Innovative Training Networks (ITN)
Call: H2020-MSCA-ITN-2017

MultidisciplinarY training network for ATrial fibRillation monItoring, treAtment and progression

Project Nº: 766082

Start date of the project: 01/11/2017

Duration: 48 months

Project Coordinator: Luca Mainardi

Deliverable D4.4

D4.4: Submission of PhD thesis draft/proposal

Submission date: 31/03/2022

This project has received funding from the European Union's Horizon 2020 research and Innovation programme under the Marie Skłodowska-Curie grant agreement No 766082.

Document Properties

Document ID	D4.4
Document Title	Submission of PhD thesis draft/proposal
Deliverable Nº	D17
Editors	Valentina Corino, Luca Mainardi
Contributors	All
Lead Beneficiary	POLIMI
Work Package Nº	3
Work Package Title	Treatment
Nature	Report
Dissemination Level	Public
Number of pages	18
Due Date (in months)	53
Submission date	31/03/2022

Distribution List

Organization	Name of recipients
POLIMI	Luca Mainardi, Josè Felix Rodriguez Matas, Valentina Corino
UMIL	Roberto Sassi
LU	Leif Sörnmo
UNIZAR	Pablo Laguna
UPV	Javier Saiz
KIT	Olaf Doessel
MEDTRONIC BRC	Mirko De Melis
MIE	Johan De Bie, Nicoletta Marzocchi
GRAD	Helena Fernandez
EMP	Francesco Onorati
KH	Claus Schmitt
HIC	Damian Sanchez-Quintana
SKANE	Pyotr Platonov
OMP	Federico Lombardi
ESR Representatives	Guadalupe Garcia Isla, Giorgio Luongo

Revision History

Rev. No.	Date of Issue	Author(s)	Brief Description of Change
0.8	18.03.2022	Valentina Corino	First draft
0.9	21.03.2022	Valentina Corino, Luca Mainardi	Second draft
1.0	30.03.2022	Valentina Corino, Luca Mainardi, All	Final draft

Table of contents

1. Summary

This document describes the status of PhD researcher of the ESRs belonging to WP4 and describes the status of their PhD thesis.

2. PhD status

Table 1 summarizes the PhD status of each ESR: starting date, current status and defense date.

	Starting date	Thesis status	Defense date
ESR10	01-07-2018	Defended	21-12-2021
ESR11	01-09-2018	Ongoing	September 2022*
ESR12	01-09-2018	Ongoing	September 2022*

* expected date

3. ESR10: Integrated and personalized computational model of atria with AF for an efficient ablation therapy

ESR10: Luca Azzolin

Motivation and aim

The incidence and prevalence of atrial fibrillation (AF) in particular is today reaching pandemic proportions. AF is the most common sustained disorder of cardiac rhythm that is estimated to affect 1.5%-2% of the general population with a prevalence that increases with age. AF is an abnormal heart rhythm characterized by rapid and irregular beating of the atria. A deeper understanding of the complex functioning of the heart can be achieved by developing computational models. The integration of computational modelling in the clinics requires a high degree of personalization, representing the patient anatomy and electrophysiology, to guide clinicians in the procedures. In this work, highly detailed computer models were leveraged to uncover the hidden AF mechanisms of initiation and maintenance and tailored virtual hearts were used to foresee the optimal treatment for a specific patient. Novel methods were developed to incorporate experimental and clinical data into models to analyze, characterize and treat AF using in-silico experiments. The full predictive potential of computational modelling was exploited to make a step forward into personalized medicine.

Methods

During my time enrolled as Early Stage Researcher in the MY-ATRIA program several studies has been addressed. At first, cardiac computational modelling was leveraged to get a better understanding of the mechanisms behind atrial fibrillation (AF) onset and perpetuation. Finally, a comprehensive platform to automatically generate personalized atrial models of patients with AF integrating multiple clinical data, assess AF vulnerability, identify ablation targets and perform virtual ablation was developed and provided. The underlying algorithms, along with the respective results achieved using them, were systematically evaluated and compared to state-of-the-art methods. In the first presented study, we quantitatively evaluated different methods to induce arrhythmia in-silico, evaluated their influence of both initiation and perpetuation of AF episodes and finally provided an fast and easily reproducible method to standardize AF vulnerability assessment of atrial models[1]. All protocols used in this study are available open source to enhance comparability, reproducibility and foster the adoption of our novel proposed method as community standard. The results obtained from the comparison with the other methods showed that our parameter-free method induced different degrees of arrhythmic complexity, unveiled more areas vulnerable to maintain AF with a lower

