Effect of Fiber Direction and Ionic Heterogeneities in Atrial Driver Location

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Abstract

Digital twins are a tool used to simulate patients with atrial fibrillation (AF). However, the level of detail needed to use this tool clinically is still unknown. This paper evaluates the effect of the inclusion of two important characteristics of atrial substrate like fiber direction (FD) and ionic heterogeneities (IH).

In this work, a bi-atrial 3D anatomical model was used to evaluate the effect of FD and IH, which were defined for each type of tissue. Multiple simulations were launched using variations of two stimulation protocols to generate arrhythmic patterns and measure the number of reentrant cases as well as the behavior of the reentries in presence or absence of FD and IH.

Inclusion of FD had a notorious effect reaching 51% of arrhythmic cases, while in its absence the percentage fell to 24%. IH did not play such an important role considering the number of arrhythmic cases, but its influence was in the type, since the number of potential locations maintaining AF increased with the addition of IH.

Adding FD has a great effect on the arrhythmic behavior of biophysical simulations. Inclusion of IH, despite being less important considering quantity in comparison to FD, has a great influence on the type and region.

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 (AF). 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 in-silico atrial arrhythmic models to faithfully reproduce different-reentrant drivers is still unknown. Fiber direction (FD) and ionic heterogeneities (IH) are two of the characteristics that can be included in the substrate of computational models. FD is a characteristic of cardiac tissue with which electric activity propagates faster in the longitudinal direction of the fiber than in the transversal direction. IH refers to the different ionic channels' densities in the cardiac tissue.

In this study the effect of the inclusion of FD and IH in the electric activity of a cardiac anatomy in chronic atrial fibrillation conditions is analyzed to determine their role in simulations.

2. Materials and Methods

2.1 Anatomical model

Simulations were performed in a specific anatomy taken from Krueger et al. [2] consisting of both right and left atria, where fiber direction of every node is included and regions are differentiated, which are: left and right atria (LA and RA, respectively), pulmonary veins (PV) crista terminalis (CT), pectinate muscles (PM), sinusal node (NS), Bachmann's bundle (BB), cava veins (CV), tricuspid valve (TV), mitral valve (MV), fosa ovalis (FO), cavo-tricuspid isthmus (CTI) and left and right atrial appendages (LAA and RAA), as seen in Figure 1A.

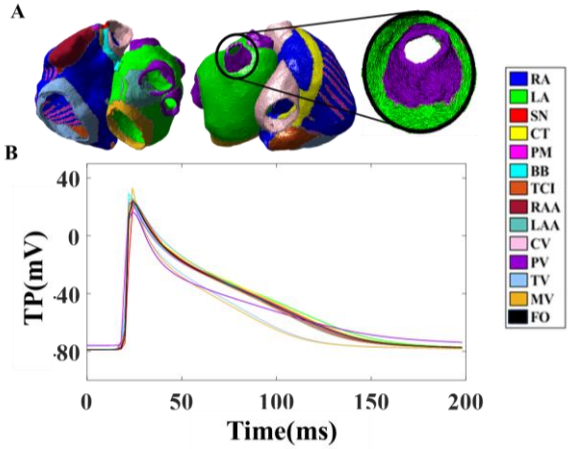

Figure 1. A) Anatomic model with the different tissues. B) Transmembrane potential for each tissue.

Each region was differentiated by the cocient between longitudinal and transversal diffusion, also called anisotropy. IH were introduced changing the values of ionic currents for each type of tissue by applying multiplying factors obtained in the literature [3-5].

2.2 Simulations

The simulations were performed in a self-owned solver [6] that used GPU to solve the monodomain differential equations of Koivumäki's cellular model [7]. To simulate a chronic AF model, electrical remodeling 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 INCX 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 applied.

