Physiology 520

Lab 10 – 23 March 2023

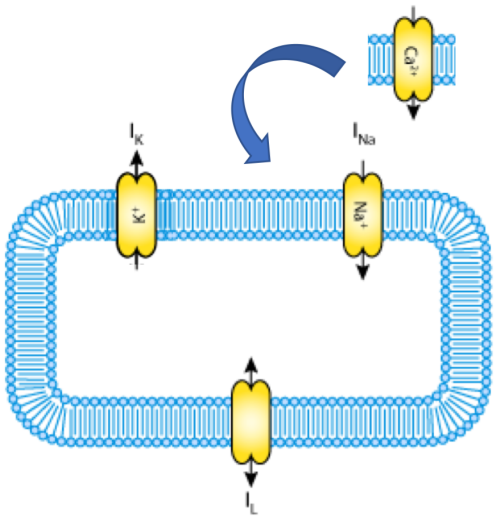

Figure 1. Schematic of ion channels, included in the Noble model of the Purkinje fiber electrophysiology (*J Physiol* **160**:317-352, 1962). A fourth channel representing one of the earlier versions of L-type calcium channel current (from Luo CH and Rudy Y. *Circ Res* **74**:1071-1096, 1994) will be added to the three existing channel currents: the fast Na^+ (I_{Na}), the K^+ (I_K), and the leak (I_{leak}).

In this lab we will make some further modifications to the Noble model (Noble D. *J Physiol* **160**: 317-352, 1962) where we have now included an L-type calcium current The point here is to understand how our working model can be used to represent the slightly different behavior of a human induced pluripotent stem cell derived cardiomyocyte (hiPSC-CM)

1) hiPSC-CMs have been observed to express genes encoding ion channels at different levels than is seen in human adult ventricular cardiomyocytes (hAVCMs). In particular, L-type Ca^{2+} is overexpressed, Na^+ is slightly underexpressed and the inward rectifier, K_1 is dramatically underexpressed. This change in gene expression can be assumed to relate to the channel density in the membrane and therefore can be represented in these models as a change in conductance parameters. A lower expression would translate to lower conductance. Using your modified Noble model from last week (or using the version in the lab folder if yours is still not working) modify it further to reflect a 50% increase in L-type Ca^{2+} conductance, a 10% decrease in fast Na^+ conductance and a 35% reduction in I_{K1} what happens to the action potential when compared to the action potential with values assumed for an hAVCM? What does this mean if we are testing a drug on these cells that blocks time-dependent K^+ channels?

2) To see if this very simple model can be used to represent actual hiPSC-CM action potential data we have included a dataset for a paced monolayer of hiPSC-CMs purchased from the vendor WiCell in Madison, Wisconsin. The first column in the datafile represent the time and the second column is the fluorescence intensity of a voltage sensitive dye which is related to voltage but is not calibrated to give actual voltage values. The data file is a text file named WiCell_Data.txt and can be found in the Week 8 Lab folder. You will first need to find a way to load this data into you code and then plot it out to see if everything looks right. Since this data is in arbitrary units of fluorescence intensity (a.u.) we will have to find a way to compare your model output in mV to the a.u. of the data. Often both data and model output are normalized by subtracting off a minimum value and dividing everything by the maximal value minus the minimal value. In effect, scaling both data and model to have a response between 0 and 1. Plotting the data along with the simulation will show you that something has to be changed to make the model fire at the appropriate times to match the data. Now that these are lined up in some manner what do you need to change in the model to make the action potential similar in shape to the data. Use your knowledge of what ion channels are active in different parts of the action potential to make these adjustments. You will definitely need to change some conductances and possibly initial conditions and/or stim current amplitude to get the simulation to describe the data. Extra credit for anyone who can even represent the slight depolarization shown in the data during the resting membrane portion of the action potential.

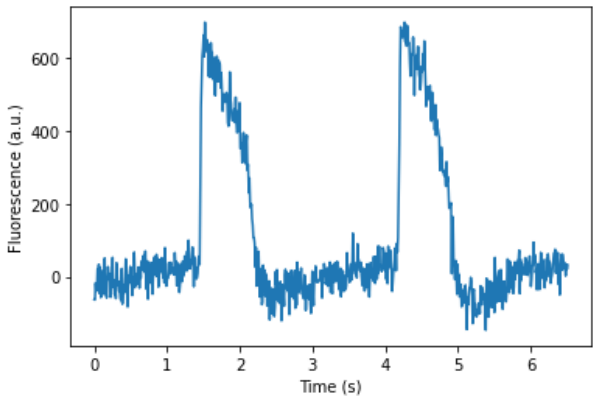

Figure 2. Intensity of a voltage sensitive fluorescent dye in arbitrary units as a function of time for a small well of WiCell hiPSC-CMs. These cells are from a cell line derived from a female patient and are paced at approximately 22.2 beats/min or about 0.37 Hz.