

Investigating Calcium-Mediated Arrhythmias via a Computational Model of a Rabbit Atrial Myocyte

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Abstract

The system of transverse and longitudinal sarcolemmal tubules (T-system) is observed to remodel in atrial fibrillation (AF) and heart failure (HF). The resulting calcium dysregulation has been suggested to underlie disruptions in excitation-contraction coupling, and increase the frequency of arrhythmic events at the cellular scale; however, these mechanisms and their importance are yet to be fully described. A 3D, stochastic, spatio-temporal model of the rabbit atrial myocyte has been developed in order to study calcium-mediated arrhythmic phenomena. Preliminary findings suggest a relationship between the severity of detubulation, and the promotion of spontaneous activity, due to a lower threshold of Ca^{2+} concentration for propagation in detubulated regions caused by the absence of pumps which extrude local Ca^{2+} from the cell.

1. Introduction

The morphology of T-systems in atrial myocytes is conjectured to be remodelled within atrial fibrillation (AF) and heart failure (HF) [1], two cardiac conditions of increasing incidence [2], with one condition often leading to the development of the other [2, 3]. Patho-physiological aberrations in calcium (Ca^{2+}) handling systems, considered

to involve alterations in T-system structure and remodelled channel expression, are suggested to promote both disrupted excitation-contraction coupling and an increasing frequency of arrhythmic events at the cellular scale [4]; the importance of T-system remodelling in the development of pro-arrhythmic events such as spontaneous Ca^{2+} remains unclear [1].

We aimed to develop a multi-scale, rabbit-specific atrial myocyte model, incorporating the necessary 3D, stochastic, spatial-temporal Ca^{2+} handling dynamics required to produce a platform capable of studying Ca^{2+} -mediated arrhythmia mechanisms.

2. Methods

A contemporary model describing rabbit atrial electrophysiology produced by Aslanidi *et al.* [5, 6] (Figure 1A), was integrated with our model describing stochastic, spatio-temporal Ca^{2+} dynamics [7, 8] (Figure 1B). Atrial T-system remodeling, associated with HF, was incorporated in isolation from other forms of remodeling which may occur, through the removal of sarcolemmal ion channel currents from individual CRUs randomly, varying both total percentage detubulation of the cell, and the patch size of detubulated regions (Figure 1C).

Rapid pacing protocols were applied to load the sarcoplasmic reticulum (SR) Ca^{2+} content, to promote the propagation of spontaneous Ca^{2+} waves; a general implementation of a pro- Ca^{2+} overload condition was also

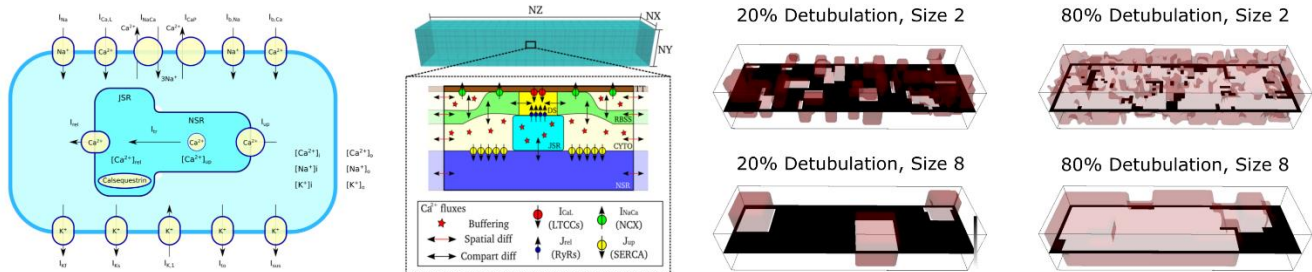


Figure 1 - Structure of the models used. Membrane current formulations from the Aslanidi *et al.* model of a rabbit left atrial myocyte (A) were incorporated into the Colman *et al.* stochastic Ca^{2+} framework (B). Patches of detubulation (C) were introduced through the removal of sarcolemmal ion channels, at various sizes to detubulate some percentage of the cell to represent T-system remodeling.

