Title: Automated Threshold Detection and Input Resistance Measurements for Characterizing Morphologically Realistic Compartmental Models of Neurons

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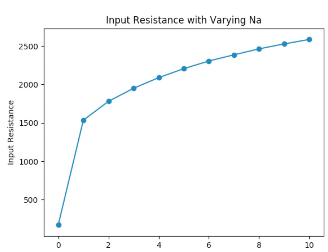
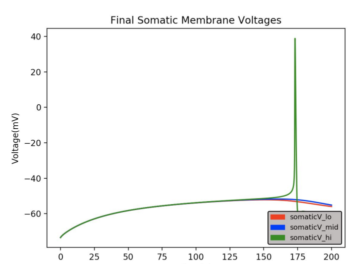
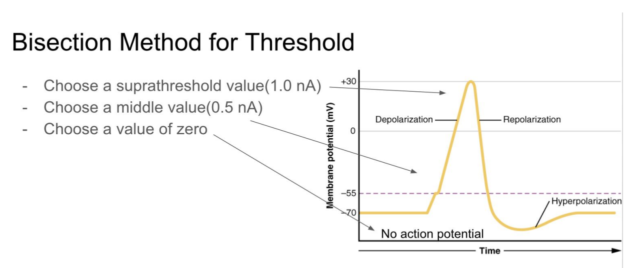
Introduction: The USC Viterbi's Center for Neural Engineering (CNE) is developing a large-scale neuronal network model of a rat hippocampus with morphologically realistic neurons which are represented using compartmental models. An evolutionary multi-objective optimization framework is being used to constrain the model parameters. Due to the large number of parameters for each model, each of the objectives needs to be efficient and robust; this study investigates two of the objectives, action potential threshold, and input resistance. The first goal of this project was to identify the minimum current amplitude necessary to elicit an action potential (AP). This was then used to constrain the current amplitudes used to measure input resistance to ensure that they were subthreshold. The study also explored how different experimental conditions, such as sodium level and current amplitude sign, affected input resistance measurements.

Materials and Methods: This computational study was performed using NEURON, a simulation environment for modeling individual neurons and networks of neurons, and it was scripted using Python. A dentate gyrus granule cell model was used in this work. To determine the threshold, the bisection method was applied to automate threshold identification by repeatedly bisecting the range of current amplitudes and selecting the subinterval in which there was no AP at the lower value and an AP at the higher value. After the first bisection, the algorithm used the midpoint of the two values to create the next bisection. The algorithm continued until the relative error of the last two iterations were below some error tolerance. The current amplitude identified during threshold detection was used to determine the range of currents used to measure input resistance. Input resistance was calculated using three conditions: all positive, all negative, and both negative and positive ranges of current amplitudes to assess their effect on calculated input resistance. Finally, sodium conductance values were varied to characterize its effect on input resistance.

Results and Discussion: For the granule cell model, the bisection method resulted in 0.111267 nA as the minimum current amplitude that triggered an AP, -52.160568 mV as the somatic voltage at which the neuron generated an AP and a relative error of 0.004779 at which the bisection method terminated. For all three positive/negative conditions (i.e., all positive, all negative, and half of each), the cells' default sodium conductance was 0.84 S/cm^2. Sodium conductance was varied by multiplying the default value with 11 scalars between 0 and 10.0. The results indicate that the all-positive condition is the most sensitive to Na changes. For the all-negative condition, the input resistance remained constant around 174 MΩ. For the combination condition, the input resistance ranged from 170 to172 MΩ. This represents a middle ground between positive and negative conditions.







Conclusions: The bisection method to determine threshold is an efficient and accurate method as the threshold is monotonically approached in neurons. The successful implementation of the bisection method allowed for an automated method to constrain the amplitudes used to characterize input resistance to ensure subthreshold activity. Finally, purely negative values should not be used to measure input resistance because it ignores the contributions of voltage-dependent ion channels, such as sodium, to the input resistance. These threshold and input resistance methods will be used as objectives within an evolutionary multiobjective optimization framework for future neuron model parameter optimization.