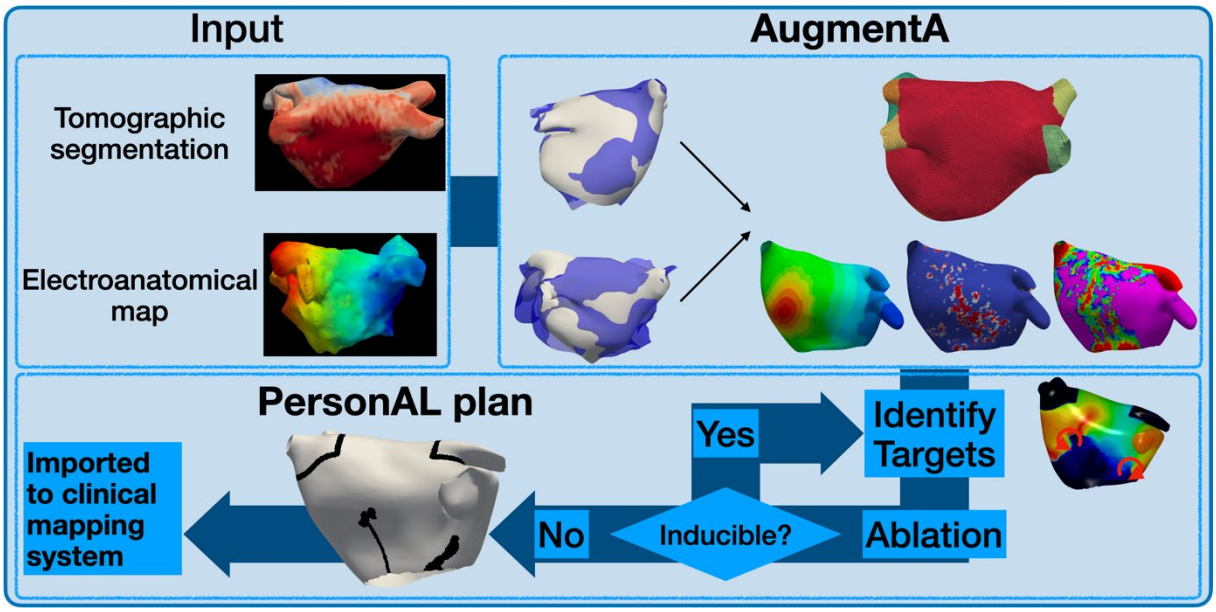
number of stimuli, being therefore computationally inexpensive. Therefore, our study highlighted and confirmed the impact of the choice of the inducing protocol on AF onset and perpetuation. Considering the findings of the previous study, the influence of heterogeneity in atrial anatomical thickness on initiation and maintenance of AF was investigated[2]. Arrhythmic episodes were initiated on atrial models with different degrees of augmented heterogeneous anatomical thickness. Long-living re-entrant drivers (RDs) were detected and tracked over time to analyze AF dynamics. Our work showed that RDs steer towards borders between regions with various thickness and are maintained in the proximity of steep rims. In addition, higher thickness heterogeneity increased arrhythmia complexity and unveiled new vulnerable areas prone to AF initiation and perpetuation. Therefore, we concluded that gradient and smoothing of anatomical thickness had an influence on both AF inducibility and maintenance, mostly in the right atrium (RA). Finally, we proposed wall thickness gradient and curvature as complementary a priori measures to investigate substrate arrhythmogenicity and suggest areas to target for ablation. Considering the insights got in the previous studies, the final study leveraging atrial digital twins for AF vulnerability assessment and personalized ablation was conducted. An automated algorithm fitting a bi-atrial statistical shape model (SSM)[3,4] to atrial geometries derived from clinical data augmenting missing anatomical structures was implemented[5]. Fiber arrangement and anatomical regions annotation were automatically integrated in the models. The framework was tested on both a geometry coming from an electroanatomical map and a magnetic resonance imaging segmentation. The resulting SSM instances represented very well the original atrial anatomies and were able to infer the shape of the RA when using information from the left atrium (LA) only. Finally, a unique pipeline to generate anatomical and functional digital twins from either tomographic imaging or electroanatomical maps was developed and tested on a cohort of 29 patients[6]. The platform pre-process geometries derived from clinical data and an anatomically personalized atrial model including region annotation and fiber orientation is delivered. Then electrophysiological parametrization is performed to minimize the difference between the simulated and the clinical local activation time map. A comprehensive comparison with state-of-the-art methods is presented. Our pipeline provided ready-to-use personalized computer models derived from clinical data outperforming other methods in representing the depolarization wave propagation in the myocardium. The presented platform is currently under patenting process. The unique level of personalization achieved with this work gave us the chance of addressing the urgent need of a tool to help clinicians to tailor ablation strategies in patient with persistent AF[7]. A technology to assess AF vulnerability and propose personalized ablation lines (PersonAL) on patient-specific atrial models was therefore developed. Along with our tailored ablation plan, different standard-in-practice ablation strategies were tested and the ablation success, defined as AF termination or conversion to atrial tachycardia (AT), was evaluated. The pipeline was applied to 29 LA anatomical and functional digital