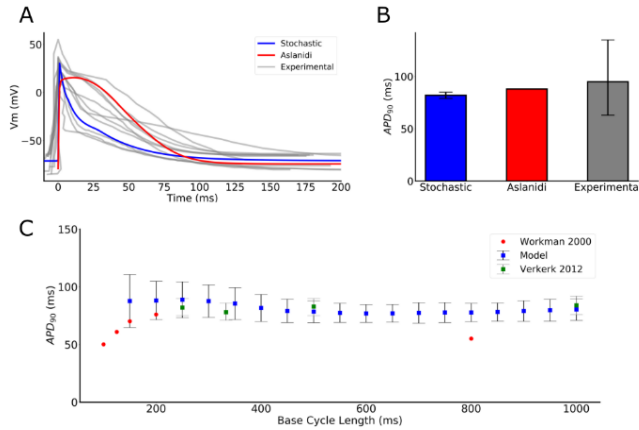


Figure 2 - Action potential (AP) dynamics. A) Rabbit left atrial APs of the newly developed (blue) and Aslanidi *et al.* (red) models (Figure 1), along with a range of experimental APs on rabbit left atrial myocytes. B) The AP duration (APD) of the Stochastic, Aslanidi *et al.* and experimental APs shown in A. C) The AP restitution curves from Workman *et al.* [5] and Verkerk *et al.* [6]

considered, representing remodeling and/or an intervention such as isoprenaline. All simulations presented in this study took place in cells of full-size (a network of 15 x 20 x 65 CRUs along the X, Y and Z axes respectively).

3. Results

3.1. Action potential dynamics

The stochastic model developed produces an action potential within the ranges of experimental data (Figure 2A), and has morphological differences to the original model, such as a visible spike in the rapid upstroke and a triangular morphology, primarily determined by a

significantly different CaT morphology, the sodium-calcium exchanger, and I_{CaL} Ca^{2+} -induced inactivation, resulting from Both the Stochastic and Aslanidi *et al.* models fall well within the range of experimental APDs (Figure 2B) at a base cycle length of 500ms. The AP restitution curve displays that the stochastic model produces APDs which agree with the AP restitution studies by Verkerk *et al.* [9] (Figure 2C), and Workman *et al.* [10].

3.2. Effects of detubulation on stimulated Ca^{2+} -wave propagation.

The degradation of the T-system was shown to produce a cytosolic Ca^{2+} transient (CaT) with a progressively slower upstroke as the density of the T-system was reduced (Figure 3A). The peak of the CaT decreases slightly due to the lower number of L-type Ca^{2+} channels present within the cell, but was not significantly smaller in the fully detubulated cell compared to control. The slower upstroke was a result of fewer CRUs activating instantly (corresponding to those not coupled to a cluster of LTCCs) and thus being activated by slower propagation of Ca^{2+} from the T-system positive regions. (Figure 3B).

Propagation of Ca^{2+} throughout the Y-Z plane of the cell is shown in each of the three cases of detubulation (Figure 3C).

The control cell shows familiar, near-simultaneous fast rise of intracellular Ca^{2+} , followed by isotropic decay. The fully detubulated cell displayed rapid rise along the cell surface, which diffuses through the cell, exciting neighboring CRUs through a diffusion-recruitment process which is significantly slower than a cell with a full T-system. The partially detubulated cell displays a combination of both behaviors, with unaffected regions undergoing the rapid, near-simultaneous increase in Ca^{2+} throughout the cell, followed by the Ca^{2+} -wave propagating slowly into the detubulated regions.

