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Doctoral Thesis

Post-processing of ECGI to detect atrial drivers

PhD in Technologies for Health and Well-Being

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October 2024

Agradecimientos

Es mucha la gente a la que le tengo que agradecer la consecución de esta tesis. Por un lado están aquellos de los que he aprendido día a día. Personas que me han hecho crecer científica y académicamente y han supuesto un apoyo cotidiano sin el cuál hubiese estado perdido. En especial quiero dar las gracias a María y Andreu. Por enseñarme todo lo que sé y las infinitas posibilidades que se abren ante mi.

Tampoco puedo dejarme a mis compañeros y amigos de laboratorio. Tengo que agradecer a Arantxa, Ismael, Jorge, Rubén, Clara, Marta, María C, María M, Raúl, Inés, Andrea, Jorge V., Pedro y a Ramón la maravillosa convivencia que tenemos, así como todas sus aportaciones y consejos. Sin vuestro trabajo esta tesis no hubiese sido posible.

También tengo que agradecer a todo el equipo de Corify Care su desempeño y buen hacer. Sin ellos, los resultados de esta tesis tendrían mucho menos sentido. Especialmente a David, cuya guía y entusiasmo han sido de gran ayuda. Mil gracias compañeros.

Por otro lado están aquellos que, si bien no han participado científicamente en el desempeño de esta tesis, han supuesto un apoyo tan incondicional como indispensable. Gracias mamá, papá. Gracias también a mis hermanos y a toda mi familia. Siempre os he sentido a mi lado.

Por último no puedo dejar de mencionar a mis amigos tanto del instituto como de la carrera. Porque habéis sido un gran apoyo y una fuente fundamental de evasión ante el estrés y la frustración. Esta tesis también es vuestra.

List of Figures

2.1	Scheme of systemic and pulmonary circulation systems. This schematic was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com	9
2.2	Electrical conduction system in the heart. This schematic was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com	10
2.3	Ventricular (A) and atrial (B) action potentials with indications of the different phases and ion currents traces through time. Figure adapted from [1].	11
2.4	Current classification of AF according to guidelines. Modified figure from [Joglar <i>et al.</i> 2024]	13
2.5	Atrial fibrillation (AF) episode driven by a fast rotor. Periodic electrograms (EGMs) are present in the rotor area with a dominant spectral peak matching the rotor's frequency, the fastest in the atria. At the rotor's periphery, disrupted propagation causes variable EGM morphology and fractionation with multiple spectral peaks. More distal sites exhibit decreased activation rates, resulting in fewer wavebreaks and more regular activity [Guillem <i>et al.</i> 2016]	15
2.6	The original cut-and-sew (Cox-maze III) procedure [Ruaengsri <i>et al.</i> 2018].	18
2.7	Diagram of different LATs definitions computed on unipolar (UNI) and bipolar (BI) EGMS. (B) maximum negative dV/dt , (C) maximum absolute voltage $ V $, (D) maximum absolute slope $ dV/dt $ and (E) minimum voltage [Cantwell <i>et al.</i> 2015].	23
2.8	A) 2D view of 64-lead catheter employed in FIRM ablation [Narayan <i>et al.</i> 2012]. A reentrant circuit can be observed in the right atria while a focal source is presented in the left. B) Example of a bicameral DF mapping obtained with sequential EAM by Atienza <i>et al.</i> [Atienza <i>et al.</i> 2009].	25
2.9	Electrode configuration in the standard ECG [Sanchez 2008].	26
2.10	Comparison of between ECG signals in SR and AF [Sanchez 2008].	27
2.11	Acorys vest for BSPM map vest with 128 electrodes (Corify Care, Spain).	28

2.12	Recorded electrograms (EGMs) and ECGs, along with their dominant frequency (DF) distribution, in a sample patient without a significant left-to-right DF gradient. A) EGMs recorded at various atrial sites and their corresponding power spectra. B) Selected body surface potential mapping leads and their corresponding power spectra. C) Intracardiac DF map with black arrows indicating regions of high DF. D) DF map on the torso surface, with superimposed electrode locations from panel B [Guillem <i>et al.</i> 2013].	30
2.13	Pipeline of an ECGI study performed in the atria. First the vest of electrodes is placed on the patient to performed an MRI or CT. A geometrical model of the heart and torso is obtained. The electrical signals of the torso are recorded by means on BSPM and used to solve the inverse problem. Finally the electrical activity of the atria is presented in a realistic 3D model [Molero Alabau 2023]	31
2.14	Different cardiac sources definitions typical used In forward formulations [Cluitmans <i>et al.</i> 2018].	33
2.15	L-Curve plot with the residual and regularization terms in the axes. The solution of the optimal λ is at the corner of the curve indicated by a dashed line.	37
2.16	A non-invasive complexity mapping validation using global intracardiac basket catheters [Rodrigo <i>et al.</i> 2020]. B Validation of DF mapping using global intracardiac basket catheter [Rodrigo <i>et al.</i> 2021].	38
2.17	Example of a block line in a ventricular ECGI LAT map. A) Two signals at both sides of the conduction block line. The vertical line indicate the LAT marked in each signal. A high temporal delay between LAT annotated is observed in spite of their proximity. B) ECGI -LAT map (left) and reference LAT map. The reference propagation is smoother than the one reconstructed with ECGI [Duchateau <i>et al.</i> 2016].	40
3.1	Examples of ECGI signals with a large and small OI (first row, first and second columns respectively). Additionally, the characteristic D function of each signal is presented below with the area of the largest negative deflection highlighted in yellow.	45

- 3.2 Bayesian Framework framework. The workflow for two different ECGI signals is presented. The first signal (first row) is a signal where exists a good agreement between both methods. The second signal on the other hand, there is a large discrepancy between the methods. In the first step, D signal is computed to identify the location of negative deflections. Then the OI is computed in each atrial node. The positions with a high OI value are used as anchor points to interpolate LATs in the rest of the atria. A p.d.f. is obtained in each atrial node. These curves are finally cobined with the D signals obtained in step 1 using Bayes theorem. The posterior p.d.f. (solid black line) is then used to estimate the final LAT. 48
- 3.3 A) Comparison of posterior and anterior views of LAT maps (first and second rows respectively). Reference LAT map (obtained from simulated EGMs) is presented in the first column. The second and third columns showed the ECGI-LAT maps computed using the $-dV/dt$ and the Bayesian methods. B) Correlation values between each method and the reference LAT maps obtained in all the 62 simulated beats. C) Root Mean Squared values between each method and the reference LAT maps obtained in all the 62 simulated beats. D) Location mismatch computed as the geodesic distance in the EAS. 50
- 3.4 A) Example of slow conduction lines (in green). In the left there is the line obtained in our reference LAT map, in the middle the lines provided by the $-dV/dt$ method and in the right the resulting lines of applying the Bayesian algorithm. B) Representation of the percentage of area accommodating a slow conduction. C) Comparison of the mean errors of LAT spatial gradients under three different noise levels. 52
- 3.5 A) From left to right: catheter contact points in the atrial anatomy, interpolated LAT map and standard deviation associated to each interpolated value. B) First column: posterior (up) and anterior (down) views of interpolated LAT values presenting a standard deviation below 5 ms. Second column: LAT maps obtained from applying the $-dV/dt$ method to ECGI signals. Third column: LAT maps obtained from applying our Bayesian framework to ECGI signals. . . 54
- 3.6 Comparison of Intracavitary and Non-Invasive Cardiac Activation Maps: Panel A displays an intracavitary local activation time (LAT) map obtained during coronary sinus pacing in the presence of a cavotricuspid isthmus block line created by radiofrequency (RF) ablation. Panel B illustrates the same activation sequence acquired non-invasively by Electrocardiographic Imaging (ECGI) using the classical $-dV/dt$ method. Panel C presents the activation sequence also captured by ECGI but derived through our novel Bayesian LAT estimation method, demonstrating enhanced localization of the blockage line. Conduction block lines are shown in white whereas regions in gray represent lack of reliable LATs 55

4.1	A) Torso model used in the experimental analysis. The white dots represent electrode locations on the torso surface. An example of a BSPM signal is presented in the right side. This signal includes the pacing stimulation and the fibrillation induction. B) Heart model. The area covered by the sock is represented in gray. The locations of the epicardial electrodes is depicted with dots in different colors depending on the drug influencing the area (dofetilide or pinacidil). An example of a fibrillation EGM signal registered on the ventricular epicardium is shown in the right side.	62
4.2	Examples DF epicardial maps during ventricular fibrillation represented in a 2D grid. The largest gradients are observed in pinacidil recordings, baseline contains gradients of intermediate magnitude and the lower frequencies and gradients are observed under dofetilide infusion.	62
4.3	Processing pipeline employed in simulations. First APs were simulated and extracellular potentials calculated. The activation frequency was calculated directly from APs using the upstroke as activation time. The forward problem was solved to transfer the information from heart EGM to a torso model with 128 simulated electrodes. White noise was included. The inverse problem was solved for a range of different regularization parameters and the DF maps were computed on each solution. Finally the DF map obtained from the LC solution was compared with the MMAE solution using the frequencies estimated in APs as gold-standard.	63
4.4	A) Lambda range selected to compute DF map in simulation 2. This range was adjusted to include a high power ratio in the frequency band of interest and a consistently high correlation between DF maps of consecutive lambdas. B) Lambda range selected in a patient recording using the same approach. C) and D) Examples of lambda ranges selected from the animal model of ventricular fibrillation.	66
4.5	A) Posterior and anterior views of the of the LC, LR and gold standard DF maps. The 3 first columns correspond to the first simulation, and the 3 last to the second. B) HDF areas obtained for simulation 1 and 2.	67
4.6	Estimation certainty maps within a $\pm 0.2\text{Hz}$ interval around the DF estimated by our LR method.	68
4.7	A) Example of the distribution of DFs in the epicardial surface of the animal ventricular model. The upper map represents the reference DF map computed in epicardial EGMs. The second the ECGI DF map obtained with the LC method and the bottom map the resultant DFs of the LR method. B) TH sensitivity and specificity of each approach is presented. C) Probabilities associated to LR-DF map. D) Percentage of nodes with a error higher than 1 cm using DF-LC and DF-LR methodologies.	70

4.8	A) and B), DF maps obtained in window 3 with LC and LR methods respectively. C) Estimation probability map provided by the LR method within an interval of $\pm 0.2\text{Hz}$. D) Mean absolute difference of DF maps obtained by the LC, LR and high confidence LR nodes in consecutive time windows.	71
5.1	Information about simulations 1 and 2 is presented in the first and second rows of panels respectively. Panels A and E show a pre-ablation instant of the simulated action potentials while panels B and F show the action potentials after ablation. In C and g, ECGI-derived rotor histograms of the pre-ablation periods are shown. Postablation histograms are presented in panels D and H.	82
5.2	A) Recall, Precision and F-score values obtained in the validation data set for all the recordings used in the evaluation. B) and C), Manually labelled and automatically detected rotor histograms obtained from recordings 9 (left) and 3 (right) respectively. The recall, precision and F-score values calculated in recording 9 were 0.87, 0.92 and 0.87 while the recall, precision and F-score values of recording 3 are 0.66, 1 and 0.7 respectively.	83
5.3	(A, B) Illustration of the regional anatomical division of the atria; C) and D) relative errors obtained in each of the atrial regions; E) Mean number of annotated and detected PSs in different atrial regions across the validation dataset. The mean absolute error between these two magnitudes is also presented in black. LB: Left Body; PPVV: Pulmonary Veins; ROOF: Roof; LAAP: Left Atrial Appendix; SEPTO: Septum; RB: Right Body; SVC: Superior Cava Vein; IVC: Inferior Cava Vein; RAAP: Right Atrial appendix	84
5.4	Number of rotors obtained in all the patients: In blue are represented patients staying in sinus rhythm (No recurrence) and in orange patients returning to arrhythmia 6 months after PVI (Recurrence). The number of rotors was calculated in the whole atria in two different scenarios regarding the number of turns used to filter the PS: A) Number of rotors obtained without any turn filtering; B) Number of rotors spinning for at least one turn.	85
5.5	(A,B) Proportion of PSs per second detected in different regions in each studied group: in blue is presented the data from patients that remained in sinus rhythm 6 months after ablation (Non-recurrence), and in orange patients that returned to arrhythmia (Recurrence). In panel (A), are presented the results obtained when all the reentries are considered in the analysis. In panel (B), the same results are shown, when only the reentries lasting for more than 1 turn. The distribution of statistical p/values obtained for each regions are presented din panel (C).	86

5.6	(A,B) PS histograms with and without filtering. (C) Percentage of PSs found in all the different atrial regions when no filtering strategies are applied. No statistically significant differences are observed. . . .	91
A.1	Validation of $-dV/dt$ LAT measures and standard deviation errors. The colors indicate point density. A) Comparison of $-dV/dt$ LATs to the reference LATs obtained from simulations. B) LAT error obtained from $-dV/dt$ against the OI value of ECGI. C) Evolution of the real and estimated standard deviation error for different OI intervals.	110
B.1	3D operations applied in the rotor detection algorithm and correspondent cross-sectional views: 1) The topological charge is calculated out of the input phase maps using 3D convolution operations. 2) A threshold is applied to obtain a binary 3D volume containing the space-temporal locations of phase singularities. 3) 3D dilation is applied on this volume in order connect close phase singularities and conform the space-temporal trajectories of rotors. 4) Skeleton of dilated volume is calculated and branch points are detected in order to remove crossing points in the trajectories. 5) Region growing is applied to the skeletonized volume in order to cluster the trajectories.	112
B.2	Geometrical conformalization process [?].	113
B.3	Proportion of PSs per second detected in different regions in each studied group: in blue is presented the data from patients that remained in sinus rhythm 6 months after ablation (Non recurrence), and in orange patients that returned to any sort of arrhythmia (Recurrence). Panels A and B present PS distributions in recordings obtained with adenosine injection and panels C and D without adenosine. On the other hand, A and C (left column) present the data when all the rotors, independently from their number of turns, were considered in the analysis. Finally, panels B and D (right column) present the PS obtained when applying a threshold of 1 turn.	114

Contents

1	Introduction	1
1.1	Motivation	2
1.2	Objectives	4
1.3	Structure of the thesis	5
2	State of the Art	7
2.1	Cardiac Physiology	7
2.2	Physiological Electrical Conduction in the Heart	8
2.3	Action Potential	10
2.4	Atrial Fibrillation	12
2.4.1	Clinical Perspective	12
2.4.2	Atrial Fibrillation Mechanisms	13
2.4.3	Atrial Fibrillation Management	16
2.5	Non-Pharmacologic Treatments	16
2.6	Invasive Cardiac Mapping	18
2.6.1	Signals in the EP-LAB	20
2.6.2	AF Characterization in the EP-Lab	22
2.7	Surface Diagnostic Technologies	24
2.7.1	Electrocardiogram in AF	24
2.7.2	Body Surface Potential Mapping	27
2.7.3	Body Surface Potential Mapping in AF	28
2.8	Electrocardiographic Imaging	29
2.8.1	Forward Problem	32
2.8.2	Inverse Problem	34
2.8.3	ECGI for AF Characterization	36
3	Bayesian framework for atrial LAT estimation in ECGI	41
3.1	Introduction	41
3.2	Materials and Methods	43
3.2.1	Datasets for Evaluation: In-Silico Data	43
3.2.2	Datasets for Evaluation: Clinical Data	43
3.2.3	Methodologies to measure LATs: Classical LAT estimation method	44
3.2.4	Methodologies to measure LATs: LAT Organizational Index	45
3.2.5	Methodologies to measure LATs: Bayesian LAT Estimation	46
3.2.6	Evaluation Metrics and Statistics	49
3.3	Results	49
3.3.1	LAT Results in Automata Database	49
3.3.2	Robustness of the Bayesian Method Against Artificial Block Lines	51

3.3.3	LAT Results in Patients	51
3.4	Discussion	53
3.4.1	Validation Results	56
3.4.2	LAT Variance Estimation	57
3.4.3	Organizational Index Threshold	57
3.4.4	Limitations and Future Work	58
3.5	Conclusions	58
4	Chapter 4: Probabilistic Dominant Frequency Estimation in AF from ECGI. A proof of Concept	59
4.1	Introduction	59
4.2	Materials and Methods	60
4.2.1	In silico Data Collection and Preprocessing	60
4.2.2	Experimental Data Collection and Preprocessing	61
4.2.3	Inverse problem and dominant frequency estimation	63
4.2.4	Evaluation of Dominant Frequency Estimation Methods	64
4.3	Results	64
4.3.1	Lambda Range selection	64
4.3.2	DF Evaluation	65
4.3.3	DF estimation probability	67
4.3.4	DF estimation in Langerndorff data	68
4.3.5	DF estimation in patient data	69
4.4	Discussion	69
4.4.1	DF Mapping Validation	72
4.4.2	Lambda Range selection	73
4.4.3	Limitations and Future Work	73
4.5	Conclusion	74
5	AF driver Detection in Pulmonary Vein Area by ECGI: Relation with a Favorable Outcome of Pulmonary Vein Isolation	75
5.1	Introduction	76
5.2	Materials and Methods	77
5.2.1	Study Population	77
5.2.2	Ablation and Electroanatomical Mapping	78
5.2.3	Data Acquisition and Preprocessing	78
5.2.4	Rotors and Phase Singularities Detection	79
5.2.5	Rotor Metrics and Clinical Outcome Study	79
5.2.6	Validation Dataset	80
5.2.7	Evaluation Metrics	80
5.3	Results	81
5.3.1	Validation of the Rotor Detection Algorithm in Simulations	81
5.3.2	Validation of the Rotor Detection Algorithm in Patients	81
5.3.3	Relation between rotors and PVI outcome	82
5.4	Discussion	84

5.4.1	Algorithm Evaluation	87
5.4.2	ECGI in the Detection of AF Sources	87
5.4.3	PS Detection and Rotor Tracking with ECGI	88
5.4.4	Noninvasive atrial substrate evaluation in AF patients	89
5.4.5	Clinical Implications	92
5.4.6	Limitations and Future Work	92
5.5	Conclusions	92
6	Chapter 6: Discussion and conclusion	93
6.1	Main findings	93
6.2	Comparison with previous studies	94
6.3	Limitations	97
6.4	Conclusions	98
6.5	Guides for future work	99
7	Chapter 7: Contributions	103
7.1	Main Contributions of this thesis	103
7.1.1	Journal Papers	103
7.1.2	International Conferences	104
7.1.3	National Conferences	104
7.2	Contributions related to this thesis	104
7.2.1	Journal Papers	104
7.2.2	International Conferences	104
7.2.3	Supervision of Master thesis	105
7.3	Patents	105
7.4	Awards	105
7.5	Research Stays	105
7.6	Research Projects and Funding	105
	Appendices	107
A	Appendix Chapter 3	109
A.1	Gaussian Process Input parameters	109
B	Appendix Chapter 5	111
B.1	Rotor Detection Algorithm	111
B.2	Processing of geometrical models	112
B.3	Extended Results with Adenosine	113
	Bibliography	115

Abstract: Atrial fibrillation (AF) is a leading cause of stroke, heart failure and mortality. This disease is characterized by complex and dynamic electrophysiological mechanisms that are not fully understood yet, leading to suboptimal treatments and patient management. The technologies nowadays available in the clinics still have some limitations for AF characterization. The use of traditional electrocardiogram is enough to diagnose AF, but not to determine the origin of the disease. In the last years, different in-silico, experimental and clinical studies have significantly advanced our understanding of AF, suggesting that AF may be driven by specific atrial regions exhibiting recurrent high-frequency patterns and reentrant activity. However, current mapping systems are only designed to characterize regular arrhythmias being very difficult to identify actual drivers among the complex and dynamic patterns present in AF.

In this context, Electrocardiographic Imaging (ECGI) emerges as an important development in the management and treatment of AF patients. This non-invasive technology provides global reconstructions of the electrical propagation in the heart which potentially confers the capacity of characterizing diffuse and time-changing mechanisms in AF. However, the non-invasive reconstruction of complex AF-signals and post-processing strategies to identify drivers are still under development and evaluation. This thesis aims to contribute to the assessment, analysis, and understanding of AF through the development and validation of novel diagnostic algorithms in ECGI.

The characterization of the electrical propagation in sinus rhythm can give relevant information about potential arrhythmogenic areas. Slow conduction areas or propagation blockages can be anchor points for AF. A significant focus of this research is the development of a novel Bayesian framework for the estimation of local activation times (LAT) using ECGI data. Traditional LAT estimation methods often suffer from inaccuracies due to temporal and spatial smoothing in the ECGI solution, which can lead to artificial conduction block lines. The proposed Bayesian approach combines information from ECGI deflections with a spatial propagation model. We compared the traditional LAT method used in the literature with our Bayesian framework. Both approaches were tested on an insilico dataset during sinus rhythm and different pacing positions. In this setup, our Bayesian framework provides more accurate and smoother LAT maps than the well-established traditional criterion, leading to better location of the earliest and latest activation sites and less artificial lines of block. Additionally, we tested the clinical applicability of this methodology by assessing two different activation sequences on real patients. In this setup, our Bayesian framework demonstrated a better interpretability and coincidence with electro-anatomical mapping.

We also evaluated ECGI to characterize atrial substrate during AF. Specifically, the regional activation rate was estimated by means of dominant frequency (DF) computation. For this purpose, we developed a new probabilistic approach and

compared it with the traditional DF estimation method. The findings from in-silico simulations indicate a similar performance from both methods in terms of DF error. However, the new methodology was able to robustly filter some harmonic components that can affect the detection of the HDF. Additionally, the experimental validation in a ventricular fibrillation animal model demonstrated that our new methodology was more accurate, preserving better the HDF areas in this realistic setup. We also quantified and compared the temporal stability of both methods in a real AF episode. Our new method presented higher temporal stability measured as the similarity between consecutive DF maps.

Finally, we used ECGI to detect the reentrant activity during AF in real patients, quantifying the overall complexity of the arrhythmia and measuring the distribution of the reentrant activity in different atrial regions. A higher number of stable reentries in all the atria was observed in AF patients with a poor pulmonary vein isolation (PVI) outcome a year after the intervention. This result was attributed to a higher complexity of the AF in this group of patients. Additionally, a higher prevalence of reentrant activity in the pulmonary veins (PV) was found in those patients that remained in sinus rhythm after PVI. This observation constitutes a direct relationship between the expected AF mechanism and the electrophysiological parameters provided by ECGI. Finally, we corroborated the importance of applying proper filtering strategies in the detection of rotors.

The results obtained from this thesis provide additional evidence on the potential of ECGI to characterize AF. New methodologies to improve the accuracy and robustness of ECGI are also presented as well as potential clinical applications. In this way, this work constitutes a step forward in developing ECGI to provide non-invasive descriptions of individualized AF episodes, which may facilitate and improve treatment and patient stratification in the future.

Keywords: Atrial Fibrillation, ECGI, Atrial Drivers, Local Activation Time.

Resumen: La fibrilación auricular (FA) es una de las principales causas de accidentes cerebrovasculares, insuficiencia cardíaca y mortalidad. Esta enfermedad se caracteriza por mecanismos electrofisiológicos complejos y dinámicos que aún no se comprenden completamente, lo que conduce a tratamientos subóptimos y una gestión ineficaz de los pacientes. Las tecnologías disponibles actualmente en la práctica clínica presentan limitaciones para la caracterización de la FA. Aunque el uso del electrocardiograma tradicional es suficiente para diagnosticar la FA, no permite determinar el origen de la enfermedad. En los últimos años, estudios *in silico*, experimentales y clínicos han avanzado significativamente en la comprensión de la FA, sugiriendo que puede ser mantenida por regiones auriculares específicas que exhiben patrones recurrentes de alta frecuencia y actividad reentrante. Sin embargo, los sistemas de mapeo actuales están diseñados principalmente para caracterizar arritmias regulares, lo que dificulta la identificación de los mecanismos mantenedores de la misma entre multitud de patrones complejos y cambiantes.

En este contexto, la imagen electrocardiográfica (ECGI, por sus siglas en inglés) surge como un avance importante en la gestión y tratamiento de los pacientes con FA. Esta tecnología no invasiva proporciona reconstrucciones globales de la propagación eléctrica en el corazón, lo que potencialmente permite caracterizar mecanismos difusos y cambiantes en la FA. Sin embargo, la reconstrucción no invasiva de señales complejas de FA y las estrategias de postprocesado para identificar mecanismos aún están en desarrollo y evaluación. Esta tesis tiene como objetivo contribuir a la evaluación, análisis y comprensión de la FA mediante el desarrollo y validación de nuevos algoritmos diagnósticos en ECGI.

La caracterización de la propagación eléctrica en ritmo sinusal puede proporcionar información relevante sobre posibles áreas arritmogénicas. Las áreas de conducción lenta o bloqueos de propagación pueden ser puntos de anclaje para la FA. Un enfoque importante de esta investigación es el desarrollo de un nuevo marco bayesiano para la estimación de los tiempos de activación local (LAT, por sus siglas en inglés) utilizando datos de ECGI. Los métodos tradicionales de estimación de LAT a menudo presentan inexactitudes debido al suavizado temporal y espacial en la solución de ECGI, lo que puede llevar a la generación de líneas artificiales de bloqueo en la conducción. El enfoque bayesiano propuesto combina información de las deflexiones de ECGI con un modelo de propagación espacial. Comparamos el método tradicional de estimación de LAT utilizado en la literatura con nuestra metodología. Ambos enfoques fueron probados en un conjunto de datos *in silico* durante el ritmo sinusal y en diferentes posiciones de estimulación. En este contexto, nuestro marco bayesiano proporcionó mapas de LAT más precisos y suaves que el criterio tradicional, mejorando la localización de los sitios de activación más temprana y tardía y reduciendo las líneas de bloqueo artificiales. Además, evaluamos la aplicabilidad clínica de esta metodología analizando dos secuencias de activación en pacientes reales. En este contexto, nuestro método demostró una mejor interpretabilidad y coincidencia con el mapeo electroanatómico.

También evaluamos el ECGI para caracterizar el sustrato auricular durante la FA. Específicamente, se estimó la tasa de activación regional mediante el cálculo de la frecuencia dominante (DF, por sus siglas en inglés). Para ello, desarrollamos un nuevo enfoque probabilístico y lo comparamos con el método tradicional de estimación de DF. Los resultados de las simulaciones in silico indicaron un rendimiento similar de ambos métodos en términos de error de DF. Sin embargo, la nueva metodología fue capaz de filtrar de manera robusta algunos componentes armónicos que pueden afectar la detección de la HDF (frecuencia dominante más alta). Además, la validación experimental en un modelo animal de fibrilación ventricular demostró que nuestra nueva metodología fue más precisa, preservando mejor las áreas de HDF. También cuantificamos y comparamos la estabilidad temporal de ambos métodos en un episodio real de FA. Nuestro nuevo método presentó una mayor estabilidad temporal, medida como la similitud entre mapas consecutivos de DF.

Finalmente, utilizamos ECGI para detectar la actividad reentrante durante la FA en pacientes reales, cuantificando la complejidad general de la arritmia y midiendo la distribución de la actividad reentrante en diferentes regiones auriculares. Se observó un mayor número de reentradas estables en todas las aurículas en pacientes con un mal resultado tras el aislamiento de las venas pulmonares (PVI) un año después de la intervención. Este resultado se atribuyó a una mayor complejidad de la FA en este grupo de pacientes. Además, se encontró una mayor prevalencia de actividad reentrante en las venas pulmonares en aquellos pacientes que se mantuvieron en ritmo sinusal después del PVI. Esta observación constituye una relación directa entre el mecanismo esperado de la FA y los parámetros electrofisiológicos proporcionados por el ECGI. Finalmente, corroboramos la importancia de aplicar estrategias de filtrado adecuadas en la detección de rotores.

Los resultados obtenidos en esta tesis proporcionan evidencia adicional en cuanto al potencial del ECGI para caracterizar la FA. También se presentan nuevas metodologías para mejorar la precisión y robustez del ECGI, así como sus posibles aplicaciones clínicas. De este modo, este trabajo constituye un avance en el desarrollo del ECGI para proporcionar descripciones no invasivas de episodios de FA, lo que puede facilitar y mejorar el tratamiento y la estratificación de pacientes en el futuro.

Resum: La fibril·lació auricular (FA) és una de les principals causes d'accidents cerebrovasculars, insuficiència cardíaca i mortalitat. Aquesta malaltia es caracteritza per mecanismes electrofisiològics complexos i dinàmics que encara no es comprenen completament, fet que condueix a tractaments subòptims i una gestió ineficaç dels pacients. Les tecnologies disponibles actualment en la pràctica clínica presenten limitacions per a la caracterització de la FA. Tot i que l'ús de l'electrocardiograma tradicional és suficient per diagnosticar la FA, no permet determinar l'origen de la malaltia. En els darrers anys, estudis *in silico*, experimentals i clínics han avançat significativament en la comprensió de la FA, suggerint que pot ser mantinguda per regions auriculars específiques que exhibeixen patrons recurrents d'alta freqüència i activitat reentrant. Tanmateix, els sistemes de mapatge actuals estan dissenyats principalment per caracteritzar arítmies regulars, fet que dificulta la identificació dels mecanismes que la mantenen entre la multitud de patrons complexos i canviants.

En aquest context, la imatge electrocardiogràfica (ECGI, per les seves sigles en anglès) emergeix com un avenç important en la gestió i el tractament dels pacients amb FA. Aquesta tecnologia no invasiva proporciona reconstruccions globals de la propagació elèctrica al cor, cosa que permet caracteritzar potencialment mecanismes difusos i canviants en la FA. Tot i això, la reconstrucció no invasiva de senyals complexes de FA i les estratègies de postprocessament per identificar mecanismes encara estan en desenvolupament i avaluació. Aquesta tesi té com a objectiu contribuir a l'avaluació, l'anàlisi i la comprensió de la FA mitjançant el desenvolupament i la validació de nous algorismes diagnòstics en ECGI.

obre possibles zones arrítmiques. Les zones de conducció lenta o bloquejos de propagació poden ser punts d'ancoratge per a la FA. Un focus important d'aquesta investigació és el desenvolupament d'un nou marc bayesià per a l'estimació dels temps d'activació local (LAT, per les seves sigles en anglès) utilitzant dades de l'ECGI. Els mètodes tradicionals d'estimació de LAT sovint presenten inexactituds a causa del suavitzat temporal i espacial en la solució d'ECGI, cosa que pot generar línies artificials de bloqueig en la conducció. El marc bayesià proposat combina informació de les deflexions d'ECGI amb un model de propagació espacial. Vam comparar el mètode tradicional d'estimació de LAT utilitzat en la literatura amb la nostra metodologia. Ambdós enfocaments es van provar en un conjunt de dades *in silico* durant el ritme sinusal i en diferents posicions d'estimulació. En aquest context, el nostre marc bayesià va proporcionar mapes de LAT més precisos i fluides que el criteri tradicional, millorant la localització dels llocs d'activació més primerencs i més tardans i reduint les línies de bloqueig artificials. A més, vam avaluar l'aplicabilitat clínica d'aquesta metodologia analitzant dues seqüències d'activació en pacients reals. En aquest context, el nostre mètode va demostrar una millor interpretabilitat i coincidència amb el mapatge electroanatòmic.

També vam avaluar l'ECGI per caracteritzar el substrat auricular durant la FA. Específicament, es va estimar la taxa d'activació regional mitjançant el càlcul de la

freqüència dominant (DF, per les seves sigles en anglès). Per a això, vam desenvolupar un nou enfocament probabilístic i el vam comparar amb el mètode tradicional d'estimació de DF. Els resultats de les simulacions *in silico* van indicar un rendiment similar d'ambdós mètodes en termes d'error de DF. No obstant això, la nova metodologia va ser capaç de filtrar de manera robusta alguns components harmònics que poden afectar la detecció de l'HDF (la freqüència dominant més alta). A més, la validació experimental en un model animal de fibril·lació ventricular va demostrar que la nostra nova metodologia era més precisa, preservant millor les zones d'HDF. També vam quantificar i comparar l'estabilitat temporal d'ambdós mètodes en un episodi real de FA. El nostre nou mètode va presentar una major estabilitat temporal, mesurada com la similitud entre mapes consecutius de DF.

Finalment, vam utilitzar l'ECGI per detectar l'activitat reentrant durant la FA en pacients reals, quantificant la complexitat general de l'arítmia i mesurant la distribució de l'activitat reentrant en diferents regions auriculars. Es va observar un nombre més elevat de reentrades estables a totes les aurícules en pacients amb un mal resultat després de l'aïllament de les venes pulmonars (PVI) un any després de la intervenció. Aquest resultat es va atribuir a una major complexitat de la FA en aquest grup de pacients. A més, es va trobar una major prevalença d'activitat reentrant a les venes pulmonars en aquells pacients que es van mantenir en ritme sinusal després del PVI. Aquesta observació constitueix una relació directa entre el mecanisme esperat de la FA i els paràmetres electrofisiològics proporcionats per l'ECGI. Finalment, vam corroborar la importància d'aplicar estratègies de filtratge adequades en la detecció de rotors.

Els resultats obtinguts en aquesta tesi proporcionen evidència addicional sobre el potencial de l'ECGI per caracteritzar la FA. També es presenten noves metodologies per millorar la precisió i la robustesa de l'ECGI, així com les seves possibles aplicacions clíniques. D'aquesta manera, aquest treball constitueix un avenç en el desenvolupament de l'ECGI per proporcionar descripcions no invasives d'episodis de FA, cosa que pot facilitar i millorar el tractament i l'estratificació de pacients en el futur.

Introduction

Contents

1.1	Motivation	2
1.2	Objectives	4
1.3	Structure of the thesis	5

The development of computational science and technology have supposed a great impact on many fields. Cardiology is not an exception in this regard. Nowadays physicians count with great variety of monitoring and treatment technologies that are only possible thanks to the incorporation of computers in the clinical practice. The impact of technology in the treatment of cardiac arrhythmias is particularly evident. Recent decades have seen the introduction of advanced navigation systems designed to refine the precision of interventions such as catheter ablations and implantation of rhythm management devices. These technologies offer real-time information in the form of electrical signals and imaging, which are crucial for a successful treatment. In this way, the deployment of such advanced interventional systems has substantially improved patient outcomes, reducing procedural risks and enhancing the accuracy of treatments.

Despite the technological advances in treatment, the diagnosis and evaluation of cardiac arrhythmias predominantly rely on the electrocardiogram (ECG), a technology that has remained fundamentally unchanged for over a century. Nowadays, the ECG is still the cornerstone of cardiac diagnostics, providing vital information about the electrical activity of the heart through surface electrodes. However, interpretation of the ECG is not trivial at all, requiring from a deep understanding of cardiac electrophysiology only acquired after years of training. Furthermore, for most of the arrhythmias, it remains impossible to determine the electrophysiological mechanism and regions involved in their maintenance with ECG. This information is usually only accessible through invasive electro-anatomical (EAM) studies that require navigation systems.

Atrial fibrillation (AF) is a particularly complex arrhythmia which is characterized by irregular and fast activation patterns of the atrial tissue. The mechanisms of this disease are generally unknown, patient-specific and very difficult to identify even by means of invasive EAM studies. In this way, Electrocardiographic Imaging (ECGI) emerges as an important development for management and treatment of AF patients. ECGI is a non-invasive technology that extends the capabilities of the conventional ECG. This method utilizes a dense array of electrodes placed all

over the chest to capture the spatial electrical distribution, offering a more detailed and comprehensive view of the heart's electrical activity than the traditional ECG. Specifically, ECGI captures the electrical activity of the heart in the torso and presents this information in a 3D model of the heart. This new representation facilitates the interpretation of the surface signals and provides localized information about the electrical propagation in the heart. This is why ECGI has the potential for identifying arrhythmia sources and tailoring individualized treatment strategies, constituting a step forward in personalized medicine.

In this context, this thesis explores the potential of ECGI to provide clinically relevant information for the treatment and management of AF patients, contributing to development of the technology by proposing new post-processing algorithms to improve the characterization of AF.

1.1 Motivation

According to the Global Burden of Disease project, about 46.3 million people worldwide had AF in 2016. The future perspective for the development of AF in the western world is not optimistic either. Historical data from the Framingham Heart Study shows that over the last 50 years, the prevalence of atrial fibrillation (AF) has increased threefold [Kornej *et al.* 2020]. Moreover, AF has been identified as a risk factor for many severe and life-threatening diseases such as stroke, heart failure, or cognitive decline [Penado *et al.* 2003] [Hui *et al.* 2015]. As a result, AF has been related to a death risk of 1.5 to 3.5 fold and a reduction in the quality of life in more than 60% of patients suffering this disease [Potpara *et al.* 2021].

Despite the burden in terms of public-health entailed by AF, and the huge effort made to treat it, current therapies remain sub-optimal. Antiarrhythmic drugs have demonstrated to be effective only in paroxysmal AF patients, with success rates non superior to 70% [Komatsu 2012]. Additionally, rate control therapy does not treat the AF itself, just prevents some of the risk and symptoms derived from the arrhythmia. Catheter ablation on the other hand has raised as a promising complementary treatment in this context, demonstrating reductions in hospitalizations, mortality and recurrences of cardiac arrhythmias with respect to antiarrhythmic drugs [Asad *et al.* 2019]. This procedure consists in inserting a catheter in the vascular system to reach the cardiac cavities and isolate electrically potential arrhythmogenic areas.

One of the most important breakthroughs in terms of catheter ablation was done by Dr. Haissaguerre in 1998, who identified the pulmonary veins as a predominant site of AF initiation [Haissaguerre *et al.* 1998]. Since then, pulmonary vein isolation (PVI) by means of catheter ablation has become the standard treatment performed on top of medication. This anatomical ablation has demonstrated to be the best therapeutic option up to date. Nonetheless, around a 20% of paroxysmal AF patients recur to AF a year after the intervention and a modest success rate of 50% has been demonstrated in persistent AF patients [Kistler *et al.* 2023, Tzeis *et al.* 2024].

