Development of a 3D computational model of centripetal calcium wave propagation in atrial cells

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Calcium is an important cell messenger, that mediates in many physiological processes. Ca^{2+} takes part, for instance, in oocyte activation at fertilization, axonal growth, gene expression, or excitation-contraction coupling in myocytes, where an increase in the concentration of intracellular calcium initiates the contraction of the cell. Any dysfunction in the handling of Ca^{2+} can thus lead to serious pathologies.

Inside cardiac cells, most intracellular Ca^{2+} is stored in a complex structure called sarcoplasmic reticulum (SR). Ca^{2+} is released from this internal network via the Ryanodine Receptors (RyR, red and black dots in Fig. 1) when a threshold calcium concentration in the cytoplasm is achieved. This happens due to a small influx of calcium through the L-type calcium channels (LCC, blue dots in Fig. 1) during the cardiac action potential. RyRs open and close collectively in clusters forming functional units known as Calcium Release Units (CaRU), which are often confronted to a cluster of LCCs. In each CaRU the number of RyR and LCC is small (of the order of 10-100 of the former and 5-10 of the latter), thus, its dynamics is intrinsically stochastic. CaRUs are distributed inside the cell, resulting in random and discrete Ca^{2+} release events, known as Ca^{2+} sparks. The (seemingly deterministic) global calcium signal appears from the coordination of several tens of thousands of these CaRUs.

Even though the same mechanism triggers the transient elevation of Ca^{2+} in both ventricular and atrial myocytes, there are substantial differences in the intracellular structures. In ventricular cells, the CaRUs arrange along invaginations of the cell membrane, called transversal tubules (t-tubules), that define regions known as z-planes. These regions are repeated every $\sim 1.5\mu$m along the longitudinal direction. The absence of t-tubules in the z-planes of atrial myocytes produces inhomogeneous spatio-temporal calcium patterns when the calcium release occurs. In particular, the excitation starts at the cell membrane and then propagates to the interior. This is a key difference between atrial and ventricular cells. In the latter, the opening of LCC channels along the t-tubules synchronizes the release of calcium from the SR. In the former, synchronization is due to this inward wave.

We have developed a 3D computational model to study inward wave propagation in atrial cells. RyR distribution is shown in Fig. 1 where we have adapted the method in [1] to develop a 3D algorithm to create a CaRU structure. This algorithm performs Monte-Carlo simulations of stochastic self-assembly of RyR clusters using a simple growth model with three probabilities. In particular, our study is focused on the gap between external (cell membrane) and internal spaces. Because of this cleft, in normal conditions, the internal RyRs remain closed during the excitation-contraction (EC) coupling and calcium is only released on the periphery (Fig. 2).

However, during atrial fibrillation (AF) the cell structure changes and this gap could eventually be reduced. With our model, we aim to understand the effects of gap reduction on the centripetal wave propagation. Besides, because of the submicron spatial discretization, the model is well suited to study the effects of changes in the microstructure (position of the RyR clusters, inhomogeneities, etc). Both situations, gap reduction [2] and changes in CaRU distribution [3] promote the internal excitation leading to complex spatio-temporal patterns of intracellular Ca^{2+} signal propagation. With this in mind, our simulations illustrate that subtle changes in cell structure may have non-intuitive effects on Ca^{2+} signal initiation.

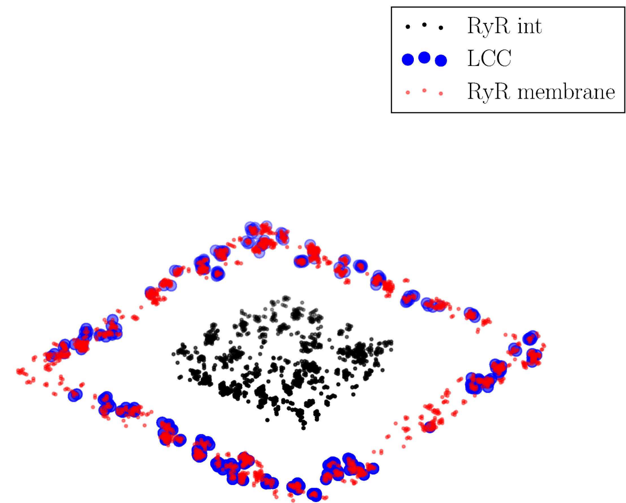

Fig. 1. Spatial distribution of RyRs and LCCs within a z-plane.

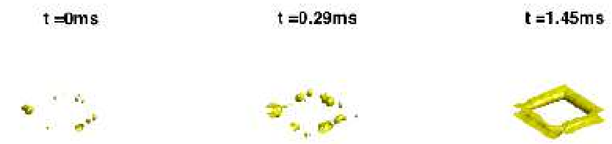

Fig. 2. 3D calcium profiles at different times. With this model, we can study calcium firing and diffusion within a z-plane.

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