Electro-Mechanical Coupling in Human Atrial Cardiomyocytes: Model Development and Analysis of Inotropic Interventions

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

Human-based computational models are a powerful tool that complements the experimental approaches and can improve our understanding of individual components of the heart by integrating them into one system. This paper aims to couple and calibrate a human atrial electro-mechanical model to analyse the coupling effects and inotropic interventions on human atrial electrophysiology, calcium dynamics, and active isometric contraction on a cellular scale.

A human atrial electrophysiology model was coupled with one of the recently developed biophysically detailed contraction models. A collection of human atrial experimental data has been presented to calibrate the coupled model. The calibrated electro-mechanical human atrial model yielded action potential, calcium transient and active tension that were validated against the experiments and conclusions were drawn to explain the mismatch between in-silico and in-vitro experiments on inotropic interventions.

The coupled and calibrated human atrial electro-mechanical model and simulation framework developed in this study serves as a pathway for future investigations of the effect of contractile performance and inotropic interventions on the electrophysiology of the atria.

1. Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia characterized by adverse changes in electrophysiology (EP) and intracellular Ca^{+2} signalling of atrial myocytes [1]. Contractile remodelling is the major consequence of impaired electrical activation and Ca^{+2} handling. AF-induced contractile dysfunction is involved in thrombogenesis and in progression to heart failure [2].

Computational modelling and simulation is a powerful tool to accelerate the mechanistic understanding of AF and to plan and evaluate therapeutic interventions. Several atrial cellular models have been proposed that provide substantial insights into the pathophysiology of the atrial cell usually through separate tracks of EP and contractility [3]. Hence, an integrated electro-mechanical (EM) model of human atrial cardiomyocyte is lacking.

This study aims to investigate the coupling effects in human atrial EP, calcium dynamics and active isometric contraction, and the inotropic effects by varying the rate and its dependence on force. For this purpose, human atrial action potential (AP) and contraction model are coupled and calibrated using experimental data. For choice of AP model, we consider a detailed ionic model, Courtemanche 1998 (CRN) [4] whereas, for the contraction part a recent model by Regazzoni-Dede-Quarteroni based on Mean Field approximation, RDQ-MF 2020 [5] was employed. RDQ-MF is computationally efficient and biophysically detailed model for cardiac force generation.

This simulation framework serves as a roadmap for human-based integrated simulation of EP, calcium dynamics and contractility in atrial cardiomyocytes. The proposed model also highlights the limitation of rate adaption on inotropic properties of the heterogeneous excitation and mechanical coupling and can be adapted as a pathway in making the right choice of the models for ensuring a strong coupling.

2. Method

2.1. Electro-mechanical myocyte model

The EM coupling of human atrial cardiomyocytes was modelled through the integration of the AP model, CRN and a recently developed biophysically detailed contractile model, RDQ-MF 2020 model. The bidirectional coupling was achieved as previously reported in [6]. Briefly, a strongly coupled model was developed by incorporating, 1) a dynamic calcium transient generated from AP model serving as an input to the contraction model; 2) the effect of active contractions was fedback into the AP model.

The fundamental contractile units of muscle cell are the sarcomeres that generate active tension T_{active} in a myocardial cell [7]. In RDQ-MF model, this process has been split into two parts, 1) the activation of regulatory units (RU), protein complexes of troponin (TRPN) and tropomyosin (TM) residing on the thin filament, actin as shown in Figure 1. Rise of Ca transient via Calcium-induced Calcium-release (CICR) process, activates these RU hence resulting in muscle contraction. 2) Cross bridge (XB) cycling, which is achieved by the interaction of activated RUs, the actin with the thick filament, the myosin that generates T_{active} by consuming the chemical energy stored in ATP [8].

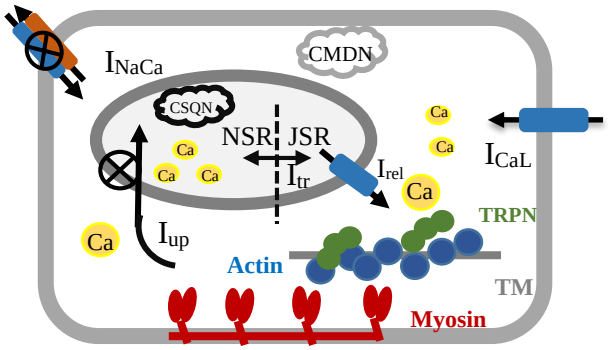

Figure 1: Electro-mechanical cell model coupling

In CRN model, the amount of calcium bound to cytosol buffers i.e., Calmodulin (CMDN) and TRPN is described through a combined scheme and provides a steady-state approximation of the phenomenon. Therefore, to ensure EM coupling, the combined buffering scheme was separated, keeping an algebraic formulation for the CMDN buffer and including dynamic calcium buffering for TRPN. We defined the amount of calcium bound to TRPN ($[Ca^{+2}]_{TRPN}$) as, the fraction of TRPN units with calcium bound to its regulatory binding site ($CaTRPN$) multiplied by a constant maximum concentration of calcium ions that can bind to TRPN ($[Ca^{+2}]_{TRPN,max}$ = 0.07 mM), leading to

$$\frac{d[Ca^{+2}]_{TRPN}}{dt} = [Ca^{+2}]_{TRPN,max}\frac{dCaTRPN}{dt} \quad (1)$$