These results evidence the complexity of AF and the presence of additional mechanisms outside the PV. Different theories about the nature of these mechanisms have been postulated in the past with no actual consensus. However, one important message can be extracted from all of them: Mechanisms involved in AF are patient-specific and dynamic, evolving in time as AF progresses. This way of understanding AF highlights the importance of providing personalized therapeutic strategies.

Several efforts to provide a mechanistic-based ablations have been done in the past with promising but non-reproducible outcomes

[Narayan *et al.* 2012, Haïssaguerre *et al.* 2006, Atienza *et al.* 2009]. Different factors such as the absence of a clear definition of AF-driver or standard protocols for AF induction and mapping contribute to this lack of reproducibility. However, the main limitation for effectively identifying driving sources in AF is fundamentally technical. AF is characterized by chaotic, irregular and unpredictable electrical activity. This characteristic hampers the identification of recurrent patterns using navigation systems, which only provide electrical information of very limited patches of tissue simultaneously.

In contrast, inverse reconstruction of the heart’s electrical activity offer global patterns of the arrhythmia propagation which potentially confers the capacity of characterizing diffuse and time-changing mechanisms. There are two main modalities of inverse reconstructions. Catheter-based imaging is an invasive modality used as part of clinical electrophysiology (EP) procedures. This modality reconstructs the electrical potential on the inner walls of the heart chambers by using data collected from multielectrode non-contact probes positioned inside the heart [Grace *et al.* 2019, Shi *et al.* 2020]. The classical inverse reconstruction modality is electrocardiographic imaging (ECGI). This technology can be seen as an extension of conventional ECG because it employs surface measurements to estimate the electrical activity of the heart [Hernandez-Romero *et al.* 2023]. As this modality is non-invasive, large volumes of data can be recorded and analyzed (inside and outside the EP lab), being not only suitable for personalized ablation guidance, but also for therapy stratification and patient management. However, despite the potential advantages of ECGI for AF characterization, the electrical complexity and irregularity of AF makes from this arrhythmia the most challenging to map noninvasively.

Another important limitation regarding the use of ECGI is the lack of consensus and research on the post-processing strategies for electrophysiological information extraction. One example is the estimation of local activation times (LAT) with ECGI. The characterization of the propagation in sinus rhythm with LAT mapping can provide relevant information about possible arrhythmogenic areas [Invers-Rubio *et al.* 2024], however the most common methodology employed for LATs estimation in ECGI has been directly inherited from invasive navigation systems with no adaptation to the morphology and characteristics of ECGI signals.

Further research and standardization is also needed for parameters measured during AF. Dominant frequency (DF) mapping is a popular subrogate for activa-

tion frequency estimation. The ablation of high dominant frequency sites with the consequent decrease of activation frequency gradients has been correlated with SR maintenance after the intervention [Atienza *et al.* 2009]. Although, different studies have demonstrated the feasibility of measuring activation frequency with ECGI [Rodrigo *et al.* 2017b, PEDRÓN-TORRECILLA *et al.* 2016], this parameter is still not used in the clinical practice due to technical limitations. The development of new postprocessing strategies to identify reliable sites of fast activation are needed for a robust and comprehensive characterization of AF. Additionally, many different methodologies for reentry detection with ECGI has been proposed in the past [Bray & Wikswo 2002, Rantner *et al.* 2007, Rodrigo *et al.* 2017c]. This great variability of methodologies has lead to disperse conclusions about the use of ECGI for catheter ablation guidance. Therefore, further efforts must be made to evaluate the detection of reentries with ECGI and to relate this measure with the clinical outcome of patients undergoing ablation.

In this way, given the potential advantages of ECGI in the characterization of AF and the consequent benefits in terms of patient stratification and treatment, it is of great importance to do research on new post-processing strategies with the objective of evaluating and improving ECGI capacities.

1.2 Objectives

The main objective of this thesis is to contribute to the evaluation, analysis, and understanding of atrial fibrillation (AF) through the development and validation of novel diagnostic algorithms in ECGI, aiming to improve the identification of critical AF drivers through the estimation of clinically relevant electrophysiological parameters. Specifically, these parameters entail studying AF from different perspectives such as identifying disturbances in the propagation during sinus rhythm, or localizing regions of recurrent fast activation and reentrant patterns during AF. In this way, the main objectives of the thesis can be established as:

- *Develop a methodology for the estimation of local activation times (LAT) in ECGI to robustly characterize the propagation during sinus rhythm.*

A new spatiotemporal Bayesian framework will be presented for this purpose. This methodology will be assessed against the traditional method to estimate LATs in ECGI. A dataset of atrial pacing simulations will be used with the aim of comparing both algorithms quantitatively in a well-defined set of propagations. Additionally, the atrial depolarization sequences retrieved by both algorithms will be compared in P-waves from patients in order to demonstrate the direct applicability and show the advantages of the new methodology in a clinical setting. Having new spatiotemporal methodologies available that incorporate a propagation model in ECGI may be useful to avoid typical artefacts inherent from the inverse solution, allowing a better interpretation of these maps and the estimation of more reliable measures of conduction velocity which is a relevant clinical parameter in AF.

- *Evaluate the identification of AF-driving mechanisms in the form of high dominant frequencies using ECGI.*

We will propose a new methodology to robustly estimate DF maps in ECGI. This approach allows to measure the uncertainty associated to the estimates and use it to identify localized reproducible DFs. The conventional DF will be compared with our proposed methodology for DF estimation. We performed this evaluation in AF in-silico models, an animal model of ventricular fibrillation (VF) and a clinical case where we compare the temporal stability of the DFs retrieved by both methods.

- *Characterize non-invasively the prevalence of global and regional reentrant activity in AF patients and evaluate the relationship between the distribution of these highly prevalent reentry areas and the clinical outcome of patients undergoing pulmonary vein isolation (PVI).*

An algorithm for rotor detection will be presented focusing on restricting the definition of rotor to reentrant activity with spatiotemporal coherence. We will use this measure to provide the spatial distribution of the reentrant activity in the atria and correlate this distribution with the clinical outcome of AF patients undergoing PVI. This relationship is of potential interest to incorporate new personalized predictors of the clinical outcome of cardiac ablation, an intervention that is nowadays far from optimal in persistent AF patients.

1.3 Structure of the thesis

This thesis is structured in the following chapters:

- Chapter 2: State of the Art. This chapter provides a general overview on all the research done in relation with ECGI and cardiac arrhythmias, as well as the general concepts needed to understand the content of this thesis. Initially, a brief explanation of key concepts in cardiac electrophysiology is provided. Then we talk about atrial fibrillation from different perspectives. Current invasive mapping systems are also introduced, as well as their main features to characterize AF. Finally, non-invasive technologies going from the traditional ECG to modern ECGI are then explained, including their application for AF characterization.
- Chapter 3: Bayesian framework for atrial LAT estimation using ECGI. A new spatiotemporal methodology to estimate local activation times in the atria is presented and compared with the traditional methodology. Mathematical models are used to test both algorithms and provide an answer about which one offers more accurate and physiological propagations.
- Chapter 4: Probabilistic Dominant Frequency Estimation in AF from ECGI. A probe of Concept. In this chapter we test the accuracy and robustness ECGI

to determine fast activation areas driving AF. We propose a new methodology to robustly estimate DF maps in ECGI. We evaluate this methodology in AF in-silico models, animal model of ventricular fibrillation (VF) and in a real clinical case.

- Chapter 5: AF driver Detection in Pulmonary Vein Area by Electrocardiographic Imaging: Relation with a Favorable Outcome of Pulmonary Vein Isolation. In this chapter a methodology to detect reentrant activity in the atria during AF is described. Additionally, a clinical application of this methodology related to the AF stratification of AF patients is studied.
- Chapter 6: Discussion and Conclusions. The general discussion and conclusions of the thesis are presented in this chapter, including the main findings achieved in this thesis, a comparison with the most relevant and closely related work in the literature, the limitations and the future lines to continue the research presented in this thesis.
- Chapter 7: Contributions. This chapter describes the main contributions provided in the frame of this thesis and other contributions related to complementary projects. Additionally, the scientific stays done during this thesis are enumerated as well as the scientific projects that made possible this work.

The following table summarizes the main structure of the thesis, including the electrophysiological parameters studied in each chapter, as well as the cardiac rhythm involved and the dataset used.

	Chapter 3	Chapter 4	Chapter 5
Rhythm	SR/Pacing	AF	AF
Parameter of Study	LAT	DF	Rotors
Dataset	Simulations/Patients	Simulations/Animal model/Patients	Simulations/Patients

Table 1.1: Summary of main structure of the thesis including the electrophysiological parameter of study, rhythm involved and dataset type used in the studies.

State of the Art

Contents

2.1 Cardiac Physiology	7
2.2 Physiological Electrical Conduction in the Heart	8
2.3 Action Potential	10
2.4 Atrial Fibrillation	12
2.4.1 Clinical Perspective	12
2.4.2 Atrial Fibrillation Mechanisms	13
2.4.3 Atrial Fibrillation Management	16
2.5 Non-Pharmacologic Treatments	16
2.6 Invasive Cardiac Mapping	18
2.6.1 Signals in the EP-LAB	20
2.6.2 AF Characterization in the EP-Lab	22
2.7 Surface Diagnostic Technologies	24
2.7.1 Electrocardiogram in AF	24
2.7.2 Body Surface Potential Mapping	27
2.7.3 Body Surface Potential Mapping in AF	28
2.8 Electrocardiographic Imaging	29
2.8.1 Forward Problem	32
2.8.2 Inverse Problem	34
2.8.3 ECGI for AF Characterization	36

2.1 Cardiac Physiology

The heart is a muscular organ located in the center of the thorax whose primary function is pumping blood throughout the circulatory system. Blood circulation plays a crucial role in distributing vital nutrients and oxygen that sustain cellular homeostasis. Additionally, the circulation of blood toward the lungs is vital to enable the gas exchange, which enriches the blood with oxygen and reduces its residual carbon dioxide concentration. This is why the circulatory system is split into two circuits: systemic (or general) circulation and pulmonary circulation. In the heart, this separation is evidenced by the presence of a septal wall. In each side

of this wall, the heart is again divided into superior and inferior chambers called atria and ventricles respectively.

Systemic or general circulation describes the pathway through which oxygenated blood is pumped to the rest of the body from the heart, and deoxygenated blood is brought back. Starting from the left ventricle, oxygen-rich blood is pumped into the aorta and distributed through a vast network of arteries to various organs and tissues. As the blood delivers oxygen and nutrients, it collects carbon dioxide and other waste products, becoming deoxygenated. This deoxygenated blood returns to the heart through the venous system, entering the right atrium via the superior and inferior vena cava.

The pulmonary circulation is responsible for the exchange of gases between the blood and the air in the lungs. The deoxygenated blood abandons the right atria and falls into the right ventricle of the heart, which pumps deoxygenated blood through the pulmonary artery to the lungs. Within the lungs, carbon dioxide is expelled from the blood, and oxygen is absorbed. The oxygen-rich blood then returns to the heart via the pulmonary veins, entering the left atrium which is communicated with the left ventricle. This cycle is repeated in every single beat. In figure 2.1 the systemic and pulmonary circuits systems are illustrated. An effective circulation of blood is only possible thanks to the heart's rhythmic contractions which are governed by a specific and organized electrical activation sequences of the cardiac tissue. In the next section the cardiac conduction system that allows this kind of activation is described.

2.2 Physiological Electrical Conduction in the Heart

At the core of the heart's electrical system is the sinoatrial (SA) node, situated in the right atrium. Known as the natural pacemaker of the heart, the SA node has the unique ability to spontaneously generate action potentials (APs) that initiates the heartbeat. These are electrical impulses that rapidly propagated across the atrial myocardium, leading to the contraction of the atria and facilitating ventricular blood filling. The impulses then reach the atrioventricular (AV) node, where they are momentarily delayed. This delay ensures that the ventricles are adequately filled with blood before they contract, optimizing the efficiency of blood pumping throughout the body.

Following the AV node, the electrical signal travels down the His bundle, branching into the left (LB) and right (RB) bundle branches, and then disseminates through the Purkinje fibers to the ventricular muscle, ensuring a synchronized and forceful contraction of the ventricles from the apex to the base. This precise sequence of electrical activations is crucial for the coordinated contraction of the ventricle chambers, enabling the effective blood outflow. In figure 2.2, all the structures involved in the propagation of the electrical impulse are presented inside the heart.

The action potential (AP) constitute therefore the information channel that

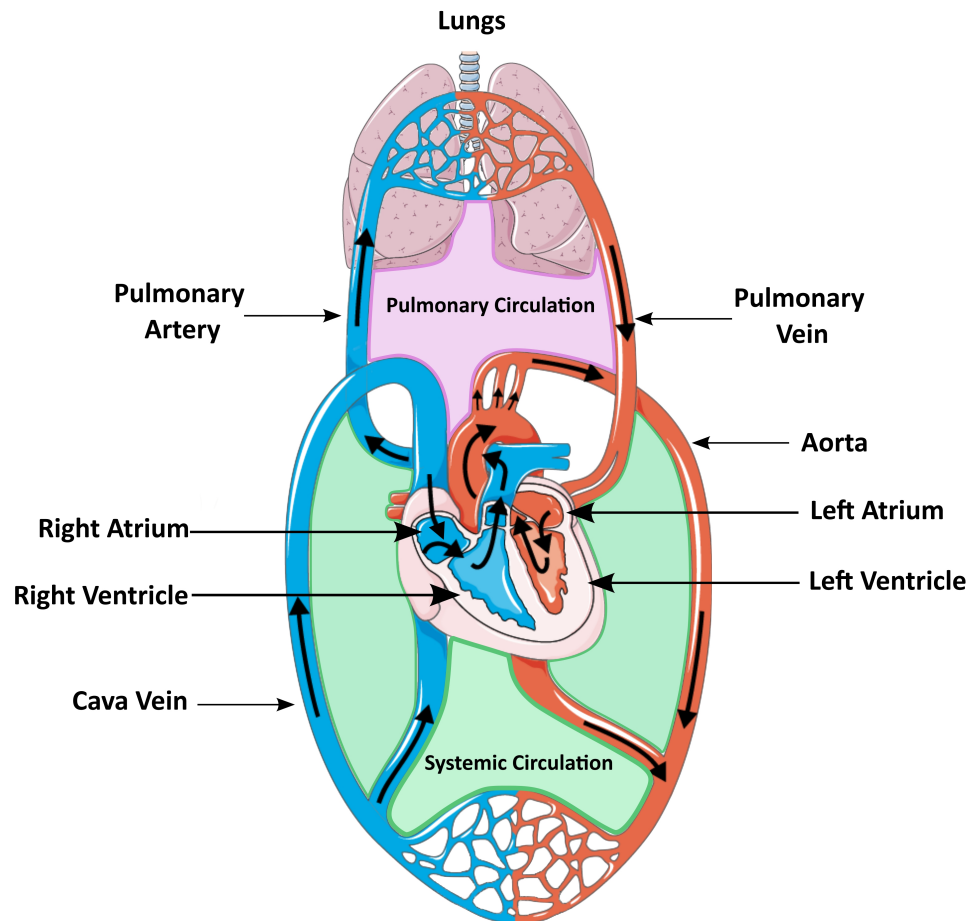


Figure 2.1: Scheme of systemic and pulmonary circulation systems. This schematic was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; <https://smart.servier.com>.

allows the rhythmic contraction of the cardiac tissue. This is characterized by a sequence of ion fluxes through specific channels in the myocardial cell membrane. This process involves a depolarization phase, where the resting voltage of the cell membrane decreases and a repolarization phase in which the cells returns to its resting potential. This cycle takes place in every single heart beat and leads to the mechanical contraction (systole) and relaxation (diastole) of the cardiac cells. In the next section we will further explain AP electrophysiology, describing the different characteristic phases and ions involved.

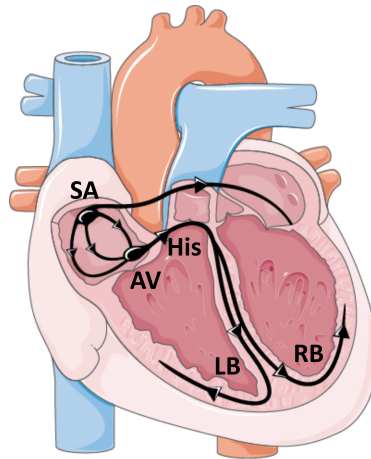


Figure 2.2: Electrical conduction system in the heart. This schematic was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; <https://smart.servier.com>.

2.3 Action Potential

The AP is defined as the transmembrane potential difference generated by the concentration of various ions across the myocardial cell membrane. The cardiac action potential unfolds in different phases, each of them characterized by a specific flux of ions facilitated by a network of ion channels, transporters, and pumps.

Initially, the resting transmembrane potential of the cardiac cells is around -80 mV. In Phase 0, the membrane potential reaches a voltage difference of -40mV which triggers the opening of voltage-gated sodium channels. This leads to a rapid influx of Na^+ ions, causing a significant rise in membrane potential, a critical step for the depolarization process. Following this, Phase 1 initiates a brief repolarization due to the outward flow of potassium ions, facilitated by the opening of potassium channels. This phase involves transient outward currents (Ito), setting the stage

for the action potential's subsequent phases. Phase 2, or the plateau phase, is characterized by a delicate balance between the influx of Ca^{2+} ions through L-type channels and the efflux of K^{+} ions, maintaining a prolonged depolarized state essential for effective ventricular contraction and blood ejection.

As the action potential progresses to Phase 3, a coordinated inactivation of calcium channels and activation of potassium currents, including the rapid delayed rectifier (IKr) and inward rectifier (IK1), repolarize the cell, allowing the membrane potential to swiftly return to its equilibrium state. Finally, Phase 4 marks the completion of repolarization, restoring the resting membrane potential through the concerted actions of the sodium-potassium pump (INaK) and sodium-calcium exchanger (INaCa). These mechanisms work to rebalance the concentrations of Na^{+} , K^{+} , and Ca^{2+} ions within and outside the cell, ensuring the cell is ready for the next activation. In figure 2.3 all the phases with the correspondent ion fluxes are detailed for a ventricular and atrial action potential.

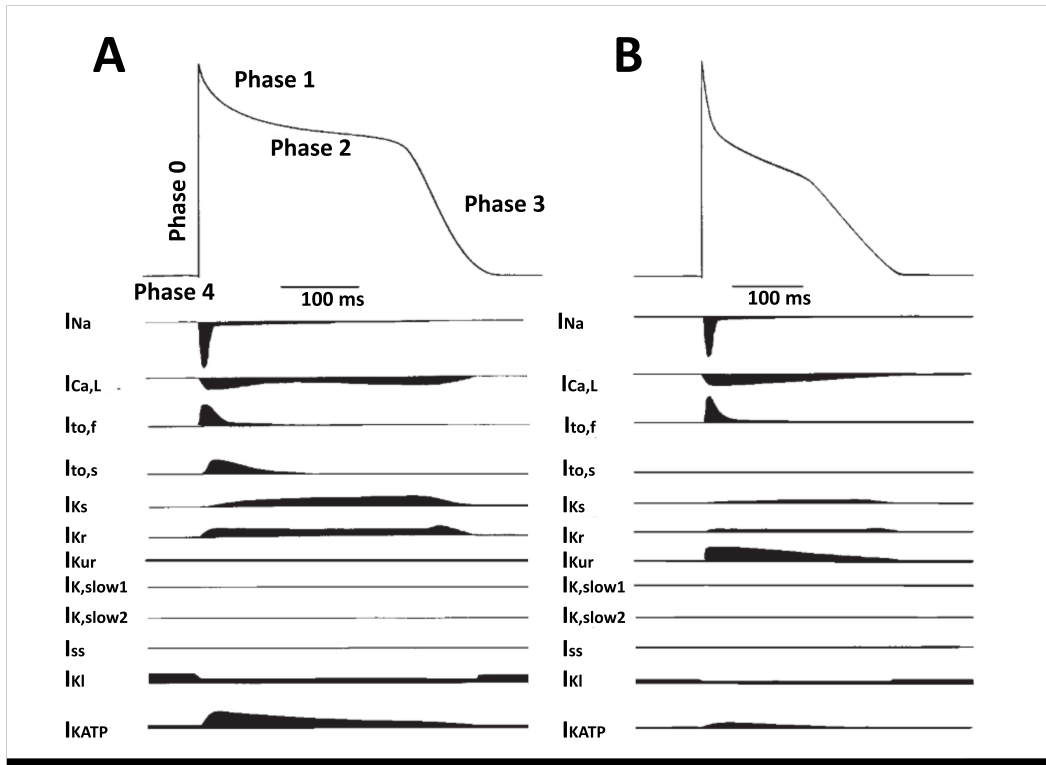


Figure 2.3: Ventricular (A) and atrial (B) action potentials with indications of the different phases and ion currents traces through time. Figure adapted from [1].

2.4 Atrial Fibrillation

AF is the most prevalent supraventricular arrhythmia [Joglar *et al.* 2024]. The prevalence and incidence of this disease underscore its status as a significant public health concern in the western world. The Global Burden of Disease (GBD) study revealed that over 59 million individuals were living with atrial fibrillation in 2019 [Roth *et al.* 2020], constituting a significant increase from the 33.5 million identified in 2010. The true prevalence is likely higher due to undiagnosed cases until symptoms or ischemic strokes occur. Epidemiological studies predict that AF prevalence will reach 15.9 million in America by 2050 [Miyasaka *et al.* 2006], and 17.9 million in Europe by 2060 [Krijthe *et al.* 2013].

Moreover, the significant impact of AF on mortality and morbidity further accentuates the need for effective treatments. AF is associated with a 1.5- to 2-fold increased risk of death stroke (AF constitutes the 20-30% of all ischemic strokes), heart failure (in 20-30% of patients), increases depression risk, and overall affects life quality in more than 60% of patients [Hindricks *et al.* 2021]. In this way, it is urgent to target AF through preventive measures, early detection, and tailored management strategies to mitigate its far-reaching effects on public health. This section describes AF from different perspectives and explains the current management strategies of the disease.

2.4.1 Clinical Perspective

AF is characterized by chaotic and rapid electrical patterns of the atria. During AF, the normal activation of the atrial tissue is disrupted preventing the atria from contracting in a synchronized manner and impairing atrial pumping. In this way, blood stagnation due to inefficient chamber emptying increases the risk of blood clot formation and stroke episodes [Hart *et al.* 1998]. Additionally, this fast and erratic propagation of electrical signals in the atria contributes to an irregular and accelerated ventricular activation rate. This is produced by a high frequency activation rate of the AV node, which finally fails to adequately block and delay the incoming stimuli producing an irregular activation rate of the ventricles.

AF significantly deteriorates the quality of life by disrupting the hemodynamic balance and elevating the risk of major cardiovascular events, thromboembolism (due to the formation of blood clots), stroke (ischemic and non ischemic), ischemic heart disease and sudden cardiac death among others [Odutayo *et al.* 2016]. Despite the impact of AF in terms of health risks and quality of life, the great variability of AF mechanisms, atrial regions involved, and natural evolution of the disease pose huge diagnostic challenges. Clinicians are forced to rely only on symptom recurrence for AF characterization. The current classification scheme of AF, although recognizes this disease as progressive, is purely based on arrhythmia duration, distinguishing AF episodes as first detected, recurrent (including paroxysmal and persistent forms), and permanent [Joglar *et al.* 2024]. Table 2.4 presents detailed definitions of the different AF stages included in the clinical guidelines.

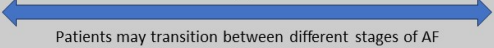
1	2	3				4
At risk for AF	Pre-AF	AF				Permanent AF
						
Presence of modifiable and non-modifiable risk factors associated with AF. Modifiable Risk Factors: • Obesity • Lack of Fitness • Hypertension • Sleep Apnea • Alcohol • Diabetes Non-Modifiable Factors: • Genetics • Male Sex • Age	Evidence of structural or electrical findings further predisposing a patient to AF: • Atrial Enlargement • Frequent Atrial Ectopic • Short Burst of Atrial Tachycardia • Atrial Flutter • Other High AF risk scenarios*	Paroxysmal AF (3A) AF that is intermittent and terminates within <7 days of onset	Persistent AF (3B) AF that is continuous and sustains for >7 days and requires intervention	Long-Standing persistent AF (3C) AF that is continuous for more than <12 month in duration	Successful AF ablation (3D) Freedom from AF after percutaneous or surgical intervention to eliminate AF	No further attempts at rhythm control after discussion between patient and clinician

Figure 2.4: Current classification of AF according to guidelines. Modified figure from [Joglar *et al.* 2024]

2.4.2 Atrial Fibrillation Mechanisms

Understanding the mechanisms underlying atrial fibrillation (AF) is crucial for advancing treatment and management strategies. Clinical observations, as well as in-vitro and in-silico experiments have led to various hypotheses about AF mechanisms. These theories range from identifying specific electrical patterns driving the arrhythmia to an understanding of AF based on structural heart changes.

There is a general agreement about the initiation of AF. In early stages, AF is driven by focal activity or triggers originated outside the sinus node. It has been shown that the pulmonary veins (PPV) is a region particularly frequent for this ectopic activity [Haissaguerre *et al.* 1998]. Several electrophysiological and structural characteristics of PPVs favors the appearance of ectopic beats in this area. For example, action potential duration is particularly short in the PPVs and the presence of delayed afterdepolarizations more frequent than in the rest of the atria, predisposing to autonomous activation and increasing the vulnerability to AF induction [Tzeis *et al.* 2024]. Other areas such as the superior cava vein (SCV), the ligament of Marshall, and the left atrial appendage (LAA) present triggering activity, however their relation with AF initiation is not clear [Santangeli & Marchlinski 2017].

The scientific explanation about the mechanisms that maintain AF episodes remains controversial. One of the most popular theories about these mechanisms is the multiwavelet mechanism proposed by Garrey [Garrey 1924]. This theory suggests that AF is maintained by multiple wavelets interacting and colliding with structural obstacles and conduction dissociation, perpetuating the arrhythmia [Tzeis *et al.* 2024].

In this way, the multiple wavelets mechanism implies that a large portions of the atrial tissue must be treated to restore sinus rhythm, as the arrhythmia arises from a diffuse phenomenon. Some observations coming from clinical studies performed in persistent AF patients support this idea as additional sources beyond the pulmonary veins have been found. These observations indicate that the pulmonary veins alone may not always be sufficient as treatment targets and validates the idea of AF as a diffuse disease [Lin *et al.* 2013, Lim *et al.* 2017].

In contrast, the Mother Rotor Hypothesis is a theory that describes the mechanisms behind AF maintenance as localized, suggesting that AF is perpetuated by a stable rotors, which serve as sources of high-frequency wavefronts [Guillem *et al.* 2016]. This theory offers an explanation of why chaotic electrical activity is observed even when the arrhythmia is driven by a few sources. Figure 2.5 illustrates the organization of AF proposed by this theory. A stable rotor with organized voltage signals is highlighted in blue. This area presents high-frequency activation and organized spectrum. Due to the physiological limit in the conduction velocity of the tissue, the waves emanating from the rotor break in its periphery, giving rise to chaotic electrical activity characterized by fractionation. Finally, the electrical activity is reorganized in further areas after some wavefronts disappear by collision. Some studies based on Langerndoff-perfused hearts or optical mapping recordings have corroborated experimentally some claims of this theory. For example, Mandapati *et al.* found a strong correlation between the rotation period of rotors and the dominant frequency (DF) at the same site [Mandapati *et al.* 2000]. Additionally, other studies observed in AF models that the propagation of waves was mostly leading from the high-frequency to the low-frequency areas [Mansour *et al.* 2001]. In this way, the Mother Rotor theory represents a more optimistic view than the multi-wavelet in terms of understanding the specific mechanism of AF in each patient and applying localized treatments to restore sinus rhythm.

However, despite the promising results of dominant frequency (DF) mapping for identifying AF drivers, particularly in paroxysmal AF [Matsuo *et al.* 2012], evidence in persistent AF is less consistent. Some studies report no added benefit of targeting high-DF regions over conventional pulmonary vein isolation (PVI) [Sanders *et al.* 2005, Salinet *et al.* 2014], which justifies the use of additional features to characterize rotational activity.

Finally, a novel perspective on AF development, particularly in the context of structural heart disease, involves the concept of Endo-Epi Dissociation. This theory maintains that the anatomical structure of the atria in addition to the progression of fibrotic tissue provides a good substrate for 3-dimensional intramural reentry and AF maintenance [Tzeis *et al.* 2024]. Several studies have observed by means of high density mapping how the activation of the endocardium and the epicardium is uncorrelated during AF in animal models [Hansen *et al.* 2018, Eckstein *et al.* 2011]. This findings have also been corroborated in patients during surgical procedures. This theory provides an elegant explanation of why in many cases treatments applied in the endocardium do not result in AF termination.

The divergence of theories about AF mechanisms has been present in the sci-

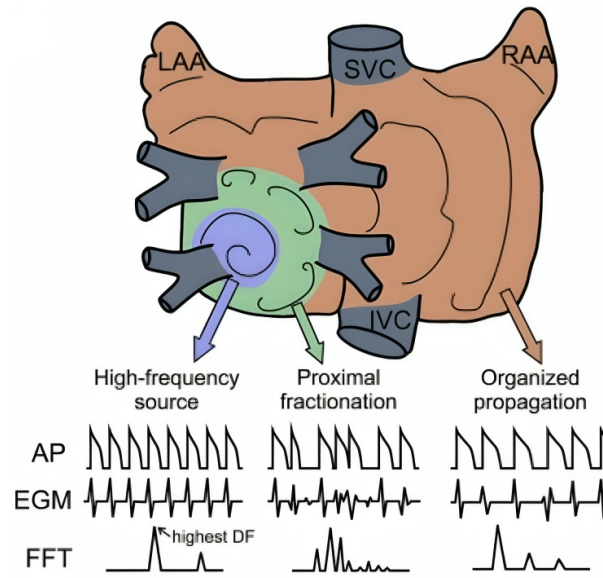


Figure 2.5: Atrial fibrillation (AF) episode driven by a fast rotor. Periodic electrograms (EGMs) are present in the rotor area with a dominant spectral peak matching the rotor’s frequency, the fastest in the atria. At the rotor’s periphery, disrupted propagation causes variable EGM morphology and fractionation with multiple spectral peaks. More distal sites exhibit decreased activation rates, resulting in fewer wavebreaks and more regular activity [Guillem *et al.* 2016]

entific community from a long time. Some difficult but key aspects that may be perpetuating this theoretical discrepancy on AF mechanisms are the different models used (clinical, animal), varying definitions of mechanisms (e.g., how reentry is characterized), and the diverse technologies employed to assess these mechanisms.

2.4.3 Atrial Fibrillation Management

The management of Atrial Fibrillation (AF) represents a significant challenge due to the complexity and variability of the initiation and maintenance mechanisms. This has led to a diverse range of treatment strategies, including both pharmacologic and non-pharmacologic approaches.

Pharmacological Treatments

Pharmacologic therapies primarily consist of antiarrhythmic drugs, such as rhythm control and chemical cardioversion aiming to reduce AF episodes, or cardiac frequency control and anticoagulation used to avoid the typical symptoms and risks associated with AF. The importance of applying early rhythm control in early stages and shifting toward rate control strategies as AF progress is a common practice widely accepted after the evidence provided by recent studies. For example, the use of antiarrhythmic drugs like dronedarone has been associated with a reduction in hospitalization for cardiac reasons and deaths [Hohnloser *et al.* 2009], and Flecainide intake after the first cardioversion showed a drop in AF recurrence [Kirchhof *et al.* 2012a]. Additionally, traditional concerns regarding the complication of rhythm control have been mitigated in studies such as the EAST-AFNET 4 trial, where no differences in the number of hospitalizations and risk of safety outcomes were found between rate control and rhythm control strategies [Kirchhof *et al.* 2020].

However, in patients with permanent AF characterized by significant atrial tissue remodeling, pharmacological rhythm control fails more frequently and the focus shifts towards rate, risks and symptoms control rather than rhythm restoration.

Anticoagulants play a crucial role in this regard. This drug reducing reduces the risk of thromboembolism, a serious complication associated with AF. The loss of atrial contraction in AF patients leads to stasis of blood in the atria, increasing the risk of clot formation and subsequent thromboembolic events. While anticoagulants are effective in mitigating this risk, they also elevate the likelihood of bleeding complications, underscoring the need for careful management.

2.5 Non-Pharmacologic Treatments

Non-pharmacologic approaches include electrical cardioversion, a medical procedure that involves delivering a synchronized electric shock to the heart through electrodes placed on the chest, momentarily interrupting the heart's electrical activity, and

restoring the normal rhythm. This technique, particularly when combined with antiarrhythmic drugs, can decrease recurrence rates in persistent AF patients without structural heart disease [Alegret *et al.* 2008]. However, the aim of this procedure by itself is limited to restore sinus rhythm and not preventing the occurrence of new AF episodes.

Given the limited knowledge available about the maintenance mechanisms of AF, the first surgical procedures aiming to restore sinus rhythm were fully based on anatomical structures. In this line, various techniques were introduced in the 1980's, such as left atrial isolation [Cox *et al.* 1991], the Guiraudon corridor technique [Defauw *et al.* 1992], and the atrial transection procedure [Cox 2011]. However, these methods were ultimately abandoned because they failed to prevent AF and restore normal sinus rhythm [Ruaengsri *et al.* 2018].

The first functional technique was developed by Cox. Called the Cox-maze (CM) procedure, it was first performed in 1987. This method involved creating multiple incisions in the left and right atria to isolate the pulmonary veins and posterior left atrium, interrupting circuits believed to cause AF. The initial CM I procedure had issues with left atrial dysfunction and did not generate a proper sinus node response, leading to high pacemaker implantation rates [Edgerton & Edgerton 2009]. The CM II improved sinus node function by relocating the atriotomy, but it was the CM III which further refined the technique that became a gold standard by adjusting the septal incision, enhancing left atrium exposure, improving atrial function, and reducing the need for pacemakers and AF recurrence [Edgerton & Edgerton 2009]. This technique showed a 95% success rate at 10 years after the intervention [Calkins *et al.* 2007, Cox *et al.* 2000]. Schaff *et al.* [Schaff *et al.* 2000] reported its safety and efficacy, with an early mortality rate of 1.4% and a 3.2% rate of postoperative pacemaker implantation. However, despite its effectiveness, CM III was rarely performed due to its complexity and aggressiveness. Figure 2.6 presents a diagram of the different incisions performed in the atria in the CM III procedure.

The development of modern ablation devices simplified the procedure, leading to the more accessible and less invasive interventions. Ablation therapy is a technique in which a thin and flexible tube called catheter is inserted through the blood vessel system, usually in the groin or neck, and guided to the heart. Once in position, the catheter delivers energy—such as radiofrequency or cryotherapy—to the targeted tissue, creating small scars that block or eliminate electrical pathways. This therapy has been proved to be superior to antiarrhythmic drugs in both patients with paroxysmal and persistent AF [Calkins *et al.* 2009]. Studies such as The Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial validated the safety of AF ablation in AF patients at risk of stroke [Packer *et al.* 2019]. Furthermore, in AF patients suffering from heart failure with reduced ejection fraction (HFrEF), outcomes were enhanced through AF catheter ablation when compared to a combined drug therapy approach that included rate control and antiarrhythmic medications [Kim *et al.* 2022].

Pulmonary vein isolation (PVI) has become the standard ablation treatment for

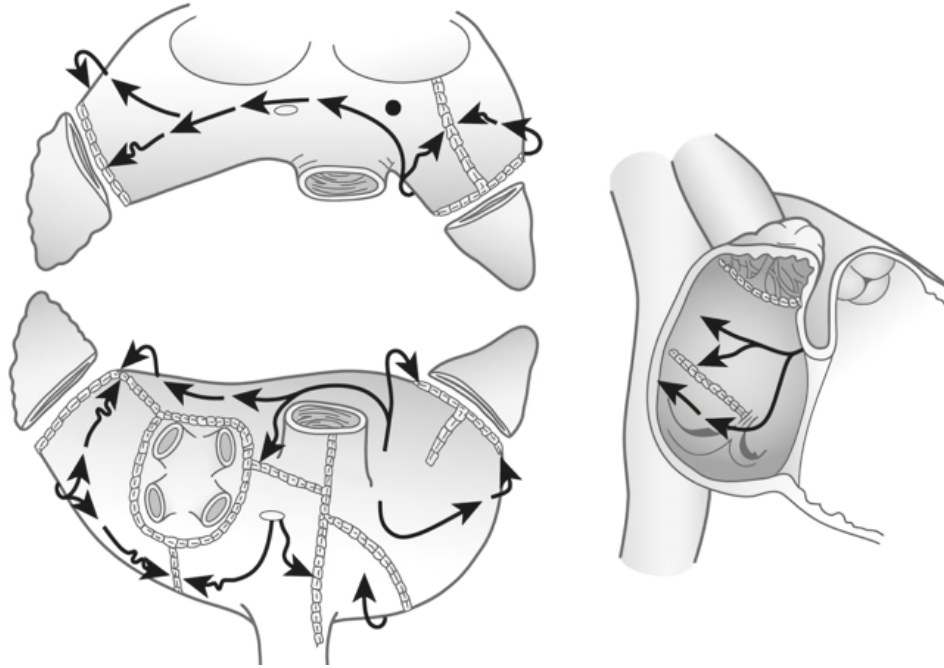


Figure 2.6: The original cut-and-sew (Cox-maze III) procedure [Ruaengsri *et al.* 2018].

patients unresponsive to pharmacological interventions. This technique was proposed by Dr. Haissaguerre in 1998, when he showed that many patients presented spontaneous focal sources originated in the pulmonary veins [Haissaguerre *et al.* 1998]. This treatment is specially effective in paroxysmal AF patients with up to 85% of patients staying in sinus rhythm one year after the intervention. However, in persistent AF patients, the effectiveness drops to 28% [Chao *et al.* 2012, Tsai *et al.* 2022]. This dramatic decrease evidences how additional mechanisms outside the pulmonary veins appear as the disease progresses, and highlights the need for personalized and mechanistic-based ablation strategies. In this way, a thorough analysis and characterization of atrial substrate is needed to apply a specific treatment for each patient. Electroanatomical mapping (EAM) systems have been developed for this endeavor. This invasive mapping systems display electrical and anatomical information combined in order to identify possible arrhythmogenic mechanisms.