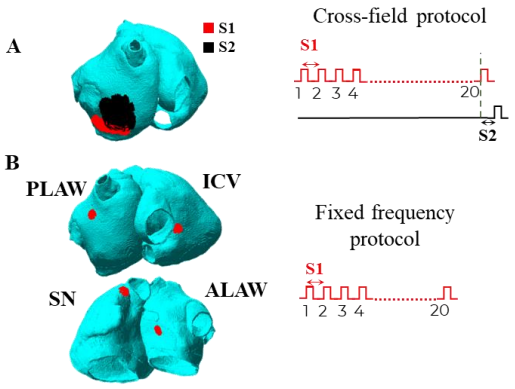

Figure 2. Stimulation zones and sequences of stimuli of A) Cross-field protocol. B) Fixed frequency protocol.

To generate arrhythmic activity, two different protocols were used. First, the cross-field protocol, and second, a fixed frequency protocol (Figure *2*). The cross-field protocol consisted in an S1-S2 type protocol with stimulations in two regions of the posterior left atrial wall (Figure *2*A), where the times between S1 went from 150 to 200ms in 10ms intervals, while S2 time values had values from 60% to 80% of the corresponding S1 in intervals of 4ms. The fixed frequency protocol consisted on 20 pulses distanced a specific value of time (Figure *2*B, 150 to 200 every 10ms). In this case, the stimulation zones were 4 points in the atria of approximately 0.5cm of diameter, resembling a pacing catheter. Two of the points were located in the left atria, one in the anterior wall and another one in the posterior wall, and the other two points were in the right atria, one located in the sinus node and the other in the inferior vena cava. This protocol with the 4 points provided 156 simulations.

Simulations lasted for 8 seconds, where the stimulation protocols were included within. When the 8 seconds finished, the presence of arrhythmic activity was analyzed, as well as the type of it, whether it was anatomical or functional.

2.3 Phase mapping

The position of the reentrant pattern was analyzed with phase mapping, a tool that allows the identification of phase singularities in the anatomy. This method was used to evaluate phase maps obtained with Hilbert transform, in which phase singularities were identified as points surrounded by linearly-increasing phases from $-\pi$ to π, lasting at least one full rotation [8]. This was applied on a low-resolution model (4000 nodes, 2.4 ±0.4mm inter-node distance). Anatomical reentries were identified as simulations whose phase singularities were clustered at anatomical obstacles (veins, valves), and, otherwise, they were classified as functional reentries. When inconclusive phase maps appeared, the simulations were visualized through action potential (AP) propagation movies to determine the type of reentry.

3. Results

Presence or absence of FD and IH in simulations produced a different behavior in the reentrant activity. In the Figure 3 different examples are shown of the variations that have been produced using the cross-field protocol, with different time steps to see the movement of the firstly generated functional reentry. In the A panel the movement of a functional reentry in the posterior left atrial wall can be seen. Despite a slight movement, it remains as functional. On the other hand, in B and C panels two cases are presented where the reentrant activity starts as functional but due to the rotor movement towards an anatomical obstacle, it ends as anatomical. In the case of B panel only FD was included in the model, and the rotor's movement follows the FD of the tissue towards the right pulmonary veins, turning into an anatomical reentry. Lastly, in the C panel, the simulated cardiac model only included IH in the substrate. In this case the rotor drifts attracted by the heterogeneities of the pulmonary veins and goes from a functional reentry to an anatomical one in the left pulmonary veins.

