A Novel Human Atrial Electromechanical Cardiomyocyte Model with Mechano-Calcium Feedback Effect

Fazeelat Mazhar[1], Francesco Regazzoni[2], Chiara Bartolucci[1], Cristiana Corsi[1], Luca Dedè[2], Alfio Quarteroni[2,3], Stefano Severi[1]

[1]University of Bologna, Cesena, Italy
[2]Politecnico di Milano, Milan, Italy
[3] École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Abstract

Electromechanical coupling is crucial for modeling a realistic representation of Ca^{+2} transient and Ca^{+2} cycling. Cellular Ca^{+2} dynamics in atria differ fundamentally from the ventricles. A biophysically detailed electrophysiology model is hence necessary to reproduce the experimentally observed phenomena like Ca^{+2} wave propagation in human atrial myocytes. In this work, we present a novel detailed and yet computationally efficient electrophysiology model, its coupling with a contraction myofilament model and the effect of mechano-calcium feedback on coupling.

This novel electromechanical model was calibrated for a collection of human atrial data and was evaluated by reproducing the rate adaptation property of action potential, Ca^{+2} transient and the active force. The aim of this article is to present a new electromechanical model for human atrial myocyte and to analyse the mechanism behind the rate adaptation.

1. Introduction

Electromechanical (EM) coupling consists of a series of events triggered with the membrane depolarization by action potential (AP), followed by the Ca^{+2} release from the sarcoplasmic reticulum (SR) via the Ca^{+2}-induced-Ca^{+2}-release (CICR) mechanism that initiates contraction. Within the EM coupling, the bidirectional coupling is achieved by adding feedback effect of Ca^{+2} sequestered by cytosolic buffers also termed as mechano-calcium feedback (MCF).

Atrial EM coupling and Ca^{+2} signaling has been documented as critically different from the ventricular tissues while also sharing some common similarities. One of the major difference lies in the structural arrangement in the atrial myocytes of T-tubules, which are either missing or have a very irregular arrangement [1]. Consequently, Ca^{+2} release in atrial myocytes is spatially heterogeneous throughout the cell, rising from the periphery and propagating to the center [2][3] hence lacking the 'local control' phenomena of Ca-SR release [4].

Computational atrial models detailed in Ca^{+2} transport, can act as an established complement to the experimental approach in elucidating the mechanism that underlies the atrial EM coupling. In this paper, a novel AP model, the modified version of Koivumäki 2011 [5] (MKM2022) which represents a fine tradeoff between the complex spatiotemporal Ca^{+2} dynamics and computational cost, has been proposed. This model is coupled with a mean-field approximation based contraction model by Regazzoni-Dede-Quarteroni group (RDQ2020) [6].

The need for a novel model formulation and its coupling was demonstrated in our previous work [7] where the coupling and calibration of the Courtemanche [8] AP model and the contraction model, RDQ2020, have been analysed. However, the model was not able to reproduce one of the important phenomena, the force-frequency relationship for human atrial cardiomyocytes. The reason for this discrepancy was seen in the Ca^{+2}-transient (CaT) rate adaptation trend. In this work, our aim is to present a novel human atrial EM coupled model and MCF effect analysis on the electrophysiology, CaT and the active force. The electromechanical model was first calibrated and then evaluated using rate adaptation phenomena.

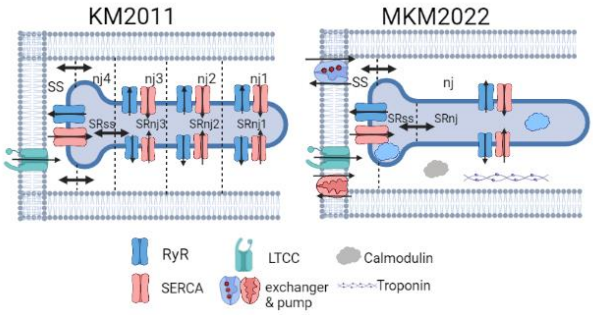

Figure 1: Model description and comparison of Koivumaki (KM2011) model schematic with modified-KM2011 (MKM2022).