The following section provides a description of these systems, as well as an extended explanation on how to interpret the EAM signals and the different techniques employed up to date to identify AF mechanisms.

2.6 Invasive Cardiac Mapping

EAM is an invasive technique used in cardiology to characterize cardiac arrhythmias. This instrumental procedure is useful to guide ablation treatments of various

types of arrhythmias including atrial fibrillation (AF).

Data acquisition is achieved by introducing mapping catheters in the vessel system in order to reach the cardiac chambers. The electrical signals for a small area of cardiac tissue are collected by touching the cardiac surface with an array of electrodes attached to the tip of the catheter. Multiple locations are measured in this way by moving the tip in a sequential process [Roney 2015]. Electroanatomic mapping combines electrical data from the heart with geometrical information, providing a combined representation of electrophysiology and cardiac anatomy to identify the mechanism and origin of the arrhythmia. Initially, two pioneering non-fluoroscopic catheter localization systems were developed and are still in use today. The first system, originally known as LocaLisa® and now incorporated into the NavX® system, operates by generating three low-amplitude, high-frequency current fields across three axes over the patient’s thorax [Wittkamp *et al.* 1999]. This setup calculates the position of an electrode within the thorax relative to a reference electrode, which can be positioned either in the heart or on the torso surface. A comparable approach is employed by the Ensite® system, which has become a key component of the NavX® platform. The second system, known as CARTO®, utilizes three patches to generate magnetic fields beneath the patient’s thorax. Within the tip of the ablation catheter, a magneto sensor measures the strength of these magnetic fields, allowing for the calculation of the catheter tip’s position [Knackstedt *et al.* 2008].

The new developments related to catheter navigation and data visualization have made from EAM a standard in the treatment of several cardiac arrhythmias such as atrial flutter, ventricular tachycardiac or atrial fibrillation. However, despite the important role of electroanatomic mapping systems, they present several limitations. For example, the complexity of these systems entails a steep learning curve, necessitating specialized training for healthcare providers, which can impact procedural efficiency until proficiency is reached [Romero *et al.* 2016]. Moreover, the high costs associated with both the systems and their disposable components can restrict accessibility, especially in resource-constrained environments. Integration challenges with other imaging modalities, such as MRI or CT scans, can affect the accuracy of the generated maps, thereby impacting procedural outcomes. Furthermore, while procedures guided by these systems are minimally invasive, risks associated with catheter manipulation—like perforation or damage to cardiac structures—remain, alongside general anesthesia risks. Additionally, the behavior of inherent temporal variability of some cardiac arrhythmias such as AF is not properly captured with these systems. Catheters are only able to measure the electrical activity on very limited portions of tissue, hampering the characterization of AF dynamics and leading to incomplete treatment strategies.

Some advances in inverse reconstruction of the electrical activity using non-contact mapping systems try to tackle this limitation. This technology reconstructs the electrical potential on the inner walls of the heart chambers by using data collected from multielectrode non-contact probes positioned inside the heart [Grace *et al.* 2019, Shi *et al.* 2020]. However, non-contact catheter mapping

presents several challenges that limit its effectiveness in certain clinical scenarios. First, distinguishing between ventricular repolarization, atrial depolarization, and early diastolic activity can be difficult due to the reliance on isopotential maps, particularly during early diastole, which is challenging to map accurately. Another major drawback is the deterioration in virtual electrogram quality as the distance from the multielectrode array (MEA) increases beyond 4 cm. This often necessitates repositioning the MEA to obtain adequate isopotential maps, which can prolong procedures and reduce mapping efficiency. Additionally, the current technology is limited in substrate mapping, especially for identifying scarred or diseased tissue, making it less reliable for detailed structural analysis of the heart tissue. These limitations highlight the need for more robust mapping tools in complex electrophysiological cases [Friedman 2002].

These limitations highlight the need for continuous advancements in electroanatomic mapping technology, and the development of other alternative mapping techniques to enhance its cost-effectiveness and safety, as well data acquisition to better address complex cardiac arrhythmias with these systems. Nonetheless, a lot of information can be extracted from EAM to understand cardiac arrhythmias. In the following sections the signals acquired in EAM as well as the different parameters that can be derived from these signals are described.

2.6.1 Signals in the EP-LAB

The electrodes placed on the tip of mapping catheters used in EAM capture voltage signals that we call electrograms (EGMs). These represent the electrical potential field generated by the heart. Cardiac excitation involves distributed currents, each contributing to this potential field based on the principle of superposition. Unlike these currents, the potential field extends outside the cardiac tissue filling all the surrounding space and decaying in magnitude by a factor of $1/r$ with the distance to the electrical source. This characteristic confers to the EGMs some degree of spatial resolution. If electric potential were measurable only at the source current and zero elsewhere, spatial resolution would be perfect, allowing electrodes to record exclusively local activity. In contrast, if potential did not diminish with distance, spatial resolution would be non-existent, making it impossible to determine the location of a current source based on electrogram amplitude. However, potential magnitude decreases with distance, introducing some level of blurring, meaning an electrode records activity from both the tissue directly beneath it (close field) and the surrounding area (far field). In this way, spatial resolution is defined by the size of this "nearby region" the electrode measures [Spector 2016]. This concept is essential to interpret and understand the relationship between heart's electrical activity and the voltage measures recorded by the electrodes.

Several factors affect the spatial resolution of electrodes such as size, length, or the distance to the tissue. However, one of the most relevant is the configuration of the electrode which gives place to two different types of electrogram measurements: unipolar and bipolar. In nature, there is no such a thing as unipolar measurements,

as all the voltage values must always be measured with respect to a reference. The main difference between unipolar and bipolar electrograms in the EP lab is the location of the reference electrode. While the reference is situated far away from the heart in unipolar measurements, in bipolar signals it is placed close to the cardiac tissue, at only a few mm from the measuring electrode. In this way, the reference electrode of unipolar electrograms does not capture any electrical activity coming from the heart and the measuring voltage includes a mixture of close and far field. In contrast, in bipolar signals, the far field captured by the reference and the measuring electrode are almost identical (as they are very close to each other) and therefore cancelled from the measurement. Although the size of tissue area in contact with the electrodes is larger in the bipolar configuration, the cancellation of far field voltage characteristic from bipolar electrograms accentuates the voltage changes present in the tissue immediately beneath the pair of electrodes. This feature makes the bipolar configuration particularly suited for enhancing spatial resolution.

Another important source of information to understand EGMs is the morphology. This morphology is used as a clinical surrogate to characterize atrial substrate. For example, the presence of EGM fractionation may be an electrical manifestation of fibrosis and slow conduction [de Bakker 2019], both necessary components for re-entry and therefore possible ablation targets. The morphology of electrogram signals is also affected by the electrode configuration. A unipolar electrogram typically begins with a flat baseline when an activation wave is distant, followed by an upward deviation as the wave approaches. When the wave passes the electrode, the electrogram peaks and then transitions to a negative deflection that reaches negative amplitudes. The instant at which the wave passes right under the electrode can be distinguished by a momentary zero amplitude in this deflection. When the wave moves away, the amplitude eventually returns to zero. Sharpness and amplitude variations help distinguish between near-field (sharp and pronounced) and far-field (rounded) signals. Unlike unipolar signals, bipolar electrogram morphology is dependent on the wavefront's direction. The amplitude of these signals is larger when the wavefront moves parallel to the line connecting the electrodes and weakest when perpendicular. Additionally, the waveform morphology varies based on whether the wave approaches from the cathode or anode side, which can provide valuable insights for identifying the origin of a wavefront. However, when the catheter is on top of a focal activation site it is impossible to determine which electrode is indeed measuring the activation using the bipolar configuration. This is why electrophysiologists usually record simultaneously in both configurations, bipolar and unipolar at the same time.

Although electrogram signal interpretation can provide a deep understanding of the cardiac arrhythmia, checking all the signals is not feasible in the clinical practice, so electrophysiologists usually employ different surrogate parameters calculated on top of the electrograms. In the following section the most relevant measurements employed to characterize AF are described.

2.6.2 AF Characterization in the EP-Lab

The main goal of the different electrophysiological parameters computed in EAM is to identify AF driving mechanisms or potential arrhythmogenic areas. In this way, any electrical characteristic related to the AF mechanisms hypothesized up to date are measured and analyzed with navigation systems, constituting potential targets for ablation.

Some studies have observed a progressive regional decrease in the electrical conduction velocity (CV) in AF patients [Heida *et al.* 2021]. This parameter shows a large variability between different atrial regions in AF patients conferring a great potential to characterize atrial substrate [Meijer *et al.* 2023]. Although, slow conduction velocity areas have not been postulated as a popular ablation target, the presence of slow CVs outside the PPVV ablation has been correlated to AF after PVI [Qi *et al.* 2024]. Conduction velocities are measured by computing the relationship between the local activation time (LAT) at different locations and the distances between the measured sites. The LAT obtained on EGM signals is a subrogate of the mean depolarization time of the cardiomyocytes located in the vicinity of the electrode. This time is computed differently depending on the EGM recording configuration. In unipolar signals, it is defined as the time instant in which the largest down-slope takes places, and in bipolar EGMs it can be calculated in different ways such as the maximum absolute voltage, maximum absolute slope, or the minimum voltage [Cantwell *et al.* 2015]. In Figure 2.7 examples of activation marks obtained for unipolar and bipolar signals are presented.

Equivalent information to CV is obtained from Isochronal Late Activation Times (ILAMS) introduced by Irie *et al.* [Irie *et al.* 2015]. This parameter measures the spatial concentration of isochrones. Although ILAMS are more popular in ventricular tachycardia ablation, the presence of these deceleration zones computed as 4 or more isochrones in 1 cm have also been linked to AF recurrence after PVI [Kuo *et al.* 2023].

The presence of low-voltage areas have been correlated with EGM fractionation and fibrosis [Bijvoet *et al.* 2022]. In fibrotic areas there is no electrical conduction and are usually surrounded by remodeled regions that slow the electrical propagation, constituting perfect anchor points for reentry. Voltage mapping consists in measuring the amplitude of electrogram signals. Although it may seem a simple parameter to measure, there are different dilemma around voltage mapping that still must be clarified. For example, the use of unipolar vs. bipolar catheters. There are several factors that act as confounders in bipolar signals such as wavefront directionality and electrode spacing. Some studies support that there is no critical differences between both recording modalities in the determination of low-voltage areas [Nairn *et al.* 2020], but others suggest the opposite [van Schie *et al.* 2021]. Additionally, it is difficult to establish a proper threshold to distinguish between high and low voltage areas. Some studies have evidenced that this parameter is also dependent on the mapping rhythm (SR or AF) [Lahuerta *et al.* 2022]. In summary, the large variability introduced in low-voltage measures by the threshold

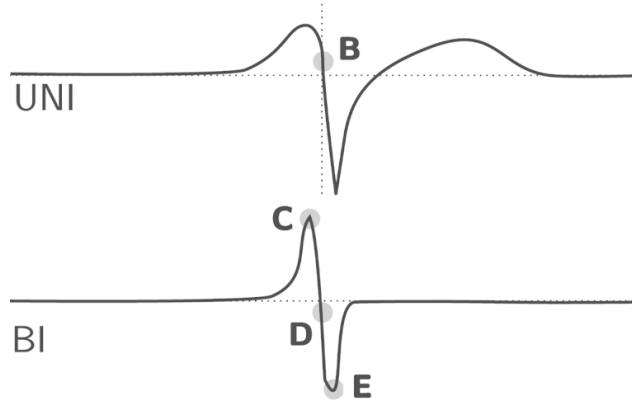


Figure 2.7: Diagram of different LATs definitions computed on unipolar (UNI) and bipolar (BI) EGMS. (B) maximum negative dV/dt , (C) maximum absolute voltage $|V|$, (D) maximum absolute slope $|dV/dt|$ and (E) minimum voltage [Cantwell *et al.* 2015].

selection, atrial rhythm, and recording modality have motivated the development of new parameters to identify fibrosis such as fractionation.

Fractionated electrograms are not only characterized by low-amplitude, but also by the presence of multiple and complex deflections. Both EnsitéTM and CartoTM systems incorporate fractionation mapping which combines different metrics related to the EGM deflections [Aksu *et al.* 2020, Calò *et al.* 2008, Wu *et al.* 2008]. The ablation of complex fractionation atrial electrograms to treat AF became very popular in the last years. However, after several studies, this ablation technique performed on top of PVI was not proved to be more effective than PVI alone, resulting in an increase of atrial tachycardias, fluoroscopy and procedural time [Parameswaran *et al.* 2021, Estner *et al.* 2011, Providência *et al.* 2015, Hunter *et al.* 2011]. In addition, other authors questioned the presence of a direct relationship between fractionation and any relevant electrophysiological information. In [Lau *et al.* 2015], fractionation was compared to other complexity measures of AF such as conduction velocity or electrical dissociation, providing poor correlation between them. A possible explanation for these results is the presence of different mechanism causing EGM fractionation. Some of them not directly related to the cardiac substrate, but to electrical propagations playing a passive role in AF maintenance [Jadidi *et al.* 2012]. For example: wavefront collision or wavebreaks. Additionally, measuring artifact (movement of cardiac tissue or electrical recording from other muscles) or remote activation capture (far field) can lead to false positive detection of fractionation [van der Does & de Groot 2017]. In this way, all these factors relegate voltage and fractionation mapping as a complementary tool to characterize the atrial substrate during AF and prevent them from being a complete and self-explanatory tool to guide ablation.

The description of AF driving sources as high-frequency, hierarchical, and local-

ized reentrant patterns have inspired ablation strategies based on characteristic propagation patterns [Jalife *et al.* 1998]. In this line, Narayan *et al.* developed the focal impulse rotor modulation (FIRM) technique. This mapping technology incorporated a 64-lead basket catheter to map and ablate stable rotors in both atria [Narayan *et al.* 2012], and showed improved outcomes compared to pulmonary vein isolation (PVI) alone [Narayan *et al.* 2014]. However, technical limitations such as poor contact of the basket catheter in complex structures or the lack of standardized preprocessing strategies to filter far-field noise, limited signal quality and made impossible to replicate the results obtained by Dr. Narayan [Benharash *et al.* 2015, Tilz *et al.* 2021].

Other authors have focused in the activation frequency to identify AF drivers. The so called dominant frequency (DF) of EGM is used as a surrogate parameter of the activation frequency which is usually computed as the maximum peak of the frequency spectrum of an EGM signal. Atienza *et al.* implemented DFs computation in sequential mapping and studied the effectiveness of ablating maximum DF sites on top of PVI [Atienza *et al.* 2009]. In this study he observed how a significant decrease in left to right DF gradients was associated to SR maintenance after the intervention. The posterior RADAR-AF study performed in a large population of AF patients concluded that this technique could offer a value in paroxysmal AF patients in terms of AF freedom 1 year after the intervention. However, these results were questioned by other authors arguing that sequential mapping do not capture the temporal variability of DFs during AF and therefore this parameter does not constitute a robust marker to ablate AF drivers [Habel *et al.* 2010, Jarman *et al.* 2012].

2.7 Surface Diagnostic Technologies

2.7.1 Electrocardiogram in AF

Electrocardiography (ECG) is the most popular and established diagnostic technique in cardiology. This technology has become the standard for diagnosing different cardiac conditions such as atrial and ventricular arrhythmias. Regarding AF, ECG has reached special importance, as the AF symptoms are hugely variable and easily referable to other conditions [Rodrigo Bort 2016].

The first ECG prototype developed by Willem Einthoven in 1806 involved placing electrodes on the arms and legs in a triangular configuration which surrounds the electrical activity of the heart in the frontal plane [Einthoven 1906]. This setup not only enabled the first clinically useful ECG but also laid the foundation for the standard electrocardiographic procedures used today. In order to interpret the information provided by the ECG, is essential to understand the physical relationship between the different electrical lines (or leads) obtained by the ECG electrode configuration, and the electrical propagation of the heart.

In the standard ECG, three electrodes are strategically placed to form Einthoven's triangle, typically placed on the right arm, left arm, and left foot. The differences of the electrical potential in the triangle vertices is then measured, creating Leads

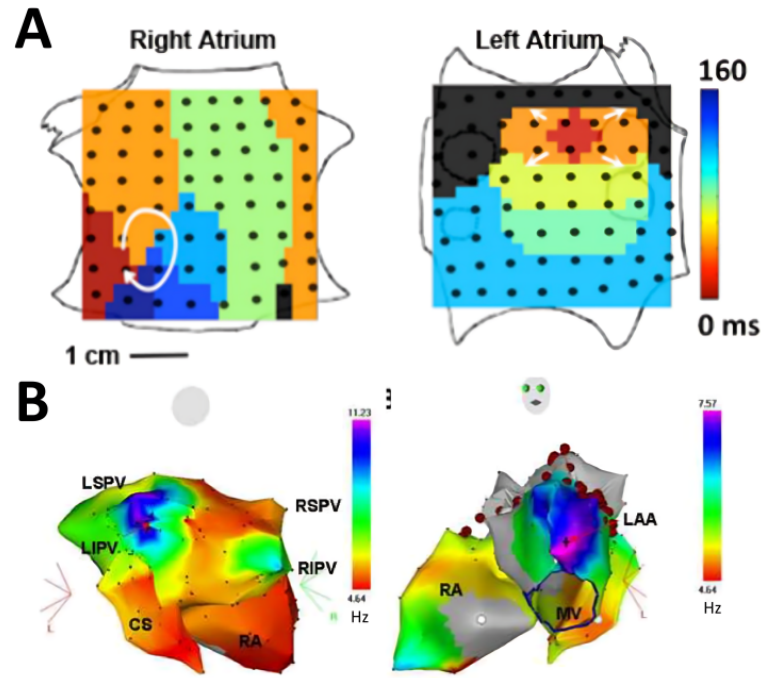


Figure 2.8: A) 2D view of 64-lead catheter employed in FIRM ablation [Narayan *et al.* 2012]. A reentrant circuit can be observed in the right atria while a focal source is presented in the left. B) Example of a bicameral DF mapping obtained with sequential EAM by Atienza *et. al.* [Atienza *et al.* 2009].

I, II, and III. With this configuration, three additional leads can be obtained as the difference of the potential measured in each electrode and the average potential of the other two. These are known as augmented leads (aVR, aVL, and aVF). Outside Eindhoven's triangle we can find the precordial leads (V1 – V6). These are derived from additional electrodes placed on the anterior and left side of the chest. The precordial leads are referenced with respect to the Wilson Central Terminal (WCT) which is a virtual electrically located in the center of the Eindhoven's triangle. Each precordial lead measures the electrical activity from different angles in the axial plane enhancing the three-dimensional assessment of cardiac activity. In figure 2.9 the configuration of the electrodes in a standard 12-lead ECG is presented.

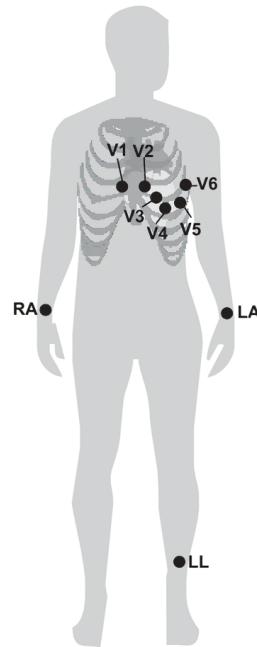


Figure 2.9: Electrode configuration in the standard ECG [Sanchez 2008].

The propagation of the depolarization and repolarization in the heart can be modeled as a moving dipole. In the ECG, the direction of this dipole throughout the cardiac cycle is represented by projecting the dipole in direction of the different leads. In this way, each lead represents how much the depolarization or repolarization wavefront travel in a particular direction.

The different phases of the cardiac cycle are therefore represented in the ECG as characteristic waveforms and deflections in the leads. For example, the P wave indicates atrial depolarization, the QRS complex represents ventricular depolarization, and the T wave reflects ventricular repolarization. The atrial repolarization is hidden by the QRS complex which happens simultaneously and has a larger amplitude

than the atrial repolarization. Additional information can be found in the segments and intervals located between the different waveforms. For example the RR interval represents the time between ventricular contractions (cardiac frequency). The PQ segment reflects the atrioventricular delay, the QT is a surrogate of the action potential duration, the ST provides information about the repolarization time of the ventricles, the TP is the resting time of both atria and ventricles when no electrical activity is propagating in the heart and the TQ segment represent the resting time of the ventricles exclusively [Sanchez 2008]. Figure 2.10.A provides an overview of all the waves and segments in a healthy propagation.

Diagnostic evaluation through ECG involves looking for alterations in these waveforms that indicate specific problems in the electrical propagation. In figure 2.10 an ECG signal of a subject in SR is compared (up) to an ECG during AF. The pattern observed in AF is characterized by the absence of P-wave, with an atrial cycle length usually below 200ms and an irregular RR interval [Tzeis *et al.* 2024].

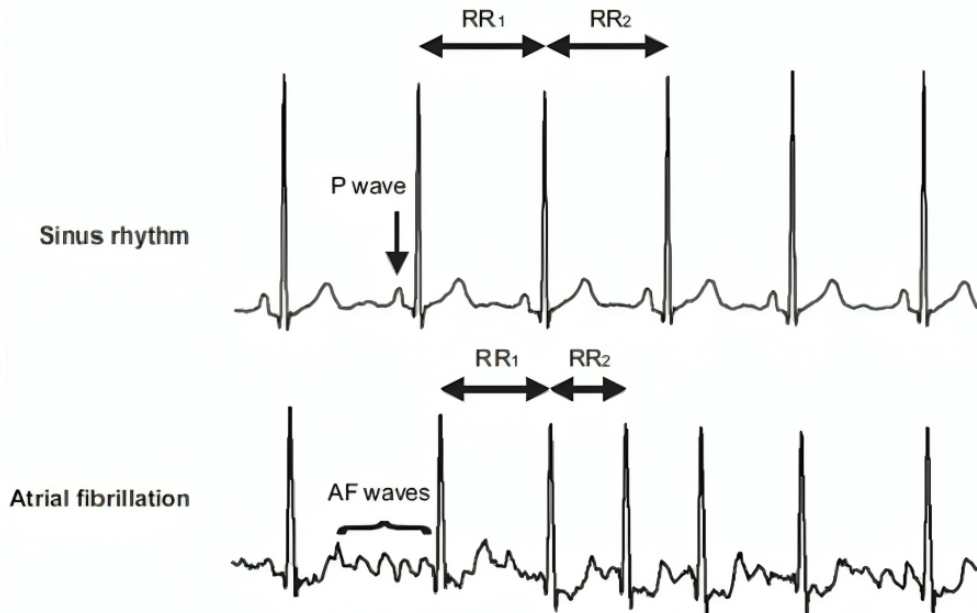


Figure 2.10: Comparison of between ECG signals in SR and AF [Sanchez 2008].

2.7.2 Body Surface Potential Mapping

Body Surface Potential Mapping (BSPM) represents a significant advancement in electrocardiography. This technology captures the surface voltage signals in a high number of locations covering a large surface of the human torso (See figure 2.11). The minimum number of electrodes has been stipulated between 23 and 30 [Guillem *et al.* 2009], but this number usually reaches a set of 128 or 256, providing a detailed depiction of cardiac activity and including more information than the

traditional 12-lead ECG, which only captures electrical signals from nine specific sites.

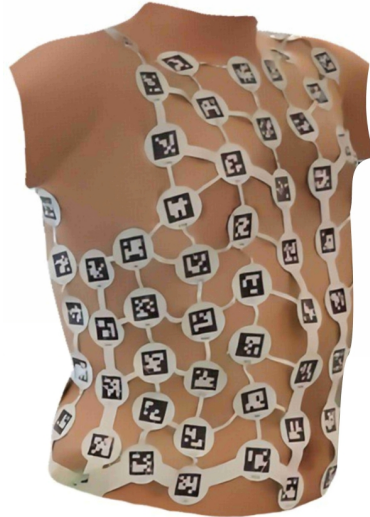


Figure 2.11: Acorys vest for BSPM map vest with 128 electrodes (Corify Care, Spain).

However, nowadays, the dominance of ECG over BSPM in clinical practice is undeniable. Different technical factors like its complexity, the specialized equipment and expertise required, and the lack of standardization in the number and location of the electrodes in BSPM have contributed to the use of ECG. Additionally, theoretical results indicating that simple pathologies with uniform electrical patterns can be represented by a single electrical dipole have contributed to the idea that the 12-lead ECG provided enough information [Burger & Milaan 1946]. In this line, the work performed by Frank et. al. reported that the 95 per cent of the electrical activity distributed in the torso in a normal QRS complex could be approximated by a single point dipole [Frank 1954].

In the last decades, other studies have demonstrated that BSPM contain more clinically relevant information than the ECG [Taccardi *et al.* 1998]. This is specially true for complex arrhythmias such as AF, where multiple wavefronts, resulting in varied electric potentials result in several maxima and minima on the torso [Sanchez 2008]. BSPM has also been probed to have additional applications like Brugada syndrome characterization [Bruns *et al.* 2002], the location of accessory pathways in Wolf-Parkinson-White patients [Tseng *et al.* 1998], or the identification of electrical circuits in atypical flutters and atrial tachycardias [Marques *et al.* 2020].

2.7.3 Body Surface Potential Mapping in AF

As mentioned in the previous section, the natural complexity of AF invalidates the dipole model to characterize the whole electrical propagation in the heart. In this

way, BSPM is specially useful to characterize electrical propagation patterns during AF. Guillem *et al.* was the first showing surface atrial propagation patterns during AF [Sanchez 2008]. In a posterior study she also characterized the global distribution of atrial DFs and even identified the atrial chamber presenting the highest dominant frequency, demonstrating a correspondence between the DF distribution of the atria and the torso [Guillem *et al.* 2013]. She found this relationship by recording simultaneously the EGM signals from the atria and BSPM. In figure 2.12, examples of frequency spectra of different simultaneous intracavitary and surface signals are presented. In panels C and D the resultant DF maps obtained invasively and non-invasively are shown. It can be observed how the highest DF located in the anterior wall of the right atrium is also projected in the right-anterior side of the torso.

Later, the minimal configuration of electrodes in order to differentiate between left and right dominant frequencies was determined by Rodrigo *et al.* [Rodrigo *et al.* 2017a]. This author also demonstrated that the origin of the reentrant activity can be localized to some extent with BSPM. Specifically, he discriminated between left and right atrium reentries through the analysis of surface phase signals [Rodrigo *et al.* 2014]. All these results demonstrate that surface signals encode relevant information to characterize AF when measured from an enough number of locations.

Additionally, other studies have focused on quantifying the complexity of AF patterns in BSPM by means of spatiotemporal decompositions of the signals. Bonizzi *et al.* developed an automatic pipeline to assess the organization of AF by measuring the reflection of the spatial complexity and temporal stationarity of wavefront patterns using principal component analysis (PCA) [Bonizzi *et al.* 2010]. He identified a significant inverse correlation between complexity and stationarity in AF patterns and was able to classify patients in different complexity clusters. Later, other studies also applied spatiotemporal decompositions to evaluate AF organization and identify correlations between AF complexity and catheter ablation outcome. For example, Meo *et al.* also used a PCA-based approach and introduced a nondipolar component index (NDI) to assess AF complexity. She observed how more organized AF episodes were associated with a successful ablation outcome in a set of 97 persistent AF patients [Meo *et al.* 2018]. In the same line, McCann *et al.* proposed 2 new parameters to measure AF copmplexity: error-ratio, normalized root-mean-square error and error-ratio, mean-absolute error. These were compared to the NDI proposed by Meo. *et al.*, finding similar discrimination power between these and the NDI in terms on catheter ablation outcome [McCann *et al.* 2022].

2.8 Electrocardiographic Imaging

Electrocardiographic Imaging (ECGI) is a non-invasive mapping technology that provides a global reconstruction of the electrical activity of the heart. This is achieved by integrating a three-dimensional model of the torso and the heart with

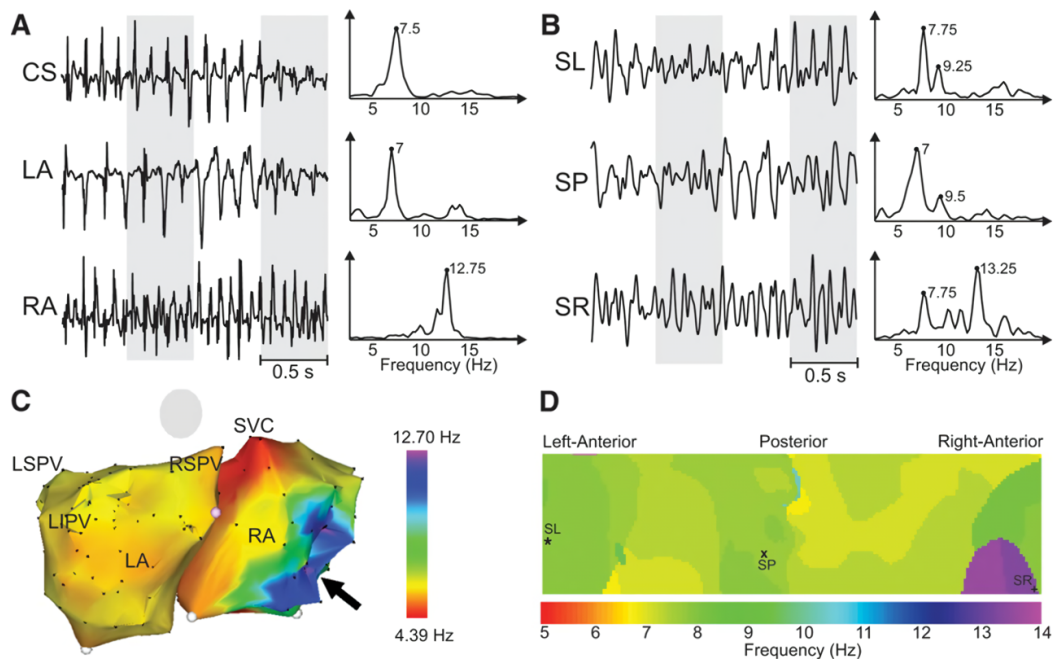


Figure 2.12: Recorded electrograms (EGMs) and ECGs, along with their dominant frequency (DF) distribution, in a sample patient without a significant left-to-right DF gradient. A) EGMs recorded at various atrial sites and their corresponding power spectra. B) Selected body surface potential mapping leads and their corresponding power spectra. C) Intracardiac DF map with black arrows indicating regions of high DF. D) DF map on the torso surface, with superimposed electrode locations from panel B [Guillem *et al.* 2013].

the electrical activity data collected on body surface. In order to avoid simplistic reconstructions of the heart's electrical activity, torso signals are recorded using many electrodes (usually between 128 and 256) with BSPM. In this way, the traditional pipeline employed to obtain ECGI maps consists in acquiring the geometrical information of the torso and the heart by means of medical imaging modalities such as MRI or a CT scan. The patient must wear the vest of electrodes during the image acquisition in order to annotate the location of all the electrodes in the torso. With the geometrical information, the forward problem of electrocardiography is solved. This problem provides the mathematical relationship between the electrical activity of the heart and the voltage signals measured in the torso. The patient is then ready to record the surface voltages which are used to solve the inverse problem of electrocardiography. This problem essentially consists in inverting the relationship obtained in the forward solution, allowing to compute the electrical activity of the heart from the signals measured in the torso. Finally, the electrical activity of the heart is visualized in a realistic 3D model. Figure 2.13 provides an overview of an ECGI study performed in the atria.

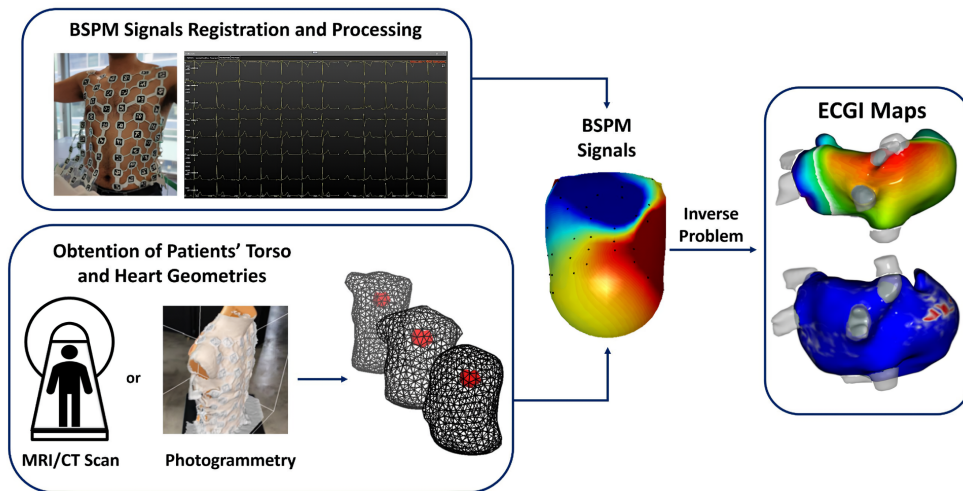


Figure 2.13: Pipeline of an ECGI study performed in the atria. First the vest of electrodes is placed on the patient to performed an MRI or CT. A geometrical model of the heart and torso is obtained. The electrical signals of the torso are recorded by means on BSPM and used to solve the inverse problem. Finally the electrical activity of the atria is presented in a realistic 3D model [Molero Alabau 2023]

ECGI provides strategical advantages over the traditional EAM. For example, it can be used as a powerful tool to stratify patients in complex arrhythmias as it is a non-invasive technology. Additionally, in contrast to current EAM systems, ECGI provides instantaneous global information of the electrical activity in the heart. This is again specially useful in dynamic cardiac arrhythmias such as AF or in therapies in which fast mapping is of great importance, like cardiac

resynchronization (CRT) where different stimulation configurations must be tested [Tam *et al.* 2024, Elliott *et al.* 2020]. ECGI has also helped in the characterization and treatment of different ventricular arrhythmias. For example it has been successfully used to locate isthmus and potential channels for reentry in ventricular tachycardias [Graham & Schilling 2021, Wang *et al.* 2011]. Regarding the atria, ECGI has also been used to identify reentrant circuits in atypical flutter [Wang *et al.* 2007], which are generally impossible to identify with conventional ECG.

In the following sections, an overview of the mathematical formulations and techniques employed to solve the forward and inverse problems of electrocardiography are provided. Additionally, an extensive description of the use of ECGI in AF is presented, highlighting current achievements but also the limitations of the technology.

2.8.1 Forward Problem

The goal of the forward problem of electrocardiography is to relate the torso electrical potentials measured on the surface with a specific cardiac source [MacLeod & Buist 2010]. The propagation of the cardiac sources to the torso surface is formulated as a volume conductor. This formulation always requires from two ingredients: the anatomical relation between the heart and the torso (usually provided with medical imaging such as CT or MRI) and the description of the cardiac electrical sources. Specifically, a cardiac source is an electrophysiological parameter or representation used to describe the electrical activity of the heart. In this way, the volume conductor formulation describing the forward model must be adapted to the cardiac source used. In figure 2.14 the three most common cardiac sources are depicted.

Historically, the cardiac sources have been modeled using discrete representations. The rationale behind this kind of formulations is that a very simple current source is equivalent to the electrical activity of the whole heart when observed from some distance [MacLeod & Buist 2010]. Some examples of these formulations are the single or multiple equivalent dipoles [Messinger-Rapport 1988] or a more complex equivalent dipole layer [Van Oosterom & Oostendorp 2004]. These models constitute equivalent models to the electrical activity of the heart but do not represent any physiological parameter. In this way, the lack of direct physiological links makes experimental and clinical validation of this formulation challenging, as these models do not correspond to observable cardiac variables [Cluitmans *et al.* 2018].

The Transmembrane Voltage-Based Model (TMV) is noted for its close approximation to actual cardiac electrical sources. It utilizes the transmembrane voltage across cardiomyocyte membranes or its continuum approximation as a source model, including transmural reconstructions of cardiac electrical currents, something particularly useful to study depolarized, repolarized, ischemic, and fibrotic zones within the heart [He *et al.* 2003, Wang *et al.* 2009]. Although in this case the formulation is representing cardiac sources as an explicit electrophysiological parameter (currents across cell membranes) TMV are not directly measurable at an organ level,

and therefore its experimental and clinical validations are impossible.

The Extracellular Potential-Based Model uses the potentials produced in a closed surface encompassing the cardiac electrical currents, which constitute a complete equivalent representation of these sources [MacLeod & Buist 2010]. The closed surfaces is conveniently defined as either the ventricular or atrial epicardial surfaces allowing for the derivation of electrograms, which, in this case are directly measurable in the clinical practice. However, while this approach provides detailed surface data and facilitates measurements through experimental or catheter-based procedures, it lacks information about transmural propagation. Despite this limitation, the practical application of extracellular potential-based models, especially in commercial ECGI systems, makes from this model the most clinically relevant.

Additionally, the Activation/Recovery-Based Models offer a streamlined approach by directly imposing as cardiac sources local activation or recovery times, circumventing the need for intermediate reconstruction of TMVs or extracellular potentials. This model, exemplified by the Equivalent Double Layer (EDL) model and the 3D Cardiac Electrical Imaging (3DCEI) model, simplifies the parameterization of cardiac electrophysiology but relies heavily on accurate initial estimates of activation and recovery times for successful application [Han *et al.* 2011, Erem *et al.* 2014].