The definition for $[Ca^{+2}]_i$ from CRN model was modified in such a way,

$$\frac{d[Ca^{+2}]_i}{dt} = \beta^*_{Cai}\left(\left(-I_{pCa} - I_{Cab} + 2I_{NaCa,i}\right)\frac{A_{cap}}{2Fv_{myo}} - J_{up}\frac{v_{nsr}}{v_{myo}} + J_{diff,Ca}\frac{v_{ss}}{v_{myo}} - \frac{d[Ca^{+2}]_{TRPN}}{dt}\right), \quad (2)$$

where

$$\beta^*_{Cai} = \frac{1}{1+\frac{[CMDN]K_{CMDN}}{([Ca^{+2}]_i+K_{CMDN})^2}} \quad (3)$$

and all other variables are defined in [4]. Here $\frac{dCaTRPN}{dt}$ from equation (1) has been computed from RDQ-MF model. In this way, the bidirectional coupling was achieved by subtracting the effect of $\frac{dCaTRPN}{dt}$ from $[Ca^{+2}]_i$ as shown in equation (2). Hence, an EM system of nonlinear equations can be produced that determines the coupling effect on EP, CaT and active contractions of a single cell.

Table 1: Human Atrial experimental data used for calibration of EM coupling model. Tmax: peak tension, ttp: time to peak tension, TT: twitch time, rt50, rt90: relaxation time at 50% and 90% of Tmax, CaT: Calcium transient.

Reference	Tissue preparation	Biomarker
Schotten et. al 2002, *CardiovasRres*	Right atrial appendages from patients of mitral valve surgery (1Hz, 37°C, n=31)	*Tmax*, rt90
Schwinger et al. 1998, *Molecular & Cellular Biochemistry*	Right atrial trabeculae from patients who underwent aortocoronary bypass operations. (1Hz, 37°C, n=9)	*Tmax*
Sossalla et al. 2009, *JACC*	Thin right atrial trabeculae were micro-dissected (n=79)	*Tmax*, *ttp*, rt50, rt90
[10] L S. MAIER et al. 2000, *AJP-Heart*	Right atrial trabeculae from patients undergoing aortocoronary bypass operation (37°C, n=15)	*ttp*, *TT*, rt50,rt95 CaT
Flesch et al. 1997, *JPET*	Isolated electrically driven (1Hz, 37°C) human right atrial trabecula from non-failing hearts. (n=15)	*ttp*, rt50
Brixius et al. 1997, *JAPPL*	Right atrial tissue from patients having aortocoronary bypass surgery. (n=19)	*ttp*, rt50 CaT

2.2. Experimental Data

Human experimental recordings used for EM coupled model calibration have been summarized in Table 1. A cardiac myocyte removed from its normal environment, where it interacts with several other cells, has a significant impact on its electrical and mechanical functionality [9]. Therefore, it is very hard to translate the electro-mechanics recorded at an isolated cellular level to organ level. Hence, instead of employing data from a single cardiac myocyte, we have calibrated our model using tissue level preparations that allow the myocytes to be studied in an environment that more closely mimics how they are found

in the heart.

2.3. Parameters Calibration

The coupled EM model was calibrated against human experimental recordings to achieve more atrial-specific characteristics. Ca sensitivity plays a crucial role to assess the mechanical behavior of the muscle other than the force-pCa curve. An increased Ca sensitivity indicates that the muscle requires less free Ca^{+2} to generate force but in this process many factors work in collaboration. The equilibrium dissociation constant, K_d (in mM) is the ratio of dissociation K_{off} (in ms^{-1}) to association K_{on} of Ca-TRPN. Human atrial myocytes have less Ca sensitivity hence providing increased K_d than ventricular myocytes [11]. In accordance, K_d was manually tuned to value in a range of 0.5-0.86 µM as reported in [12,13].