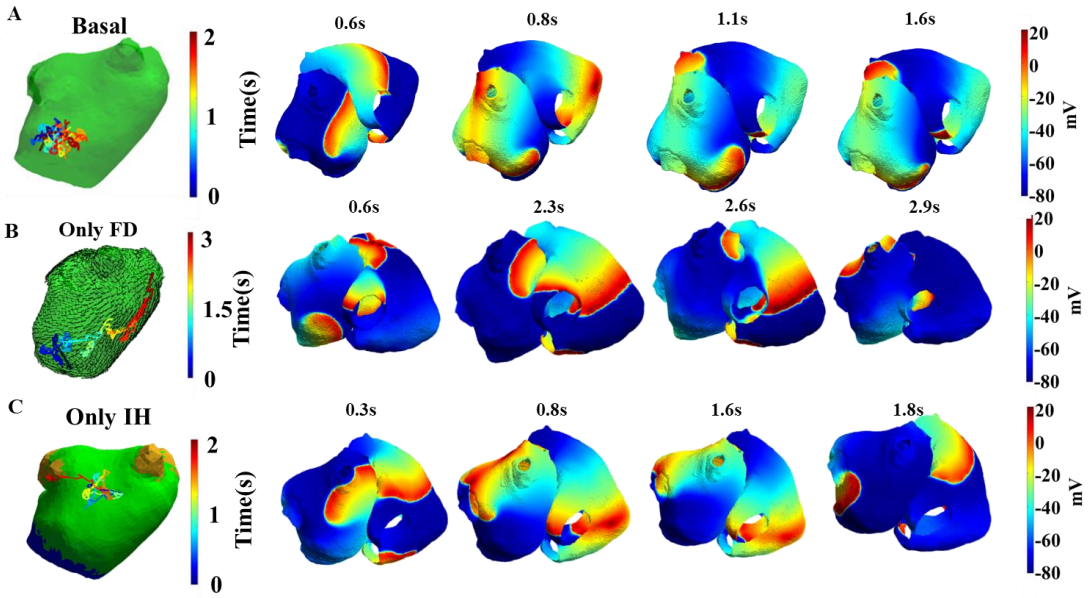

Figure 3. Examples of reentry drift for the cross-field protocol. A) Stable functional reentry in absence of ionic heterogeneities and fiber direction. B) Functional reentry that turns into anatomical at RPV in presence of fiber direction. C) Functional reentry that turns into anatomical at RPV in presence of fiber direction. C) Functional reentry that turns into anatomical at LPVs in presence of ionic heterogeneities. Left: anatomical model of LA (green: LA wall; blue: mitral valve; yellow: pulmonary veins; arrows: fiber direction) with the phase singularity meandering tracked in colors. Right: Transmembrane potential at 4 different instants of each simulation.

In Figure *4* bar charts with a summary of the analyzed cases are shown, with the percentage of caused arrhythmic patterns differentiated by their type for both stimulation protocols. In the A panel the reentrant cases for all four possible combinations of FD and IH are shown, as well as the type of reentry of them, for the cross-field protocol. When FD was included, the percentage of reentrant cases went up to 50% compared to the 20% when not included. Regarding IH, there is no difference practically in terms of quantity of reentries. Considering the type of the arrhythmia, presence of IH alongside FD does not cause a strong variation in the type of reentry either (7% vs 5% of functional reentries). If FD is not present, the inclusion of only IH involves no functional reentries (0 vs 5%). In the B panel, showing the fixed frequency protocol results, presence of FD has a higher percentage of arrhythmic cases than when it is absent, going to 40% vs 15% respectively, independently of the stimulation site. IH has no influence in the number of reentries, happening the same phenomenon as in the cross-field protocol. Considering their type, FD has a higher impact than IH, since the functional cases observed are 2/0% when FD is included and 7/5% when it is not.

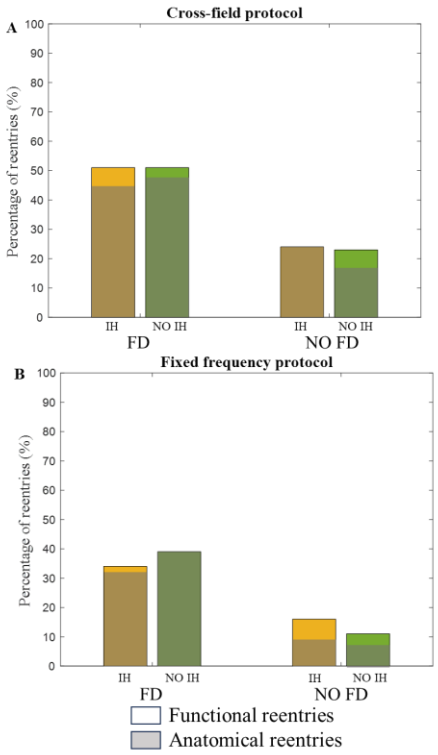

Figure 4. Bar charts with percentage of arrhythmic cases differentiated between functional and anatomical as results of A). Cross-field protocol. B) Fixed frequency protocol.

