Solving Calcium Spatiotemporal Diffusion Using COMSOL Multiphysics® Software

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Introduction: This project involves a simplified biological problem that was used to test the potential of COMSOL 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 transverse-tubule (TT) network on intracellular calcium (Ca^{2+}) diffusion. Although TT structures seem to vary in atrial myocyte according to species, in some, including humans, the atrial myocytes seem to have a less organized TT network in comparison to their ventricular counterpart. Therefore, we used COMSOL to compare Ca^{2+} diffusion in a simplified cardiac myocyte model with and without TTs.
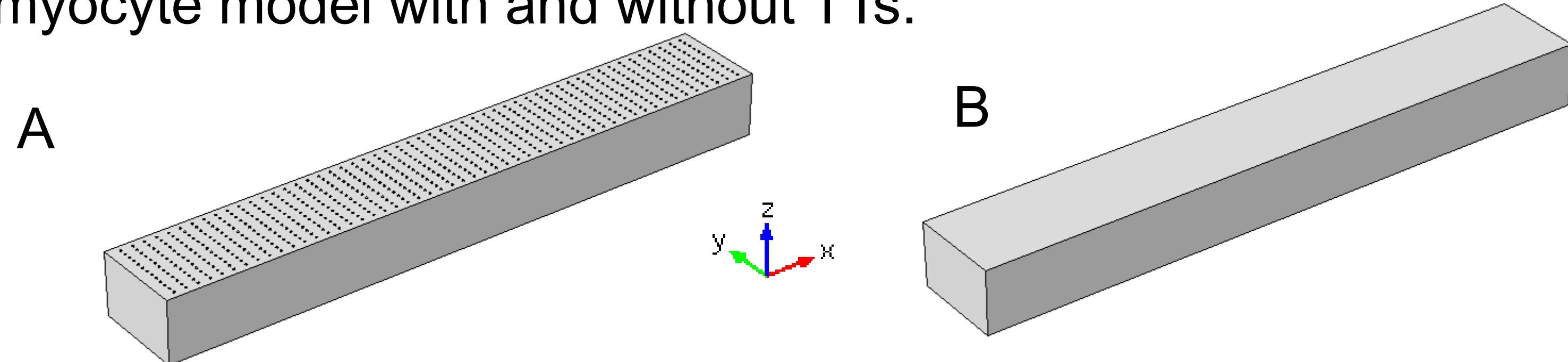

Figure 1. Model Geometry. (A) Model of a cardiac myocyte with a t-tubular network. (B) Geometry without t-tubules.

Methods: The first part of this project involved modeling Ca^{2+} diffusion with an organized TT network. We used the structural dimensions published by Chen-Izu and colleagues to determine TT spacing within the ventricular myocytes. Furthermore, we used the TT diameter dimensions that were confirmed by the aqueous diffusion pathway study of Parfenov et al. Then we modeled a similar model without TT to explore the cases in which atrial cells might lack these structures. The Ca^{2+} membrane fluxes were solved in Matlab using Grandi et al. detailed ionic ventricular and atrial myocyte models respectively. We used COMSOL's Transport of Diluted Species physics to solve the diffusion equation in the geometry as portrayed in Fig. 1, and we used a sweep mesh with triangular elements. Finally we studied the role of diffusivity which is affected by various Ca^{2+} buffers within the cytosol.

Governing equations: $\dfrac{\partial [Ca^{2+}]}{\partial t} = \nabla \cdot (D_{Ca^{2+}} \cdot \nabla [Ca^{2+}])$, $\nabla [Ca^{2+}] = \dfrac{J_{Ca^{2+}}}{D_{Ca^{2+}}}$

