Calcium Entrained Arrhythmias

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Defects in cardiac Ca^{2+} dynamics result in cardiac arrhythmias that can be fatal. Our work investigates fundamental mechanisms that underlie Ca^{2+} -dependent arrhythmias. Specific molecular, genetic, structural and signaling defects develop as a result of diverse specific disease or conditions (e.g. myocardial infarction, heart failure, pharmacologic treatments and diverse inherited traits) and these underlie the changes in Ca^{2+} signaling. Here we report on our current work that uses a multi-scale, systems biology approach that enables us to combine state-of-the-art experiments with detailed stochastic computational models.

The overall plan is to develop a robust experimentally constrained model to permit us to understand how Ca^{2+} sparks trigger and sustain Ca^{2+} waves. This is our current focus. The work uses single ventricular myocytes as an experimental preparation and as a model system. In these and all experiments we are examining the roles of the Ca^{2+} signaling proteins and cellular electrical activity. This work enables detailed 1D, 2D and 3D modeling of cells and should enable us to investigate how Ca^{2+} instability arises, and how it may lead to novel electrical activity and arrhythmia.

A second aspect of the effort is to determine how Ca^{2+} waves propagate from cell to cell. Related to this investigation is our examination of how Ca^{2+} waves entrain electrical activity. To accomplish these aims we are working on several aspects of this project in parallel. The modeling is fully informed and constrained by experimental findings. For the models to be successful, their outputs need to reliably mesh with and predict specific experimental findings.

Today we will report on our current work to understand and model $[Ca^{2+}]_i$ dynamics using both models and experiments. One area of specific interest is the Na^+/Ca^{2+} exchanger (NCX). This is a Ca^{2+} activated electrogenic transport protein and is one of the critical components of the heart cell that links $[Ca^{2+}]_i$ changes with membrane current. Thus when there is a large increase in $[Ca^{2+}]_i$, as there is with every heartbeat, there is a parallel inward (depolarizing) current. Abnormal Ca^{2+} signals such as Ca^{2+} waves also activate the NCX current (I_{NCX}) which may trigger an extrasystole and hence produce an arrhythmia. Modeling the NCX is thus very important but, to date, inadequate. We have thus been investigating this electrogenic transporter in on-going work. We have also been examining the subcellular and nanoscopic characterization of $[Ca^{2+}]_i$ that activates I_{NCX} . This involves modeling local Ca^{2+} signals that arise from the junctional sarcoplasmic reticulum (jSR) at high temporal and spatial resolution. As a result of these interactions, we have been modeling both aspect of this behavior and this work involves the three PIs. Published experiments and new work in our labs seek to constraint key features of the NCX model.

In out attempt to link local signals to whole cells signaling, we have developed a whole cell stochastic model of EC coupling that includes all 20,000 Ca^{2+} release units (CRUs) (with over 1,000,000 stochastic channels) (Williams *et al.*, 2011). The CRU includes the transverse tubules and jSR that contain clusters of about 50 RyR2's. We have thus been able to characterize the mechanisms of the sarcoplasmic reticulum (SR) Ca^{2+} leak explaining recent experiments using only know components of the myocyte. We have not only been testing the mathematical model of Ca^{2+} signaling but using super-resolution imaging (with several collaborators) to examine the arrangements of the RyR2s in the CRUs (Wagner *et al.*, 2012). This information has helped us better understand functional changes in cardiac Ca^{2+} signaling in

disease. Two extensions of this work involve testing how Ca^{2+} wave propagation occurs. One element is a cellular model with a one-dimensional network of cardiac myocytes that lets us explore how Ca^{2+} overload leads to spontaneous Ca^{2+} release and how this triggers myocyte depolarization. This on-going work is complemented by high resolution 3D modeling of a single heart cell and (at extremely high resolution) the CRU. This complements experiments examining Ca^{2+} release, Ca^{2+} sparks and Ca^{2+} waves in Langendorff perfused hearts.

References

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