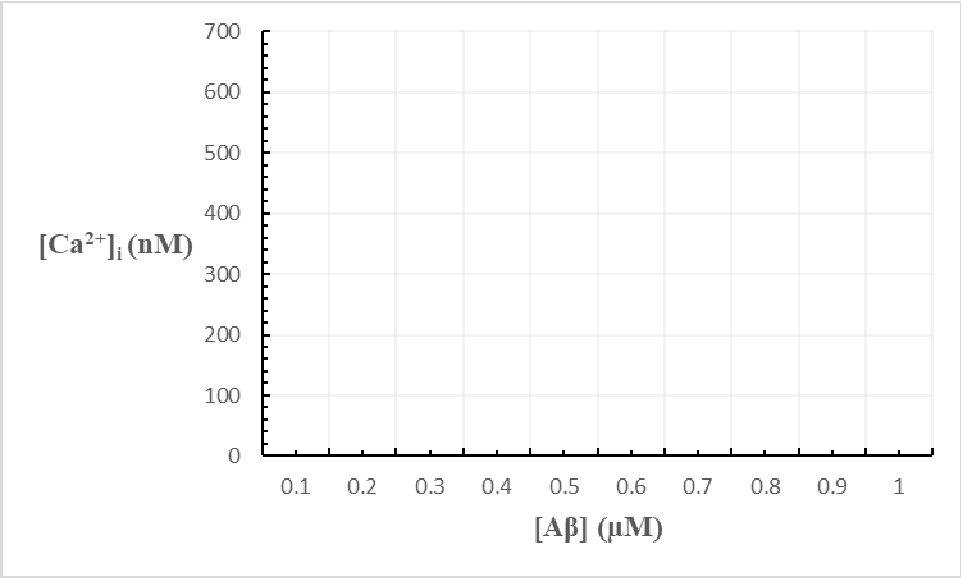
5. After a brief introduction, let's get down to business. First of all, we need a control recording, i.e. when Aβ concentration is 0 (representing the healthy condition). Click "remove aBeta" and then "run model".

6. Now that we have a control recording, lets apply Aβ. Click "confirm" to set "aBeta concentration factor" to 1 and click "run model" again (right-click on the graph and select "Keep lines" if you'd like to keep the results of previous simulations). Consider the differences at the same section between Aβ concentrations and between different sections at the same concentration, what do you see? Consider both bAP amplitude and Ca^{2+} transient changes. $\bar{g}_{I_A}$ changes are implemented in "aBeta.hoc" file in the following way:

gkabar_kap *= (1-aBeta_concentration_factor*.315) for soma

gkabar_kap *= (1-aBeta_concentration_factor*.465) for dendrites

7. Now try varying Aβ concentration between 0 and 1. You may wish to first compare a few low concentration runs, however, later on try comparing the results at 0.7µM Aβ and 0.8µM Aβ. Do the results follow a linear pattern when comparing numerically identical concentration differences (for example 0.3µM with 0.4µM and 0.7µM with 0.8µM)? To read off $[Ca^{2+}]_i$, left-click on the graph displaying Ca^{2+} transients in various parts of the cell. The basal $[Ca^{2+}]_i$ in a CA1 pyramidal cell is somewhere around 50nM, therefore 5E-5 in the gaph is 50nM, 0.0001 is 100nM and so on. You can use the empty graph below to plot a few points and see whether the results follow a linear pattern.



8. Try inputs of various frequency. You can set them in the model folder, file named "fig2A_c961662.hoc". Close the NEURON simulator if you have it running, open this file with a text editor, at the top you'll see two variables – "noSpikes" and "frequency". You can try, for example, theta or gamma band frequencies, respectively 4-11Hz or 25-80Hz. Save the changes and restart the NEURON simulator if you didn't exit it beforehand.

Try exploring various morphological application patterns (in NEURON GUI – buttons just below "run model"). Try applying Aβ only to the soma ("apply aBeta to soma" button) and compare the obtained recordings to Aβ application only to oblique (middle column – "apply aBeta to oblique dendrites button") or apical dendrites ("apply aBeta to apical dendrites" button just below "run model"). Which regions of application produce the most/least dramatic shifts in activity?

Additional problems

1. It has been long known that excessive Ca^{2+} activity causes apoptosis. Which parts of the hippocampal pyramidal cell show the highest increase in $[Ca^{2+}]_i$? In which parts of the hippocampal pyramidal cell do you expect $[Ca^{2+}]_i$ rise high enough to trigger cell apoptosis?
2. Based on the Ca^{2+} control hypothesis of synaptic plasticity, speculate what effects would Aβ have on plasticity and via which mechanisms?
3. Morse et al. (2010) identified three factors for the nonlinear increase of oblique dendrite intracellular Ca^{2+} transients, can you speculate what they are?

References

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