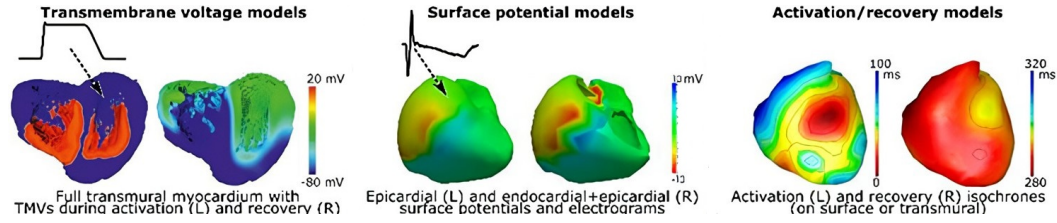


Figure 2.14: Different cardiac sources definitions typical used in forward formulations [Cluitmans *et al.* 2018].

The mathematical complexity of the volume conductor model adapted to any of the cardiac sources explained above, makes impossible to obtain an analytical solution in realistic anatomical domains. In this way, it becomes necessary to employ discretization strategies to solve the forward problem. The main objective of these methodologies is to transform the analytical formulation in the form of differential equations into a linear system. In this linear system both, the solution (torso potential) and input information (cardiac source) are represented as vectors containing discrete spatial values of these variables in their entries. The relationship between the cardiac sources and the torso voltage is encapsulated in a matrix and constitutes the result of applying a discretization. Equation 2.1 represents this relationship, where x is the cardiac source, the matrix A is the forward operator, y the voltage in the torso, and n represents the noise.

$$y = A \cdot x + n \quad (2.1)$$

The choice of a numerical approach for solving forward problems in electrocardiography largely depends on the specific formulation, with no universally best method for all cases [Gulrajani 2005]. The Finite Difference Method (FDM) is often used for its straightforward application. However, it requires from orthogonal and regular grids to represent the solution domain, which is not always optimal to describe the shape of complex geometries such as the cardiac or torso anatomies. The Boundary Element Method (BEM) exclusively focuses on computing the a solution in the boundary surfaces of the domain, in this case, the external surfaces of the torso and the heart. This property makes from BEM a cheap computational method, which is additionally suited to model inhomogeneities in the conductivities of the tissue, but not anisotropy. The Finite Element Method (FEM) and Finite Volume Method (FVM) are favored for their ability to handle general scenarios with inhomogeneous and anisotropic conductivities. However, FEM requires a significant effort in mesh construction, as well as tedious and complex adjustments in the mesh in case of anatomical changes, presenting a major barrier to their practical use [MacLeod & Buist 2010].

2.8.2 Inverse Problem

As explained in the previous section, the forward problem has the fundamental goal of stablishing a mathematical relation between cardiac sources and torso voltage signals. The inverse problem focuses on reversing this relationship in order to face a more interesting problem from a clinical perspective: estimating the cardiac sources from torso voltage measurements. This is why the inverse problem cannot generally be solved without solving first the forward problem.

If the forward problem is formulated as a linear system as stated in equation 2.1, it may seem clear that the solution of the inverse problem must be the result of inverting the matrix A . However, there are two main problems arising when trying to invert this matrix. First, there is no guarantee that A is squared and therefore may not be invertible. Initially, this limitation may not seem to be very important as this problem can be solved by means of a mean squared error minimization.

$$x = \operatorname{argmin} \{ \|Ax - b\|_2 \} \quad (2.2)$$

Where the solution is:

$$x = (A^T A)^{-1} A^T b \quad (2.3)$$

However, the second problem becomes evident when formulating the previous equation. A is an ill-conditioned matrix and the expression $A^T \cdot A$ even more [Pullan *et al.* 2005]. In this way, as the forward operator A is ill-conditioned, the inverse problem becomes ill-posed. In practice, this means that any small perturbation or error in the torso potential b , or in the geometrical information encoded in A , translates into huge errors in the vector solution x . Thus, in order to find

realistic solutions for x , additional constraints and prior knowledge on the problem must be included in the formulation.

The different approaches to constraint the inverse problem can be classified into two main categories: deterministic and probabilistic. In probabilistic formulations x and n (see equation 2.1) are considered as random vectors. The main goal of this approach is to find the vector x that maximizes the posterior probability $P(x|y)$. That is, the probability of a voltage distribution in the heart (x) given a specific set of voltage signals in the torso (y). A probability density function must be assumed for vector x , but also for the noise n introduced by the acquisition system. In the simplest scenario, x and n are assumed to be normally distributed, with 0 mean and constant standard deviation. If the forward operator A is also considered linear, then the maximization of the posterior distribution $P(x|y)$ has a closed solution. This solution is commonly named the Maximum a Posteriori (MAP) and has the following expression:

$$\hat{x}_{MAP} = \left(A^T C_n^{-1} A + C_x^{-1} \right) A^T C_n^{-1} y \quad (2.4)$$

Where C_n and C_x are the noise and solution covariance matrices.

Deterministic methods are more widely used in practice. These follow two main strategies, either approximate the forward operator A with another one A_r that is better conditioned, or find the best-fit solution satisfying additional constraints by means of Tikhonov regularization [Pullan *et al.* 2005]. In order to approximate the forward operator with another well-conditioned A_r matrix, an spectral decomposition of this operator is usually done and the highest frequency components are removed from the forward matrix. This decreases the condition number of the operator reducing the effect of the noise in the solution when inverting the matrix A . The Singular Value Decomposition (SVD) is a popular methodology for this purpose, this is why this approach is called Truncated Singular Value Decomposition (TSVD).

Tikhonov regularization is probably the most used technique to solve the inverse problem. It has been widely used in AF for DF estimation [Rodrigo *et al.* 2021, Rodrigo *et al.* 2017b], and reentrant activity estimation [Rodrigo *et al.* 2017b], but also in other rhythms such as SR [Gao *et al.* 2019], and atrial tachycardias [Shah *et al.* 2013, Cheniti *et al.* 2019]. In Tikhonov regularization, the following expression is minimized to obtain the solution $\hat{x}_\lambda$:

$$\hat{x}_\lambda = \operatorname{argmin} \left\{ \|A(x) - b\|_2^2 + \lambda^2 \|R(x)\| \right\} \quad (2.5)$$

In this equation, the error generated by the forward propagation of the solution candidate x is minimized in combination with another functional that tries to constrain this solution. This last part depends on the regularization parameter λ and the regularization term R which specifies the type of constraint to be applied. The typical regularization matrices used in the inverse problem are the zero-order Tikhonov, where $R = I$; the first order, where $R = G$ being G the discrete approximation of the spatial gradient; and second-order with $R = L$, a discrete

approximation of the spatial Laplacian. In this way, the zero-order Tikhonov regularization constraints the Euclidean norm of the solution x , the first order the differences between the close spatial values of x or steepness of the solution and the second-order provides smooth solutions where no sudden changes in the gradient can take place. Different studies have evaluated the accuracy of each Tikhonov regularization in terms of voltage signals [Karoui *et al.* 2018, Milanič *et al.* 2014] and other electrophysiological parameters measured on top of the inverse solution [Molero *et al.* 2021a]. No consensus have been reached so far about the advantages of any regularization. This is why the most generalized regularization employed so far is the zero-order as it is the simplest. The general solution for this formulation can be written as follows:

$$\hat{x} = \left(A^T A + \lambda^2 I \right)^{-1} A^T y \quad (2.6)$$

In this way, the last component to be estimated in order to solve the previous expression is the regularization parameter λ . This parameter balances the influence or importance of the regularization term in the solution x . The most popular methods to find an optimal λ parameter are the L-curve optimization, and the Composite Residual and Smoothing Operator (CRESO) [Hernandez-Romero *et al.* 2023].

The L-curve criterion [Hansen 1992] involves plotting the regularization objective function against the residual term using different λ values. The resultant curve has an L-shape in which the "corner" represents the ideal balance between over-regularization and under-regularization. Figure 2.15 demonstrates the typical shape of these regularization curve and the optimal value λ , corresponding to the solution in the corner of the function. This value is usually determined by computing the curvature κ of the curve and finding the maximum value according to the following equation:

$$\arg \max \frac{f''}{\left[1 + (f')^2 \right]^{3/2}}. \quad (2.7)$$

The Composite Residual and Smoothing Operator (CRESO) criterion is also used to select the regularization parameter (λ) by maximizing the difference between the derivatives of the residual and smoothing terms [Franzone *et al.* 1985]. Specifically, CRESO chooses the smallest λ_t that results in a local maximum of the function $C(\lambda_t)$, defined as [Pullan *et al.* 2005]:

$$C(\lambda_t) = \|\phi_H(x, \lambda_t)\|_2^2 + 2\lambda_t^2 \frac{d}{d\lambda} \|\phi_H(x, \lambda_t)\|_2^2 \quad (2.8)$$

Where $\|\phi_H(x, \lambda_t)\|_2^2$ represents the solution regularized by λ_t .

2.8.3 ECGI for AF Characterization

Several clinical studies have reported the temporal instability of AF-driving mechanism [Habel *et al.* 2010, Kogawa *et al.* 2015]. This dynamic nature of AF makes

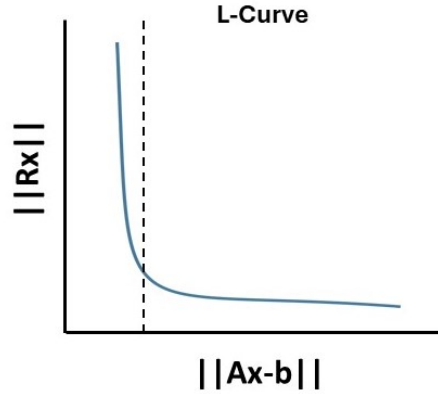


Figure 2.15: L-Curve plot with the residual and regularization terms in the axes. The solution of the optimal λ is at the corner of the curve indicated by a dashed line.

really challenging to capture AF-drivers by means of conventional sequential EAM [Tzeis *et al.* 2024]. In contrast, ECGI provides global reconstructions of the electrical propagation in the heart which potentially confers the capacity of characterizing diffuse and time-changing drivers in AF.

In this way, AF is probably the cardiac arrhythmia in which conventional invasive mapping is more limited and ECGI can provide more value. However, is also the most challenging arrhythmia in terms of epicardial voltage reconstruction. Several factors such as the presence of multiple wavefronts, the residuum from ventricular activity cancellation, the low SNR and the presence of fibrotic tissue may pose additional challenges in the reconstruction of epicardial potentials in ECGI. Indeed, several studies have reported poor correlation between intracavitary and ECGI voltage and phase signals [Rodrigo *et al.* 2017b, PEDRÓN-TORRECILLA *et al.* 2016]. However, other non-invasive parameters such as DF in AF or arrhythmia complexity estimated via reentry location have been demonstrated to correlate well with invasive measurements. For example, Torrecilla *et. al* reported a relative error in non-invasive DF mapping less than 10% with respect intracavitary DF estimation [PEDRÓN-TORRECILLA *et al.* 2016]. These results were correlated by Rodrigo *et. al* who observed an error of 2.3% after filtering the spectra by organizational index [Rodrigo *et al.* 2021]. An example of the correspondence between intracardiac maps and ECGI is presented in figure 2.16. Additionally, the non-invasive estimation of the complexity of AF in different areas was evaluated by the same author using intracavitary basket catheters [Rodrigo *et al.* 2020]. This complexity was measured as the concentration of long-lasting reentries in different areas. A good correspondence between the high complexity areas estimated non-invasively and measured intracardially was observed (see figure 2.16).

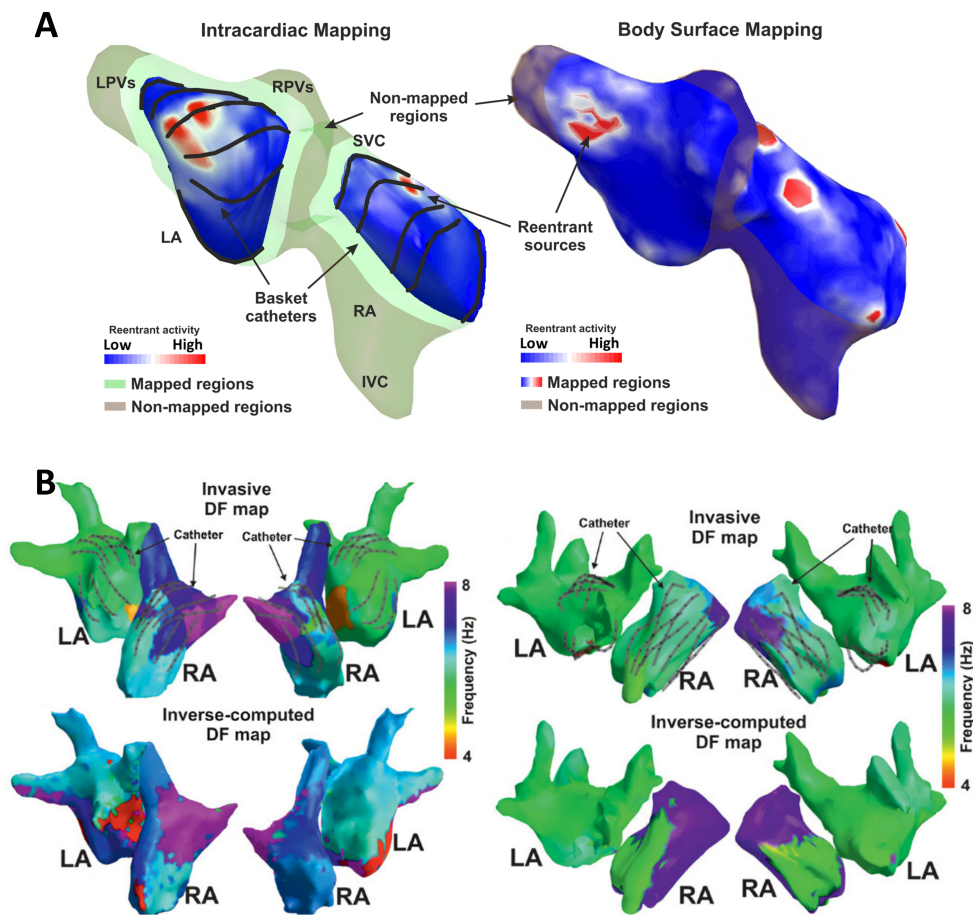


Figure 2.16: A non-invasive complexity mapping validation using global intracardiac basket catheters [Rodrigo *et al.* 2020]. B Validation of DF mapping using global intracardiac basket catheter [Rodrigo *et al.* 2021].

Apart from the technical validation, several studies have also reported clinical advantages of using ECGI for AF-driver identification. For example, Haissaguerre et. al., tested an ECGI ablation strategy guided by cumulative maps of focal and reentrant activity measured non-invasively [Haissaguerre et al. 2014]. They included 103 patients with persistent AF demonstrating that the mean ablation time can be reduced with ECGI. Furthermore, a higher degree of fractionation in reentry areas was identified with ECGI, providing clinical evidence of the detections. Additionally, locations critical to maintenance of AF identified using catheter measures were also co-localized by ECGI in [Cuculich et al. 2010]. The ablation of this sites confirmed by ECGI restore sinus rhythm demonstrated the clinical applicability of ECGI to treat AF. Gao et. al observed in a heterogenous cohort of long-lasting and persistent patients how AF acute termination was possible in a 68% of the patients using ECGI guidance in a stepwise ablation strategy. More recently, the studies TARGET-AF1 and TARGET-AF2 demonstrated efficacy of including ECGI ablations guidance on top of PVI in persistent AF patients. Specifically, in TARGET-AF1 reported a freedom of AF and AT achievement of 65%, and a 75% of AF freedom after a year from the procedure [Honarbakhsh et al. 2022]. The TARGET-AF2 trial focused on redo patients, reporting a lower efficacy in this population of patients, but a 75% freedom of AF in the follow up of the total population of patients [Dhillon et al. 2023].

ECGI has also been used in sinus rhythm to characterize AF substrate. In [Invers-Rubio et al. 2024], ECGI was used to assess the regional atrial conduction velocities noninvasively in a cohort of 52 AF patients. They identified a relationship between the regional CVs and the clinical outcome of patients undergoing PVI. Specifically, patients without slow-conduction areas (mean conduction velocity < 0.78 m/s) presented significantly lower 12-month AF recurrence than those with 1 or more slow-conduction areas. This is the first and only study that demonstrates the capability of ECGI technology to characterize atrial substrate in sinus rhythm. This analysis was performed considering the regional mean CV in 18 different atrial regions and not punctually in all the nodes of their atrial model. This local averaging mitigates the effect of artificial conduction block lines introduced by the inverse problem, making their analysis more robust.

The origin of the artifactual conduction block lines mentioned above lies in the estimation of LAT that serve as input to the CV computation. So far, LATs have mostly been calculated in ECGI signals using the standard method employed in unipolar EGMs [Moore et al. 2023, Shah et al. 2013, Schill et al. 2020]. As mentioned in previous sections, this method consists in finding the most prominent negative deflection in the signal. However, the spatial smoothing produced by the regularization of the inverse problem modifies the morphology of inverse computed EGMs, and introduces artefactual deflections [Schuler et al. 2021]. This phenomenon may result in a selection of wrong deflections as the activation time. In figure 2.17, an example of a conduction block line in an ECGI-LAT is presented with the referenced propagation sequence. LATs obtained using the negative deflection approach are shown in two signals. Although the real activation sequence is smooth

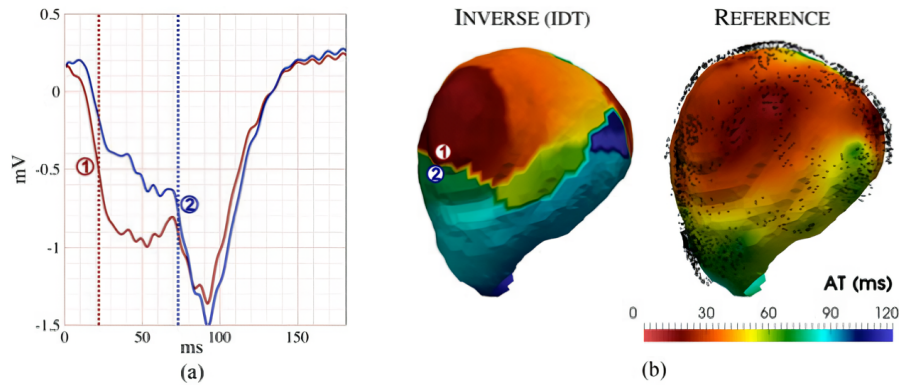


Figure 2.17: Example of a block line in a ventricular ECGI LAT map. A) Two signals at both sides of the conduction block line. The vertical line indicate the LAT marked in each signal. A high temporal delay between LAT annotated is observed in spite of their proximity. B) ECGI -LAT map (left) and reference LAT map. The reference propagation is smoother than the one reconstructed with ECGI [Duchateau *et al.* 2016].

(Reference map), this method estimates very different activation times in two close signals, introducing an artificial conduction block in the reconstructed propagation. In order to solve this problem, some studies have introduced new methodologies that incorporate the spatial distribution of the LAT to improve the selection of the EGM deflection [Cluitmans *et al.* 2022, Duchateau *et al.* 2016]. These methodologies provide smoother maps with more physiological propagations, but they have been developed and validated only in ventricular signals.

In this way, although there is scientific evidence demonstrating that ECGI provides clinically relevant information during AF and SR, there are still technical challenges to face in order to extend ECGI capabilities and robustness.

Bayesian framework for atrial LAT estimation in ECGI

Contents

3.1	Introduction	41
3.2	Materials and Methods	43
3.2.1	Datasets for Evaluation: In-Silico Data	43
3.2.2	Datasets for Evaluation: Clinical Data	43
3.2.3	Methodologies to measure LATs: Classical LAT estimation method	44
3.2.4	Methodologies to measure LATs: LAT Organizational Index	45
3.2.5	Methodologies to measure LATs: Bayesian LAT Estimation	46
3.2.6	Evaluation Metrics and Statistics	49
3.3	Results	49
3.3.1	LAT Results in Automata Database	49
3.3.2	Robustness of the Bayesian Method Against Artificial Block Lines	51
3.3.3	LAT Results in Patients	51
3.4	Discussion	53
3.4.1	Validation Results	56
3.4.2	LAT Variance Estimation	57
3.4.3	Organizational Index Threshold	57
3.4.4	Limitations and Future Work	58
3.5	Conclusions	58

3.1 Introduction

Local activation time (LAT) mapping plays a crucial role in understanding cardiac arrhythmias. Electrophysiologists usually use invasive measurements to obtain detailed information on the activation sequence in the heart. The current standard procedure to directly measure LATs is electro-anatomical mapping (EAM). In this approach, an intracavitary catheter records the extracellular potentials (EGMs) in a small portion of cardiac tissue by direct contact. This is a sequential process in

which several activation cycles are required to map the entire atrial anatomy. In each measurement, a surrogate of the activation time in the depolarization is obtained by localizing the steepest negative deflection of invasive electrograms (namely $-dV/dt$ method). LATs obtained from different EGM signals are referenced to the activation time measured in a fixed position recorded with an additional catheter. This approach is therefore time-consuming, invasive and exclusive for repetitive arrhythmias.

Electrocardiographic Imaging (ECGI) provides panoramic and instantaneous reconstructions of the electrical activity of the heart, addressing from a theoretical point of view, all the limitations present in EAM. This technology makes use of a set of non-invasive voltage signals measured on the torso surface, a geometrical model of the torso and the cardiac anatomy to solve the inverse problem of electrocardiography. There are several formulations of the solution to this problem, some aim at retrieving directly the activation time sequence [He *et al.* 2002], and others solve for the voltage signals. Voltage formulations though, require less assumptions and result to be more versatile, allowing to measure different electrophysiological parameters in the inverse solutions such as LATs, voltage amplitude, activation frequency, making from the voltage formulation the most popular choice in ECGI.

The reconstruction of cardiac voltages in ECGI is an ill-posed problem. The regularization performed to solve this problem smooths spatially and temporally the reconstructed signals, leading to two main challenges when trying to estimate LATs. First, temporal smoothing increases the duration of deflections augmenting at the same time the uncertainty on when to place the activation mark. Additionally, it has been proven how spatial smoothing adds artifactual deflections to the temporal course of ECGI signal [Schuler *et al.* 2021]. This phenomenon may result in a selection of artifactual deflections to determine the activation time. Although LATs have mostly been calculated in ECGI signals using the standard $-dV/dt$ method [Moore *et al.* 2023][Shah *et al.* 2013][Schill *et al.* 2020], the limitations of this approach are well known, which encourage the development of new spatiotemporal approaches.

In this work we propose a new methodology to estimate LATs with ECGI and present its application to estimate atrial activation sequences. This methodology is formulated as a Bayesian framework that combines information coming from ECGI and a data-driven propagation model of the atrial electrical activity. We assessed our new method against the classical $-dV/dt$ approach in a dataset of in-silico pacing models and in two patients: One in sinus rhythm and another during pacing after cavotricuspid isthmus (CTI) ablation. The results obtained are finally discussed in combination with other spatiotemporal methods present in the literature [Cluitmans *et al.* 2022][Duchateau *et al.* 2016]. We hypothesize that our new method provides smoother and more accurate LAT maps than the traditional $-dV/dt$ approach.

3.2 Materials and Methods

In this section, we introduce the datasets used to test our new Bayesian framework. We start by describing the in-silico data, which provides a well-known gold standard for Local Activation Times (LATs). We then present two clinical cases where we could check the clinical applicability of our new algorithm. Electroanatomical Mapping (EAM) was used to understand the real activation sequence of the patient. Next, we explain both the traditional and new methods used to estimate LATs. Finally, we detail the metrics used to evaluate each method’s performance.

3.2.1 Datasets for Evaluation: In-Silico Data

In order to evaluate our LAT algorithm, we have created a synthetic database where ECGI was simulated. We run an automata model over a volumetric bi-atrial mesh with an average edge length of 1.6 mm and 58529 nodes [Herrero-Martin *et al.* 2022]. The simulation database included pacing and sinus rhythm simulations. The pacing simulations consisted of 30 random stimulation locations. For each location, two simulations were generated, one with a cycle length of 100 ms and other of 150 ms. To obtain these cycle lengths, the diffusion coefficients of the model were uniformly scaled in the atria. We then computed EGM signals from APs applying the methodology explained in [PEDRÓN-TORRECILLA *et al.* 2016]. Body surface potential signals were calculated from simulated EGMs in a subset of 128 virtual electrodes located in our torso model. The passive conductor formulation and the boundary element method for discretization were applied to solve the forward problem. Three different levels of zero-mean Gaussian noise were added in the BSPM (10 dB, 3 dB, 3 dB). This lead to a total of 180 pacing simulations (30 locations x 2 cycle lengths x 3 levels of noise =180). A similar protocol was followed for the sinus rhythm simulation yielding to a total of 6 simulations (1 location x2 cycle lengths x 3 levels of noise =6). Finally, Tikhonov 0-order regularization and the L-curve method were used to solve the inverse problem as described in previous works [Salinet *et al.* 2021] [PEDRÓN-TORRECILLA *et al.* 2016].

Rhythm	N places	Noise Level (SNR dBs)	Cycle length (ms)	Total Maps
Pacing	30	10, 3, 0	100	180
SR	1	10, 3, 0	100	6

Table 3.1: Population of automata simulations

3.2.2 Datasets for Evaluation: Clinical Data

In order to demonstrate that the analysis performed in simulations is reproducible in clinical data, both LATs methods were compared on ECGI recordings obtained from real patients, where endocardial LATs were available and used as a gold standard.

First, we generated an intracavitary comprehensive activation map within the atrial geometry by interpolating intracavitary LAT measurements recorded by the

navigation system. A Gaussian Process (GP) interpolation was used for this purpose. This GP model was constructed following the outline previously described in [Coveney *et al.* 2020]. However, in this case we considered the variance of the measured intracavitary LATs σ_i as zero. The model returns a probability density function (pdf) per node from which we derive the expected LAT value and the uncertainty associated to the interpolation (standard deviation). In order to validate our algorithm only with reliable endocardial LATs, we discarded the interpolated LATs with a standard deviation larger than 5ms.

Regarding the non-invasive data, 10 second BSPM signals were recorded in a 64-electrode vest with 1 kHz sampling frequency. In these segments, a P-wave was selected for ECGI reconstruction. Signals were visually inspected in order to remove the leads with poor quality or bad contact. The remaining signals were filtered with a 0.05-500 Hz bandpass filter and with a notch filter at 50 Hz to remove power interference. Torso geometry was acquired by photogrammetry and the atrial geometry was personalized via MRI. The imageless ECGI ACORYS system from Corify Care was used to integrate all this information and solve the inverse problem using the same approach as in simulations. We performed an ECGI study to a 55-year-old male patient with persistent atrial fibrillation. Intracavitary LAT maps were recorded to obtain the activation sequence in the left atrium during sinus rhythm. The patient was cardioverted and mapped using NavX[®] system before pulmonary vein isolation (PVI). The clinical parameters include a history of nine years with AF, a body mass index of 32.6, arterial hypertension, a left ventricular ejection fraction of 69%, and a CHA₂DS-VASc₂ score of 1.

Additionally, we tested our Bayesian LAT algorithm in the presence of a real and localized conduction blockage. We studied the electrical activation sequence in a 74-year-old female with persistent AF after Cavo-tricuspid isthmus ablation. The isolation line was confirmed by the physician via intracavitary LAT mapping during coronary sinus pacing. ECGI data was acquired during this maneuver which was performed after a redo ablation of the right pair of pulmonary veins. This patient presented arterial hypertension, dyslipidemia and was treated with antiarrhythmics (flecainide) and anticoagulant (dabigatran) drugs.

3.2.3 Methodologies to measure LATs: Classical LAT estimation method

We computed LATs from the generated ECGI signals using the classical $-dV/dt$ method. In this approach, the activation time is defined at the moment where the steepest voltage downslope takes place during the depolarization. We derived a characteristic function D to determine the presence of negative deflections in ECGI signals. To do so, the temporal derivative of each signal was calculated. Positive values were set to zero in the derivative in order to remove information coming from positive deflections. Finally, the absolute value of dV/dt is computed. Equations 3.1 describes these operations mathematically:

$$D = \begin{cases} -v' & \text{if } v' < 0 \\ 0 & \text{if } v' > 0 \end{cases} \quad \text{where } v' = \frac{dv}{dt} \quad (3.1)$$

Where v' is the temporal derivative of voltage v . In this method, the LAT is set to the maximum peak present in D .

3.2.4 Methodologies to measure LATs: LAT Organizational Index

Reliability on LATs was assessed by computing an organizational index (OI). This parameter measures the predominance of the largest downslope in ECGI signals [Duchateau *et al.* 2016]. In this way, signals with high OI are characterized by a single dominant deflection where the LAT can be clearly identify. Mathematically, it is defined as the ratio of the largest peak area A_j , over the area under the function D .

$$OI = \operatorname{argmax}_j \left(\frac{A_j}{\int D dt} \right) \quad (3.2)$$

The areas A_j of every peak j in D were calculated by local integration. Figure 3.1 shows an example of two different ECGI signals and their correspondent OI. The first one (left) presents a high OI as there is only one large negative deflection. In the second one, (right) the OI is small because there are multiple downslopes with similar energy. The correspondent LAT assigned to each ECGI signal are also shown in blue.

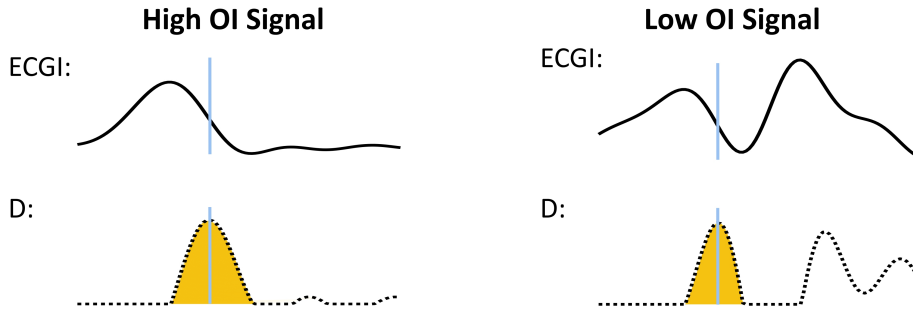


Figure 3.1: Examples of ECGI signals with a large and small OI (first row, first and second columns respectively). Additionally, the characteristic D function of each signal is presented below with the area of the largest negative deflection highlighted in yellow.

We set an OI threshold T in order to identify those ECGI signals that provide a reliable LAT estimate. An analysis of the selection of T was performed in our automata database (see appendix A).

3.2.5 Methodologies to measure LATs: Bayesian LAT Estimation

Our Bayesian LAT estimation uses as input the traditional LAT map and the deflection information D obtained in equation 3.1. With these data, we first build a model that assumes smooth propagation and then combine this a priori with the deflection data D . The following subsections explain this framework in detail.

3.2.5.1 Building a propagation model: Gaussian Process interpolation

We built a data-driven propagation model by interpolating LATs in low-confidence locations of the atria. This model uses as inputs high-confidence LATs obtained with the standard $-dV/dt$ method, and measures associated to the uncertainty of these LATs. High-confidence LAT estimates were identified using the OI described in the previous section. In this way, LATs belonging to ECGI signals with an OI higher than a threshold T were considered to be high confidence and used to interpolate the LATs in the rest of the atria. The uncertainty of LATs provided by the $-dV/dt$ method was quantified as the standard deviation of the expected error. The estimated standard deviation of these errors were introduced in a probabilistic interpolation model that quantifies the uncertainty of the interpolated value based on its location. Specifically, the interpolation model was formulated as a Gaussian Process (GP) following the methodology described in [Coveney *et al.* 2020]. In Gaussian Processes, a function f is fitted to a set a of noisy observations y_i specified at locations x_i . This is done under the assumption that all the data is distributed following a multivariate normal distribution:

$$\begin{cases} f(x) \sim \mathcal{GP}(0, \tau^2 k(x, x')), \\ y_i = f(x_i) + \varepsilon_i, \quad \text{where } \varepsilon_i \sim \mathcal{N}(0, \sigma_i^2) \end{cases} \quad (3.3)$$

In our case, y_i corresponds to reliable LATs (with high OI) and x_i to the locations (manifold nodes) where those LATs are located. The variance σ_i^2 associated to each measurement y_i was estimated by fitting a gaussian mixture model to the D function obtained in each high-confidence node x_i . This was done by considering the function D_i associated to the node x_i (see figure 1) as a probability density function. In order to fit the model, D_i was sampled generating a dataset of points that constituted the input of the gaussian-mixture fitting algorithm. In this way, we defined y_i and σ_i^2 as the mean and variance of the fitted gaussian distribution corresponding to the largest peak in D_i .

In the GP model, the covariance between LATs $\Sigma(x, x')$ is a function of the spatial location x_i in the atria. This information is specified in the term: $\tau^2 k(x, x')$, where τ^2 is an hyperparameter and $k(x, x')$ is a kernel function describing the spatial relationship between LATs. In order to define $k(x, x')$, we adapted the Euclidean Matern 3/2 function to a 3-dimensional manifold domain and built a vector basis that encodes the atrial anatomy [Coveney *et al.* 2020]. This procedure consists in expressing our stationary kernel $\Sigma(x, x')$ as a function of the

spectral density $S(\omega)$ and the eigensolutions of the atrial-mesh Laplacian operator [Solin & Särkkä 2020][Solin & Kok 2019].

$$\text{Cov}(f(x_i), f(x_j)) = \hat{k}(x_i, x_j) = \sum_{k=1}^M \sqrt{\lambda_k} \phi_k(x_i) \phi_k(x_j) \quad (3.4)$$

Where $\phi_k(x)$ are the eigenfunction resultant from solving the following the system:

$$\begin{cases} -\nabla^2 \phi_k(x) = \lambda_k \phi_k(x), & x \in \Omega \\ \nabla \phi_k(x) \cdot \mathbf{n}_{\partial\Omega} = 0, & x \in \Omega \end{cases} \quad (3.5)$$

Being λ_k the eigenvalues associated with the eigenfunctions $\phi_k(x)$, Ω the domain defined by the atrial mesh and ∇^2 the Laplacian operator applied on the atrial mesh. Given its robustness, we decide to use the tufted Laplacian implementation proposed in [Sharp & Crane 2020]. The expression of Matern 3/2 spectral density function is presented in equation 3.6:

$$S(\omega) := \frac{2^{\frac{d}{2}} \pi^{\frac{d}{2}} \left(\nu + \frac{d}{2}\right) (2\nu)^\nu}{\Gamma(\nu) l^{2\nu}} \left(\frac{2\nu}{l^2} + 4\pi^2 \omega^2\right)^{-(\nu + \frac{d}{2})} \quad (3.6)$$

Where ν is the smoothness, l is the length-scale, d the dimensionality ($d = 2$) and Γ is the Gamma function. In this way, the spectral density function $S(\omega)$ defines the structure of our kernel. This particular approach has the advantage of decoupling the covariance structure of choice, and our vector basis, allowing a more efficient tuning of the hyperparameters.

Once the multivariate Gaussian model is defined, the low-confidence LATs distributions are estimated as the conditional distribution $Z | Y$. Where Z is a vector of low-confidence LATs and Y the vector of high-confidence LATs (y_i). Gaussian distributions possess the algebraic property of having a conditioning closed form. This property allows to express the conditional distribution $Z | Y$ as another Gaussian distribution in terms of the means and covariance matrices of both data sets, Z and Y . The mathematical expression is presented in equation 3.7:

$$Z | Y \sim \mathcal{N}(\mu_Z + \Sigma_{ZY} \Sigma_{YY}^{-1} (Y - \mu_Y), \Sigma_{ZZ} - \Sigma_{ZY} \Sigma_{YY}^{-1} \Sigma_{YZ}) \quad (3.7)$$

Where μ represent the mean, and Σ the covariance and cross-covariance matrices. Combining the distributions in $Z | Y$ and Y we finally obtain our propagation model $GP | D$ which provides the probability density function of activation at each node.

3.2.5.2 Posterior Bayesian distribution and LAT estimation

In this step, we combine the information coming from the ECGI deflections D , and the propagation model $GP | D$ we built in the last section. We do this by applying Bayes theorem in each atrial node:

$$P(D | GP) = \frac{P(GP | D) \cdot P(D)}{P(GP)} \quad (3.8)$$

This expression returns a posterior probability density function (pdf) in each node. We use this function to derive our optimal LAT. For that, we minimize a quadratic cost function by calculating the minimum variance estimator, which is essentially the expected value of our posterior distribution:

$$LAT = E[D | GP] \quad (3.9)$$

In figure 3.2, a general overview of the whole framework is provided. There, the calculation of the final Bayesian posterior distribution in two different nodes is presented. In node number one, there is a great agreement between the LAT provided by the propagation model GP|D (pink line) and the LAT obtained from the deflection curve D (blue line). In this way, there is not a great update on the location of the LAT in the posterior estimate (red line). In contrast, in node two the ECGI-deflections and the propagation model suggest distant time locations for the activation. Based on both curves, the posterior pdf finally centers the most probable time near a smaller deflection between both estimates.

