An experimentally derived Ca^{2+} model for the studying effects of drugs on cardiac myocytes

M.S. Imtiaz, D.F. van Helden and D.R. Laver, School of Biomedical Sciences and Pharmacy, The University of Newcastle, Callaghan, NSW 2308, Australia.

Ca^{2+} release from the sarcoplasmic reticulum (SR) not only underlies heart muscle contraction but also contributes to the cardiac rhythm by modulating action potential frequency of sinoatrial node cells. We have used experimental data to develop a detailed three-dimensional mathematical model of Ca^{2+} cycling in single cardiac cells that can be coupled to whole cell membrane potential models.

We began by formulating a calcium cycling unit (CCU) where each CCU is composed of: 1) A ryanodine receptor (RyR) cluster (arranged in concentric volumes), with formulation of the RyR in the cluster based on experimental data from lipid bilayer measurements; 2) Terminal SR; 3) Network SR; 4) SERCA which transports Ca^{2+} from the bulk cytoplasm to the network SR; and 5) Various Ca^{2+} buffers in all the compartments of the CCU and cytoplasm are also included. Geometric dimensions and other parameter (such as diffusion rate) were based on available experimental data.

CCUs were placed in the three-dimensional cytoplasmic space at required density and arrangement. This three-dimensional Ca^{2+} system has the ability to interface with whole cell membrane potential models. The averaged response of all CCUs represents the whole cell Ca^{2+} system interacting with membrane ionic currents.

The cardiac cell model could be stimulated locally and globally to study the emergence of sparks, and generation and propagation of Ca^{2+} waves. Data from bilayer experiments during drug application or other pathological conditions can be provided to the CaS and resultant Ca^{2+} dynamics (sparks, waves, etc) can be simulated. Furthermore, the resultant change in the whole cell (ventricular, atrial or sinoatrial) action potential can also be studied in silico.

In conclusion, our study provides a novel data-driven tool whereby bilayer RyR data can now be included in a realistic model to understand how drugs/pathologies change Ca^{2+} cycling, and its subsequent effects on Ca^{2+} sparks, waves, and action potentials. This will facilitate our understanding of the role Ca^{2+} plays in cardiac pacemaking and contraction under drug application and pathological conditions.