twins generate with our previous work[6]. The optimal ablation targets are established using multiple information from non-invasive and intracardiac mapping systems to discriminate arrhythmogenic sites. AF episodes are initiated with our novel proposed inducing protocol[1], and RDs are automatically identified and targeted for ablation. The process of arrhythmia vulnerability assessment and identification and ablation of emerging RDs is iterated until the models are AF non-inducible. The first application of the PersonAL strategy had a success of over 98%, better than all other tested anatomical and substrate approaches. However, with a clear characterization of the arrhythmogenic substrate and techniques aiming to isolate these AF-perpetuating areas led to high success (89-90%). Nonetheless, the amount of inactive tissue after ablation strategies targeting arrhythmogenic substrate was more than 20%, compared to only 5-6% using the PersonAL plan. In addition, no further AF episode could be induced after a second iteration of the PersonAL strategy. The possibility of importing the PersonAL plan onto the original mapping system integrating ablation lines predicted by a computer model into the clinical workflow proved the clinical feasibility of our technology.

Main findings

The general aim of my research was to standardize and guide AF assessment and therapy planning helping clinicians leveraging computer simulations for an improved patient outcome. In this PhD, novel mathematical tools were implemented and the predictive power computational models was exploited to better understand AF onset and perpetuation mechanisms, leading to relevant insights in the human atrial patho-physiology. The studies presented promote new state-of-the-art in digital twins for healthcare and in personalized medicine.

Novel technologies to process and augment clinical data, to merge multi-datasets, to reproducibly compute and automatically integrate fiber orientation, to evaluate AF vulnerability, to build patient-specific virtual hearts, to identify AF drivers, to propose the optimal tailored ablation strategy and predict patient outcome, to import the final ablation plan in the original mapping system. Summarizing, our studies lay the foundations for a better cardiac arrhythmia management and treatment guided by personalized computational models. Thus, the individual patient's discomfort, the ablation procedural time, the recurrence rate of AF, and finally the socio-economic burden of AF might be alleviated. We are confident that the synergistic work between academics, clinicians and engineers will eventually improve patient's care standardizing personalized therapies.



Workflow to guide tailored ablation strategies in patients with atrial fibrillation.

References

[1] Azzolin L, Schuler S, Dössel O, Loewe A. A Reproducible Protocol to Assess Arrhythmia Vulnerability : Pacing at the End of the Effective Refractory Period. Frontiers in Physiology 2021;12:656411. https://doi.org/10.3389/fphys.2021.656411.

[2] Azzolin L, Luongo G, Rocher S, Saiz J, Doessel O, Loewe A. Influence of Gradient and Smoothness of Atrial Wall Thickness on Initiation and Maintenance of Atrial Fibrillation. Computing in Cardiology Conference (CinC), 2020. https://doi.org/10.22489/CinC.2020.261.

[3] Nagel C, Schuler S, Dössel O, Loewe A. A bi-atrial statistical shape model for large-scale in silico studies of human atria: Model development and application to ECG simulations. Medical Image Analysis 2021;74:102210. https://doi.org/10.1016/j.media.2021.102210.

[4] Nagel C, Luongo G, Azzolin L, Schuler S, Dössel O, Loewe A. Non-Invasive and Quantitative Estimation of Left Atrial Fibrosis Based on P Waves of the 12-Lead ECG-A Large-Scale Computational Study Covering Anatomical Variability. Journal of Clinical Medicine 2021;10. https://doi.org/10.3390/jcm10081797.

[5] Azzolin L, Nagel C, Nairn D, Sanchez J, Zheng T, Eichenlaub M, et al. Automated Framework for the Augmentation of Missing Anatomical Structures and Generation of Personalized Atrial Models from Clinical Data. Computing in Cardiology Conference (CinC), 2021.

[6] Azzolin L, Eichenlaub M, Nagel C, Nairn D, Sánchez J, Unger L, et al. AugmentA: Patient-specific Augmented Atrial model Generation Tool. Medrxiv 2022. https://doi.org/10.1101/2022.02.13.22270835.

