Substrate-Specific Simulations of Atrial Fibrillation Reproducing Electrophysiological Clinical Markers

María Termenón-Rivas, Javier Barrios-Álvarez de Arcaya, Giada S. Romitti, Pau Romero, Dolors Serra, Ignacio García-Fernandez, Miguel Lozano, Rafael Sebastian, Alejandro Liberos, Miguel Rodrigo

CoMMLab, Universitat de València, València, Spain

Abstract

Digital Twins able to reproduce patient-specific electrical patterns during atrial fibrillation (AF) could help to identify the optimal therapy. Calibration of atrial simulation parameters is mandatory to reproduce observed clinical markers such as cycle length (CL) or conduction velocity (CV).

A realistic 3D atrial anatomy including fiber orientation, conduction anisotropy and ion channel heterogeneities across atrial regions was built to simulate AF patterns. Functional reentries were simulated under different degrees of electrical remodeling and tissue diffusion (healthy to chronic AF), then CV and CL were measured at different atrial regions.

The heterogeneous model allowed to simulate differences in transmembrane potential curves as reported in bibliography. As expected, CV at atrial regions increases with increasing diffusion, whereas CL decreases with electrical remodeling, from healthy to chronic AF substrate.

Electrical remodeling and diffusion factors can be used to calibrate AF models to clinically measured CV and CL markers. This will permit Digital Twins to reproduce the patient-specific electrophysiological patterns simulating AF progression and test potential therapies.

1. Introduction

Cardiac arrhythmias are one of the main causes of mortality and morbidity in developed countries, with atrial fibrillation (AF) being the most prevalent cardiac arrhythmia [1]. Approximately, 1% of the population suffers from this pathology [2]. However, the specific mechanisms of AF initiation and maintenance are not yet fully understood. Computational modeling of atrial electrophysiology allows a better understanding of experimental data and pathologies, facilitating diagnosis and treatment selection.

Obtaining a Digital Twin of each individual patient's atrium would allow to reproduce their specific AF phenotype and predict the potential outcome of specific therapies. However, this requires adapting the mathematical models to reproduce the patient's electrical activity, since a large variability has been reported for clinical markers such as cycle length (CL) and conduction velocity (CV), which can range from 130 to 300 ms and from 0.1 m/s to 1 m/s, respectively.

The aim of this work is to study the relationship between simulation parameters and clinical markers in order to adapt realistic computational models. This will be carried out in a detailed 3D model including substrate heterogeneity, fiber direction and electrical remodeling to faithfully reproduce the electrical activity of AF in realistic substrates.

2. Materials and Methods

2.1. Heterogeneous atrial model

The 3D model of human atria shown in Figure 1a was used, which includes fiber orientation and atria division into different regions [3]: right atrium (RA), left atrium (LA), sinoatrial node (SAN), crista terminalis (CT), pectinate muscles (PM), Bachmann bundle (BB), right atrial appendage (RAA), left atrial appendage (LAA), inferior vena cava (IVC), superior vena cava (SVC), cavotricuspid isthmus (CTI), mitral valve (MV), tricuspid valve (TV), pulmonary veins (PV) and fossa ovalis (FO).

Differences between atrial regions at cellular scales were included in the model. Based on the work of Krueger [3], anisotropy was included as variations in the transverse and longitudinal diffusion values of each region as shown in Table 1. In addition, we included a specific cellular model for each atrial region based on previous experimental [4,5] and simulation studies [6-10]. Using Koivumäki's model [11] as a basis, we modified the conductivities of 5 ionic currents: I_{to}, I_{CaL}, I_{Kr}, I_{K1} and I_{Ks} as shown in Table 2. Tissue propagation was based on the

monodomain model and solved with a dt of 10 μs on a custom-made GPU solver [12].

