PROCESSING THE INTRACARDIAC ELECTROGRAM FOR ATRIAL FIBRILLATION ABLATION

by

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Abstract

Atrial fibrillation (AF) is a major global health issue as it is the most prevalent sustained supraventricular arrhythmia. Catheter-based ablation of some parts of the atria is considered an effective treatment of AF. The main objective of this research is to analyze atrial intracardiac electrograms (IEGMs) and extract insightful information for the ablation therapy. Throughout this thesis we propose several computationally efficient algorithms that take streams of IEGMs from different atrial sites as the input signals, sequentially analyze them in various domains (e.g., time and frequency), and create color-coded three-dimensional map of the atria to be used in the ablation therapy.
Acknowledgments

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Mohammad Hassan Shariat
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Part I

Introduction
Notations and Table of Definitions

In this thesis, scalar values are shown with non-bold letters; whereas, vectors and matrices are shown with boldface small and capital letters, respectively. The real part, imaginary part, absolute value, and complex conjugate of a complex number $Z$ are denoted by $\text{Re}\{Z\}$, $\text{Im}\{Z\}$, $|Z|$ and $Z^*$, respectively; $j \triangleq \sqrt{-1}$, and the phase angle of a complex number $Z$ in radians is denoted by $\text{angle}(Z) \in [-\pi, \pi]$. The set of all the $M \times N$-dimensional real and complex matrices are shown with $\mathbb{R}^{M \times N}$ and $\mathbb{C}^{M \times N}$, respectively; the set of all the $K$-D real and complex vectors are denoted by $\mathbb{R}^K$ and $\mathbb{C}^K$, respectively.

The $N$-dimensional (N-D) identity matrix, the $M$-D zero vector, the $N$-D vector of one, the Frobenius norm of matrix $A$, the $i$, $j$th entry of the matrix $A$, and the union of two sets $A$ and $B$ are respectively denoted by $I_N$, $0_M$, $1_N$, $\|A\|$, $[A]_{i,j}$ and $A \cup B$. The Hermitian/Conjugate transpose and transpose of $A$ are respectively shown as $A^H$ and $A^T$. Furthermore, the trace of the matrix $A$, the $a$th to $b$th elements of the vector $x$, the Kronecker product, and the diagonal matrix with elements of $x$ on its diagonal are denoted by $\text{tr}(A)$, $[x]_{a:b}$, $\otimes$, and $\text{diag}(x)$, respectively. The Kronecker delta is denoted as $\delta_i$, where $\delta_0 = 1$ and $\delta_i = 0$, for $i \neq 0$. 
Notation \( \mathbf{x} \sim \mathcal{N}(\mathbf{m}, \Sigma) \) shows that the random vector \( \mathbf{x} \) has the Gaussian distribution with the mean vector \( \mathbf{m} \) and covariance matrix \( \Sigma \). Notation \( x \sim U[a, b] \) means that a random variable \( x \) is uniformly distributed between \( a \) and \( b \). Mean±STD is used to report the mean and standard deviation (STD) of the variables. The expected value of a random vector \( \mathbf{x} \) and its empirical/sample expected value are denoted by \( E\{\mathbf{x}\} \) and \( \hat{E}\{\mathbf{x}\} \), respectively. Notation \( y \overset{\mathcal{H}_0}{\gtrless} \eta \), means that the hypothesis \( \mathcal{H}_0 \) is rejected if \( y > \eta \) and the hypothesis \( \mathcal{H}_0 \) is failed to be rejected if \( y < \eta \).

The following table shows the abbreviations used in this manuscript. To improve the readability of the text, the definition and abbreviation of these words are expressed at the first appearance of them in each chapter (definition is followed by the abbreviation in parentheses).

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>AA</td>
<td>Accumulator Array</td>
</tr>
<tr>
<td>ABPR</td>
<td>Active Interval to the Baseline Power Ratio</td>
</tr>
<tr>
<td>AD</td>
<td>Activation Duration</td>
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<tr>
<td>AE</td>
<td>Absolute Error</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>AI</td>
<td>Active Interval</td>
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<td>AntW</td>
<td>Anterior Wall</td>
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<tr>
<td>AO</td>
<td>Activation Onset</td>
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<td>AT</td>
<td>Activation Time</td>
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<td>AV</td>
<td>Atrioventricular</td>
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<td>AZ</td>
<td>Active Zone</td>
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<td>Abbreviation</td>
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<tr>
<td>CC</td>
<td>Computational Complexity</td>
</tr>
<tr>
<td>CCW</td>
<td>counterclockwise</td>
</tr>
<tr>
<td>CCV</td>
<td>Cardiac Conduction Velocity</td>
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<tr>
<td>CCVV</td>
<td>Cardiac Conduction Velocity Vector</td>
</tr>
<tr>
<td>CFAE</td>
<td>Complex Fractionated Atrial Electrogram</td>
</tr>
<tr>
<td>CFE</td>
<td>Complex Fractionated Electrogram</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CL</td>
<td>Cycle Length</td>
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<tr>
<td>CLI</td>
<td>Cycle Length Iteration</td>
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<tr>
<td>CoM</td>
<td>Center of Mass</td>
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<td>CS</td>
<td>Cumulative Sum</td>
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<tr>
<td>CW</td>
<td>Clockwise</td>
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<td>Double-Electrode Pair</td>
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<td>DF</td>
<td>Dominant Frequency</td>
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<td>DI</td>
<td>Detected AI</td>
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<td>EDF</td>
<td>Electrode Dominant Frequency</td>
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<td>FAI</td>
<td>False Alarm AI</td>
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<tr>
<td>FIR</td>
<td>Finite Impulse Response</td>
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<td>FFT</td>
<td>Fast Fourier Transform</td>
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<td>FNI</td>
<td>False Negative Interval</td>
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<td>FNR</td>
<td>False Negative Rate</td>
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<td>False Positive Interval</td>
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<td>FPR</td>
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<tr>
<td>GD</td>
<td>Gradient Descent</td>
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<tr>
<td>GLRT</td>
<td>General Likelihood Ratio Test</td>
</tr>
<tr>
<td>HT</td>
<td>Hough Transform</td>
</tr>
<tr>
<td>IEGM</td>
<td>Intracardiac Electrogram</td>
</tr>
<tr>
<td>i.i.d.</td>
<td>independent identically distributed</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
</tr>
<tr>
<td>LAA</td>
<td>Left Atrial Appendage</td>
</tr>
<tr>
<td>LAnt</td>
<td>Left Antrum</td>
</tr>
<tr>
<td>LIPV</td>
<td>Left Inferior Pulmonary Vein</td>
</tr>
<tr>
<td>LSPV</td>
<td>Left Superior Pulmonary Vein</td>
</tr>
<tr>
<td>LTI</td>
<td>Linear Time Invariant</td>
</tr>
<tr>
<td>LLR</td>
<td>Log-Likelihood Ratio</td>
</tr>
<tr>
<td>LS</td>
<td>Least Square</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>MA</td>
<td>Manual Annotation</td>
</tr>
<tr>
<td>MCL</td>
<td>Mean Cycle Length</td>
</tr>
<tr>
<td>MGLRT</td>
<td>Modified General Likelihood Ratio Test</td>
</tr>
<tr>
<td>MitIs</td>
<td>Mitral Isthmus</td>
</tr>
<tr>
<td>ME</td>
<td>Mean Error</td>
</tr>
<tr>
<td>MinV</td>
<td>Minimum Velocity</td>
</tr>
<tr>
<td>ML</td>
<td>Maximum Likelihood</td>
</tr>
<tr>
<td>MrgI</td>
<td>Merged AI</td>
</tr>
<tr>
<td>mS or msec</td>
<td>millisecond</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>MMTD</td>
<td>Modified Maximum Time Difference</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum Time Difference</td>
</tr>
<tr>
<td>mv</td>
<td>Millivolt</td>
</tr>
<tr>
<td>MVUE</td>
<td>Minimum Variance Unbiased Estimator</td>
</tr>
<tr>
<td>NAE</td>
<td>Normalized Absolute Error</td>
</tr>
<tr>
<td>N-D</td>
<td>N-Dimensional, e.g., 2-dimensional (2-D)</td>
</tr>
<tr>
<td>NLEO</td>
<td>Non-Linear Energy Operator</td>
</tr>
<tr>
<td>NMSE</td>
<td>Normalized Mean Square Error</td>
</tr>
<tr>
<td>pdf</td>
<td>Probability Density Function</td>
</tr>
<tr>
<td>PDE</td>
<td>Partial Differential Equation</td>
</tr>
<tr>
<td>PostW</td>
<td>Posterior Wall</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>RA</td>
<td>Right Atrium</td>
</tr>
<tr>
<td>RAnt</td>
<td>right antrum</td>
</tr>
<tr>
<td>RDF</td>
<td>Regional Dominant Frequency</td>
</tr>
<tr>
<td>RIPV</td>
<td>Right Inferior Pulmonary Vein</td>
</tr>
<tr>
<td>RSPV</td>
<td>Right Superior Pulmonary Vein</td>
</tr>
<tr>
<td>RV</td>
<td>Right Ventricle</td>
</tr>
<tr>
<td>S or s or sec</td>
<td>Second</td>
</tr>
<tr>
<td>SA</td>
<td>Sinoatrial</td>
</tr>
<tr>
<td>Sept</td>
<td>Septum</td>
</tr>
<tr>
<td>SF</td>
<td>Separating Functions</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>SFET</td>
<td>Separating Function Estimation Tests</td>
</tr>
<tr>
<td>SI</td>
<td>Similarity Index</td>
</tr>
<tr>
<td>SpI</td>
<td>Split AI</td>
</tr>
<tr>
<td>SS</td>
<td>Sweep Speed</td>
</tr>
<tr>
<td>STD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>STFT</td>
<td>Short Time Fourier Transform</td>
</tr>
<tr>
<td>TPI</td>
<td>True Positive Interval</td>
</tr>
<tr>
<td>TPR</td>
<td>True Positive Rate</td>
</tr>
<tr>
<td>TS</td>
<td>Test Statistic</td>
</tr>
<tr>
<td>UQRDF</td>
<td>Upper Quartile Regional Dominant Frequency</td>
</tr>
<tr>
<td>VD</td>
<td>Variance Difference</td>
</tr>
<tr>
<td>VR</td>
<td>Variance Ratio</td>
</tr>
<tr>
<td>VV</td>
<td>Velocity Vector</td>
</tr>
<tr>
<td>WB</td>
<td>Wave Break</td>
</tr>
<tr>
<td>WBR</td>
<td>Wave Break Rate</td>
</tr>
<tr>
<td>XNOR</td>
<td>Logical complement of the exclusive OR</td>
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</table>
Chapter 1

Background and Outline of the Thesis

1.1 Cardiac Conduction System

The heart is a muscle which is responsible for circulation and pumping blood throughout the body. It has four chambers; including two atria at the top and two ventricles at the bottom. The deoxygenated blood from the body enters the right atrium (RA), is sent to the right ventricle (RV) by the RA, and then the RV pumps the blood to the lungs. The oxygenated blood returns from the lungs to the left atrium (LA), is forced into the left ventricle (LV), and is pumped from there to all the body tissues except the lungs [6].

A properly scheduled sequence of the contractions of the chambers, regulated/controlled by electrical impulses, is a critical factor in blood circulation. In a healthy heart, the sinoatrial (SA) node, located on the RA, generates/fires an electrical impulse (also known as the electrical wavefront) that propagates throughout the atria
and contracts these chambers, and then reaches the atrioven-
tricular (AV) node. After a small delay caused by the AV node, the impulse enters the wall between the
two ventricles at the His bundle. The wavefront then divides into rapidly conducting
bundles with branches to the LV and RV and contacts the ventricles [6,7].

Study of the electrical activities of the heart provides critical information about
its functioning. These activities can either be recorded using the noninvasive/invasive
recording [6–8], or can be simulated using available mathematical models for heart
electrical wavefront propagation [9–12]. Intracardiac electrograms (IEGMs) can be
collected using a minimally invasive procedure, and they can efficiently be processed
and used to treat various cardiac diseases, such as atrial fibrillation (AF) [13].

1.2 Atrial Fibrillation (Prevalence; Cost; Morbidity and Mortality)

The most common sustained supraventricular arrhythmia is AF [14,15]. This
arrhythmia, for which the regular electrical wave propagation does not exist, is a
major global health issue and is the focus of this research.

Atrial fibrillation occurs in approximately 1–2% of the general population, and its
prevalence highly depends on age, race, and gender (males are more often affected by
AF than females) [14–16]. Around 300000 Canadians and over six million Europeans
suffer from AF, and as the population ages, AF prevalence is predicted to at least
double in the next 50 years [16]; the median age of AF patients is about 75 years
old and approximately 70% are 65-85 years old [17]. This disease affects around 8
percent of individuals older than 80 years [18]. AF is an extremely costly public

health problem with the annual cost per patient close to $3600 U.S. [17,19–21]. Hospitalization due to AF accounts for 33% of all admissions for cardiac arrhythmias [16] and is the primary cost driver (52%) [17]. Morbidity and mortality associated with AF is very high as it is a major risk factor for strokes [16,17,22,23]. Indeed, one in five of all strokes is attributed to AF; these are more severe than strokes of other origins and often result in long-term disability or death [15,16]. Patients with AF have significantly higher mortality than non-AF subjects; i.e., death rates are almost doubled by AF [16,23].

1.3 Surface Electrocardiogram During AF and Different Types of AF

AF can be identified using the noninvasive surface electrocardiogram (ECG), i.e., the surface ECG shows irregular R-R intervals that do not follow a repetitive pattern and also there are no distinct P waves on the surface ECG during AF [16,17]. The P waves of an ECG of a patient with AF are replaced with oscillatory or fibrillatory waves of different duration and amplitude. The ventricular response (QRS) is usually rapid (between 90 and 170 beats per minute) [18]. Figure 1.1 shows a sample 12-lead ECG of a patient with AF and the transition to sinus rhythm. For this patient, AF terminated as a result of the catheter ablation therapy (see Section 1.5). This figure indicates that before time=6s, the surface ECG shows the characteristics of an ECG during AF; however, after that, the ECG becomes regular, corresponding to the sinus rhythm.

AF can be categorized into several types: paroxysmal, persistent and permanent [16,17]. Paroxysmal AF is a self-terminating arrhythmia usually within 48 hours.
Persistent AF, on the other hand, lasts longer than 7 days and terminates after intervention (drugs or direct current cardioversion) [16, 17]. Permanent AF is long-lasting arrhythmia where cardioversion has failed or has not been attempted [17, 18].

1.4 Mechanisms Underlying AF

Despite the significant prevalence of AF, the perpetuating sources are not clearly known [15, 17, 24, 25]. Theories of the mechanism of AF includes two main processes which are described in the automatic focus theory and multiple-wavelet hypothesis [16, 17, 24]. Based on the automatic focus theory, one or multiple ectopic foci in both atria disturb the regular wavefront propagation. The automatic focus theory gained a lot of attention after observation that several focal sources for AF could be identified in humans and ablation of these sources could extinguish AF [17, 26, 27]. While most of the focal sources are identified around pulmonary veins (PVs), up to 20% may be non-PV in origin, i.e., foci are observed in the superior vena cava, crista terminalis, left posterior free wall, and coronary sinus [17, 25, 27, 28].

Based on the multiple-wavelet hypothesis, conduction of several wavelets propagating through the atria perpetuate AF [16, 24, 29]. According to this hypothesis, fractionation of wavefronts propagating through the cardiac tissue results in self-perpetuating daughter wavelets [17]; where the number of wavelets at any time depends on many parameters including the refractory period and cardiac conduction velocity in various atrial sites [17].
Figure 1.1: Top: a sample 12-lead ECG during AF and the transition to sinus rhythm. For this patient, AF terminated as a result of the catheter ablation therapy. The surface ECG shows irregular R-R intervals during AF (Time < 6s) and there are no distinct P waves on the surface ECG (see lead II). For the ECG signals on the right hand side of the figure (Time > 6s), regular R-R intervals and distinct P waves are present. Bottom: lead II is enlarged for better demonstration of the ECG during AF and sinus rhythm.
The previously described mechanisms for AF perpetuation are not mutually exclusive and might co-exist at various times [16,17]. Patients with paroxysmal AF are more likely to have a focal mechanism [25].

1.5 AF Treatments and Catheter Ablation Therapy

There are several major approaches to treat AF, and the treatment that each patient receives depends on many factors including type, duration and severity of symptoms of AF, patient age and associated medical conditions [17]. Drug therapy is the first form of treatment for most patients. There are two general approaches for medical management of patients with AF: rate-control and rhythm-control strategies. In the rate-control strategy, the main goal is to control the ventricular rate with no commitment to restore sinus rhythm. In the rhythm-control strategy, however, the goal is to restore and maintain sinus rhythm [17,18,30]. Calcium channel blockers (e.g., Diltiazem and Verapamil), β blockers (e.g., Atenolol, Bisoprolol, and Carvedilol) and digoxin are some examples of rate-control drugs. Sodium channel blockers (e.g., Flecainide, Propafenone, and Quinidine) and potassium channel blockers (e.g., Amiodarone and Sotalol) are some drugs that are used for rhythm control [16,17,30].

Ablation of the some parts of the atria is another approach for AF treatment. This can be done by using surgical ablation in the Cox-Maze procedure [31] or by catheter ablation therapy [18]. Despite the high success rate of the Cox-Maze procedure, the use of this AF treatment is limited due to the risk of open heart surgery and significant complications, including stroke (0.5%), bleeding caused by multiple incisions (4.9%)
and sinus node dysfunction with a requirement for permanent pacing (5.8%) [25, 30]. Furthermore, a 30-day mortality rate of using this procedure is approximately 2% [25].

Catheter ablation therapy, which is a minimally invasive procedure, is more frequently used and is the focus of this thesis. In this approach, a mapping catheter is inserted into a blood vessel, usually in the groin, and is guided into heart. The mapping catheter is used to collect intracardiac electrograms (IEGMs) of various atrial sites and to create a 3-dimensional (3-D) map of atria. Finally, an ablation catheter is used to eliminate sites targeted for ablation [32].

Depending on the type of the mapping catheter, common cardiac mapping systems that are currently used can be categorized into various types: continuous, sequential, contact, and non-contact systems [33]. The proposed methods throughout this thesis are mainly designed considering that a small catheter with a high density of electrodes is used for data collection. Considering the structure of data collection, sequential mapping is the most desirable approach and is used here. Indeed, in sequential mapping, a small catheter is moved through the chamber of interest and collects the IEGMs from several sites sequentially. The sequential mapping with small catheters, such as a Reflexion Spiral (St. Jude Medical) or Lasso (Biosense-Webster, Inc.) catheter, is the most common mapping approach for the ablation therapy procedure mainly because the small catheters are easier to control and are less expensive [34]. However, deploying these catheters requires more time to collect data sequentially from various atrial sites.
In continuous mapping, however, a large catheter with a sizable number of electrodes collects the IEGMs [35–37], e.g., the continuous contact mapping using a basket catheter is studied in [38,39] and continuous non-contact mapping is investigated in [40]. In this approach, the cardiac map can be created quickly after analysing a few wavefronts. While large catheters can generate a cardiac map quickly, their limitations are incomplete endocardial coverage of some cardiac zones (e.g., the atrial appendage cannot be mapped properly by these catheters) and risk of systemic thromboembolism during mapping; furthermore large catheters are expensive they are not useful to guide pulmonary vein isolation [41].

Atrial IEGMs might be efficiently processed and used to guide the ablation of putative perpetuating sources of AF [13]. Available commercial software that is used for AF ablation therapy processes IEGMs to quantify areas with complex fractionated electrograms (CFAEs) or regions with high dominant frequency for the operator; as prior works suggest that ablation of these sites improve clinical success [42–44]. Although the algorithms used in these programs are able to process the IEGMs in real-time and are computationally efficient, recent robust clinical data shows that the success rate of ablation therapy based on them is not satisfactory [45–47], justifying further research in this field.

The main objective of this research is to analyze atrial IEGMs and extract insightful information for catheter-based ablation of the atria to treat AF. We propose some algorithms that process the IEGMs in various domains (e.g., time and frequency) and generate an ablation map, a 3-D map of the atria, to expose patterns in AF that provides mechanistic insight and point to source location. The proposed methods
have low computational complexities to make the real-time processing of the data gathered during ablation therapy possible.

1.6 Outline of the Thesis

Performance of the algorithms which process IEGMs highly depends on the accuracy of estimating the time that electrical waves pass the area under the electrodes. Estimating the activation times (ATs) of the electrodes from IEGMs during AF is very challenging as electrical activities of the atria are quite irregular, and the amplitudes and morphologies of the active zones in IEGMs continuously change. Estimating the ATs of IEGMs is usually the first processing step in cardiac mapping systems. In Chapters 2 and 3, we study the AT estimation of IEGMs during AF.

In Chapter 2, we propose a new activation detector which is based on the test of the equality of the variance of two segments of IEGMs. At any time $t$, we consider two sets of IEGM data: 1) data in a bounded interval around $t$, 2) data in bounded intervals around the first interval. We show that the activation zone can be extracted by comparing the variance of these two sets.

In Chapter 3, we study the problem of identification of the active intervals (AIs) of IEGMs, i.e., AI extraction which consists of estimating the beginning and duration of the AIs is investigated in this chapter. We formulate the problem of the IEGM’s AIs extraction as a sequence of hypothesis tests; we derive five test statistics (TSs) and show that the onset and duration of the AIs of the IEGMs can be extracted by threshold crossing the TSs.
Significant interest was generated from the recent studies showing multiple rotor activities in human during AF [35–37,48]. Based on these findings, the main objective in Chapters 4 and 5 is to localize the tip of spiral wave reentries as it is believed that the success of the ablation therapy highly depends on the accuracy of localizing these sources.

