Role of fiber direction and ionic heterogeneities in atrial arrhythmia simulations

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Abstract

Digital twins are useful tools to simulate atrial fibrillatory behavior in patients with atrial fibrillation (AF). However, the degree of complexity needed for their clinical use is still unclear. The usage of fiber direction (FD) and ionic heterogeneities (IH) can be a key factor to improve digital models when simulating AF conditions.

FD and IH were included in a 3D anatomical model of the atria. Multiple stimulation protocols to induce AF were simulated in this model, adding and suppressing the effect of FD and IH on it.

FD had an important role as its inclusion produced 51% of the protocols to generate arrhythmic behavior, whereas without FD only a 24% of the total cases were arrhythmic. On the other side, IH did not produce notorious differences when it was removed from simulations, since the percentage of reentries were 38% when they were included to 37% when they were not. In average, arrhythmic patterns were generated in 37% of simulations, amongst them, 4% were functional reentries and 33% were anatomic reentries.

Inclusion of FD in detailed simulation is necessary in order to induce fibrillatory patterns similar to those reported in clinical practice. This will allow a better fit of digital models to their respective patient data.

1. Introduction

Cardiac arrhythmias are one of the main causes of mortality in developed countries. Amongst them, the one that is produced the most is atrial fibrillation. The mechanisms that underlie this pathology are still not understood, however. With the aim of the better comprehension of it, in-silico models are used [1], where different anatomies with its different scenarios can be simulated, such as the generation of reentrant patterns, obtaining information of the beginning and maintenance of arrhythmia mechanisms. Moreover, thanks to these simulations, a proper diagnosis and optimal treatment can be dictated for every particular arrhythmia.

The degree of detail of these models is still an undetermined aspect when it comes to reproduce realist reentrant behaviors in patient-specific anatomies. Fiber direction (FD) is a factor to be included, since heart fibers do not propagate way transversally and longitudinally, so diffusion must be defined both directions for each tissue [2]. Another important factor are ionic heterogeneities (IH), as different ionic concentrations and ionic channel densities have been reported for different atrial tissues, resulting in different electrophysiological behaviors.

In this study, the effect of FD and IH applied in a realistic anatomy with chronic atrial fibrillation was analyzed and so their individual impact in the initiation of arrhythmic patterns can be evaluated.

2. Materials and methods

2.1. Anatomic model

An anatomic model was used based on the atrial anatomy proposed by Krueger et al [3], containing both right and left atria, where FD and HI were included. In this anatomy, different tissues and regions can be distinguished, such as right atria (RA), left atria (LA), sinus node (SN), crista terminalis (CT), pectinate muscles (PM), Bachmann bundle (BB), cavo-tricuspid isthmus (CTI), right appendage (RAP), left appendage (LAP), venae cavae (VC), pulmonary veins (PV), tricuspid valve (TV), mitral valve (MV), and fossa ovalis (FO), as they can be seen in Figure 1A

The fiber FD was defined in each atrial region by their anisotropy, characteristic that is applied by varying transversal and longitudinal diffusion in the different tissues. Their specific values are shown in Table 1.

On the other side, IH were introduced varying ionic currents' values for each tissue. These values were extracted from the bibliography [4-8]. Table 2 shows the relative factors applied to the ionic currents to achieve tissue heterogeneity. Left atria's condition was considered as basal.

Table 1. Transversal diffusions and diffusion ratios

Region	Transversal diffusion ($\mu m^2/ms$)	Ratio longitudinal/transversal diffusion
RA, LA	0,12	3,75
SN	0,44	1
CT	0,12	6,56
PM	0,05	23,25
CTE,CV, LA,RA	0,12	1
MV,TV,FO	0,08	17

Four different models were generated combining these two variations, in presence and absence of FD and IH. When FD was not included, diffusion ratios were set to make propagation isotropic (ratio of longitudinal to transversal diffusion equal to 1). In absence of IH, the whole atria was considered to have basal (LA) conditions.

Table 2. Relative ionic heterogeneities

Region	g_{to}	g_{CaL}	g_{Kr}	g_{K1}	g_{Ks}
RA	1	1	0,625	1	1
LA, SN, BB	1	1	1	1	1
CT	1,35	1,6	0,9	1	1
PM	1,05	0,95	0,9	1	1
CTI, RA, FO	1	1	0,7906	1	1
LA	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. Simulations

A self-owned Solver [9] was used to perform the simulations, that used GPU to solve the differential equations of Koivumäki's cellular model [10]for each node of the anatomical model.