[7] Azzolin L, Eichenlaub M, Nagel C, Nairn D, Sanchez J, Unger LA, et al. Atrial digital twins to assess arrhythmia vulnerability and guide personalized ablation strategies for atrial fibrillation. In Proceedings 2021.

4. ESR11: Assessment of AF therapies targeting ion channels and neural components

ESR11: Chiara Celotto

Motivation and aim

The autonomic nervous system (ANS) has been increasingly linked to the onset and perpetuation of atrial fibrillation (AF) [1, 2, 3]. The cardiac ANS can be divided into its extrinsic and intrinsic components, with the latter being organized in an epicardial neural network of interconnecting axons and clusters of autonomic ganglia known as ganglionated plexi (GPs) [4, 5]. Although atrial GPs comprise both sympathetic and parasympathetic fibers, predominance of parasympathetic innervation has been shown.

Both branches of the ANS are known to be involved in the onset of AF, with strong evidence on hyperactivity of the parasympathetic branch being associated with the development of paroxysmal AF (pxAF) [6]. Cholinergic stimulation, through its neurotransmitter acetylcholine (ACh), activates the ACh-activated potassium current, which causes concentration-dependent shortening of the action potential (AP) duration (APD) and hyperpolarization of the resting membrane potential. These effects, in turn, lead to shortening of the wavelength of reentry (WL) and increase the vulnerability to atrial arrhythmias.

Despite the high incidence of AF, there is still a significant unmet clinical need for more effective and safer antiarrhythmic therapies that overcome the limited efficacy and side effects of present treatments. Class III antiarrhythmic drugs bind to and inhibit the potassium channels controlling AP repolarization, causing an increase in APD and hence a lengthening of the WL. To minimize potentially hazardous side effects at the ventricular level, potassium currents that are primarily expressed in the atria are being examined as prospective targets for AF therapy. In this regard, recent research has demonstrated that blocking small-conductance calcium-activated potassium (SK) channels by pharmacological compounds may compensate for cholinergic effects in the atria [7].

In another line of research, some studies have investigated the nonlinear interaction between vagal and sympathetic neural pathways modulating atrial electrical activity. In Sousunov et al. [8], low β-adrenergic stimulation was found to considerably antagonize ACh-induced APD shortening, thus acting as a ``brake'' to limit the effects caused by cholinergic stimulation on atrial AP. Isoproterenol (Iso) is a non-specific β-adrenergic agonist, which modulates repolarization by facilitating calcium release from the sarcoplasmic reticulum and increasing the delayed rectifier potassium current [9]. Based on the tight relationship between ANS and AF,

some studies have shown that targeting GPs with catheter ablation in addition to pulmonary vein isolation improves the outcomes of pxAF ablation [10, 11, 12]. This requires accurate location of GPs for ablation to be effective, which deserves further investigation.

In this study, the individual and combined effects of SK channel block (SKb) and β-adrenergic stimulation by Iso to counteract ACh-induced deleterious effects on human atrial electrophysiology were analyzed [13, 14, 15].

In a second research line, the feasibility to locate parasympathetic innervation regions in human atria directly from electrograms (EGMs) to aid cardioneuroablation procedures [16] was investigated. In both lines of research, *in silico* modeling and simulation were used to aid in the understanding of the mechanisms underlying the action of antiarrhythmic therapies targeting ion channels and neural components and to advance in their potential clinical use.

Methods

To simulate atrial electrophysiology and assess model independence of the obtained results, different atrial AP models were used, namely those developed by Courtemanche et al. [17], Grandi et al. [18] and Skibsbye et al. [19]. In all these models, ANS modulation descriptions in terms of cholinergic stimulation by ACh and β-adrenergic stimulation by Iso were introduced, if these were not available. Additionally, a formulation of the I_{SK} current was introduced in the Grandi and Courtemanche models. Persistent AF (psAF) variants of the models were implemented in all cases. The constructed cellular models were used as a basis to conduct single cell simulations as well as bidimensional tissue simulations by solving the monodomain model using the finite element method [20, 21].

The effects of application of Iso and/or SKb were assessed both transiently and at steady state. In the transient state, the ability of the two simulated therapies to terminate a stable rotor in a cholinergic AF model was evaluated. After generating the rotors, doses of up to 1 μM Iso and/or full SKb were progressively applied following pharmacokinetics representative of a range of drug association rates. At steady state, results were evaluated in terms of the induced prolongation of APD at 90% repolarization with respect to APD measured under ACh. Homogeneous and heterogeneous ACh spatial tissue distributions were considered. ACh concentrations spanning from 0 to 0.1 μM were examined.