In addition, XB cycling kinetics K_{basic} (in ms^{-1}) was also optimized along with the value of K_{off}. Human atrial twitches and CaT are shorter in time than ventricles [10] therefore the optimization of model RU and XB kinetics parameters were achieved by using human atrial experimental data as listed in Table 1 based on biomarkers of ttp, rt90, rt50 and the beating frequency. The calibration of EM kinetics parameters has been shown in Figure 3 in Results section. The calibration was performed using *fminsearch* optimization function to find local minima in Matlab. The model biomarkers were tuned in accordance with the experimental data to adopt atrial physiology.

3. Results

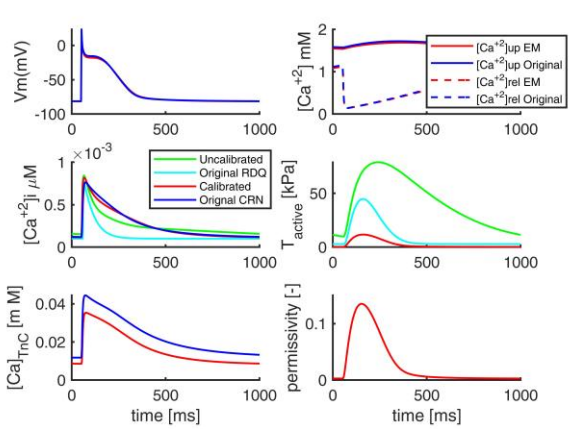

Figure 2: Simulation of EM coupled human atrial cell model (in red) vs original CRN model (in blue). Upper panel shows effect of contraction on AP, SR Ca^{+2} content. Middle panel shows CaT and Tactive also including un-calibrated EM model i.e., RDQ with CRN CaT (in green) and the original RDQ model i.e., RDQ with the analytically simulated CaT(in cyan). Lower panel shows Ca bound to TRPN and permissivity.

Figure 2 illustrates the comparison of AP, CaT, active isometric tension T_{active}, contractility for calibrated EM model (in red) with original CRN model (in blue). For CaT and T_{active} we have also included original RDQ (in cyan) and un-calibrated EM model curves. The stimulus of 2 nA was applied at t = 50 ms to the cell for a duration of 2ms. Initial conditions were recorded by running original CRN model at 1 Hz for 200 beats. The EM model was then run for 20 beats to achieve steady state.

Coupling affects the AP by slight shortening of the early phase of repolarization as shown in Figure 2. CaT of the calibrated model follows the original CRN trend. A minor decrease can be seen by sarcoplasmic reticulum (SR) Ca^{+2} uptake. The middle panel of Figure 2 also demonstrates T_{active} development with sarcomere length (SL) fixed at 2.2 µm. The calibrated tension twitch is fast in activation and relaxation than the uncalibrated and original RDQ twitches. The lower panel shows a reduction in Ca bound to TRPN peak than the original CRN which is the consequence of a slight increasing CaT peak. Another parameter, permissivity is the number of myosin heads that are in a permissive state and it is proportional to the amount of force generated. The plot corresponds to a very small amount of permissive myosin heads.

EM model was calibrated based on the biomarkers as shown in Figure 3. After calibration the kinetics of EM model were tuned as follows: K_d=0.865e-3, K_{off}=180e-3 and K_{basic}=20e-3. This calibration effect has been already depicted in Figure 2. Moreover, the model cooperativity was also slightly enhanced by making γ=20. In terms of biomarkers, the comparison of the calibrated model with the un-calibrated one can be seen in Figure 3. The un-calibrated model shows slower kinetics i.e., a delayed ttp, slow relaxation and a large twitch time.

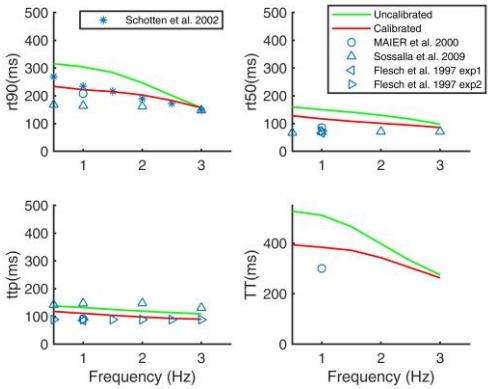

Figure 3: EM model kinetics calibration based on biomarkers extracted from human atrial experimental data.

The inotropic property of the model was assessed by running the model at frequencies varying from 0.5 to 3Hz. Rate adaption by the coupled model demonstrates a negative inotropic effect as shown in Figure 4 (left panel). All the experimental data shows a positive force-frequency relation whereas our model is not following this trend. On right, CaT generated from our AP model has been plotted in the systolic phase which also depicts a decreasing trend

with increase in frequency. Similarly, CaT from our EM model also follows the EP CaT with respect to changing frequency.