Electrical remodeling caused by chronic AF was introduced by including the following variations to the basal model: an increase in I_{k1} conductivity of 80%, an increase in the maximum value of I_{NCX} of 37,5%, in the ratio between PLB and SERCA of 13%, in the sensitivity of RyR to $[Ca^{2+}]_{SR}$ of 75% and a reduction of SERCA expression of 12%, a reduction of I_{to} conductivity of 33%, a reduction in I_{kur} conductivity of 16%, a reduction in I_{CaL} of 44%, and a reduction in SLN to SERCA of 30%. Also, a 25% reduction on the general diffusion was included.

With the purpose of simulating pro-arrhythmic activity in this anatomy, a S1-S2 protocol was paced using the regions marked in Figure 1C. Time intervals of activation ranged between 150 and 200ms every 10ms for S1, whereas S2 ranged between 60 and 80% of the corresponding S1 value in steps of 4ms.

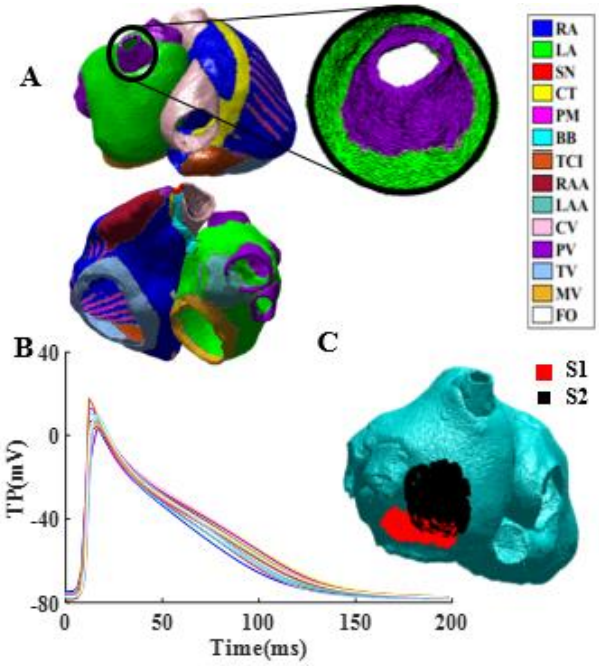

Figure 1. A) Atrial anatomy with the different regions. B) Transmembrane potentials of atrial regions. C) Stimulation zones for the S1-S2 protocol.

All simulations were stabilized with a battery of 20 S1 pulses in the model including both FD and IH. After these pulses, the S2 pulse was applied, as well as the change of conditions of FD and IH. This new situation was maintained until simulation time reached 10 seconds, and it was analyzed if there was reentrant activity and its type, anatomical or functional.

3. Results

Different combinations of S1 and S2 in presence and absence of FD and IH resulted in different arrhythmic patterns. Anatomical reentries were observed in pulmonary veins, inferior cava vein and mitral valve, as well as functional reentries in the left atria's posterior wall and in the septum. There were multiple cases when no arrhythmic pattern was generated. In Figure 2 three examples of reentries are shown: panel A shows a functional reentry in the posterior wall of the left atria. Panels B and C show two anatomical reentries, one in the inferior vena cava and another one in left pulmonary veins, respectively.

Results of simulations are shown in Figure 3 for every combination of model conditions, including or suppressing FD and IH, for the different values of S1 and S2. Black colored cells are the ones that were not simulated, red colored cells are cases where there was no reentry produced, darker green cells represent anatomical reentries, and lighter green cells are functional reentries.

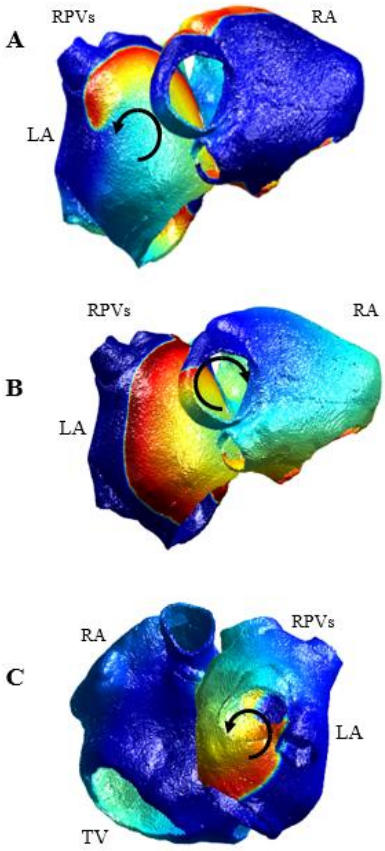

Figure 2.A) Functional reentry with FD and IH and S1=190 and S2=142ms. B) Anatomical reentry with FD and no IH and values of S1=170 and S2=132ms. C) Anatomical reentry without FD nor IH and values of S1=190 and S2=142ms.