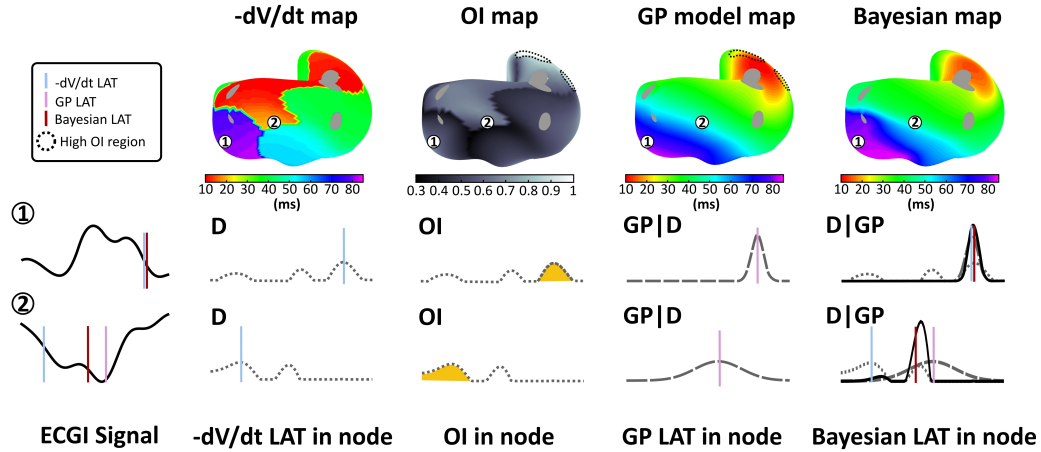


Figure 3.2: Bayesian Framework framework. The workflow for two different ECGI signals is presented. The first signal (first row) is a signal where exists a good agreement between both methods. The second signal on the other hand, there is a large discrepancy between the methods. In the first step, D signal is computed to identify the location of negative deflections. Then the OI is computed in each atrial node. The positions with a high OI value are used as anchor points to interpolate LATs in the rest of the atria. A p.d.f. is obtained in each atrial node. These curves are finally cobined with the D signals obtained in step 1 using Bayes theorem. The posterior p.d.f. (solid black line) is then used to estimate the final LAT.

3.2.6 Evaluation Metrics and Statistics

Pearson correlation and the root mean squared error (RMSE) were calculated in all the maps in order to assess their similarity with our gold-standard (LAT maps calculated in simulated EGMs). Additionally, the geodesic distances between the reference and estimated earliest and latest activation sites were measured for each method. The earliest and latest activation sites were defined as the location of the minimum and maximum LATs respectively. We also quantified the presence of slow conduction lines (SCL) as the percentage of atrial surface with a CV lower than 0.1 m/s. Additionally, the root mean squared error norm (RMSEN) of spatial LAT gradients were calculated and compared in both methods [Duchateau *et al.* 2016].

All the analysis were performed under three different signal to noise ratio (SNR) levels in the BSPM: 10, 3 and 0 dbs. The noise was injected into the system before solving the inverse problem. The Shapiro-Wilk test was applied to check normality of the data. In normal data, the two-sample t-test was used to evaluate differences between groups. Wilcoxon rank sum test was performed in non-normally distributed data to assess statistical difference.

3.3 Results

3.3.1 LAT Results in Automata Database

In Figure 3.3A, the anterior and posterior views of the reference LAT calculated in one simulation (first column) are shown. The LATs obtained applying the $-dV/dt$ method and the Bayesian approaches on ECGI signals are presented in the second and third columns respectively. This example illustrates the smoothing effect achieved with Bayesian estimation, which notably enhances the localization of the earliest and latest activation sites. According to Figure 3.D, there is a consistent reduction in the location error of the earliest activation sites when comparing the $-dV/dt$ method with Bayesian LAT maps across all simulated Signal-to-Noise Ratio (SNR) levels (1.8 ± 0.9 cm vs 1.3 ± 0.7 cm for 10 dBs, 2.6 ± 1.2 cm vs 1.6 ± 0.9 cm for 3 dBs, and 2.4 ± 1.2 cm vs 1.6 ± 1.0 cm for 0 dBs). This trend is also observed for the location of the latest activation sites (2.5 ± 1.6 cm vs 2.3 ± 1.8 cm for 10 dB, 2.9 ± 1.9 cm vs 2.3 ± 2.0 cm for 3 dB, 3.0 ± 1.9 cm vs 2.3 ± 2.1 cm for 0 dB). Furthermore, Bayesian LAT estimation not only provides a better correlation with the references LAT maps compared to the traditional method (0.81 ± 0.06 vs 0.91 ± 0.07 for 10 dBs, 0.78 ± 0.08 vs 0.89 ± 0.09 under 3dBs of SNR and 0.75 ± 0.09 vs 0.87 ± 0.14 with 0 dBs) but also demonstrates a lower Root Mean Square Error (RMSE) (16.5 ± 6.5 vs 11.1 ± 6.5 ms for 10 dBs, 18.5 ± 8.1 vs 12.2 ± 5.3 ms for 3 dBs, and 19.1 ± 8.6 vs 13.7 ± 8.0 ms for 0 dBs). All statistical tests conducted returned a p-value lower than 0.001, demonstrating how the Bayesian approach significantly improves the accuracy and reliability of activation times in ECGI, even under different noise levels.

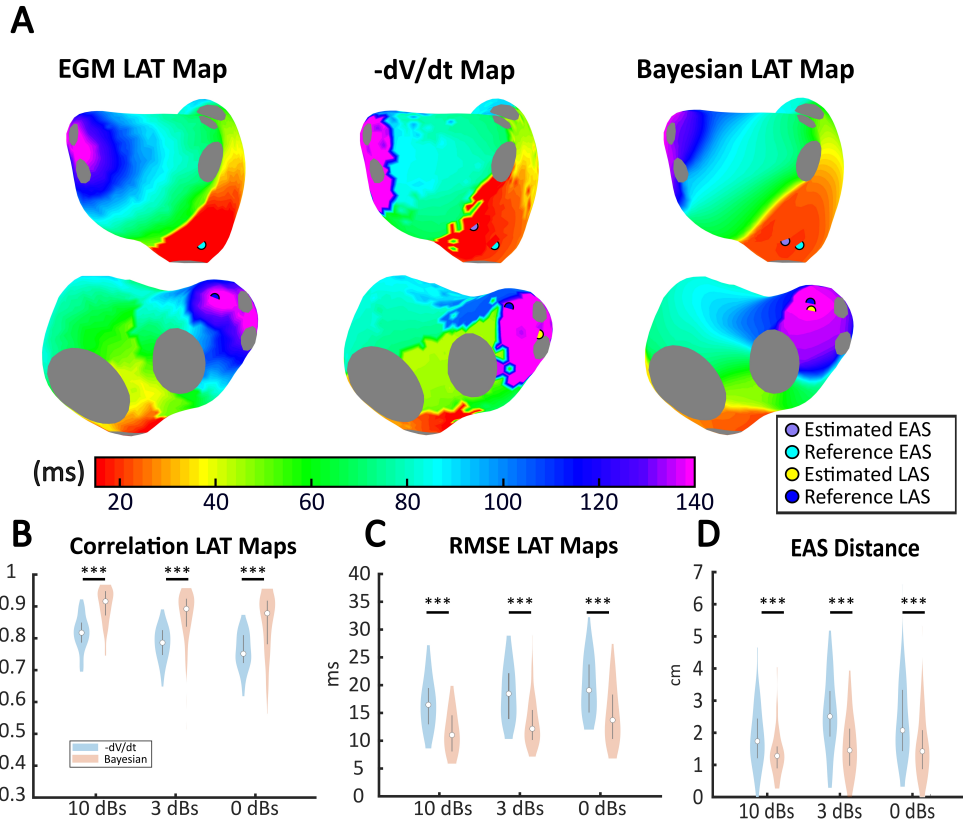


Figure 3.3: A) Comparison of posterior and anterior views of LAT maps (first and second rows respectively). Reference LAT map (obtained from simulated EGMs) is presented in the first column. The second and third columns showed the ECGI-LAT maps computed using the $-dV/dt$ and the Bayesian methods. B) Correlation values between each method and the reference LAT maps obtained in all the 62 simulated beats. C) Root Mean Squared values between each method and the reference LAT maps obtained in all the 62 simulated beats. D) Location mismatch computed as the geodesic distance in the EAS.

3.3.2 Robustness of the Bayesian Method Against Artificial Block Lines

The analysis on the presence of artificial lines of block (LoB) is presented in figure 3.4. Panel A exemplifies the overrepresentation of artificial LoB in LAT maps calculated with the $-dV/dt$ method. In this example, the EGM-propagation (reference data) presents a small and short LoB in the posterior atrial septum which is the result of the physiological propagation that takes place through the atrial bridges that communicate the left and right atria. Both ECGI-LAT algorithms, $-dV/dt$ and Bayesian, introduce longer lines in this area, slightly displaced towards the left atrium. However, the $-dV/dt$ LAT map contains additional SCLs surrounding the left pair of pulmonary veins which are not present neither in the Bayesian, nor in the reference LAT maps.

The results of the systematic analysis conducted on the presence of LoB is presented in figure 3.4B. These results show a higher presence of artificial LoB in the LAT maps calculated in ECGI signals. However, the % of surface presenting artificial LoB is significantly reduced when using the Bayesian framework (0.52 ± 0.80 % vs 2.52 ± 1.87 %). The smoothness characteristic from Bayesian LAT maps also improves the estimation of the spatial activation gradients. In panel C, the RMSEN of these gradient vectors are presented. In all the noise levels evaluated, the Bayesian LAT estimation present lower error norms (4.0 ± 0.9 vs 5.0 ± 1.1 ms/mm for 10 dBs, 4.3 ± 1.3 vs. 5.6 ± 1.3 ms/mm for 3 dBs, and 4.7 ± 0.9 vs. 6.0 ± 1.5 ms/mm for 0 dBs).

3.3.3 LAT Results in Patients

The sinus activation sequence of patient 1 obtained from EAM is presented in figure 3.5. Information such as catheter measurement positions recorded from the navigation system (on the left) and the standard deviation in the LAT interpolation (on the right) is included. Regions with fewer catheter contacts exhibit increased interpolation uncertainty, represented as higher standard deviation values in the last map of panel A. The interpolated activation pattern obtained aligns with typical sinus rhythm propagation. However, the LATs were referenced to the first activation in the left atria leading to a shortened total propagation time.

Our Bayesian framework eliminates artificial LoB also in clinical data when compared to the classical $-dV/dt$ method. We established the same criterium employed in the simulation dataset to define a LoB: a conduction velocity below 0.1 meters per second. In panel B, the LAT maps obtained from EAM and ECGI are compared presenting low conduction areas in white and high uncertainty (std < 5 ms) regions in gray. In the first column, the EAM LATs are shown. This map presents a smooth transition between the EAS in the top of the roof and LAS in the inferior left-side of the posterior wall. In contrast, the LAT map obtained with classical $-dV/dt$ method (middle column) shows only three main areas: a very early activation in the roof, very late activation in the left-inferior portion and

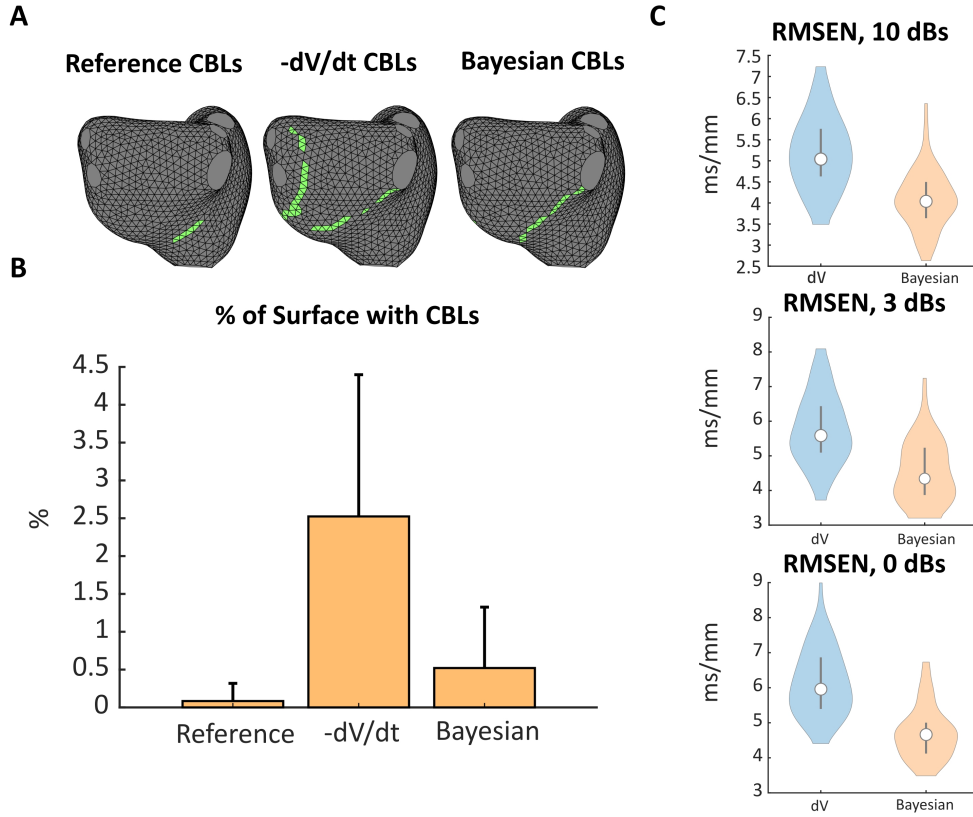


Figure 3.4: A) Example of slow conduction lines (in green). In the left there is the line obtained in our reference LAT map, in the middle the lines provided by the $-dV/dt$ method and in the right the resulting lines of applying the Bayesian algorithm. B) Representation of the percentage of area accommodating a slow conduction. C) Comparison of the mean errors of LAT spatial gradients under three different noise levels.

an intermediate activation in the right side of the atrium. All of them separated by LoB. In contrast, the Bayesian distribution of the LATs is similar to the one observed in EAM. This map (third column) presents a smooth transition where the location of the earliest and latest activation sites are in the same regions to those shown in EAM.

Additionally, even if the position of the EAS does not look perfect in the LAT map obtained with our Bayesian method, the activation pattern is way more accurate in the new algorithm also in terms of earliest activation site (EAS) estimation. This EAS covers both pairs of PPVV in the traditional method while it only represents a small portion of the atrial tissue in the electroanatomical mapping (EAM). The EAS constitutes an area way smaller when estimating the activation sequence with the new methodology. Moreover, this spot is displaced towards the right pair of PPVV also in the EAM, something that is recovered only when using our method.

We also compared the behavior of both LAT methods in the presence of a real conduction block. In figure 3.6, intracavitary and non-invasive activation maps are exemplified in a patient with a CTI ablation line during coronary sinus pacing. In panel A, the intracavitary LAT map is presented showing the electrical propagation circuit around the tricuspid valve and the correspondent conduction blockage in the isthmus. In panels B and C, ECGI activation maps are depicted using the classical $-dV/dt$ method and our Bayesian method respectively. Both ECGI maps show a conduction block line in the CTI. However in the classical $-dV/dt$ method this line prolongs to the septum reaching the mitral valve (MV) in the left atrium. In this way, the reentrant circuit represented in this map extends through the posterior wall of the atria leading to a misinterpretation of the real reentrant circuit. In contrast, the Bayesian estimation provides a smooth propagation path around the tricuspid valve preserving in this way the real activation sequence.

3.4 Discussion

A novel Bayesian framework for estimating Local Activation Times in Electrocardiographic Imaging signals has been introduced. This innovative method combines information from ECGI deflections with a multivariate-gaussian model fitted to high-confidence measures. We compared the traditional $-dV/dt$ method with our Bayesian framework. Both approaches were tested on in-silico dataset during sinus rhythm and different pacing positions. Three noise levels were included in body surface signals before computing ECGI to test the robustness of the algorithms. We observed how our Bayesian framework provides more accurate and smoother LAT maps than the well-established $-dV/dt$ criterion, leading to better location of the earliest and latest activation sites and less artificial SCLs. Two different activation sequences of real patients were also studied with our Bayesian method.

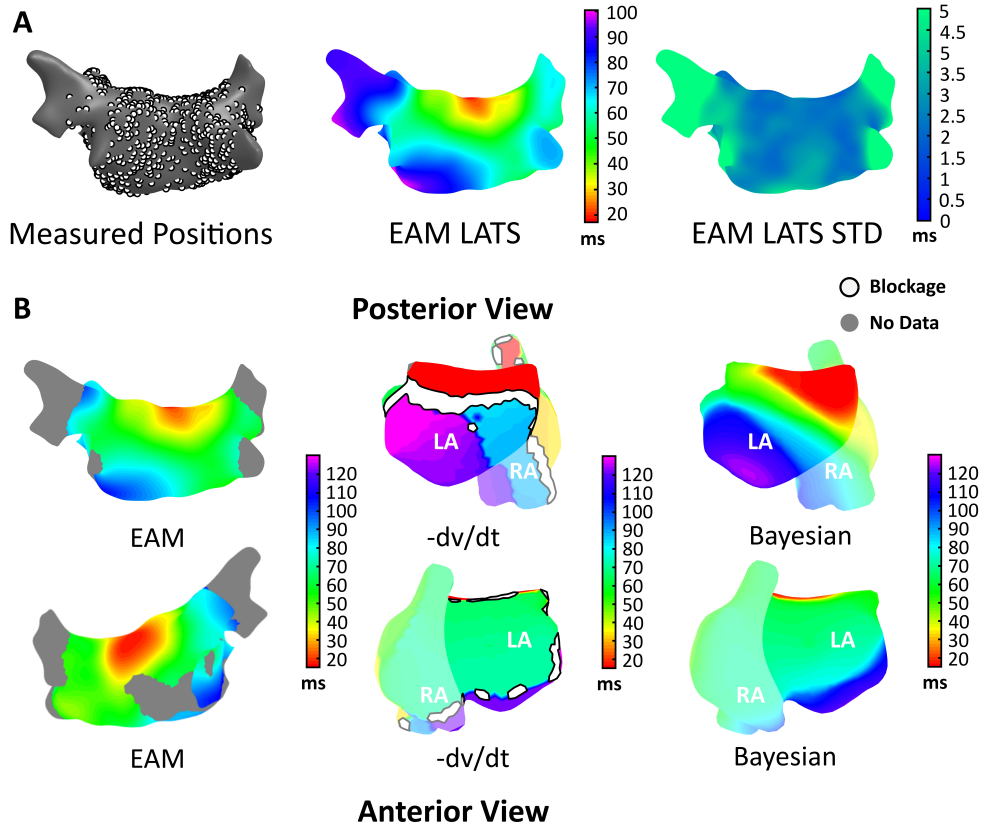


Figure 3.5: A) From left to right: catheter contact points in the atrial anatomy, interpolated LAT map and standard deviation associated to each interpolated value. B) First column: posterior (up) and anterior (down) views of interpolated LAT values presenting a standard deviation below 5 ms. Second column: LAT maps obtained from applying the $-dV/dt$ method to ECGI signals. Third column: LAT maps obtained from applying our Bayesian framework to ECGI signals.

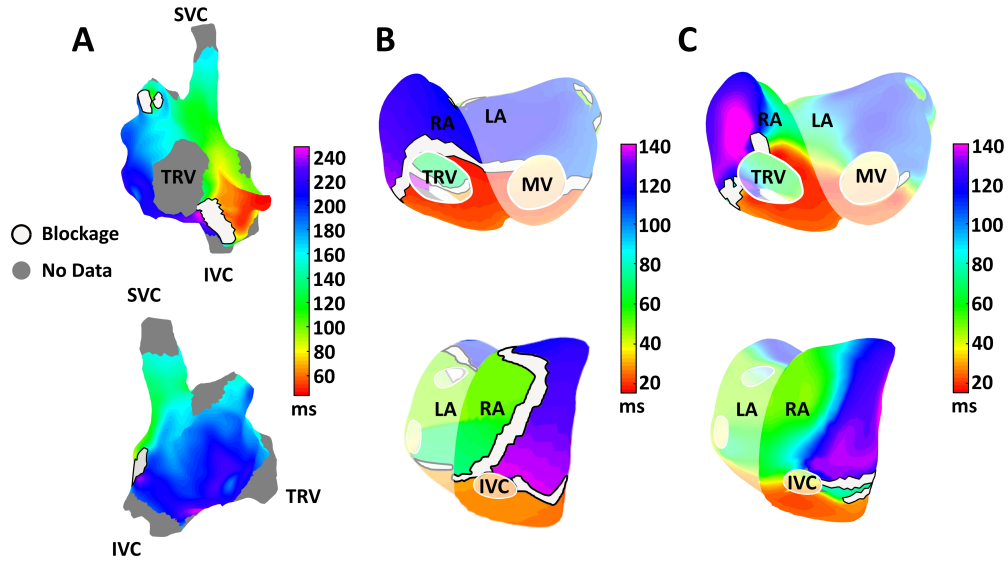


Figure 3.6: Comparison of Intracavitary and Non-Invasive Cardiac Activation Maps: Panel A displays an intracavitary local activation time (LAT) map obtained during coronary sinus pacing in the presence of a cavotricuspid isthmus block line created by radiofrequency (RF) ablation. Panel B illustrates the same activation sequence acquired non-invasively by Electrocardiographic Imaging (ECGI) using the classical $-dV/dt$ method. Panel C presents the activation sequence also captured by ECGI but derived through our novel Bayesian LAT estimation method, demonstrating enhanced localization of the blockage line. Conduction block lines are shown in white whereas regions in gray represent lack of reliable LATs

3.4.1 Validation Results

Our spatiotemporal Bayesian framework provided smoother and more accurate maps than the $-dV/dt$ method. This was true in atrial simulations where we observed a reduction in the presence of LoB and also in our clinical episode. The advantages of spatiotemporal methods over the classical pure-temporally based LAT estimation have already been highlighted in the past [Punske *et al.* 2003] [Cluitmans *et al.* 2016][Cluitmans *et al.* 2022][Coveney *et al.* 2019].

Erem *et. al.* proposed the optimization of a functional integrating temporal and spatial gradients to identify LATs in fractionated EGMs [Erem *et al.* 2011]. Cluitmans *et. al.* tested and compared this approach to the traditional $-dV/dt$ method in simulated ventricular EGM recordings and experimental and clinical ECGI signals [Cluitmans *et al.* 2022]. The application of the spatiotemporal optimization in EGMs increased the accuracy of activation and recovery times in ventricular simulations. This improvement was explained by the selectivity of the spatiotemporal method to identify the correct deflection in highly fractionated EGM signals, avoiding the presence of local outliers in the LATs. Although they did not observe a quantitative improvement of LAT maps in animal ex-vivo or torso-tank ECGI data (at least in terms of mean LAT errors), they could see how their spatiotemporal method provided smoother maps with fewer local outliers even in clinical data. Additionally, the distance mismatch between the EAS identified with ECGI and the reference position was found to be reduced from 3.6 cm to 2.3 cm when using their spatiotemporal approach. The distance errors reported by Cluitmans *et. al.* are higher than our noisier scenario (SNR of 0dBs) where the Bayesian estimation was below 2cm. However it is true that the distance reported in [Cluitmans *et al.* 2022] was measured in an ex-vivo set-up with additional geometrical errors that we didn't include in our simulations.

Duchateau *et. al.* introduced a delayed-based spatial coherent LAT estimator. This method combines in an optimal way the activation times obtained in ECGI signals (using $-dV/dt$ method), and the temporal delays estimated between neighboring nodes [Duchateau *et al.* 2016]. The algorithm was tested on ventricular ECGI data in two different validation setups: ventricular simulations and clinical epicardial mapping. Their results demonstrated a reduction in the mean LAT-RMSE across various simulations compared to the standard $-dV/dt$ method (10.4 ± 1.5 vs 14.4 ± 3.6 ms). The same trend was observed when comparing both algorithms in clinical epicardial data (23.2 ± 8.4 vs 28.6 ± 10.1 ms). The spatial gradients of LATs provided by both methods were also studied, in which the spatiotemporal methodology exhibit an enhancement of these maps of 2.9 ± 0.7 vs. 6.0 ± 2.7 ms/mm of error, corresponding to a $47.2 \pm 13.7\%$ of relative error reduction. When comparing the accuracy of LAT maps in terms of RMSE, the errors in the Bayesian framework were slightly higher than those reported by Duchateau in ventricular simulations (11.1 ± 6.5 under 10 dBs of SNR vs 10.4 ± 1.5 ms). The same is true when comparing the errors of spatial LAT gradients (4.0 ± 0.9 vs. 2.9 ± 0.7 ms/mm). However, they did not specify the noise level included in their

simulations, which complicates the comparison of the results.

3.4.2 LAT Variance Estimation

Our framework combines in an optimal way information coming from ECGI deflections and a multivariate-gaussian distribution model. This model, generated by a Gaussian process, relies on a subset of activation times and their corresponding variances to infer the LAT-distribution in the entire atria. Specifically, we use locations with high OI where voltage signals feature a single deflection. In these sites, the deflection energy is better approximated by single-pure gaussian distribution, and we can accurately characterize the total LAT variance (see Appendix A for further details on the relationship between OI and standard deviation error). In this way, we only introduce in the model nodes in which our variance estimation error is small, reducing at the same time errors derived from the gaussian distribution assumption in the LATs.

The estimation of the variances is crucial to obtain realistic probability distributions in our model. This consideration is shared with other methods that integrate information from multiple sources. For instance, Duchateau et. al. employed the variance of LAT errors to effectively combine deflection and delay information in a linear least-squared formulation [Duchateau *et al.* 2016]. To estimate LAT variances, a model relating the OI measured in the signals and the variance of LAT errors was built. This model was trained using ventricular simulations and then transferred to patient signals. Although this method proved to overcome the temporal $-dV/dt$ method also in clinical ventricular recordings, the exclusive use of ventricular simulations in the training may be a limitation when applying this model in atrial signals.

In contrast, our Bayesian framework includes the estimation of the LAT variance in the workflow. This ensures that our variance estimation does not rely on assumptions inherent in simulations, providing a more robust and general representation of the LAT distributions in our model.

3.4.3 Organizational Index Threshold

We incorporated the implementation of the OI proposed in [Duchateau *et al.* 2016]. This parameter measures the dispersion of the energy associated with the deflections in ECGI signals. We hypothesized that the standard $-dV/dt$ method would concentrate lower errors in atrial sites with voltage signals presenting high OI values.

Our findings, also in line with those of Duchateau et al., demonstrated how this parameter is indeed heteroscedastic (see Appendix A), and therefore specific to detect small LAT errors in the atria but not large errors. Despite this, the specificity of the OI to identify locations with a small LAT error proved valuable in identifying a subset of high-confidence LATs from which we could build an electrical propagation model in the entire atria.

3.4.4 Limitations and Future Work

One limitation to highlight concerning the propagation model of the Bayesian methodology is its exclusive applicability to non-reentrant rhythms. This limitation is common for all the spatiotemporal LAT methods developed up to date. We plan to extend this methodology to reentrant arrhythmias by incorporating new probabilistic interpolation methods in the phase domain. This could generalize the current approach to any type of arrhythmia. Additionally, an important limitation of this study is the limited size of the human datasets, which hampers the generalization of the technique. We plan to increase the number of patients in the future for further validation in clinical data.

3.5 Conclusions

The classical $-dV/dt$ methodology used in EAM to estimate LATs is fully suitable for ECGI signals. Specifically, selecting the LAT as the moment of steepest negative deflection in ECGI leads to artificial block lines in the activation sequence. The Bayesian methodology presented in this study is more accurate than the propagation obtained with classical $-dV/dt$ LAT maps. The combination of information from ECGI deflections and a propagation model provide smoother and more physiological activation maps that preserve better the real activation sequence avoiding artificial conduction block lines. Additionally, the location of the earliest and latest activation sites is also improved with the proposed method which also resulted more robust against lower SNR in the BSPM.

Chapter 4: Probabilistic Dominant Frequency Estimation in AF from ECGI. A proof of Concept

Contents

4.1	Introduction	59
4.2	Materials and Methods	60
4.2.1	In silico Data Collection and Preprocessing	60
4.2.2	Experimental Data Collection and Preprocessing	61
4.2.3	Inverse problem and dominant frequency estimation	63
4.2.4	Evaluation of Dominant Frequency Estimation Methods	64
4.3	Results	64
4.3.1	Lambda Range selection	64
4.3.2	DF Evaluation	65
4.3.3	DF estimation probability	67
4.3.4	DF estimation in Langerndorff data	68
4.3.5	DF estimation in patient data	69
4.4	Discussion	69
4.4.1	DF Mapping Validation	72
4.4.2	Lambda Range selection	73
4.4.3	Limitations and Future Work	73
4.5	Conclusion	74

4.1 Introduction

There is scientific evidence demonstrating that atrial fibrillation (AF) can be originated and maintained by localized high activation frequency areas [Mandapati *et al.* 2000]. Additionally, the ablation of these high frequency sites with a has been linked to long-term sinus rhythm maintenance after the intervention [Atienza *et al.* 2009]. However, identifying fast activation areas during AF is

still challenging as current endocardial mapping can only provide sequential measurements that do not capture the temporal variability of AF [Habel *et al.* 2010]. Recently, Electrocardiographic Imaging (ECGI) has been proposed as an alternative technology to measure the atrial activation frequency [PEDRÓN-TORRECILLA *et al.* 2016]. ECGI is a non-invasive mapping technology that provides a global reconstruction of the electrical propagation in the heart. This exclusive characteristic of ECGI potentially confers the capacity of characterizing diffuse and time-changing drivers in AF [Tzeis *et al.* 2024]. Several studies have demonstrated the feasibility of using the dominant frequency (DF) mapping on inverse-computed electrograms (iEGMs) as a subrogate of the activation frequency in the atria [Rodrigo *et al.* 2017b, Rodrigo *et al.* 2021]. In this way, DFs may be used to locate the fastest activation areas as the regions harboring the highest dominant frequency (HDF) in the atria and identify a potential target for ablation.

The typical approach followed to estimate DF in ECGI is by localizing the peak of maximum amplitude in the spectrum of inverse iEGMs. However, ECGI provides over-smoothed solutions due to the bad conditioning of the inverse problem. This phenomenon leads to spatial mixing of the spectral content and may affect on the estimation of DFs. We hypothesize that the use of information from different regularization solutions can improve the estimation of the activation frequency during fibrillation. Specifically, we think that combining DF maps from a coherent set of ECGI solutions may improve the general distribution of DFs and provide more robust maps.

In this study we present a methodology to robustly estimate DF maps in ECGI. This approach allows to measure the uncertainty associated to the estimates and use it to identify localized reproducible DFs. The conventional DF obtained from the L-Curve regularization (LC-DF) was compared with our proposed Lambda-Range DF method (LR-DF). This approach experimentally builds a probability density function (PDF) and calculates the DF as the frequency that minimizes the maximum absolute error in the estimated PDF. We performed this evaluation in AF in-silico models, an animal model of ventricular fibrillation (VF) and compared the temporal stability of the DFs retrieved by both methods in a real clinical case.

4.2 Materials and Methods

4.2.1 In silico Data Collection and Preprocessing

Two AF episodes of 10s duration were simulated using a realistic 3D model of the atrial anatomy, consisting of 284,578 nodes and 1,353,783 tetrahedrons of an average inter-nodal distance of $673.4 \pm 130.3 \mu\text{m}$ [Rodrigo *et al.* 2017c]. Specific distributions of electrical remodelling and slow conduction areas were included in the models to generate and maintain re-entrant propagation patterns. Electrogram signals in the epicardium were then computed from the simulated transmembrane potentials in a uniform mesh of 4098 unipolar EGMs around the epicardial surface

at a distance of 1 mm. This was done under the assumption of a homogeneous, unbounded, and quasi-static conducting medium by summing up all effective dipole contributions throughout the entire model [PEDRÓN-TORRECILLA *et al.* 2016]. Body surface potentials (BSPM) were obtained by solving the forward problem of electrocardiography with the boundary element method. Zero-mean Gaussian noise was added to the resultant BSPM. The standard deviation of these noise was computed to obtain a mean signal to noise ratio of 20 dB. Finally, a 0.5-20 Hz bandpass filter was applied to improve signal quality.

4.2.2 Experimental Data Collection and Preprocessing

Regarding the experimental ex-vivo data, a heart was excised from a pig and perfused in Langendorff mode with a mixture of blood and Tyrode. Details on the instrumentation and experimental setup are explained in [Bear *et al.* 2021]. Briefly, an epicardial sock with 108 electrodes and 8 to 14 mm spacing between them was attached to the ventricles. The heart was then transferred to a human torso-shaped tank fitted with 256 electrodes with 30 to 60 mm spacing. The epicardial potentials and torso voltages were simultaneously recorded during ventricular fibrillation which was induced by means of an S1-S2 protocol. The torso model used in this experiments is represented in panel A of figure 4.1. The white dots on the torso indicate surface electrode locations.

A total of 24 recordings of 10s of duration were obtained in this setup. In order to include a wider variety of dominant frequency values and spatial gradients, these 24 episodes were obtained in three different conditions: under the infusion of Dofetilide ($n = 8$), Pinacidil ($n = 8$), and in baseline ($n = 8$, no drugs). The left anterior descending artery (LAD) was cannulated and used to perfuse Dofetilide. Pinacidil on the other hand was administrated through the aorta. In figure 4.1.B a model of the heart is presented. There, the LAD and aorta are visible in blue and red colors respectively. The area covered by the sock of electrodes is colored in gray where the dots indicate electrode locations.

Figure 4.2 shows 3 images of the DF epicardial distribution in baseline conditions and under the infusion of dofetilide and pinacidil. The largest gradients are observed in pinacidil recordings, baseline contains gradients of intermediate magnitude and the lower frequencies and gradients are observed under dofetilide infusion. The inverse problem was solved to estimate ventricular voltage. Two DF methods were assessed using the measured epicardial electrograms.

In addition to the experimental data, BSPM signals of a persistent AF patient (female, 70 years old) were recorded before PVI using 128 electrodes with a 1 kHz sampling frequency. Signals were filtered with a 0.05-500 Hz bandpass filter. Torso geometry and electrode positions were recorded by photogrammetry. The atrial anatomy and fibrosis distribution were obtained from a late gadolinium enhancement MRI (LGE-MRI). A 3D geometrical model of both atria was generated and registered into the torso shape recorded by photogrammetry using ACORYS system, Corify Care SL (Madrid, Spain).

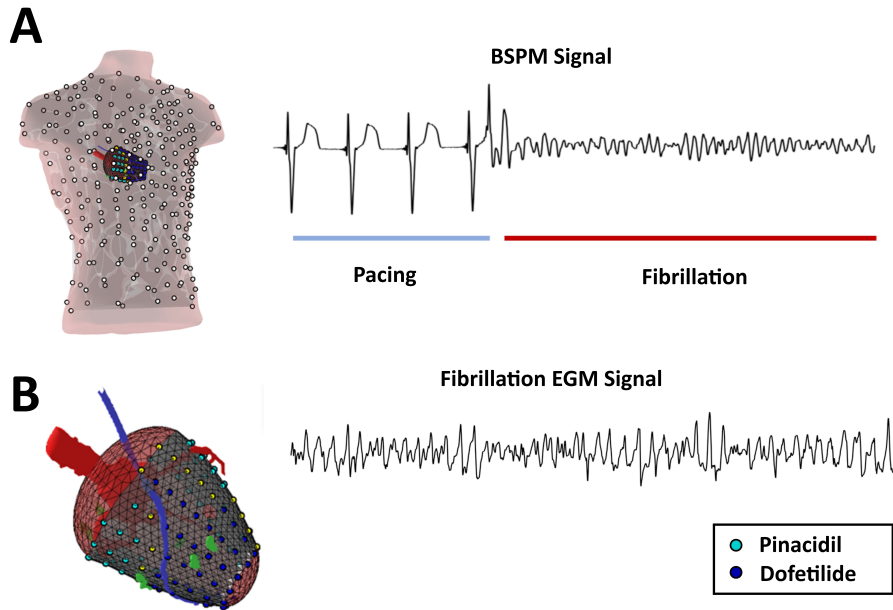


Figure 4.1: A) Torso model used in the experimental analysis. The white dots represent electrode locations on the torso surface. An example of a BSPM signal is presented in the right side. This signal includes the pacing stimulation and the fibrillation induction. B) Heart model. The area covered by the sock is represented in gray. The locations of the epicardial electrodes is depicted with dots in different colors depending on the drug influencing the area (dofetilide or pinacidil). An example of a fibrillation EGM signal registered on the ventricular epicardium is shown in the right side.

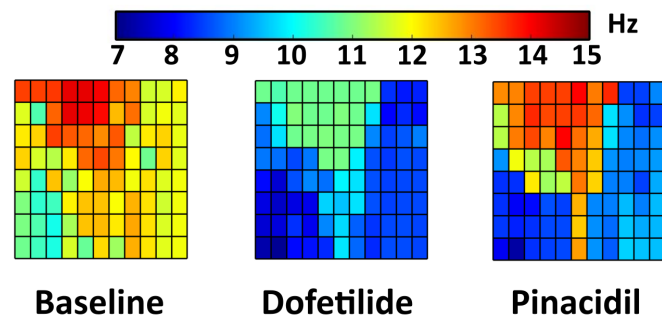


Figure 4.2: Examples DF epicardial maps during ventricular fibrillation represented in a 2D grid. The largest gradients are observed in pinacidil recordings, baseline contains gradients of intermediate magnitude and the lower frequencies and gradients are observed under dofetilide infusion.

4.2.3 Inverse problem and dominant frequency estimation

We solved the inverse problem by applying 0-order Tikhonov regularization. With this procedure, inverse computed electrograms (icEGMs) were obtained for 41 different regularization parameters (λ) in the range $[10^{-12}, 10^{-2}]$. DF maps were computed for each of these solutions. The DF was considered as the peak with maximum amplitude in the spectrum, which was calculated using Welch's periodogram with a Hamming window of 8192 points, 4s length and 50% overlap.

