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Cytosolic and nuclear calcium dynamics interaction in a three-dimensional ventricular E-Cell (3Dv E-Cell)

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Earlier simulation studies have modelled the nucleus as a region lacking a releasable calcium pool with lower diffusion coefficient (about 50 $\mu m^2/s$) compared with cytoplasm (about 300 $\mu m^2/s$), where nuclear calcium rises only because of passive diffusion [1]. However, the magnitude and duration of nuclear calcium transient can be both significantly greater than that of cytosolic calcium transient, which indicates other potential nuclear calcium release sources [2].

Given the importance of nuclear calcium in the regulation gene transcription and expression, we introduce a nulcear envelope into the 3Dv E-Cell, which has been used to model stochastic intracellular calcium wave phenomena of an isolated ventricular cell [3], as a barrier with low diffusion coefficient $D_{NE} < 5$ $\mu m^2/s$ to maintain spatial heterogeneity, and nuclear calcium handling as a CICR type process with longer Ca^{2+} release duration (about 200 ms) and relative high diffusion coefficient (about 200 $\mu m^2/s$).

A nuclear envelope with a very low diffusion coefficient (D_{NE} = 0.1 $\mu m^2/s$), isolates the nucleus from the cytosol, and cytosolic calcium waves neither enter the nucleus nor initiate nuclear calcium transients. The nucleus acts simply as an obstacle that splits the calcium wave front into two fronts that travel around the nucleus.

For intermediate values (D_{NE} = 1.0 $\mu m^2/s$) a Ca^{2+} wave can trigger a confined nuclear Ca^{2+} transient, and lead to a nuclear Ca^{2+} excitation. Since the nucleus has a much longer Ca^{2+} release duration, nuclear Ca^{2+} concentration remains at a high level for a relatively long period after the cytosolic Ca^{2+} wave passed. At higher values (D_{NE} = 5.0 $\mu m^2/s$) a nuclear calcium transient can be activated when cytosolic calcium wave reached an end of the elongated nucleus. The nuclear Ca^{2+} transient can re-invade neighbouring cytosol and trigger a Ca^{2+} wave. This can allow a Ca^{2+} spark located near the nucleus to be amplified by the nuclear transient and nuclear envelope, and initiate a spontaneous cytosolic Ca^{2+} wave due to a high D_{NE}. Examples of these phenomena are illustrated in Fig. 1.

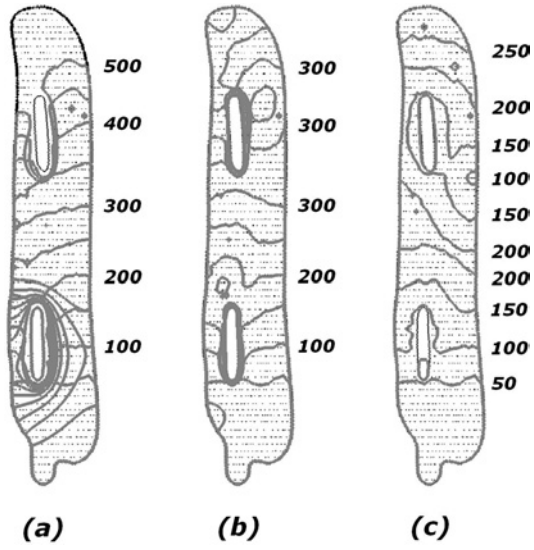

Fig. 1 Effects of the nuclear envelope diffusion coefficient on nuclear-cytosolic calcium transient coupling on intracellular calcium wave patterns. Isochrones of 20μM [Ca^{2+}] are shown with time steps of 50ms. At t = 0ms, a stimulus is applied at the bottom end of the cell by increasing calcium concentration to 50 μM, with (a) D_{NE} = 0.1 $\mu m^2/s$, (b) D_{NE} = 1.0 $\mu m^2/s$, (c) D_{NE} = 5.0 $\mu m^2/s$.

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4-Aminopyridine-sensitive Ca^{2+} store in frog ventricle

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It is believed that a functionally significant intracellular Ca^{2+} store is absent in frog ventricle and that they depend on extracellular Ca^{2+} for contraction [1]. A series of findings in our lab has convinced us that there must be a functionally significant Ca^{2+} store in frog ventricle. Based on a previous report, we used 4-aminopyridine (4-AP), on frog ventricular strips [2].

Hearts were isolated from frogs (*Rana hexadactyla*) which were anesthetized with ether and pithed. 2 mm thick ventricular strips were prepared and mounted in a temperature controlled (25-28 °C) bath perfused with oxygenated solution of the following composition (in mmol L^{-1}): 117 NaCl, 3 KCl, 1 $CaCl_2$, 1 $MgCl_2$, 0.2 NaH_2PO_4, 0.8 Na_2HPO_4, 10 glucose, pH 7.4. Free end of the strip was connected to a force-transducer and force of contraction was recorded on a computer. The strip was paced with field