# Bioengineering/Physiology 6003
# Modeling and Simulation Lab

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December 6, 2010

## 1 Purpose and Background

### 1.1 Purpose

The purpose of this lab is to gain some exposure to two examples of programs for modeling and simulation of cells and ion channels. Each of these models allows access to many different parameters of the action potential and associated cellular parameters and this provide a means of investigating cell function. Each of the specific tasks below will also familiarize you with the response of the cell to variations in parameters that arise in sickness and in experiments and thus seek to deepen your appreciation of the salient mechanisms. For this second goal, assume that the models you are using are accurate and use them to explore and test your knowledge of the mechanics that drive the electrical behavior of a cell.

### 1.2 Background

Most of the background of the models is covered in the notes from the BE 6003 lectures on modeling and simulation of ion channels and cells. There are many programs that implement the simulation of the electrical activity of excitable membranes in the nerve and heart and we have chosen two examples to provide at least a brief exposure. The physiological and mechanistic background comes from all of your lectures to date. The two examples of programs are:

**OpenCell** is an open source tool environment for developing, visualization and analysis of mathematical models via a graphical user interface. It makes use of the CellML format for storage and exchange of computer-based mathematical models. OpenCell is being developed at the Auckland Bioengineering Institute and built on top of the Mozilla platform. Detailed information can be found at:

http://www.cellml.org/tools/opencell

**JSim** is an open source Java-based simulation system for building quantitative numeric models and analyzing them with respect to experimental reference data. JSim's primary focus is in physiology and biomedicine, however its computational engine is quite general and applicable to a wide range of scientific domains. JSim models may intermix ODEs, PDEs, implicit equations, integrals, summations, discrete events and procedural code as appropriate. JSim's model compiler can automatically insert conversion factors for compatible physical units as well as detect and reject unit unbalanced equations. JSim also imports the SBML and CellML model archival formats. Detailed information can be found at:

http://nsr.bioeng.washington.edu/jsim/

## 2 Lab Procedure

### 2.1 Lab Preparation

1. Read over the documentation available for the programs at
   http://www.physiome.org.nz/cellml/tools/opencell/help/manual.html for cellml and

http://nsr.bioeng.washington.edu/jsim/docs/User.html for JSim.
2. Download and install OpenCell and JSim on your computer.

### 2.2 Lab Day Setup

1. Meet at CVRTI, old conference room.
2. Come prepared with a laptop (if available) and thumb/USB drive
3. Familiarize yourself with OpenCell. OpenCell provides a user interface that allows you to adjust parameters and visualize the effects. Use the model of ten Tusscher et al (2004). Vary parameters and perform simulations with the model. Export simulation results in CSV format.
4. Explore JSim. Once familiar with the operation of the program, run simulations with the following two models
   • Cell Physiology/Fibroblast
   • Cell Physiology/Action potential/ten Tusscher Noble Noble Panfilov 2004
   and plot the results.
5. Carry out the specific exercises in Sections 2.3.1 and 2.3.2 below.

### 2.2 Capturing images

For the report on this lab, you can use either built in printing functions of the programs or a screen capture utility to grab images. After capturing, the screen shot is copied to the clipboard and can be pasted into any paint or image processing program and saved in a variety of image formats.

### 2.3 Lab Exercises

#### *2.3.1 OpenCell*

After carrying out the explorations described in Section 2.2, above, use the program and the model of ten Tusscher et al (2004) to explore the following questions:
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. The goal of this set of simulations is to see if the program replicates this behavior. Set up at least five combinations of stimulus strength and duration and observe the resulting action potential amplitudes and durations. Record the settings that you find and save an image of the action potential and relevant currents for each case.
2. In order to simulate for the cardiac myocyte the experiments performed out by Hodgkin and Huxley on the nerve axon, carry out a set of simulations in which you systematically alter the concentration difference of sodium between the intracellular and extracellular spaces (use reasonable values, holding the intracellular concentration constant) and observe the effects on action potential shape and amplitude. Again, for each case, save an image and/or the time signals for action potentials and relevant currents in external files for later display. Why does the action potential not disappear completely even when the sodium concentration difference approaches zero? What is providing the inward current in this case? Make sure to use the flexibility of the simulation and display options of OpenCell to make visible the data to support your conclusions. The goal of the exercise is for you to use a realistic model explore the mechanisms as they are presented in classes and skeptically evaluate their accuracy.