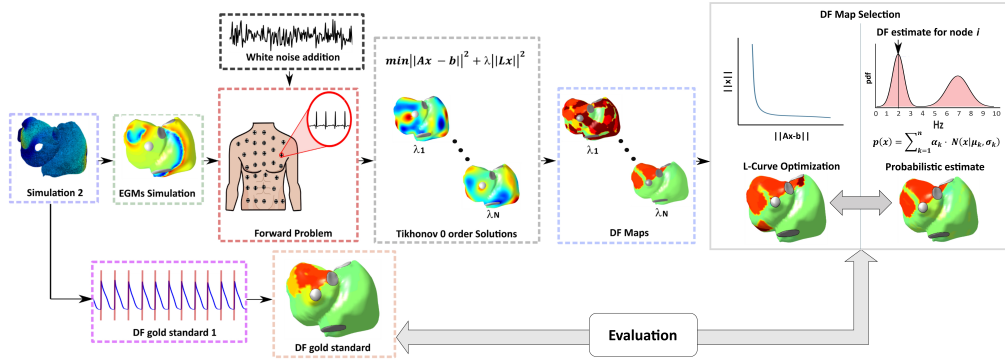


Figure 4.3: Processing pipeline employed in simulations. First APs were simulated and extracellular potentials calculated. The activation frequency was calculated directly from APs using the upstroke as activation time. The forward problem was solved to transfer the information from heart EGM to a torso model with 128 simulated electrodes. White noise was included. The inverse problem was solved for a range of different regularization parameters and the DF maps were computed on each solution. Finally the DF map obtained from the LC solution was compared with the MMAE solution using the frequencies estimated in APs as gold-standard.

Pearson correlation coefficients between DF maps from consecutive λ values were computed together with the normalized power within the 0.5-12 Hz band for each of the 41 sets of spectra calculated. A range of λ values with consistently high correlations and power spectral content in the band of interest was manually selected, and their corresponding icEGMs were used to compute the final DF. A probability density function was obtained by fitting a gaussian mixture model to the DF distribution computed from the selected icEGMs. In this way, the multi-modal nature of DFs present in the fibrillation are accounted and collected in our model. The final estimation probability was calculated using equation 4.1 in an interval of $\pm 0.5\text{Hz}$ around the DF estimate.

$$p(x) = \sum_{k=1}^n \alpha_k \cdot N(x | \mu_k, \sigma_k) \quad (4.1)$$

where α_k is the probability of a DF value to belong to a particular population of frequencies following a gaussian distribution, μ_k is the mean of each gaussian

distribution and σ_k is the standard deviation. The DF associated to each atrial location was estimated as the peak with maximum amplitude in this probability density function.

Finally, the L-curve methodology was applied to determine the optimal lambda and rescue its DF map (LC) [Hansen & O’Leary 1993]. This map was compared to the final DF estimate obtained using the lambda-range (LR) approach explained above. The whole pipeline followed in in-silico data is presented in figure 4.2.

4.2.4 Evaluation of Dominant Frequency Estimation Methods

In simulations, the gold standard activation frequency was determined by counting the activations present in the computed transmembrane potentials. In the ventricular animal model, the activation frequency was calculated as the maximum peak in Welch’s -periodogram computed on the measured epicardial electrograms (EGMs). To compare the performance between the proposed LR method and the standard LC in the context of a clinical application, we calculated the highest dominant frequency (HDF) regions with both methods and compared with the gold standard. The HDF in each map was obtained as the region containing a frequency above the 95-percentile interval. We quantified the sensitivity and specificity of the HDF regions in both methods. The root mean squared error between DF maps was computed in both data sets, and the percentage of electrodes with a DF error higher than 1 Hz was calculated in the epicardial recordings obtained from our animal model.

Temporal reproducibility of the DF maps obtained from the patient was quantified by splitting a 30 second ECGI recording into 10s windows with 50% overlap. The mean absolute difference between DF maps from consecutive windows was computed in three scenarios: using LC maps, LR maps containing DFs values from all the atria and LR maps with only the atrial nodes presenting an estimation probability higher than 0.7.

We checked the normality of all the parameters using the Kolmogorov-Smirnov test. For comparisons between two groups, Student’s t-tests were used for independent samples if the data were normally distributed. If the data were not normally distributed, the Mann-Whitney U-test was applied.

4.3 Results

4.3.1 Lambda Range selection

In the simulated AF episodes we selected the range of λ values (10^{-9} to $5.62 \cdot 10^{-5}$) that maximized the power within the spectral band of interest in AF and the correlation between DF maps from consecutive λ values. Specifically, we set the boundaries of these ranges in the solutions of maximum slopes of correlations that also contains a high spectral power in the 3 to 12 Hz band. Figure 4.4.A shows the variation of these parameter in this range, where the correlation with the gold

standard activation frequency is also maximized. The λ value selected by the L-curve optimization method lies within this same range but is close to its lower boundary. In panel B, we can see the same analysis applied to the clinical data. In this case, maximization of both, the spectral power in the band of interest and the correlation between DFs from consecutive λ values lies within the $3 \cdot 10^{-6}$ to $3 \cdot 10^{-4}$ range, a narrower interval than the one obtained for the simulations. The lambda value selected by the L-curve optimization is again within this range. In panels C and D the ranges selected for two recordings obtained from the experimental model of ventricular fibrillation are presented. In C a favorable scenario is presented where the selection of the lambda range was easily identified given the stable plateau of consecutive correlations. In contrast, panel D the selection of the range is less clear. There is a wider region of high correlations and the differences between the high and low correlation ranges is smaller than in the previous example. The mean lambda ranges obtained in this the whole set of VF recordings was $4.5 \cdot 10^{-5}$ to $2.0 \cdot 10^{-2}$.

4.3.2 DF Evaluation

DF maps obtained by LC and LR methods, together with the gold standard are depicted in figure 4.4. In both simulations, the gold standard presents two different activation frequencies. The LC and LR methods showed small differences in distribution of the DFs observed in the gold standard. However, additional frequencies are present when using the LC method that interfere in the interpretation of the DF map.

In simulation 1, the right atria harbors the HDF area, with an activation frequency of 5.5 Hz. The LC method presents a wider penetration of the right atrial activation frequency into the left atrium, right below the right inferior pulmonary vein which is not that evident in the LR method. Additionally, a small and localized regions of HDF higher than the gold standard HDF is present in the right atrium posterior wall.

In simulation 2, the HDF present in the gold standard is localized in the left-atrial roof also at a frequency of 5.5 Hz. An additional region at 5.5 Hz in the inferior side of the left-atrial posterior wall is observed when DF are estimated using the LC regularization. This false HDF site is corrected in the DF map provided by the LR method. Artificial high frequency spots are also observed in the LC-DF map of simulation 2. One in the right atrium, just below the superior cava vein, and another one in the inferior side of the left atrium posterior wall. These two false-HDF are also corrected in the LR-method. DF estimation in the anterior wall is similar in both methods. In contrast to the posterior wall, the anterior wall is homogeneously activated at just one frequency. This reduces the spatial mixing of spectral components allowing a good DF estimate even with the traditional DF method.

In table 4.1 the sensitivity and specificity of each method in the identification of the HDF is presented. Additionally, the root mean squared errors (RMSE) of the DF maps are also shown. Regarding the sensitivity and specificity, if we consider

Lambda Range selection in Different Datasets

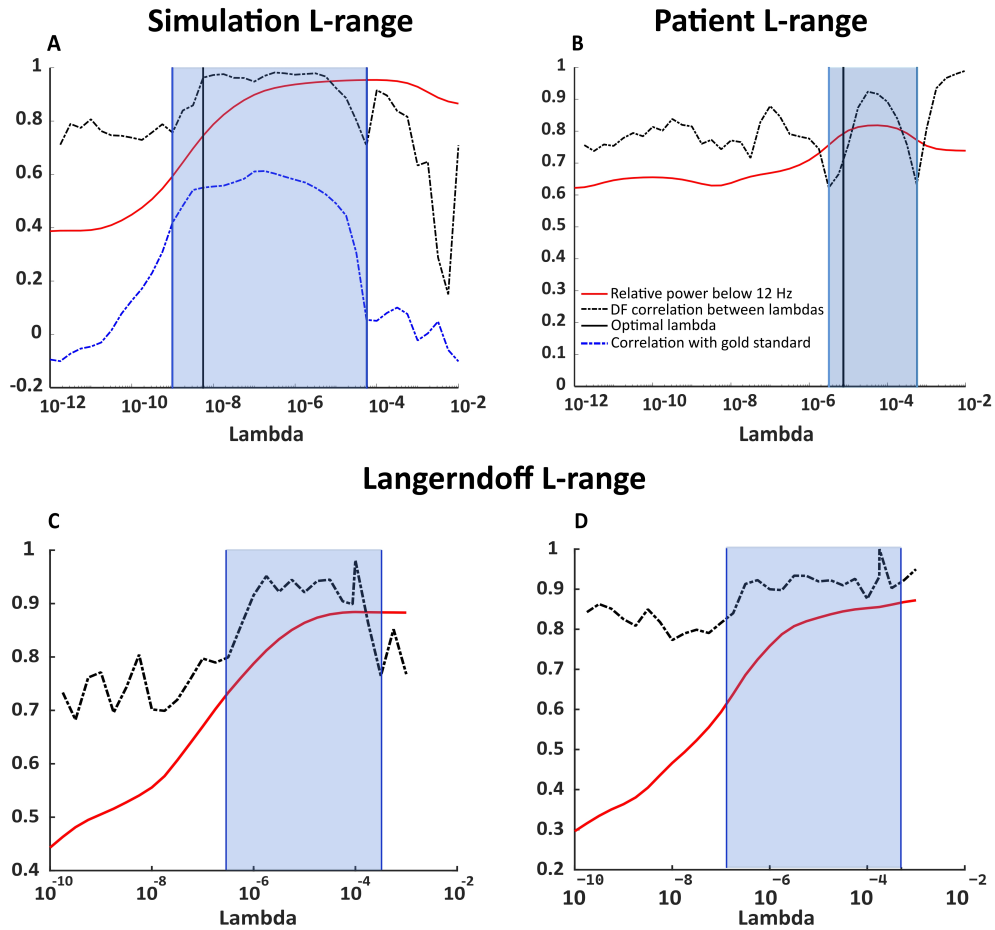


Figure 4.4: A) Lambda range selected to compute DF map in simulation 2. This range was adjusted to include a high power ratio in the frequency band of interest and a consistently high correlation between DF maps of consecutive lambdas. B) Lambda range selected in a patient recording using the same approach. C) and D) Examples of lambda ranges selected from the animal model of ventricular fibrillation.

Method	Sensitivity		Specificity		RMSE	
	LC	LR	LC	LR	LC	LR
Sim. 1	0.01	0.93	0.99	0.78	0.32	0.37
Sim. 2	0.00	0.90	0.98	0.92	0.41	0.73

Table 4.1: Sensitivity and specificity of the LC and LR methods for each of the simulations.

the definition of HDF as DFs above the 95-percentile the LC completely misleads the identification of these areas with sensitivities of 0.01 and 0. This is due to the presence of harmonics in the ECGI solution, which are effectively corrected with the new methodology. However, if we assume that these harmonics can be easily identified by the clinicians, the sensitivity and specificity of the LC in identifying the HDF increases to 0.90 and 0.95 in the first simulation and to 0.76 and 0.89 in the second. These are similar values to those obtained with our LR-method. The RMSE suggests that the LR method can retrieve more accurately the distribution of DFs in the atria although both methods present small errors.

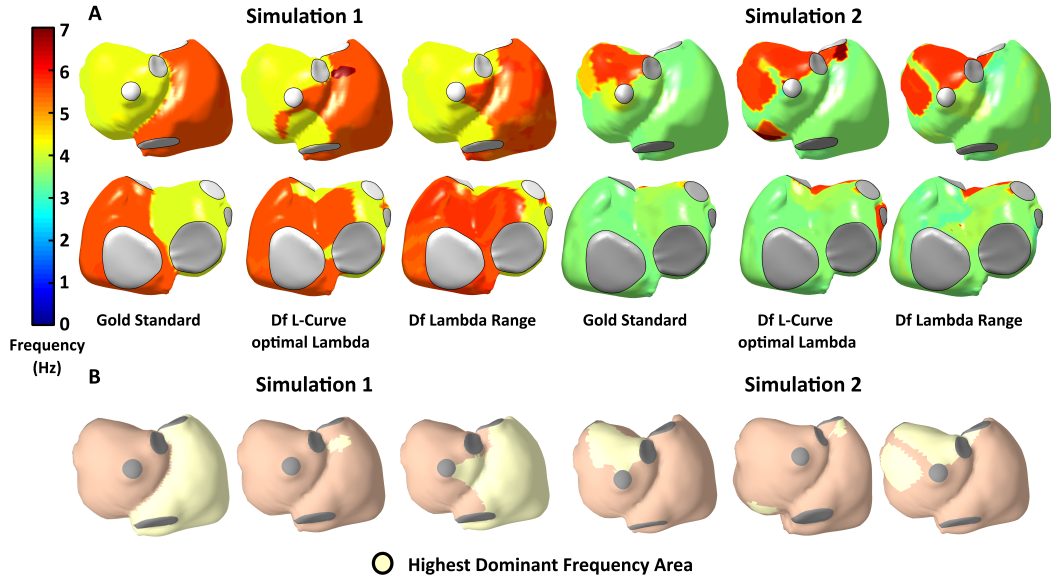


Figure 4.5: A) Posterior and anterior views of the of the LC, LR and gold standard DF maps. The 3 first columns correspond to the first simulation, and the 3 last to the second. B) HDF areas obtained for simulation 1 and 2.

4.3.3 DF estimation probability

In Figure 4.6, probability maps related to the DF estimation are shown. In both simulations, there is a general drop of the probability in the boundaries between

different DF regions. This observation would be consistent with the presence of mixed spectral content in the vicinity of two different DF regions.

Another area with a high uncertainty in both simulations is the septum. This is a specially challenging region to obtain reliable solutions when solving the inverse problem. The concavity of the geometry in this area affects the solution when applying the BEM.

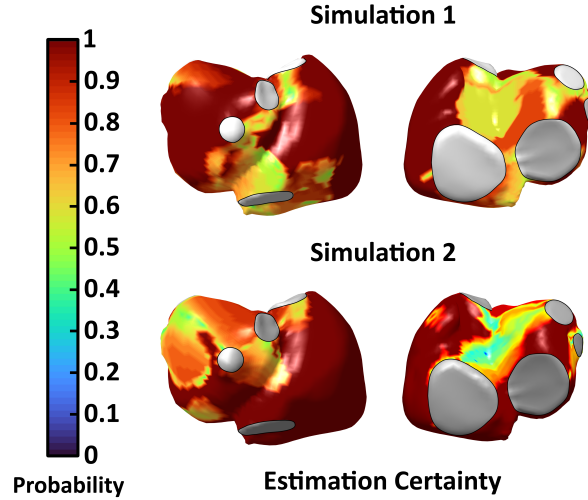


Figure 4.6: Estimation certainty maps within a $\pm 0.2\text{Hz}$ interval around the DF estimated by our LR method.

4.3.4 DF estimation in Langerndorff data

The performance of the LR algorithm in Langendorff data was validated by comparing the estimated DF against the gold standard of activation frequencies directly estimated in electrogram signals (EGM-DF). The results are summarized in Figure 4.7, which provides a comprehensive comparison across various parameters including DF maps, sensitivity, specificity, and percentage of nodes with wrong DFs.

The maps in panel A illustrate an example of the spatial distribution of dominant frequencies across the ventricles as derived from different methods. The first map illustrates the DF distribution measured with epicardial EGMs. Inspection of the LC and LR maps below reveals a closer alignment of the LR method with the EGM-DF map. The LC method showed more noticeable deviations from the EGM measurements. For example, an artificial high frequency band of DFs is observed in the inferior left corner of the array. In panel C, an example of the DFs probability distribution obtained with the LR methodology is presented. Like in simulations, in this map lower probabilities are located in the transitions zones with high DF gradients. Additionally, the electrode array in the left inferior corner of the grid is also shown as a high uncertainty area.

Sensitivity and specificity analyses were conducted to evaluate the ability of the algorithms to correctly identify the highest dominant frequency region under various conditions, including Baseline, Dofetilide, and Pinacidil infusion. The LR method consistently demonstrated higher sensitivity compared to the LC approach across all conditions, signifying a better capability to detect true dominant frequencies in baseline conditions (0.47 ± 0.15 vs 0.71 ± 0.07 , median $\pm$ interquartile range) and with drug infusion. Specificity was also observed to be slightly higher for the LR DF method in baseline conditions (0.87 ± 0.04 vs 0.94 ± 0.01), but also under the influence of Dofetilide (0.84 ± 0.04 vs 0.90 ± 0.03), and Pinacidil perfusion (0.86 ± 0.04 vs 0.90 ± 0.02), showing a robust performance.

The global root mean squared error between estimated and gold standard DF maps was lower in the LR method (1.06 ± 1.25 vs 0.89 ± 0.85) as well as the percentage of electrodes with an error greater than 1 Hz. This was consistent across all pharmacological conditions tested, including Baseline (30.55 ± 9.33 vs 18.29 ± 7.14), Dofetilide (22.45 ± 7.42 vs 16.55 ± 6.24), and Pinacidil (33.10 ± 6.52 vs 26.85 ± 3.63). All the mentioned comparisons resulted statistically significant with a $p < 0.05$.

4.3.5 DF estimation in patient data

DF maps were computed in 5 consecutive time windows using the LC and LR methods. The estimated DF maps in the third window using both methods are shown in figure 4.8 A and B as an example. The HDF area was found below the left inferior pulmonary vein, which was consistent in all the 5 windows analyzed. The probability map associated to the LR DFs also presents consistent high values in the core of the HDF region (see figure 4.8.C) suggesting a robust estimation of the DF in this area.

Temporal stability of DF maps using both, LC and LR methods were quantified and presented in figure 4.8.D. There, the mean absolute differences between DFs in consecutive windows are compared. These differences were larger in the LC method than in the LR method (1.38 ± 0.11 Hz vs. 1.16 ± 0.09 Hz). When comparing the mean absolute error between consecutive maps only in high confidence regions (probability > 0.7) the mean differences decreases to 0.64 ± 0.34 Hz. In this way, DF estimated with LR method are more temporally stable than the LC-DFs. Additionally, LR method provides an uncertainty measure that constitute an alternative way to identify stable DF.

4.4 Discussion

This study presents a new methodology for DF estimation in ECGI. It provides an alternative approach to regularize the inverse problem of electrocardiography by means of a probabilistic framework. Information from a range of ECGI solutions is used to obtain a robust DF map and to quantify the uncertainty of the estimates. The validation suggest that the new LR DF algorithm offers superior accuracy and

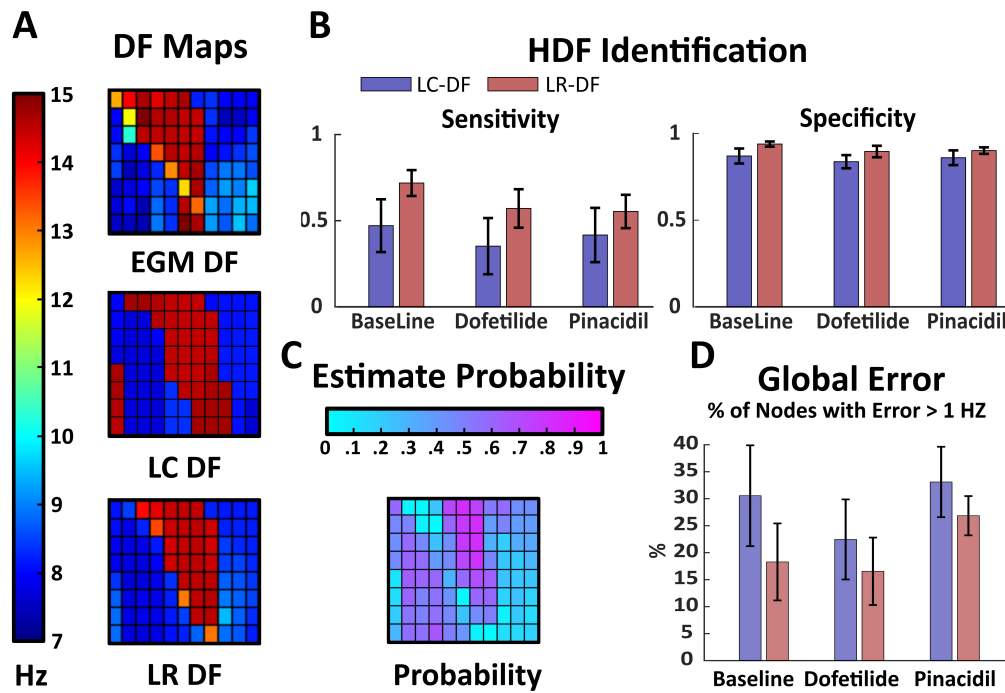


Figure 4.7: A) Example of the distribution of DFs in the epicardial surface of the animal ventricular model. The upper map represents the reference DF map computed in epicardial EGMs. The second the ECGI DF map obtained with the LC method and the bottom map the resultant DFs of the LR method. B) TH sensitivity and specificity of each approach is presented. C) Probabilities associated to LR-DF map. D) Percentage of nodes with a error higher than 1 cm using DF-LC and DF-LR methodologies.

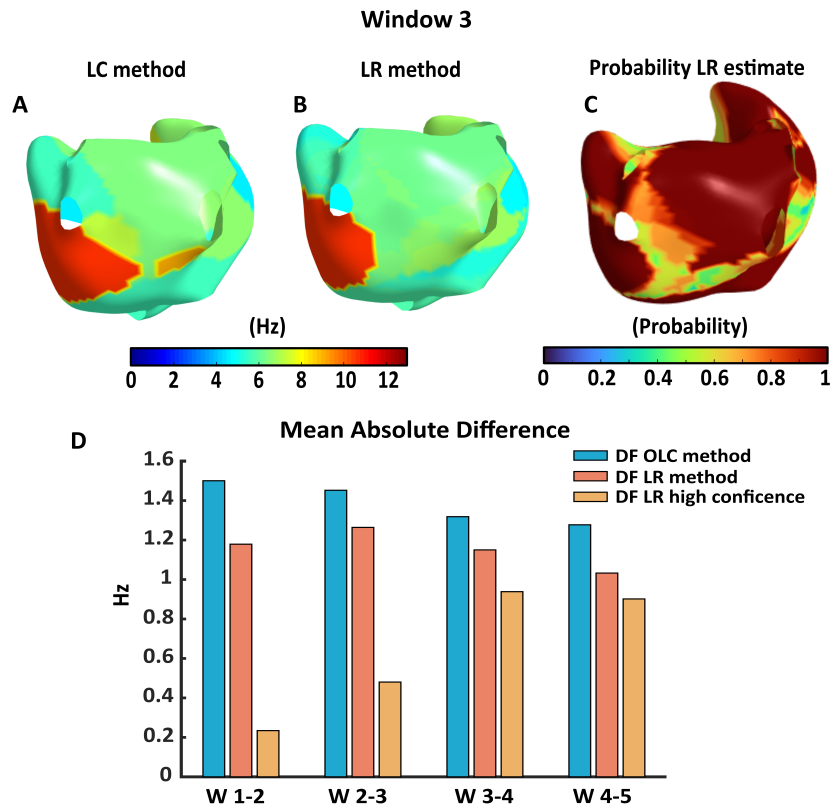


Figure 4.8: A) and B), DF maps obtained in window 3 with LC and LR methods respectively. C) Estimation probability map provided by the LR method within an interval of $\pm 0.2\text{Hz}$. D) Mean absolute difference of DF maps obtained by the LC, LR and high confidence LR nodes in consecutive time windows.

reliability in terms of DF and in the location of the HDF region compared to the conventional LC DF method.

4.4.1 DF Mapping Validation

We included in-silico, experimental and clinical data to validate our proposed DF algorithm and compare it with the standard methodology employed in the literature. Other studies have already evaluated the performance of the standard LC-DF methodology in mathematical simulations. For example, in [Rodrigo *et al.* 2017b], an in-silico evaluation of the identification of the HDF was performed using 30 different mathematical models of AF. For the same noise level of 20 dBs a mean concordance value above an 80% between the simulated and estimated HDF areas was obtained. We observed similar results for both LC and LR methods with sensitivities around a 90%. Pedrón-Torrecilla *et. al.* also observed low errors in non-invasive DF maps when evaluated in mathematical models (around 5% of relative error) [PEDRÓN-TORRECILLA *et al.* 2016]. However, in this study the relative error was computed in terms of mean squared spectral differences and not using the DF. In this way, our results align with those reported in the literature and support that the standard LC method employed in simulations accurately retrieves the spectral content of AF. However, we observed artificial HDF areas due to the presence of harmonic frequencies in the range of [3-12Hz]. Although these harmonics can be easily identified in computer simulations, in patient data we do not have a gold standard to rule out these contributions and therefore these may interfere in the interpretation of the maps. This is why special care must be taken to compute the HDF from DFs obtained by the LC method. The LR method demonstrated to overcome this limitation inherent to DF estimation in AF signals.

The differences between the LC and LR methods regarding DF mapping found in experimental data were more pronounced. In the pig model the global RMSE error in the DF was significantly lower in the LR method as well as the sensitivity and specificity in the identification of the HDF. This was true in all the tested conditions (baseline, dofetilide and pinacidil). In this setup, the inverse problem is prone to be worse conditionate than in simulations, as geometrical errors are also included in the resolution. This may be the reason why the LR method, which makes use of different regularization solutions, is more robust than the standard LC method for DF estimation. Additionally, an important particularity of our experimental setup is the use of ventricular fibrillation episodes. Unlike AF, VF surface potentials exhibit stronger temporal variability, with increasing complexity as the episode sustains. In order to account for this increased level of complexity characteristic from VFs, we evaluated our algorithm under different condition. Using drugs such as dofetilide and pinacidil which potentially reduce and increase the activation frequency of the arrhythmia and its complexity. In this way, we observed how our methodology overcame the traditional DF estimation method independently of the arrhythmia complexity.

We also quantified and compared the temporal stability of both methods in a real

AF episode. The LR method presented higher temporal stability measured as the similarity between consecutive DF maps. Additionally, the high-confidence regions contained more stable DFs throughout time than the global LR-DF maps. Several clinical studies have reported the temporal variability of dominant frequencies measured from intracavitary signals and how sequential mapping is not optimal to capture its dynamic behavior [Habel *et al.* 2010, Kogawa *et al.* 2015]. This is why different attempts to identify recurrence in fast activation areas have been done in the past using global mapping technologies. For example, Li *et al.* employed non-contact mapping to identify dominant patterns in the spatial distribution of the HDF [Li *et al.* 2021]. He found a significantly lower standard deviation of DFs belonging to repetitive patterns. Although the technology and methodological approach are different, these results align with the higher stability of DF we observed in high probability areas, highlighting the potential clinical relevance of these locations as they may constitute ablation triggers under the right conditions. However, additional research is needed to evaluate the temporal stability of high DF and high probability areas in a large cohort of patients.

4.4.2 Lambda Range selection

The optimal lambda value found by the L-curve lied into our proposed lambda range in all the different setups and clinical conditions. The wider ranges of solutions were found in simulations (10^{-9} to $5.62 \cdot 10^{-5}$), followed by the ventricular animal models ($4.5 \cdot 10^{-5}$ to $2.0 \cdot 10^{-2}$) and the real AF episode ($3 \cdot 10^{-6}$ to $3 \cdot 10^{-4}$). In this way, the amplitude of this range seems to be correlated with the level of uncertainty in the system, obtaining wider ranges in problems that are better conditioned.

4.4.3 Limitations and Future Work

An important aspect of our methodology is the selection of a set of inverse solutions for estimating a DF map. In this study, we did not provide an automatic method for determining the range of lambda values. Instead, we used the correlation between DF maps and spectral power in the AF frequency band as a guide for selection. Specifically, we set the boundaries of these ranges in the solutions of maximum slopes of correlations if this range includes also a high spectral power in the 3 to 12 Hz band. However, defining these ranges consistently proved challenging in some experimental recordings. In the future, we plan to explore additional parameters in the inverse solutions to develop a more robust algorithm for selecting the inverse solutions involved in the calculation of DF maps.

We also plan to perform a direct comparison between the ECGI DF methods evaluated in this study and intracavitary DFs. We plan to perform this evaluation in the future, ensuring that the electro-anatomical mapping protocol allows for enough frequency resolution.

Finally, some of the conclusions drawn are based on results from an animal model of ventricular fibrillation. Some technical differences arise when leading with

atrial fibrillation such as the need for a QRS cancellation and having a worse signal to noise ratio in the body signals. However, we still consider this dataset valid, as we did not use it to compare with results obtained from DF estimates in AF, but as a benchmark to compare the performance of two algorithms applied under the same conditions.

4.5 Conclusion

Overall, our results suggest that, in addition to the L-curve, other methods based on spectral parameters can be used to obtain an accurate solution of the inverse problem of electrocardiography for DF estimation. Furthermore, the optimal solution found with the L-curve is improved when making use of a set of solutions with different λ values, providing accurate results and additional information on the estimation uncertainty.

AF driver Detection in Pulmonary Vein Area by ECGI: Relation with a Favorable Outcome of Pulmonary Vein Isolation

Contents

5.1	Introduction	76
5.2	Materials and Methods	77
5.2.1	Study Population	77
5.2.2	Ablation and Electroanatomical Mapping	78
5.2.3	Data Acquisition and Preprocessing	78
5.2.4	Rotors and Phase Singularities Detection	79
5.2.5	Rotor Metrics and Clinical Outcome Study	79
5.2.6	Validation Dataset	80
5.2.7	Evaluation Metrics	80
5.3	Results	81
5.3.1	Validation of the Rotor Detection Algorithm in Simulations	81
5.3.2	Validation of the Rotor Detection Algorithm in Patients	81
5.3.3	Relation between rotors and PVI outcome	82
5.4	Discussion	84
5.4.1	Algorithm Evaluation	87
5.4.2	ECGI in the Detection of AF Sources	87
5.4.3	PS Detection and Rotor Tracking with ECGI	88
5.4.4	Noninvasive atrial substrate evaluation in AF patients	89
5.4.5	Clinical Implications	92
5.4.6	Limitations and Future Work	92
5.5	Conclusions	92

5.1 Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting millions globally and posing significant challenges in cardiovascular healthcare [Members *et al.* 2023]. Characterized by rapid and disorganized atrial activity, AF substantially increases the risk of stroke and heart failure [Kirchhof *et al.* 2012b]. Despite advancements in treatment, the management of AF, particularly in its persistent forms, remains complex and often unsatisfactory.

The landmark study performed by [Haissaguerre *et al.* 1998] fundamentally shifted the treatment paradigm for AF. The high concentration of ectopic beats observed in the pulmonary veins made from pulmonary vein isolation (PVI) the primary treatment strategy for AF. While PVI has demonstrated effectiveness in paroxysmal AF with approximately 70-80% remaining free of arrhythmia after the first procedure [Calkins *et al.* 2017], the success rate is notably lower in patients with persistent AF where only about 50% achieve arrhythmia freedom after the initial ablation [Brooks *et al.* 2010]. This highlights a critical need for improved patient selection and stratification methodologies in PVI.

The heterogeneity in AF pathophysiology needs from a personalized approach. Current research underscores the importance of identifying AF drivers. Rotors, also known as functional reentries, are a type of local driver characterized by rotational activation patterns that sustain disorganized electrical propagation in the heart [Jalife 2003]. These phenomena have been extensively theorized and represented in numerous in-silico and animal models [Mandapati *et al.* 2000, Pertsov *et al.* 1993], demonstrating their role in the continued disturbance of normal cardiac rhythm. Yet, pinpointing rotors within clinical settings continues to be a challenging endeavor. Various obstacles prevent from a clear identification of rotors in the electrophysiology (EP) lab, including their continuous movement within the atria or the presence of transmural reentrant circuits. However, the current primary challenge is technological. The existing sequential mapping systems lack the capability for a comprehensive global analysis of the arrhythmia making the detection and continuous monitoring of rotors very challenging.

Recent advances in non-invasive imaging, particularly Electrocardiographic Imaging (ECGI), have opened new avenues for understanding and managing AF. ECGI allows for global and non-invasive mapping of the heart's electrical activity, offering potential for identifying AF drivers and refining treatment strategies. This new understanding may help to stratify non-invasively patients that may benefit from PVI from those who will return to arrhythmia after the intervention, saving resources and minimizing unnecessary risks for some patients. The most extended methodology used nowadays to localize rotors using ECGI is based on the detection of phase singularities (PSs) in phase maps [Li *et al.* 2020, Rodrigo *et al.* 2017c, Molero *et al.* 2021b, Haissaguerre *et al.* 2014]. Many strategies have been developed so far to identify PSs automatically [Li *et al.* 2020]. However, the lack of standardized postprocessing techniques to identify PSs in phase maps obtained from ECGI and technological limitations associated to ECGI validation have raised skep-

ticism on the use of phase maps and confusion about the electrophysiological interpretation of phase singularities (PS) [Podziemski *et al.* 2018, Cluitmans *et al.* 2018].

This chapter explores the novel use of ECGI for detecting rotors in the atrial tissue, focusing on the pulmonary vein area. We examine the relationship between rotor density in this region and the outcomes of PVI, using a cutting-edge rotor detection algorithm. Our findings have significant implications for predicting PVI success and could lead to more personalized treatment approaches and better stratification strategies for AF patients.

5.2 Materials and Methods

5.2.1 Study Population

The acquisition protocol employed in this study received the necessary ethical approval from the ethics committee of Hospital Gregorio Marañón in Madrid, Spain, under the reference number 475/14. Informed consent was obtained from all participants, affirming their understanding and voluntary involvement in the study. The study cohort comprised 29 patients diagnosed with atrial fibrillation (AF), including a subpopulation of 7 men and 22 women with an average age of 62.63 years (standard deviation ± 14.26 years). This population included 27 re-do patients (93.10%) and counted with two groups according to the AF stage: 16 patients with paroxysmal AF, characterized by sudden onset and resolution, and 13 patients with persistent AF, known for more prolonged and stable episodes. Prior to undergoing a PVI procedure, a subset of 6 patients had been prescribed antiarrhythmic drugs (detailed demographics and medical history are presented in Table 5.1).

After PVI, patients were observed for a period of 6 months to assess the procedure's efficacy, during which they were divided into two categories based on their clinical outcomes. Fifteen patients who maintained normal sinus rhythm were classified as 'Non-recurrence', indicating successful treatment outcomes. The remaining 14 patients who experienced any form of arrhythmia including AF or atrial flutter, were grouped under 'recurrence'. To validate the clinical outcomes, standard 12-lead ECGs were employed, providing a comprehensive evaluation of the heart's electrical activity. Additionally, quality-of-life questionnaires were utilized to assess the impact of the treatment on patients' day-to-day wellbeing, offering a holistic view of the intervention's success [Molero *et al.* 2021b].

**Chapter 5. AF driver Detection in Pulmonary Vein Area by ECGI:
78 Relation with a Favorable Outcome of Pulmonary Vein Isolation**

		All Patients	Non-recurrence	Recurrence
		(n = 29)	(n = 15)	(n = 14)
Male (%)		7 (24.14%)	6 (40.00 %)	1 (7.14 %)
Age (Years)		62.63 $\pm$ 14.26	58.13 $\pm$ 15.06	64.57 $\pm$ 13.18
Paroxysmal AF (%)		16	11 (73.33 %)	5 (35.71 %)
Valvuloplasty (%)		14	8 (53.33 %)	6 (42.86 %)
Medical Therapy	Beta-blockers	1	1	0
	Flecainide	1	1	0
	Amiodarone	6	3	3
Medical Therapy After Ablation	Beta-blockers	15	5	10
	Flecainide	2	2	0
	Amiodarone	12	5	7
Patients with Previous Ablation		27 (93.10%)	14 (93.33 %)	13 (92.86 %)

Table 5.1: Description of the population used in the study.

5.2.2 Ablation and Electroanatomical Mapping

In all 29 patients, circumferential pulmonary vein isolation (PVI) was achieved using point-by-point ablation with irrigated catheters (Cool-Flex, TactiCath, Sapphire-Blue from St. Jude Medical). Ablation energies between 25 to 35 W were delivered to each pair of pulmonary veins through conventional radiofrequency ablation. For 3-dimensional electroanatomic mapping, FIRMap 64-pole mapping catheters were sequentially inserted into the right and left atrium using the NavX system (St. Jude Medical). Access to the atria was gained through the femoral vein, reaching the right atrium and subsequently the left atrium via transeptal puncture. In cases where patients presented in sinus rhythm, electrical burst pacing was used to induce AF [Rodrigo *et al.* 2020].

5.2.3 Data Acquisition and Preprocessing

Body Surface Potential Maps (BSPM) were recorded in all the patients during AF right before circumferential PVI. A set of 57 electrodes were employed to record the signals. The acquisition and preprocessing protocols employed in this study were already presented previously [Molero *et al.* 2021b] [Rodrigo *et al.* 2020]. As an overview, BSPM signals were recorded with a 1kHz sampling frequency and filtered using a 0.05-500Hz bandpass filter. The geometry of the torso and electrode positions were determined using photogrammetry and the anatomy of the atria was segmented from MRI/CT images. A total of 57 segments with similar durations (4.06 ± 0.311 s) were included in the analysis. Additionally, other 57 segments were recorded during adenosine injection in order to compare the clinical results obtained from adenosine-free signals (see supplemental material). These segments were manually segmented to ensure the acquisition lied within adenosine injection and a good signal quality. Regarding signal processing, the baseline was removed using a low-frequency polynomial fitting. The signal was then filtered using a 10th Butterworth band-pass filter with cut-off frequencies of 2 and 45 Hz. In order to re-

move the ventricular activity, QRS cancellation was performed following a temporal PCA separation approach [Castells *et al.* 2005]. The inverse problem was then computed using the boundary element method formulation, and zero-order Tikhonov regularization with L-curve optimization methods for matrix inversion. Once the 3D voltage maps were obtained, these were transformed into 2D squared images using a Teichmüller external mapping approach, guaranteeing a uniform conformal distortion of the 3D point cloud surface [Meng *et al.* 2016] (See appendix B for more information). Finally, phase maps were computed from 2D voltage maps by means of the Hilbert transform.