In the study on GP ablation, cholinergic release sites were modeled as circular ACh patches. Different distributions and sizes of these ACh patches as well as various fibrotic patterns accounting for either uniform diffuse or non-uniform diffuse fibrosis in the atrial tissue were investigated. The Courtemanche model was used to simulate cellular electrophysiology. Tissue models representative of non-AF, pxAF and psAF were built. In this case, only planar

wavefronts representing electrical propagation under sinus rhythm were simulated. Unipolar EGMs were computed in a 16 x 16 electrode mesh with an inter-electrode spacing of 2 mm. Different distances of the electrodes to the tissue (0.5, 1 and 2 mm) and addition of noise levels with SNR values of 0, 5, 10, 15 and 20 dB were tested.

Main findings

It was found that cholinergic stimulation by ACh hyperpolarized the resting membrane potential and shortened the APD, with dose-dependant effects. At the cellular level, I_{SK} inhibition was able to antagonize parasympathetic effects induced by physiological ACh doses. 1 µM Iso had a variable response, with shortening or prolongation of the APD depending on the AP morphology, in agreement with experimental results [8, 9]. The combination of SKb and Iso largely restored to basal levels the APD shortening induced by ACh for most AP shapes represented by the different cell models. At the tissue level, the combination of SKb and Iso notably reversed ACh-mediated APD shortening at steady state, thus increasing the WL for reentry and consequently reducing vulnerability to AF [14].

When evaluating the ability of SKb and Iso to terminate a stable rotor, it was found that the combination of the two as well as Iso alone terminated the rotors under all tested ACh concentrations. Individual application of SKb stopped the rotor only for the lowest tested ACh concentration (0.01 µM). Different handling dynamics of Iso and SKb had no impact on rotor termination, only delaying the termination time [15].

Regarding GP location, a novel method to identify parasympathetically-stimulated regions based on EGM analysis was developed[16]. The amplitude of the atrial EGM repolarization wave was found to be representative of the presence or absence of ACh release sites, with larger positive amplitudes indicating that the electrode was positioned over a region with high ACh level. The optimal thresholds for detecting ACh release sites were determined using statistical analysis. The repolarization amplitude allowed for successful identification of ACh sites in all non-AF, PxAF and PsAF tissues, with minimum and mean accuracy of 0.8 and 0.91, respectively. The algorithm performed better in the absence of fibrosis or when fibrosis was uniformly diffuse, with a mean accuracy of 0.94 in contrast with a mean accuracy of 0.89 for non-uniform diffuse fibrotic cases. The algorithm was robust against noise and performed successfully for all the tested ranges of electrode-to-tissue distances.

References

[1] Chen J, Wasmund SL, Hamdan MH. Back to the Future: The Role of the Autonomic Nervous System in Atrial Fibrillation. Pacing and Clinical Electrophysiology, 29(4):413–421, April 2006.
[2] Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the Autonomic Nervous System in

