Channel Sensitivity Analysis in a Ventricular Myocyte Model

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Introduction

A computational model of a ventricular myocyte can be tested upon in much different ways than would be possible with a physical heart. While a normal heart cell can only be tested on under specific conditions and a finite number of times, a model allows the experimenter the opportunity to completely control the conditions, as inputs, and for a significantly larger amount of runs. In this project, the aim was to use computational tools that take advantage of these facts, in order to determine the significance of the parameters that dictate each channel. Even though each channel requires the inputs of a certain set of parameters, each one is not as significant as the other. Through many runs and manipulation of the parameters, this project set out to determine which parameters were the most significant, for each channel in the Shannon-Bers ventricular myocyte model. With this analysis, we will be able to determine the best targets for pharmacological agents, and see whether those that are already out on the market, are performing their desired effect on the most optimal part of the channel.

Background

The basis for this project comes from the computational model of a ventricular myocyte. The Shannon-Bers model is very robust at properly modeling action potentials, calcium influx and other experimentally testable results. This model is comprised of many sets of differential equations, that are used in order to mimic the results of a real ventricular myocyte channel. Each of these equations are dictated by many different parameters, that correspond to different attributes that can normally be found in the cell. It is the aim of this project to determine the relative significance of each of these parameters, which vary from channel to channel.

Methods:

MatLab

MatLab is a computational program, that can be used to solve mathematical problems. The Shannon-Bers model that was used for this project, was coded into MatLab format. All of the actual coding and manipulation of the base parameters, was done through the use of MatLab. The code was modified in order to determine the maximum calcium transients and the action potential duration. Much of this previous code manipulation was done thanks to a previous PRIME project, by Mike Lo. With the calcium transient and action potential duration as outputs, it was easier to see and quantify the significance of each parameter. Since the original output of the Shannon-Bers model came in graphical form, this modification allowed us to better analyze the results.

Nimrod/G

The Nimrod portal was the key to being able to run a sufficient number of trials. Through this system, set up at Monash, in Melbourne Australia, we were able to import the model and adjust the parameter and run settings. Once the model was imported and adjusted to run through the portal, we were able to adjust the parameter settings. While looking at the channel of interest, all the parameters within that channel were set to run in an interval of plus and minus 10% of their steady state values. All other parameters that were not a part of the channel, were held constant. The parameters within the desired channel were set to randomly choose points within this range, and then the model was run multiple times. Depending on the channel and the amount of parameters, Nimrod/G could produce thousands of jobs. All of the data that was produced was then collated into a single file, in order to be analyzed later.

Nimrod/E & Statistical Analysis

It is through Nimrod/E that most of the data should have been analyzed, but unfortunately, it was not working for most of my duration at Monash. Once Blaire Bethwaite was able to make Nimrod/E partially usable, the Daniel and Lenth plots that were produced split up each parameter, so they did not fully show the effect of each. Thanks to the help of Neil Diamond and David Albrecht, we were able to start analyzing the data, using R. With the collated data produced from the I_Ks channel, Neil was able to begin working on a response surface design, in order to analyze the data. This includes a fractional factorial design, a center point and star points. Through Neil and David, we were able to begin analyzing the data, and will eventually be able to produce a wireframe plot to display the data.

Future Work

Once we have the first set of data analyzed, we will be able to use it as a framework for the analysis of the rest of the channels. With all of the data already produced, we only need a way to display the significance of each parameter. I will be in contact with Blaire, Neil and David through email, so that once the first set of data is analyzed, I will be able to continue on and finish the analysis of the rest of the channels.

Conclusion

This project has shown me the true inner-workings of research. I was able to produce large sets of data, but without the proper tools to analyze them, the numbers are meaningless. Luckily I had people around me that were extremely helpful. This entire experience has been great and I hope to finish up the project when I get back home.

References

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