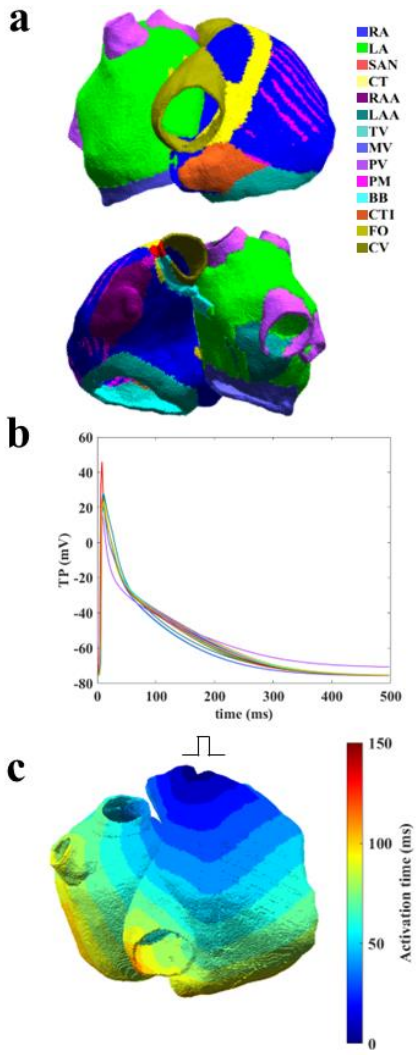

Figure 1. a) Atrial regions. b) Transmembrane potential curves for regions in a). c) Activation time map.

Table 1. Transversal and longitudinal diffusion values.

Atrial region	Transversal diffusion ($\mu m^2/ms$)	Longitudinal diffusion ($\mu m^2/ms$)
RA, LA	0.1200	0.4500
SAN	0.4392	0.4392
CT	0.1200	0.7872
PM	0.0480	1.1160
BB	0.2892	1.1221
RAA, LAA, IVC, SVC, CTI	0.1200	0.1200
MV, TV, PV, FO	0.0840	0.3049

Table 2. Relative values of ion channel conductance in atrial regions with respect to the baseline model.

Atrial region	g_{to}	g_{CaL}	g_{Kr}	g_{K1}	g_{Ks}
RA	1	1	0.625	1	1
LA, SAN, BB, IVC, SVC	1	1	1	1	1
CT	1.35	1.6	0.9	1	1
PM	1.05	0.95	0.9	1	1
CTI, RAA, FO	1	1	0.7906	1	1
LAA	0.65	1.05	2.75	1	1
MV, TV	1.05	0.65	3	1	1
PV	1.35	0.4	2	0.7	1

2.2. Heterogeneous model simulations

After stabilizing the heterogeneous atrial model following a pacing protocol at 5 Hz for 4 seconds, reentrant activity was generated in the left atrial septum using an S1-S2 protocol. Two sets of simulations were performed: i) varying the diffusion percentages (25%, 50%, 75% and 100%) together with a 125% remodeling; and ii) varying the remodeling percentages (25%, 50%, 75%, 100% and 125%) with a 25% diffusion. Note that a remodeling percentage of 0% and a diffusion percentage of 100% represents healthy atrial conditions. Increasing the remodeling percentage implies progressing from healthy to chronic AF (cAF), for a remodeling of 100%, and long-standing AF when exceeding this percentage. To create the FAc model, the following currents were modified from Koivumäki's model in all regions of the atrium: SERCA expression (-16%), PLB to SERCA ratio (+18%), SLN to SERCA ratio (-40%), maximal I_{NCX} (+50%), sensitivity of RyR to $[Ca^{2+}]_{SR}$ (+100%), conductance of I_{CaL} (-59%), conductance of Ito (-44%), conductance of I_{Kur} (-22%) and conductance of I_{K1} (+100%). For the 25%, 50% and 75% remodeling models, the values of the modified currents were obtained as a linear interpolation between the healthy case and the cAF model, while the currents of the 125% remodeling model were calculated by linearly extrapolating.

2.3. Measurement of cycle length and conduction velocity

Seven points covering the surface of both atria were selected to measure clinical markers: LA, MV, PV, CT and RAA and two in RA wall. These points, represented in Figure 2a, were used to measure CL and CV using 2s of each simulation after the functional reentry was stabilized.