2. Method

2.1 MKM2022 model

A physiological representation of Ca^{+2} release and

uptake dynamics was obtained from Koivumaki 2011 [5] and was simplified to enhance its computational efficiency. Figure 1 shows a comparison of cell level model description for the MKM2022 and the original one KM2011. Apart from structural changes, the major atrial-specific phenomenon that activates contraction is the Ca^{+2} diffusion where Ca^{+2} wave propagates from subspace (ss) towards the central/non-junctional (nj) region of the cell and then combines with several proteins that regulate muscle force. Ca^{+2} diffusion was made faster in the new model by relying on the original diffusion distance, this also corresponds to one of the characteristic features of the atria [9]. Additively, the contractile myofilament buffer, troponin (TRPN) was added to the model in accordance with [10].

2.2 EM coupling

MKM2022 AP model was coupled with a biophysically detailed cardiac force generation model RDQ2020 [6]. The MKM2022 model is modified by replacing the instantaneous troponin with the dynamic effect coming from the RDQ model. The bidirectional EM coupling was achieved by using CaT from MKM2022 (Cai_{nj}) as an input to RDQ2020 and then the dynamic effect of Ca^{+2} bound to TRPN ($\frac{d[Ca^{+2}]_{TRPN}}{dt}$) is feedback to the AP model to analyze the MCF effect as shown in the modified differential equation for Cai_{nj} ,

$$\frac{dCai_{nj}}{dt} = beta_{nj} * \frac{JCa}{VnjTot} - \frac{d[Ca^{+2}]_{TRPN}}{dt}$$

where $\frac{d[Ca^{+2}]_{TRPN}}{dt} = TnC_{maxi} * dTnC$, $dTnC$ is the fraction of troponin C units with calcium bound to its regulatory binding site and it comes from RDQ2020 model and is given as,

$$TnC = \sum x\_RU * X_{so}(SL) + B_{nso}\left(1 - X_{so}(SL)\right)$$

where x_RU is the state variable related to troponin units in the single-overlap zone while B_{nso} is the ratio of bounded troponin units in the no-overlap zone and $X_{so}(SL)$ is the function of the size of the single overlap zone that models the effect of sarcomere length (SL) changes. In our coupled model the focus is on active force (T_{active}) under isometric conditions and, hence, we have fixed SL to 2.2µm. Having this coupled model, calibration of the contraction parameters was performed to adopt atria-like physiology. This calibration was based on experimental data available for human atrial myocytes as discussed in [7]. Briefly, the cross bridge cycling transition rate and the Ca^{+2} sensitivity were retuned with respect to a set of time based biomarkers of T_{active} i.e., relaxation time at 50% and 90% of peak values (rt50 rt90), time to peak (ttp), and twitch time (TT). This calibration was performed at basal frequency of 1Hz and the results were also portrayed at other frequencies as shown in Figure 3 of Results section.

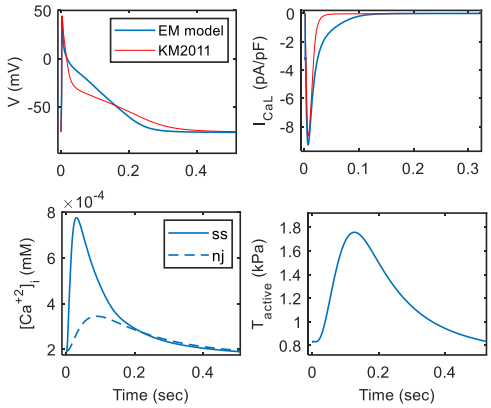

Figure 2: Upper panels: comparison of AP and I_{CaL}-curves from MKM2022 model with KM2011. Lower panels: show the CaT in ss and nj region along with T_{active} generated by coupling.

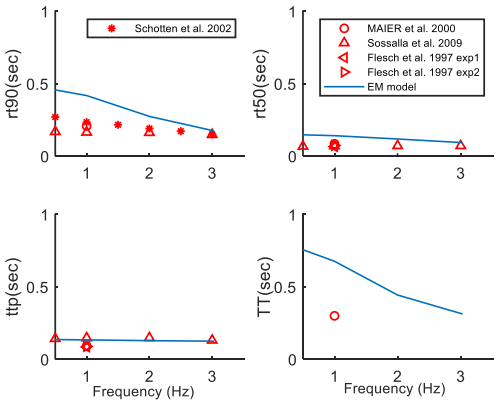

Figure 3: EM model kinetics calibration based on biomarkers extracted from human atrial experimental data.