In Chapters 4, based on the Hough transform (HT) [49], we propose a general framework to estimate unknown parameters of the electrical propagation waves with arbitrary parametric shapes. There, localization of a single Archimedean spiral wavefront with unknown parameters, including unknown angular speed, initial rotation phase, distance between successive arms of the spiral, and location of its tip is studied; the HT is used to reduce the computational complexity (CC) of tip localization.

In Chapter 5, we consider a more general case where the spiral wavefront rotation direction is also unknown and can be either clockwise (CW) or counterclockwise (CCW). Assuming that the activation times (ATs) of the IEGMs and locations of electrodes of a catheter are known, we propose a method with less CC to estimate all the wavefront parameters.

A cardiac conduction velocity map can provide insightful information regarding the mechanisms initializing and sustaining complex arrhythmias, such as AF [50, 51]. The cardiac conduction velocity estimation using the ATs and locations of the catheter’s electrodes is studied in Chapters 6, 7 and 8.

In Chapters 6, we analyse the cardiac velocity estimation error of two computationally efficient heuristic estimators: 1- maximum time difference (MTD) and 2-
In the MTD, the estimated velocity is a vector in the direction of the vector that connects the first to the last catheter’s activated electrode, and the magnitude of the velocity vector (VV) is estimated as the ratio of the distance between two electrodes to the delay between their ATs. In the MinV, using a similar procedure as the MTD, we assign a VV to each available electrode pair of the catheter, and the VV with the smallest magnitude is selected as the final estimated VV. We derive the average absolute value of the velocity estimation error of the MTD and MinV methods for a planar wavefront in a two-dimensional case and show that the performance of MTD is worse than MinV.

In Chapter 7, we modify the MTD method and show that modified MTD (MMTD) is more robust to the AT estimation error and is able to determine the VV of the planar wavefronts more accurately.

In practice, the ATs and locations of the electrodes are estimated, and if their estimation errors are not taken into consideration, they may significantly degrade the quality of the velocity estimation. Thus, in Chapter 8, we assume that the locations and the ATs of the catheter’s electrodes are contaminated with white Gaussian noise with known variances, and we derive the maximum likelihood (ML) cardiac velocity estimator for the planar wavefront. In Chapters 6-8, we study the VV estimation using the IEGMs collected from only one cardiac site. In Chapters 9 and 10, cardiac conduction VV (CCVV) estimation in sequential mapping is considered.

In Chapters 9, we assume that the IEGMs of several cardiac sites are sequentially recorded, their ATs are extracted, and the corresponding wavefronts are specified. The locations of the mapping catheter’s electrodes and the ATs of the wavefronts
are used for the CCV estimation. We assume that the extracted ATs include some estimation errors, which we model with zero-mean white Gaussian noise values with known variances. Assuming stable planar wavefront propagation, we derive the ML CCVV estimator, when the synchronization times between various recording sites are unknown. We analytically evaluate the performance of the CCV estimator and provide its mean square estimation error.

In Chapters 10, we study the CCVV estimation in sequential recording. Assuming the zero-mean Gaussian AT estimation error, we propose a method for ML estimation of the CCVV when the variance of the AT estimation error is unknown.

Finally, in the last chapter, Chapter 11, we introduce regional dominant frequency (RDF) and show that it can be used to identify and characterize variation and disorganization in wavefront propagation or wave breaks (WBs) at each recording site. Our results suggest that the WB analysis based on the RDF can provide insightful information regarding the wavefront propagation that potentially can be used in the catheter ablation therapy.
Part II

Active Interval Extraction
Chapter 2

Activation Detection of Intracardiac Electrograms During Atrial Fibrillation Based on the Variance Equality Test

2.1 Abstract

Performance of the algorithms which process intracardiac electrograms (IEGMs) highly depends on the accuracy of estimating the times that electrical waves pass the area under the electrodes. Estimating these activation times (ATs) from IEGMs during atrial fibrillation (AF) is extremely challenging as electrical activities of atria are very complex, non-stationary, and irregular. In this chapter, we propose a new activation detector which is based on the test of the equality of variance of two sets of data. At any time $t$, we consider two sets of IEGM data: 1) data in a bounded interval around $t$, 2) data in bounded intervals around the first interval. We show that the activation zone can be extracted by comparing the variance of these two
sets, i.e., we introduce a new preprocessing approach and show that it can effectively highlight activation zones of IEGMs. Our simulation results on bipolar atrial IEGMs gathered during AF confirm the efficiency of the proposed preprocessing method.

2.2 Introduction

Accuracy of AT estimation is among the important factors that determines the performance of the algorithms which process IEGMs [52–57]. Estimating the ATs of the electrodes from IEGMs during AF is very challenging as electrical activities of the atria are quite irregular, and the amplitudes and morphologies of the active zones in IEGMs continuously change [58, 59]. Existence and propagation of multiple wavelets [15] and spiral wave reentry [15,36,60] are considered as causes of the complex non-stationary IEGMs during AF [58] (also see Section 1.4).

To extract the active zones of electrograms, several preprocessing steps are usually executed on IEGMs. These steps are designed such that the processed signals show different behavior for active and non-active electrograms' zones, e.g., the proposed method in this chapter produces large magnitude signals in the active zones and low magnitude signals elsewhere. Various linear time invariant (LTI) bandpass/lowpass filters and a non-linear operator (such as a rectifier) can be used for activation extraction [1–5,61].

Careful study of IEGMs during AF reveals that while the amplitudes and morphologies of the active zones are different, the variances of the active zones are higher than the variance of nearby nonactive regions; thus, by analyzing the changes in the
variances of the different electrograms’ regions, we can extract the active zones. In this chapter, based on the test of equality of the variance of two sets of Gaussian data, we introduce a new preprocessing approach and show that it can effectively highlight local active areas of IEGMs. Indeed, at any time \( t_c \), we consider two sets of IEGM data:

1. data in a bounded interval around \( t_c \),

2. data in bounded intervals on the right and left sides of the first interval.

The variances of these sets are equal if the ratio of the maximum likelihood (ML) estimate of their variances is less than a threshold. We propose to use the ratio of estimated variances of the sets (variance of the center segment over the variance of the outer segments) as a non-linear operator for activation detection. Our simulation results on bipolar atrial IEGMs gathered during AF confirm the efficiency of the proposed preprocessing method.

### 2.3 Activation Detection Based on the Variance Equality Test

In this section, first, in Theorem 1, we present a hypothesis test for the equality of the variances of two sets of Gaussian data. Later, we describe how this test can be used for activation detection of atrial IEGMs.

**Theorem 1.** Consider two sets of real data \( X = \{x_1, \ldots, x_N\} \) and \( Y = \{y_1, \ldots, y_M\} \). The elements of \( X \) are independent identically distributed (i.i.d.) Gaussian random variables with mean \( m_x \) and variance \( \sigma^2_x \), i.e., \( x_i \sim N(m_x, \sigma^2_x) \) for \( i = 1, \ldots, N \).
2.3. ACTIVATION DETECTION BASED ON THE VARIANCE EQUALITY TEST

Similarly, elements of $Y$ are i.i.d. with $y_i \sim \mathcal{N}(m_y, \sigma_y^2)$ for $i = 1, \ldots, M$. The following hypothesis test can be used to check the equality of the variance of sets $X$ and $Y$ [62]

\[
\begin{cases}
    \mathcal{H}_0 : \sigma_x^2 = \sigma_y^2, \\
    \mathcal{H}_1 : \sigma_x^2 > \sigma_y^2.
\end{cases}
\]  

The null hypothesis ($\mathcal{H}_0$) is rejected if the following statistic is larger than a predetermined threshold

\[F(X, Y) = \frac{(M - 1) \sum_{i=1}^{N} (x_i - \hat{m}_x)^2}{(N - 1) \sum_{i=1}^{M} (y_i - \hat{m}_y)^2},\]  

where the maximum likelihood (ML) estimates for mean values $m_x$ and $m_y$ are respectively

\[\hat{m}_x \overset{\text{def}}{=} \frac{1}{N} \sum_{i=1}^{N} x_i \quad \text{and} \quad \hat{m}_y \overset{\text{def}}{=} \frac{1}{M} \sum_{i=1}^{M} y_i,\]

and $F$ statistic has the F-distribution with $N - 1$ and $M - 1$ degrees of freedom.

Theorem 1, shows that we reject the hypothesis $\sigma_x^2 = \sigma_y^2$ if the ratio of the estimated variances of two sets of data is larger than a threshold. In the rest of this section we describe the proposed preprocessing steps that stem from (2.2) and highlight the active zones of atrial IEGMs.

Let $z(t)$ show the filtered IEGM of the atrium sampled at time $t$. At any sampled time $t_c$, we create two sets of data $X(t_c)$ and $Y(t_c)$ to calculate the numerator and denominator of (2.2), respectively, as $F(t_c) \overset{\text{def}}{=} F(X(t_c), Y(t_c))$. The first set, $X(t_c)$,
2.3. ACTIVATION DETECTION BASED ON THE VARIANCE EQUALITY TEST

\[
Y(t_c) \overset{\text{def}}{=} \left\{ z(t) : t \in \left[ t_c - \frac{W_c}{2} - W_s, t_c - \frac{W_c}{2} \right] \cup \left( t_c + \frac{W_c}{2}, t_c + \frac{W_c}{2} + W_s \right) \right\}
\]

includes samples of \( z(t) \) in the bounded interval around \( t_c \), that is

\[
X(t_c) \overset{\text{def}}{=} \left\{ z(t) : t \in \left[ t_c - \frac{W_c}{2}, t_c + \frac{W_c}{2} \right] \right\},
\]

where \( t \in [t_1, t_2] \) denotes all the samples in \([t_1, t_2]\) and \( W_c > 0 \) determines the cardinality of \( X \). The second set, \( Y(t_c) \), defined in (2.4), is the union of the data \( z(t) \) in bounded intervals on the right and left sides of \( X(t_c) \) where \( W_s \) determines the cardinality of \( Y \).

Figure 2.1 shows an example of the atrial IEGM for \( 1 \leq t \leq 2.1 \). In this figure, the data sets used in calculating \( F(1.34) \) and \( F(1.79) \) are shown when \( W_c = W_s = 60 \text{ mS} \). It is clear that the ML estimate of the variance of \( X(1.34) \) is significantly larger than the one estimated from \( Y(1.34) \); thus, \( F(1.34) = F(X(1.34), Y(1.34)) \approx 6 \) becomes a large number. In contrast, \( F(1.79) \approx .01 \) is a small number because the estimated variance of \( X(1.79) \) is significantly smaller than the one estimated from \( Y(1.79) \). This example demonstrates how operator \( F(\cdot) \) amplifies the active zones of atrial IEGMs. Therefore, we propose the following processing steps to analyze IEGMs:

- Bandpass filter atrial IEGM (pass band: \( f_1 - f_2 \)).
- At any sample time \( t_c \), calculate \( F(X(t_c), Y(t_c)) \).
- Clip the large peaks of \( F(X(t_c), Y(t_c)) \), i.e., if \( F(X(t_c), Y(t_c)) > \eta \), set \( F(X(t_c), Y(t_c)) \)
Figure 2.1: Segments of data which are used to calculate $F(1.34)$ and $F(1.79)$ of a sample IEGM equal to $\eta$.

- Apply a lowpass filter with cutoff frequency $f_c$.

Note that several other processing steps (e.g., adaptive/variable thresholding [63] or wavelet transform [61]) must be applied on processed IEGMs data to estimate the AT of IEGMs; however, in this chapter, we do not focus on them.
2.4. RESULTS

Figure 2.2: Ten bipolar IEGMs gathered from the left atrium of a patient with paroxysmal AF and their corresponding normalized proposed preprocessed signals; the dashed rectangles show the activation zones that the proposed method extracted which other studied methods in Figure 2.3 missed.

2.4 Results

In this section, we apply the proposed preprocessing steps on IEGMs recorded with a Reflexion Spiral™ catheter (St. Jude Medical). The data are collected from the left atrium of a patient with paroxysmal AF using ten bipolar electrodes of the catheter with the sampling frequency of $F_s = 2034.5$. The pass band of $f_1 = 40, f_2 = 250$ Hz is considered for the bandpass filter of the proposed method which leads to baseline wander removal; the cutoff frequency of the lowpass filter in the last stage of the proposed processing is set to $f_c = 20$ Hz; both the FIR filters have the order of 70 with the Kaiser window with the parameter $\beta = 2, [3-5]$. We use $\eta = 10$ for the signal clipper in the third step and set $W_c = W_s = 60$ mS in $\mathcal{F}$; thus, we have...
$N = 122, M = 244$. Parameters $W_c$ and $W_s$ should be set based on the IEGM activation durations and durations of non-active zones, respectively. Our results confirm that the selected values are acceptable.

To reduce the computational complexity of the proposed method, we assume that the mean of the input signal to the operator $F$ is zero and instead of (2.2), we use the following operator which can be computed in an efficient way

$$\tilde{F}(X, Y) = \frac{M \sum_{i=1}^{N} x_i^2}{N \sum_{i=1}^{M} y_i^2}. \quad (2.5)$$

Consider an IEGM with $T_d$ second duration where $T_d \gg \max\{W_c, W_s\}$; to find the output of $\tilde{F}$ operator, we need to calculate almost $2T_dF_s$ and $6T_dF_s$ real number multiplications and summations, respectively.

Figure 2.2 shows 2.5 seconds of raw\(^1\) and normalized\(^2\) processed IEGMs using the proposed method.

For comparison purposes, the outcomes of some other algorithms are shown in Figure 2.3. Figures 2.2 and 2.3 show that all the studied methods are able to highlight isolated activations with large magnitudes; however, these methods produce different results for the activation with small magnitudes. The dashed rectangles in Figure 2.2 show the activation zones that the proposed method extracted which other simulated methods in Figure 2.3 missed. To closely compare various methods, the fourth bipolar

\(^1\)Power line interference, ventricles\(^7\) activities, and baseline wander are removed from the data.
\(^2\)Maximum magnitude of the processed data is one.
Figure 2.3: Ten bipolar IEGMs gathered from the left atrium of a patient with AF and the normalized preprocessed signals using approaches in [1–5]
2.4. RESULTS

IEGM channel is shown in Figure 2.4. This figure shows that both non-linear energy operator (NLEO) [1, 2] and Rectifier[^3] [3–5] create small peaks for some active zones; whereas, the proposed processing generates clear peaks for all the active zones of the IEGMs.

The ATs obtained from the proposed processing are shown in Figure 2.5. These ATs are found by comparing the processed signal and a fixed threshold. Based on the estimated ATs, there are 16 wavefronts [64] where consecutive wavefronts are shown with different colors. This figure confirms that all the detected activations are consistent across various electrodes (each wavefront hits all the catheter’s electrodes within an expected short time interval).

[^3]: The block diagram for this approach is similar to the proposed method when the operator $F$ and clipper are replaced with a rectifier.
2.5 Conclusion

In this chapter, based on the test of the equality of variance of two sets of data, we proposed new preprocessing steps which highlight the active zones of IEGMs. At any time $t$, we defined the operator $F$ in (2.2) as the ratio of variances of two sets obtained from IEGM around time $t$. This operator is used for activation detection; i.e., the proposed IEGM preprocessing steps include a bandpass filter, the operator $F$, a signal clipper, and a lowpass filter. We applied our proposed method on bipolar atrial IEGMs of a patient with AF and showed that it can effectively extract the

Figure 2.5: The ATs of IEGMs obtained by comparing the proposed processed signals and a fixed threshold. The ATs are marked with small vertical lines on the IEGMs. Sixteen wavefronts are shown in this figure where consecutive wavefronts are shown with different colors. The dashed rectangles show the activations that the proposed method detected which other simulated methods missed.
activation zones even when the amplitudes of the IEGMs are small.
Chapter 3

Bipolar Intracardiac Electrogram Active Intervals
Extraction During Complex Arrhythmias

3.1 Abstract

Identifying the active intervals (AIs) of the intracardiac electrogram (IEGM), which consists of jointly estimating the beginning and duration of the AIs, can provide diagnostic information for various arrhythmias. The AI estimation is very challenging during complex arrhythmias, such as atrial fibrillation (AF), due to the variable amplitude, morphology and duration of the AIs. We formulate the problem of the AI extraction (estimation of the onset and duration of AI) as a sequence of hypothesis tests; where, in each test, we compare the variance of a small piece of the bipolar IEGM with its adjacent segments. We propose a modified general likelihood ratio (MGLR) and separating function estimation tests; we derive five test statistics (TSs), and show that the AIs can be obtained by threshold crossing the TSs. We also propose a computationally efficient approach for the implementation of the derived
3.2. INTRODUCTION

Identifying the active segments of the intracardiac electrograms (IEGMs) is among the critical processing steps in the cardiac electro-anatomic mapping systems [13,65]. The ability to precisely determine the activation time (AT) of the IEGM is the defining factor for the accuracy of the created cardiac maps [66], yet it can present significant challenges when IEGMs are recorded during complex arrhythmias due to the variable amplitude, morphology and duration [43]. This has significantly hampered attempts to visualise activation patterns of putative sources of atrial fibrillation (AF) perpetuation, the most challenging complex arrhythmia. Accurate measures of active intervals (AIs) during human arrhythmias, which include the estimation of the onset
and duration of the AI, would be highly valuable in automated analysis.

The locations of electrodes from the catheter and their ATs can be used for cardiac conduction velocity estimation and may be deployed to create a wavefront propagation/activation map [67,68]. The electrodes’ locations and ATs may also be analysed to identify sites with early activation in the ablation therapy procedure [13]. In addition, they can be processed to localize the focal sources that sustain AF [28,65]. The ATs are used for the IEGM cycle length (CL) estimation, and sites with small CLs are considered as candidate ablation sites [69].

Different AI properties and patterns reflect the characteristics of the atrial tissues, and regions with the most irregular and disorganized AIs can be assumed to be crucial for AF maintenance [70]. Index of synchronisation that represents the probability of finding synchronous activations in intra-atrial bipolar IEGMs is among the features that measures organization of arrhythmias and requires accurate AI extraction [71]. The activation duration (AD) is also an insightful feature of the bipolar IEGM that provides information about various arrhythmias [72]. The ADs are inversely related to the organization of arrhythmias, as complex IEGMs usually have longer ADs [73]. The activation recorded from the areas with slow conduction speed also have long and fractionated electrograms with multiple deflections. Localizing these areas, which are responsible for the formation of the reentrant circuit/excitation, is critical in the success of the ablation therapy of different arrhythmias [36,60]. The regularity index, which is an estimate of the probability of finding two similar AIs in the IEGM segment, is another useful feature that requires the precise AT and AD identification [54,73]. Ablation of the low voltage sites with electrical activities with durations of more than
70% of the CLs is shown to improve the ablation success rate in persistent AF [74]; identifying these sites also requires accurate estimation of the AIs.

In this chapter, we study the problem of the bipolar IEGM AI extraction, and our goal is to estimate the activation onset (AO) and duration (AD). We formulate the problem of the AI identification as sequential hypothesis testing problems; where, in each test, we compare the variance of a small segment of the IEGM with its adjacent segment. We consider two hypothesis tests and derive five different test statistics (TSs) for them. Two of the TSs are based on the modified version of the general likelihood ratio tests (GLRTs) [75], and the other three are based on the separating function estimation tests (SFETs) [76]. The derived TSs are applied to the IEGMs, and subsequent AIs are extracted by thresholding the resulting TSs.

Our IEGM dataset is described in Section 3.3. Details of our proposed methods including efficient implementation of them are presented in Section 3.4. Our results and discussions are expressed in Sections 3.5, and we conclude the chapter in Section 3.6.

Here, scalar values are shown with non-bold letters; whereas, vectors and matrices are shown with boldface small and capital letters, respectively. Notation \( y \gtrless_{\mathcal{H}_0}^{\mathcal{H}_1} \eta \), means that the hypothesis \( \mathcal{H}_0 \) is rejected if \( y > \eta \), and \( \mathcal{H}_0 \) is failed to be rejected if \( y < \eta \). The \( N \)-dimensional (\( N \)-D) identity matrix, the \( M \)-D zero vector, the Frobenius norm of matrix \( A \), the set of all the \( K \)-D real vectors, the expected value of the random vector \( x \), and the union of two sets \( A \) and \( B \) are respectively denoted by \( I_N, O_M, \| A \|, R^K, E\{ x \} \) and \( A \cup B \). For the \( S \)-D vector \( y \), the operator \( \Phi(y) \) is defined as \( \Phi(y) = \frac{S}{2} \ln(\frac{2\pi e}{S} \| y \|^2) \). Notation \( x \sim \mathcal{N}(0_K, \Sigma) \) shows that the \( K \)-D vector \( x \) has the zero-mean Gaussian distribution with the covariance matrix \( \Sigma \). Finally,
mean±std is used to report the mean and standard deviation (std) of the variables.

3.3 Material; IEGM Dataset

IEGM segments were collected from sixteen patients (Age: 62.4 ± 8.2 years, four females, four paroxysmal AF and twelve persistent AF) who presented in sustained AF and have undergone catheter ablation at Kingston General Hospital. For each patient, the bipolar electrograms of several sites in the left atrium were sequentially collected using the EnSite Velocity system (St. Jude Medical, St Paul, MN, USA) prior to any radiofrequency ablation by the irrigated-tip ablation catheter Therapy™ Cool Flex™ or TactiCath™ Quartz (St. Jude Medical). Either the Reflexion HD™ or the Reflexion™ Spiral (St. Jude Medical) catheter (with 20 electrodes with 1mm width) was used for the IEGM collection. The bipolar pair electrodes spacing for Reflexion HD™ is 2mm; whereas, for Reflexion™ Spiral, it is 1mm. The sampling frequency of the IEGM collection was $f_s = 2034.5$Hz, and data was filtered with 30Hz high-pass and 300Hz low-pass filters. In 10 patients, ablation terminated AF to sinus rhythm (6), and atrial tachycardia (4); a further 6 patients underwent direct current cardioversion.

