Development of a computational model of calcium signalling in cardiac cells at the submicron scale

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

In cardiac cells, calcium is mostly stored inside a network called sarcoplasmic reticulum (SR). Calcium ions can leave the SR through specific channels (Ryanodine receptors or RyRs). Clusters of RyRs (CaRU) are placed at the membrane of the SR. Around 50-70 RyRs form one cluster and there are roughly 20000 clusters inside the cell, placed at a distance of $\sim 1\mu$m. RyRs are sensitive to the calcium concentration, so that, a small spontaneous release of calcium (because of a random RyR aperture), defined as a spark, can turn on to more apertures of neighbouring RyRs (in a process called calcium-induced calcium release), leading to a cascade effect that causes an intracellular wave. Exactly how many RyRs participate in a Ca^{2+} spark is still debated. The clustering size of RyRs and its spatial distribution is crucial to develop sparks. In atrial fibrillation (AF), myocytes have been shown to have 50% higher spark frequency and more probability to develop macrosparks [1].

To study this, we model the calcium dynamics and diffusion in an atrial cell at the submicron scale (100nm). Several detailed models have considered the dynamics of calcium in ventricular cardiac cells [2]. In these, the presence of T-tubules (invaginations of the cell membrane into the intracellular space), provides a rapid coordination of the clusters of RyRs. Since atrial cells do not present T-tubules, this coordination is mediated by an inwardly propagating intracellular calcium wave. We generate a simplified cell geometry and, after that, we couple the calcium fluxes from several compartments (SR, intracellular and extracellular domains), taking also into account buffering effects. An important characteristic of our model is the consideration that, at each point of the domain, we have both cytosolic and SR calcium concentrations, $c_i(\mathbf{r},t)$ and $c_{sr}(\mathbf{r},t)$, i.e., we consider a bidomain calcium model. In both domains calcium ions can diffuse, with effective diffusion coefficients that result from homogenization of the underlying complex structure. Thus, we solve the set of PDEs, given by:

$$\begin{cases} \dfrac{dc_i(\mathbf{r},t)}{dt} = J_i(\mathbf{r}) + \nabla\cdot[D_i(\mathbf{r})\nabla c_i(\mathbf{r},t)] - J_b(\mathbf{r}) \\ \dfrac{dc_{sr}(\mathbf{r},t)}{dt} = \dfrac{v_i}{v_{sr}} J_{sr}(\mathbf{r}) + \nabla\cdot[D_{sr}(\mathbf{r})\nabla c_{sr}(\mathbf{r},t)]\,, \end{cases} \quad (1)$$

where $D_i(\mathbf{r})$ and $D_{sr}(\mathbf{r})$ are the diffusion coefficients, v_i/v_{sr} is the ratio of cytosolic to SR volume and $J_i(\mathbf{r})$, $J_{sr}(\mathbf{r})$ and $J_b(\mathbf{r})$ represent the currents in both cytosol and SR domains. We use the same currents as in [2].

The cardiac cell is modelled as a two dimensional square with $L_x = 100\mu m$ and $L_y = 15\mu m$. The spatial grid belongs to the submicron scale and it is defined as $dx = 0.1\mu m$. CaRUs placed on the perimeter follow an exact periodic distribution with a period $T_x = T_y = 0.8\mu m$. In front of all these exterior CaRUs there are L-type calcium channels (LCC) groups. Inside the cell, CaRUs are placed following a Gaussian distribution centred at the z-planes with a given average distance between CaRUs set as $T_x = 1.6\mu m$ and $T_y = 0.5\mu m$. Then, we identify the SR structure with periodic narrow strips (0.3μm width) with a predefined period (T_x). All these geometrical considerations are shown in the figure 1.

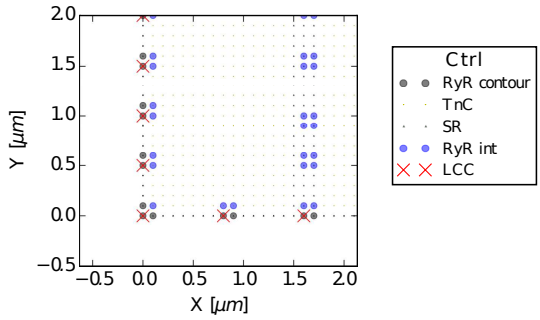

Figure 1: Circles (black and blue) represent RyRs, red crosses are LCC groups, black triangles indicate the SR zone, and yellow dots are the TnC zone.

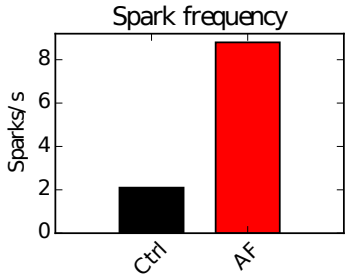

Figure 2: AF shows an increase in spark frequency with respect to Control.

The model reproduces experimental data in both normal and diseased cells (Control and AF). In figure 2 we show that, in abnormal myocytes with AF (where more scattered is the CaRU distribution), the spark probability increase heavily. Thus, this indicates that the spatial distribution of CaRUs plays an important role in the transition to AF.

[1] N. Macquaide et al., Cardiovascular Research, **108** (2015), pp. 387-398.

[2] E. Alvarez-Lacalle et al., **114**, 10 (2015), pp. 108101.