Purkinje Fiber Action Potential Model (McAllister 1975)

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 McAllister-Noble-Tsien (MNT) model [1] simulates the action potential in cardiac Purkinje fibers. This model has provided a wealth of information on the electrical conduction system in the heart [2, 3, 4]. 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 it reproduces the natural rhythmic depolarizations of the Purkinje fiber. In addition, two currents describe potassium efflux during repolarization, and the model includes two chloride currents.

The purpose of this study is to implement the MNT model and compare the Purkinje action potential to the action potential in the squid giant axon.

The MNT model uses ten state variables:

1. \( V_m \), membrane potential
2. \( m \), sodium activation gate
3. \( h \), sodium inactivation gate
4. \( d \), slow sodium activation gate
5. \( f \), slow sodium inactivation gate
6. \( q \), chloride inactivation gate
7. \( r \), chloride inactivation gate
8. \( s \), potassium pacemaker gate
9. \( x_1 \), plateau potassium gate
10. \( x_2 \), another plateau potassium gate

These state variables are handled much the same way as those in the Hodgkin-Huxley model. The complete MNT 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 MNT Purkinje fiber model. The simulation should cover 4 seconds using a time step $\Delta t = 0.01$ milliseconds.

Generate plots of the membrane potential and currents versus time. Plot the gates and time constants versus $V_m$ for the $m$, $h$, and $s$ gates. Compute the action potential amplitude, the maximum upstroke velocity ($dV/dt_{\text{max}}$), and the duration at 90% repolarization ($\text{APD}_{90}$). What is the intrinsic period of the action potentials? How does the action potential change shape when the sodium conductance is reduced to 25% of its original value? Does the amplitude, $dV/dt_{\text{max}}$, and/or the period change? You should read the original article [1] and one with corrections [2] for more information.

### Purkinje Fiber Action Potential Model (McAllister 1975)

Currents are given in $\mu$A/cm², conductances in mS/cm², and potentials in mV. Note that l'Hôpital’s rule must be applied to the last term of $J_{K1}$ in addition to some opening rates.

- $J_{\text{ion}} = J_{\text{Na}} + J_{\text{si}} + J_{\text{K1}} + J_{\text{K2}} + J_{x1} + J_{x2} + J_{\text{qr}} + J_{\text{Na,b}} + J_{\text{Cl,b}}$ ion current
- $J_{\text{Na}} = \overline{g}_{\text{Na}} \cdot m^3 \cdot h \cdot (V_m - E_{\text{Na}})$ fast Na⁺ current
- $J_{\text{si}} = (\overline{g}_{\text{si}} \cdot d \cdot f + \overline{g}_{\text{si}}' \cdot d') \cdot (V_m - E_{\text{si}})$ secondary inward current
  
  where $d' = 1 / \{1 + \exp[-0.15(V_m + 40)]\}$
- $J_{\text{qr}} = \overline{g}_{\text{qr}} \cdot q \cdot r \cdot (V_m - E_{\text{Cl}})$ transient Cl⁻ current
- $J_{K2} = s \cdot \overline{J}_{K2}$ pacemaker K⁺ current
- $\overline{J}_{K2} = 2.8 \{\exp[0.04(V_m + 110)] - 1\} / \{\exp[0.08(V_m + 60)] + \exp[0.04(V_m + 60)]\}$
- $J_{K1} = \overline{J}_{K2} / 2.8 + 0.2 (V_m + 30) / \{1 - \exp[-0.04(V_m + 30)]\}$ background K⁺ current
- $J_{x1} = x_1 \cdot 1.2 \{\exp[0.04(V_m + 95)] - 1\} / \exp[0.04(V_m + 45)]$ nonlinear plateau K⁺ current
- $J_{x2} = x_2 \cdot (25 + 0.385 V_m)$ linear plateau K⁺ current
- $J_{\text{Na,b}} = 0.105 (V_m - E_{\text{Na}})$ background Na⁺ current
- $J_{\text{Cl,b}} = 0.01 (V_m - E_{\text{Cl}})$ background Cl⁻ current

Nernst potentials, conductances, and membrane capacitance:

- $E_{\text{Na}} = 40$
- $E_{\text{Cl}} = -70$
- $E_{\text{si}} = 70$
- $C_m = 10 \mu$F/cm²
- $\overline{g}_{\text{Na}} = 150$
- $\overline{g}_{\text{si}} = 0.8$
- $\overline{g}_{\text{si}}' = 0.04$
- $\overline{g}_{\text{qr}} = 2.5$
The initial values of the state variables are:

\[ V_m = -80 \text{ mV} \quad q = 2.156 \times 10^{-6} \]
\[ m = 0.01946 \quad r = 0.1190 \]
\[ h = 0.85910 \quad s = 0.7791 \]
\[ d = 0.002089 \quad x_1 = 0.02694 \]
\[ f = 0.7725 \quad x_2 = 0.01986 \]

The nine gates are governed by the opening and closing rates (in msec\(^{-1}\)):

\[
\begin{align*}
\alpha_m &= \frac{V_m + 47}{1 - \exp[-(V_m + 47)/10]} \quad \beta_m = 40 \exp[-(V_m + 72)/17.86] \\
\alpha_h &= 0.0085 \exp[-(V_m + 71)/5.43] \quad \beta_h = \frac{2.5}{1 + \exp[-(V_m + 10)/12.2]} \\
\alpha_d &= \frac{0.002 (V_m + 40)}{1 - \exp[-(V_m + 40)/10]} \quad \beta_d = 0.02 \exp[-(V_m + 40)/11.26] \\
\alpha_f &= 0.000987 \exp[-0.04(V_m + 60)] \quad \beta_f = \frac{0.02}{1 + \exp[-(V_m + 26)/11.49]} \\
\alpha_q &= \frac{0.008V_m}{1 - \exp[-V_m/10]} \quad \beta_q = 0.08 \exp[-V_m/11.26] \\
\alpha_r &= 0.00018 \exp[-(V_m + 80)/25] \quad \beta_r = \frac{0.02}{1 + \exp[-0.087(V_m + 26)]} \\
\alpha_s &= \frac{0.001 (V_m + 52)}{1 - \exp[-(V_m + 52)/5]} \quad \beta_s = 5.0 \times 10^{-5} \exp[-(V_m + 52)/14.93] \\
\alpha_{x_1} &= \frac{0.0005 \exp[(V_m + 50)/12.1]}{1 + \exp[(V_m + 50)/17.5]} \quad \beta_{x_1} = \frac{0.0013 \exp[-(V_m + 20)/16.67]}{1 + \exp[-(V_m + 20)/25]} \\
\alpha_{x_2} &= \frac{1.27 \times 10^{-4}}{1 + \exp[-(V_m + 19)/5]} \quad \beta_{x_2} = \frac{0.0003 \exp[-(V_m + 20)/16.67]}{1 + \exp[-(V_m + 20)/25]}
\end{align*}
\]


