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 D2.4

# D2.4: 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 | D2.4 |
| Document Title | Submission of PhD thesis draft/proposal |
| Deliverable Nº | D9 |
| Editors | Valentina Corino, Luca Mainardi |
| Contributors | All |
| Lead Beneficiary | POLIMI |
| Work Package Nº | 3 |
| Work Package Title | Basic Research: Atrial Arrhythmia Mechanisms |
| Nature | Report |
| Dissemination Level | Public |
| Number of pages | 19 |
| Due Date (in months) | 53 |
| Submission date | 31/03/2022 |
| | |

# Distribution List

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## 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 |

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# 1. Summary

This document describes the status of PhD researcher of the ESRs belonging to WP2 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 |
|---|---|---|---|
| ESR1 | 01-10-2018 | Ongoing | December 2022* |
| ESR2 | 26-10-2018 | Ongoing | December 2022* |
| ESR3 | 01-07-2018 | Defended | 16-12-2021 |
| ESR4 | 01-11-2018 | Submitted | July 2022 * |

* expected date

# 3. ESR1: Bottom up study on the implications of interatrial block in the mechanisms of atrial fibrillation

ESR1: Jordan Elliott

## Motivation and aim

To better understand atrial behavior and the underlying mechanisms of atrial electrophysiology, computer models have been used to shed light on different characteristics that should be considered in the further steps of cardiac mapping and, in turn, in planning personalized therapy for patients with atrial arrhythmias. The influence of variability on electrophysiological behavior of the atria for patients with normal atrial anatomy for both healthy and AF remodeled tissue was studied. The aim of this project is to further the understanding of the impact of different interatrial conduction defects on the electrophysiological behavior in the atria. Through the investigation of cellular variability in atrial tissue, this study shows the impact of cellular heterogeneity on the behavior of the atria under healthy conditions and after AF remodeling.

## Methods

Through the use of the POM approach [5], cellular heterogeneity was introduced to isolated atrial tissue samples and whole atrial anatomical models. A non-bias population of 200,000 unique action potential models was created using the Courtemanche-Ramirez-Nattel (CRN) cellular model [3]. To create these unique action potential models, 9 maximum channel conductances: gNa, gTo, gKur, gKr, gKs, gK1, gCaL, gNaK and gNaCa, were varied between −100% to +200% of the standard value, using the Monte Carlo sampling method. Each unique combination of parameters was stimulated with 101 impulses at a BCL of 1000ms, with stimulus duration 1ms, amplitude -45pA/pF. The action potential resulting from the last impulse was saved and used for classification based on action potential morphology. From the population of 162,971 stable action potential models, smaller populations were extracted based on action potential morphology matching experimental data previously published[1-2][4][6-15] for 8 atrial regions. The set biomarker values for each atrial region are presented in the table below.

| | RMP | APA | APD20 | APD50 | APD90 |
|---|---|---|---|---|---|
| RA | −78 ± 12 | 116.6 ± 14 | 30 ± 18 | 72.2 ± 37 | 200 ± 62 |
| RAA | −79 ± 6.6 | 124.1 ± 19 | 30 ± 18 | 105.6 ± 36 | 190 ± 22 |
| LA | −78 ± 5.4 | 112.4 ±13 | 30 ± 18 | 54.7 ± 17 | 174 ± 34 |
| LAA | −73.8 ± 6.6 | 128 ± 19 | 30 ± 18 | 89.7 ± 13 | 160 ± 22 |
| AVR | −73.8 ± 1.4 | 127.3 ± 21 | 30 ± 18 | 38 ± 21 | 170 ± 29 |
| CT/BBra | −77 ± 1.9 | 134.8 ± 19 | 30 ± 18 | 119.3 ± 32 | 219 ± 64 |
| BBla | −77 ± 1.9 | 124.1 ± 19 | 30 ± 18 | 94.2 ± 32 | 172 ± 32 |
| PM | −75.9 ± 12 | 131.6 ± 16 | 30 ± 18 | 74.5 ± 17 | 172 ± 19 |

*Table: Mean and standard deviation of the AF remodelled biomarkers for each atrial region.*

Using the regional populations, cellular heterogeneity was introduced into 10 geometrically identical atrial models. A regionally homogeneous model was created for comparing results and determining the impact of cellular heterogeneity on whole atrial behavior. Electric propagation in the atria was model through the monodomain model. Atrial regions conduction velocity were calibrated using isolated tissue samples. To further stabilize each whole atrial model as a single unit, 10 stimuli were initiated in the SA nodes, at a BCL of 800ms, with an amplitude of 50mV and stimulus duration of 2ms. A further single stimulus was applied to each atrial model for analysis.

