Bioengineering 6000
Homework Assignment # 1
Simulation of Cardiac Action Potentials

Rob MacLeod and Quan Ni

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1 Introduction

The goal of this assignment is to experiment with a numerical simulation of the cardiac action potential. The form of this simulation is just as described in class, using the Hodgkin-Huxley formalism and differential equations to reproduce the currents responsible for the action potential. As we saw in class, To simulate the cardiac action potential, it is necessary to expand the number of channels from the simple squid giant axon case, and also to alter the dynamic behavior of these currents compared with the original work of Hodgkin and Huxley.

The background for the simulations you will find in your notes from class on the Luo-Rudy model, implemented according to the first edition (*i.e.,* based on the 1991 and 1994 papers[1, 2]. Below is a description first of how to obtain and use the code and then of what I would like you to investigate with it.

Additional background is in the accompanying pdf document called background.pdf so please make sure to read it first.

2 The Code

The programs to perform the simulation are all written in MATLAB—they are m-files and thus completely readable and editable by each of you. Feel free to experiment with your copy of the files and investigate the structure of the code and numerical methods employed. For details or questions about MATLAB, contact me (macleod@sci.utah.edu) or see the associated references from my web site.

To make the code work, perform the following steps:

1. Follow the link from the class web site
   www.sci.utah.edu/~macleod/bioen/be6000/homeworks/cell/code.zip
   and you will have a zipped file with a directory full of the the m-files.

2. Start MATLAB and make sure the current MATLAB path includes the directory with all the m-files. Then execute the sample driver program called "`Map_demo`" (just type `Map_demo` at the command prompt). After a short delay (A few seconds to perhaps a minute depending on how fast your computer is) You should see a plot containing six different graphs from the simulation.

3. Use the `Map_demo.m` file as a starting point for your own simulations and then investigate how to change parameters there, in the `Map.m`, and in the `Constant.m` files, which are called by any driver program for a simulation.

3 The Assignment

Note: the report from this assignment must be typeset and include graphs of your results. See the homework tips site for details. I appreciate people who can write sentences and prepare decent looking reports. So please take the time to organize the report clearly, and integrate the output from the simulations into the document. I anticipate reports in the range of 3-6 pages in length (including figures) but there are no restrictions or requirements (in either direction) so please **write concisely** and answer the questions directly.

The `Map_demo.m` file provides a template that can be the starting point for this set of simulations. **Note that that in the `Map_demo.m` program, the action potential functon `Map`, is called with three parameters for the stimulus: the amplitude, onset time, and offset time; the difference between these last two values is the stimulus duration. Look at the documentation in the `Map.m` file for details.**

1. You have learned the action potentials only fire if the stimulus strength rises above a threshold and that any stimulus beyond that threshold elicits essentially the same action potential ("all or nothing"). The goals of this set of simulations is to see if the program (and perhaps reality) replicates this behavior and to determine which conditions are necessary for stimulation of an action potential.

   (a) By adjusting values of stimulus amplitude and duration, create simulations of membrane potentials that result from stimuli that are a) below, b) near, and c) above the threshold. Adjust values of intensity and duration in small increments in order to pinpoint combinations of values that just barely illicit a viable action potential, even if this means fractions of milliseconds or μA/cm^2.

   (b) Create an overlap plot (action potentials all displayed on the same set of axes) that summarize your results. Make sure to include in the plot at least 2–3 combinations of stimulation that do not elicit an action potentials, 2–3 that just barely result in an some sort of action potential, even one of reduced amplitude, and 1–2 that generate normal action potentials. Be aware that you a probing a highly nonlinear behavior (all-or-nothing), so select values of stimulus pulses thoughtfully.

   Questions for the report: What do these results tell you about how the (simulated) cell responds to stimulation? Do your results validate the all-or-nothing behavior you expected?

   (c) Now, by varying stimulus strength and duration, generate at least 20 combinations of these two parameters that each just barely generate a more or less normal action potential. Again, fine adjustments will be necessary. Make sure your values of duration and intensity span a reasonable range as well—you are exploring the relationship between stimulation duration and intensity. Tabulate these values of amplitude and duration and plot them in their own graph (does not matter which one goes on which axis).

   (d) Try and fit some simple functions to the resulting curve and then interpret the meaning of these curves in the context of what is necessary for stimulation of a membrane or cell

to be successful. **Questions for report:** Can you explain a method or system, perhaps a formula, for determining whether a specific intensity/duration combination is likely to be enough to stimulate an action potential?

2. In order to simulate the experiments performed by Hodgkin and Huxley on the nerve axon, carry out a set of simulations in which you systematically alter the concentration *gradient* of sodium (use reasonable values, holding the intracellular concentration constant) and observe the effects on action potential shape and amplitude.

   Questions for report: Why does the action potential not disappear completely even when the sodium concentration gradient approaches zero? What is providing the inward current in this case?

3. Perform at least one more experiment using the simulation to answer a question/hypothesis of *your* choosing and document the results. Feel free to alter anything in the model (not just ion concentrations), but justify your choices in terms of either normal or pathophysiology. Be careful to adjust parameters that are actually variables in the simulation code, *e.g.,* the channel kinetics that are hard wired into the program assume a temperature of 37° so varying temperature will not produce sensible results.

   Discuss the results in terms of your qualitative knowledge of cellular electrophysiology.

Submit the assignmemt in paper or electronic form by Monday, February 13, 2012.

References

[1] C.H. Luo and Y. Rudy. A model of the ventricular cardiac action potential. *Circ. Res.*, 68(6):1501–1526, 1991.

[2] C.H. Luo and Y. Rudy. A dynamic model of the cardiac ventricular action potential: I. Simulations of ionic currents and concentration changes. *Circ. Res.*, 74(6):1071–1096, 1994.