Locations of the different arrhythmic mechanisms are shown in Table *1*. The various places of possible reentries were mitral valve (MV), left and right pulmonary veins (LPV, RPV), inferior cava (IC), atrial septum (AS) or posterior left atrial wall (PALW), being the two latter ones locations of functional reentries and the rest locations of anatomical reentries. Inclusion of IH alone reduced the potential driving regions (2 regions), while inclusion of FD increases this number to 4-5.

Table 1. Locations of the drivers for the different cases.

	Driver sites
Basal	MV. LPV, AS, PLA
Only IH	MV, LPV
Only FD	MV, IC, LPV, RPV, PLA
FD+IH	MV, IC, AS, PLA

4. Conclusion and discussion

In this study, 404 simulations were performed where the influence of FD and IH on arrhythmic activity in biophysical simulations has been seen. The inclusion of FD shows an increase in the number of arrhythmic cases compared to when it is absent for both protocols, being the percentage of reentrant cases of 51% with FD against a 23-24% when FD is not included for the cross-field protocol, and a 35% against a 15% for the fixed frequency protocol. On the other hand, IH do not have such a notorious effect in the number of reentries since the percentages do not change with their inclusion in the simulations, but they do have a stronger effect in the type of reentries.

IH have an attractive effect of reentries towards pulmonary veins, as mentioned by Calvo et al.[5]. This effect is very notorious when, in the cross-field protocol, IH is the only modification in the model since there are not functional reentries. As it is shown in B panel of Figure *3*, the reentry begins as functional, but due to the attractive effect of IH it drifts towards the left pulmonary veins. This effect is mitigated when FD is also included in the model since functional reentries can be found when FD and IH are simultaneously included on the model.

For the fixed frequency protocol, the addition of FD not only generates more reentries, but also nearly the totality of them are anatomical, when, if FD is not present in the model the proportion between anatomical and functional reentries is similar. With these results, the inclusion of both characteristics proves to be important, whether it is for the number of reentries or for their type.

The limitations of this work are, the use of just one anatomy and the stimulation from a limited number of atrial zones, and, for future work, we address stimulating from different atrial zones with patient-specific anatomies.

Acknowledgments

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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] M. W. Krueger, G. Seemann, K. Rhode, D. U. J. Keller, C. Schilling, A. Arujuna, J. Gill, M. D. O'Neill, R. Razavi and O. Dossel, "Personalization of atrial anatomy and electrophysiology as a basis for clinical modeling of radio-frequency ablation of atrial aibrillation," *Tmi*, vol. 32, *(1)*, pp. 73–84, 2013..

[3] 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.

[4] A. Dasí, A. Roy, R. Sachetto, J. Camps, A. Bueno-Orovio and B. Rodriguez, "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.

[5] C. Calvo, M. Deo, S. Zlochiver, J. Millet and O. Berenfeld, "Attraction of rotors to the pulmonary veins in paroxysmal atrial fibrillation: A modeling study," *Biophysical Journal*, vol. 106, *(8)*, pp. 1811–1821, 2014.

[6] V. M. Garcia-Molla 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, 2014. 10.1016/j.compbiomed.2013.10.02

[7] J. T. Koivumäki, R. B. Clark, D. Belke, C. Kondo, P. W. M. Fedak, M. M. C. Maleckar and W. R. Giles, "Na+ current expression in human atrial myofibroblasts: identity and functional roles," *Frontiers in Physiology*, vol. 5, pp. 275, 2014.

[8] M. Rodrigo et al. "Technical considerations on phase mapping for identification of atrial reentrant activity in direct- and inverse-computed electrograms".2017. Circulation, Arrhythmia and Electrophysiology. doi: 10.1161/circep.117.005008

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