## Main findings

There was no significant difference in the activation across the atria resulting from cellular heterogeneity. The total activation time in the homogeneous atrial model was 146ms and the total activation time was 147ms across all heterogeneous atrial models. Repolarization across the atria, however, showed significant differences between the regionally homogeneous and heterogeneous atrial models. The repolarization patterns remained consistent across the 10 heterogeneous models. This suggests the visual difference was not specific to a single variable model but was a result of the intrinsic cellular heterogeneity. Figure 1 shows the repolarization across homogeneous and heterogeneous atrial models from 150ms to 240ms after initially stimulating the sinoatrial node. Showing the repolarization across the atria from anterior and posterior viewpoints. This figure clearly highlights differences in repolarization as a result of cellular heterogeneity. The LA region repolarizes quicker in the homogeneous atria than the heterogeneous atria, whereas the reverse is observed in the right atria.

Atrial activation, or the depolarization phase, is not significantly impacted by the introduction

of cellular heterogeneity in the atrial model. With only slight differences in activation across the atria, and total activation times differing by 0-1ms due to variability, it is clear that the depolarization across the atria is not impacted by variability when regional models are calibrated using isolated tissue samples. Observable and significant differences, however, were observed in the repolarization phase as a result of the introduction of cellular heterogeneity. Through the use of multiple heterogeneous atrial models, it has been shown that the impact of heterogeneity is consistent across multiple models, and models and is not unique to a single heterogeneous model.

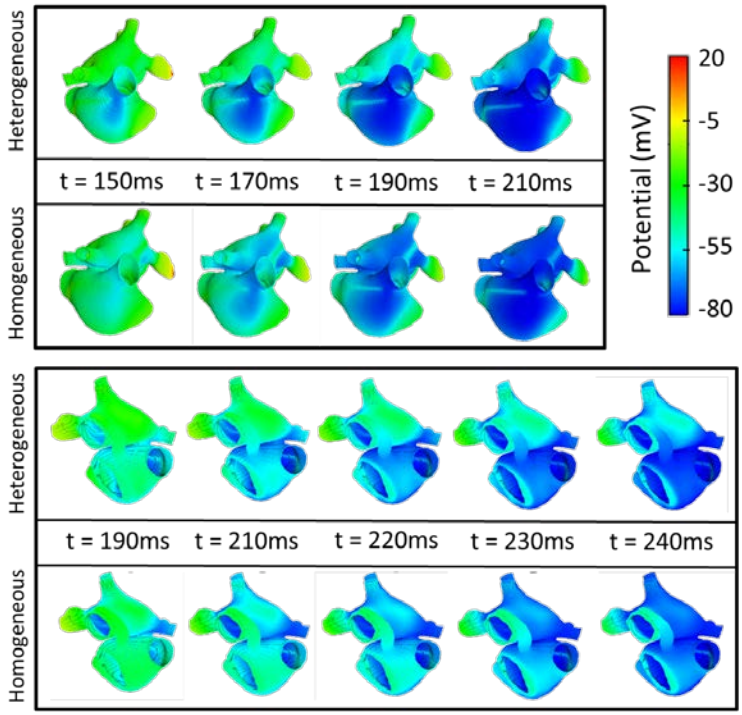


*Figure 1 Repolarization across the atria over time. The heterogeneous model is presented above the associated timeframe, and the equivalent regionally homogeneous model is presented below the timeframe.*

The significant changes in repolarization due to heterogeneity could result in changes to the window of vulnerability across the atria and impact the propagation and maintenance of re-entries. With APD determining the refractory period and the window of vulnerability in atrial tissue, it is a key determinant of the susceptibility to re-entries. The observed changes in the repolarization across the atria as a result of cellular heterogeneity could significantly impact the progression and maintenance of re-entries and atrial fibrillation.

# References

[1] Adeniran, I.; Maciver, D.H.; Garratt, C.J.; Ye, J.; Hancox, J.C.; Zhang, H. Effects of Persistent Atrial Fibrillation-Induced Electrical Remodeling on Atrial Electro-Mechanics—Insights from a 3D Model of the Human Atria. PLoS ONE 2015, 10.

[2] Bosch, R.F.; Zeng, X.; Grammer, J.B.; Popovic, K.; Mewis, C.; Kühlkamp, V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. Cardiovasc. Res. 1999, 44, 121–13.

[3] Courtemanche, M.; Ramirez, R.J.; Nattel, S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am. J. Physiol. Circ. Physiol. 1998, 275.

[4] Dobrev, D.; Graf, E.; Wettwer, E.; Himmel, H.; Hála, O.; Doerfel, C.; Christ, T.; Schuler, S.; Ravens, U. Molecular basis of downregulation of G-protein-coupled inward rectifying K(+) current (I(K,ACh) in chronic human atrial fibrillation: decrease in GIRK4 mRNA correlates with reduced I(K,ACh) and muscarinic receptor-mediated shortening of action potentials. Circulation 2001, 104, 2551–2557.