5.2.4 Rotors and Phase Singularities Detection

The details on the proposed rotor detection algorithm are explained in appendix B but the general workflow of the algorithm is described in this section. The first stage on the detection algorithm consists in the identification of the center of rotation of rotors, namely phase singularities (PSs), on a given time instant. In this study, PS are defined as locations in the atria surrounded by the whole activation cycle, or equivalently, the full range of phases $[-\pi, \pi]$ obtained by applying the Hilbert transform on inverse computed electrograms. PSs are identified by the topological charge [Bray & Wikswo 2002]. Then, PSs non complying with a gradual spatial progression of phases between $-\pi$ and π in their surroundings [Rodrigo *et al.* 2017c] were discarded. After having identified PSs we then connect them spatiotemporally into rotors and through filaments in order to both discard transient PSs that appear for a short period of time most likely corresponding to changes in direction of the propagation front- and connect PSs whose tracking is transiently lost. Rotors filaments were then dilated using a prism-shaped kernel in the direction of the trajectory, and skeletonized in order to cluster and identify the trajectories. Finally, the number of turns is quantified in each rotor and PSs belonging rotors that spin for less than a given number of turns are discarded for further analysis.

5.2.5 Rotor Metrics and Clinical Outcome Study

Two different parameters were calculated to study the relationship between the detected reentrant activity, and the clinical outcome of the patients after PVI. The first parameter was the number of rotors or clusters in the whole atria per unit time. The second set of parameters was the percentage of PSs at 9 different atrial regions. This percentage was calculated as the number of PSs detected at a particular atrial region over the total number of PS detected. After clustering PSs into rotors, the mentioned metrics were obtained in two different conditions: considering all the detected rotors and PS, or keeping only those rotors (and correspondent PSs) that spin for at least 1 turn. These two implementations were applied to recordings obtained with and without adenosine injection. Finally, Mann-Whitney's U test was used in order to compare the value of all the calculated rotors and PSs ratios in the 'Non recurrence' and 'Recurrence' group.

5.2.6 Validation Dataset

The proposed methodology for rotor detection in ECGI data was evaluated both using recordings from patients and simulated data. Specifically, two mathematical models with well-defined location of reentries were employed. To identify the reentries maintaining the arrhythmia, we performed a virtual ablation in the middle of the fibrillatory episode. Then we solved the inverse problem and applied the rotor detection algorithm presented in this study to compare the pre- and post-ablation scenarios (see supplementary materials for further details on the simulations).

Regarding the validation in patients, a dataset of 9 ECGI segments were selected from the main database of patients. These episodes were blindly labeled by an operator indicating the areas with reentrant activity. The labeling was performed by visual inspection of the signals and phase maps considering two main conditions to indicate the presence of a reentry. First, the pattern should spin for at least 1 turn and second, a linear progression of the phases around the detected singularities should be observed.

5.2.7 Evaluation Metrics

The performance of the algorithm was evaluated using the precision (P) and recall (R), defined in equations 5.1 and 5.2:

$$P = \frac{TP}{TP + FP} \quad (5.1)$$

$$R = \frac{TP}{TP + FN} \quad (5.2)$$

Where TP are the true positive detections, FP the false positive and FN the false negative. Precision (P) is a measure of how much the proposed algorithm overestimates the presence of PSs. On the other hand, recall (R) measures how often PSs are undetected. All the PSs detected within a tolerance distance of 5 mm from a manually labelled PS were considered true positives. In contrast, false positives were annotated when more than one PS was detected in the 5 mm surrounding area of a labelled PS. False negatives were identified as the absence of any detected PS withing a 5 mm distance from a labelled PS. In order to include the precision and recall information in only one parameter, the F_β score was also computed [Li *et al.* 2020] (see equation 5.3). This parameter allows to weight the relevance of the precision and recall in the final score through the constant β . In this study the same value presented in the literature of $\beta = 2$ was used for better comparison.

$$F_\beta = (1 + \beta^2) \frac{P \cdot R}{\beta^2 \cdot P + R} \quad (5.3)$$

Finally, the regional accuracy of the algorithm was also evaluated. For that, the atrial geometries of all the patients were divided into 9 different regions depicted in

figure 5.3. The number of PS manually labelled in the validation data set was then compared to the number of PS detected by the algorithm in every region. The mean absolute error between these two quantities and the relative error were calculated. This last was defined as the ratio between the mean absolute error and the mean number of PSs labelled in each region.

5.3 Results

5.3.1 Validation of the Rotor Detection Algorithm in Simulations

The simulated AF episodes are illustrated in figure 5.1. In the first AF episode (figures 5.1 A-D), a reentry driving the arrhythmia was localized near the left pair of PPVVs. In figures 5.1.A and 5.1.B the transmembrane potentials of two different pre and post-ablation instants in this episode are presented. The reentry was identified in ECGI signals by using our rotor detection algorithm after forward and inverse propagations. The rotor histograms summarizing the whole reentrant activity in the pre-ablation period is shown in figure 5.1.C. We can observe how most of the reentrant activity is located near the left pair of pulmonary veins. A virtual ablation in the PPVV area was able to stop the arrhythmia and therefore, no reentrant activity is observed after the ablation (figure 5.1.D). In contrast, in the second episode (figures 5.1 E-H) reentrant activity is spread throughout different atrial locations far from the PPVV. When applying PVI, the electrical activity is prevented from entering in the PPVVs and the dynamics of the arrhythmia are modified (see figure 5.1.F). However, PVI is not able to eliminate rotors present in the right atrial posterior wall, leaving some pro-arrhythmic mechanisms intact outside the PPVV (5.1.H).

5.3.2 Validation of the Rotor Detection Algorithm in Patients

In Figure 5.2.A the global recall, precision and F-score values obtained for all the recordings in the validation dataset are represented. The mean F-score, precision and recall values of all these recordings were 0.84, 0.84 and 0.85 respectively. The lowest recall was found in recording 3 with a value of 0.66, and the lowest precision was found in the recording number 5 with a value of 0.65. In Figure 5.2.B and 5.2.C a comparison of the rotor histograms obtained in two different recordings are presented: recording 9 with a high recall value (0.87), and recording 3 with a low recall (0.66). In this example, it is shown how, in spite of missing some of the reentry areas (mostly in the right pair of PPVV), a map with very similar locations of the main reentrant activity is obtained.

The accuracy of the algorithm was also evaluated regionally. The proposed division for the atria is shown in figures 5.3.A and 5.3.B. Regarding the local accuracy in each of these regions, the mean number of detected and annotated PSs along with the mean absolute error between these two magnitudes are presented in figure 5.3.E. In general, it can be observed a good correspondence between the annotated

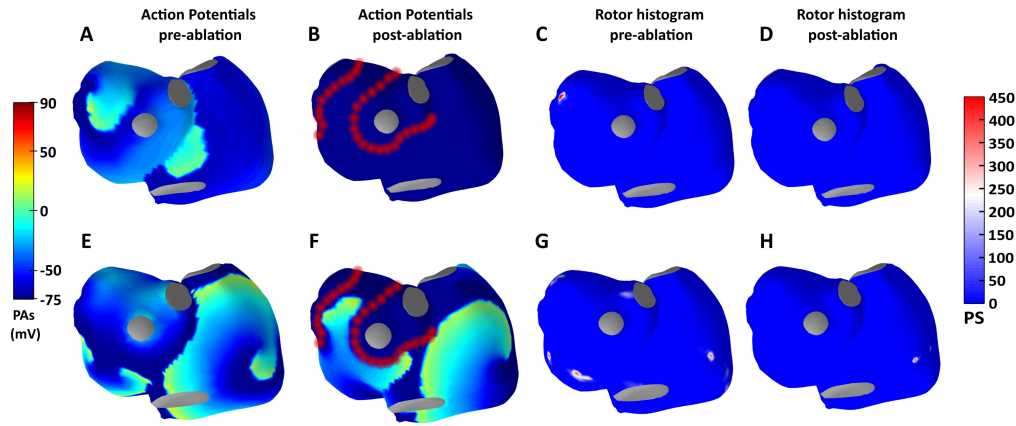


Figure 5.1: Information about simulations 1 and 2 is presented in the first and second rows of panels respectively. Panels A and E show a pre-ablation instant of the simulated action potentials while panels B and F show the action potentials after ablation. In C and G, ECGI-derived rotor histograms of the pre-ablation periods are shown. Postablation histograms are presented in panels D and H.

and detected PSs with a mean absolute error of 7.9 PSs across all the regions. The areas with higher absolute errors were the RB (23,22 PSs) followed by the LB (18,11) which are also the largest regions in the proposed atrial segmentation. Regarding the relative error, it ranged between 0 and 67% with a mean value of 16.11%. The SVC is the atrial structure with lower relative error and RAPP the one with the largest. The distribution of the relative errors in the rest of atrial regions is presented in figures 5.3.C and 5.3.D.

5.3.3 Relation between rotors and PVI outcome

In figure 5.4 the number of rotors per second obtained in the whole atrium is presented for both studied groups: patients that remained in sinus rhythm and patients that returned to arrhythmia 6 months after PVI (AF-recurrence). The number of rotors was quantified in two different ways: including all the rotors detected (any turns, figure 4.A) and discarding those rotors spinning for less than 1 turn (figure 5.4.B). Patients with an unsuccessful PVI had more rotors in the whole atria than patients remaining in sinus rhythm 6 months after the ablation. This difference was more noticeable when all the rotors detected were considered in the analysis, median values 54.83 ± 10.43 vs 70.92 ± 27.77 ($p < 0.01$, figure 5.4.A). However, when keeping only rotors that spin for at least 1 turn, the difference is still preserved although the significance lowers down (3.59 ± 2.67 vs 4.31 ± 2.78 , $p < 0.05$, figure 5.4.B).

In both groups, higher concentrations of PS are found in the regions located

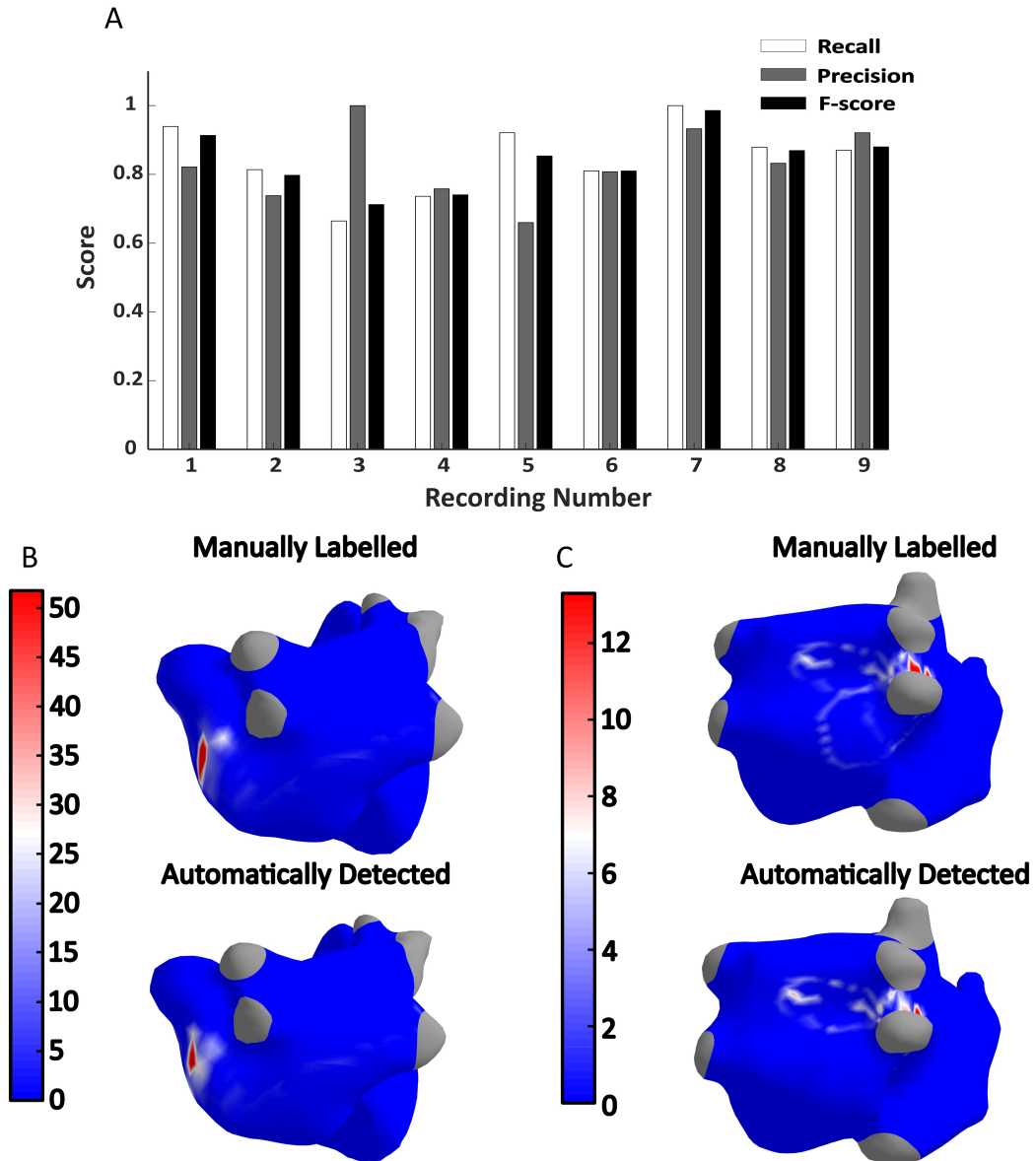


Figure 5.2: A) Recall, Precision and F-score values obtained in the validation data set for all the recordings used in the evaluation. B) and C), Manually labelled and automatically detected rotor histograms obtained from recordings 9 (left) and 3 (right) respectively. The recall, precision and F-score values calculated in recording 9 were 0.87, 0.92 and 0.87 while the recall, precision and F-score values of recording 3 are 0.66, 1 and 0.7 respectively.

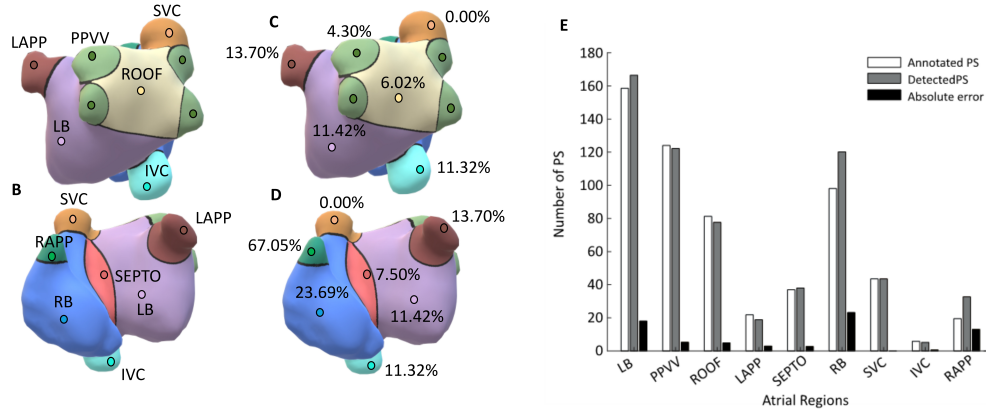


Figure 5.3: (A, B) Illustration of the regional anatomical division of the atria; (C) and (D) relative errors obtained in each of the atrial regions; (E) Mean number of annotated and detected PSs in different atrial regions across the validation dataset. The mean absolute error between these two magnitudes is also presented in black. LB: Left Body; PPVV: Pulmonary Veins; ROOF: Roof; LAAP: Left Atrial Appendix; SEPTO: Septum; RB: Right Body; SVC: Superior Cava Vein; IVC: Inferior Cava Vein; RAAP: Right Atrial appendix

in the left atria. This result is in line with the general belief that most of the initiation mechanisms of AF are present in the left atrium. In a regional level, a larger proportion of PS in the PPVV was always found in the non-recurrence group. This last finding is expected given the assumption that the mechanisms driving AF are more frequently located in the PPVV in patients with a successful PVI. This difference is presented in figure 5.5.B for stable reentries, that is, reentries spinning for at least 1 turn (10.20 ± 12.40 vs 5.19 ± 9.13 , $p > 0.05$), but also in figure 5.5.A where all the PS detected are included in the analysis. The statistical differences obtained in the different atrial regions are presented in figure 5.5.C, where it is shown that the PPVV and LAPP areas are the only areas presenting p-values lower than 0.05.

5.4 Discussion

In this study, a rotor detection algorithm was presented and validated. The proposed methodology for rotor detection was applied in two groups of AF patients identifying a higher prevalence of PS in the PPVV area in subjects with a favorable outcome after PVI. This results suggest a link between the identified reentrant activity and the mechanism sustaining AF.

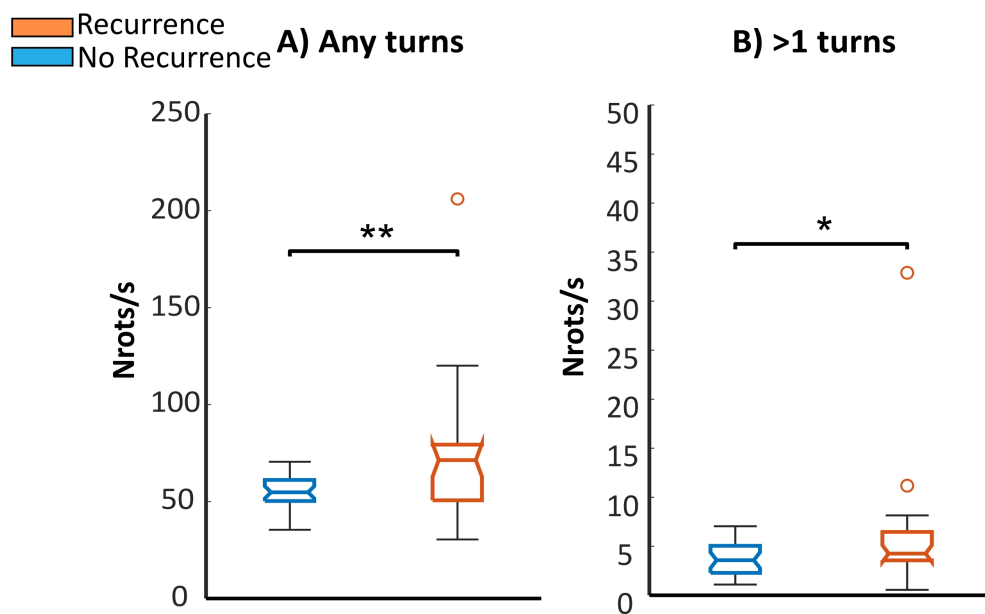


Figure 5.4: Number of rotors obtained in all the patients: In blue are represented patients staying in sinus rhythm (No recurrence) and in orange patients returning to arrhythmia 6 months after PVI (Recurrence). The number of rotors was calculated in the whole atria in two different scenarios regarding the number of turns used to filter the PS: A) Number of rotors obtained without any turn filtering; B) Number of rotors spinning for at least one turn.

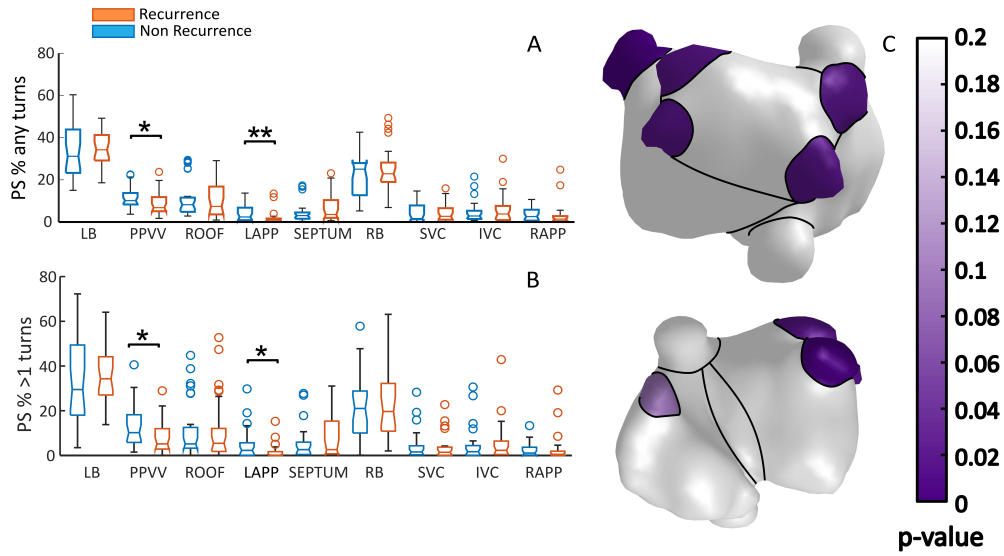


Figure 5.5: (A,B) Proportion of PSs per second detected in different regions in each studied group: in blue is presented the data from patients that remained in sinus rhythm 6 months after ablation (Non-recurrence), and in orange patients that returned to arrhythmia (Recurrence). In panel (A), are presented the results obtained when all the reentries are considered in the analysis. In panel (B), the same results are shown, when only the reentries lasting for more than 1 turn. The distribution of statistical p/values obtained for each regions are presented in panel (C).

5.4.1 Algorithm Evaluation

In terms of global performance, the use of simulations showed a precise localization of the main reentrant activity during AF, as well as a mechanistic explanation on why PVI works in the first simulation, with a localized reentry in the PPVV area, and not in the second, with multiple spread drivers. Regarding labeled data coming from AF patients, it was found that the F-score value obtained (0.84) outperforms other algorithms presented in the literature. A closely related study in this regard is [Li *et al.* 2020], where the same definitions of precision, recall and F-score values were used. In this study, 4 different rotor detection algorithms were tested in 2D geometries obtaining F-scores values ranging between 0.527 and 0.831. Similarly, these algorithms were validated in non-invasive ECGI phase maps obtained from AF patients, where the presence of rotors was manually labeled by an operator.

In the same way, the performance of our algorithm was also evaluated locally in 9 different regions. The mean discrepancy present in all areas between the detected and annotated PSs was 16.11%. An abnormally high relative error in the RAPP region (67%) was observed. The origin of this high error must be related to the low number of PSs detected in the RAPP. This factor increases the effect of miss detections in the relative error value.

5.4.2 ECGI in the Detection of AF Sources

The existence of well localized mechanism driving AF has been reported by means of invasive and non-invasive mapping techniques [Narayan *et al.* 2012] [Haïssaguerre *et al.* 2006] [Gao *et al.* 2019]. This finding has justified the use of personalized driver-specific ablation strategies to terminate AF. In this line, Narayan *et al.* showed that focal impulse and rotor modulation ablation (FIRM), in combination with PVI, had a higher successful rate in long-term AF termination than standard PVI alone [Narayan *et al.* 2012]. Haïssaguerre *et al.*, also tried a similar ablation strategy, but this time obtaining the cumulative maps of focal and reentrant activity from ECGI mapping [Haïssaguerre *et al.* 2013]. They guided ablation in 103 patients with persistent AF demonstrating that the mean ablation time can be reduced guiding the procedure with non-invasive ECGI mapping. Furthermore, a higher degree of fractionation in reentry areas identified with ECGI was found, providing clinical evidence of the detections.

In spite of the clinical evidence showing the potential advantages of a personalized ablation strategies, the positive results obtained in the mentioned studies have not been reproducible. A possible reason for this may be the lack of robustness of the overall approach and a dependence on the operator expertise to determine what is a reentry. In our pipeline, we include a full methodology that allows to remove the human factor by automatically computing the number of turns of the rotors and filtering the PSs with no linear progression of phases in their surroundings.

5.4.3 PS Detection and Rotor Tracking with ECGI

Other ECGI PS detection methods have been developed in the past. Specifically, Rodrigo et. al. proposed a methodology to detect reentries directly on 3D atrial meshes. There, PS were detected at nodes in which the full range of phases $[-\pi, \pi]$ was observed in their surroundings. Additionally, the spatial progression of the phases was checked to be ‘linear’ around each PS. The resultant PS were then tracked to obtain filaments or rotors by imposing a radius distance criterium. This methodology was validated in AF simulations [Rodrigo *et al.* 2017c] [Rodrigo *et al.* 2017b].

Other studies have proposed to detect reentries by means of local activation time (LAT) mapping [Vandersickel *et al.* 2019] [Rogers *et al.* 1999]. However, this approach is hardly transferable to ECGI during AF since there is no consistent method for detecting LATs during irregular rhythms. Additional challenges causing the lack of standard methods are the inherent spatial smoothing present on ECGI electrograms and the presence of remaining far-field artifacts that lead to false positive detections of PS. In this context, phase mapping has been postulated as an alternative way to detect reentries in ECGI [Haissaguerre *et al.* 2013] [Dhillon *et al.* 2022]. Phases provide equivalent information about the electrical propagation encoded in the low-frequency content of the signals with no need for LAT detection. Given the exposed advantage, we decided to stick to a phase-mapping based approach, but updating our methodology according to the results obtained in [Li *et al.* 2020]. In this work, algorithms based on topological charge, a metric closely related to the curl of the electrical propagation, presented the highest performance for PS detection. In addition, around the PSs obtained from topological charge, a checkup of linearity in the surrounding phases was included. This feature overcomes the presence of false positive PS at locations with complex or fractionated signals [Rodrigo *et al.* 2017c]. Additionally, we perform PS detections in a 2D domain in order to speed up the calculations. For that, we employ a transformation that assures a homogeneous distribution of nodes in the atria, and provides a direct transformation of the data to a 2D grid, where we can efficiently track rotors. Furthermore, having a homogeneous disposition of nodes is also very convenient in some steps of our methodology like phase linearity checking around PSs, or counting the number of turns per rotor. Other 2D-3D transformations, such as the universal atrial coordinates (UAC) system have been proposed in the past [Roney *et al.* 2019]. However, our methodology is better suited for our purpose than UAC. First, our transformation is fully automatic and does not require from manual landmark placement. Additionally, UAC was conceived for data transferring between different patients and does not result in a uniform grid with preservation of distances in the original mesh.

The methodology for rotor tracking was also updated in this study. It consists in combining neighbor voxels containing a PS into filaments. The methodology is completely based in image processing operations such as voxel dilation and skeletonization which present two main advantages with respect to the previous approach. The

first one comes from the efficiency of convolutional operations such as dilation or skeletonization performed on image stacks. The second one is about specificity. Our tracking algorithm is more specific when combining PS into rotors than imposing a radius around each PS in space. This is because a prism-shaped dilation kernel is applied following the direction of the trajectory of the rotor at each voxel, preventing the algorithm from combining independent filaments together that eventually get too close in space. A similar methodology was applied in [Clayton & Holden 2004], where filaments in simulated ventricular fibrillation episodes were created by linking together voxels in a 3D space. In contrast with our algorithm, the method used in Clayton et. al. uses a grassfire algorithm instead of dilation and skeletonization operations to obtain filaments. This approach has the advantage that no kernel needs to be specified like in our approach, however the computational time needed to run it is higher. Finally, another important difference between our method and the one employed by Clayton et al. is that we count the number of turns of each rotor by taking into account the surround phases of the filament. This last step allows us to filter out rotors with a low number of turns.

5.4.4 Noninvasive atrial substrate evaluation in AF patients

The results obtained in this study suggest that ECGI provides relevant information about the functional state of the atria in AF patients. In a prior study we already related the stability of rotor-derived metrics with ablation outcome [Molero *et al.* 2021b] but we could not relate the location of these rotors with the success of PVI, in the same line as other studies [Dhillon *et al.* 2022]. In this study we have developed a new methodology for rotor tracking that allows for a more restrictive definition of a rotor, specifically suited for analysis of ECGI data, a context with low spatial resolution and loss of tracking due to remaining far-field components. In addition to the methodological differences for PS detection and rotor tracking explained in the previous section, we also explored regional differences in the presence of reentries. For that purpose, we divided the atria in 9 different areas where the prevalence of reentries was estimated as the percentage of PS. Additionally, we computed a different global parameter, the total number of rotors detected in the atria per unit time. Regarding the number of rotors per second found in the atria, a larger number was detected in the recurrence group, reflecting a possible higher complexity of the electrical activation patterns in patients with poor PVI outcome. This finding is in concordance with the reproducibility results obtained by Molero et. al. A possible explanation supporting this findings is the detection of changes in the direction of wavefronts as PS. Relative to this, Podziemski et. al. established a relationship between PSs obtained from phase maps and spots of conduction block [Podziemski *et al.* 2018]. In this way, recurrence patients with a higher prevalence of complex atrial substrate may have more conduction block spots that produce this effect. Another explanation is the detection of hidden transmural rotors where only part of the rotor cycle is visible in the epicardium. In this regard, Clayton et. al. observed in in-silico simulations of ventricular fibrillation (VF) that

only 65% of reentries touched the epicardium and most of them for less than one cycle [Clayton & Holden 2004].

In addition to factors that are actually related to the dynamics and complexity of the arrhythmia, the presence of far field artifacts and the limited spatial resolution reduce the accuracy of ECGI to provide the exact location of reentries. In this scenario, post-processing algorithms employed on top to the ECGI signals are of great importance to detect rotors robustly. Indeed, some studies quantifying the amount reentries in the PPVV have found a great overlap between recurrence and non-recurrence AF patients using CardioInsight system [Dhillon *et al.* 2022][Gao *et al.* 2019]. In our study, we also observed how the number of rotors overlapped between the studied groups. However, with our methodology, in contrast with the previous ones, we obtained statistically significant differences in the number of rotors and the proportion of phase singularities in the PPVV. In figure 5.6 it can be observed how when keeping only PS with a linear progression of phases in their surroundings, the areas showing a high prevalence of reentries shrinks down. In this example, red areas of high PS prevalence outside the roof of the atria are removed, keeping only a small core. This filtering has therefore an effect on the percentage of PS calculated in the different areas. When comparing these percentages in the recurrence and non-recurrence group of patients with no filtering strategy, we see how all the statistical differences observed with our post-processing algorithm disappear, with a $p=0.579$ in the PPVV. This observation highlights the importance of the methodology to observe differences in the reentrant activity when comparing recurrence and non-recurrence AF patients after PVI.

Finally, a higher prevalence of PSs in the PPVV area was quantified in patients with a favorable outcome after PVI. According to our results, the application of a threshold of one turn enhances the differences in the prevalence of PSs in the PPVV area as compared to other regions. In this regard, it was observed how the significant difference found in the LAPP obtained when including all the PS in the analysis (no turn filtering), was reduced when only PS belonging to long-lasting rotors (1 turn or more) are included in the analysis. A possible explanation for this reduction is the role of the LAPP as an anatomical obstacle, leading to direction changes in the propagation of wavefronts that do not cover an entire turn. In this way, the application of a threshold of 1 turn seems to reduce the relevance of this secondary patterns in the analysis, enhancing the importance of the mechanisms present in the PPVV. Additionally, this analysis was also performed during adenosine injection (see the Appendix B). Adenosine is a drug that stops the ventricular activity, providing a more favorable scenario for the inverse problem. Again, similar tendencies and significant differences in the proportion of phase singularities were found between the studied groups. The coherence in the results obtained under different filtering and adenosine conditions suggest that the presented approach is robust against far field artifact coming from the ventricular activity.

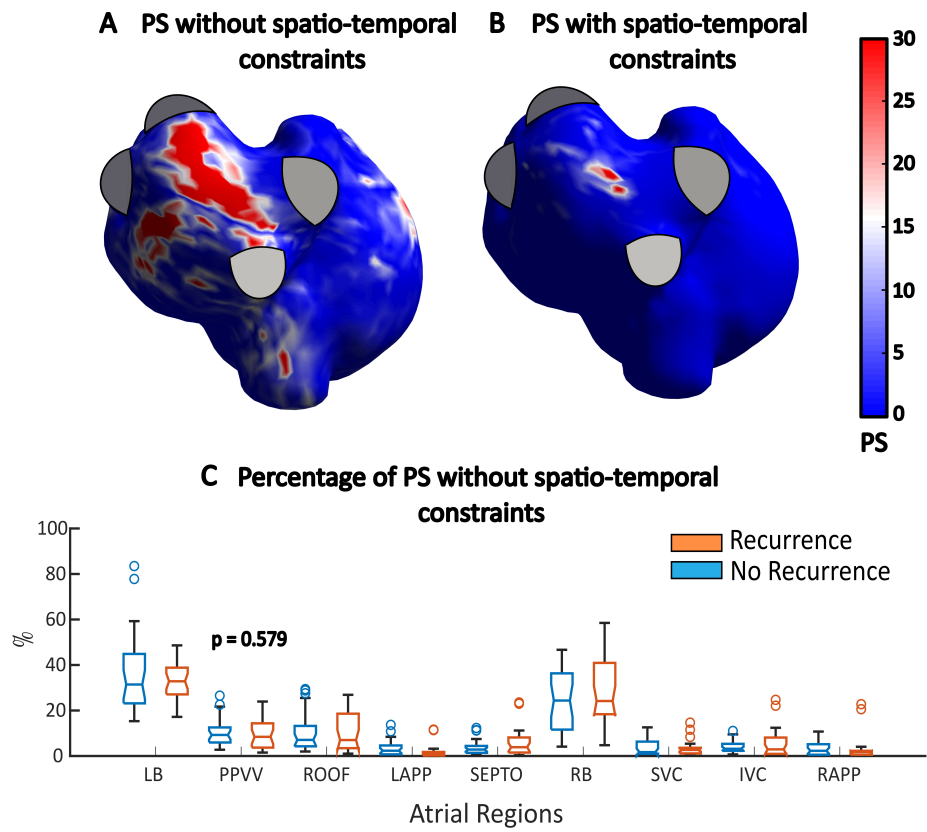


Figure 5.6: (A,B) PS histograms with and without filtering. (C) Percentage of PSs found in all the different atrial regions when no filtering strategies are applied. No statistically significant differences are observed.

5.4.5 Clinical Implications

The efficacy of PVI in AF patients decreases as the disease progresses due to the higher complexity and variety of mechanisms involved in the arrhythmia [Haïssaguerre *et al.* 2006][Haïssaguerre *et al.* 2013]. This progression leads to a lower success of PVI in patients with an advanced disease. In this study, we observed that the prevalence of reentries measured as singularity points in non-invasive phase mapping is a predictive factor of the clinical outcome of patients undergoing PVI. Therefore, this finding can help clinicians to stratify patients non-invasively before any electrophysiological study, saving in this way resources and reducing risks for patients who will not benefit from PVI.

5.4.6 Limitations and Future Work

Some of the characteristics of the dataset employed, such as the large prevalence of previous ablations or valvuloplasties are very particular of our population. Additionally, due to the lack of a standardized gold-standard in rotor detection with ECGI technology, we have opted for manually labelling ECGI data, which may somehow bias our results. In the future, we plan to continue the validation of the algorithm presented in this study, by comparing the locations of reentries to low voltage areas obtained with electroanatomical mapping.

5.5 Conclusions

In this study we have shown that ECGI allows detecting the spatial dominance of the reentrant activity at different atrial regions during AF. A higher concentration of PSs in the PPVV was found in those patients that remained in sinus rhythm 6 months after PVI, showing a direct relationship between the expected AF mechanism and the electrophysiological parameters provided by ECGI.

The results of this study may help in the future to predict which patients will benefit from a PVI procedure. Furthermore, we have shown that the approach employed is robust and valid for non-invasive applications like personal AF studies or patient stratification.

Chapter 6: Discussion and conclusion

Contents

6.1	Main findings	93
6.2	Comparison with previous studies	94
6.3	Limitations	97
6.4	Conclusions	98
6.5	Guides for future work	99

This chapter offers a discussion of the results presented in this thesis. Initially, it reviews and contrasts the key findings of the thesis. A contextualization of these results is then provided, relating these findings to prior studies published in the field. The main limitations encountered in this research are enumerated and the primary conclusions are presented. Finally, the chapter concludes describing future research lines, emphasizing areas of this thesis that require further investigation.

6.1 Main findings

Electrocardiographic Imaging (ECGI) is quickly becoming more important in the cardiac arrhythmias research field. Its use is growing in areas like Cardiac Resynchronization Therapy (CRT), Ventricular Tachycardia (VT), Ventricular Fibrillation (VF), Premature Ventricular Contractions (PVCs), and atypical atrial flutters (AFL). As the use of ablation to treat Atrial Fibrillation (AF) becomes more common, the importance of ECGI in making these procedures more accurate and effective is also increasing. This research provides additional evidence on how ECGI can change the way cardiac care is personalized and improved.

We first concentrated efforts on improving the characterization of sinus rhythm propagation with the aim of building the foundation to robustly identify slow conduction areas. The presence of artificial conduction block lines in ECGI activation mapping was corroborated when employing the standard definition of LAT based on deflections. For that reason we proposed a spatiotemporal Bayesian framework for LAT estimation which combines information from ECGI deflections with a propagation model. We demonstrated how incorporating a propagation model that also

includes spatial information provides a substantial improvement in terms of earliest and latest activation site location, isochrone estimation and in the reduction of artificial conduction block lines.

We evaluated ECGI to detect dominant frequencies (DF) in atrial fibrillation (AF) and compared our new probabilistic approach to the traditional DF estimation method. The findings from in-silico simulations and a clinical case study indicate that similar performance from both methods can be expected in these simple scenarios in terms of DF error. However the new methodology was able to robustly filter some harmonic components that can affect the detection of the HDF. Moreover, the experimental validation in a ventricular fibrillation animal model demonstrated that our new methodology was more accurate preserving better the HDF areas. This constitutes a more realistic setup than the simulations where geometrical errors are also included in the system. In this setup, we observed how the use of several inverse solutions provide higher robustness to the DF maps. Finally, we also quantified and compared the temporal stability of both methods in a real AF episode, demonstrating how the proposed LR method presents higher temporal stability measured as the similarity between consecutive DF maps.

In chapter 5, we observed how ECGI allows detecting the spatial dominance of the reentrant activity in different atrial regions during AF episodes. A higher concentration of PSs in the PPVV was found in those patients that remained in sinus rhythm 6 months after PVI. This observation constitutes a direct relationship between the expected AF mechanism and the electrophysiological parameters provided by ECGI. We also observed a higher number of rotors in the whole atria in patients that did not respond to the ablation. This result was attributed to a higher complexity of the AF also outside the PPVV. Additionally, we corroborated the importance of applying proper filtering strategies in the detection of rotors as we observed substantial differences in the regional concentrations of PS.

