An Improved Hodgkin-Huxley Model (Sangrey 2004)

Simulation Project

Report due on Friday, December 22, 2017, by noon (12:00 pm)
Late reports: 20% will be deducted for each hour after the deadline.

The MATLAB scripts and functions you wrote as part of Homework Assignments 8, 9, and 10 are the starting point. You will modify your scripts and/or functions, and possibly create new ones, to conduct this experiment and analyze the results.

Report: Your report should be targeted to an audience that understands the Hodgkin-Huxley model, but not your topic of study. The report must include a statement of the problem (or the question being studied), the methods used to solve the problem (including equations and numerical algorithms), and the results of your investigation. Figures or graphics may be integrated with the text or arranged sequentially immediately after the references. The report must close with a discussion section, where the results and their implications are described. Plots must show appropriately labeled axes, including units. Appendices will contain your scripts and any lengthy derivations. Full citations to any reference materials used in your study must be included.

Score: The projects will be graded 80% for your analysis (the content of the report) and 20% for the style of the report. Superior reports will include analysis beyond what is required.

The original Hodgkin-Huxley model [1] was not only a major breakthrough in quantitative electrophysiology, it also built the framework for numerous new models of other cell types [2, 3, 4, 5]. Even so, several investigators have developed “improved” electrical models of the squid axon membrane based on modern interpretations of newer experimental data [6, 7]. At the macroscopic (membrane) level, the Hodgkin-Huxley model is known to underestimate the action potential amplitude, upstroke velocity \( \frac{dV}{dt_{\text{max}}} \), and repolarization velocity of the measured action potential. The improved model of Sangrey and colleagues [7] was developed to specifically address these issues.

The purpose of this study is to implement the improved model of Sangrey et al. and compare its characteristics to those in the original Hodgkin-Huxley model of the squid giant axon.

The improved Sangrey model uses the same four state variables as the original model. The key differences between the improved model and the original are:

<table>
<thead>
<tr>
<th>parameter</th>
<th>symbol</th>
<th>units</th>
<th>Hodgkin-Huxley</th>
<th>Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>leak Nernst potential</td>
<td>( E_L )</td>
<td>mV</td>
<td>-55</td>
<td>-65</td>
</tr>
<tr>
<td>( \text{Na}^+ ) conductance, maximum</td>
<td>( g_{\text{Na}} )</td>
<td>mS/cm²</td>
<td>120</td>
<td>130</td>
</tr>
<tr>
<td>( \text{K}^+ ) open probability</td>
<td>(none)</td>
<td>(none)</td>
<td>( n^4 )</td>
<td>( n^6 )</td>
</tr>
<tr>
<td>( n ) initial value</td>
<td>(none)</td>
<td>(none)</td>
<td>0.27293</td>
<td>0.19550</td>
</tr>
<tr>
<td>( m ) initial value</td>
<td>(none)</td>
<td>(none)</td>
<td>0.03689</td>
<td>0.01799</td>
</tr>
<tr>
<td>( h ) initial value</td>
<td>(none)</td>
<td>(none)</td>
<td>0.69572</td>
<td>0.92236</td>
</tr>
</tbody>
</table>
Another key improvement is a more rapid closing rate for potassium channels; the original Hodgkin-Huxley formulation is

\[
\beta_h = \frac{1}{1 + \exp\left[\frac{-(V_m + 30)}{10}\right]}
\]  

(1)

whereas the improved formulation is

\[
\beta_h = \frac{1.8}{1 + \exp\left[\frac{-(V_m + 16)}{10}\right]}
\]  

(2)

Aside from the above modifications, the two models should be identical to insure a valid comparison. When conducting their comparison, Sangrey et al. used the following parameters in the original and improved models:

- stimulus current \(J_{\text{stim}} = 50 \mu\text{A/cm}^2\)
- stimulus duration of 0.25 msec
- time step, \(\Delta t = 0.005\) msec
- simulation time = 15 msec
- temperature = 6.3 °C
- \(E_{Na} = 50\) mV
- \(E_K = -70\) mV
- \(V_{rest} = -65\) mV

Show the parallel conductance model of the improved membrane. Generate plots of the membrane potential, currents, and gates. Compute the action potential amplitude, the duration at 90% repolarization (APD\(_{90}\)), the maximum upstroke velocity \((dV/dt)_{\text{max}}\), and the maximum repolarization velocity \((dV/dt)_{\text{min}}\). Plot the \(h\) gate time constant versus \(V_m\) for both models. Compare the potassium channel conductance in the two models. How would a lower \(K^+\) channel open probability affect the repolarization velocity and APD\(_{90}\)? You may want to consult the original article [7] for more information.