[5] Elliott J, Belen MK, Mainardi L, Rodriguez Matas JF (2021) A Comparison of Regional Classification Strategies Implemented for the Population Based Approach to Modelling Atrial Fibrillation. Mathematics 9:1686. https://doi.org/10.3390/math9141686

[6] Feng, J.; Yue, L.; Wang, Z.; Nattel, S. Ionic Mechanisms of Regional Action Potential Heterogeneity in the Canine Right Atrium. Circ. Res. 1998, 83, 541–551.

[7] Kim, B.-S.; Kim, Y.-H.; Hwang, G.-S.; Pak, H.-N.; Lee, S.C.; Shim, W.J.; Oh, D.J.; Ro, Y.M. Action potential duration restitution kinetics in human atrial fibrillation. J. Am. Coll. Cardiol. 2002, 39, 1329–1336.

[8] Li, D.; Zhang, L.; Kneller, J.; Nattel, S. Potential Ionic Mechanism for Repolarization Differences between Canine Right and Left Atrium. Circ. Res. 2001, 88, 1168–1175.

[9] Loose, S.; Mueller, J.; Wettwer, E.; Knaut, M.; Ford, J.; Milnes, J.; Ravens, U. Effects of IKur blocker MK-0448 on human right atrial action potentials from patients in sinus rhythm and in permanent atrial fibrillation. Front. Pharmacol. 2014, 5, 5–26.

[10] Martinez-Mateu, L.; Romero, L.; Ferrer-Albero, A.; Sebastian, R.; Rodriguez Matas, J.F.; Jalife, J.; Berenfeld, O.; Saiz, J. Factors affecting basket catheter detection of real and phantom rotors in the atria: A computational study. PLoS Comput. Biol. 2018, 14.

[11] Muszkiewicz, A.; Liu, X.; Bueno-Orovio, A.; Lawson, B.; Burrage, K.; Casadei, B.; Rodriguez, B. From ionic to cellular variability in human atrial myocytes: an integrative computational and experimental study. Am. J. Physiol. Heart Circ. Physiol. 2018, 31.

[12] Pau, D.; Workman, A.J.; Kane, K.A.; Rankin, A.C. Electrophysiological and arrhythmogenic effects of 5-hydroxytryptamine on human atrial cells are reduced in atrial fibrillation. J. Mol. Cell. Cardiol. 2007, 42, 54–62.

[13] Workman, A.J.; Kane, K.A.; Rankin, A.C. The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation. Cardiovasc. Res. 2001, 52, 226–235.

[14] Yue, L.; Feng, J.; Gaspo, R.; Li, G. R.; Wang, Z.; & Nattel, S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circulation research, 1997, 81(4), 512–525.

[15] Zrenner, B.; Ndrepepa, G.; Karch, M.R.; Schneider, M.A.; Schreieck, J.; Schömig, A.; Schmitt, C. Electrophysiologic characteristics of paroxysmal and chronic atrial fibrillation in human right atrium. J. Am. Coll. Cardiol. 2001, 38, 1143–1149.

# 4. ESR2: Detailed 3-D computer models of human atria and torso for studying atrial fibrillation initiation and progression

ESR2: Rebecca Belletti

## Motivation and aim

The aim of this research project is the assessment of the effects of three gain-of-function mutations related to episodes of atrial fibrillation (AF) - KCNH2 T895M, KCNH2 T436M, and KCNE3-V17M using simulations of the cardiac electrophysiology, at multi-scale levels. The genetic mutations taken into account affect genes encoding potassium channel protein structures in asymptomatic patients and are known to modify the $I_{Kr}$ and $I_{to}$ currents. The generation of substrates more prone to arrhythmias was studied using detailed mathematical models and performing computational simulations on single-cell, tissue and 3D bi-atrial morphologies, presenting anatomical details and electrophysiological heterogeneities. This investigation represents a step forward in the understanding of the initiation and progression of AF and of the underlying mechanisms of the fibrillatory events induced by the mutations.

## Methods

The original mathematical formulations of the $I_{Kr}$ and $I_{to}$ ionic currents published by Courtemanche et al. [1] were modified by means of reparameterization to account for the effects of these mutations. A genetic algorithm was used to tune the parameters' values to reproduce the alterations produced by the mutations as reported experimentally [2], [3]. The resulting models accurately reproduced the dynamics of the mutated ion channels, as illustrated in Figure 1A. The integration of such mutated currents into the Courtemanche model together with electrical remodeling to reproduce pulmonary vein (PV), right (RA), and left atrium (LA) tissues resulted in twelve versions of the human atrial action potential model and allowed the analysis of the mutations' impact on action potentials and ionic currents. Moreover, the characterization of the susceptibility to arrhythmia in presence of the genetic defects was conducted by studying the temporal vulnerability in tissue and in 3D bi-atrial model simulations.