Boundary Condition: $J_{Ca^{2+}} = J_{lcc} + J_{ncx} + J_{pmca} + J_{bca}$
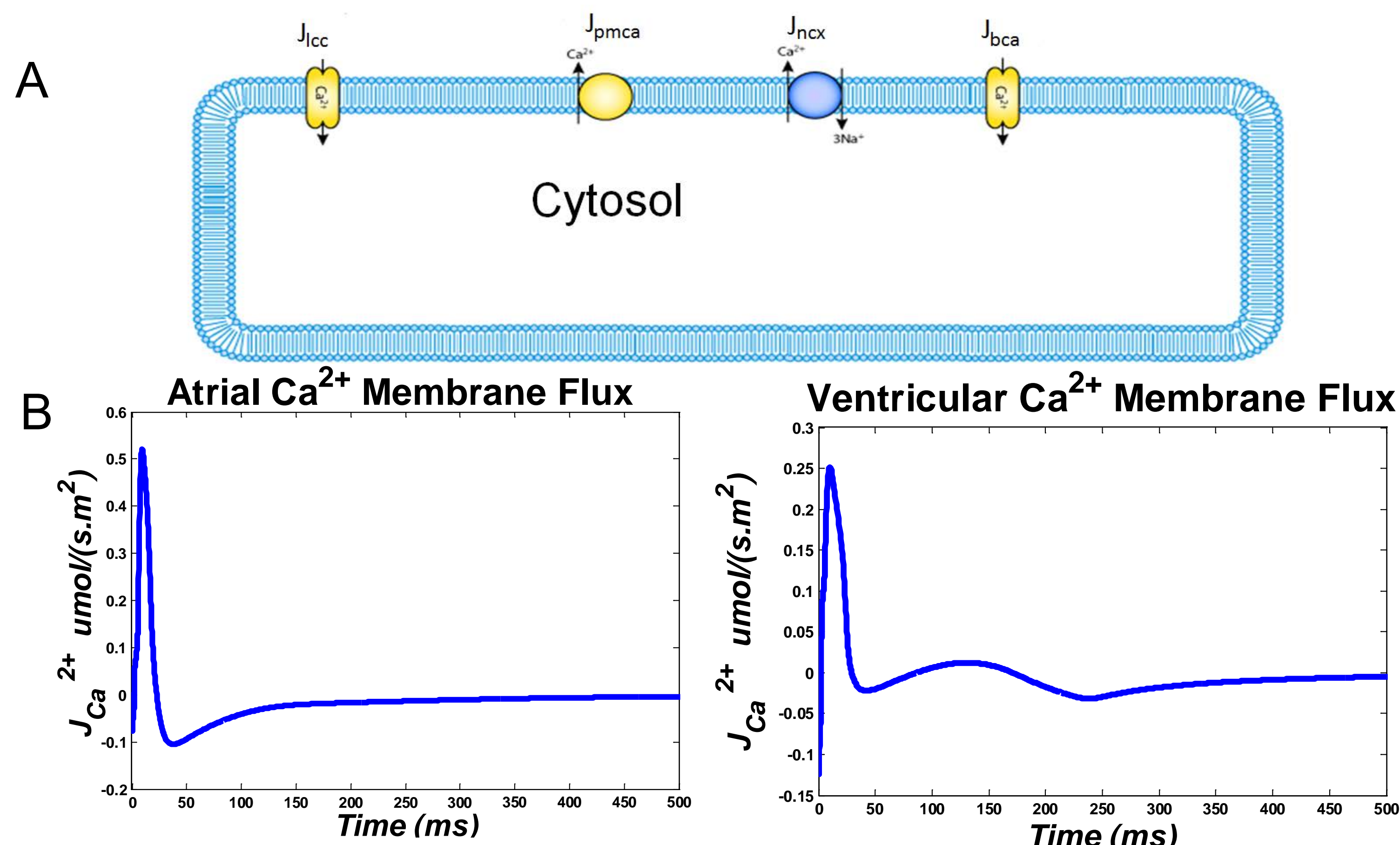
Initial Conditions: $[Ca^{2+}]_i = 100\ nM$

Figure 2. Ca^{2+} ionic fluxes. (A) Schematics indicating the fluxes through ionic channels and pumps: L-type Ca^{2+} channel flux (J_{lcc}), plasma membrane Ca^{2+} ATPase flux, Na^+-Ca^{2+} exchanger flux (J_{ncx}), background balancing Ca^{2+} flux (J_{bca}). (B) Boundary fluxes.