The CL was obtained from the transmembrane potential curve of each of these 7 points by averaging the time between consecutive activations (fig 2c).

To measure the CV, 4 points were selected at 5 mm surrounding each of the 7 measurement points (fig 2b). A planar wave conduction was fit by least-squares to the respective activation instants, from which the propagation direction and CV were extracted. Finally, the CV was obtained as the average value of all activations.

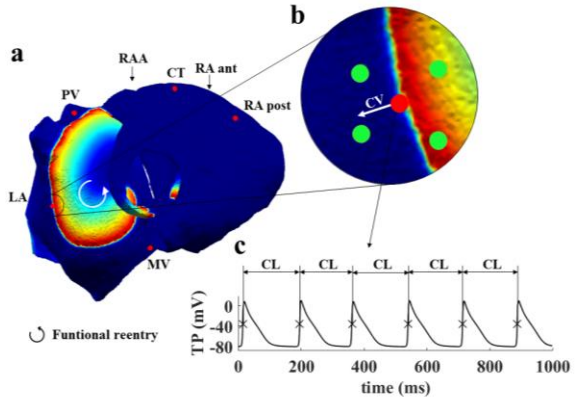

Figure 2. a) Points to measure CL and CV. b) Detail of 4 points used to measure CV. c) Transmembrane potential to determine CL.

3. Results

3.1. Electrophysiological model evaluation

The atrial model reproduced differences in transmembrane potential curves across different regions (fig 1b), obtained for a pacing simulation at 2 Hz for healthy conditions. LA tissue showed an action potential duration (APD_{90}) of 232 ms, whereas the atrioventricular rings, TV and MV, presented the shortest action potentials with APD_{90} of 210 ms and 206 ms, respectively. In contrast, the CT had the longest APD_{90} (256 ms), and the PVs presented an earlier repolarization but longer APD_{90}.

Figure 1c shows the local activation map for the pacing simulation from the SAN at 2 Hz, where the entire atrium takes 114 ms to depolarize. The effect of anisotropy can be observed as a faster conduction zone corresponding with the CT that causes a triangular profile in the isochrones.

3.2. Conduction velocity fitting

Figure 3 shows the CV obtained in each of the 7 measurement zones for simulations with 125% remodeling and diffusion variation from 25% to 100%. As expected, an increase in diffusion caused an increase in CV across all regions of the atrium. For example, in the LA increasing diffusion from 25% to 100% provoked a CV increase from 231.68 mm/s to 584.49 mm/s.

The heterogeneities and anisotropy of the model had a direct impact in the measured CVs. Thus, the CT is the fastest region and the RAA the slowest, with CVs of 959.65 mm/s and 379.36 mm/s, respectively, for 100% diffusion.

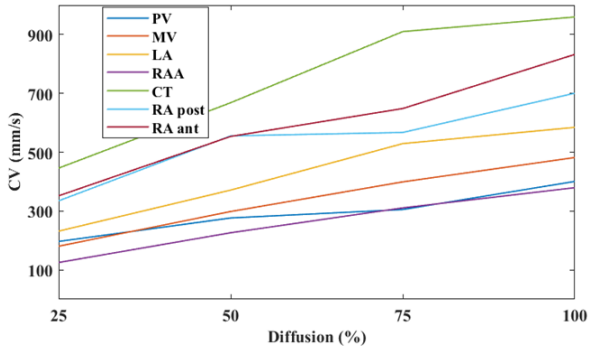

Figure 3. CV for 125% electrical remodeling.

3.3. Cycle length fitting

The effect of electrical remodeling on CL is shown in Figure 4a, which represents the values measured at the 7 points of the atrium in the simulations with 25% diffusion.

At points in the LA, PV and MV regions the CL decreased with increasing remodeling. For example, at the LA point a CL of 229.71 ms was measured for 25% remodeling and 172.40 ms for 125%. Note that, from 25% to 75% remodeling the conduction ratio from LA to RA was approximately 4:3 (fig 4b), where for every 4 cycles of potential at the LA 3 cycles are conducted to the RA. For 100% remodeling conduction to the right atrium was reduced to a ratio of 2:1 (fig 4c), causing an increase in CL.