## Main findings

The presence of the three mutations lead to an overall more arrhythmogenic substrate. At the single-cell level, these genetic defects shortened the action potential durations (APD) to different extents, depending on the mutation under study, as can be seen in Figure 1B where the simulated action

potentials, $I_{Kr}$ and $I_{to}$ traces in the left atrium are represented. In presence of KCNH2 T436M, APDs shortened by 9% in the RA and by 13% in LA and PV. The KCNH2 T895M induced an APD reduction of 18% in RA, 23% in LA and 24% in PV. Finally, the KCNE3-V17M mutation provoked an APD shortening of 46% in RA, 51% in LA and 47% in PV. This was a direct consequence to higher current densities respect to the healthy case, as can be seen in Figure 1B). The presence of the genetic mutations increased the susceptibility to arrhythmias by promoting the rotor's initiation and maintenance, by shifting the vulnerable windows (VW) to shorter S1–S2 time intervals and by sustaining spiral waves that perpetuate until the end of the simulation [4].

The mutation showing the highest pro-arrhythmic effects was KCNE3-V17M with the widest sustained VW and the smallest meandering rotor's tip areas. The VW shift was more evident for the KCNE3-V17M mutation, and it is progressively less pronounced for the KCNH2 T895M and KCNH2 T436M mutations. The increased vulnerability to arrhythmias and rotor's stability was tissue-dependent: susceptibility to the rotor's initiation was higher in PV tissue, but rotors were more easily maintained in LA. Phase analysis allowed the tracking of rotors' tips trajectories that helped understanding the temporal dynamics and evolution of the rotors and unveiling a more stable behavior in the presence of the KCNE3-V17M mutation and in the pulmonary vein region [4]. Finally, in 3D whole atria simulations, the presence of the mutations also increased the vulnerability to re-entry. Figure 1C depicts examples of arrhythmic episodes in the presence of each of the mutations. Different types of arrhythmic behavior were observed depending on the mutation. The KCNH2 T436M mutation favored the generation of macro re-entries and rotors, to a lesser extent, in RA perpetuated for a minimum of 3.8 s and for a maximum of 5 s (Figure 1C, left column). In the presence of the mutation KCNH2 T895M, macro re-entries perpetuating until the end of the simulations (5s) were generated (Figure 1C, middle column). Complex arrhythmogenic patterns arises in the case of the KCNE3-V17M mutation with multiple wave break, collisions and the formation of several instable rotors in both RA and LA (Figure 1C, right column). This multi-scale study provides useful insights into the mechanisms underlying fibrillatory events caused by the KCNH2 T895M, KCNH2 T436M, and KCNE3-V17M mutations, such as the abbreviated APD and higher temporal vulnerability. The different dynamics arisen from the presence of the three mutations underlined the importance of a personalized intervention strategy to efficiently address such pathologies. This investigation can be considered a step forward in demonstrating the importance of the development of personalized anti-arrhythmic drugs, personalized therapeutical treatments based on the characteristics of the genotype and, therefore, patient-specific ablation strategies. Furthermore, prevention strategies by early identification of patient at risk of developing AF later in life can lead to an improvement in AF management.

# References

[1] M. Courtemanche, R. J. Ramirez, and S. Nattel, "Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model," *Am. J. Physiol. -Heart Circ. Physiol.*, vol. 275, pp. 301–321, 1998, doi: 10.1152/ajpheart.1998.275.1.H301.

[2] K. Hayashi *et al.*, "Functional Characterization of Rare Variants Implicated in Susceptibility to Lone Atrial Fibrillation," *Circ. Arrhythmia Electrophysiol.*, vol. 8, no. 5, pp. 1095–1104, 2015, doi: 10.1161/CIRCEP.114.002519.

[3] A. Lundby, L. S. Ravn, J. H. Svendsen, S. Haunsø, S. P. Olesen, and N. Schmitt, "KCNE3 mutation V17M identified in a patient with lone atrial fibrillation," *Cell. Physiol. Biochem.*, vol. 21, no. 1–3, pp. 47–54, 2008, doi: 10.1159/000113746.

[4] R. Belletti, L. Romero, L. Martinez-Mateu, E. M. Cherry, F. H. Fenton, and J. Saiz, "Arrhythmogenic Effects of Genetic Mutations Affecting Potassium Channels in Human Atrial Fibrillation: A Simulation Study," *Front. Physiol.*, vol. 12, no. May, pp. 1–16, 2021, doi: 10.3389/fphys.2021.681943.