IEGM segments with various durations were randomly selected from available sets of signals. Segments with very small power or those with fragmented/continuous fractionated electrograms without isoelectric intervals in which the activation intervals were not distinguishable, were excluded; we also excluded segments in which the ventricle far field signals were strongly present. Thus, 36 segments were excluded by visual investigation and the remaining 324 segments had a duration of 3.8 ± 2.1sec
(median 3.2sec; range 1.4 to 11.3sec), and total duration of all segments together was 1231sec (20.5 minutes).

3.4 Proposed AI Extraction Methods

Study of the IEGMs of complex arrhythmias reveals that one of the main characteristics of the AIs is that the variances of the IEGM signals in those segments are higher than their neighbouring zones/intervals. The comparison of the variance of each segment of the electrogram with its adjacent segments is the basis of our proposed method. To find the AIs of the IEGM, we execute a sequence of hypothesis tests. In each test, we consider a specific part of the IEGM and compare its variance with the variances of its adjacent IEGM segments. More specifically, at any time $n$, we define two vectors $\mathbf{x}_{n,m} \in \mathbb{R}^m$ and $\mathbf{y}_{n,m} \in \mathbb{R}^{2T}$ that are comprised of the segments of the IEGM as follows:

\[
\mathbf{x}_{n,m} \overset{\text{def}}{=} [\text{IEGM}(n), \ldots, \text{IEGM}(n + m - 1)]^T, \tag{3.1}
\]

\[
\mathbf{y}_{n,m} \overset{\text{def}}{=} [\mathbf{x}_{n-T,T}^T, \mathbf{x}_{n+m,T}^T]^T. \tag{3.2}
\]

Figure 3.1 shows various examples of the IEGM segments. As it is shown in this figure, $\mathbf{x}_{n_i, m_i}$ includes the IEGM segment starting from $n_i$ with length $m_i$ that is surrounded by the IEGM segments in $\mathbf{y}_{n_i, m_i}$. Vector $\mathbf{y}_{n_i, m_i}$ itself consists of two IEGM segments $\mathbf{x}_{n-T,T}$ and $\mathbf{x}_{n+m,T}$, each with $T$ samples; one starts from $n_i - T$ and ends at $n_i - 1$, and the other one starts from $n_i + m_i$ and ends at $n_i + m_i + T - 1$.

In this chapter, we assume that $T$ is a known fixed value that is specified based
on the minimum time delay between two consecutive AIs (minimum silent interval between two AIs). Whereas, $m$ is an unknown AD that can be any value between $m_{\text{min}}$ and $m_{\text{max}}$, i.e., $m \in M = [m_{\text{min}}, m_{\text{max}}]$, where $m_{\text{min}}$ and $m_{\text{max}}$ show the sample duration of the smallest and largest possible AD, respectively. Here, we empirically selected $T = 122$ (equivalent to the number of samples in a 60msec segment); we also use $m_{\text{min}} = 30$ and $m_{\text{max}} = 407$, i.e., we assume that AD can be between 15msec to 200msec. These values are selected based on the histogram of the AD of manually annotated IEGMs (less than 0.5% of all the annotated AIs have ADs which were not in [15-200]msec).
We assume that $x_{n,m} \sim \mathcal{N}(0_m, \theta_{x,n,m} I_m)$ and $y_{n,m} \sim \mathcal{N}(0_{2T}, \theta_{y,n,m} I_{2T})$ are independent Gaussian random vectors. In the following two sections, our aim is to extract the AOs and ADs of the IEGMs by testing the variances of $x_{n,m}$s and $y_{n,m}$s. Consequently, we propose several hypothesis tests and obtain related TSs. Finally, to extract AIs, TSs should be compared with some thresholds; here, these thresholds are specified based on the iterative method proposed in [77], in which the blanking period of 50msec is used.

The modified GLR (MGLR) and SFE approaches are studied in Sections 3.4.1 and 3.4.2, respectively.

### 3.4.1 Modified GLR Tests (MGLRTs) for AI Extraction

The variance of the AI of the IEGM is higher than the variance of its adjacent segments, and this is reflected in our problem formulation under $\mathcal{H}_1$. In the next two subsections, we study two tests with different $\mathcal{H}_0$s. In the test in subsection 3.4.1, we check to see if the variance of $x_{n,m}$ is higher than the variance of $y_{n,m}$, as opposed to the case where the variance of $x_{n,m}$ is Less than or Equal to the variance of $y_{n,m}$. The proposed TS for this test is referred to as the LE. In the studied test in subsection 3.4.1, we check if the variance of $x_{n,m}$ is higher than $y_{n,m}$ in contrast to the case where the variances of $x_{n,m}$ and $y_{n,m}$ are Equal (the proposed TS for this test is referred to as the Eq).

In the GLRT, the log-likelihood ratio (LLR) of the available signal under different hypotheses should be optimized over all the unknown parameters. The durations of
the activations are unknown and optimization of the LLR over \( m \) leads to a sequence of tests with a different number of IEGM samples (the length of \( x_{n,m} \) is \( m \); whereas, the length \( y \) is fixed and is \( 2T \)). Thus, in this chapter, we propose the MGLR and modified LLR (MLLR) to take into consideration the variation of the number of sample sizes under different hypotheses. In particular, we propose to normalize the LLR over the number of samples. The GLR-based methods tend to overestimate the AD; whereas, the MGLR methods provide more accurate estimation of the AD. Our results also confirmed that this modification significantly improves the quality of AI extraction.

**MGLRT 1: the variance of \( x_{n,m} \) is less than or equal to that of \( y_{n,m} \) under \( \mathcal{H}_0 \)**

Consider the hypothesis test

\[
\mathcal{P}_1 : \begin{cases} 
\mathcal{H}_0 : \theta_{x,n,m} \leq \theta_{y,n,m}, \\
\mathcal{H}_1 : \theta_{x,n,m} > \theta_{y,n,m}.
\end{cases}
\]  

(3.3)

In Appendix 3.A, we prove that the MGLR for (3.3) is

\[
\text{LE} : \max_{m_1 \in M} \left( \frac{(g_{n,m_1} - h_{n,m_1})U_{n,m_1} + h_{n,m_1}}{m_1 + 2T} \right) - \\
\max_{m_0 \in M} \left( \frac{(h_{n,m_0} - g_{n,m_0})U_{n,m_0} + g_{n,m_0}}{m_0 + 2T} \right) \overset{\mathcal{H}_1}{\geq} \eta, \]

(3.4)
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where

\[ g_{n,m} \overset{\text{def}}{=} -\Phi(x_{n,m}) - \Phi(y_{n,m}), \]

\[ h_{n,m} \overset{\text{def}}{=} -\Phi([x_{n,m}^T, y_{n,m}^T]^T), \]

\[ U_{n,m} \overset{\text{def}}{=} \begin{cases} 1, & \text{if } \frac{||x_{n,m}||^2}{m} - \frac{||y_{n,m}||^2}{2T} > 0 \\ 0, & \text{Otherwise} \end{cases} \]

MGLRT 2: the variance of \( x_{n,m} \) is equal to that of \( y_{n,m} \) under \( H_0 \)

The GLR test for \( P_1 \) given in (3.4) requires the maximization of the probability density function (pdf) of the observation over \( m \) for both \( H_0 \) and \( H_1 \). In the following, we propose a test that only requires the optimization of \( m \) under \( H_1 \). Note that under \( H_1 \), when \( n \) is the onset of an AI, the optimum \( m \) shows the AD of that AI. If the segments under the test, \( (x_{n,m} \text{ and } y_{n,m}) \), are parts of the isoelectric line or parts of the AI, the variances of them should be equal. If the middle segment \( x_{n,m} \) is in the AI, while \( y_{n,m} \) comprises some parts of the isoelectric line, the variance of \( x_{n,m} \) is expected to be larger than that of \( y_{n,m} \). In the test considered in this subsection, under \( H_1 \) we assume that \( m, \theta_{x,n,m}, \text{ and } \theta_{y,n,m} \) are unknown. Under \( H_0 \), on the other hand, we assume that \( \theta_{x,n,m} \text{ and } \theta_{y,n,m} \) are equal and unknown; whereas, \( m \) is known and is the argument that maximizes the pdf under \( H_1 \). The considered test is

\[ P_2 : \begin{cases} H_0 : \theta_{x,n,m_1} = \theta_{y,n,m_1} = \theta_{n,m_1}, \\ H_1 : \theta_{x,n,m} > \theta_{y,n,m}, \end{cases} \] (3.5)
3.4. PROPOSED AI EXTRACTION METHODS

where

\[
m_1 = \arg\max_{m \in \mathcal{M}} \frac{(g_{n,m} - h_{n,m})U_{n,m} + h_{n,m}}{m + 2T}.
\] (3.6)

In Appendix 3.B, we derive the MGLR for (3.5) as

\[
\text{Eq: } \frac{(g_{n,m_1} - h_{n,m_1})U_{n,m_1}}{m_1 + 2T} \overset{\mathcal{H}_1}{\gtrless} \eta.
\] (3.7)

3.4.2 Separating Function Estimation Tests for AI Extraction

In the following two subsections, we provide two separating functions (SFs) [76] for test (3.3), and based on them, propose three detectors for the AIs extraction. The definition of the SF is presented here [76]. Let \( \Theta_0 \) and \( \Theta_1 \) be disjoint subsets of \( \mathbb{R}^E \).

Then, the function \( g : \mathbb{R}^E \to \mathbb{R} \) is called an SF for \( \Theta_0 \) and \( \Theta_1 \) if it continuously maps the parameter sets \( \Theta_0 \) and \( \Theta_1 \) into two separated real intervals.

Variance Difference (VD) SF

Let \( \theta \) denote the vector of the unknown variances \( \theta_{n,m} \defeq [\theta_{x,n,m}, \theta_{y,n,m}]^T \). Considering the definition of the SF [76], it is straightforward to check that the variance difference \( g_1(\theta_{n,m}) = [1, -1] \theta_{n,m} = \theta_{x,n,m} - \theta_{y,n,m} \) is a SF for two disjoint subsets \( \Theta_0 = \{ \theta_{n,m} | \theta_{x,n,m} \leq \theta_{y,n,m} \} \) and \( \Theta_1 = \{ \theta_{n,m} | \theta_{x,n,m} > \theta_{y,n,m} \} \) in (3.3).

Lemma 1. For a given \( m \), the minimum variance unbiased estimator (MVUE) of
3.4. PROPOSED AI EXTRACTION METHODS

\( g_1(\theta_{n,m}) \) in \( \Theta_0 \cup \Theta_1 \), denoted by \( T(x_{n,m}, y_{n,m}) \), is

\[
T_1(x_{n,m}, y_{n,m}) = \frac{\|x_{n,m}\|^2}{m} - \frac{\|y_{n,m}\|^2}{2T}.
\] (3.8)

Proof: See Appendix 3.C.

Based on the variance difference SF, we propose (3.9) (referred to as the VD) for the AIs extractions

\[
\text{VD : } \left( \frac{\|x_{n,m}\|^2}{m_1} - \frac{\|y_{n,m}\|^2}{2T} \right) \overset{H_1}{\gtrsim} \overset{H_0}{\eta}.
\] (3.9)

where \( m_1 \) is obtained from (3.6).

Variance Ratio (VR) SF

It is straightforward to check that \( g_2(\theta_{n,m}) = [\theta_{n,m}]_1/\theta_{n,m} - 1 = \theta_{x,n,m}/\theta_{y,n,m} - 1 \) is a SF for two disjoint subsets \( \Theta_0 = \{ \theta_{n,m} | \theta_{x,n,m} \leq \theta_{y,n,m} \} \) and \( \Theta_1 = \{ \theta_{n,m} | \theta_{x,n,m} > \theta_{y,n,m} \} \) in (3.3).

Lemma 2. For a given \( m \), the MVUE of \( g_2(\theta_{n,m}) \) in \( \Theta_0 \cup \Theta_1 \) does not exist.

Proof: See Appendix 3.D.

Therefore, we use the ML estimate of \( g_2(\theta_{n,m}) \), denoted by \( T_2(x_{n,m}, y_{n,m}) \)

\[
T_2(x_{n,m}, y_{n,m}) = \frac{2T\|x_{n,m}\|^2}{m\|y_{n,m}\|^2} - 1,
\] (3.10)
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and propose the following AI detector (referred to as the VR1):

\[
\text{VR1} : \left( \frac{T}{m_1} \frac{\|x_{n,m_1}\|^2}{\|y_{n,m_1}\|^2} \right) \frac{\mathcal{H}_1}{\mathcal{H}_0} \geq \eta,
\]

(3.11)

where \( m_1 \) is obtained from (3.6).

We also propose the following similar AI detector

\[
\text{VR2} : \max_{m \in \mathcal{M}} \left( \frac{T}{m} \frac{\|x_{n,m}\|^2}{\|y_{n,m}\|^2} \right) \frac{\mathcal{H}_1}{\mathcal{H}_0} \geq \eta.
\]

(3.12)

The AT estimation method that is proposed in [78] uses the variance ratio; however, in that paper it is assumed that the durations of activations are fixed and known (the AD of 60msec is used in [78]). In this chapter, on the other hand, we consider different ADs for various AIs which can be any value between \( m_{\text{min}} \) and \( m_{\text{max}} \).

3.4.3 Efficient Implementation of the Proposed TSs

The proposed TSs in (3.4), (3.7), (3.9), (3.11), and (3.12), respectively referred to as LE, Eq, VD, VR1 and VR2, require optimization of TSs over \( m \) which can be done using an exhaustive search. For this aim, for each sample \( n \), we calculate the TSs for all the possible \( m \) in \( \mathcal{M} = \{m_{\text{min}}, m_{\text{min}} + m_{\text{res}}, \ldots, m_{\text{max}}\} \) and find the best possible \( m \) for each TS at time \( n \). Therefore, the TSs should be calculated many times, and the computational complexity (CC) of AI extraction depends on the number of samples of the IEGM segment and \( |\mathcal{M}| \) (cardinality of the set \( \mathcal{M} \)), which itself depends on the possible range of the AD \( [m_{\text{min}}, m_{\text{max}}] \) and the resolution of searching for the optimum AD \( (m_{\text{res}}) \). Consequently, it is important to find a computationally
efficient method to implement these TSs. All the aforementioned detectors depend on the norm of various segments of the electrogram ($\|x_{n,m}\|^2$ and $\|y_{n,m}\|^2$). Using the following cumulative sum (CS) of the power of the IEGM

$$CS_n = \sum_{u=0}^{n} |IEGM(u)|^2,$$

(3.13)

we can express $\|x_{n,m}\|^2$ and $\|y_{n,m}\|^2$ as

$$\|x_{n,m}\|^2 = CS_{n+m-1} - CS_{n-1},$$

(3.14)

$$\|y_{n,m}\|^2 = CS_{n+m+T-1} - CS_{n-T-1} - \|x_{n,m}\|^2.$$  

(3.15)

Computation of the CS for an IEGM with $N$-sample duration requires $N$ multiplications and $N-1$ additions, and computation of $\|x_{n,m}\|^2$ and $\|y_{n,m}\|^2$, respectively, require one and two additions. Thus, to calculate $\|x_{n,m}\|^2$ and $\|y_{n,m}\|^2$ for $n = 1, \ldots, N$ and $m \in \mathcal{M}$, we need to execute $3N|\mathcal{M}| + N-1$ additions and $N$ multiplications. It can be verified that the proposed methods require $O(N|\mathcal{M}|)$ operations to calculate the TSs for an IEGM with $N$ samples, which confirms the efficacy of using the CS in the proposed methods.

The grid size of $m_{\text{res}} = 20$ samples is used for AI extraction, i.e., for each estimator, we search among $|\mathcal{M}| = 19$ uniformly distributed ADs between 15 to 200msec and choose the best possible AD for each TS ($m_{\text{res}}$ is the number of samples in a 10msec segment). The impact of decreasing $m_{\text{res}}$ beyond 20 on the performance of the proposed methods is negligible; thus, we chose that value for the CC concern.
3.4.4 Evaluations of the Proposed Methods

IEGM segments were annotated by two independent experts; expert number 1 (E1) annotated 187 segments and E2 annotated 313 segments. One of the segments, which is the IEGM collected from one of the electrodes of the catheter, was presented to the expert and the annotation was done solely based on that segment. The annotators were able to change the amplifying/scaling factor of the IEGM presentation and also could vary the electrogram sweep speed (SS). Most of the segment annotations were done when the SS was 100mm/sec, and a few of them were done with the SS of 200 or 50mm/sec. Both annotators were also asked to annotate 50 segments with the least similarity index (defined later in this section) with the Eq method for the second time. During both rounds of the MA, E1 and E2 were blind to the output of our AI estimators or their previous annotation. Consequently, the number of segments with one to four MAs were respectively 127, 138, 39, and 20. The total of 12702 AIs were annotated by specifying the onset and the end of the activations during 671.6 minutes; the time spent for each AI annotation was 3.2 ± 1sec.

The following AIs were specified after comparing the extracted AIs and those obtained from MA: 1- True positive interval (TPI): the estimated AI has an overlap with only one of the manually annotated AIs (overlap should be more than 30% of the AIs), and no other estimated AI has any overlap with that annotated AI; 2- False negative interval (FNI): no AI is estimated during the manually annotated AI; 3- False positive interval (FPI): there is no annotated AI during the estimated AI. The TPI, FNI, and FPI rates are reported as percentages of the total number of manually annotated AIs. The positive predictive value (PPV), which is the number of TPIs
3.4. PROPOSED AI EXTRACTION METHODS

divided by total number of TPIs and FPIs, is also reported.

The center of mass (CoM) or barycenter of the AI is considered as the AT \([55,79]\) and is used to estimate the mean CL (MCL) of the segments; for this aim, the time delay between the CoMs of the consecutive AIs were obtained, and the MCL was estimated as the mean of those values (excluding 5% of the points from the top and bottom tails of a data set).

The estimation error of the onset, AD, end and MCL of the proposed methods were obtained by comparing them with MA. Suppose that \(x\) is a parameter obtained from the MA, and \(\hat{x}\) is an estimated value using one of the proposed methods, then the error and normalized absolute error (NAE) of \(x\) are defined as \(x - \hat{x}\) and \(|x - \hat{x}|/|x|\), respectively.

We also used the similarity index (SI) to assess the consistency between MAs, and also to measure the consistency between the proposed methods and MAs. Consider two methods X and Y that are used to extract the AIs of an IEGM segment; the SI of X and Y, is defined as the ratio of the time duration that their extracted intervals are similar to the total duration of the segment. To calculate SI between X and Y for an IEGM segment, we first extract the AIs of that segment using methods X and Y. Then, for each method, we assign “1” to the IEGM samples that are in the extracted AIs and “0” to the other samples. Thus, we create two binary streams for X and Y. The SI of X and Y is the average of the logical complement of the exclusive OR (XNOR) of those binary sequences. The SI of two methods varies between zero and one; it tends to one, as the similarity of the specified AIs of the methods increases.
3.4. PROPOSED AI EXTRACTION METHODS

To analyze the regularity of the studied segments, we report the organization index [80] and the number of occurrences [81,82] of them. The organization index, which is the ratio of areas under the dominant frequency (DF) and its first three harmonics to total spectral area from 2.5 Hz up to, but not including, the fifth harmonic can be used to quantify the regularity of IEGM segments; the organization index close to 1 indicates a narrow peak of the DF, and values close to zero indicates broad spectral DF and disorganized AF [80]. The number of occurrences, defined as the percentage number of points along the baseline of the electrogram, is another effective indicator of the AF organization [81,82], that is also reported.

The Wilcoxon signed-rank test [83,84] is used to compare the absolute error of the MCL estimation of the proposed methods; and t-test is used to check if the proposed methods provide biased estimations of the onset, duration and end of AIs (P value less than 0.05 is considered statistically significant).

3.4.5 Other Related Methods

The Teager-Kaiser (TK) energy operator is used in [85,86] for the AI extraction. The nonlinear TK operator uses information of the frequency and the amplitude of electrogram to extract the AIs [52,85–88]; we studied this method (referred to as TK) and compared it with our proposed methods.

In [77], the cycle length iteration (CLI) method is proposed for activation detection, improving the MCL estimation of the commonly used techniques. However, the
CLI method only extracts the local activation times of IEGMs without providing information regarding the duration of AI. Thus, we use the proposed method in [73, 82] to obtain the AD for the AT extracted from CLI; we refer to this method for AI extraction as “CLI-AD”. The AD in [73, 82] is estimated as the length of the window containing 90% of the total activation power, where the activation power is defined as the sum of the squared electrogram on a time window with duration $W$ centered on the estimated activation time. The length of time window used in [73, 82] is 60msec, and in [55] is 90msec, which limits the maximum AD value to 90msec. Here, we use a longer window size of $W = 120$msec as it produces better consistency with the manual annotation. Increasing $W$ beyond 120msec degrades the performance of CLI-AD as in many cases the window with long duration includes more than one AI. The CLI-AD and TK approaches are compared with the proposed methods and manual annotations in terms of the TP, FP, and FN rates, as well as the SI and accuracy of AI estimation.

The inverse of the DF provides an estimate of the MCL without extraction of the AIs of the IEGMs. The DF of the IEGM is estimated from the power spectrum of the IEGM [5, 80], and the accuracy of the estimated MCL ($1/\text{DF}$) is compared with the proposed methods.
3.5 Results and Discussion

3.5.1 IEGM Characteristics

The power of the 324 selected segments was 32.9±60mv²/sec (median 14.4mv²/sec; range 0.1 to 548mv²/sec). Based on the annotated segments, the AD of the AIs was 60.7±29msec (median 55msec; range 11 to 635msec); the MCL of the segments was 182.4±35.7msec (median 173.5msec; range 119.4 to 303.8msec, which is equivalent to 3.3 to 8.4 activations/second). The DF of the segments was 5.6±1.1Hz (median 5.7Hz; range 3.2 to 12.1Hz). The organization index of the studied segments was 0.49±0.11 (median 0.5; range 0.1 to 0.8) and their number of occurrences was 62±14% (median 65%; range 15 to 87%). These reported values confirm that the selected segments are very diverse, and they consist of a wide range of physiologically relevant IEGMs with different levels of complexities/fractionation/organization.