Results: Figure 3 shows Ca^{2+} diffusion in a simplified myocyte model with TT and depleted intracellular stores. Our results seem to indicate that low diffusivity plays an important role in decreasing the $[Ca^{2+}]$ amplitude in the center of the model geometry. Figure 4 shows Ca^{2+} diffusion with similar conditions in a model that lacks TTs. These results suggest that the t-tubular network plays an important role in synchronizing and speeding Ca^{2+} diffusion. Moreover, the effect of lowering Ca^{2+} diffusivity is more pronounced in the cellular model that lacks t-tubules.
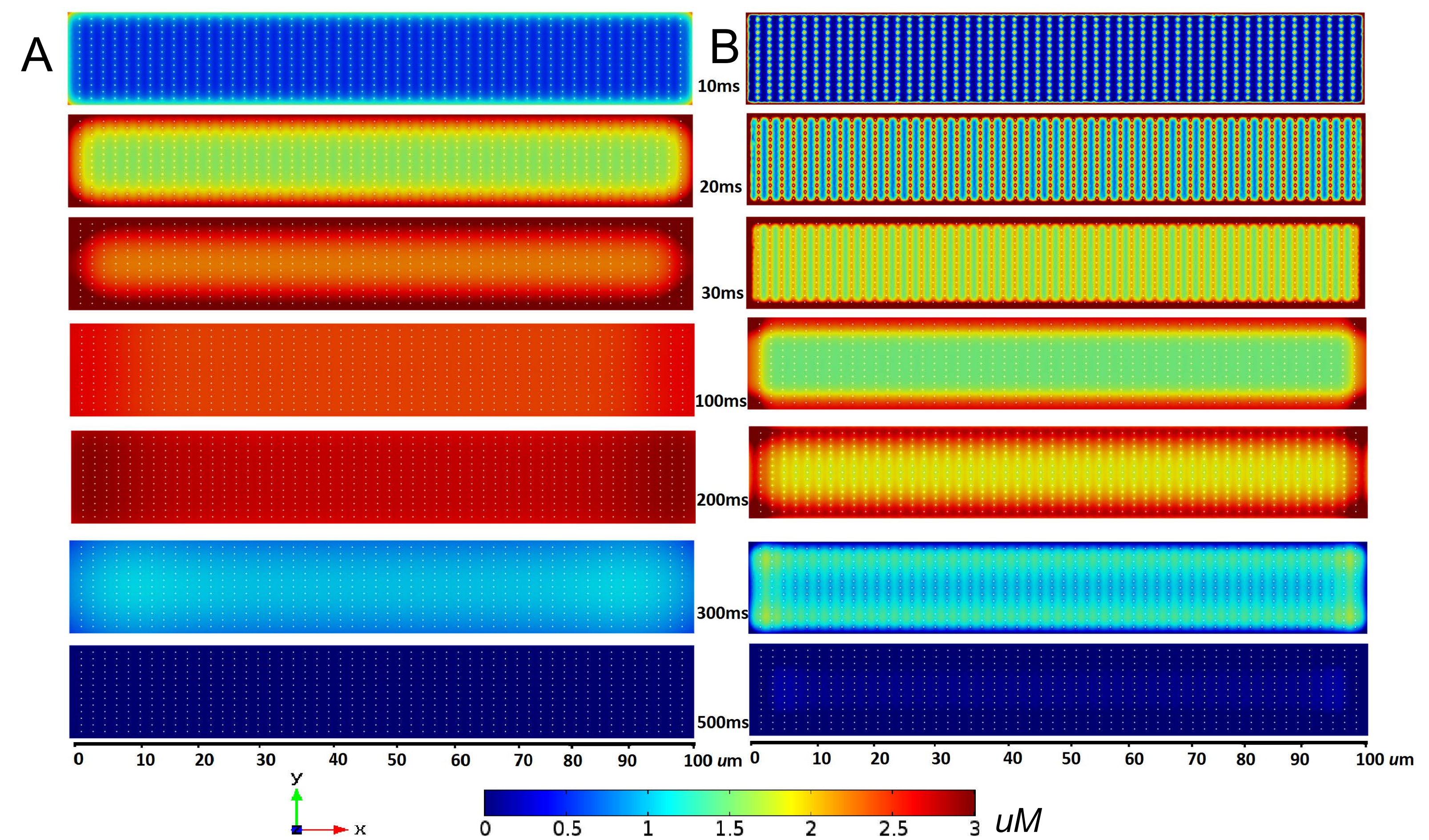

