BME 307 Bioelectricity Fall 2018

Bursting Action Potential in Pancreatic $\beta$-Cells (Bertram 2000)

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.

Beta cells ($\beta$-cells) are the primary type of cell in the islets of the pancreas. $\beta$-cells store and release insulin to maintain glucose homeostasis in the body. Similar to pacemaker cells in the heart, $\beta$-cells fire spontaneously, but they exhibit “bursting” where the action potential has many peaks. This phantom burster model of pancreatic $\beta$-cells [1] includes a potassium current activated by cytosolic calcium, and another potassium current activated by ATP. The formulation of this model follows that of the Hodgkin-Huxley model: nonlinear membrane conductances are modeled using a saturation value and gating variables, but the open probabilities are developed using an activation function with a time constant.

The purpose of this study is to implement the $\beta$-cell model and analyze the effect of a calcium-mediated conductance on the action potential’s bursting rate.

The $\beta$-cell model uses four state variables:

1. $V_m$, membrane potential
2. $n$, potassium activation gate
3. $r$, calcium-activated potassium activation gate
4. $s$, ATP-activated potassium activation gate

In the original research paper [1], the $r$ gate is called the $s_1$ gate, and the $s$ gate is called the $s_2$ gate.

These state variables are handled much the same way as those in the Hodgkin-Huxley model. The complete $\beta$-cell 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 β-cell model. Since the cell will spontaneously depolarize, the simulation will not include a stimulus current. The final simulation should cover 6000 milliseconds using a time step \( \Delta t = 0.01 \) milliseconds.

Generate plots of the membrane potential, the sum of currents \( J_R + J_S \), and the \( r \) and \( s \) gates versus time; these should resemble Figure 2 in the original research paper [1]. Compute the action potential amplitude, maximum upstroke velocity \( dV/dt_{\text{max}} \), and the duration at 90% repolarization (APD90). Plot the voltage-dependent time constant for the \( n \) gate versus \( V_m \).

Vary maximum calcium-activated potassium conductance \( \bar{g}_R \) from 13 to 20 pS/cm², then plot the number of action potential peaks versus \( \bar{g}_R \). What is the experimentally observed range of bursting oscillations in β-cells? You may want to consult the original article [1] for more information.

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**Bursting Action Potential in Pancreatic β-Cells** (Bertram 2000)

Conductances are given in pS/cm², capacitances in femtoF/cm², and potentials in mV.

\[
\begin{align*}
J_{\text{ion}} &= J_{\text{Ca}} + J_K + J_R + J_S + J_{\text{leak}} \\
J_{\text{Ca}} &= \bar{g}_{\text{Ca}} \cdot m_\infty \cdot (V_m - E_{\text{Ca}}) \\
&\text{where } m_\infty = \frac{1}{1 + \exp \left( -\left( V_m + 22 \right) / 7.5 \right)} \\
J_K &= \bar{g}_K \cdot n \cdot (V_m - E_K) \\
J_R &= \bar{g}_R \cdot r \cdot (V_m - E_K) \\
J_S &= \bar{g}_S \cdot s \cdot (V_m - E_K) \\
J_{\text{leak}} &= g_L \cdot (V_m - E_L)
\end{align*}
\]

ion current

calcium current

potassium current

calcium-activated potassium current

ATP-activated potassium current

leak current

Nernst potentials, conductances, and cell capacitance:

\[
\begin{align*}
E_{\text{Ca}} &= 100 & \bar{g}_{\text{Ca}} &= 280 & \bar{g}_R &= 20 \\
E_K &= -80 & \bar{g}_K &= 1300 & \bar{g}_S &= 32 \\
E_L &= -40 & g_L &= 25 & C_m &= 4524
\end{align*}
\]

The initial values of the state variables are:

\[
\begin{align*}
n &= 0.03244 & s &= 0.43931 \\
r &= 0.64195 & V_m &= -43.4 \text{ mV}
\end{align*}
\]
The three gates are governed by the activation functions and time constants (in ms):

\[
\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}
\]

\[
\frac{dr}{dt} = \frac{r_\infty - r}{\tau_r}
\]

\[
\frac{ds}{dt} = \frac{s_\infty - s}{\tau_s}
\]

\[
n_\infty = \frac{1}{1 + \exp[-0.1 (V_m + 9)]}
\]

\[
\tau_n = \frac{8.3}{1 + \exp[0.1 (V_m + 9)]}
\]

\[
r_\infty = \frac{1}{1 + \exp[-2 (V_m + 40)]}
\]

\[
\tau_r = 1,000 \text{ ms}
\]

\[
s_\infty = \frac{1}{1 + \exp[-2.5 (V_m + 42)]}
\]

\[
\tau_s = 120,000 \text{ ms}
\]

Finally, the membrane potential is governed by:

\[
\frac{dV_m}{dt} = -J_{\text{ion}}/C_m
\]