6.2 Comparison with previous studies

The identification of arrhythmogenic areas with ECGI during sinus rhythm via LAT mapping is not a common practice. The main reason is that the definition of activation time as the time of maximum downslope is not directly transferable to ECGI signals. Although some studies have relied on this definition [Graham *et al.* 2019], it is well known that the regularization performed to solve the inverse problem leads to temporal and spatial smoothing on the reconstructed signals, introducing artificial block lines and affecting the interpretation of LAT maps [Schuler *et al.* 2021].

Several spatiotemporal methods have been developed in the past to mitigate the presence of artificial block lines, mostly focusing on ventricular propagation sequences. Erem *et. al.* proposed the optimization of a functional integrating temporal and spatial gradients to identify LATs in fractionated EGMs [Erem *et al.* 2011]. Cluitmans *et. al.* tested and compared this approach to the traditional deflection-based method in simulated ventricular EGMs and experimental and clinical ECGI

signals [Cluitmans *et al.* 2022]. Duchateau *et al.* introduced a delay-based spatial coherent LAT estimator that optimally combines ECGI activation times with temporal delays between neighboring nodes [Duchateau *et al.* 2016]. All these LAT methodologies provided smooth and more physiological propagations, but more importantly, they demonstrated a higher accuracy than the standard deflection-based method in terms of isochrone estimation and earliest activation site location.

It is difficult to provide a clear comparison between all these spatiotemporal methods and our Bayesian framework. The differences in the validation datasets such as ventricular propagation instead of atrial pacing, and the use of simulation with predictable differences in the signal to noise ratio are confounding factors. However, some results indicate that our Bayesian framework is at a similar level of accuracy than the rest of spatiotemporal methodologies. For example, in terms of EAS location Cluitmans *et al.* reported errors close to 2 cm, while our algorithm presented errors of around 1.5 cm in atrial simulations. Additionally, the isochronal errors of the delay-based methodology presented by Duchateau *et al.* in ventricular simulations are comparable with the errors we obtained in the atria (10.4 ms vs 11.1 ms of RMSE). Our framework has an advantage with respect to the spatiotemporal model presented by Duchateau though. It includes the computation of the error variance in the LAT estimation workflow, ensuring that our variance estimation does not rely on assumptions inherent to simulations and providing a more robust and general representation of the LAT distributions in our model. Similar performances has been observed in all the spatiotemporal methodologies indicating that there is small room for improvement in the estimations of single-beat LAT maps just applying new post-processing strategies. Nonetheless, one of the strengths of ECGI is its capacity to process and analyze long-time signals with several beats. We think that there is still a great potential to identify recurrent blocks or slow conduction areas more robustly by combining the propagations of many beats.

The estimation of fast activation areas is an important parameter to identify AF-drivers. This is why several studies have evaluated the accuracy of ECGI to identify the HDF during AF. For example, in [Rodrigo *et al.* 2017b], an in-silico evaluation of the identification of the HDF was performed, with concordances of around an 80% between the simulated and estimated HDF areas. Pedrón-Torrecilla *et al.* also observed low errors in non-invasive DF maps when evaluated in mathematical models (around 5% of relative error) [PEDRÓN-TORRECILLA *et al.* 2016]. In chapter 4, the errors obtained in in-silico trials by these authors were corroborated where a similar performance of the standard DF and our proposed methodology were observed. However, our proposed DF estimation method outperformed the traditional one in more realistic setups such as animal models. Moreover, it provides additional information regarding the confidence of the DF estimate. We observed how the high-confidence areas contained more stable DF values in time and explored the idea of using these information to identify recurrent fast activation patterns. This idea though, is not new. Li *et al.* developed a clustering algorithm of HDF patterns in AF patients using intracavitary non-contact mapping [Li *et al.* 2021]. A significantly lower standard deviation in the DF obtained in recurrent patterns was

observed in comparison with other regions. Although the technology and methodological approach are different, our results align with the observed higher stability of DF in high probability areas. This underscores the potential clinical relevance of these locations, as they may serve as ablation triggers under the right conditions. However, further research is required to evaluate the temporal stability of high DF and high probability areas in a larger cohort of patients.

Another important perspective of this thesis is related to the detection of reentrant activity in AF. There are different approaches already published in the literature to detect reentrant activity. The most popular methods are based on the detection of singularities in the phase domain (PS). A great overview of this kind of methodologies is presented in [Li *et al.* 2020], where four different methods to identify PS in 2D images and 3D triangulations are compared. One of the main conclusions of the study was that the post processing strategy to identify reentries in phase maps has a huge impact. However, the methodologies that resulted in a higher accuracy were those based on topological charge computation. Rodrigo *et al.* also investigated the technical considerations to take into account when detecting reentries in non-invasive phase maps [Rodrigo *et al.* 2017c]. He reported that without the proper post-processing strategies, it is possible to detect even more PS in random EGM propagations than in AF episodes driven by rotors. Additionally, the presence of wave-breaks and conduction blocks can also lead to false positive detections of PS [Podziemski *et al.* 2018]. These findings evidenced the need of additional filtering strategies to avoid false positive detections. Fortunately, checking that the progression of phases around a PS candidate is linear and gradual demonstrated to be an effective filtering strategy to discard artificial PS [Rodrigo *et al.* 2017c]. Other important filtering strategy proposed by Rodrigo *et al.* to remove spurious PS detections consisted in tracking PS, combining them into rotors and measuring the rotational activity through time. In this way, reentries lasting for less than 0.5 turns were not considered as rotors. In chapter 5, we included the knowledge accumulated in the field to develop a rotor detection algorithm incorporating a careful definition of a rotor (taking into account all the technical considerations proposed by Rodrigo), an efficient rotor tracking method, and an homogeneous 2D domain that minimizes computational errors.

The technical considerations mentioned for PS filtering and rotor tracking have been validated in the past. The location of reentries detected non-invasively was correlated with areas of disorganized activity measured in invasive panoramic contact mapping, finding a nice correspondence between both technologies [Rodrigo *et al.* 2020]. In this thesis, we further validated this methodology using manual annotations in non-invasive phase maps. Using this approach, we observed that our implementation fulfilled all the technical considerations necessary to detect PS. Additionally, we also obtain similar clinical results to those reported in [Rodrigo *et al.* 2020]. In this study, Rodrigo observed a higher concentration of reentries in the whole atria in those patients that did not respond well to the ablation. In chapter 6, a significantly higher number of rotors per second were present in patients who returned to AF during our blanking period. Another study presenting results in the same line

is [Molero *et al.* 2021b], where the reentrant activity measured with ECGI resulted significantly more reproducible in patients that responded to PVI. In this way, the compilations of these results suggest that ECGI is able to provide a clinically relevant measure of the complexity of AF.

Finally, we provided a regional parametrization of the reentrant activity distribution on top of the measures evaluated in previous studies. We quantified the prevalence and distribution of the reentrant activity prior the ablation and studied the relationship of these with the clinical outcome of AF patients undergoing PVI. In this regard, we observed a larger concentration of reentries in the PPVV area in patients that remained in sinus rhythm 6 months after the ablation. The idea that ECGI can determine the location of recurrent reentrant activity during AF has been supported by other interventional studies focused on evaluating the use ECGI as an ablation guidance [Haissaguerre *et al.* 2014, Gao *et al.* 2019, Honarbakhsh *et al.* 2022, Dhillon *et al.* 2023]. Although in this thesis the estimation of the reentrant distribution was evaluated for stratification, not to guide ablations.

6.3 Limitations

In-silico models were used to validate most of the algorithms proposed in this thesis. These mathematical models were automata rule-based, meaning they do not include detailed electrophysiological descriptions at cellular level. However, all the parameters validated in this dataset were present at a tissue level. Additionally, the forward propagation model employed in these simulations did not include inhomogeneities or anisotropy due to inner organs in the torso. Although this simplification may have an impact in the calculations of surface signals, previous studies sustain that its effect is relatively low [Ferrer *et al.* 2015]. Finally, our models counted with static geometries. As is usual in the field, no relative movement between the atrium and the torso due to respiration, or heart beat was included throughout AF simulations. The use of static geometries may condition better the inverse problem than it should be in the clinical practice, where some level of geometrical uncertainty is unavoidable. These mathematical models were used in all cases to compare methodologies, and despite all the mentioned simplifications, the analysis performed in real AF patients showed coherent results with those obtained in simulations.

Another limitation to highlight concerning the propagation model of the Bayesian methodology is its exclusive applicability to non-reentrant rhythms. The propagation model built is based on a probabilistic interpolator that assumes the interpolation variable (in our case time) is not wrapped in the domain. This leads to local inaccuracies in reentrant rhythms where the initiation and the end of the activation cycle co-localize. However, this is a common limitation present in all the spatio-temporal LAT methods developed up to date. Additionally, this study was quantitatively validated exclusively in in-silicon models. Although, two application examples are provided in real patients, more validation in real P-waves is needed.

In chapter 4, we provided validation on simulated data. However, the number of simulations must still be increased to extract robust conclusions about the differences in the performance of both DF methods compared. We also evaluate our new DF methodology in experimental and clinical data. The animal model used consisted of ventricular fibrillation, which does not include some technical challenges typically present in AF such as the need for a QRST cancellation and having a low signal to noise ratio in the body signals. However, we did not use this dataset to compare our results with DF computed in AF, only as a benchmark to compare the performance of two algorithms applied under the same conditions. Regarding the clinical data, a direct comparison between the ECGI DF methods evaluated in this study and intracavitary DFs is missing. We plan to perform this evaluation in the future, ensuring that the electroanatomical mapping protocol allows for enough frequency resolution.

In chapter 5, it should be mentioned that some of the characteristics of the dataset of AF patients, such as the large prevalence of previous ablations or valvuloplasty are particular of our population. To ensure that these conclusions are more generalizable to all AF patients, a larger population is needed with differentiated groups of patients such as persistent and paroxysmal AF, or first-procedure and redo ablations. Finally, we would have liked to combine the DF estimation presented in chapter 4 with the reentrant activity estimations from chapter 5 to provide a more complete characterization of AF in these court of patients. However, the ECGI signals employed in chapter 5 were recorded using an old version of ECGI which only included 57 surface electrodes while the ECGI system from chapter 4 had 256. We cannot be certain that this drop in spatial resolution will allow to capture well the distribution of DFs. Additionally, we mentioned how in chapter 4 we only included animal models of ventricular fibrillation and AF simulations with no ventricular contributions. These scenarios do not contemplate QRST cancellation, which is a typical technical challenge in real AF episodes. Adenosine signals recorded in chapter 5, would have provided a nice control scenario to validate DFs with no QRST cancellation. However, due to technical limitations, the length of ECGI signals recorded during adenosine injection is too short to perform any spectral analysis. Therefore, given the use of different ECGI technologies and the limitations to estimate DFs with adenosine, we have decided to record a new dataset of AF episodes employing an acquisition protocol that allows to perform a combined DF-Reentry analysis. Unfortunately, the collection of these data lies outside the scope of this thesis and was included as future work.

6.4 Conclusions

The main objective of this thesis was to contribute to the evaluation, analysis, and understanding of atrial fibrillation (AF) through the development and validation of novel diagnostic algorithms in ECGI. This general objective has been faced in the different chapters by the proposal and assessment of different approaches to

characterize AF non-invasively. The following list summarizes the main objectives of each chapters:

- **Objective:** Develop a methodology for the estimation of local activation times (LAT) in ECGI to robustly characterize the propagation during sinus rhythm.

Response: We proposed a novel spatiotemporal LAT estimator and demonstrated that our methodology provides more accurate and smoother LAT maps than the standard criterion of the largest negative deflection, leading to better location of the earliest and latest activation sites and less artificial lines of block.

- **Objective:** Evaluate the identification of AF-driving mechanisms in the form of fast activation sites using ECGI.

Response: Other methods based on spectral parameters can be used to obtain an accurate solution of the inverse problem for DF estimation. Furthermore, the optimal solution found with the L-curve is improved when making use of a set of solutions with different λ values, providing accurate results and additional information on the estimation uncertainty.

- **Objective:** Characterize non-invasively the prevalence of reentrant activity, globally and regionally in AF patients, and evaluate the relationship between the distribution of these high prevalent reentry areas and the clinical outcome of AF patients undergoing pulmonary vein isolation (PVI).

Response: We demonstrated that significant differences in the number of rotors can be distinguished between responders and non-responders to PVI. Additionally, ECGI allowed measuring the spatial distribution of the reentrant activity at different atrial regions during AF episodes. With this measure, we observed a positive relationship between the concentration of reentries in the pulmonary veins and the clinical outcome of patients undergoing PVI. That is, patients with a higher prevalence of reentrant activity in the pulmonary veins before the ablation responded better to PVI than those with a high concentration outside the veins.

6.5 Guides for future work

Several new ideas should be explored based on the results obtained in this thesis. Regarding the probabilistic framework to estimate LAT maps presented in chapter 3, a natural next step is to make use of the probability density functions (pdf) obtained with our method to compute CV maps as proposed by Convey et. al. for intracavitary signals. This approach would provide not only a CV map but also their correspondent pdf, and therefore a quantitative level of the uncertainty associated to different atrial regions. Furthermore, applying these methodology in ECGI by means of our Bayesian framework opens the possibility of combining the

pdf of many CV maps to obtain a more robust estimate in a feasible clinical time. Specifically, the clinician could stimulate the atrium via pacing from different sites to compute a CV map from each location using our methodology and ECGI. These maps could then be combined in an optimal way using their resultant pdfs in order to obtain a more robust CV map. The rationale behind this approach is the following: large-uncertainty areas in the CVs resultant from a specific stimulation site may be reduced when the CV maps obtained from other activation sequences are incorporated, decreasing in this way the overall uncertainty. In the future, we plan to incorporate the computation of this probabilistic CV maps in our framework, as well as provide a stimulation protocol for an optimal estimation. Another methodological improvement is the adaptation of the LAT estimator to regular reentrant arrhythmias. This is a common limitation of all the spatiotemporal methodologies to estimate LATs. In the future, we plan to develop a new probabilistic interpolator in the phase domain, generalizable to reentrant propagations and based on Gaussian Process and Markov Chain Monte Carlo sampling.

Apart from the methodological extensions, additional preprocessing strategies may be included and tested in the future to estimate LAT maps. For example, LAT maps could be computed on an average beat instead of using a single-beat strategy. This would feed our algorithm with less noisy signals and may increase the accuracy of the resultant LAT maps. Additionally, working on average beats could help in the development of a robust delineator for P-waves in body surface signals, avoiding in this way the need of manually segmenting the P-wave from real ECG signals. In the future, a study evaluating the advantages of applying our LAT estimator over an averaged beat should be performed.

Regarding the identification of DFs, additional validation in real patients must be provided. We would like to study the reproducibility of these maps in a large time-scale (several minutes) using ECGI signals from AF patients and compare this reproducibility with the standard DF estimation. We also want to include intracavitary validation. In this sense, basket catheters that record globally the atrial activation are an option. However, we know from past experiences in our laboratory it is a challenge to determine what electrodes are properly in contact with the atrial tissue, making sometimes the electrode selection impossible for a proper analysis. Because of this, an initial validation using conventional EAM will be performed with the objective of checking that the recurrent areas of fast activation in ECGI are indeed faster than other regions when measured endocardial.

Several efforts to guide ablations using ECGI have been done in the past with focus on reentrant activity [Haïssaguerre *et al.* 2006] and DFs [Atienza *et al.* 2009]. In this thesis, we have developed methodologies to identify AF-drivers based on the detection of reentrant activity and high activation frequencies independently. In the future we plan to propose a unique parameter that combines these two perspectives to provide the probability of a region to contain a driver. Rodrigo proposed a strategy in this line consisting on filtering the ECGI solution around the HDF to identify the dominant reentries [Rodrigo *et al.* 2017b]. However, we know that temporal variation of the activation frequency may have a great impact

on the determination of the HDF, and if we want to identify recurrent mechanisms in long periods we have to think in new strategies that can adapt to the variability in the activation frequency. In this way, we plan to test the use of high-confidence DF sites to identify recurrent fast activations areas and combine this information with reentrant activity in a prospective ablation study. This strategy could be used to guide the interventions based on driver detections outside the PPVV in persistent AF patients or even redo ablation procedures.

Finally, this thesis provides additional evidence on the possibility of stratifying AF patients based on personalized electrophysiological parameters. The next step to take in this direction is to a refined prediction model for PVI outcome using additional ECGI parameters and clinical information. This model, if useful, could have a great impact in the clinical practice, saving costs, risks and improving the efficacy of PVI due to a better patient selection.

Chapter 7: Contributions

Contents

7.1 Main Contributions of this thesis	103
7.1.1 Journal Papers	103
7.1.2 International Conferences	104
7.1.3 National Conferences	104
7.2 Contributions related to this thesis	104
7.2.1 Journal Papers	104
7.2.2 International Conferences	104
7.2.3 Supervision of Master thesis	105
7.3 Patents	105
7.4 Awards	105
7.5 Research Stays	105
7.6 Research Projects and Funding	105

This chapter describes the main contributions provided in the frame of this thesis and other contributions related to complementary projects. Additionally, the scientific stays done during this thesis are enumerated as well as the scientific projects that made possible this work.

7.1 Main Contributions of this thesis

7.1.1 Journal Papers

- **C. Fambuena-Santos**, I. Hernández-Romero, R. Molero, A. M. Climent, and M. S. Guillem, “AF driver detection in pulmonary vein area by electrocardiographic imaging: Relation with a favorable outcome of pulmonary vein isolation,” *Front. Physiol.* 14, 1– 11. <http://dx.doi.org/10.3389/fphys.2023.1057700>.
- **C. Fambuena-Santos**, C, Herrero, S. Ros, E. Invers, L. Mont, I. Hernández-Romero, F. Atienza, A. M. Climent, M.S. Guillem, “Bayesian framework for atrial LAT estimation using ECGI”. Submitted.
- I. Hernández-Romero, R. Molero, **C. Fambuena-Santos**, C. Herrero-Martín, A. M. Climent, and M. S. Guillem, “Electrocardiographic imaging in the atria,” *Med. Biol. Eng. Comput.*, vol. 61, no. 4, pp. 879–896, Apr. 2023 <http://dx.doi.org/10.1007/s11517-022-02709-7>.

7.1.2 International Conferences

- **C. Fambuena-Santos**, I. Hernández-Romero, R. Molero-Alabau, A.M. Climent, M.S. Guillem Sánchez. An evaluation on the clinical outcome prediction of rotor detection in non-invasive phase maps. Computing in Cardiology, 2021. <https://doi.org/10.22489/CinC.2021.251>.
- **C. Fambuena-Santos**, I. Hernández-Romero, C Herrero-Martín, J. Reventós-Presmanes, E Invers-Rubio, L. Mont, A.M. Climent, M.S. Guillem, "Probabilistic Dominant Frequency Estimation in AF From ECGI," 2022 Computing in Cardiology (CinC), 2022, doi: 10.22489/CinC.2022.362.

7.1.3 National Conferences

- **C. Fambuena-Santos**, I. Hernández-Romero, R. Molero, F. Atienza, A. M. Climent, and M. S. Guillem, Detección de Actividad Reentrante en Fibrilación Auricular mediante Imagen Electrocardiográfica: Relación con el Resultado Favorable tras Aislamiento de Vena Pulmonares. Congreso Nacional de la Sociedad Española de Cardiología, Mallorca, Spain, 2022.

7.2 Contributions related to this thesis

7.2.1 Journal Papers

- I. Reinal, I. Ontoria-Oviedo, M. Selva, M. Casini, E. Peiró-Molina, **C. Fambuena-Santos**, Andreu M. Climent, Julia Balaguer, Adela Cañete, Jaume Mora, and et al. 2023. "Modeling Cardiotoxicity in Pediatric Oncology Patients Using Patient-Specific iPSC-Derived Cardiomyocytes Reveals Downregulation of Cardioprotective microRNAs" Antioxidants 12, no. 7: 1378. <https://doi.org/10.3390/antiox12071378>.
- Gutiérrez-Fernández-Calvillo, M. A. Cámara-Vázquez, I. Hernández-Romero, M. S. Guillem, A. M. Climent, **C. Fambuena-Santos**, O. Baequero-Pérez 'Non-invasive estimation of atrial fibrillation driver position using long-short term memory neural networks and body surface potentials', Computer Methods and Programs in Biomedicine, 246, p. 108052. doi: <https://doi.org/10.1016/j.cmpb.2024.108052>

7.2.2 International Conferences

- **C. Fambuena-Santos**, I. Llorente-Lipe, S. Ros2, J. Sánchez, F. Atienza, A.M. Climent, M.S. Guillem, 'Estimation of Ventricular Ectopic Beat Origin with ECGI'. EHRA Congress, Germany, 2024.

7.2.3 Supervision of Master thesis

- Personalización de modelos computacionales eléctricos auriculares mediante el problema inverso de la electrocardiografía. Iván Suárez Vera. Mark: 9.

7.3 Patents

- R. Molero, **C. Fambuena-Santos**, J. Milagro, A.M. Climent, M. S. Guillem, ‘Method for analyzing arrhythmia’. The patent is currently in the PCT (Patent Cooperation Treaty) phase of international application. PCT/EP2022/074485.

7.4 Awards

- 2021 – Rosanna Degani Young Investigator Award Finalist – Computing in Cardiology Conference, Brno, Czech Republic. “An evaluation on the clinical outcome prediction of rotor detection in non-invasive phase maps”.
- 2022 – Best poster award - Computing in Cardiology Conference, Tampere, Finland. “Probabilistic Dominant Frequency Estimation in AF From ECGI”.

7.5 Research Stays

During the development of this thesis a research stay has been conducted on Inria Institute (Bordeaux, France) and EP Solutions (Yverdon-les Bains, Switzerland) with dates May 2021 – July 2021 and January 2023 – April 2023. The research project corresponding to chapter 4 of these thesis was developed during these secondments.

7.6 Research Projects and Funding

This thesis has been funded by the European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 860974, PersonalizeAF. Additionally, this work has been developed as part of a national project funded by the Spanish Agencia Estatal de Investigación with title: Desarrollo de una herramienta de mapeo panorámico para la evaluación de sustratos electro-estructurales para guiar la ablación de la fibrilación auricular utilizando AI (PID2020-119364RB-I00).

Appendices

Appendix Chapter 3

A.1 Gaussian Process Input parameters

As explained in the methodology, the Gaussian Process interpolator requires a set of LAT estimates obtained using the $-dV/dt$ method, and the standard deviation error associated to these estimates. Then, based on the OI of the signals, a set of high-confidence LATs are used to interpolate the activation times in the whole atrial geometry. This appendix provides an overview of the accuracy of the $-dV/dt$ method in general and the relationship between the OI and the standard deviation of the LAT errors.

In figure A.1 an evaluation of these parameters is presented. The LATs derived from the $-dV/dt$ method are plotted against the gold-standard LATs directly obtained from the simulations. A positive correlation of $C=0.84$ was obtained and the linear regression model fitted to the data presented a slope of 0.87 showing a good correspondence between the estimated and the real LATs. In figure A.1.B it can be observed that the LAT error in ECGI signals with low OI present higher standard deviation, which proved the heteroscedasticity of the data. This outcome is expected, as signals with low OI typically exhibit more deflections compared to signals with a high OI and, therefore, are more prone to LAT estimation errors.

In order to determine the OI threshold T used to identify high-confidence LATs, we studied how well our framework was able to estimate the standard deviation error using different thresholds. In figure A.1.C. the evolution of the estimated and the real standard deviation errors is presented for signals with different OI indexes. That is, the standard deviation error estimate in our framework by means of the gaussian mixture model fitting, and the real standard deviation error of the $-dV/dt$ method measured with respect to the gold standard LATs. It can be observed how our methodology underestimates the standard deviation of LAT error in signals with low OI (57.9 vs 3.8 in the 0-0.1 interval) but converges to the real standard deviation in high-OI signals (10.3 vs 9.6 ms in the 0.8-0.9 interval). For that reason we selected a threshold of 0.8, above which we find an error between the estimated and the real standard deviation of 0.7 ms.

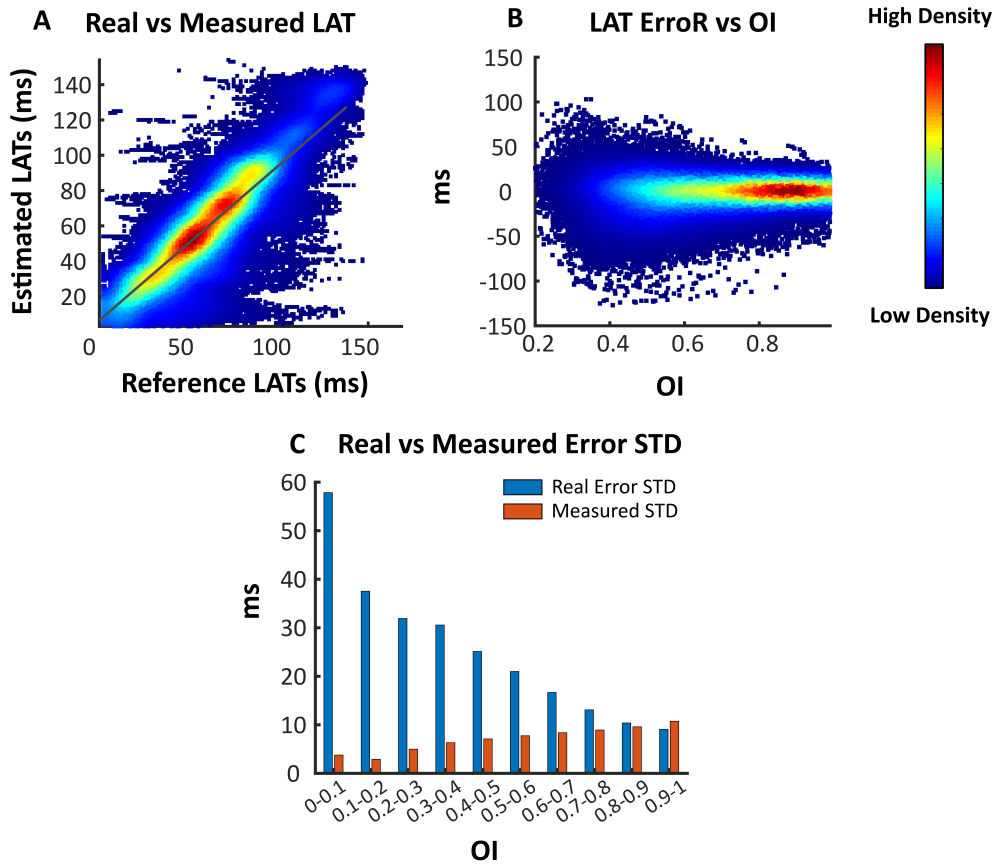


Figure A.1: Validation of $-dV/dt$ LAT measures and standard deviation errors. The colors indicate point density. A) Comparison of $-dV/dt$ LATs to the reference LATs obtained from simulations. B) LAT error obtained from $-dV/dt$ against the OI value of ECGI. C) Evolution of the real and estimated standard deviation error for different OI intervals.

Appendix Chapter 5

B.1 Rotor Detection Algorithm

The workflow of the proposed rotor detection algorithm is depicted in Figure B.1. The input data for this algorithm is a set of instantaneous 2D phase maps stacked in a volume. In this structure, the first 2 dimensions contain the spatial distribution of phases and the third dimension corresponds to time. PSs are initially detected by calculating the topological charge C at every pixel of the volume (see equation B.1) [Guillem *et al.* 2016][Cluitmans *et al.* 2018][Podziemski *et al.* 2018].

$$C = \oint \nabla \Theta \cdot d\mathbf{r} \quad (\text{B.1})$$

Where θ are the phase values in a closed curve $\mathbf{r}$ around each PS. If the absolute value of the topological charge C obtained was larger than a certain threshold, the pixel was considered as a possible phase singularity. Only the PSs presenting a gradual spatial progression between 0 and 2π in their surroundings were considered as real rotations, the rest were filtered [Rodrigo *et al.* 2017c]. The remaining PS were then stored as a volume of binary images encoding their spatiotemporal locations, where 1 indicated the presence of a PS and 0 the absence. Then, 3D binary dilation was performed using equation B.2:

$$A \oplus B = \bigcup_{b \in B} A_b \quad (\text{B.2})$$

Where B is the 3D volume encoding the location of the PSs, A is a 3 by 3 structural element containing ones and A_b is a translated instance of A by b pixels. This operation allows connecting neighbouring PS and fill the gaps produced by misdetections. The dilation was always performed in the direction of the filament in order to reduce interferences with other trajectories. However, occasionally dilation may also connect non-related filaments. The locations in the volume where two or more different trajectories are connected are called crossing points. In order to identify these crossings, binary skeletonization was applied by using the built-in MATLAB function `bwmorph`. Converging trajectories were split by deleting the crossing points. Then, region growing algorithm was applied to classify the resulting trajectories into different rotors.

Finally, the number of turns of each rotor was estimated. For that, the phase evolution throughout the spatiotemporal trajectory of the rotor was unwrapped in 4 different positions around each phase singularity. A first order polynomial curve

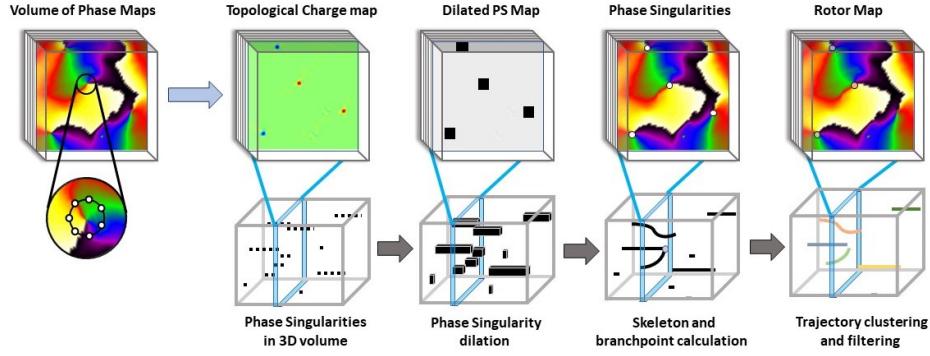


Figure B.1: 3D operations applied in the rotor detection algorithm and correspondent cross-sectional views: 1) The topological charge is calculated out of the input phase maps using 3D convolution operations. 2) A threshold is applied to obtain a binary 3D volume containing the space-temporal locations of phase singularities. 3) 3D dilation is applied on this volume in order connect close phase singularities and conform the space-temporal trajectories of rotors. 4) Skeleton of dilated volume is calculated and branch points are detected in order to remove crossing points in the trajectories. 5) Region growing is applied to the skeletonized volume in order to cluster the trajectories.

was fitted to these phase evolution and the mean squared error between the phase progression and the fitted model was computed in the four locations. The number of turns of the rotor was calculated as the range of phase covered in the position with the lowest mean squared error divided by 2π .

B.2 Processing of geometrical models

Atrial geometries present complex anatomical structures. In order to avoid inhomogeneities in the distribution of nodes that may affect the accuracy of the inverse problem solution and posterior PS detection, we applied the framework presented in [?]. Additionally, this framework provides a way to reliably transform the electrophysiological data from 3D to 2D, allowing us to efficiently process the data with our rotor detection algorithm. The first step consists in applying to the atrial geometry a remeshing algorithm presented in [Choi *et al.* 2015]. This method parameterize the geometrical model in a spherical domain (Praun and Hoppe, 2003). The data is then resampled in this domain in such a way that can be easily reorganized and uniformly distributed in a 2D grid. Specifically, the new set of nodes is obtained from a uniform triangulation of spherical mesh using an octahedron-based subdivision [Gu *et al.* 2002]. Then, the nodes obtained from the spherical parametrization of the atria, and the nodes obtained from the spherical parametrization of a 2D uniform grid are connected. The connectivity between the nodes is optimized using

the convex hull algorithm in the spherical domain [Barber *et al.* 1996]. Finally, in order to obtain the electrophysiological data in the 2D grid domain, the data is interpolated in the uniform sampling domain [Amidror 2002]. This methodology is generally presented in figure B.2, where the data can be directly open into a 2D grid.

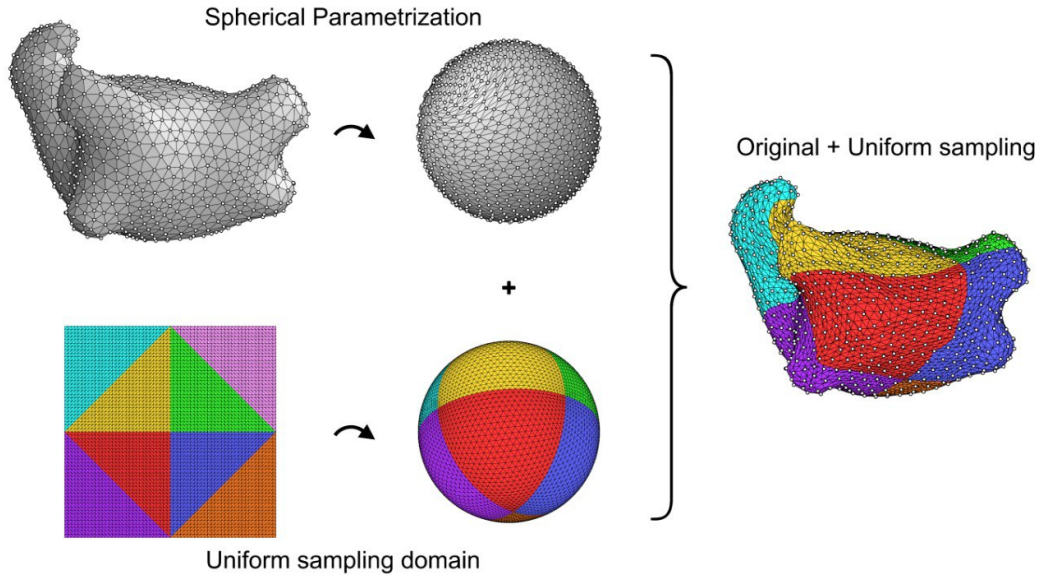


Figure B.2: Geometrical conformalization process [?].

B.3 Extended Results with Adenosine

In this section the results obtained in segments recorded during adenosine injection are presented and compared to the results obtained without adenosine. Specifically, the proportion of PS in the same 9 atrial regions were calculated. In figure B.3 below, this proportions are presented using adenosine (first row of panels, B.3.A and B.3.B) and without adenosine (second row of panels, B.3.C and B.3.D). Additionally, the same analysis was performed considering all the PS (panels B.3.A and B.3.C) and removing all the PS belonging to rotors that spin for less than 1 turn (panels B.3.B and B.3.D). Similar regions with statistically significant differences in the proportion of PS and tendencies are observed with and without adenosine. In total, only 3 different regions present statistically significant differences considering all the studied scenarios: PPVV, LAAP and SEPTUM. More importantly, the PPVV is the only region in which a significantly higher prevalence of reentries was observed in all the studied condition including adenosine injection. In fact, the difference between the studied groups is highlighted by its adenosine (12.09% vs 6.49%, $p < 0.01$). Something noticeable when analyzing adenosine recordings, is that the application of a 1-turn filtering on the PSs seems to have a larger effect than in

non adenosine recordings. For example, it can be observed how the differences in the proportion of PS in the PPVV increase more when applying the turn filtering. Additionally, the number of regions with significant differences is reduced from 3 to 1 in adenosine recordings. With the data collected it is very difficult to distinguish whether the mentioned differences observed when including adenosine are due the effect of adenosine accentuating the activity in the pro-arrhythmic areas, or it is simply because the absence of QRS complexes provide more reliable information of the atrial activity. However, the results obtained show that is still possible to see similar distribution of phase singularities along the atria and a constant higher prevalence of reentries in the PPVV in non recurrence patients without the use of any drug.

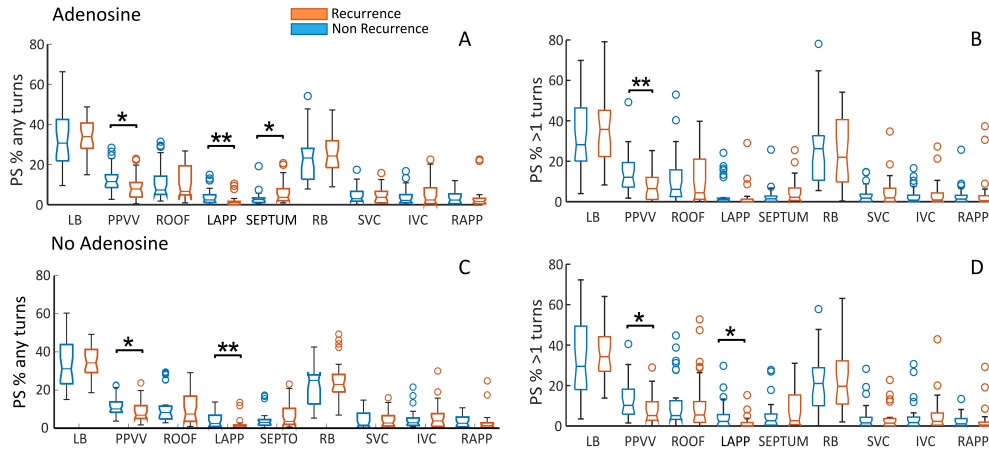


Figure B.3: Proportion of PSs per second detected in different regions in each studied group: in blue is presented the data from patients that remained in sinus rhythm 6 months after ablation (Non recurrence), and in orange patients that returned to any sort of arrhythmia (Recurrence). Panels A and B present PS distributions in recordings obtained with adenosine injection and panels C and D without adenosine. On the other hand, A and C (left column) present the data when all the rotors, independently from their number of turns, were considered in the analysis. Finally, panels B and D (right column) present the PS obtained when applying a threshold of 1 turn.

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