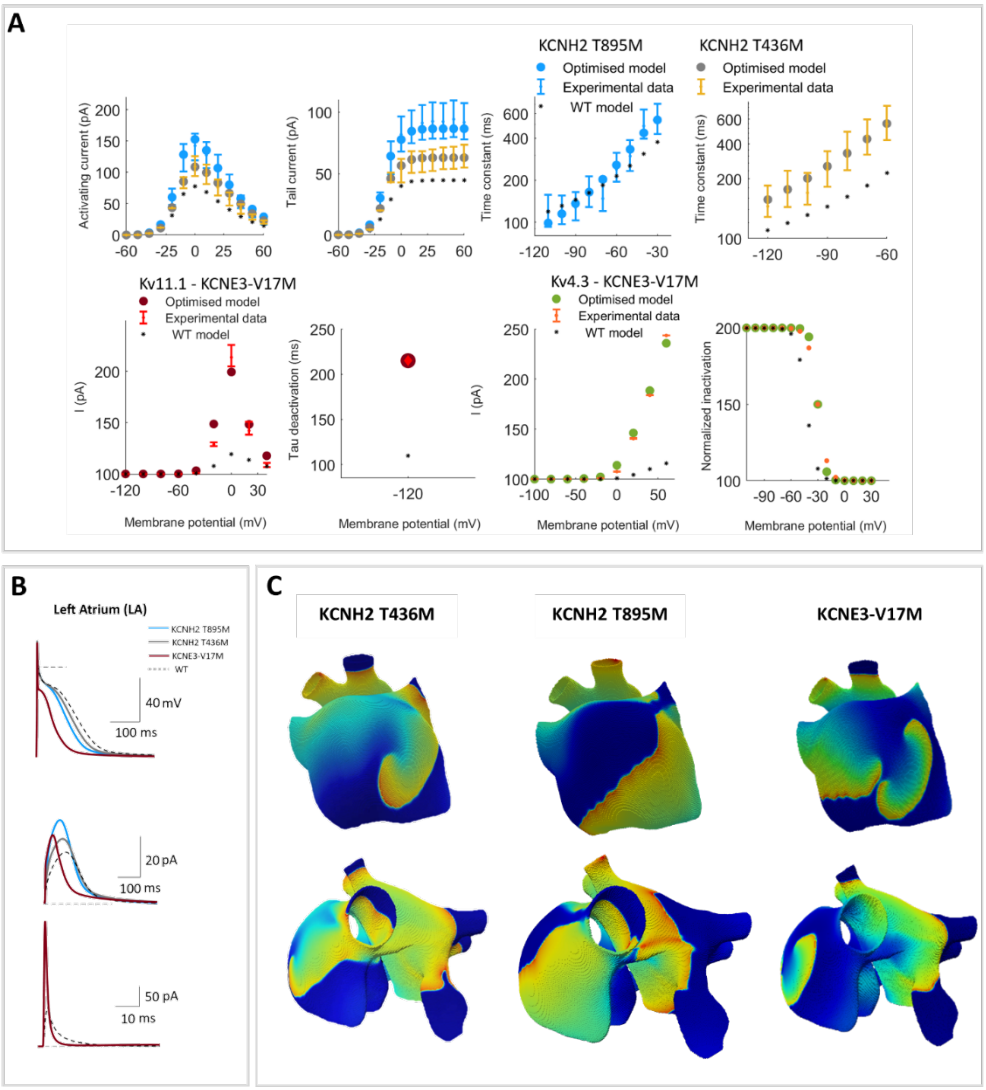


*Figure 1 - Resulting $I_{Kr}$ and $I_{to}$ currents, time constants and inactivation curves of KCNH2 T436M (grey), KCNH2 T895M (blue) and KCNE3-V17M (Kv11.1 in red and Kv4.3 in green) mutations (panel A). Simulated effects of the mutations in human single cell models of left atrium; action potential (top), $I_{Kr}$ current (middle) and $I_{to}$ current (bottom) (panel B). Simulation of different arrhythmic behaviour in presence of KCNH2 T436M, KCNH2 T895M and KCNE3-V17M in 3D atrial models (panel C).*

# 5. ESR3: Body Surface Potential Maps and ECG-signals of AF lead

ESR 3: Giorgio Luongo

## Motivation and aim

The general aim of this project is to develop electrocardiogram- (ECG) and machine learning-based tools to support physicians in the characterization, diagnoses, ablation procedure planning, and complication prediction for patients with atrial fibrillation (AFib) and atrial flutter (AFlut). These can be used to reduce the invasive procedure time and, therefore, the related costs by supporting the physicians in finding diagnoses, personalizing treatment, and improving the patient outcomes. Two major topics are incorporated into this project: The characterization and discrimination of different AFlut mechanisms, and the localization of AFib drivers with acute ablation success prediction, and AFib complications' risk analysis. The leading aims of the first study are: Improve AFlut mechanism characterization implementing novel biosignal approaches to extract valuable features; Evaluate the influence of atrial and torso geometries on ECG and therefore on feature extraction and classification; Discriminate several AFlut mechanisms using both in silico and clinical ECG data with a machine learning-based approach and using findings from the first two studies.