3. Results

EM coupling of the human atrial model has been shown in Figure 2, where the upper panels show the AP and L-type Ca^{+2} current (I_{CaL}) for MKM2022 (in blue) in comparison to the original model KM2011 (in red). The new model has a lengthened early repolarization phase (or a more pronounced plateau) followed by shortening of the late repolarization APD. I_{CaL} current now has a lower peak with less inactivation than the KM2011 model. The lower panel (on left) shows the CaT in ss and nj regions, where the delay of ttp between ss and nj is quite evident. On the right lower panel, we have active force T_{active} obtained as a result of EM coupling. All the results were obtained by running the coupled model at 1Hz pacing frequency and 800 beats.

Figure 3 shows calibration of EM model based on the biomarkers extracted from human data. The model exhibits frequency-dependent acceleration of relaxation (FDAR), a process that is important for speeding up relaxation at high heart rates from physiological point of view.

3.1 Rate adaptation

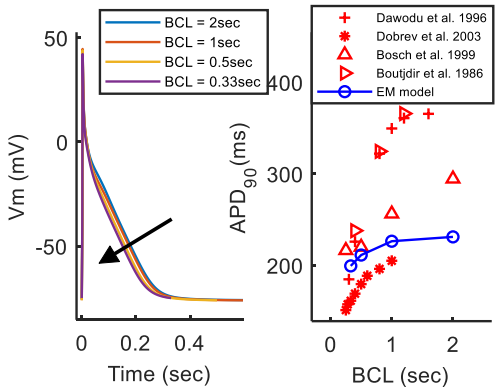

Figure 4: AP curves (on left) and rate dependent APD_{90} data points (on right) in comparison with the human atrial experimental data.

Rate adaptation property of APD, T_{active} and the CaT was demonstrated by simulating the cell model for physiological range of basic cycle length (BCL) varying from 2 to 0.33sec. The initial conditions used were the steady state variables recorded by running the model at basal BCL of 1 sec and 800 beats. Afterwards, for rate adaptation, each BCL was simulated for 300 beats in order [2 1 0.5 0.33] sec. Hence, the curves thus obtained are a steady state representation with respect to varying BCL.

Increasing the pacing rate reduces the APD at 90% of repolarization (APD_{90}) in a biphasic manner (Figure 4 right panel), phase 1 BCL 2→1sec shows a flat rate dependence APD_{90} whereas for phase 2, BCL 1→0.33 sec shows a sharp dependence. This trend has been shown by many experiments as represented by markers in Figure 4. Given the sparse set of data, the model was replicating this biphasic trend qualitatively.

A dome-shaped frequency-dependent relationship of T_{active} can be seen in experiments as shown in Figure 5 (left panel). The percentage change in force for our model is showing an increasing trend throughout the frequencies. The right panel shows an increasing trend of percentage change in CaT with respect to frequency.

4. Discussion & Conclusions

In this work, a modified version of the human atrial AP model KM2011 has been proposed. The model is computationally efficient and reproduces the experimentally observed complex Ca^{+2} transport mechanism. This AP model is then utilized to develop a

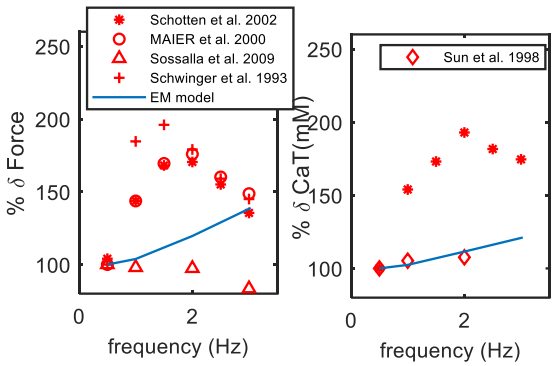

Figure 5: A dome shaped force-frequency relationship (on left) has been compared with human atrial experimental data. Systolic CaT (on right) from nj region has also been plotted with the data.

fully coupled EM model with proper consideration of feedforward and feedback pathways (the MCF) in the Ca^{+2} handling. In particular, we have evaluated this EM model by reproducing a correct frequency-dependent T_{active}, APD_{90} and CaT relationship and have focused on the mechanism behind the adaptation.