Atrial Fibrillation. Circulation Research 2014; 114(9):1500–1515.
[3] Ching-Tai Tai. Role of Autonomic Influences in the Initiation and Perpetuation of Focal Atrial Fibrillation. Journal of Cardiovascular Electrophysiology 20001; 12(3):292–293.
[4] Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, Distribution, and Variability of the Epicardiac Neural Ganglionated Subplexuses in the Human Heart. The Anatomical Record 2000; 259(4):353–382.
[5] Stavrakis S, Po S. Ganglionated Plexi Ablation: Physiology and Clinical Applications. Arrhythmia & Electrophysiology Review 2017; 6(4):186.
[6] Iso K, Okumura Y, Watanabe I, Nagashima K, Takahashi K, Arai M, Watanabe R, Wakmatsu Y, Otsuka N, Yagyu S, Kurokawa S, Nakai T, Ohkubo K, Hirayama A. Is Vagal Response During Left Atrial Ganglionated Plexi Stimulation a Normal Phenomenon? Circulation: Arrhythmia and Electrophysiology 2019; 12(10):e007281.
[7] Skibsbye L, Poulet C, Diness JD, Bentzen BH, Yuan L, Kappert U, Matschke K, Wettwer E, Ravens U, Grunnet M, Christ T, Jespersen T. Small-Conductance Calcium-Activated Potassium (SK) Channels Contribute to Action Potential Repolarization in Human Atria. Cardiovascular Research 2014; 103(1):156–167.
[8] Sosunov EA, Anyukhovsky EP, Rosen MR. Adrenergic-Cholinergic Interaction that Modulates Repolarization in the Atrium is Altered with Aging. Journal of Cardiovascular Electrophysiology 2002; 13(4):374–379.
[9] González-de la Fuente M, Barana A, Gómez R, Amorós I, Dolz-Gaitón P, Sacristán S, Atienza F, Pita A, Pinto Á, Fernández-Avilés F, Caballero R, Tamargo J, Delpón E. Chronic Atrial Fibrillation Up-Regulates 1-Adrenoceptors Affecting Repolarizing Currents and Action Potential Duration. Cardiovascular Research 2013; 97(2):379–388.
[10] Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortoriello V, Landoni G, Zangrillo A, Lang C, Tomita T, Mesas C, Mastella E, Alfieri O. Pulmonary Vein Denervation Enhances Long-Term Benefit After Circumferential Ablation for Paroxysmal Atrial Fibrillation. Circulation 2004; 109(3):327–334.
[11] Pokushalov E, Romanov A, Shugayev P, Artyomenko S, Shirokova N, Turov A, Katritsis DG. Selective Ganglionated Plexi Ablation for Paroxysmal Atrial Fibrillation. Heart Rhythm 2009; 6(9):1257–1264.
[12] Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid Pulmonary Vein Isolation Combined with Autonomic Ganglia Modification: A Randomized Study. Heart Rhythm 2011; 8(5):672–678.
[13] Celotto C, Sanchez C, Laguna P, Pueyo E. Calcium-Activated Potassium Channel Inhibition in Autonomically Stimulated Human Atrial Myocytes. In 2019 Computing in Cardiology (CinC) (Singapore: IEEE), Vol. 46, pp. 1–4.
[14] Celotto C, Sanchez C, Mountris KA, Laguna P, Pueyo E. SK Channel Block and Adrenergic Stimulation Counteract Acetylcholine-Induced Arrhythmogenic Effects in Human Atria. In 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) (Montreal, QC, Canada: IEEE), 2303–2306.
[15] Celotto C, Sanchez C, Mountris KA, Laguna P, Pueyo E. Rotor Termination in Cholinergic Paroxysmal Atrial Fibrillation by Small-Conductance Calcium-Activated K+ Channels Inhibition and Isoproterenol: a Computational Study. In 2021 Computing in Cardiology (CinC) (Brno: IEEE). Vol. 48, pp 1–4.
[16] Celotto C, Sánchez C, Mountris KA, Laguna L, Pueyo E. Location of Parasympathetic Innervation Regions From Electrograms to Guide Atrial Fibrillation Ablation Therapy: An in silico Modeling Study. Frontiers in Physiology 2021; 12:1020.
[17] Courtemanche M, Ramirez RJ, Nattel S. Ionic Mechanisms Underlying Human Atrial Action Potential Properties: Insights from a Mathematical Model. American Journal of Physiology-Heart and Circulatory Physiology 1998; 275(1):H301–H321.
[18] Grandi E, Pandit SV, Voigt N, Workman AJ, Dobrev D, Jalife J, Bers DM. Human Atrial Action Potential and Ca2+ Model: Sinus Rhythm and Chronic Atrial Fibrillation. Circulation

Research 2011; 109(9):1055–1066.
[19] Skibsbye L, Jespersen T, Christ T, Maleckar MM, van den Brink J, Tavi P, Koivumaki JT. Refractoriness in Human Atria: Time and Voltage Dependence of Sodium Channel Availability. Journal of Molecular and Cellular Cardiology 2016; 101:26–34.
[20] Mountris KA, Pueyo E. The Radial Point Interpolation Mixed Collocation Method for the Solution of Transient Diffusion Problems. Engineering Analysis with Boundary Elements 2020; 121:207–216.
[21] Mountris KA, Pueyo E. A Dual Adaptive Explicit Time Integration Algorithm for Efficiently Solving the Cardiac Monodomain Equation. International Journal for Numerical Methods in Biomedical Engineering 2021; page e3461.
[22] Po SS, Nakagawa H, Jackman WM. Localization of Left Atrial Ganglionated Plexi in Patients with Atrial Fibrillation. Journal of Cardiovascular Electrophysiology 2009; 20(10):1186–1189.

5. ESR12: Characterization of Propagation Patterns and Atrial Substrate with Novel Electrograms-Based Approaches in Multi-Electrode Arrays