4. Discussion and Conclusions

This study demonstrates that detailed simulations of the atrial substrate, including fiber direction, ionic heterogeneity and electrical remodeling, can reproduce clinical markers as CV and CL in ranges observed in clinical practice. Calibration curves were obtained at 7 atrial regions able to link clinically measurable markers, CV and CL, as a function of the parameters used to perform simulations: electrical remodeling and diffusion. It has been obtained that CV increases with increasing diffusion percentage, covering the range from 231.68 mm/s to 584.49 mm/s in the LA, and from 100 to 900 mm/s in the whole atria. Conversely, increasing the electrical remodeling resulted in a decrease in CL, from 229.71 to 172.40 ms in the LA, and ranging from 160 to 350 ms across both chambers.

The detailed atrial model with anisotropy and substrate heterogeneities was used to measure the CV in presence of chronic AF substrate. Different conduction velocities were obtained for each atrial region, observing variations also reported in bibliography [2].

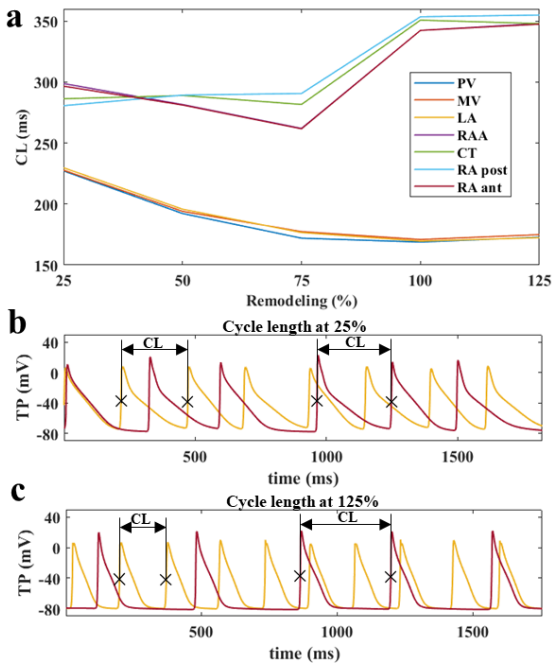

Figure 4. a) CL for 25% diffusion. b) Transmembrane potential curves at LA (yellow) and RA (red) points for 25% remodeling (b) and 125% remodeling (c).

Regarding the measurements on the TP curve, the lowest APD_{90} was obtained in the TV and MV (206 ms and 210 ms, respectively) and the highest in the CT (256 ms). These results agree with those obtained in experimental studies [4]. In addition, a decrease in amplitude (from 102.31 mV to 87.86 mV) were obtained in the PVs, as measured in [5].

This study shows a single CV calibration curve for a single value of 125% remodeling, as well as a CL curve for 25% diffusion. It is necessary to extend these calibration tables to fit CL and CV for any substrate condition, in order to cover all potential clinical situations. This study focuses on the arrhythmic condition on the LA, as it is known the relevance of this region in AF maintenance. However, other AF maintenance mechanisms, such as multiple waves or micro-reentries, and other dominant regions should be considered.

The results obtained in this investigation demonstrate diffusion and electrical remodeling can be adapted on computational models to reproduce the CL and CV values measured in patients. This will allow the creation of Digital Twins by adapting the percentage of remodeling and diffusion of the simulations performed to the ranges corresponding to the clinical markers measured in the patient. Even sweeps of simulations can be performed to reproduce the temporal dynamism of the markers. In this way, it will be possible to reproduce not only the anatomy but also the specific AF phenotype of each patient, to identify the specific mechanisms of AF and predict the efficacy of each therapy.

Acknowledgments

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Address for correspondence:

Miguel Rodrigo Bort.
Av. de la Universidad s/n, 46100, Burjassot, Valencia, Spain.
miguel.rodrigo@uv.es.