The reentries corresponding to a S1 with the value of 150ms were located all in the mitral valve, for all the combinations of FD and IH. In the case of the model that included FD and IH, all anatomical reentries with S1 of 170 and 180ms were located in the inferior vena cava, except the case of S1=180ms and S2=136ms, that was located in the left superior pulmonary vein. Functional reentries with FD and IH were located in the posterior wall of the left atria and in the septum, as it is shown in the panel A of the Figure 3. In the 4 combinations of FD and IH, every anatomic reentry corresponding to a S1 of 150ms was typical *flutter* located in the mitral valve.

When FD was included but IH was not, the reentries that share type with the ones on the table where FD and IH were included, all the cases of S1=170 and 180ms, share the same location. The anatomical reentry of S1=190 and S2=136ms was located on the left superior pulmonary vein. If FD was suppressed but IH was conserved, reentries, that were all anatomical, were surrounding the left pulmonary veins.

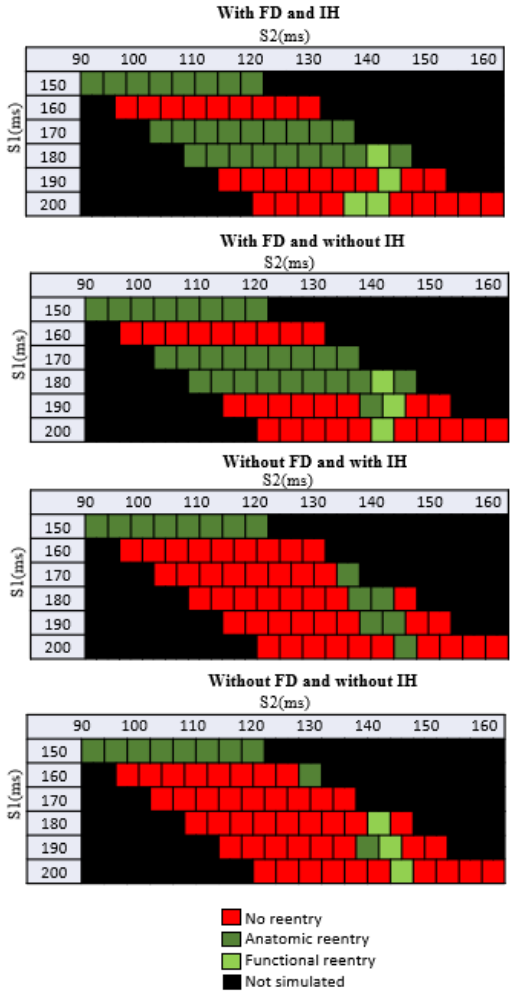

Figure 3. Arrhythmic cases simulated

When both FD and IH were suppressed, anatomical reentries that were not done using S1=150ms were placed in the left superior pulmonary veins, whereas functional reentries were located in the posterior wall and in the septum.

In Table 3 a summary of the results is shown. There were more arrhythmic cases when FD was applied, where 51% of the simulations were arrhythmic in presence or absence of IH. If FD was not included, reentrant cases went down to 24% in presence of IH and to 23% if absence of IH.

Table 3. Simulations results.

	Total arrhythmic cases (%)	Anatomic reentrant cases (%)	Functional reentrant cases (%)
FD/IH	51	44	7
FD/No IH	51	47	4
No FD/IH	24	24	0
No FD/No IH	23	17	5

Considering initiated arrhythmic patterns, the case with both FD and IH was the one with the highest number of fibrillatory patterns, but there was practically no difference in the number of fibrillatory patterns when IH was suppressed. If FD was eliminated but IH was maintained, every reentry was anatomical. Lastly, when no FD nor IH were in the model, only 17% of total cases were anatomical, whereas percentage of fibrillatory patterns was 5%.