3.5.2 Performance of the Proposed Methods

Table 3.1 shows the TP, FN, FP rates, as well as PPV, of all the extracted AIs from all the segments, when the total number of manually annotated AIs were 12702. The values written in parentheses besides the FP rates (FN rates) show the percentage of FPs (FNs) that were caused by the split (merge) of AIs; where the split AI is defined when more than one AI have overlaps with a single annotated AI, and merged AI is when a single AI is estimated during the occurrence of more than one annotated AI. The TK approach has the highest FNR and this approach has a high tendency to merge AIs. The CLI-AD approach, however, has the highest FPR, and it tends to
Table 3.1: The true positive rate (TPR), positive predictive value (PPV), false negative rate (FNR), and false positive rate (FPR) of all the extracted AIs in percent. The value written in parenthesis beside the FPR (FNR) shows the percentage of FP (FN) that were caused by the split (merge) of AIs.

<table>
<thead>
<tr>
<th>Method</th>
<th>TPR</th>
<th>PPV</th>
<th>FPR (split)</th>
<th>FNR (merge)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGLR LE (3.4)</td>
<td>97.8</td>
<td>98.4</td>
<td>1.6 (34)</td>
<td>1.3 (26.2)</td>
</tr>
<tr>
<td>MGLR Eq (3.7)</td>
<td>97.8</td>
<td>98.6</td>
<td>1.4 (41.1)</td>
<td>1.4 (20.5)</td>
</tr>
<tr>
<td>SFE VD (3.9)</td>
<td>96.3</td>
<td>98.5</td>
<td>1.4 (51.1)</td>
<td>2.9 (3.8)</td>
</tr>
<tr>
<td>SFE VR1 (3.11)</td>
<td>97.1</td>
<td>98.8</td>
<td>1.1 (38.2)</td>
<td>2 (20.5)</td>
</tr>
<tr>
<td>SFE VR2 (3.12)</td>
<td>95.5</td>
<td>99</td>
<td>1 (38.2)</td>
<td>3.5 (19.5)</td>
</tr>
<tr>
<td>TK [85]</td>
<td>86.5</td>
<td>97.9</td>
<td>1.9 (30.3)</td>
<td>4 (87.6)</td>
</tr>
<tr>
<td>CLI-AD [73,77]</td>
<td>94.7</td>
<td>97</td>
<td>2.9 (87.5)</td>
<td>2.8 (11.4)</td>
</tr>
</tbody>
</table>

Error and absolute error (AE) of the onsets, durations, and ends of the TP-extracted AIs, as well as the MCLs for all the segments are reported in Table 3.2. The mean and std of the absolute error of the onset of the AI was smaller than that of the end of the AI for all the proposed methods, except VD.

The reported values in Table 3.2 for the onset, duration and end of the AIs estimation error are based on the TP-extracted AIs. Thus, values in Table 3.1 should be considered while analysing data in Table 3.2. For example, the TPR of the TK method (86.5%) was much smaller than the other studied methods, and many fractionated AIs identified by other methods were missed by TK and consequently not used for error analysis, resulting in improved error for the onset/duration/end of AI estimations. However, the low TPR drastically increased the MCL estimation error of the TK method.

Bias of the extracted features of the AIs of the proposed methods can be obtained
Table 3.2: The error and absolute error (AE) of the activation onset (AO), activation duration (AD), and end of the true positive active intervals, as well as the error and absolute error of the mean cycle length (MCL) of all the segments (all values are in msec). The normalized AE of the AD and MCL estimation for all the segments are reported in percents.

<table>
<thead>
<tr>
<th>Method</th>
<th>AO (annotated - estimated) in msec</th>
<th>AD (annotated - estimated) in msec</th>
<th>end (annotated - estimated) in msec</th>
<th>MCL (annotated - estimated) in msec</th>
<th>AO (estimated) in msec</th>
<th>AD (estimated) in msec</th>
<th>end (estimated) in msec</th>
<th>MCL (estimated) in msec</th>
<th>AD (estimated) in percent</th>
<th>MCL (estimated) in percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE</td>
<td>-2.1±13.1</td>
<td>-9.3±29.1</td>
<td>-11.4±22.7</td>
<td>0.8±10.3</td>
<td>8.6±10.1</td>
<td>20.3±22.9</td>
<td>16.4±19.4</td>
<td>4.1±9.5</td>
<td>36.6±46.2</td>
<td>2±4.6</td>
</tr>
<tr>
<td>Eq</td>
<td>-4.1±13.0</td>
<td>-1.9±25.8</td>
<td>-6.0±19.3</td>
<td>0.1±10.3</td>
<td>8.7±10.5</td>
<td>17.2±19.3</td>
<td>13.0±15.5</td>
<td>4.2±9.4</td>
<td>30±34.7</td>
<td>2.1±4.6</td>
</tr>
<tr>
<td>VD</td>
<td>-18.3±14.1</td>
<td>25.3±25.7</td>
<td>7.0±18.9</td>
<td>-2.0±14.7</td>
<td>18.6±13.7</td>
<td>29.0±21.3</td>
<td>13.3±15.1</td>
<td>5.8±13.7</td>
<td>48.7±27.7</td>
<td>3±8</td>
</tr>
<tr>
<td>VR1</td>
<td>0.4±15.9</td>
<td>-12.6±32.4</td>
<td>-12.3±23.4</td>
<td>-0.8±11.5</td>
<td>10.3±12.1</td>
<td>23.9±25.2</td>
<td>17.4±19.8</td>
<td>4.5±10.6</td>
<td>42.9±49.2</td>
<td>2.3±5.3</td>
</tr>
<tr>
<td>VR2</td>
<td>1.4±17.6</td>
<td>-14.4±35.4</td>
<td>-13.0±25.7</td>
<td>-3.6±12.9</td>
<td>11.1±13.7</td>
<td>26.8±27.3</td>
<td>19.2±21.4</td>
<td>6.4±11.8</td>
<td>47.7±51.3</td>
<td>3.6±6.9</td>
</tr>
<tr>
<td>TK</td>
<td>-1±15.3</td>
<td>2.7±29.6</td>
<td>1.7±22</td>
<td>-19.1±100.5</td>
<td>8.6±12.7</td>
<td>19.4±22.5</td>
<td>13.5±17.4</td>
<td>22.9±99.7</td>
<td>33±33.6</td>
<td>11±42.4</td>
</tr>
<tr>
<td>CLI-AD</td>
<td>-10.9±21.5</td>
<td>10.9±30.9</td>
<td>0.0±25.9</td>
<td>-2.1±19.9</td>
<td>16.5±17.6</td>
<td>24.2±22.2</td>
<td>18.6±18.1</td>
<td>8.1±18.3</td>
<td>34±26.5</td>
<td>4.5±11.3</td>
</tr>
<tr>
<td>DF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-4.2±16.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-19.3±14.3</td>
<td>-</td>
<td>4.9±7.3</td>
</tr>
</tbody>
</table>
by analyzing the difference of the features of TPIs of them and the corresponding AIs of the MAs. Based on the t-test, all the studied methods provide biased estimations of the onset, duration and end of the AIs ($P < 0.0001$), and the amount of bias varies among different methods. For example, the LE method is a biased estimator of the onset of the AI (t-test value: -18.07, degrees of freedom: 12423, std: 13.12, and $P < 0.0001$); however, the amount of bias is negligible as the 95% CI for the bias was between -2. and -1.9msec. The 95% CI for the bias of the onset of the AI for the Eq, VD, VR1, and VR2 were [-4.3,-3.9], [-18.6,-18.1], [0.1,0.7], and [1.1,1.7]msec, respectively. Therefore, the biases of the onset estimation of all the proposed methods, except the VD approach, is negligible. The 95% CIs for the biases of the end of the extracted AIs for the LE, Eq, VD, VR1, and VR2 methods were [-11.8,-11], [-6.3,-5.7], [6.6,7.3], [-12.7,-11.8], [-13.5,-12.6]msec, respectively. On average, LE, Eq, VR1, and VR2 overestimated the end of the AIs; whereas, VD underestimated it. The 95% CIs for the bias of the extracted AI durations for the LE, Eq, VD, VR1, and VR2 methods were [-9.8,-8.8], [-2.4,-1.5], [24.8,25.7], [-13.2,-12.1], and [-15.1,-13.8]msec, respectively. Thus, LE, Eq, VR1 and VR2 overestimated the activation durations; whereas, VD underestimated the duration.

The CIs for the biases of the onset, duration, and end of AIs of the TK method were [-4.9,-4.4], [9.9,10.8], and [5.3,6]msec, respectively; and for the CLI-AD method were [-13.7,-13.2], [14.3,15.1], and [0.9,1.6]msec, respectively.

The reported CIs for biases of AI onset and end can be used to modify the proposed methods. For example, since the VD method, on average, overestimates (underestimates) the start (end) of the AIs, we can add a positive (negative) constant to the
estimated AOs (ends) of the AI, where the constant values should be close to the bias of the VD estimator.

Based on the Wilcoxon signed-rank test, the AE of the MCL of all the proposed methods were significantly less than that of DF and TK. Furthermore, the AE of the MCL of LE and Eq were significantly less than CLI-AD. The mean NAE of the MCL estimation of the proposed methods were less than 4%, and were less than the TK, CLI-AD, and DF methods. The best average NAE of the AD estimation of the TP detected AIs for the studied methods was 30%, achieved by the Eq method. To find an acceptable bound for the NAE of the AD, we considered all the segments that are annotated by both experts and measured the inconsistency among the two annotators; this provided us with a minimum achievable NAE. Assuming that the ADs of one of the MAs were the true values and those from the other one were the estimated values, the NAE of the AD estimation for the segments with two MAs was 25.1±28.2%. Thus, the average NAE of the AD estimation of the Eq method was less than 5% above the absolute normalized difference between annotators. The main reason for the high values of the NAE of the AD estimation (even between annotators) is that for the AIs with a short duration, a small amount of error leads to a high normalized error, and those high values significantly increase the mean and std of the error.

The SIs between the MAs and the LE, Eq, VD, VR1, VR2, TK, and CLI-AD methods for all the segments were 89.2±3.6%, 91.1±3.1%, 84.8±4.2%, 87.7±3.8%, 86.1±4.7%, 85.9±15.5%, and 86.5±4.2%, respectively. The accuracy of the MA depends on many parameters, such as the level of the expertise and fatigue of the
annotator, as well as the SS and amplifying factor during annotation. To verify the accuracy and consistency of the MA and to show that our proposed methods are as effective as the MA, we asked both experts to repeat the annotation for 50 segments with least similarity with the Eq method. The second round of MA was done at least 15 days after the first one; the Eq method was chosen for comparison as it had the highest average SI with MA among the studied methods. The SI between the first and second rounds of MA of E1 was 87±4.2 and for E2 the SI was 91.2±2.7. For the segments that were annotated by both experts, the SI between two MAs was 90±3.3. The SI between two experts for the concatenated segments was 93.2%. The SI between the MAs and the LE, Eq, VD, VR1, VR2, TK, and CLI-AD methods for the concatenated segments were respectively 89.6%, 91.4%, 84.9%, 87.9%, 86.1%, 86.2%, and 86.6% (if more than one annotation was available for a segment, the consistent parts of the MAs were used for the SI calculation). These values show a high level of consistency between our proposed methods and the MAs, e.g., the SI of the Eq method and MA was 98% of the SI between the MAs.

Manual assessment of AIs based on the visual judgement of the IEGMs is very time consuming, and considering the usual density of recording sites per patient, the MA leads to an unacceptable situation during an interventional procedure. To show that the proposed methods are applicable in practice, we analysed all the available IEGMs of 16 patients. For this aim, the IEGMs of all the recording sites were sequentially fed to the MATLAB (Mathworks, Natick, MA) environment and the proposed methods were deployed to extract the AIs of each site. Note that, at each site, 10 bipolar IEGMs that were simultaneously recorded were analysed for AI extraction. In total, the IEGMs of 335 atrial sites with a duration of 27.9±12.3 seconds were analysed.
and the computational time of these processes in a computer equipped with 3.6 GHz Intel® Core™ i7-4790 processor are reported here. The upper quartile computation time required to extract the AIs of one-second IEGMs of 10 bipolar channels using the LE, Eq, VD, VR1, and VR2 methods were 82.2, 65.9, 87.1, 84.8, and 86.7msec, respectively. Thus, less than half a second was required to analyze 5sec (commonly used segment duration) IEGMs of a high density mapping catheter with 10 bipolar electrodes, confirming clinical applicability of the proposed methods.

It is worth emphasizing that modification of the GLR test significantly improved the quality of the proposed methods, as the estimation error of the duration and the end of the AIs extracted from the GLR test was larger than those obtained from the proposed MGLR. For instance, the SI of the LE method that is based on the MGLR was 32.2% higher than that obtained from the GLR, which shows the importance of our modification. The SI improvement achieved by using the MGLR for the Eq, VD, and VR1 methods were 30.2%, 6.5% and 1.8%, respectively; the VR2 does not use the MLLR for the AD estimation, and consequently, did not change.

Also note that the proposed methods do not rely on regular cardiac activations (like those that are present in the tachycardia), and they do not use any independent reference IEGM for time synchronization. This is in contrast to [79, 89], where a reference electrogram, recorded from a catheter placed in the coronary sinus, is used to extract the AI of IEGMs of patients with atrial tachycardia. Here, we only use the local recorded bipolar IEGMs, because in complex arrhythmias, such as the AF, the cardiac electrical activations are temporarily and spatially heterogeneous, and usually, there is no single stable wavefront propagation. Consequently, the proposed
method in [79,89] for the AI estimation cannot be used for AF; however, the local activation time estimation methods in these papers can be used for the extracted AI. For instance, the CoM of the AI or the maximum negative slope of the unipolar electrogram within the AI can be considered as the local activation time [79,89].

Although the maximum negative slope of the unipolar electrogram provides an accurate estimate of the AT, the sensitivity of the unipolar recording to noise contamination and remote activations restricts their clinical application [13]. The bipolar recordings, which are commonly used, on the other hand, only reflect the local activations and was the focus of this chapter. However, morphologies of the activations of the bipolar recordings are influenced by the wavefront orientation with respect to the interpolar axis and also interpolar distance; furthermore, the exact spatial location of the measurement of bipolar recordings is not clear [13,68,90]. The proposed methods in this chapter extract the onset and duration of the AIs and provide a possible time window for AT, which enable us to benefit from the unipolar recording for accurate AT estimation (as described in [79,89]), and compensate the aforementioned drawbacks of processing bipolar recordings.

3.6 Conclusion

In this chapter, we formulated the problem of AI extraction as a sequence of hypothesis tests on the variances of different parts of the IEGMs and derived five TSs for this purpose. The TSs LE in (3.4), Eq in (3.7), VD in (3.9), VR1 in (3.11), and VR2 in (3.12) are extracted based on the modified GLRT or SFET. We verified the proposed methods by applying them to several IEGM segments collected from
sixteen patients with paroxysmal or persistent AF, and showed that the extracted AIs are consistent with those obtained from the expert MA. For example, the TPRs of the LE and Eq was 97.8%, and their FPRs were less than 1.6%. Furthermore, we proposed an efficient method for implementing the TSs and showed that the clinical application of all the proposed methods is feasible. We also used the SI to highlight the improvement achieved by modifying the GLRT; for instance, the SI of the LE method that is based on the proposed MGLR is 32.2% higher than that obtained from the GLR. We showed that the automated analysis/annotation of the IEGMs obtained from human AF is feasible using the proposed methods for the activation assessment. This innovation is a major building block that enables realtime study of the complex activation patterns during arrhythmias.
3.A. Modified GLR test for $P_1$ given in (3.3)

The joint distribution of the independent Gaussian vectors $x_{n,m}$ and $y_{n,m}$ is given in (3.16).

$$f(x_{n,m}, y_{n,m}|m, \theta_{n,m}) = \frac{\exp\left(-\frac{||x_{n,m}||^2}{2\theta_{x,n,m}} - \frac{||y_{n,m}||^2}{2\theta_{y,n,m}}\right)}{(2\pi \theta_{x,n,m})^{\frac{m}{2}}(2\pi \theta_{y,n,m})^T},$$  \hspace{1cm} (3.16)

where $\theta_{n,m}^{\text{def}}=[\theta_{x,n,m}, \theta_{y,n,m}]^T$ is the variance vector.

The GLR test for (3.3) obtained by comparing the log-likelihood ratio (LLR)

$$\text{LLR}^{P_1}_n = \max_{m, \theta_{n,m}} \ln f(x_{n,m}, y_{n,m}|n, m, H_1) - \max_{m, \theta_{n,m}} \ln f(x_{n,m}, y_{n,m}|n, m, H_0)$$

and a threshold [75]. The optimization of the LLR over $m$ leads to a sequence of tests with a different number of IEGM samples under two hypotheses. Thus, we propose to modify the LLR in order to account for different sample sizes under $H_0$ and $H_1$. 

Appendix

3.A Modified GLR test for $P_1$ given in (3.3)
3.A. MODIFIED GLR TEST FOR $P_1$ GIVEN IN (3.3)

We propose the following Modified GLR (MGLR)

$$\text{MGLR} : \text{MLLR}^P_{n_{\mathcal{H}_1}} \gtrless \eta,$$

where the MLLR is the LLR divided by the number of samples as

$$\text{MLLR}^P_{n_{\mathcal{H}_1}} = \max_{m, \theta_{n,m}} \frac{\ln f(x_{n,m}, y_{n,m} | n, m, \mathcal{H}_1)}{m + 2T} - \max_{m, \theta_{n,m}} \frac{\ln f(x_{n,m}, y_{n,m} | n, m, \mathcal{H}_0)}{m_0 + 2T}. \quad (3.17)$$

Maximization of the LLR in the GLRT usually leads to the $m$ which is larger than the AD. However, the normalization factor $m + 2T$ that is included in the MLLR effectively restricts the overestimation of the ADs in the MGLRT.

The MLLR can be expressed as

$$\text{MLLR}^P_{n_{\mathcal{H}_1}} = \max_{m_1} \left( \max_{\theta_{n,m}} \frac{\ln f(x_{n,m_1}, y_{n,m_1} | n, m_1, \mathcal{H}_1)}{m_1 + 2T} \right) - \max_{m_0} \left( \max_{\theta_{n,m}} \frac{\ln f(x_{n,m_0}, y_{n,m_0} | n, m_0, \mathcal{H}_0)}{m_0 + 2T} \right), \quad (3.18)$$

$$= \max_{m_1} \left( \max_{\theta_{n,m}} \frac{\ln f(x_{n,m_1}, y_{n,m_1} | n, m_1)}{m_1 + 2T} \right) - \max_{m_0} \left( \max_{\theta_{n,m}} \frac{\ln f(x_{n,m_0}, y_{n,m_0} | n, m_0)}{m_0 + 2T} \right), \quad (3.19)$$

To simplify MLLR$^P_{n}$, we first solve the inner optimizations in (3.19) [91], i.e., find the maximum likelihood (ML) estimates of $\theta_{x,n,m}$ and $\theta_{y,n,m}$ under $\mathcal{H}_0$ and $\mathcal{H}_1$ and substitute the ML estimates in (3.19). The ML estimates of $\theta_{x,n,m}$ and $\theta_{y,n,m}$ under
\( H_0 \) denoted respectively by \( \hat{\theta}_{x,n,m|H_0} \) and \( \hat{\theta}_{y,n,m|H_0} \) can be obtained from

\[
[\hat{\theta}_{x,n,m|H_0}, \hat{\theta}_{y,n,m|H_0}] = \arg \max_{\theta_{n,m}} f(x_{n,m}, y_{n,m}|n, m)
\]

\[
\text{s.t. } \theta_{x,n,m} \leq \theta_{y,n,m}
\]

Consider the relaxed version of (3.20) in which constraint \( \theta_{x,n,m} \leq \theta_{y,n,m} \) does not exist. For the relaxed problem, the ML estimates of variances is found by setting the derivative of the pdf in (3.16) with respect to variances equal to zero, i.e.,

\[
\frac{\partial f(x_{n,m}, y_{n,m}|n, m, H_0)}{\partial \theta_{x,n,m}} = 0,
\]

\[
\frac{\partial f(x_{n,m}, y_{n,m}|n, m, H_0)}{\partial \theta_{y,n,m}} = 0.
\]

The following \( \hat{\theta}_{x,n,m} \) and \( \hat{\theta}_{y,n,m} \) satisfy (3.21) and (3.22)

\[
\hat{\theta}_{x,n,m} = \frac{||x_{n,m}||^2}{m} \quad \text{and} \quad \hat{\theta}_{y,n,m} = \frac{||y_{n,m}||^2}{2T}.
\]

If \( \hat{\theta}_{x,n,m} \leq \hat{\theta}_{y,n,m} \), i.e., \( ||x_{n,m}||^2/m \leq ||y_{n,m}||^2/2T \), the solution of the relaxed problem is the same as the solution of the original problem, and we conclude that \( \hat{\theta}_{x,n,m|H_0} = \hat{\theta}_{x,n,m} \) and \( \hat{\theta}_{y,n,m|H_0} = \hat{\theta}_{y,n,m} \). Note that in this case \( \hat{\theta}_{y,n,m|H_0} \geq \hat{\theta}_{x,n,m|H_0} \), and the estimated variances are the critical points of \( f(x_{n,m}, y_{n,m}|n, m, H_0) \) as they satisfy (3.21) and (3.22).