#### *2.3.2 JSim*

Work through the simulations of the following assignments:

#### Electrical Modeling of Membrane

**Objective**: Gain insights into modeling of the relationship between transmembrane voltage $V_m$ and electrical stimuli.
**Assignment:**

1. Configure the fibroblast model as capacitive, i.e., without ion channel currents. Set the stimulus start to 0.1 s, duration to 1 ms, amplitude to 0.2 nA and frequency to 1 Hz. Run the simulation for 6 s. Plot $V_m$ and explain it! Why does the membrane not exhibit repolarization?
2. Add a background current with a conductance Gb of $10^{-3}$ μS and a reversal potential $E_b$ of -84 mV to the model. Applying the upper stimulus protocol, calculate and plot $V_m$. Explain the simulation results in the framework of a parallel resistor-capacitor circuit.

### Markov Modeling of Ion Channels

**Objective**: Investigate parameterization and dynamics of Markov models.
**Assignment:**
1. Configure the fibroblast model with capacitive and the time and voltage dependent K (Shaker) currents only. Adjust resting $V_m$ to -84 mV. Choose a stimulus amplitude leading to a peak $V_m$ of +50 mV. Run the simulation for 0.5 s. Plot the Markov states and explain their changes. Why do C1,. . . , C3 exhibit two peaks, but C4 and O only one?
2. Modify the Markov model in such a manner that the peak open probability is delayed by ~20 ms while keeping the open probability above 40%. Specify your changes to the model parameters and explain your motivation for these changes.

### Electrophysiological Modeling of Cardiac Myocytes

**Objective**: Explore the role of hERG channels in repolarization of cardiac myocytes.
**Assignment:**
1. Using the ten Tusscher et al. model of human ventricular myocytes with default parameters, calculate the action potential duration to 90% depolarization (APD90). Describe your calculation of APD90.
2. Set the hERG channel conductance (gKr) to 200%, 50% and 0% and simulate the corresponding action potentials. Calculate APD90 for these conductances.
3. Relate these simulations to effects of mutations, blockers and activators of hERG channels on action potentials of cardiac myocytes.
4. What pathological consequences are caused by alterations of hERG channels?

## 3 Lab Report

**Introduction**: Begin the report with an introduction to computational modeling based on the review article that we used for preparation of the cellular modeling lecture:

http://www.sci.utah.edu/~macleod/bioen/be6003/notes/winslow2010.pdf

Describe the programs used in the computational lab in this context, in particular, what you think their purpose and capabilities are. (length of introduction: ~2 pages)

**Methods**: In the Methods section, describe briefly, in a paragraph for each exercise, what you did to use the program and specifically produce the figures in the results section—include any relevant settings you had but do not go into detail of things like how you acquired the images. Always keep in mind, the directions should be detailed enough to allow the instructors or someone with the background of your classmates to replicate the experiments. Find the correct balance between specific and general instruction and try not to replicate either the lab description (this document) or the material in the tutorials for the programs.

**Results and Discussion**: In the Results and Discussion sections, for each exercise, address the questions in the description above. Make sure to use both images and text to describe all your results. The emphasis is on qualitative mechanistic descriptions but also find ways to quantify the results where possible.

**Conclusion**: Wherever possible, compare and contrast the experience in the experimental labs and this simulation lab. Generally, what are the advantages of simulation over experiments? What can one learn from experiments that is not possible with simulation? Summarize the differences in your experiences with the two software environments. Use your specific experiences to support more general observations about experimental and simulation approaches to scientific discovery.

Lab reports are due in PDF format to Frank Sachse (fs@cvrti.utah.edu) and Rob MacLeod (macleod@cvrti.utah.edu) before 5:00 pm on December 17, 2010. For specifics on lab report format, see http://www.cvrti.utah.edu/~macleod/bioen/be6000/homeworks/homework-tips.html