ESR12: Jennifer Riccio

Motivation and aim

This project aims to improve characterization of atrial fibrillation (AF) dynamics for guiding catheter ablation and predicting its efficacy in terminating AF. It is based on the hypothesis that morphological characteristics of intracardiac electrograms (EGMs) can be used to identify ablation targets. The specifically addressed problems are 1) the identification of features from simultaneous multi-site EGMs, whose mapping can be used to guide ablation interventions and 2) the assessment of the ability of the proposed feature maps to characterize voltage, conduction velocity and fibrotic tissue. In clinical settings, unipolar and bipolar EGMs (u-EGMs and b-EGMs, respectively) are used to estimate atrial propagation and substrate parameters, which are then mapped by electroanatomic mapping (EAM) systems to identify the locations that may be responsible for the erratic propagation. However, u-EGMs are sensitive to far-field signal components and b-EGMs depend on catheter-to-wavefront orientation. Atrial substrate is typically characterized by mapping the peak-to-peak amplitude of b-EGMs. A widely-used criterion is to identify those areas with voltage lower than 0.5 mV as fibrotic, representing a potential substrate for AF maintenance and, consequently, a target for ablation. Nevertheless, b-EGMs amplitude is affected by the aforementioned catheter-to-wavefront orientation, inter-electrode distance and tissue-electrode contact. In order to try to alleviate these problems affecting AF characterization, we proposed substrate [1,2] and propagation [1,3] mapping strategies based on modifications of the omnipolar EGM (MOP-EGM) method introduced in [4], which partially overcomes orientation-dependent limitations, estimating the electric field (E-field) from the b-EGMs locally recorded at each electrode clique under the assumption of plane and homogeneous propagation within it. Atrial fibrosis detection by using a threshold on b-EGM amplitude also ignores the spatiotemporal information held in the signal morphology. Another contribution of this project is the proposal of the dominant-to-remaining eigenvalue dominance ratio (EIGDR) of the u-EGMs in cliques as a measure of the waveform spatial dispersion, assessing its ability to detect atrial fibrosis [5].

Methods

Both MOP-EGM and EIGDR methods were validated in a 2D tissue simulated with Universitat Politècnica de València (UPV). The tissue included a circular patch of diffuse fibrosis and a high-density multi-electrode array, rotated by an angle Ψ = {0°, 30°, 45°} with respect to the tissue fiber direction. Simulated u-EGMs and b-EGMs were corrupted by real patient recordings noise (Hospital Santa Marta, Lisbon), repeating both procedures for different noise levels. As was extensively discussed in [1], the E-field loop $\boldsymbol{E}(t)$ estimated by the omnipolar EGM (OP-EGM) method with the least squares, was derived after a time-alignment of b-EGMs within each clique, to compensate for the delay between its components, which would produce a 2D loop not reflecting propagation direction well. Moreover, our MOP-EGM approach introduced more robust estimates for the local propagation direction and conduction velocity (CV) within the clique if compared to the original proposals in [4]. Finally, we defined omnipolar EGMs by projecting $\boldsymbol{E}(t)$ along specific directions. Mapping strategies computed from the omnipolar estimates were compared against amplitude maps of b-EGMs in detecting fibrosis. Voltage measurements were assessed in reproducing an ideal reference map based on u-EGMs, as well.

In this project, we also proposed the EIGDR of the u-EGM signals within a clique to characterize the atrial substrate, hypothesizing that it would be correlated with the presence of fibrosis [5]. Two EIGDR values were proposed in [5] considering (R^A) or not considering (R) previous u-EGMs time alignment. The increased spatial dispersion in fibrosis suggested the use of these two measures and its ratio ΔR^A, which represents the gain in eigenvalues concentration produced by the alignment, as fibrosis markers. Their performance was evaluated in discriminating between fibrotic and non-fibrotic tissue in simulation scenarios (UPV) including variable electrode-tissue distance. The EIGDR strategy was also tested over intracavitary u-EGMs recorded at Hospital Clínic, Barcelona. Different mapping points were selected at fibrotic and non-fibrotic areas detected by magnetic resonance images co-registered with the EAM data and used as gold standard for fibrosis visualization. EIGDR-based metrics were compared against bipolar voltage maps in fibrosis detection performance.

Main findings

Voltage and CV mapping strategies based on MOP-EGM were more robust than b-EGMs and standard OP-EGM based maps, against the heterogeneity of propagation pattern and noise [1]. They showed higher accuracy in fibrosis detection (> 85% versus 80% and 70%, for MOP-EGM, b-EGMs and OP-EGM maps, respectively), with maps of peak-to-peak amplitudes of the

omnipolar EGMs also presenting better correlation with reference maps (Pearson's correlation > 0.80 versus 0.60 and 0.75, respectively) and smaller variability than bipolar maps (Fig.1 A-C). For all the considered noise levels, CV maps based on MOP-EGM approach achieved the highest accuracy (> 90%) in fibrosis identification (Fig.1 D-E). In simulation, best EIGDR performance was reached from previously time-aligned u-EGMs, achieving a fibrosis detection accuracy of 94%, higher than the 86% of bipolar voltage maps, with different noise levels and variable electrode-tissue distance (Fig.1 F-G). These findings were corroborated by preliminary results from real u-EGMs, where R^A and ΔR^A showed robustness comparable to bipolar maps. Results achieved in this project reveal that the proposed strategies are able to characterize atrial propagation and substrate, although further studies will elucidate the advantage of their use, as well as their impact in clinical practice.

