The Effects of Luminal Regulation on Local Calcium Release and Depletion in Cardiac Myocytes

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In addition to its role in bones and teeth, calcium (Ca) is one of the most important neurotransmitters in the body. The rhythmic beating of the heart derives from the alternating release and sequestration of calcium ions within and around individual cardiac muscle cells (myocytes) through a complex process involving several cellular structures and their constituent proteins. One of the proteins which is critical to this process is cardiac calsequestrin (CASQ2). Mutant versions of this protein are implicated in cardiac arrhythmias, so an improved understanding of the functioning of CASQ2 could lead to better treatments.

CASQ2 is found in a structure called the junctional sarcoplasmic reticulum (jSR), and is known to bind to intracellular calcium channels called Ryanodine receptors (RyRs). When activated, RyRs channel calcium ions from the interior spaces (lumen) of the jSR into the myoplasm of the muscle cell, triggering contraction. The rapid release of calcium by multiple RyRs clustered in a release site produces a calcium "spark"; the subsequent uptake of calcium relaxes the cell and causes a calcium "blink." The figure below (from Terentyev *et al.*, 2008) illustrates this process for four variants of CASQ2 using confocal microscopy and an indicator dye that fluoresces in the presence of calcium.

Effects of mutant calsequestrin

Terentyev et al. 2008
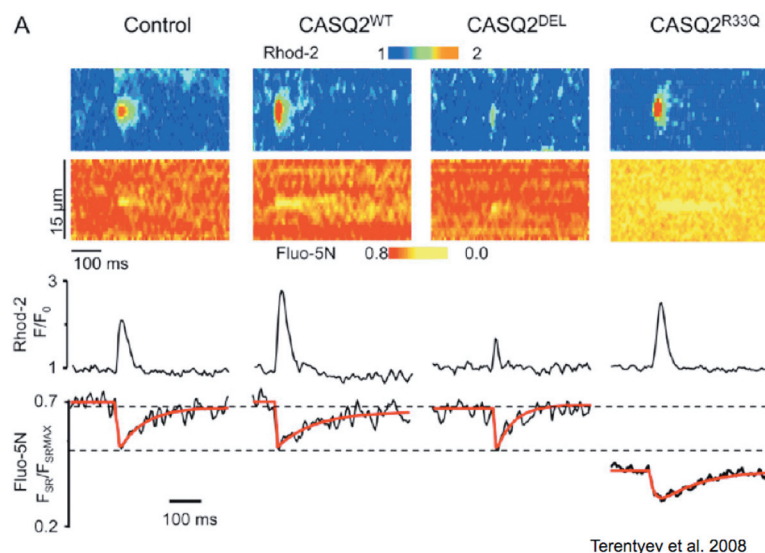
The upper sequence of images (blue panels) shows Ca levels over time within the cytosol (intracellular fluid) of a ventricular myocyte. The lower sequence (red panels) indicates corresponding Ca levels within the jSR. The line graphs represent the time profiles of the fluorescence signals. As can be seen, the different

mutants of CASQ2 produce very different calcium signaling.

My research aims to shed light on the mechanisms behind the opening and closing of intracellular calcium channels by investigating the possible roles of CASQ2 during Ca sparks and blinks. To do this, we construct ODE-based computational models of Ca release sites composed of 100 RyRs. Several different topologies of RyR were chosen for study to include several plausible roles for CASQ2. Parameter studies are being performed to compare computationally-generated sparks from various models against known experimental data. We are examining 5 different cases in our simulations, and each case requires from 5 to 25 hours of computation on a single CPU. Furthermore, we have to search for optimal solutions within a 10-dimensional parameter space, and this requires more than 1,000 runs for each case—in short, a huge amount of computing. The SciClone cluster makes this feasible by allowing us to explore tens to hundreds of solutions simultaneously, something that would be impossible to do on a personal computer or workstation.

To date, we have found that our simulations partially capture the behavior of Ca sparks and blinks, but we also see discrepancies, indicating that some of the mechanisms or parameters of the current RyR model are not represented correctly. Performing parameter studies on differing RyR topologies should allow us to simulate a spark-blink pair that is more similar to observed behavior. In finding the best topologies and parameters, we hope to learn more about the true mechanisms in CASQ2 regulation of spark-blink activity.