MODELLING THE STRUCTURE AND FUNCTION OF CARDIAC CELL TRANSVERSE-AXIAL-TUBULES

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Introduction

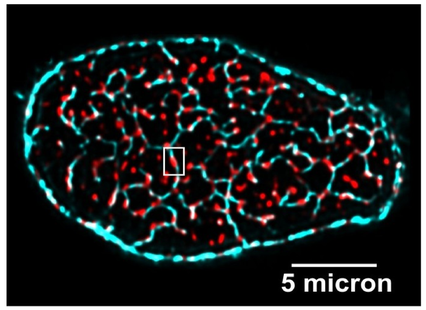
We are developing 3D computer models of cardiac cell structure and function to gain quantitative insights into the role of cell structure and spatial organisation in cell function.

A critical aspect of excitation-contraction (EC) coupling is the distribution of transverse-axial-tubules (TATs) and their proximity to ryanodine receptor channels (RyRs) on the sarcoplasmic reticulum for effective calcium-induced calcium release (CICR)

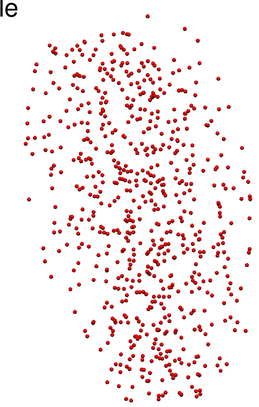
We present methods for developing anatomically realistic, and biophysically based computer models of the inter-play between TATs and RyRs across the dyadic space in a sarcomere of a whole cell.

Imaging and Image Segmentation

Based on [1], 3D confocal images of wistar rat TATs (cyan) and RyRs (red) were acquired via antibody labelling for caveolin-3 and RyR2, respectively. The images capture the whole cross-section along 4 sarcomeres in length.



Extraction of the sarcolemma (dark brown), TATs (gold) and RyRs (red cloud on right) was possible using a combination of thresholding, and binary morphology techniques. The TATs were processed into a 3D skeletonized network (as below) based on [2]



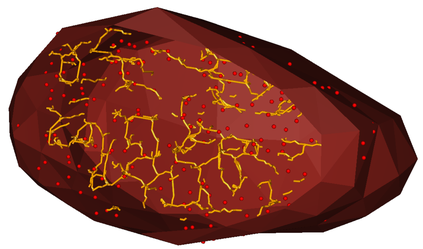
Finite Element Modelling of Cellular Structure

We employ the finite element method (FEM) to solve the partial differential equations that represent calcium dynamics within the cell.

The TATs skeleton network was converted into a network of 1D FE network in 3D space (on right).

A 2D surface mesh was fitted to the sarcolemma data based on [3] to capture the shape of the cell boundary.

The RyRs were then added to the sarcolemma boundary nodes to create a tetrahedral mesh of the 3D domain using tetgen [4] (right).



Model Equations for Calcium Dynamics in 3D

We simulate the dynamics of calcium in the different compartments of the cell as a reaction-diffusion process:

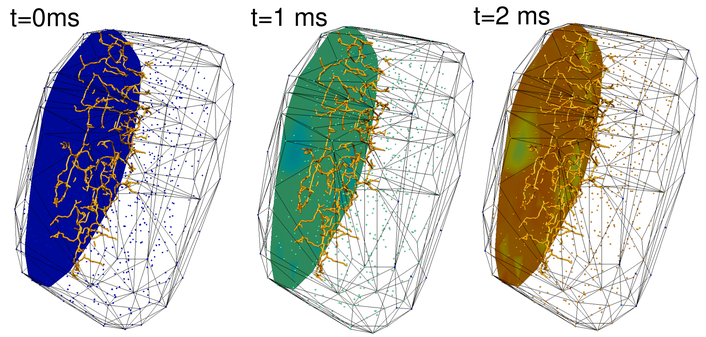
$$\partial[Ca^{2+}]_i / \partial t = D_{Ca} \nabla^2 [Ca^{2+}]_i - \Sigma R_j \quad j=1..num\ reactions$$

where $[Ca^{2+}]_i$ is the cytosolic calcium concentration, and D_{Ca} is the isotropic diffusion coefficient of calcium in the cytosol.

We use OpenCMISS, and CellML to couple the 3D diffusion equations to the reactions of ion-channel gating.

Our aim is to use biophysically-based models of ion channel kinetics that drive the calcium dynamics in and out of the cell. Initially, we will base our RyR channel kinetics on the model of Hinch et.al 2004 [5]. This model simulates CICR assuming the dyadic space is bridged by 1 L-type Ca^{2+} channel, and 1 RyR channel.

Simulation of CICR



Here we demonstrate, with a rudimentary model of RyR gating, the simulation of a calcium release event from rest at t=0, to activation of RyRs associated with t-tubules at t=1 ms, and finally the diffusion of this injected calcium in the cytosol (t=3 ms).

Conclusions and Future Work

We have developed methods to model 3D cardiac cell anatomy and function in a realistic fashion.

The next step is to incorporate Hinch model of calcium dynamics.

A first approximation to the whole cell can be obtained by concatentating copies of this volume.

We intend to incorporate all key EC proteins, and organelles for a thorough picture of intracellular calcium dynamics.

References

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[3] Fernandez et.al., Biomech. Model. Mechanobiology, 2, p139-155
[4] http://tetgen.berlios.de/
[5] Hinch et.al. Biophysical J, 87, p3723-3736

Acknowledgements

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