RyRs Coupling Causes a Calcium Leak in Cardiac Cell

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Calcium sparks are a manifestation of a functioning of the intracellular calcium release system, which can operate as a self-sustaining oscillator (clock) responsible for the automaticity of cardiac pacemaker cells. Disturbances in Ca^{2+} sparks formation can be an arrhythmogenic factor in a pacemaker cell.

Here we introduce results of a mathematical modeling of calcium sparks in cardiac cells. We developed a model of the calcium release unit which includes a single sarcoplasmic reticulum lumen, a regular 9x9 cluster of RyRs and a dyadic space. 2D diffusion problem of Ca^{2+} ions across the dyadic space was solved thereby we reproduced Calcium-Induced-Calcium-Release (CICR) effect and “domino-like” RyRs activation in the cluster.

For the rapid computations we used the finite differences method to solve the 2D problem of Ca^{2+} diffusion which is described by the standard diffusion equation. Parameters of Ca^{2+} dynamics were taken from Maltsev-Lakatta model of a rabbit pacemaker cell (Maltsev et al., Am J Phys, 2009).

RyRs’ dynamics in the cluster is described by equations of developed earlier Electron-Conformational model (ECM) of RyRs stochastic dynamics which involves the consideration of RyRs dynamics in terms of a continuous conformational degree of freedom and in energetic terms (Moskvin et al., PBMB, 2006). This approach also allows taking into account conformational coupling between RyRs.

Earlier it was shown that conformational coupling between RyRs in a cluster causes a stability of isolated from the membrane intracellular Ca^{2+} clock in a wide range of the Ca^{2+} dynamics parameters (Ryvkin, et al., Biophysics, 2015). However a sufficiently strong RyR-RyR coupling can be a reason of a “Ca^{2+}-clock sudden stop effect” which is manifested in an occasional forming of a stable open RyRs cluster (2x2, 3x3, etc.) through which a stable Ca^{2+} leak occurs.

A similar effect we observed in case of Ca^{2+} RyR-RyR interaction. This regime manifests itself in the opening of a certain number of channels in a small region. Diffusion supports channels in an open state, but spark does not propagate further. This regime is manifested at a sufficiently low diffusion rate of Ca^{2+} along the dyadic space and can explain a number of arrhythmogenic effects associated with disorders in the intracellular Ca^{2+} -release system.

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