4. Conclusion and discussion

In this study the influence of 2 parameters included in realistic biophysical simulations, FD and IH, has been studied. This allowed us to generate arrhythmic patterns similar to the ones observed in clinical practice, such as *flutter* and functional reentries near the pulmonary veins. Under similar pro-arrhythmic conditions, in terms of chronic AF electrical remodeling and S1-S2 stimulation protocols, FD presence caused the percentage of arrhythmic patterns to be higher, 51%, than when this characteristic was not included., when arrhythmic cases do not surpass 25%. On the other hand, the inclusion of IH did not provide a significant difference in the quantity of arrhythmic cases, but it does make a difference in the type of reentry.

As Calvo et al. [7] reported, IH alter the position of functional reentries, attracting them towards pulmonary veins. This can be observed in the case without FD and with IH, where the effect of IH is visible, since there are no functional reentries. Reentries start as functional, but the influence of IH causes their movement towards pulmonary veins, and they end up transforming into anatomical reentries surrounding the pulmonary veins. When there are not FD nor IH, reentries are more static and stay as functional. When FD is applied in conjunction with IH the effect of IH is mitigated since there are functional reentries.

The study presents different limitations that open new fields of research. Firstly, the combinations of S1 and S2 intervals is limited, as well as the number of locations of stimulation. Ionic heterogeneities are unique and based in experimental data that may not represent the heterogeneity present in atrial fibrillation patients. In addition, and according to the role of FD, the anatomical model and the FD is unique and these may differ between patients.

The results presented suggest that FD inclusion eases the maintenance of reentrant behaviors while IH do not show such important role. However, ionic profile presented an important role in rotor attraction, and defining the specific arrhythmic mechanism: anatomical vs functional. Simulating patient-specific anatomies may help in the understanding of individual atrial fibrillation behaviors and their optimal therapies.

Acknowledgments

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5. References

[1] O. Dössel, M. W. Krueger, F. M. Weber, M. Wilhelms and G. Seemann, "Computational modeling of the human atrial anatomy and electrophysiology," *Med Biol Eng Comput,* vol. 50, *(8),* pp. 773-799, 2012.

[2] J. Jalife, M. Delmar, J. Anumonwo, et al, "Basic Cardiac Electrophysiology for the Clinician," 2009.

[3] M. W. Krueger, G. Seemann, K. Rhode, et al, "Personalization of Atrial Anatomy and Electrophysiology as a Basis for Clinical Modeling of Radio-Frequency Ablation of Atrial Fibrillation," *Tmi,* vol. 32, *(1),* pp. 73-84, 2013.

[4] G. Schram, M. Pourrier, P. Melnyk and S. Nattel, "Differential Distribution of Cardiac Ion Channel Expression as a Basis for Regional Specialization in Electrical Function," *Circulation Research,* vol. 90, *(9),* pp. 939-950, 2002

[5] J. R. Ehrlich, T. Cha, L. Zhang et al, "Cellular electrophysiology of canine pulmonary vein cardiomyocytes: action potential and ionic current properties," *The Journal of Physiology,* vol. 551, *(3),* pp. 801-813, 2003

[6] A. Dasí, A. Roy, R. Sachetto, J. Camps et al, "In-silico drug trials for precision medicine in atrial fibrillation: From ionic mechanisms to electrocardiogram-based predictions in structurally-healthy human atria," *Frontiers in Physiology,* vol. 13, pp. 966046, 2022

[7] C. Calvo, M. Deo, S. Zlochiver, et al, "Attraction of Rotors to the Pulmonary Veins in Paroxysmal Atrial Fibrillation: A Modeling Study," *Biophysical Journal,* vol. 106, *(8),* pp. 1811-1821, 2014.

[8] G. Seemann, C. Höper, F. B. Sachse et al, "Heterogeneous three-dimensional anatomical and electrophysiological model of human atria," *Philosophical Transactions of the Royal Society of London. Series A: Mathematical, Physical, and Engineering Sciences,* vol. 364, *(1843),* pp. 1465-1481, 2006

[9] V. M. Garcia-Molla, A. Liberos, A. Vidal, et al, "Adaptive step ODE algorithms for the 3D simulation of electric heart activity with graphics processing units," *Computers in Biology and Medicine,* vol. 44, pp. 15-26, 2014.

[10] J. T. Koivumäki, R. B. Clark, D. Belke et al, "Na+ current expression in human atrial myofibroblasts: identity and functional roles," *Frontiers in Physiology,* vol. 5, pp. 275, 2014.

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