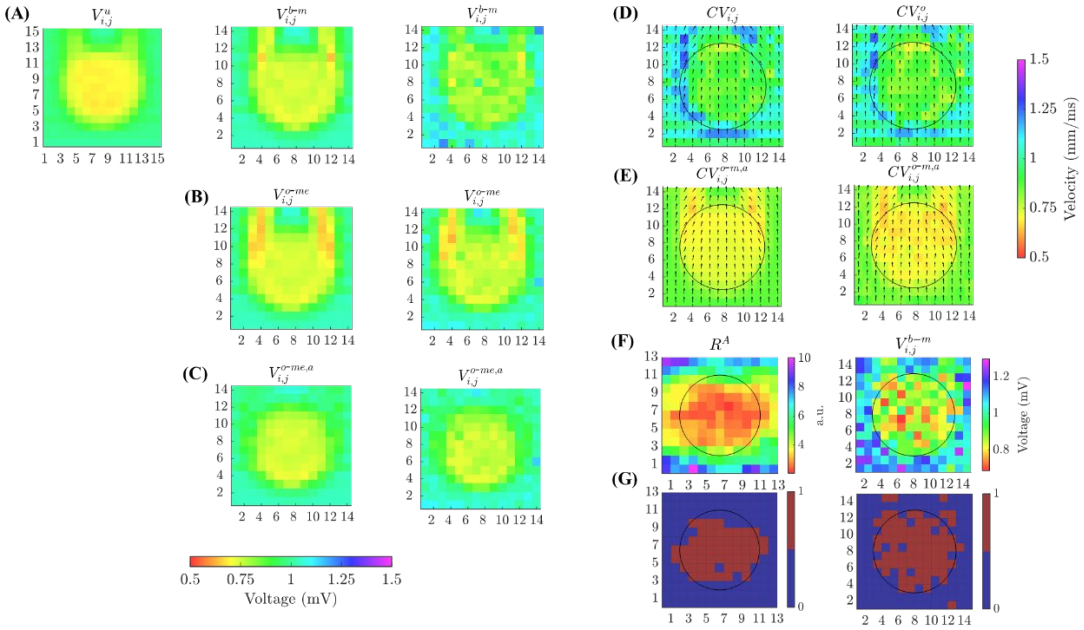


Figure 1: (A) u-EGMs (left panel) and b-EGMs (middle and right panels), (B) OP-EGM and (C) MOP-EGM based voltage maps; (D) OP-EGM and (E) MOP-EGM based velocity maps. From (A) to (E): the two middle and right columns show the same types of mapping strategies, without and with noise corrupted b-EGMs, respectively. (F) R^A map (left panel) and bipolar voltage map (right panel), performed assuming a variable electrode-to-tissue distance and noisy u-EGMs. (G) detected fibrotic areas (brown), using the thresholds that maximize detection accuracy of each map. All the maps from (A) to (F) were obtained when Ψ = 0°.

References

[1] Riccio J, Alcaine A, Rocher S, Martinez-Mateu L, Laranjo S, Saiz J, Laguna P, Martínez JP. Characterization of atrial propagation patterns and fibrotic substrate with a modified omnipolar electrogram strategy in multi-electrode arrays. Frontiers Physiology 2021;12:674223.
[2] Riccio J, Alcaine A, Rocher S, Laguna P, Saiz J, Martínez JP. Omnipolar EGM voltage mapping for atrial fibrosis identification evaluated with an electrophysiological model. Proceedings of the 28th European Signal Processing Conference (EUSIPCO 2020) 2021; 920–924.
[3] Riccio J, Alcaine A, de Groot NMS, Houben R, Laguna P, Martínez JP. Characterization of

propagation patterns with omnipolar EGM in epicardial muti-electrode arrays. Proceedings of Computing in Cardiology 2019; 46:1–4.
[4] Deno DC, Balachandran R, Morgan D, Ahmad F, Massé S, Nanthakumar K. Orientation-independent catheter-based characterization of myocardial activation. IEE Transactions on Biomedical Engineering 2017; 64:1067-1077.
[5] Riccio J, Rocher S, Martinez-Mateu L, Alcaine A, Saiz J, Martínez JP, Laguna P. Unipolar electrogram eigenvalue distribution analysis for the identification of atrial fibrosis. Proceedings of Computing in Cardiology 2020; 47:1–4.