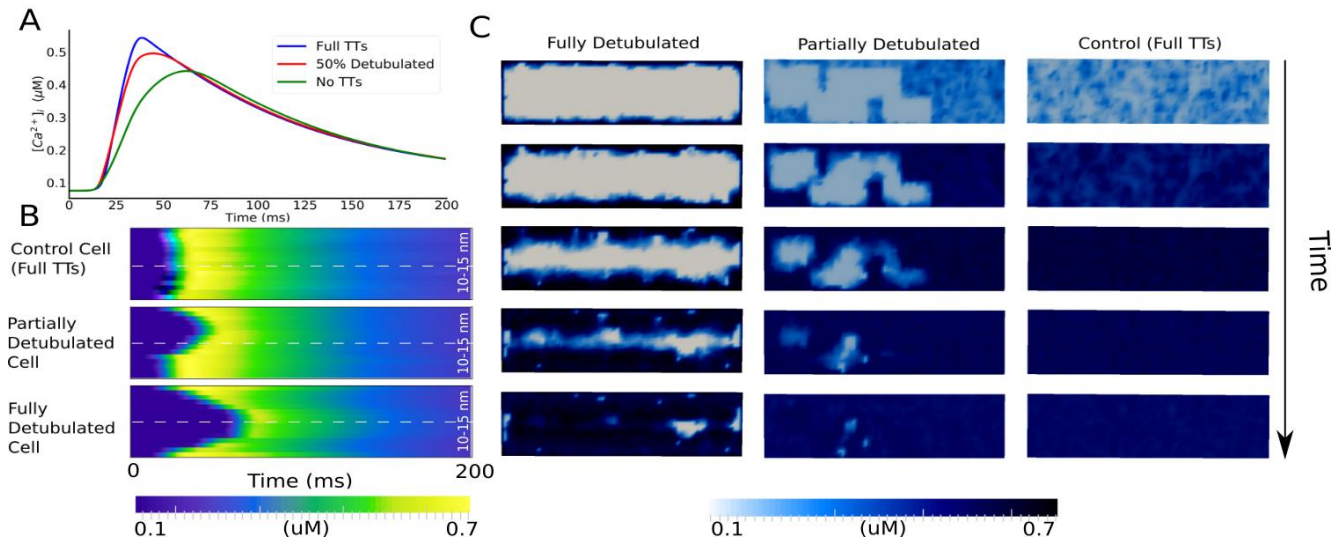


Figure 3 - Effects of detubulation on stimulated Ca^{2+} wave propagation. A) Intracellular Ca^{2+} transient for a fully, partially and none-detubulated cell in the stochastic model. B) Linescans along the X-axis of the cell over 200ms. C) Intracellular Ca^{2+} snapshots along the Y-Z plane of fully, partially and none-detubulated cells. The three cells in A, B and C are the same simulated cells.

3.3. Detubulation promotes spontaneous activity under SR Ca²⁺ loading

A total of nine simulations under each set of conditions were ran, the results of which show few, uncommon spontaneous activity among detubulated cells without the presence of a pro- Ca²⁺ loading condition, but all simulations show various magnitudes of spontaneous excitation with the presence of such a condition.

The results (Figure 4) show a positive correlation between total percentage detubulation and the relative magnitude of spontaneous activity across the nine simulations, for 20%, 40% and 60% detubulation. There was no significant difference between the average relative magnitudes at 60% and 80%. This suggests that atrial remodeling in the form of modifications to T-system morphology may promote spontaneous activity, however this relationship is not linear.

A non-significant difference on the average relative magnitude of spontaneous activity across the patch sizes at each severity of T-system remodeling also suggests that the patch size of these detubulated regions are unimportant regarding the magnitude of spontaneous Ca²⁺ activity. However, there was a correlation between detubulated regions, and the origin of spontaneous Ca²⁺ waves.

4. Discussion

The implementation of a stochastic, spatio-temporal Ca²⁺ handling framework to the Aslanidi *et al.* rabbit atrial myocyte model (Figure 1) has produced a more physiological CaT morphology while retaining a physiological AP (Figure 2A, 2B), and agreement with a range of experimental AP restitution curves (Figure C).