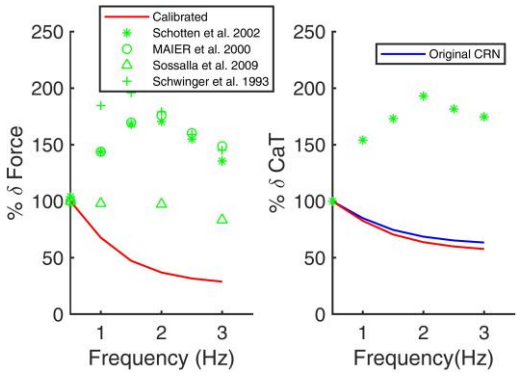

Figure 4: Force (left) and CaT (right) plotted with respect to frequency for coupled and calibrated EM model

4. Discussion & Conclusions

In this study, a strongly-coupled EM model of human atrial myocytes has been presented by the integration of existing human cellular AP and contractility model. In particular, we have incorporated the effect of contraction on AP and CaT by adding the feedback effect of Ca-TRPN buffering on AP model. To have more atria-specific behavior of the EM model we have calibrated the kinetics in accordance with human atrial experimental data. For this purpose, we have presented a collection of available data from human atrial trabeculae at body temperature.

The main findings of this study are the negative inotropic effect of our model respect to changing rate. A further investigation demonstrated a decreasing CaT with respect to increasing rate generated by both CRN and our model. The positive force-frequency relation is actually associated with a powerful continuous increase in Ca uptake by SR as reported by in-vivo experiments [10]. This mismatch of our in-silico model with the in-vivo experiments highlights the limitation of our AP model choice. CRN model has a simplistic representation of SR compartments that is far from the actual arrangement of complex SR structure. Therefore, we suggest the need for such an AP model with a more detailed spatiotemporal Ca-gradient representation like Koivumaki et al. (KM) 2011 model. This choice will come up with an obvious increased computational complexity by adding more state variables in the EM model and that would create difficulty of scaling up our cellular level model to tissue level. Therefore, a tradeoff between complexity and biophysically detailed AP model can be achieved by employing an update of CRN model i.e., Colman et al. 2013 model that incorporates a simplified but still detailed form of Ca^{+2} handling developed in KM model. Hence we aim to adopt this computationally efficient AP model as a future choice for EM coupling that hopefully will preserve the characteristics of intracellular Ca^{+2} handling in the periphery and interior sites of the cell.

Acknowledgments

This work was supported by the Italian Ministry of University and Research (Italian National Project, PRIN2017 (‘Modeling the heart across the scales’).

References

[1] P Kirchhof, et al. "2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS." *EJECTS*, vol. no. 50.5, pp. e1-e88, 2016.

[2] SA Nazir, et al. "Mechanoelectric feedback and atrial arrhythmias." *CardiovasRres* vol no. 32.1, pp. 52-61, 1996.

[3] J Heijman, et al. "Computational models of atrial cellular electrophysiology and calcium handling, and their role in AF."*J of physiology*, vol no. 594.3, pp. 537-553, 2016.

[4] M Courtemanche, et al. "Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model." *AJP-Heart* vol. 275.1, pp. H301-H321, 1998.

[5] F Regazzoni, et al. "Biophysically detailed mathematical models of multiscale cardiac active mechanics." *PLoS computational biology* vol. 16.10 pp. e1008294, 2020.

[6] V Timmermann, et al. "An integrative appraisal of mechano-electric feedback mechanisms in the heart." *Progress in biophysics and molecular biology* vol. 130 pp. 404-417, 2017.

[7] D Bers. Excitation-contraction coupling & cardiac contractile force. *Springer Science & Business Media*, vol. 237, 2001.

[8] NA Narolska, et al. "Myocardial contraction is 5-fold more economical in ventricular than in atrial human tissue." *CardiovasRes* vol. 65.1 pp. 221-229, 2005.

[9] ER Pfeiffer, et al. "Biomechanics of cardiac electromechanical coupling and mechanoelectric feedback." *J of biomechanical engineering* vol. no. 136.2, 2014.

[10] LS Maier, et al. "Ca^{+2} handling in isolated human atrial myocardium." *AJP-Heart and Circulatory Physiology* vol. no. 279.3, pp. H952-H958, 2000.

[11] I Morano, et al. "Skinned fibers of human atrium and ventricle: myosin isoenzymes and contractility." *Circulation research*, vol. no. 62.3, pp. 632-639, 1998.

[12] SP Robertson, et al. "The time-course of Ca^{+2} exchange with calmodulin, troponin, parvalbumin, and myosin in response to transient increases in Ca^{+2}." *Biophysical journal*, vol. no. 34.3, pp. 559-569, 1981.

[13] S Land, et al. "Influence of atrial contraction dynamics on cardiac function." *Inter j for numerical methods in biomedical engineering*, vol. no. 34.3, pp. e2931, 2018.

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