If \( \hat{\theta}_{x,n,m} > \hat{\theta}_{y,n,m} \), or equivalently, \( ||x_{n,m}||^2/m > ||y_{n,m}||^2/2T \), this suggests that the variance of the segment \( x_{n,m} \) is larger than the variance of the segment \( y_{n,m} \), which is not consistent with the assumption under \( H_0 \). Thus, in this case, the solution of the
relaxed problem is not the same as the solution of (3.20), and we conclude that the solution of (3.20) is located on the boundary of the constraint. Thus, we conclude that the estimated variance of both $x_{n,m}$ and $y_{n,m}$ should be equal to 

$$\hat{\theta}_{x,n,m|\mathcal{H}_0} = \frac{1}{m+2T}(|x_{n,m}|^2 + |y_{n,m}|^2).$$

Combining the above results, the ML estimates of the variances of the $x_{n,m}$ and $y_{n,m}$ under $\mathcal{H}_0$ is

$$\hat{\theta}_{x,n,m|\mathcal{H}_0} = \begin{cases} \frac{|x_{n,m}|^2}{m}, & \text{if } \frac{|x_{n,m}|^2}{m} \leq \frac{|y_{n,m}|^2}{2T} \\ \frac{|x_{n,m}|^2 + |y_{n,m}|^2}{m + 2T}, & \text{if } \frac{|x_{n,m}|^2}{m} > \frac{|y_{n,m}|^2}{2T} \end{cases} \tag{3.24}$$

and

$$\hat{\theta}_{y,n,m|\mathcal{H}_0} = \begin{cases} \frac{|y_{n,m}|^2}{2T}, & \text{if } \frac{|x_{n,m}|^2}{m} \leq \frac{|y_{n,m}|^2}{2T} \\ \frac{|x_{n,m}|^2 + |y_{n,m}|^2}{m + 2T}, & \text{if } \frac{|x_{n,m}|^2}{m} > \frac{|y_{n,m}|^2}{2T} \end{cases} \tag{3.25}$$

respectively. Similarly the ML estimates of the variances of $x_{n,m}$ and $y_{n,m}$ under $\mathcal{H}_1$ are respectively

$$\hat{\theta}_{x,n,m|\mathcal{H}_1} = \begin{cases} \frac{|x_{n,m}|^2}{m}, & \text{if } \frac{|x_{n,m}|^2}{m} \leq \frac{|y_{n,m}|^2}{2T} \\ \frac{|x_{n,m}|^2 + |y_{n,m}|^2}{m + 2T}, & \text{if } \frac{|x_{n,m}|^2}{m} > \frac{|y_{n,m}|^2}{2T} \end{cases} \tag{3.26}$$

and

$$\hat{\theta}_{y,n,m|\mathcal{H}_1} = \begin{cases} \frac{|y_{n,m}|^2}{2T}, & \text{if } \frac{|x_{n,m}|^2}{m} \leq \frac{|y_{n,m}|^2}{2T} \\ \frac{|x_{n,m}|^2 + |y_{n,m}|^2}{m + 2T}, & \text{if } \frac{|x_{n,m}|^2}{m} > \frac{|y_{n,m}|^2}{2T} \end{cases} \tag{3.27}$$
3.B Modified GLR test for \( P_2 \) given in (3.5)

\[
\ln f(x_{n,m}, y_{n,m} | \hat{\theta}_{n,m} | H_0) = \begin{cases} 
-\Phi([x_{n,m}^T, y_{n,m}^T]^T) & \text{if } \frac{|x_{n,m}|^2}{m} > \frac{|y_{n,m}|^2}{2T} \\
-\Phi(x_{n,m}) - \Phi(y_{n,m}) & \text{if } \frac{|x_{n,m}|^2}{m} \leq \frac{|y_{n,m}|^2}{2T}
\end{cases}
\]

(3.29)

\[
\ln f(x_{n,m}, y_{n,m} | \hat{\theta}_{n,m} | H_1) = \begin{cases} 
-\Phi(x_{n,m}) - \Phi(y_{n,m}) & \text{if } \frac{|x_{n,m}|^2}{m} > \frac{|y_{n,m}|^2}{2T} \\
-\Phi([x_{n,m}^T, y_{n,m}^T]^T) & \text{if } \frac{|x_{n,m}|^2}{m} \leq \frac{|y_{n,m}|^2}{2T}
\end{cases}
\]

(3.30)

Substituting \( \hat{\theta}_{y,n,m|H_j} \) and \( \hat{\theta}_{x,n,m|H_j} \) for \( j = 0, 1 \) back into MLLR\(_t^{P_1}\), the MGLR test becomes as

\[
\text{MLLR}_{t}^{P_1} = \max_{m_1} \frac{\ln f(x_{n,m_1}, y_{n,m_1} | \hat{\theta}_{n,m_1} | H_1)}{m_1 + 2T} - \max_{m_0} \frac{\ln f(x_{n,m_0}, y_{n,m_0} | \hat{\theta}_{n,m_0} | H_0)}{m_0 + 2T} \overset{H_1}{\underset{H_0}{\gtrless}} \eta
\]

(3.28)

where \( f(x_{n,m}, y_{n,m} | \hat{\theta}_{n,m} | H_0) \) and \( f(x_{n,m}, y_{n,m} | \hat{\theta}_{n,m} | H_1) \) are defined in (3.29) and (3.30), respectively.

Using (3.29) and (3.30) in (3.28), we simplify MLLR\(_{t}^{P_1}\) as (3.4).

3.B Modified GLR test for \( P_2 \) given in (3.5)

Considering the problem (3.5), the joint pdf of \( x \) and \( y \) under \( H_1 \) is similar to test \( P_1 \) and under \( H_0 \) is

\[
f(x_{n,m_1}, y_{n,m_1} | n, m_1, H_0) = \frac{\exp\left(-\frac{|x_{n,m_1}|^2 + |y_{n,m_1}|^2}{2\theta_{n,m_1}}\right)}{(2\pi\theta_{n,m_1})^{m_1 + 2T/2}},
\]

(3.31)
The MGLR test for $\mathcal{P}_2$ obtained by comparing the following MLLR and a threshold

$$
\text{MLLR}_n^{\mathcal{P}_2} = \max_m \left( \max_{\theta_{n,m}} \ln f(x_{n,m}, y_{n,m} | n, m, \mathcal{H}_1) \right) - \max_{\theta_{n,m_1}} \ln f(x_{n,m_1}, y_{n,m_1} | n, m_1, \mathcal{H}_0) \right),
$$

Following the same approach as in Appendix 3.A, the ML estimate of $\theta_{n,m_1}$ under $\mathcal{H}_0$ becomes

$$
\hat{\theta}^2_{n,m_1 | \mathcal{H}_0} = \frac{||x_{n,m_1}||^2 + ||y_{n,m_1}||^2}{m_1 + 2T},
$$

and the ML estimates of $\theta_{x,n,m}$ and $\theta_{y,n,m}$ under $\mathcal{H}_1$ are respectively given in (3.26) and (3.27). Substituting estimated variances back into MLLR$^{\mathcal{P}_2}_t$, the MGLR test becomes as (3.7).

3.C Proof of Lemma 1

The joint pdf of $x_{n,m}$ and $y_{n,m}$ when $\theta_{x,n,m}$ and $\theta_{y,n,m}$ are members of $\Theta_0 \cup \Theta_1$ can be written as

$$
f(x_{n,m}, y_{n,m} | \theta_{n,m}) = \exp\left( -\frac{||x_{n,m}||^2 - ||y_{n,m}||^2}{2\theta_{x,n,m}} \right) \frac{1}{(2\pi \theta_{x,n,m})^{\frac{1}{2}} (2\pi \theta_{y,n,m})^{\frac{1}{2}}}.
$$
Here, to find the efficient estimator (or MVUE) of \( g_1(\theta_{n,m}) = [1, -1] \theta_{n,m} \), we use Cramer-Rao Lower Bound (CRLB) [92]. The above pdf satisfies the regularity condition, i.e.,

\[
E \left[ \frac{\partial \ln f(x_{n,m}, y_{n,m}|\theta_{n,m})}{\partial \theta_{n,m}} \right] = 0, \tag{3.35}
\]

and the Fisher information matrix for \( \theta_{n,m} \) is [92]

\[
\mathcal{I}(\theta_{n,m}) = \begin{bmatrix}
\frac{m}{2 \sigma^2_{x,n,m}} & 0 \\
0 & \frac{2T}{2 \sigma^2_{y,n,m}}
\end{bmatrix}. \tag{3.36}
\]

It can be shown that the following equation is valid

\[
\frac{\partial g_1(\theta_{n,m})}{\partial \theta^T_{n,m}} \mathcal{I}(\theta_{n,m})^{-1} \frac{\partial \ln f(x_{n,m}, y_{n,m}|\theta_{n,m})}{\partial \theta_{n,m}} = \frac{m}{T_1(x_{n,m}, y_{n,m})} \frac{||x_{n,m}||^2}{m} - \frac{||y_{n,m}||^2}{2T} - \frac{(\theta_{x,n,m} - \theta_{y,n,m})}{g_1(\theta_{n,m})}, \tag{3.37}
\]

where \( \frac{\partial g_1(\theta_{n,m})}{\partial \theta^T_{n,m}} = [1, -1] \). Consequently, based on [92], we conclude that the MVUE for \( g_1(\theta_{n,m}) \) is \( T_1(x_{n,m}, y_{n,m}) \) given in (3.8).
3.D Proof of Lemma 2

Following the same procedure as in Appendix 3.C, we obtain

$$\frac{\partial g_2(\theta_{n,m})}{\partial \theta_{n,m}^T} I(\theta_{n,m})^{-1} \frac{\partial \ln f(x_{n,m}, y_{n,m}|\theta_{n,m})}{\partial \theta_{n,m}} =$$

$$\frac{\|y_{n,m}\|^2}{2T \theta_{y,n,m}} \left( \frac{2T\|x_{n,m}\|^2}{m\|y_{n,m}\|^2} - 1 - \left( \frac{\theta_{x,n,m}}{\theta_{y,n,m}} - 1 \right) \right), \quad (3.38)$$

where $\partial g_2(\theta_{n,m})/\partial \theta_{n,m}^T = [\theta_{y,n,m}^{-1}, -\theta_{x,n,m}\theta_{y,n,m}^{-2}]$. Since $h(\theta_{n,m}, y_{n,m})$ depends on both $\theta_{n,m}$ and $y_{n,m}$, we conclude that the MVUE does not exist.
Part III

Localizing Spiral Rotor Sources
Chapter 4

Localization of the Ectopic Spiral Electrical Source Using Intracardiac Electrograms During Atrial Fibrillation

4.1 Abstract

Multiple ectopic electrical sources in the atria are believed to sustain AF. Catheter-based ablation of these sources is considered an effective AF treatment. In this chapter, based on the Hough transform (HT), we propose a general framework that processes the atrial intracardiac electrograms (IEGMs) to localize the core/center point/focus of an ectopic source with a spiral wavefront shape. Using the locations of the catheter’s electrodes and the activation times of the IEGMs, we provide a method that can estimate the location of the core of a spiral wavefront to be eliminated by ablation. By providing various examples, it is shown that the proposed method can accurately localize the center point of the spiral wavefront also known as spiral rotor.
4.2 Introduction

As we discussed in Chapter 1 (see Section 1.4), despite the significant prevalence of AF, the perpetuating sources are not clearly known [15]. Investigation of atrial intracardiac electrograms (IEGMs) has shown that multiple ectopic electrical sources in the atria are believed to sustain AF [15,16]. Catheter-based ablation of these sources, in addition to the isolation of the pulmonary veins [27], are considered as common treatment of the different types of AF (paroxysmal, persistent, and permanent) [16].

Available commercial software that is used for AF ablation therapy mainly suggests the areas with complex fractionated electrograms (CFAEs) or regions with high dominant frequency to be ablated [42,43]. Although the algorithms used in these programs are able to process the IEGMs in real-time and are computationally efficient, available clinical data shows that the success rate of ablation therapy based on them is not satisfactory [45], justifying further research in this field.

Significant interest was generated from the work of Jalife showing clear rotor activity in experimental models of AF [48], and multiple rotors have recently been visualised in humans during AF by use of large basket catheters [35–37]. Based on these findings, the main objective in this chapter is to localize the tip of spiral wave reentries as it is believed that the success of the ablation therapy highly depends on the accuracy of localizing the focal and rotor sources [26, 35–37, 48, 93]. Estimating the location of the tips/center points/foci of the rotors from IEGMs as ablation candidates is very challenging and is investigated here. Note that none of the available commercial software used for the ablation therapy procedure is able to localize the
tips of the spiral wavefronts during AF.

Based on the Hough transform (HT) [49, 94–97], we propose a general framework to estimate unknown parameters of the electrical propagation waves with arbitrary parametric shapes. The HT was originally proposed in 1962 as a computationally efficient procedure for detecting lines in binary edge images [49]. Since then, it has become a very powerful processing tool in different fields and deployed not only to detect lines, but also for general curve fitting [94–97]. Here, the HT is used to find the tip of the different types of spiral wave reentries (e.g., the arithmetic/Archimedean and logarithmic spirals).

In this chapter, we assume that only one spiral wavelet propagates at the recording site, and we propose a method to estimate its tip from the IEGM’s activation times. We also assume that the propagation wave belongs to the specific family of spirals (e.g., arithmetic spiral) and estimate all the unknown parameters in that family in a two-dimensional plane. Our computer simulations show that the proposed method accurately estimates the position of the tip of the spiral.

4.3 Localizing the Tip of the Spiral Rotor

Here, we assume that the electrical wave propagation path is an arithmetic spiral; generalization of the proposed method for other waveforms is straightforward. Suppose complex points \( \{Z_i\}_{i=1}^{N} \) are located on the arithmetic spiral whose tip is located at \( P \), and the spiral rotates with the fixed angular speed \( w \). The following equation
shows the relation between $Z_i$ and the spiral parameters

$$Z_i = a\theta_i e^{j(\theta_i + \omega t_i + \theta_0)} + P, \quad (4.1)$$

where $\theta_i$ is the polar phase of $Z_i$ with respect to the origin $P$, $t_i$ is the time value, $\theta_0$ is the initial rotation phase of the spiral, $j = \sqrt{-1}$, and $a > 0$ determines the distance between successive turnings/arms of the spiral (see Figure 4.1).

Figure 4.1: Arithmetic/Archimedean spiral $Z_i = a\theta_i e^{j\theta_i} + P$ for $0 \leq \theta_i \leq 3\pi$ with its tip located at $P$

Given $\{Z_i, t_i\}$, we explain how the HT algorithm can be used to localize the rotor’s tip. To ease the understanding of the HT-based approach, we use a simple example through this section. First, we assume that the parameters $a, \theta_0$, and $w$ are known, and our goal is to estimate $P$. Later, we generalize the problem for the case where all the spiral’s parameters are unknown. Consider the scenario shown in Figure 4.2 where the spiral wavefront rotates and hits sensors $S_1, S_2, \text{and } S_3$ at time $t_1, t_2, \text{and}$
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

$t_3$, respectively. The measured signal from the catheter’s electrodes/sensors (IEGMs) are shown in Figure 4.3. Note that here we assume that the activation times (ATs) of electrodes are accurately known; in practice, these values are estimated [3, 5, 78].

Figure 4.2: Spiral wavefront that rotates clockwise with angular speed of $w$ and hits three sensors/electrodes

Figure 4.3: From top to bottom ($V_1$ to $V_3$): the IEGMs of sensors $S_1, S_2$, and $S_3$ in Fig. 4.2 that are hit by the spiral wavefront
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

Using (4.1), the spiral center $P$ can be obtained from

$$P = Z_i - a\theta_i e^{j(\theta_i + wt_i + \theta_0)}.$$  \hspace{1cm} (4.2)

Since the spiral hits the $i$th sensor at time $t_i$, the location of $S_i$, denoted by $Z_{Si}$, should satisfy the rotor equation (4.1) at time $t_i$; meanwhile, as $P$ is unknown, we are unaware of $\theta_{Si}$. If $(a, w, \theta_0)$ is known, for any $Z_{Si}$, we can obtain all possible values for $P$ by considering feasible $\theta_{Si}$ in (4.2), e.g., we may assume that $\theta_{Si} \in [0, 7]$ and obtain all the corresponding locations for $P$. Thus, location of the sensor and its ATs can be used to obtain the candidate curve for the probable tip locations. In other words, each sensor for each AT proposes the points on a curve as the candidates for being the rotor’s tip. Red, green, and blue curves in Figure 4.4 show the location of the points that have been suggested by the first, second, and third sensors, respectively. The intersections of these curves are marked with circles and show the candidate points that two or three sensors agreed on. The number written on the circle shows the number of curves that intersected at that point (number of votes that specific intersection point has received). The intersection point with the largest number is very likely to be the center of the spiral. This figure shows that all three candidate curves plotted in the $P$-plane/space intersect at only one point, i.e., the three sensors agreed on one candidate point which matches the location of the rotor’s tip. We showed how the center of the spiral can be localized by finding the intersection of several candidate curves which are plotted in the unknown-parameter-plane ($P$-plane in this example). In practice, the above procedure can be implemented using the HT algorithm, as we will briefly explain it using the previous example. Consider limited number of $\theta_j \in [0, 7]$, e.g., $\theta_j = 7(j - 1)/50$, $j = 1, \ldots, 50$; for each $\theta_j, t_i$ and $Z_{Si}$
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

\begin{align*}
\{P\} &= Z_{S1} - a\theta e^{i(\theta + wt_1 + \theta_0)} \\
\{P\} &= Z_{S2} - a\theta e^{i(\theta + wt_2 + \theta_0)} \\
\{P\} &= Z_{S3} - a\theta e^{i(\theta + wt_3 + \theta_0)}
\end{align*}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{tip_of_rotor}
\caption{Potential locations for rotor’s tip obtained using (4.2) with known \(\{w, t_i, \theta_0, a = 1\}\) for \(\theta_{S_i} \in [0, 7]\)}
\end{figure}

we can obtain the corresponding value for \(P\). Figure 4.5 shows the candidate \(P\)s obtained from \(S_1\), \(S_2\) and \(S_3\) with red, green, and blue dots, respectively. Indeed, each sensor uses its location and AT to suggest 50 points as possible tip locations. In the next step, we create a two-dimensional *accumulator array* \((AA)\). The dimension of this array is equal to the dimension of the unknown parameter space. Since the only unknown parameter in this example is \(P\), the unknown space, and therefore, the AA are two-dimensional (one dimension for the real and one for the imaginary part of \(P\)). Each element of the AA corresponds to a small area in the parameter space. This is shown in Figure 4.5 where each small square grid box is associated with one element of the AA. Note that the size of squares determines the accuracy of the
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

Figure 4.5: Practical implementation of the HT-based method for tip localization. Each small box/square in the plotted grid is associated with an element in the AA, and the number in it shows the number of candidate points that fall in the square. The center of the areas associated with the AA’s elements with value 5 are considered as the estimated tip locations (see the enlarged area).

analysis. We assign a number to each AA’s element that represents the number of the candidate points that fall in the corresponding area of that element. The assigned numbers to the unknown space grids or the AA are shown in Figure 4.5. Finally, by finding the largest AA’s elements, we can estimate the location of the rotor’s tip. For this example, we conclude that the tip is located in the areas associated with the AA’s elements with value 5 (see the enlarged area in Figure 4.5).

We described the proposed approach to estimate $P$ when $(a, w, \theta_0)$ is known.
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

Generalization of the HT-based method to the case with more unknown parameters is straightforward and described here. Suppose that \((a, w, \theta_0)\) is unknown, and it can be any member of \(\Theta = \{(a_1, w_1, \theta_{0,1}), \cdots, (a_L, w_L, \theta_{0,L})\}\). For any triplet in \(\Theta\), we can follow the same procedure as before and create the AA (we should create \(L\) AAs where \(L\) is the cardinality of \(\Theta\)). Among all the generated AAs, the one with the largest maximum value determines the unknown \((a, w, \theta_0)\) and that AA can be used for tip localization.

Let us now assume that \(a\) among \((a, w, \theta_0)\) is unknown and can be \(a = 0.5, 1, \) or 1.5.
1.5, i.e.,
\[ \Theta = \{(0.5, w, \theta_0), (1, w, \theta_0), (1.5, w, \theta_0)\} \].

We form three AAs associated with the elements of \( \Theta \). Three sub-figures in Figure 4.6(a) show the candidate points associated to the three elements of \( \Theta \) when \( S_1 \) and \( S_2 \) are used, e.g., the right sub-figure shows the suggested points by \( S_1 \) and \( S_2 \) using their ATs and assuming that \( a = 1.5 \); whereas, the left sub-figure is a similar plot assuming \( a = 0.5 \). Since the maximum values in the AAs\(^1\) associated with different \( a \)s are equal to two, we cannot properly estimate \( a \) using only \( S_1 \) and \( S_2 \). This is because all the intersection points in the three sub-figures received the same amount of votes and are equally likely the location of the spiral’s tip. Figure 4.6(b) shows the plots associated with the three elements of \( \Theta \) when \( S_1, S_2 \) and \( S_3 \) are used. The maximum value of the AAs associated with \( a = 0.5 \) or \( a = 1.5 \) is two; whereas, the maximum value of the AA associated with \( a = 1 \) is three. Thus, the estimated value for \( a \) is one, and the middle sub-figure in Figure 4.6(b) should be used to obtain the rotor’s tip.