Figure 3. Ca^{2+} Diffusion in the t-tubular model. (A) Diffusivity ($D_{Ca^{2+}}$)= 250 um^2/s. (B) $D_{Ca^{2+}}$ = 15 um^2/s.
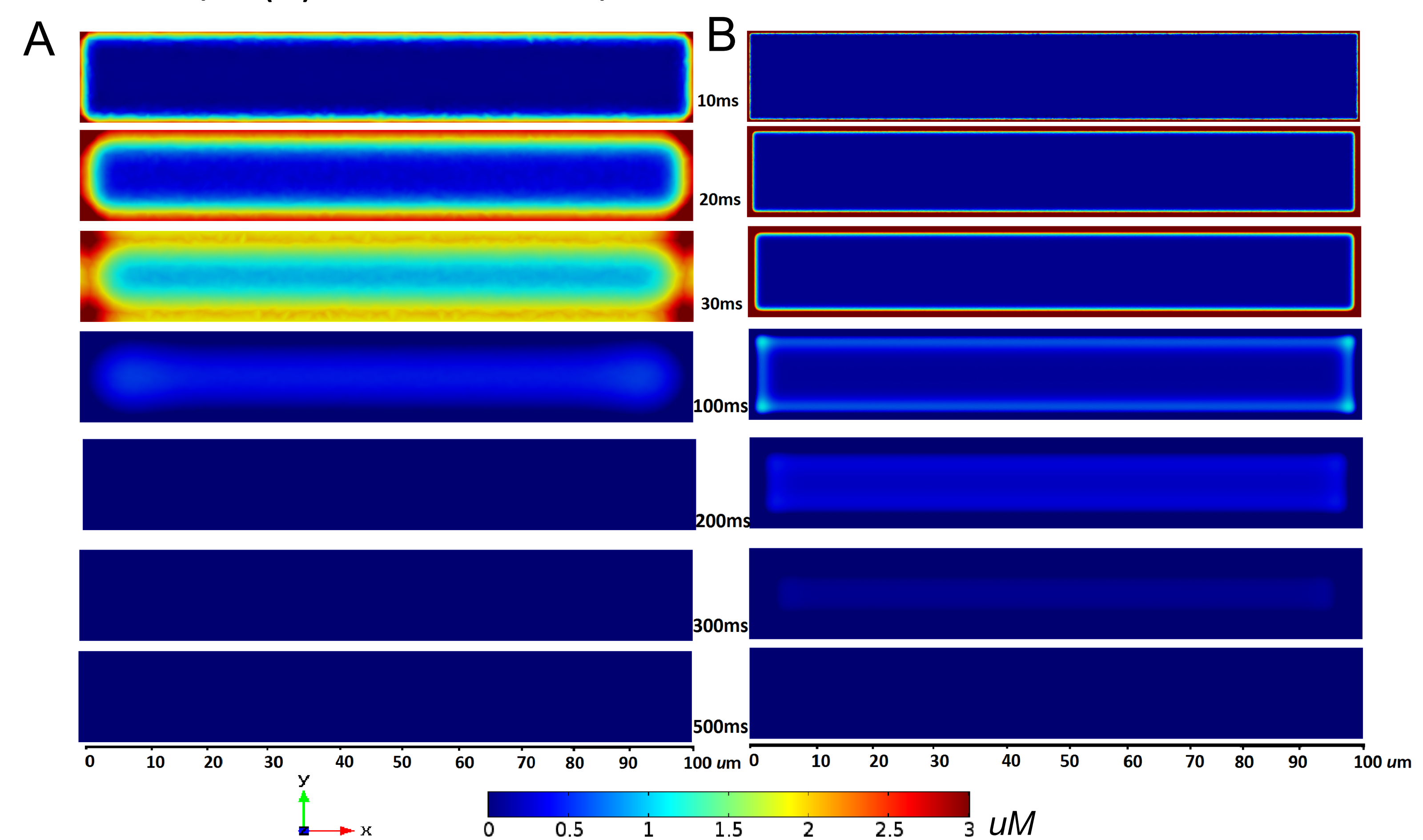
Figure 4. Ca^{2+} Diffusion in the non TT model. (A) Diffusivity ($D_{Ca^{2+}}$) =250 um^2/s. (B) $D_{Ca^{2+}}$ = 15 um^2/s.

Conclusions: COMSOL is a powerful tool to simulate physiological effects that are due to spatial control of Ca^{2+} dynamics. By integrating different modeling components, the simulations elucidate the mechanism of intracellular Ca^{2+} diffusion in altered 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 tools to aid in the understanding of intracellular calcium dynamics.

Limitations: Our model does not capture the specific Ca^{2+} buffers as only the effect of diffusivity was explored. Moreover, the intracellular Ca^{2+} stores were not modeled explicitly. Future model development will incorporate more biological complexity.

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*Modified from Cell ML repository (https://models.physiomeproject.org)