The main findings of this study are that our novel EM coupled model was able to reproduce a qualitatively correct rate-dependent adaptation of APD_{90}, CaT and the T_{active}. Experimentally, APD_{90} shows a biphasic trend with varying rate. Phase 1 where a flat rate dependence of APD_{90} was observed. This small APD rate dependence is based on the rate dependent inactivation property of I_{CaL}

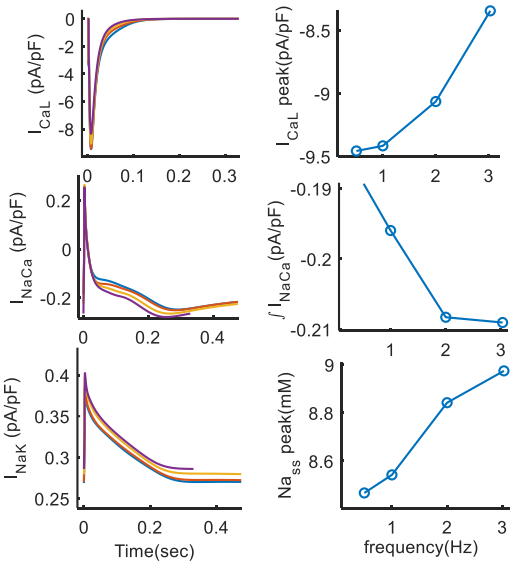

Figure 6: Membrane current rate dependence. I_{CaL} current traces (top panel, left) and peak values (top panel, right) for all rates. I_{NaCa} traces (middle panel, left) and integral normalized by BCL 1sec (middle panel, right) for all rates. I_{NaK} current traces (bottom panel, left) and the cytosolic Na^{+} accumulation (bottom panel, right) with rate.

current and this phenomenon is dominant for low frequencies only as discussed in [11]. Our model was able to reproduce this phenomenon as shown by I_{CaL} traces for different frequencies in Figure 6 (top panel left). Similarly, a rate dependent reduction in I_{CaL} peaks was also observed in Figure 6 (top panel right). Phase 2, where a sharp shortening of APD_{90} with rate was observed and the cause was cytosolic Na^{+} accumulation (a known phenomenon in ventricles). As a consequence of the rise in cytosolic Na^{+} concentration, two of the membrane currents are affected: firstly, rise in pumping function of sodium-potassium current I_{NaK}, secondly, modulation in the exchanger I_{NaCa} current activity. These two currents together create a large impact on APD at high frequencies and the shortening was also reproduced well by the model as shown in Figure 6 (middle and bottom panels).

The peak of T_{active} shows a dome-shaped trend with increasing pacing frequency. The model showed an increasing rate adaptation trend for T_{active}. The mechanism behind the force-frequency relation can be understood by looking into the CaT_{nj} rate dependence. A deeper look inside the Ca^{+2} transport system shows rising Ca^{+2} content in the SR with rate whereas, on the contrary, a decreasing release from the ryanodine receptor (RyR) gate can be observed. The reduced opening probability of the activation gate of RyR_{nj} may find its reason in reduced recovery time from inactivation at higher frequencies. Hence, CaT rate dependence trend can result from an interplay between $[Ca^{+2}]_{SR}$ and the release flux $Jrel_{nj}$. Another aspect of Ca^{+2} accumulation in the cytosol was Ca^{+2} influx in the cytosol via the reverse mode of I_{NaCa} exchanger. This was also observed by the model (Figure 6 middle panel, right) where the integral (normalized by BCL 1sec) of I_{NaCa} current is not shifting to more negative values anymore at higher frequency. Figure 7 shows the J_{rel} flux (top panel) and its decreasing trend with rate (bottom left). Though J_{NaCa} shows a very little contribution but still is acting as a medium of Ca^{+2} influx at higher

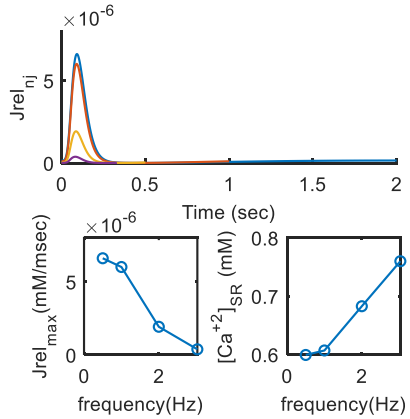

Figure 7: Top panel shows J_{rel} flux traces for different frequencies and its decreasing trend with frequency on lower left panel. $[Ca^{+2}]_{SR}$ increasing trend was shown on bottom right panel.

frequency. Hence, from our results, It can be concluded that Ca^{+2} transport system i.e., the SR is the main contributor that produces an increasing force-frequency relationship for a human atrial myocyte.

Acknowledgments

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Address for correspondence:

Stefano Severi
Department of Electrical, Electronic and Information Engineering,
University of Bologna,
Via dell'Università 50, 47522 Cesena (FC), Italy
stefano.severi@unibo.it