Bioengineering/Physiology 6003
Cellular Electrophysiological Modeling Lab

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1 Purpose and Background

1.1 Purpose

The purpose of this lab is to provide insights into cellular electrophysiology based on modeling and simulation. We will explore a previously developed electrophysiological model of a human ventricular myocyte. This and similar models describe isolated cells based on mathematical equations and different parameters. The models provide a means for investigating effects of ion channel currents on transmembrane voltages. Each of the specific tasks described below will familiarize you with the response of the cell to variations in parameters that arise in disease and in experiments. We will reveal limitations and critically evaluate the used model.

1.2 Background

Most of the background of the models is covered in the notes from the BIOEN 6003 lectures on modeling and simulation of ion channels and cells. In this computational lab, we will use **JSim** (http://nsr.bioeng.washington.edu/jsim/), which is an open source Java-based simulation system for building quantitative numeric models and analyzing them with respect to experimental 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 models in SBML and CellML format.

2 Lab Procedure

2.1 Lab Preparation

Read the following article introducing the model: http://www.ncbi.nlm.nih.gov/pubmed/14656705
The article is also in canvas (filename: tentusscher04.pdf).

2.2 Lab Day Setup

1. Come prepared with a laptop
2. Download the model (id: **ten_Tusscher_Noble_Panfilov2004)**. Run simulations and plot the results.
3. Carry out the specific exercises in Section 2.3 below.

2.3 Lab Exercises

Work through the simulations of the following assignments:

2.3.1 Electrophysiological Modeling of Cardiac Myocytes – Repolarization

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% repolarization (APD90). Describe your calculation of APD90. (5 pts)
2. Set the hERG channel conductance (g_Kr) to 200%, 50% and 0% and simulate the corresponding action potentials. Calculate APD90 for these conductances. (5 pts)

3. Relate these simulations to effects of mutations, blockers and activators of hERG channels on action potentials of cardiac myocytes. (10 pts)
4. What pathological consequences are caused by alterations of hERG channels? (10 pts)

2.3.2 Electrophysiological Modeling of Cardiac Myocytes – Ca Transients

Objective: Investigate the modulation of Ca transients by Ca channels in cardiac myocytes.
Assignment:

1. Using the ten Tusscher et al. model of human ventricular myocytes with default parameters, determine the time to peak (TTP) and the decay time constant of the intracellular calcium concentration (τ). Describe your calculation of TTP and τ. (5 pts)
2. Set the Ca channel conductance (g_CaL) to 200%, 50% and 0%. Simulate the corresponding action potentials and Ca transients. Calculate APD90, TTP and τ for these conductances. (5 pts)
3. Discuss the simulation results in the context of your knowledge of excitation-contraction coupling. (10 pts)
4. How would you improve the modeling of excitation-contraction coupling in this model? (10 pts)

3 Lab Report

Please work independently on the lab report.

Introduction: Begin the report with an introduction to computational modeling of electrophysiology of cardiac cells. The introduction could be based on the review http://www.ncbi.nlm.nih.gov/pubmed/20303361 or similar publications. Explain the applications of computational models in this research field. Describe the model used in the computational lab and its applications in this context. In particular, what are the purpose and capabilities of this and similar models? (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. 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. (Length: ~1 page)

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. Compare simulation results with previously published studies. Discuss limitations of the model that you revealed. (Length: ~2 pages)

Conclusion: What do you conclude for your investigation of the computational model? (Length: ~1 page)

The lab report will be graded with maximal 100 pts. Twenty points are for general writing style of the lab report. Twenty points are for formatting and structuring of the report and figures. Sixty points are for describing methods and results related to the tasks described in section 2.3.1 and 2.3.2.

Lab reports are due in PDF via canvas. Write the lab report as if you would write a paper for submission to a scientific journal. Follow standards for citation of literature and formats, for instance

http://www.ieee.org/publications_standards/publications/authors/authors_journals.html