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A multiscale model of calcium release reveals a novel mechanism for calcium wave initiation

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The release of Ca^{2+} from the Sarcoplasmic Reticulum (SR) of cardiomyocytes is central to both cardiac muscle contraction in response to action potentials and to cardiac pace making. Disruption of normal Ca^{2+} release results in cardiac arrhythmias [1]. During systole, Ca^{2+} is released from the SR via clusters of Ca^{2+}-activated ryanodine receptor Ca^{2+} channels (Type 2 ryanodine receptors, RyR2) in the SR membrane of the dyad (synapse of the SR and sarcolemma membranes). This release of calcium strongly reinforces local RyR2 activation, a process called calcium-induced calcium release (CICR). Eventually, Ca^{2+} release is exhausted and during diastole, Ca^{2+} is sequestered back into the SR by the ATP powered Ca^{2+} pumps (SERCA2a) in the SR membrane [1].

Brief, localised Ca^{2+} release events at single sites were first experimentally observed with fluorescent confocal microscopy by Cheng et al., [2] and dubbed Ca^{2+} sparks. These Ca^{2+} sparks are thought to be the basic quanta of global Ca^{2+} release phenomena such as Ca^{2+} waves and transients that produce cardiomyocyte contraction. Ca^{2+} waves initiate in a localised region and propagate throughout the cell. Wave propagation is believed to be due to Ca^{2+}-induced triggering between neighbouring release sites, although details of this process remain unclear and the development of a convincing Ca^{2+} wave model has proved challenging [3] [4].

Although the calcium release properties of RyR2 have been intensely studied and are very well characterised, models have not successfully integrated experiments with cellular Ca^{2+} release phenomena. For example, RyR2 sensitivity to cytoplasmic Ca^{2+} (half activation by 30 µM [5] [6] is too low to explain Ca^{2+} wave initiation via Ca^{2+} induced triggering between neighbouring release sites by the brief Ca^{2+} release that occurs in a spark. Models that force wave initiation by increasing RyR2 Ca^{2+} sensitivity generate unrealistically high spark frequencies and initiation of myriad wavelets rather than a single propagating wave [3]. Models that achieve Ca^{2+} waves by assuming that RyR2 Ca^{2+} sensitivity is high only when Ca^{2+}-stores are filled are at odds with experimental findings showing that store Ca^{2+} has a relatively minor effect on RyR2 activity [5] [6].

Here we develop a multiscale model that successfully reproduces Ca^{2+} sparks and Ca^{2+} waves in skinned ventricular myocytes that uses experimentally verified Ca^{2+}-dependent rates of RyR2 opening and closing. The model spans spatial domains of 10^{-8} to 10^{-4} m and time scales of 10^{-6} to 10 s. The model proceeds from a previous model for Ca^{2+} sparks [7] with spatial elements simplified to a 7-compartment model, each with 62 state equations. The compartment model is embedded within approximately 20,000-200,000 cubic voxels (0.25 µm edges) that comprise the model sub-cell. Dyads are distributed throughout the cytoplasm in array formations informed by super-resolution micrographs [8]. We use parallel computing to calculate Ca^{2+} release from each dyad junctions as well as Ca^{2+} diffusion, buffering and uptake by SERCA2a.

We find that as SERCA2a loads the SR to a threshold [Ca^{2+}], Ca^{2+} sparks fail to terminate and produce a prolonged (~seconds) sustained Ca^{2+} release that substantially increases CICR between dyads, sufficient to initiate a Ca^{2+} wave.

1. Bers, D.M., Cardiac excitation-contraction coupling. Nature, 2002. 415:198-205.
2. Cheng, H., et al, Calcium sparks. Science, 1993. 262:740-744.
3. Izu, L.T., et al., Ca^{2+} waves in the heart. Journal of Molecular and Cellular Cardiology, 2013. 58:118-124.
4. Colman, M.A., et al., Multi-Scale Computational Modeling. Front Physiol, 2022. 13:836622.
5. Gyorke, I. and S. Gyorke, Regulation of the cardiac RyR by luminal Ca^{2+}. Biophys. J., 1998. 75:2801-2810.
6. Walweel, K., et al., Differences in the regulation of RyR2 from human, sheep, and rat by Ca^{2+} and Mg^{2+} in the cytoplasm and in the lumen of the sarcoplasmic reticulum. J Gen Physiol, 2014. 144:263-271.
7. Cannell, M.B., et al., 3D Model of the Cardiac Dyad and Importance of Induction Decay for CICR Termination. Biophys J, 2013. 104:2149-59.
8. Hou, Y., et al., Nanoscale analysis of ryanodine receptor clusters in dyadic couplings of rat cardiac myocytes. J Mol Cell Cardiol, 2015. 80:45-55.