Ca²⁺-wave propagation for a stimulated excitation (Figure 3) produces familiar behaviors for the control cell, and a slower propagation of Ca²⁺ through a diffusion-recruitment CRU mechanism, with the partially detubulated cell displaying a combination of these behaviors. Increasing the severity of the T-system remodeling, via increasing the percentage of the cell which was modelled to be detubulated, had a positive correlation the average magnitude of spontaneous activity over the set of simulations produced (Figure 4). The results suggest that the removal of sarcolemmal ion channels as a result of T-system remodeling promotes spontaneous activity, in agreement with the findings of Song *et al.* [1] while the size of the remodeled regions have no significant effect on the average magnitude of these spontaneous events. This positive relationship may be due to a lower threshold for the propagation of a Ca²⁺-wave within the detubulated regions, and the boundaries between the tubulated, and detubulated regions juxtaposing this lower propagation threshold, and nearby CRUs coupled with L-type Ca²⁺-channels.

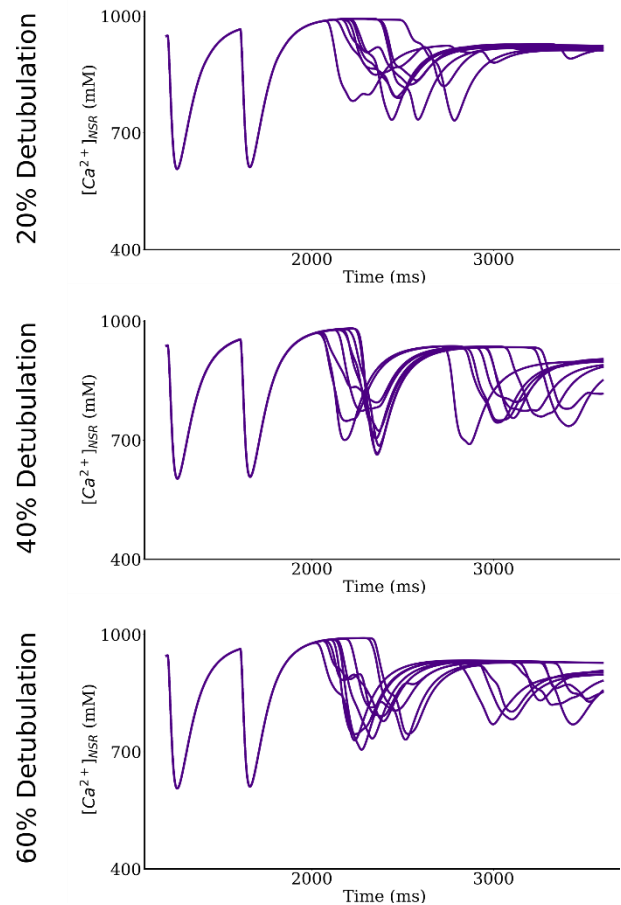


Figure 4 - Effects of detubulation on promoting spontaneous activity. A range of detubulation severities (percentage of total detubulation) and sizes (see Methods) underwent a general implementation of a Pro-Ca²⁺ loading condition, such as isoprenaline, in which I_{CaL} and SERCA activity is enhanced. Three plots of the same patch size are shown. As rabbits are known to have lower t-tubule densities, 20% detubulation can be considered as a control.

5. Conclusion

A computational model of a rabbit left atrial myocyte has been produced from the Aslanidi *et al.* rabbit atrial model, and our model of 3D, stochastic, spatio-temporal Ca²⁺ handling. The model produces a physiological AP morphology, and reproduces APD dynamics observed in experimental studies. A representation of T-system remodelling was implemented, along with a general pro-Ca²⁺ loading condition. The model is capable of producing spontaneous Ca²⁺-waves, and investigation into the relationship between T-system remodeling and spontaneous activity reveals several distinct behaviours of spontaneous Ca²⁺-wave propagation, and a correlation between increased detubulation and the magnitude of spontaneous activity.

Acknowledgements

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