All the potential candidates for being the tip of the rotor that have been confirmed by at least two sensors are shown in Figure 4.7. It is clear that if we only use the IEGM of the first and second sensors, there are seven probable values for \( P \), i.e., we have seven candidates who have each received two votes (one from \( S_1 \) and one from \( S_2 \)). However, when we consider all three sensors, there is only one point that all three agreed on and this point is associated with \( a = 1 \). Note that if \( a \) is known, there are only two candidates after using \( S_1 \) and \( S_2 \) (see the yellow circles in Figure 4.7(a));

\(^1\)We assume that the AA’s grid size is small enough that each grid box cannot contain two different candidate points.
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

Estimated tip

Tip of the rotor

(a) Probable tip locations obtained using the locations and ATs of $S_1$ and $S_2$. All candidate points similarly have been confirmed by two sensors.

(b) Probable tip locations obtained using the locations and ATs of $S_1$, $S_2$, and $S_3$. Only one point has been confirmed by three sensors.

Figure 4.7: Candidate tip locations that have been confirmed by at least two sensors when $a$ is unknown. The number written on the circle shows the number of votes that each specific point has received; the color of the circle shows the corresponding estimated value for $a$, e.g., white circles correspond to $a = 1.5$.

whereas, having ambiguity regarding the value of $a$ increases the number of potential tip locations (see Figure 4.7(a)).

In the next example, we explain the tip localization when $\theta_0$ is unknown. Consider the circular catheter with nine sensors and the spiral wavefront as shown in Figure 4.8. If $\theta_0$ is unknown, similar to the case of unknown $a$, we have to generate several AAs, each associated with a specific $\theta_0 \in [0, 2\pi]$ and the estimated $\theta_0$ is obtained from the AA with the largest maximum element.

Let us now assume that $\theta_0$ can be $\theta_0 = 0, \pi/2, \pi$, or $3\pi/2$, i.e.,

$$\Theta = \{(a, w, 0), (a, w, \pi/2), (a, w, \pi), (a, w, 3\pi/2)\}.$$
4.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

(a) Spiral wavefront rotates clockwise and hits nine sensors on the circular catheter

(b) The rotor’s tip is the intersection of several curves obtained using the location and ATs of the sensors

Figure 4.8: Spiral wave rotates clockwise with angular speed of \( w \) and hits \( i \)th sensor located at \( Z_{Si} \) at time \( t_i \). When \((a, w, \theta_0)\) is known, the rotor’s tip is the intersection of curves \( P = Z_{Si} - a\theta e^{j(\theta + wt_i)} \) for \( i = 1, \ldots, 9, \theta \in [0, 7] \).

We create four AAs associated with the elements of \( \Theta \). Each AA can be represented by a gray scale image as shown in Figure 4.9. To create these images, each element of the AAs is shown with a pixel where the higher the value of that element, the darker that pixel is represented, i.e., the element of the AA with zero value is shown with white, and the element with a value equal to nine is shown with black. The darkest pixel among all the sub-figures is in sub-figure 4.9(a) associated with \( \theta_0 = 0 \). Thus, we conclude that \( \theta_0 \) must be zero, and using sub-figure 4.9(a), we localize the rotor’s tip.

We discussed the tip localization when \( \theta_0 \) is unknown. If both \( a \) and \( \theta_0 \) are unknown, we can pursue a similar approach and create several AAs, each associated with a member of unknown space. For instance, suppose \( a \) and \( \theta_0 \) are unknown; and \( \theta_0 \) can be \( 0, \pi/2, \pi, \) or \( 3\pi/2 \), and \( a \) can be \( 0.5, 1, \) or \( 1.5 \). For this case, the unknown
Figure 4.9: Gray scale images generated from the AAs of the example in Figure 4.8 for different $\theta_0$. Each sub-figure represents an AA. Each element of the AA is shown with a pixel where the higher the value of that element, the darker that pixel is represented. The darkest pixel among all the sub-figures is in sub-figure 4.9(a), which suggests that $\theta_0$ is zero and also shows the rotor’s tip.
Figure 4.10: (a) The Mapping catheter is used to measure a spiral wavefront with its tip on the circle with radius $R$; (b) MSE of estimation of the rotor tip in cm\(^2\) as a function of $R$

Parameter space becomes

$$\Theta = \{(0.5, w, 0), (0.5, w, \pi/2), (0.5, w, \pi), (0.5, w, 3\pi/2),$$

$$\quad (1, w, 0), (1, w, \pi/2), (1, w, \pi), (1, w, 3\pi/2), (1.5, w, 0),$$

$$\quad (1.5, w, \pi/2), (1.5, w, \pi), (1.5, w, 3\pi/2)\}.$$ 

Thus, we have to form 12 AAs corresponding to the members of $\Theta$ and follow the same procedure as before. This example shows that the computational complexity (CC) of the HT-based approach significantly increases as the unknown parameters of the spiral increases\(^2\).

\(^2\)In practice, the CC is significantly higher than the described example because, here, only three (four) values are considered as the candidates for $a (\theta_0)$ which leads to the very low/poor resolutions in the $a (\theta_0)$-space.
is 1 cm) with nine electrodes that is used to localize the tip of the rotor. We consider 90 different locations on a circle with a radius $R$ as the rotor’s tip (see Figure 4.10(a)) and estimate $P$ using the proposed method assuming that $2\pi a = 3$ cm, $w = 70$ Rad/S are known. To create the AA, we assume that $|\text{Re}\{P\}| < 7$ cm and $|\text{Im}\{P\}| < 7$ cm. The grid sizes for searching in $P$-plane and $\theta_0$-plane are 1 or 0.5 cm and 3 degrees, respectively. Figure 4.10(b) shows the average mean squared error (MSE) of estimating the tip location as a function of distance from the center of the mapping catheter ($R$). This figure shows that the proposed method can localize the tip of the rotor accurately, and as we expect, the MSE of the localization is an increasing function of $R$ where the farther the rotor tip is from the center, the higher the tip localization error. This figure also shows that we can decrease the MSE by decreasing the grid size of searching in $P$-plane; however, this increases the computation complexity of the proposed method.

4.4 Conclusion

Catheter-based ablation of ectopic electrical sources in atria is a minimally invasive AF treatment. Estimating the location of the tips of the rotors from IEGMs as ablation suspicious regions is a challenging and critical issue. Herein, based on the HT, we proposed a general framework to estimate unknown parameters of the electrical propagation wave with an arbitrary parametric shape. We assumed that the propagation wave is an arithmetic spiral in a two-dimensional plane and estimated all of its unknown parameters, including the tip location. For this, using the activation times of the atrial IEGMs and the location of the catheter’s electrodes, we proposed
4.4. CONCLUSION

a method to estimate the location of the tip of a spiral rotor to be eliminated by ablation. Using synthetic IEGMs and through several examples, it was shown that the proposed framework can accurately localize the tip of the spiral rotor.
Chapter 5

Computationally Efficient Method for Localizing the Spiral Rotor Source Using Synthetic Intracardiac Electrograms During Atrial Fibrillation

5.1 Abstract

Recent studies suggest that the spiral rotors are among perpetuating sources of AF, and it is believed that the success rate of ablation therapy might be improved significantly by localizing and ablating the tip/core of rotors in atria. In this chapter, using simulated atrial IEGMs during AF, we propose a computationally efficient method for localizing the tip of the electrical rotor with an Archimedean/arithmetic spiral wavefront. The proposed method deploys the locations of electrodes of a catheter and their IEGMs activation times to estimate the unknown parameters of the spiral
wavefront including its tip location. The proposed method is able to localize the spiral as soon as the wave hits three electrodes of the catheter. Our simulation results show that the method can efficiently localize the spiral wavefront that rotates either clockwise or counterclockwise.

5.2 Introduction

As we discussed earlier, mechanisms initiating and sustaining AF are very complex and not clearly known [15,17]. Recent studies suggest that the spiral wavefronts (also known as rotors) are among perpetuating sources of AF, and it is believed that the success rate of ablation therapy might be improved significantly by localizing and ablating the tip/phase-singularity/core of rotors in atria [26,35–37,48,93]. Since none of the available commercial software currently used for the ablation therapy procedure [98] is designed to find spiral wavefronts, localizing spiral rotors has gained increasing attention over the past few years [35–37,48,57].

In [57], localization of a single Archimedean spiral wavefront with unknown parameters, including unknown angular speed ($w$), initial rotation phase ($\theta_0$), distance between successive arms of the spiral ($a$), and location of its tip ($P$) is studied. There, the Hough transform is used to reduce the computational complexity (CC) of tip localization; however, the CC of the proposed method in [57] is still high, as it requires a three-dimensional search over ($w, a, \theta_0$).

In this chapter, we consider a more general case where the spiral wavefront rotation direction is also unknown and can be either clockwise (CW) or counterclockwise
(CCW). Assuming that the activation times (ATs) of the IEGMs and locations of electrodes of a catheter are known, we propose a method with significantly less CC to estimate all the wavefront parameters. The proposed method requires the ATs of at least three electrodes; the ATs of more electrodes can be deployed to reduce the tip localization error.

5.3 Localizing the Tip of the Spiral Rotor

In this chapter, we assume that the recorded IEGMs at each catheter location are due to the electrical activities of a single arithmetic/Archemidean spiral wavefront that rotate either CW or CCW. We only consider 2-dimensional geometry and assume that all the catheter’s electrodes and the rotor are in the same plane. Given the ATs of the electrograms [2, 3, 78] and location of the electrodes [99–101], our objective is to localize tip of the spiral wavefront.

Suppose complex point \( Z_i \), at time \( t_i \), is located on the arithmetic spiral whose tip is located at \( P \), and the spiral rotates CW with the fixed angular speed \( w \). The relationship between \( Z_i \) and the spiral parameters can be expressed as

\[
Z_i = a \theta_i e^{j(\theta_i - wt_i + \theta_0)} + P,
\]

where \( \theta_i \) is the polar phase of \( Z_i \) with respect to the origin \( P \), \( \theta_0 \) is the initial rotation phase of the spiral, and \( a > 0 \) determines the distance between successive turnings/arms of the spiral (see Figure 1 in [57]). Similarly, the following equation
5.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

\[ Z = a\theta e^{j(\theta_0 - wt)} + P \]

Wavefront rotates clockwise

\[ Z = a\theta e^{-j(\theta + \theta_0 - wt + \pi)} + P \]

Wavefront rotates counterclockwise

Figure 5.1: Spiral wavefronts that rotate in different directions at time \( t = 0 \) when \( \theta_0 = 1.7\pi \) and \( \theta \in [0, 2\pi] \).

Figure 5.1 shows the considered wavefronts in this chapter. Consider that an electrical arithmetic spiral wavefront passes the area under the \( i \)th electrode located at \( Z_i \) at time \( t_i \), and the location \( Z_i \) is active at time \( t_i \) for \( i = 1, \ldots, N \). The least squares (LS) estimates of the unknown parameters of the spiral in (5.1) are the arguments that minimize

\[ e_{\text{CW}} = \sum_{i=1}^{N} |Z_i - a\theta_i e^{j(\theta_i - wt_i + \theta_0)} - P|^2. \]  

(5.3)

Similarly, the unknown parameters of the spiral with a CCW rotation, given in (5.2),
can be found by minimizing

\[ e_{CCW} = \sum_{i=1}^{N} |Z_i - a_{\theta_i}e^{-j(\theta_i - wt_i + \theta_0 + \pi) - P}|^2. \] (5.4)

Considering both CW and CCW rotors, we can localize the rotor’s tip by solving the following optimization problem

\[ [P, w, \theta_0, a] = \arg \min_{P, w, \theta_0, a} \min \{ e_{CW}, e_{CCW} \}. \] (5.5)

It is clear from (5.1) that we have \( \theta_i = |Z_i - P|/a \), and we can rewrite \( e_{CW} \) and \( e_{CCW} \) as

\[ e_{CW} = \sum_{i=1}^{N} |Z_i - |Z_i - P|| e^{j\left(\frac{|Z_i - P|}{a} - wt_i + \theta_0\right) - P}|^2, \] (5.6)

\[ e_{CCW} = \sum_{i=1}^{N} |Z_i - |Z_i - P|| e^{-j\left(\frac{|Z_i - P|}{a} - wt_i + \theta_0 + \pi\right) - P}|^2. \] (5.7)

The optimization (5.5) can be solved by using the grid search method, i.e., exhaustive search over all the possible values for the unknown parameters \( a \in [a_{\text{min}}, a_{\text{max}}], w \in [w_{\text{min}}, w_{\text{max}}], \theta_0 \in [0, 2\pi] \) and \( P \) in searching zone). Thus, the CC of solving it depends on the possible ranges for \( \theta_0, a, P, \) and \( w \) (which depend on many parameters, e.g., the size of the atrium and refractory period) and the desired accuracy (which dictates the size of the grids). In [57], assuming that the spiral rotation direction is known, the Hough transform is used to reduce the complexity of searching in \( P \)-plane; however,
the CC of the proposed method in that paper is still high as it requires a three-dimensional search over \((w, a, \theta_0)\). In the following subsection, we propose a low CC approach to localize the tip of the rotor.

### 5.3.1 Proposed Method

Consider the spiral wavefront that rotates CW and hits two electrodes located at \(Z_i\) and \(Z_j\). Using (5.1), we have

\[
(Z_i - P)(Z_j - P)^* = a^2 \theta_i \theta_j e^{i(\Delta \theta_{ij} - w \Delta t_{ij})}
\]

(5.8)

where \(\Delta t_{ij} \triangleq t_i - t_j\) and \(\Delta \theta_{ij} \triangleq \theta_i - \theta_j\) that can be expressed as \(\Delta \theta_{ij} = (|Z_i - P| - |Z_j - P|)/a = D_{ij}(P)/a\) in which \(D_{ij}(P) \triangleq |Z_i - P| - |Z_j - P|\). Note that we assume that electrodes are hit during one wavefront rotation; thus, we have \(w \Delta t_{ij} \in [-2\pi, 2\pi]\). Furthermore, \(\Delta \theta_{ij} \in [-2\pi, 2\pi]\), as we only consider a single-armed spiral. Consequently, \(\Delta \theta_{ij} - w \Delta t_{ij} \in [-4\pi, 4\pi]\). Note that the proposed method can be used to localize a meandering rotor which is stationary during the short time interval that it passes the catheter’s electrodes (spiral parameters should not vary significantly throughout largest \(\Delta t_{ij}\)). Defining \(\Phi_{ij}(P) \triangleq \text{angle}\{(Z_i - P)(Z_j - P)^*\}\) and using (5.8), for a pair of electrodes \(i\) and \(j\), we have

\[
\Phi_{ij}(P) = D_{ij}(P)/a - w \Delta t_{ij} + 2\pi q_{ij},
\]

(5.9)

where \(q_{ij} \in \{0, \pm1, \pm2\}\) is used because \(\Phi_{ij}(P) \in [-\pi, \pi]\); whereas, \(D_{ij}(P)/a - w \Delta t_{ij} \in [-4\pi, 4\pi]\). Consider another pair of electrodes \(k\) and \(l\) (located at \(Z_k\) and
5.3. LOCALIZING THE TIP OF THE SPIRAL ROTOR

For this pair, we have \( \Phi_{kl}(P) = D_{kl}(P)/a - w\Delta t_{kl} + 2\pi q_{kl} \) where \( q_{kl} \) is defined similar to \( q_{ij} \). Using the above equations for \( \Phi_{ij}(P) \) and \( \Phi_{kl}(P) \), we can obtain \( a \) and \( w \) as

\[
a = \frac{D_{ij}(P)\Delta t_{kl} - D_{kl}(P)\Delta t_{ij}}{\Phi_{ij}(P)\Delta t_{kl} - \Phi_{kl}(P)\Delta t_{ij}} \tag{5.10}
\]

and

\[
w = \frac{D_{kl}(P)\tilde{\Phi}_{ij}^{CW}(P) - D_{ij}(P)\tilde{\Phi}_{kl}^{CW}(P)}{D_{ij}(P)\Delta t_{kl} - D_{kl}(P)\Delta t_{ij}}, \tag{5.11}
\]

respectively, where \( \tilde{\Phi}_{ij}^{CW}(P) \equiv \Phi_{ij}(P) - 2\pi q_{ij} \) and \( \tilde{\Phi}_{kl}^{CW}(P) \equiv \Phi_{kl}(P) - 2\pi q_{kl} \).

A similar procedure can be followed to obtain \( a \) and \( w \) for a wavefront that rotates CCW. It can be shown that for the CCW rotor, \( a \) and \( w \) are respectively given in (5.10) and (5.11) when \( \tilde{\Phi}_{ij}^{CW} \) and \( \tilde{\Phi}_{kl}^{CW} \) are replaced by \( \tilde{\Phi}_{ij}^{CCW} \) and \( \tilde{\Phi}_{kl}^{CCW} \), respectively, where \( \tilde{\Phi}_{ij}^{CCW}(P) \equiv -\Phi_{ij}(P) - 2\pi q_{ij} \) and \( \tilde{\Phi}_{kl}^{CCW}(P) \equiv -\Phi_{kl}(P) - 2\pi q_{kl} \).

To localize the tip of the rotor, for each possible \( P \), for each available two pairs of electrodes, we estimate \( a \)s and \( w \)s for CW and CCW rotors using (5.10) and (5.11). If the estimated \( a \)s and \( w \)s are in the acceptable range \( (a \in [a_{\min}, a_{\max}] \) and \( w \in [w_{\min}, w_{\max}] \)), those values are respectively added to vectors \( \mathbf{a}_P \) and \( \mathbf{w}_P \). The median of \( \mathbf{a}_P \) (and \( \mathbf{w}_P \)) denoted by \( \bar{a}_P \) (and \( \bar{w}_P \)) is considered as a final estimated value for \( a \) (and \( w \)) for the considered \( P \). Finally, we localize the tip of the rotor by solving the following optimization problem:

\[
P = \arg \min_P \sum_{\text{electrodes pairs } i,j} \min_{\tilde{a}_{ij}} \{ \mathcal{E}_{ij}^{CW}(P), \mathcal{E}_{ij}^{CCW}(P) \}, \tag{5.12}
\]
5.4. SIMULATION RESULTS

where $\mathcal{E}^{CW}_{ij}(P) = |\Phi_{ij}(P) - D_{ij}(P)/\bar{a}_P + \bar{w}_P \Delta t_{ij} - 2\pi q_{ij}|$ and $\mathcal{E}^{CCW}_{ij}(P) = |\Phi_{ij}(P) + D_{ij}(P)/\bar{a}_P - \bar{w}_P \Delta t_{ij} - 2\pi q_{ij}|$.

The proposed method can be summarized as follows:

**Input:** Locations and ATs of the catheter's electrodes; possible range for $P, a, w$.

**For** all considered $P$s, $a_P = [\ ]$ and $w_P = [\ ]$;

**For** available pairs of electrodes, estimate $a$ and $w$ using (5.10) and (5.11) for the CW and CCW rotors.

**If** estimated $a$s and $w$s are in the acceptable range, add them to $a_P$ and $w_P$, respectively, i.e., $a_P = [a_P, a]$ and $w_P = [w_P, w]$ **end**.

**end**

$\bar{a}_P = \text{median}(a_P)$ and $\bar{w}_P = \text{median}(w_P)$. 

**end**

Find the rotor’s tip by solving (5.12).

5.4 Simulation Results

For the simulation, based on commercially available product employed in most catheter ablation procedures, we consider a circular catheter with a radius of 1.25cm that has ten bipolar electrodes. We consider 90 uniformly distributed locations on the circle with radius $R = 3$cm as locations of the spiral’s tip (see Figure 5.1). At
each location, for 100 independent simulation runs, we create a spiral wavefront that its $w$ and $a$ are randomly chosen from $[20 - 63]\text{rad/s}$ and $[3/(2\pi) - 5/(2\pi)]\text{cm}$, respectively. Each spiral either rotates CW or CCW. Here, we assume that the ATs of the IEGMs are known. In practice, these ATs can be obtained using activation extraction algorithms [2, 3, 78]. Study of the impact of the AT estimation error on the tip localization will be analysed in our future research.

Estimated tip location for the sample rotor is marked with a small square in Figure 5.1. This example clarifies that although we use exact ATs in our method, we still have some error because of limited resolution for $P$-domain search (considering the $P$-plane grids in Figure 5.1, the estimated $P$ is the closest grid point to the tip of the rotor, and therefore, is the best possible estimation).

The proposed method in this chapter requires at least one double-pair of electrodes for tip localization. Different numbers of double-electrode pairs (DEPs) are considered for this simulation; the first to twelfth pairs, respectively, are: (1,6)-(4,9); (2,7)-(5,10); (3,8)-(6,1); (4,9)-(7,2); (5,10)-(8,3); (1,4)-(9,6); (10,7)-(2,5); (2,9)-(4,7); (1,4)-(1,8); (3,10)-(4,7); (4,10)-(3,7) and (1,8)-(3,6) where the numbers in the parentheses are the numbers corresponding to the electrodes as shown in Figure 5.1. For example, to obtain the result labeled “1 DEP” in Figure 5.2, we use the first DEP which is (1,6) – (4,9), and for “2 DEPs”, we use (1,6) – (4,9) and (2,7) – (5,10).

The absolute error of estimating the spiral tip location averaged over all the independent simulation runs is shown in Figure 5.2(a) as a function of the resolution of searching in $P$-plane ($\Delta P$) when $P_{\text{max}} = -P_{\text{min}} = 5\text{cm}$. Mean relative absolute errors of $a$ and $w$ are also plotted in Figure 5.2. To better investigate the effect of the
number of the considered DEPs on the localization error, we plot the mean absolute error of estimating $P$ as a function of number of DEPs in Figure 5.3. Figures 5.2 and 5.3 confirm that we can improve the localization error by decreasing $\Delta P$ or increasing the number of the DEPs. For example, the proposed localization method with $\Delta P = 0.6$ and the number of DEPs equal to six has almost the same accuracy as the one with $\Delta P = 1$ and the number of DEPs equal to nine. Thus, depending on the available electrodes’ ATs and the desired accuracy, we can select $\Delta P$ and the number of DEPs. Figure 5.3 shows that the minimum achievable error is determined by $\Delta P$, and we can approach the minimum error by increasing the number of deployed DEPs.

