Cardiac Sinoatrial Node Pacemaker Action Potential Model (Bristow 1982)

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 sinoatrial (SA) node model [1] simulates the action potential in the primary cardiac pacemaker cell. This model has provided insights into the pacemaker activity in the heart [2, 3]. 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 SA node cell. 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 SA node model and compare its action potential to the action potential in the squid giant axon.

The SA node model uses seven 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. $s$, potassium pacemaker gate
7. $x_1$, plateau potassium gate

These state variables are handled much the same way as those in the Hodgkin-Huxley model. The complete SA 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 SA node model. The simulation should cover 1200 milliseconds using a time step $\Delta t = 0.01$ milliseconds.

Show the equivalent circuit model of the SA node membrane. Generate plots of the membrane potential and currents versus time; these should resemble Figure 5 in the original research paper [1]. Plot the gates and their time constants versus $V_m$ for the $m$, $h$, and $s$ gates. Compute the action potential amplitude, the maximum upstroke velocity ($dV/dt_{\text{max}}$), duration at 90% repolarization (APD$_{90}$), and the period of the action potential peaks. How do these change if $E_{\text{si}}$ is reduced by 40 percent? What could cause this reduction in $E_{\text{si}}$? 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$^2$, and potentials in mV. Note that l'Hôpital’s rule must be applied to the last term of $j_{K_1}$ in addition to some opening rates.

$$J_{\text{ion}} = J_{Na} + J_{\text{si}} + J_{K_1} + J_{K_2} + J_{x_1}$$

ion current

$$J_{Na} = (\bar{g}_{\text{Na}} \cdot m^3 \cdot h + \bar{g}'_{\text{Na}}) \cdot (V_m - E_{Na})$$

fast Na$^+$ current

$$J_{\text{si}} = (\bar{g}_{\text{si}} \cdot d \cdot f + \bar{g}'_{\text{si}} \cdot d') \cdot (V_m - E_{\text{si}})$$

slow inward current

where $d' = 1 / \{1 + \exp[-(V_m + 15)/6.67]\}$

$$J_{K_2} = s \cdot \bar{j}_{K_2}$$

pacemaker K$^+$ current

$$\bar{j}_{K_2} = 0.6 \{\exp[(V_m + 110)/25] - 1\} / \{\exp[(V_m + 60)/12.5] + \exp[(V_m + 60)/25]\}$$

$$J_{K_1} = 0.93 \cdot \bar{j}_{K_1}$$

$$\bar{j}_{K_1} = \bar{j}_{K_2}/0.6 + \{(V_m + 30)/5\} / \{1 - \exp[-(V_m + 30)/25]\}$$

background K$^+$ current

Note above that in the original paper the $\exp[]$ argument is missing the negative sign.

$$J_{x_1} = x_1 \cdot 2.25 \{\exp[(V_m + 95)/25] - 1\} / \exp[(V_m + 45)/25]$$

plateau K$^+$ current

Conductances, Nernst potentials, and membrane capacitance:

$$E_{Na} = 40$$

$$E_{\text{si}} = 70$$

$$C_m = 6 \mu\text{F/cm}^2$$

$$\bar{g}_{Na} = 5$$

$$\bar{g}_{\text{si}} = 0.45$$

$$\bar{g}'_{Na} = 0.075$$

$$\bar{g}'_{\text{si}} = 0.14$$

The initial values of the state variables are:

$$m = 0.17016$$

$$h = 0.02520$$

$$d = 0.00318$$

$$f = 0.26486$$

$$s = 0.89877$$

$$x_1 = 0.05037$$

$$V_m = -61.3 \text{ mV}$$
The six gates are governed by the opening and closing rates (in msec\(^{-1}\)):

\[
\alpha_m = \frac{V_m + 47}{1 - \exp\left[-\frac{(V_m + 47)}{10}\right]} \quad \beta_m = 40 \exp\left[-\frac{(V_m + 72)}{17.86}\right]
\]

\[
\alpha_h = 0.0085 \exp\left[-\frac{(V_m + 71)}{5.43}\right] \quad \beta_h = \frac{2.5}{1 + \exp\left[-\frac{(V_m + 10)}{12.2}\right]}
\]

\[
\alpha_d = \frac{0.005 (V_m + 34)}{1 - \exp\left[-\frac{(V_m + 34)}{10}\right]} \quad \beta_d = 0.05 \exp\left[-\frac{(V_m + 34)}{6.67}\right]
\]

\[
\alpha_f = 0.002468 \exp\left[-\frac{(V_m + 47)}{20}\right] \quad \beta_f = \frac{0.05}{1 + \exp\left[-\frac{(V_m + 13)}{11.49}\right]}
\]

\[
\alpha_s = \frac{0.05 (V_m + 28)}{1 - \exp\left[-\frac{(V_m + 28)}{5}\right]} \quad \beta_s = 0.00025 \exp\left[-\frac{(V_m + 28)}{14.93}\right]
\]

\[
\alpha_{x1} = \frac{0.0025 \exp\left[\frac{(V_m + 30)}{12.11}\right]}{1 + \exp\left[\frac{(V_m + 30)}{50}\right]} \quad \beta_{x1} = \frac{0.0065 \exp\left[-\frac{(V_m - 20)}{16.67}\right]}{1 + \exp\left[-\frac{(V_m - 20)}{25}\right]}
\]