The second topic described in this project covers the following aspects regarding AFib driver localization and complication prediction: Implement an in silico-based machine learning algorithm to identify the AFib drivers located near the pulmonary veins (PVs), predict the success rate of PV isolation to terminate the arrhythmia, and test it on a clinical cohort of ECGs; Identify likely connections between AFib and heart failure using beat-to-beat variation signals extracted from 1-lead ECG.

## Methods

In both the studies presented, simulated ECG signals were computed to extend a clinical dataset, or substitute it, for the implementation of novel methods applicable in clinical practice. These methods enabled the extraction of information related to AFlut and AFib activities. In the first presented study, two new recurrence quantification analysis (RQA) methods have been implemented to derive useful features for discriminating different AFlut mechanisms: individual component RQA, and spatial reduced RQA. These two methods were implemented and tuned on simulated data and tested on clinical data. Next, a thorough analysis of the influence of the atrial and torso geometries used for the simulations needed to be performed,

thus to avoid the algorithm's failure on clinical data due to overfitting to simulated data. The final AFlut study conducted was a machine learning algorithm capable of discriminating three different macro categories of AFlut (cavotricuspid isthmus-dependent, peri-mitral, and other left atrium AFlut mechanisms). New simulations were performed using a large number of atrial geometries (100). In addition, the classifier was trained using a hybrid approach (simulated plus clinical data). Thus, overfitting on the simulated data and on the atrial geometries used was drastically reduced.

In the second study, the identification of the AFib drivers located near the PVs has been performed using the 12-lead ECGs. An automated learning algorithm was trained only on in silico ECGs and then it was tested on a clinical. Moreover, analysis of the success of some common ablation procedures (i.e., PV isolation (PVI), roof line, and mitral isthmus ablation) to terminate AFib conferred more value to the implemented classification. Another key, but still unresolved, issue with AFib is its link to some even more serious cardiovascular diseases such as heart failure, and cardiomyopathy, which led us to the last work in this project: the implementation of a decision tree classifier using RR-interval series extracted from 1-lead ECG Holter signals to discriminate between AFib cases inducing heart failure in respect to AFib cases without this induction.

## Main findings

In the first presented project, the results obtained from the RQA analysis showed that some of the RQA features have the potential to discriminate between AFlut mechanisms. In particular, the focal source mechanisms showed to be significantly deterministic and laminar in contrast to microreentries. The first three principal components derived from the 12-lead ECG demonstrated the presence of relevant small or major changes in the dynamic structure of these AFlut phenomena. The proof of concept of the methods on simulated data also matched the clinical data results [1]. Regarding the influence of torso and atrial models on the ECG, poor performance in analyzing the influence of atrial models (classification accuracy of 59.8% with leave-one-atrium-out approach) demonstrated how fundamental it is to build in silico studies on a large number of atrial geometries in order to produce a faithful representation of atrial ECG variability as the one seen in clinical practice. In contrast, high performance achieved for the torso models' influence analysis (classification accuracy of 89.0% with leave-one-torso-out approach) showed that a large number of torso models is not necessarily required in the simulation framework. The torso models do not have a significant influence on the resulting ECG during AFlut in contrast to atrial models, indeed [2]. The final AFlut im-

plemented algorithm (machine learning algorithm to discriminate three different macro categories of AFlut - cavotricuspid isthmus-dependent, peri-mitral, and other left atrium AFlut mechanisms) obtained an accuracy of 82.2% on a small clinical database demonstrated how this approach is capable of identifying the location of AFlut mechanisms relying only on non-invasive signals (i.e., 12-lead ECG) [3]. The final results obtained from the latter two works also confirmed that F-wave duration is a key feature for AFlut discrimination.

In the second study, the automated learning algorithm trained only on in silico ECGs was successful in the underlying discrimination on a clinical dataset yielding a test set specificity of 82.6%, and sensitivity of 73.9%. Moreover, 93.5% of the predictions matched between two different sets of ECG segments extracted from the same patient for a consistency analysis. The successful use of computational simulations in support of clinical data, or in total replacement of them, proved the true potential of simulations in clinical practice. Moreover, 100% of PVI ablations on AFib drivers located near PVs resulted in acute termination of the arrhythmia. In contrast, the combination of all three ablation procedures almost never terminated the arrhythmia for AFib drivers located in other areas than the PVs (12.5% of the cases). Thus, the algorithm, besides localizing the location of the AFib drivers, can also predict the acute success of PVI in terminating the arrhythmia [4]. In the last work of this study, the decision tree algorithm showed that there are patterns allowing the discrimination of AFib cases inducing heart failure in respect to AFib cases without this induction (classification accuracy, and specificity of 73.5%, and 91.4%, respectively). In AFib-induced heart failure cases predicted by the algorithm, the physicians are advised to proceed with cardiological care as soon as possible (e.g., applying cardioversion) to reduce the risk of such complication [5].