5.5 Conclusion

In this chapter, we assumed that an Archimedean spiral wavefront propagates in the atria perpetuating AF. Using the ATs of the atrial IEGMs and locations of a catheter’s electrodes, we proposed a computationally efficient algorithm to localize the tip of the electrical rotor with a spiral wavefront. The angular rotation speed of the electrical wave ($w$), its direction of rotation (CW or CCW), initial rotation phase ($\theta_0$), the distance between successive arms of the spiral ($a$), and the location of the tip of the spiral wavefront ($P$) are assumed to be unknown. We proposed a method that requires at least one double-electrode pair (DEP) to estimate $P$ (ATs of at least three electrodes are required). Our simulation results confirmed the efficiency of the proposed algorithm and showed that we can improve the localization error at the expense of increasing the CC, by decreasing the resolution of searching in $P$-plane ($\Delta P$) or increasing the number of the DEPs. Our results suggested that the minimum
achievable error is determined by $\Delta P$ and we can approach the minimum error by increasing the number of DEPs used for localization.
Figure 5.1: The considered circular catheter and a sample spiral wavefront that rotates CCW. For simulation, we considered 90 uniformly distributed locations on the blue dashed circle as locations of the spiral’s tip. The estimated and actual locations of the tip of the sample rotor are shown with a small blue square and a red circle, respectively; $P$-plane grids are also plotted in the searching zone with gray lines.
Figure 5.2: From top to bottom: absolute error of $P$, relative absolute error of $a$ and $w$, as functions of $\Delta P$, averaged over all the considered values for $a, w, P$. We considered 90 different $P$s, and for each tip location, we considered 100 different values for $a$ and $w$. 
Figure 5.3: Average absolute error of $P$ as a function of the number of DEPs.
Part IV

Wavefront Dynamics
Chapter 6

Two Computationally Efficient Intracardiac Wavefront Velocity Estimators: Error Analysis for the Planar Wavefronts

6.1 Abstract

The wavefront velocity vector (VV) provides insight into the characteristics of the myocardial tissue and can be deployed to treat different heart diseases. The cardiac VV can be estimated by processing the intracardiac electrograms. In this chapter, we analyse the VV estimation error of two computationally efficient heuristic estimators: 1- maximum time difference (MTD) and 2- minimum velocity (MinV). In the MTD, the estimated velocity is a vector in the direction of the vector that connects the first to the last catheter’s activated electrode, and the magnitude of the VV is estimated as the ratio of the distance between two electrodes to the delay between their ATs. In the MinV, using a similar procedure as the MTD, we assign a VV to each available
6.2. WAVEFRONT CONDUCTION VELOCITY ESTIMATION

electrode pair of the catheter, and the VV with the smallest magnitude is selected as the final estimated VV. We derive the average absolute value and average squared absolute value of the VV estimation error of the MTD and MinV methods for a planar wavefront in a two-dimensional case and confirm the accuracy of our analysis by studding synthetic data.

6.2 Wavefront Conduction Velocity Estimation

A wavefront conduction velocity vector (VV) map can provide important information about regional electrical activations and can be used to study the characteristics of arrhythmias [13, 102]. As an example, the cardiac velocity is used to estimate the wavelength of the cardiac impulse, which is the distance traveled by the depolarization wavefront during the time the tissue restores its excitability [103]. This parameter that is calculated by multiplying the conduction velocity and the refractory period is critical for characterizing the possibility of initiation and maintenance of reentrant circuits [104].

The wavefront VV can be estimated using the activation times (ATs) of the intracardiac electrograms (IEGMs) and the relative position of multipolar catheter’s electrodes [68, and references therein] [105–108]. In the currently available cardiac mapping systems, regions with early and late ATs are color-coded and can be used to find the direction of the wavefront propagation [51,106].

In this chapter, we investigate two heuristic approaches for cardiac conduction
6.2. WAVEFRONT CONDUCTION VELOCITY ESTIMATION

VV estimation which are based on analysing sites with early and late activations: 1- *maximum time difference* (MTD) and 2- *minimum velocity* (MinV). In both methods, first, the ATs of the IEGMs are detected; then, various wavefronts are specified, and the ATs of each wavefront and the location of the electrodes at the ATs are used to estimate the VV. In the MTD velocity estimation method, the first and last electrodes of the recording catheter that are hit by the wavefront are determined; the estimated MTD wavefront VV is in the direction of the vector that connects those electrodes. Indeed, if $\Delta t$ denotes the delay between the ATs of the first and last activated electrode, $v$ is estimated as $(p_l - p_f)/|\Delta t|$, where $p_f$ and $p_l$ show the three-dimensional (3-D) catheter electrodes’ locations vectors that are activated first and last, respectively. The magnitude of the velocity is estimated as $d/|\Delta t|$, where $d = \|p_f - p_l\|$ is the distance between two electrodes ($\|\cdot\|$ denotes the Euclidean norm). Note that the estimated wavefront VV in this approach is in the direction of the electrode pair where the difference between the ATs of its electrodes is maximum. If the VV is not perpendicular to the line joining the electrodes of the pair with the maximum AT difference, the MTD produces an overestimation of the wavefront speed (e.g., see Fig. 1 in [105]), which justifies the application of the MinV method.

In the MinV method, for each possible pair of electrodes, similar to the MTD, we obtain the magnitude of the VV for that pair, and the velocity with the smallest magnitude is selected as the estimated VV in the MinV approach.

In other words, in the MTD and MinV methods, for each wavefront, the absolute value of the VV is estimated as $d_i/|\Delta t_i|$, and the direction of the VV is estimated as
the direction of the $i$th pair of electrodes where

$$i = \begin{cases} 
\arg\max_{k \in \Omega} \Delta t_k & \text{for the MTD method,} \\
\arg\min_{k \in \Omega} \frac{d_k}{|\Delta t_k|} & \text{for the MinV method,}
\end{cases} \quad (6.1)
$$

in which $\Omega$ is the set of indices of all available electrode pairs, $d_k$ and $\Delta t_k$ are the distance and time delay between the ATs of the electrodes of the $k$ pair, respectively.

If the VV of a planar wave is in the direction of the $i$th electrode pair, the VV estimation error of the heuristic methods becomes zero. However, when the VV has a different direction than the $i$th pair, the estimated VV has a larger magnitude than the actual VV. In Section 6.3, we study the VV estimation error of the MinV and MTD methods for the planar wave in 2-D and quantify the improvement achieved by using the MinV instead of the MTD. Using synthetic data, in Section 9.4, we study the accuracy of our error analysis for the MTD and MinV.

### 6.3 Error Analysis of the MTD and MinV Methods

The VV, denoted by $v$ in this chapter, is a 3-D real vector in a general case. In this section, however, we assume that the VV and all the catheter’s electrodes are in one plane; a single plane passes through all the electrodes, and the VV lies on the same plane. In this condition, we can apply an affine transformation on the VV and the catheter’s electrodes, such that all the electrodes and the VV lie on the $xy$-plane. We can obtain the original VV and electrodes’ locations by applying the inverse transform. Thus, we represent the transformed VV with a complex number where its
real and imaginary parts show the $x$ and $y$ components of the velocity, respectively. Therefore, instead of the 3-D real velocity vector $\mathbf{v}$, here, we use a complex scalar velocity value $V = |V|e^{j\theta}$ and study the error of the described heuristic methods.

Consider three pairs of electrodes as shown in Figure 6.1, where all the pairs intersect at the center point (origin). We assume that the estimated velocity is in the direction of one of these electrode pairs, and our goal is to analyse the VV estimation error. In subsection 6.3.1, we describe how to transform the mapping catheter to several electrode pairs that should be considered in error analysis. Let us define the $i$th decision region, highlighted in gray in Figure 6.1(a), as the region where for all the VVs in that zone pointing toward the origin, the direction of the $i$th pair is considered as the estimated direction for the velocity. Figure 6.1(a) also shows different decision regions with different colors that are separated with boundaries, $\mathcal{D}_s$. These boundaries and regions depend on the method that is used for the VV estimation.

Boundary $\mathcal{D}_{i,j}$ for the MTD method is a line that separates the area around the $i$th and $j$th electrode pairs, such that, if the impinging velocity lies on the boundary line, it produces similar delay between the first and last activated electrodes of the $i$th and $j$th pairs. The VV that lies on $\mathcal{D}_{i,j}$ activates the first and last electrodes of the $i$th and $j$th pairs at the same times; thus, the estimated VV using the MTD method can be in the direction of the $i$th or $j$th electrode pair.

Boundary $\mathcal{D}_{i,j}$ for the MinV, however, is such that if the velocity lies on the boundary line, the estimated VV in the directions of the $i$th and $j$th pairs have the same magnitude.
Figure 6.1: A catheter with 3 pairs of bipolar electrodes (each bipolar electrode is shown with a square). The estimated VV direction for all the vectors in the grey-highlighted zone, including the plotted sample in sub-figure (a), is equal and is plotted with a blue arrow in that zone denoted by \( \hat{v} \). Various decision regions are highlighted in different colors and are separated with boundaries, \( D_s \). The \( i \)th region is the section, where for all the VVs in that zone pointing toward the origin, the direction of the \( i \)th pair is considered as the estimated direction for the velocity.
A sample VV direction and its estimated direction using the MTD method are shown in Figure 6.1(a). The estimated VV direction for all the vectors in the grey-highlighted zone (including the plotted sample) is equal and is plotted with a blue arrow denoted by \( \hat{v} \) in Figure 6.1(a). The angular error of the VV direction estimation (\( \Psi \)) is also shown in this figure.

As Figure 6.1(b) shows, the \( i \)th decision region can be specified by \( \eta_i^- \) and \( \eta_i^+ \) where these are the angles between the \( i \)th electrode pair and boundaries \( D_{i,i-1} \) and \( D_{i,i+1} \), respectively. The following lemma specifies the boundaries of the \( i \)th pair for the MTD and MinV methods.

**Lemma 3.** For the MTD method,

\[
\tan(\eta_i^-) = \frac{d_i}{d_{i-1}} - \frac{\cos(\Delta_{i-1,i})}{\sin(\Delta_{i-1,i})}, \tag{6.2}
\]

\[
\tan(\eta_i^+) = \frac{d_i}{d_{i+1}} - \frac{\cos(\Delta_{i,i+1})}{\sin(\Delta_{i,i+1})}, \tag{6.3}
\]

and for the MinV method,

\[
\eta_i^- = \frac{\Delta_{i-1,i}}{2} \quad \text{and} \quad \eta_i^+ = \frac{\Delta_{i,i+1}}{2}, \tag{6.4}
\]

where \( d_i \) is the distance between the electrodes of the \( i \)th pair, and \( \Delta_{i,j} \) is the angular distance between the \( i \)th and \( j \)th electrode pairs (see Figure 6.1(b)). *Proof: See Appendix 6.A.*

Suppose that the direction of the \( i \)th pair of electrodes is considered as the estimated direction for the velocity. If we denote the actual and estimated velocity by \( V \)
and $\hat{V}_{H,i}$, respectively, and define the error as $e_i = V - \hat{V}_{H,i}$, we can write the following equation

$$E\{|e_i|\} = \frac{|V|}{|V|} \ln \left| \cos(\eta_i^-) \right| + \ln \left| \cos(\eta_i^+) \right| - \eta_i^- - \eta_i^+,$$

where $|V| = E\{|V|\}$ and also

$$E\{|e_i|^2\} = \frac{|V|^2}{|V|^2} \left( \frac{\tan(\eta_i^-) + \tan(\eta_i^+)}{\eta_i^- + \eta_i^+} - 1 \right),$$

where $|V|^2 = E\{|V|^2\}$. \textit{Proof:} See Appendix 6.B.

### 6.3.1 Finding Electrode Pairs of the Catheter for Error Analysis

We provided an error analysis for when all the electrode pairs pass through the origin. If the middle point of a pair does not lie on the origin, we simply shift that pair so that its middle point lands on the origin. Figure 6.2(a) shows a spiral mapping catheter and four bipolar pairs of electrodes, and Figure 6.2(b) shows the shifted versions of those pairs which are suitable for the error analysis. To obtain an accurate error analysis of the described heuristic methods for a specific catheter shape, we should consider all the possible pairs of the electrodes. All the considered electrode pairs should then be shifted, such that their middle point is on the origin. If an electrode pair falls in the convex hull created by the shifted electrodes, it means that that pair cannot be the pair with the first-last ATs. Thus, we should exclude that pair for the error analysis of the MTD approach. For instance, in Figure 6.2(b), the violet electrode pair falls in the convex hull of the shifted electrodes and should not
Figure 6.2: (a) A spiral catheter and 4 electrode pairs. (b) The pairs are shifted, such that their middle points lie on the origin. The convex hull of the shifted pairs are highlighted in cyan. The violet pair that falls in the convex hull should (not) be considered for the error analysis of the MinV (MTD).

be considered for error analysis of the MTD method; whereas, it should be considered for the MinV because the estimated VV of that pair might have the minimum magnitude. Since some of the pairs used in the MinV analysis are removed from the MTD approach, we expect the MTD to have a higher estimation error. Note that the computation complexity of the MinV is higher than the MTD, as in the MinV, the magnitude of the VV is calculated for every possible pair.

In this section, we also assumed a 2-D catheter. In some cases, we can project 3-D catheter electrodes in a 2-D plane and use the aforementioned analysis to study the velocity estimation error. For example, Figure 6.3-a shows part of a left atrial shell of a patient and a Reflexion Spiral™ catheter (St. Jude Medical) that is used for signal collection. We can project the catheter on a 2-D plane, where the plane is
6.3. ERROR ANALYSIS OF THE MTD AND MINV METHODS

Figure 6.3: 

- **a**: Part of a left atrial shell and a Reflexion Spiral™ catheter (St. Jude Medical).
- **b**: Spiral catheter that is projected catheter on a 2-D plane and is rotated to lie on the $x-y$ plane.
- **c**: Electrode pairs of the spiral catheter shown in **b** that are shifted such that their middle points lie on the origin (The black pairs should not be considered for the error analysis of the MTD; whereas, they should be included in the error analysis of the MinV method).

The catheter shown in Figure 6.3-**b** can be used for error analysis. Subfigure **c** shows all the electrode pairs of the spiral catheter in subfigure **b** that are shifted such that their middle points lie on the origin. The black lines show the electrode pairs that fall in the convex hull of the shifted electrodes. These pairs should not be considered for the error analysis of the MTD; whereas, they should be considered for the MinV. Only the green lines in the subfigure **c** should be used to obtain the expected velocity.
estimation error of the MTD.

6.4 Simulation Results

In this section, we investigate the performance of the studied heuristic methods for the VV estimation. Here, we consider 2-D planar wavefronts with velocity \( V = |V|e^{i\theta} \) that hit a circular catheter with radius \( r = 1.25 \) cm and \( N \) electrodes. We assume that \( 40 \leq |V| \leq 200 \) cm/s. We considered 360 different values for the phase of the VV \( \theta = 1^\circ, 2^\circ, \cdots, 360^\circ \) and for each \( \theta \), we generate 50 VVs with different values for \( |V| \) that are randomly selected from 40 to 200 \( (|V| \sim U(40, 200)) \). For each VV, we generated the ATs of the electrodes and used them in the heuristic estimators. For the MTD method, if we only consider the electrode pairs that pass through the center of the catheter (pairs along the diameter of the circular catheter), we can simplify (6.5) and (6.6). In this case, \( \Delta_{i-1,i} = \Delta_{i,i+1} = 2\pi/N \) and \( d_i = d_{i-1} = d_{i+1} = 2r \). Using (6.2) and (6.3), we have \( \eta^-_i = \eta^+_i = \pi/N \) for \( i = 1, \ldots, N/2 \). Consequently, \( e_1 = \cdots = e_{N/2} \) and (6.5) and (6.6), respectively, become

\[
E\{|V - \hat{V}_{MTD}|\} \approx -N|V|/\pi \ln \cos(\pi/N), \quad (6.7)
\]
\[
E\{|V - \hat{V}_{MTD}|^2\} \approx N|V|^2/\pi \tan(\pi/N) - 1. \quad (6.8)
\]
Figure 6.1: Relative absolute estimation error of the VV of the MTD and MinV methods averaged over 18000 independent VVs as a function of the total number of electrodes in a circular catheter $N$. Derived estimation errors for the MTD (given in (6.7) and (6.8) for circular catheter) are also plotted.

For the MinV, for the circular catheter, we have $\eta_i^- = \eta_i^+ = \pi/(2N)$, and (6.5) and (6.6) can be simplified as

\[
E\{|V - \hat{V}_{\text{MinV}}|\} \approx -2N|V|/\pi \ln \cos(\pi/(2N)),
\]

\[
E\{|V - \hat{V}_{\text{MinV}}|^2\} \approx 2N|V|^2/\pi \tan(\pi/(2N)) - 1.
\]

Figure 6.1 shows the average of the relative estimation error of the MTD and MinV methods versus $N$. Equations (6.7)-(6.10) are also plotted in Figure 6.1; which precisely match their empirically estimated values. This figure also shows that the MinV has a better accuracy than the MTD method (see the modified MTD method in [109]).
6.5 Conclusion

In this chapter, we studied two simple approaches for the wavefront VV estimation: 1) MTD and 2) MinV. The estimated VV in the MTD is in the direction of the vector that connects the first to the last activated electrode of the catheter; the magnitude of the estimated VV is the ratio of the distance between two electrodes to the delay between their ATs. In the MinV method, using a similar method to the MTD, we assign a VV to each available electrode pair, and the VV with the smallest magnitude is selected as the final estimated VV. The aforementioned wavefront VV estimation methods overestimate the magnitude of the VV. We analysed the quality of the VV estimation of the MTD and MinV methods and derived the average (squared) absolute value of the VV estimation error of these methods for a planar wavefront in a 2-D case. We proved that the MinV has a better accuracy than the MTD method (at the expense of being more computationally complex). We also showed that both studied methods can have an acceptable VV estimation accuracy when the total number of the catheter’s electrodes is large. Finally, our simulation results confirmed the accuracy of our error analysis for the MTD and MinV.
6.A. PROOF OF LEMMA 1

Appendix

6.A. Proof of Lemma 1

6.A.1 Boundary Lines of the MTD Method

Our aim here is to find the boundaries of the $i$th pair for the MTD method. When the VV lies on $D_{i,i-1}$, we have $\Delta t_i = \Delta t_{i-1}$, where $\Delta t_i = d_i \cos(\eta_i^-)/|V|$ and $\Delta t_{i-1} = d_{i-1} \cos(\eta_{i-1}^+)/|V|$ are the AT delays between the electrodes of the $i$th and $i-1$th pairs, respectively, and $d_i$, $\eta_i^-$, and $\eta_i^+$, are shown in Figure 6.1(b). Thus, $\Delta t_i = \Delta t_{i-1}$ becomes

$$d_i \cos(\eta_i^-) = d_{i-1} \cos(\eta_{i-1}^+). \quad (6.11)$$

Considering Figure 6.1(b), we also have

$$\eta_i^- + \eta_{i-1}^+ = \Delta_{i-1,i}. \quad (6.12)$$
Following the same procedure for $D_{i,i+1}$, we have
\[
d_i \cos(\eta_i^+) = d_{i+1} \cos(\eta_i^-) \quad \text{and} \quad \eta_i^+ + \eta_i^- = \Delta_{i,i+1}. \tag{6.13}
\]
Substituting (6.12) in (6.11), after some manipulations, we obtain (6.2). Similarly, from (6.13) we can write (6.3).

6.A.2 Boundary Lines of the MinV Method

Here, our aim is to find the boundaries of the $i$th pair for the MinV method. When the VV lies on $D_{i,i-1}$, we have $d_i/\Delta t_i = d_{i-1}/\Delta t_{i-1}$. Using $\Delta t_i = d_i \cos(\eta_i^-)/|V|$, $\Delta t_{i-1} = d_{i-1} \cos(\eta_{i-1}^+)/|V|$ and (6.12), we conclude that on $D_{i,i-1}$, we have $\eta_i^- = \eta_{i-1}^+ = \Delta_{i-1,i}/2$. Similarly, on the boundary $D_{i,i+1}$, we have $\eta_{i+1}^- = \eta_i^+ = \Delta_{i,i+1}/2$.

6.B Proof of (6.5) and (6.6)

Suppose that the direction of the $i$th pair of electrodes is considered as the estimated direction for the VV. If we denote the actual and estimated velocity by $V = |V|e^{j\theta}$ and $\hat{V}_{H,i} = |V_{H,i}|e^{j\theta_{H,i}}$, respectively, the estimation error is
\[
e_i = V - \hat{V}_{H,i} = |V|e^{j\theta}(1 - e^{-j\Psi_i}/\cos(\Psi_i)) \tag{6.14}
\]
where $\Psi_i = \theta - \hat{\theta}_{H,i}$ is the error in the velocity direction estimation, $|\hat{V}_{H,i}| = d_i/\Delta t_i$, and $|V| = d_i \cos(\Psi_i)/\Delta t_i$. 

