Solving Calcium Spatiotemporal Diffusion Using COMSOL Multiphysics® Software

L. Garber[1], G. S. B. Williams[2], W. J. Lederer[2]

[1]Fischell Department of Bioengineering, University of Maryland, Baltimore, MD, USA
[2]Center for Biomedical Engineering & Technology, University of Maryland, Baltimore, MD, USA

Abstract

Introduction

This project involves a simplified biological problem that was used to test the potential of COMSOL Multiphysics® software for cardiac myocyte spatial modeling. We made several assumptions to simplify the biological complexity and to highlight the geometrical structures (i.e., lack of sarcoplasmic reticulum, lack of contractile apparatus). We explored the role of the t-tubular network on intracellular calcium diffusion. Although t-tubular structures seem to vary in atrial myocyte according to species, is some, including humans, the atrial myocytes seem to have a less organized network of transverse t-tubules in comparison to their ventricular counterpart. It is to this end that we used COMSOL to compare calcium diffusion in a simplified cardiac myocyte model with and without t-tubules.

Methods and Use of COMSOL

The first part of this project involves modeling Ca2+ diffusion with an organized t-tubular network. We used the structural dimensions published by Chen-Izu and colleagues to determine t-tubular spacing within the ventricular myocytes. Furthermore, we used the t-tubule diameter dimensions that were confirmed by the aqueous diffusion pathway study of Parfenov et al. Then we simulated a similar model without t-tubules to study the cases in which atrial cells might lack these structures. The calcium membrane fluxes were solved in MATLAB® using Grandi et al. detailed ionic ventricular and atrial myocyte models respectively. We used the Transport of Diluted Species physics in COMSOL to solve the diffusion equation in the geometry as portrayed in Figure 1 and we used a physic-controlled mesh which triangular elements. Finally we studied the role of diffusivity which is affected by various Ca2+ buffers within the cytosol.

As portrayed in Figure 3&4, our results suggest that the t-tubular network plays an important role in synchronizing and speeding calcium diffusion. Moreover, the effect of lowering diffusivity is more pronounced in the cellular model that lacks t-tubules.

Conclusions

COMSOL is a powerful tool to simulate important physiological effects that are due to spatial control of calcium dynamics. By integrating different modeling components, the simulations elucidate the mechanism of intracellular calcium diffusion by altering model structures. Although these models will continue to be upgraded to integrate additional cellular complexity, the current simulations provide clues to enhance experimental validation and to develop additional tools to aid in the understanding of intracellular calcium dynamics.

Reference

References
1. Chen-Izu Y, McCulle SL, Ward CW, Soeller C, Allen BM, Rabang C, Cannell MB, Balke CW, Izu LT. Three-dimensional distribution of ryanodine receptor clusters in cardiac myocytes. Biophys J. 2006 Jul 1;91(1):1-13.
2. Parfenov AS, Salnikov V, Lederer WJ, Lukyánenko V. Aqueous diffusion pathways as a part of the ventricular cell ultrastructure. Biophys J. 2006 Feb 1;90(3):1107-19.
3. Jafri MS, Rice JJ, Winslow RL. Cardiac Ca2+ dynamics: the roles of ryanodine receptor adaptation and sarcoplasmic reticulum load. Biophys J. 1998 Mar;74(3):1149-68. Erratum in: iophys 1998 Jun;74(6):3313.
4. Michailova A, DelPrincipe F, Egger M, Niggli E. Spatiotemporal features of Ca2+ buffering and diffusion in atrial cardiac myocytes with inhibited sarcoplasmic reticulum. Biophys J. 2002 Dec;83(6):3134-51.
5. Kushmerick MJ, Podolsky RJ. Ionic mobility in muscle cells. Science. 1969 Dec 5;166(3910):1297-8.
6. Grandi E, Pasqualini FS, Bers DM. A novel computational model of the human ventricular action potential and Ca transient. J Mol Cell Cardiol. 2010 Jan;48(1):112-21.
7. Grandi E, Pandit SV, Voigt N, Workman AJ, Dobrev D, Jalife J, Bers DM. Human atrial action potential and Ca2+ model: sinus rhythm and chronic atrial fibrillation. Circ Res. 2011 Oct 14;109(9):1055-66.

Figures used in the abstract

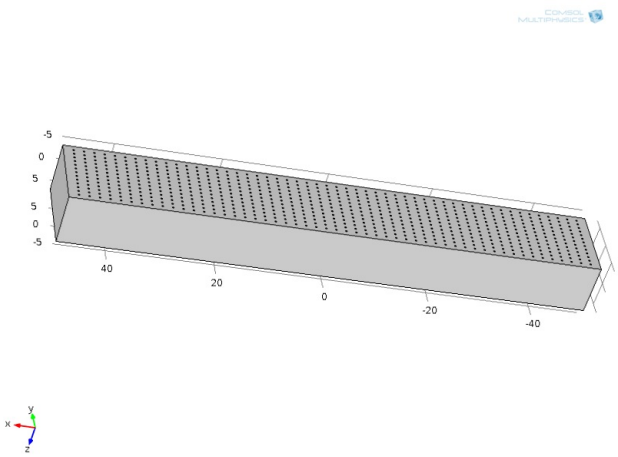

Figure 1: Geometry.

Governing equation: $\frac{\partial[Ca^{2+}]}{\partial t} = \nabla \cdot (\mathrm{D}Ca^{2+} + \nabla[[Ca^{2+}])$

Initial Conditions: $[Ca^{2+}]_i\ (t = 0) = 100 \cdot 10^{-6}\ mM$

$[Ca^{2+}]_o\ (t = 0) = 1.8\ mM$

Boundary Condition: $J_{Ca^{2+}} = J_{lcc} + J_{ncx} + J_{pmca} + J_{bkca}$

Figure 2: Equations used in this study.

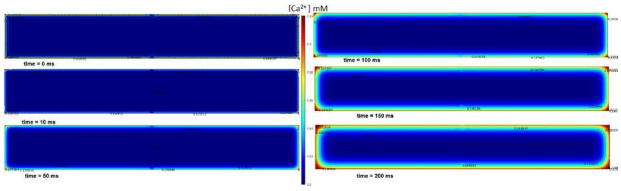

Figure 3: Results: Atrial Myocyte.

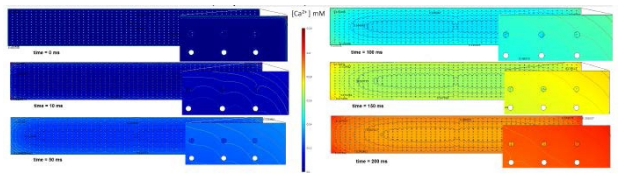

Figure 4: Results: Ventricular myocyte.