# References

[1] Luongo G, et al. Non-Invasive Characterization of Atrial Flutter Mechanisms Using Recurrence Quantification Analysis on the ECG: A Computational Study. IEEE Transactions on Biomedical Engineering 2021;68(3):914-925.

[2] Luongo G, et al. Automatic ECG-based Discrimination of 20 Atrial Flutter Mechanisms: Influence of Atrial and Torso Geometries. 2020 Computing in Cardiology.

[3] Luongo G, et al. Hybrid Machine Learning to Localize Atrial Flutter Substrates Using the Surface 12-lead ECG. EP Europace 2022.

[4] Luongo G, et al. Machine learning enables noninvasive prediction of atrial fibrillation driver location and acute pulmonary vein ablation success using the 12-lead ECG. Cardiovascular Digital Health Journal 2021;2(2):126-136.

[5] Luongo G, et al. Machine Learning Using a Single-Lead ECG to Identify Patients With Atrial Fibrillation-Induced Heart Failure. Frontiers in Cardiovascular Medicine 2022.

# 6. ESR4: Atrial Complex Networks in Endocavitary Recordings During Atrial Fibrillation

ESR4: Muhamed Vila

## Motivation and aim

In current clinical practice, ablation treatment of atrial fibrillation (AF) is mainly restricted to a standard procedure called pulmonary vein isolation (PVI). However, AF mechanisms may vary from patient to patient, thus a standard procedure may not suffice. Recent progress indicates that the future treatment of AF should be tailored to the individual patient in an attempt to achieve optimal success rate [1]. To aggravate the problem, PVI often results into another atrial arrhythmia, called atrial flutter (AFL) [2]. Even though new technologies and techniques are emerging in the recent years to tackle atrial arrhythmias, these findings have not been found consistent, and it has become clear that such a development will not be possible without further advancement of signal processing techniques [1]. Also, it is clear that patient-specific signal-guided approaches to ablation are expected to gain further importance in the future, requiring novel methods which can handle the strongly variable organization of atrial signals, as well as the increasing number of simultaneously recorded signals. In this project, integrated and personalized models of the atria, comprising of signals, three-dimensional meshes and complex networks, are investigated to support physicians during the therapy. This multidomain approach has the potential to be used during PVI procedure for personalized treatment of atrial arrhythmias and to speed up the planning of the ablation therapy by identifying, nearly real-time, the mechanism sustaining the arrhythmia.

## Methods

A novel approach, called “directed network mapping”, was designed to represent the electrical activity in the atria during atrial arrhythmias. It creates a directed network by processing electrograms (EGMs) acquired during sequential mapping in an electrophysiologic study, to model the electrical propagation on the atrial inner surface [3]. To create the network, a set of EGMs collected from moving catheters, their 3D positions over time and the geometrical model of the atria are necessary. The network nodes are defined as specific locations on the atrial surface, and the network edges represent the directed electrical propagation from one location to a nearby one (Fig.1A). Atrial conduction paths can be identified based on the time delay between activations collected at two locations at close distance. From the created network, it is possible to automatically identify arrhythmia mechanisms, using standard tools

from network theory, such as depth first search to travel along the nodes, or by computing the outdegree of a node to identify focal points [3]. Indeed, the main advantage of modeling the electrical activity using a directed network is the fact that a plethora of efficient algorithms already exist to "query" and analyze the model in the field of graph theory. Furthermore, we investigated on the potential of directed networking mapping in supporting the planning of the ablation treatment. Specifically, suggesting a set of possible ablation lines suitable to terminate reentrant activities, recommended automatically by a computer program using graph theory algorithms.

