Human Node of Ranvier Action Potential Model (Schwarz 1995)

Simulation Project

Report due on Thursday, December 20, 2018, by 3:00 pm in my mailbox (Pastore 125) or my office at Schneider Electric. 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 Hodgkin-Huxley model laid the groundwork for the development of models for numerous other cell types. One important model describes the membrane’s electrical characteristics in the node of Ranvier in humans [1]. This work is important because myelinated nerve damage is one effect of multiple sclerosis. The formulation follows that of the Hodgkin-Huxley model: nonlinear membrane conductances are modeled using a saturation value and activation or inactivation gates, with voltage-dependent opening and closing rates. This model is more complex, however, because the sodium current is derived from the Goldman-Hodgkin-Katz equation. In addition, two currents (one “fast” and the other “slow”) describe potassium efflux during repolarization.

The purpose of this study is to implement the Ranvier node model and compare its action potential and currents to those in the squid giant axon.

The Ranvier node model uses five state variables:

1. \( V_m \), membrane potential
2. \( m \), sodium activation gate
3. \( h \), sodium inactivation gate
4. \( n \), fast potassium activation gate
5. \( s \), slow potassium activation gate

These state variables are handled much the same way as those in the Hodgkin-Huxley model. The complete Ranvier node model is listed below. The simulation will generate a membrane action potential (a non-propagating action potential at a point).
Modify the Hodgkin-Huxley scripts to implement the Ranvier node model. The simulation should cover at least 8 milliseconds using a time step $\Delta t = 0.001$ milliseconds. A stimulus current of $0.0005 \, \mu A/cm^2$ should be applied for 0.6 milliseconds.

Generate plots of the membrane potential, currents, and gates. Plot the gates’ time constants versus $V_m$. Compute the action potential amplitude, duration at 90% repolarization ($APD_{90}$), the maximum upstroke velocity $dV/dt_{\text{max}}$, and maximum repolarization velocity $dV/dt_{\text{min}}$. The upstroke velocity here and in the Hodgkin-Huxley model will be very different — what does this suggest about propagation velocity in the myelinated nerve versus the unmyelinated nerve? In the Ranvier model, how does repolarization velocity change when the slow potassium current is removed? You may want to consult the original article [1] for more information.

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Currents are given in $\mu A/cm^2$, conductances in $mS/cm^2$, potentials in $mV$ (except in $J_{Na}$; see note below), and concentrations in mM. Note that l’Hôpital’s rule must be applied to almost all of the opening and closing rates.

$$J_{\text{ion}} = J_{Na} + J_{Kf} + J_{Ks} + J_{\text{leak}}$$

**ion current**

$$J_{Na} = m^3 \cdot h \cdot P_{Na} \cdot \frac{V_m F^2}{RT} \cdot \frac{[Na^+]_o - [Na^+]_i \cdot \exp \left( \frac{V_m F}{RT} \right)}{1 - \exp \left( \frac{V_m F}{RT} \right)}$$

**Na$^+$ current**

In the $J_{Na}$ equation above, membrane voltage $V_m$ must be expressed in volts (not millivolts), so $J_{Na}$ will be in $A/cm^2$. You will need to convert this to $\mu A/cm^2$ to compute $J_{\text{ion}}$.

Carefully check the units in the $J_{Na}$ equation; there is another unit conversion required.

$$J_{Kf} = g_{Kf} \cdot n^4 \cdot (V_m - E_K)$$

**fast K$^+$ current**

$$J_{Ks} = g_{Ks} \cdot s \cdot (V_m - E_K)$$

**slow K$^+$ current**

$$J_{\text{leak}} = g_L \cdot (V_m - E_L)$$

**leak current**

Nernst potentials, conductances, and other parameters:

$$E_K = -83.8 \quad g_{Kf} = 15 \times 10^{-6} \quad [Na^+]_o = 154 \quad \text{temp} = 20 \, ^\circ C$$

$$E_L = -84.0 \quad g_{Ks} = 30 \times 10^{-6} \quad [Na^+]_i = 35 \quad P_{Na} = 3.52 \times 10^{-9} \, \text{cm}^3/\text{sec}$$

$$g_L = 30 \times 10^{-6} \quad C_n = 1.4 \times 10^{-6} \, \mu F/cm^2$$

The initial values of the state variables are:

$$V_m = -84 \, mV \quad m = 0.03821$$

$$n = 0.25667$$

$$h = 0.69823 \quad s = 0.20124$$
The four gates are governed by the opening and closing rates (in msec$^{-1}$):

\[
\begin{align*}
\alpha_m &= \frac{1.86 (V_m + 18.4)}{1 - \exp\left[-(V_m + 18.4)/10.3\right]} \\
\beta_m &= \frac{-0.086 (V_m + 22.7)}{1 - \exp\left[(-V_m - 18.4)/9.16\right]} \\
\alpha_h &= \frac{-0.0336 (V_m + 111)}{1 - \exp\left[(-V_m - 111)/11\right]} \\
\beta_h &= \frac{2.3}{1 + \exp\left[(-V_m - 28.8)/13.4\right]} \\
\alpha_n &= \frac{0.00798 (V_m + 93.2)}{1 - \exp\left[-(V_m + 93.2)/1.1\right]} \\
\beta_n &= \frac{-0.0142 (V_m + 76)}{1 - \exp\left[(-V_m - 76)/10.5\right]} \\
\alpha_s &= \frac{0.00122 (V_m + 12.5)}{1 - \exp\left[-(V_m + 12.5)/23.6\right]} \\
\beta_s &= \frac{-0.000739 (V_m + 80.1)}{1 - \exp\left[(-V_m - 80.1)/21.8\right]}
\end{align*}
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