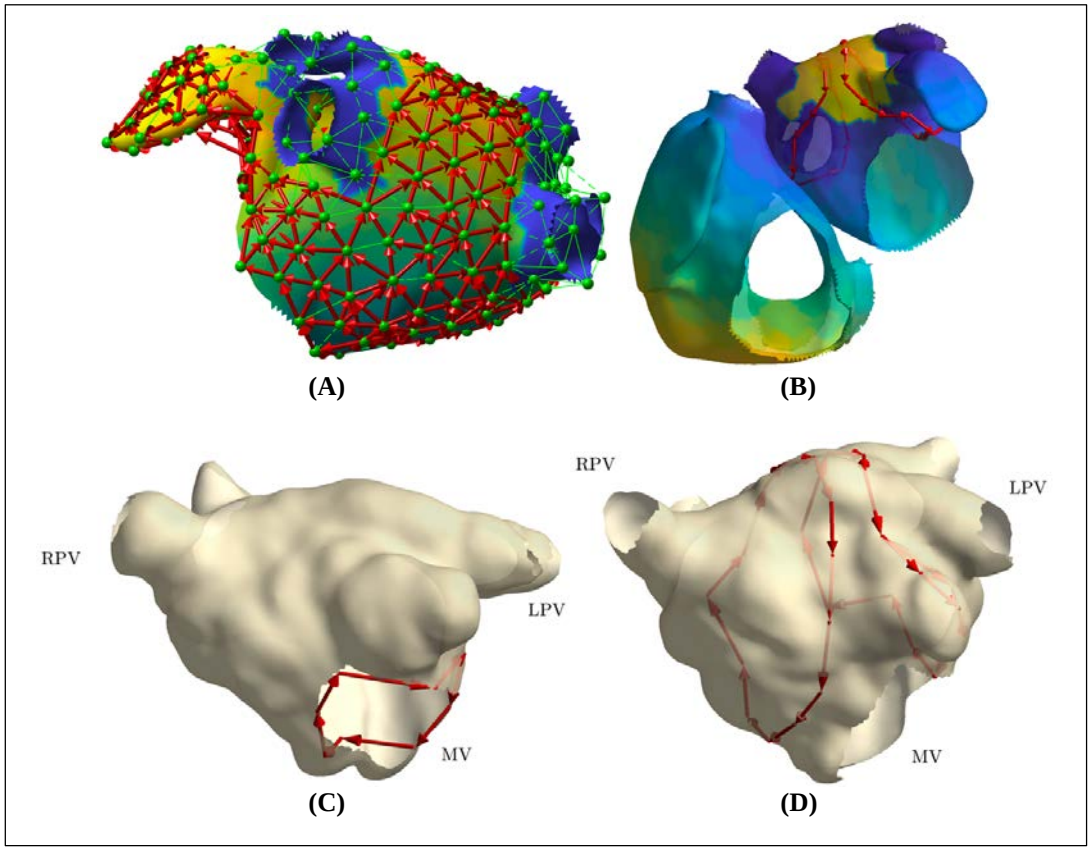


*Figure 1: (A) Entire directed network (in red) after processing all signals at each node (in green) to determine the existence and direction of the electrical propagation between nodes, in one of the simulated cases. The color map represents the LAT value across the atrial surface referenced to the activation of a specific node in the mesh. (B) Cycles detected in a simulated case of figure-of-eight reentry. (C) Cycles detected in a clinical case of macroreentry around mitral valve. (D) Cycles detected in a clinical case of figure-of-eight around. Only one cycle randomly selected from each group has been plotted in red color. The figure is adapted from [3].*

## Main findings

The network-based mapping approach was used for automatically detecting various types of mechanisms of atrial arrhythmias, such as focal, microreentry, macroreentry, and rotor-driven AF. It was applied to a broad range of simulations and clinical cases of AFL and AF. First, we showed that directed network mapping can be used to accurately represent the electrical propagation pattern in sinus rhythm [3]. Second, directed network mapping was able to correctly locate macroreentries in *in-silico* AFL models, where we tested 6 different scenarios [3]. Then, we tested the technique on 10 clinical cases of AFL and compared the results with clinical reports by expert electrophysiologists. Overall, the algorithm proved to be satisfactory according to the clinicians' opinion with respect to the complex cases analyzed and showed the potential for clinical use with an accuracy of 80% [3]. As a proof-of-concept, we also demonstrated that directed network mapping can be used to represent the electrical activity in the atria during AF, where the network was leveraged to detect rotors in *in-silico* heart model [4]. Finally, we developed a recommender system able to suggest the ablation strategy to interrupt all AFL mechanisms in place. In order to recommend the strategy, an optimization problem was designed. Finding the optimal solution of the problem could be possible only for a small set of ablation lines to recommend. To address the issue, we designed a heuristic-based algorithm, far more efficient, to provide a solution, though suboptimal. The algorithm was tested on the same simulations and clinical cases, and achieved promising results. The results of this study will be submitted soon to a prestigious scientific journal.

## References

[1] Rottner L, Bellmann B, Lin T, et al. Catheter Ablation of Atrial Fibrillation: State of the Art and Future Perspectives. Cardiol Ther. 2020;9(1):45-58.
[2] Chugh A, Oral H, Lemola K, et al. Prevalence, mechanisms, and clinical significance of macroreentrant atrial tachycardia during and following left atrial ablation for atrial fibrillation. Heart Rhythm. 2005;2(5):464-471.
[3] Vila M, Rivolta MW, Luongo G, et al. Atrial Flutter Mechanism Detection Using Directed Network Mapping. Front Physiol. 2021;12:749635. Published 2021 Oct 26.
[4] Vila M, Rocher S, Rivolta MW, Saiz J, Sassi R. Directed Network Mapping Approach to Rotor Localization in Atrial Fibrillation Simulation. *Annu Int Conf IEEE Eng Med Biol Soc*. 2021;2021:730-733.