It can easily be shown that \(|e_i| = |V||\tan(\Psi_i)|\). The velocity direction error \(\Psi_i\) has the uniform distribution between \(-\eta_i^-\) and \(\eta_i^+\), i.e., \(\Psi_i \sim U[-\eta_i^-, \eta_i^+]\). Thus, the mean absolute error for \(e_i\) is

\[
E\{|e_i|\} = \frac{|V|}{\eta_i^- + \eta_i^+} \int_{-\eta_i^-}^{\eta_i^+} |\tan(\Psi)| \, d\Psi,
\]

which can be simplified as (6.5). Similarly, \(E\{|e_i|^2\}\) can be written as (6.6), where to derive these equations we have used \(\int \tan(x) \, dx = -\ln|\cos(x)|\) and \(\int \tan(x)^2 \, dx = \tan(x) - x\).
Chapter 7

Modified Maximum Time Difference Intracardiac Wavefront Conduction Velocity Estimation

7.1 Abstract

In this chapter, we modify the maximum time difference (MTD) method, introduced in the previous chapter. In the MTD, first, the ATs of the electrograms are extracted, and the corresponding wavefronts are estimated. For each wavefront, the VV is estimated as the vector connecting the first to the last activated electrodes of the catheter divided by the time duration between the activation of those two electrodes. In the proposed modified MTD (MMTD) approach, which is slightly more computationally complex than the MTD, we divide the ATs of each considered wavefront into two groups, such that one group contains the electrodes with early activations, and the other contains those with late activations. We properly assign a time value and a location value to these groups and follow the same procedure as the MTD method to estimate the wavefront VV using the assigned values. Using synthetic data, we show
that the proposed MMTD improves the quality of the wavefront VV estimation of the MTD method, i.e., the MMTD is more robust to the AT estimation error and is able to determine the VV of the planar wavefronts more accurately.

7.2 Cardiac Conduction Velocity Estimation

As we discussed in the previous chapter, a wavefront conduction velocity map can provide valuable information regarding the mechanisms initializing and sustaining complex arrhythmias, such as atrial fibrillation. For example, cardiac regions with slow conduction velocity are considered as a prerequisite for forming reentrant wavefronts [50, 51].

The conduction velocity vector (VV) at any point on the cardiac tissue can be estimated by analysing the local intracardiac electrograms (IEGMs) [68, and reference therein] [89, 106, 108], i.e., the ATs of the IEGMs are estimated [2, 5, 78], and these ATs, in conjunction with the estimated positions of the catheter’s electrodes [99,110], are used for the wavefront conduction VV estimation. In currently practiced catheter mapping, regions with early and late ATs are highlighted in different colors, which can be used to find the direction and speed of the wavefront propagation [51, 106]. Estimating the wavefront VV using the ATs and locations of the first/earliest and last/latest activated electrodes of the catheter is studied in [111], in which the VV estimation performance of the maximum time difference (MTD) method is investigated when the IEGMs’ ATs are accurately known. In the MTD approach, after estimating the ATs of the IEGMs and obtaining wavefronts, the velocity is estimated as the displacement vector between the first and the last activated electrodes of the
catheter divided by the time delay between the ATs of those electrodes.

When the VV of a planar wave is in the direction of the electrode pair with maximum time difference, the VV estimation error of the MTD becomes zero; however, if the VV has a different direction than that pair, the MTD overestimates the VV, i.e., the estimated VV has a larger magnitude than the actual velocity [111] [105, see Fig. 1]. For the case where the ATs of the IEGMs are accurately known, the average absolute VV estimation error of the MTD is derived in [111] for the planar wavefront, and it is shown that although the MTD is very computationally efficient and simple to implement, its performance is not good when the number of the catheter’s electrodes that are in contact with the cardiac tissue is not large. Furthermore, since the MTD only relies on the locations and the ATs of the electrodes with the earliest and latest ATs, its accuracy closely depends on the quality of the AT and location estimation of those two electrodes.

To cope with these drawbacks of the MTD, in Section 7.3, we propose a slightly more computationally complex version of the MTD. In the proposed modified MTD (MMTD) method, based on the ATs, we categorize the catheter’s electrodes into two groups, such that the first group contains the electrodes with early activations, and the second one contains those with late activations. A time value and a location value are properly assigned to each of the groups and those values are used for the VV estimation. Our simulation results are presented in Section 9.4, in which by using synthetic data for the planar wavefront, we compare the performance of the proposed MMTD velocity estimator and the MTD.
7.3 Modified MTD Cardiac Conduction Velocity Estimation

The MTD only uses the locations and ATs of the first and last activated electrodes of a catheter for each wavefront. Here, we introduce another simple method which deploys the ATs and locations of other electrodes to improve the quality of the VV estimation. Similar to the MTD, in this modified approach, we first estimate the ATs of the IEGMs and specify the wavefronts. After that, we divide the ATs of each wavefront into two groups, such that the ATs of the first group are closer to the smallest/first AT, and the ATs of the second group are closer to the largest/last AT of the wavefront. The first group contains the electrodes with early activations denoted by *Early AT Group* (EG); whereas, the second one contains those with late activations denoted by *Late AT Group* (LG). Note that subscripts $e$ and $l$ are used to denote the EG and LG, respectively. We assign a time and location value to each group and use those values to estimate the VV. The following location value $p_e$ and time value $t_e$ are assigned to the EG and are used to represent that group

$$p_e = \sum_{i \in \Omega_e} w_i p_i, \quad t_e = \sum_{i \in \Omega_e} w_i t_i, \quad (7.1)$$

where the members of $\Omega_e$ are the electrodes’ numbers that are in the EG, $p_i$ is a real vector with length 3 that shows the 3D position of the $i$th electrode of the catheter, and $w_i$s are some positive weighting coefficients that sum up to 1. Similarly, the location $p_l$ and time value $t_l$ that represent the LG are

$$p_l = \sum_{i \in \Omega_l} q_i p_i, \quad t_l = \sum_{i \in \Omega_l} q_i t_i, \quad (7.2)$$
where the members of $\Omega_t$ are the electrodes’ numbers that are in the LG, and $q_i$s are some positive weighting coefficients that sum up to 1. We denote the cardinalities of $\Omega_e$ and $\Omega_l$ with $M_e$ and $M_l$, respectively.

For example, Figure 7.1 shows the IEGMs collected using a circular catheter with eight bipolar electrodes. The ATs of the EGMs are marked with red dashed lines. The ATs of two wavefronts are highlighted in this figure and are used for the velocity estimation. For the wavefront highlighted in green, the first and last activated electrodes are the 4th and 8th electrodes, respectively. Thus, the estimated VV using the MTD method is in the direction of the vector that connects those electrodes. Similarly, the estimated MTD VV for the wavefront highlighted in blue is in the direction of the vector that connects the 2nd to the 6th electrode. Considering the depicted EGMs in Figure 7.1, for the wavefront highlighted in blue when $M_e = M_l = 2$, we have $\Omega_l = \{7, 8\}$ and $\Omega_e = \{3, 4\}$; for the wavefront highlighted in green when $M_e = M_l = 3$, we have $\Omega_e = \{3, 4, 5\}$ and $\Omega_l = \{1, 7, 8\}$.
Figure 7.1: Two wavefronts and the EG and LG for the MMTD. For the wavefront highlighted in green (blue), the first and last activated electrodes are the 4th and 8th (2nd and 6th) electrodes, respectively. Thus, the estimated \( \hat{V} \) using the MTD is in the direction of the vector that connects those electrodes as shown at the bottom of each wavefront. Two examples of the EGs and LGs that are used in the MMTD estimator are also specified with blue and red ellipsoids, respectively, when \( M_e = M_t = M \); e.g., for the blue highlighted wavefront, when \( M = 2 \), we have \( \Omega_e = \{1, 2\} \) and \( \Omega_t = \{5, 6\} \).
7.3. MODIFIED MTD CARDIAC CONDUCTION VELOCITY ESTIMATION

The following weighting coefficients are used in (7.1) and (7.2) for the Exponential Combination

\[ w_i = \frac{\exp(-\alpha \frac{t_i - t_{\text{min}}}{\Delta T})}{\sum_{k \in \Omega_e} \exp(-\alpha \frac{t_k - t_{\text{min}}}{\Delta T})}, \quad \text{for} \quad i = 1, \ldots, M_e, \quad (7.3) \]

\[ q_i = \frac{\exp(-\alpha \frac{t_{\text{max}} - t_i}{\Delta T})}{\sum_{k \in \Omega_l} \exp(-\alpha \frac{t_{\text{max}} - t_k}{\Delta T})}, \quad \text{for} \quad i = 1, \ldots, M_l, \quad (7.4) \]

where \( t_{\text{min}} \) and \( t_{\text{max}} \) are the minimum and maximum ATs of the wavefront, respectively, \( \Delta T = t_{\text{max}} - t_{\text{min}} \) is the wavefront duration, and \( \alpha \) is a positive scalar that determines the exponential decay constant of the weighting coefficients. Note that for very large \( \alpha \), \( t_e \) and \( t_l \) become very close to \( t_{\text{min}} \) and \( t_{\text{max}} \), respectively; thus, the difference between the MTD and the modified method becomes smaller. In Section 9.4, we provide a proper approach to specify \( \alpha \) to improve the VV estimation.

We can also use the following Linear Combination coefficients that only depend on the wavefront’s ATs

\[ w_i = \frac{t_{\text{max}} - t_i}{\sum_{j \in \Omega_e} (t_{\text{max}} - t_j)}, \quad \text{for} \quad i = 1, \ldots, M_e, \quad (7.5) \]

\[ q_i = \frac{t_i - t_{\text{min}}}{\sum_{j \in \Omega_l} (t_j - t_{\text{min}})}, \quad \text{for} \quad i = 1, \ldots, M_l. \quad (7.6) \]

Finally, using the representing values of the EG \((p_e, t_e)\) and the LG \((p_l, t_l)\), the velocity vector \( \mathbf{v} \) is estimated as

\[ \mathbf{v} = \frac{p_l - p_e}{t_l - t_e}. \quad (7.7) \]
7.4 Simulation Results

In this section, we consider the circular catheter with a radius of 1.25cm and \( N \) bipolar electrodes that are uniformly distributed on it. We assume that the catheter and the VV lie on the \( xy \)-plane, and we represent the VV with a complex value \( V = |V|e^{j\theta} \), where its real (imaginary) part shows the \( x \) (\( y \)) component of the velocity. The minimum and maximum wavefront speeds in our simulations are 40 and 200cm/s, respectively [36]. All the results presented in this section are obtained by averaging over 180000 independent simulation runs; i.e., we consider 360 different values for the phase of the VV (\( \theta = 1^\circ, 2^\circ, \cdots, 360^\circ \)) and for each \( \theta \), we generate 500 VVs with different values for \( |V| \) that are randomly selected from the values between 40 and 200. For each VV, we generate the ATs of the electrodes; to include the AT estimation error, we add zero-mean independent identically distributed additive Gaussian noises with the standard deviation of \( \sigma_T \) to the ATs of the wavefront. The contaminated ATs are then used in the MTD, MMTD, or MinV [111] method for the VV estimation. Throughout this section, we further assume that the cardinality of \( \Omega_e \) and \( \Omega_l \) in the MMTD are equal (\( M_e = M_l = M \)) and use (7.3) and (7.4) to calculate \( w_i \) and \( q_i \), respectively. In the first simulation, our aim is to obtain proper \( \alpha \) for the MMTD in different conditions. Decaying constant \( \alpha \) can be selected, such that the VV estimator provides a good average performance. To find \( \alpha \), we generate several VVs and estimate them using the proposed MMTD with different \( \alpha \)s; the best \( \alpha \) is the one that minimizes the average absolute error of the VV. Figure 7.1 shows the mean relative absolute error of the VV estimation (\( |V - \hat{V}|/|V| \)) as a function of the \( \alpha \) for \( M = N/2 \) and various \( \sigma_T \). This figure shows that the optimum \( \alpha \) is a...
7.4. SIMULATION RESULTS

Figure 7.1: Relative absolute error of the VV estimation of the MMTD method as a function of weights exponential decay constant $\alpha$.

function of the catheter shape, $M, N, \sigma_T$. The optimum value for $\alpha$ that minimizes the average absolute estimation error of the VV in different simulation conditions is reported in Table 7.1. This table can be used to obtain $\alpha$, when $\sigma_T$ is known. If $\sigma_T$ is unknown, we can select $\alpha$ which has a proper mean relative error for various $\sigma_T$. For instance, we can select $5 \leq \alpha \leq 7$ which has an acceptable relative VV estimation error for various $M, N, \sigma_T$ (see yellow highlighted zone in Figure 7.1).

In the next simulations, we compare the performance of the MTD and MMTD. Figure 7.2, shows the polar plot of these estimators when the optimum $\alpha$s in Table 7.1 are used in the MMTD. For the curves in this figure, the radius shows the relative absolute error of the VV estimation in dB, and the angle is the VV phase ($\theta$). The total number of electrodes of the catheter for this simulation is either $N = 4$ or $N = 10$, and $M = 1, \cdots, N/2$. Angle positions of the electrodes are also shown.
Table 7.1: Optimum $\alpha$ that minimizes the average relative absolute velocity estimation error of the MMTD for the circular catheter with radius 1.25cm with $N$ bipolar electrodes that are uniformly distributed on it.

<table>
<thead>
<tr>
<th>$(N, M)$</th>
<th>$\overrightarrow{\sigma_T}$</th>
<th>0.1 ms</th>
<th>1 ms</th>
<th>5 ms</th>
<th>10 ms</th>
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</table>

with the filled circles in Figure 7.2. This figure shows that the MMTD has a smaller average error than the MTD for most $\theta$s. However, when $\theta$ is in the direction of the one of the electrode pairs, the estimation error of the MTD becomes close to zero, and the MMTD has a larger error than the MTD.

Figure 7.3 shows the relative absolute error of the VV estimation as a function of $N$ for different AT noise variances. For the MMTD, $M = N/2$ and the optimum $\alpha$, reported in Table 7.1, are used. This figure confirms that the proposed MMTD can improve the average absolute error of the MTD approach. Figure 7.3 also shows that, similar to the MTD, the average absolute error of the MMTD is a decreasing function of $N$. However, the decrease in the average absolute error of the MMTD approach is less than the one of the MTD method.

Figure 7.4 shows the relative absolute error of the VV estimation as a function of
7.4. SIMULATION RESULTS

When AT noise is negligible ($\sigma_T = 0.1\text{ms}$) and $M = N/2$. This figure shows that the MMTD with $\alpha = 5$ has a similar performance to the one with the optimum $\alpha$, when $N \geq 6$. Based on this figure, the MinV [111] estimates the VV more accurately than the MTD which is consistent with [111]; also this figure shows that the MMTD outperforms both the MTD and MinV.

Figure 7.5: The relative absolute error of the VV estimation as a function of $M$ for $\sigma_T = 0.1, 10\text{ms}$ when the optimum $\alpha$s, reported in Table 7.1, are used.

Finally, Figure 7.5 shows the average relative absolute error of the VV estimation as a function of $M$ for different $\sigma_T$ when $\alpha$s reported in Table 7.1 are used. It is clear that the largest decrease in the relative error of the MMTD is achieved when $M$ is increased from one to two. Note that the MMTD approach with $M = 1$ becomes the MTD method. This figure shows that when the ATs are accurately estimated, improvement obtained by increasing $M$ beyond two is negligible.
7.5 Conclusion

In this chapter, we studied the cardiac conduction velocity estimation using the IEGMs and proposed the modified MTD (MMTD). In the MTD, for each wavefront, the estimated VV is in the direction of the vector that connects the first to the last activated electrode of the catheter; the magnitude of the estimated VV is obtained by dividing the distance between two electrodes to the delay between their ATs. In the MMTD, on the other hand, we divide the ATs of the wavefront into two groups, EG and LG. The EG contains $M_e$ electrodes with early activations, and the LG contains $M_l$ electrodes with late activations. We assign a time value (weighted mean of the ATs) and a location value (weighted mean of the electrodes’ locations) to each group, and the estimated wavefront VV is in the direction of the vector that connects the assigned location of the EG to that of the LG. Using synthetic data, we obtained proper exponential decay constants that are used for the weighted mean calculation in various conditions. We also showed that the MMTD improves the wavefront VV estimation of the MTD and is more robust to the AT estimation error.
Figure 7.2: Polar plot with the radius of the relative absolute error of the VV estimation in dB, and the angle of the VV phase $\theta$. The optimum $\alpha$s (Table 7.1) are used in the MMTD; $N$ is either 4 or 10, and $M = 1, \cdots, N/2$. 
Figure 7.3: The relative absolute error of the VV estimation as a function of $N$ for different $\sigma_T$. The error of the MTD is shown with dashed lines. For the MMTD (solid lines), $M = N/2$, and the optimum $\alpha$s in Table 7.1 are used.
Figure 7.4: The relative absolute error of the VV estimation as a function of $N$ when $\sigma_T = 0.1$ms. For the MMTD, $M = N/2$ and either $\alpha = 5$ or the optimum $\alpha$s, reported in Table 7.1, are used.
Chapter 8

Maximum Likelihood Wavefront Conduction Velocity Estimation in the Presence of Ambiguities in the Locations and Activation Times of the Recording Points

8.1 Abstract

The cardiac conduction velocity vector (CCVV) or wavefront velocity vector (VV) can be estimated using the intracardiac electrograms; i.e., the activation times (ATs) and locations of the recording catheter’s electrodes are used for the VV estimation. In practice, the ATs and locations of the electrodes are estimated, and if their estimation errors are not taken into consideration, they may significantly degrade the quality of the velocity estimation. Thus, in this chapter, we assume that the locations and the ATs of the catheter’s electrodes are contaminated with white Gaussian noise with known variances, and we derive the maximum likelihood (ML) cardiac velocity
estimator for the planar wavefront. We further calculate the ML estimate of the AT that the planar wavefront reaches at any given location. Our simulation results show the efficiency of the proposed ML estimators for the velocity and AT, and they also confirm the validity of the derived relations for the covariance of the error of the estimators.

8.2 Introduction

The cardiac conduction velocity vector (CCVV) map, which describes the speed and direction of the wavefront propagation at desired locations on the cardiac shell, can provide insight into the mechanisms triggering and sustaining arrhythmias [102]. The CCVV can be estimated by processing the intracardiac electrograms (IEGMs), i.e., it can be obtained by analysing the activation times (ATs) and the locations of the catheter’s electrodes [67, 68, 109, 112]. Estimation of the intracardiac AT is challenging, especially during complex arrhythmias such as atrial fibrillation, mainly because the morphologies, durations and amplitudes of the active zones of IEGMs vary from one activation to the next. Consequently, the AT estimation methods [1, 4, 78] always obtain the ATs with some degree of ambiguity. Furthermore, the techniques that are used to localize the catheters’ electrodes and track their movements in the cardiac chambers also have some errors, as the common magnetic-based [113] and impedance-based [114] cardiac mapping systems have limited catheter localization accuracy [115, 116].
Therefore, in practice, the exact ATs and locations of the electrodes are not available, and if their estimation errors are not taken into consideration, they may significantly degrade the quality of the velocity estimation. Here, we consider both catheter localization and AT estimation error and propose a CCVV estimator, i.e., we assume that the ATs and locations of catheter’s electrodes are contaminated with white Gaussian noise, and we derive the maximum likelihood (ML) estimate of the wavefront VV and the AT at a desired point \( p_d \). We also calculate the covariance of the velocity and AT estimation error as a function of the shape of the mapping catheter and the quality of the estimations of the electrodes’ locations and ATs.

### 8.3 Cardiac Conduction VV Estimation

In this chapter, we consider the problem of the CCVV estimation for the planar wavefront in the isotropic medium. We assume that the electrical wavefront and the recording catheter are in the same plane, and the planar wavefront hits the catheter, such that it passes the area under the \( i \)th electrode located at \( p_i \in \mathbb{R}^{3 \times 1} \) at time \( t_i \).

Our aim is to find the AT and velocity at a desired location \( p_d \). If \( t_d \) shows the AT at \( p_d \), we have

\[
t_i = t_d + (p_i - p_d)^T \frac{v}{\|v\|^2}, \quad \text{for} \quad i = 1, \cdots, N. \tag{8.1}
\]

We can rewrite (8.1) in terms of the estimated ATs (\( \tilde{t}_i \)) and measured electrodes’ locations (\( \tilde{p}_i \)) as

\[
\tilde{t}_i = t_d + \frac{v^T}{\|v\|^2} (\tilde{p}_i - p_d + n_{p_i}) + n_{t_i}, \quad \text{for} \quad i = 1, \cdots, N \tag{8.2}
\]
where \( n_t \) is the AT estimation error for the \( t_i \), and \( n_{p_i} \in \mathbb{R}^{3 \times 1} \) represent the localization error of the \( i \)th bipolar electrode of the catheter. The sets of equations in (8.2) can be expressed as

\[
\tilde{\mathbf{t}} = \left[ \mathbf{P}, \mathbf{1}_N \right] \begin{bmatrix} \mathbf{v}^T \\ t_d \end{bmatrix}^T + \mathbf{n}_t + \mathbf{N}_p \frac{\mathbf{v}}{\| \mathbf{v} \|^2},
\]

(8.3)

where \( \mathbf{P} \triangleq \mathbf{C} - 1_N \mathbf{p}_d^T, \) \( \mathbf{C} \) contains the estimated locations of the catheter’s electrodes, \( \tilde{\mathbf{t}} \) is made of the estimated ATs of the electrodes, \( \mathbf{N}_p \) and \( \mathbf{n}_t \) represent the localization error and AT estimation error of the catheter’s electrodes as defined below:

\[
\mathbf{C} = \begin{bmatrix} \tilde{\mathbf{p}}_1, \cdots, \tilde{\mathbf{p}}_N \end{bmatrix}^T \in \mathbb{R}^{N \times 3}, \quad \mathbf{N}_p = \begin{bmatrix} \mathbf{n}_{p_1}, \cdots, \mathbf{n}_{p_N} \end{bmatrix}^T \in \mathbb{R}^{N \times 3},
\]

\[
\tilde{\mathbf{t}} = \begin{bmatrix} \tilde{t}_1, \cdots, \tilde{t}_N \end{bmatrix}^T \in \mathbb{R}^{N \times 1}, \quad \mathbf{n}_t = \begin{bmatrix} n_{t_1}, \cdots, n_{t_N} \end{bmatrix}^T \in \mathbb{R}^{N \times 1}.
\]

To simplify the formulation, we assume that the average of all the estimated ATs is zero, and the average of the locations of all the catheter’s electrodes is the origin. Thus,

\[
\sum_{i=1}^N \tilde{t}_i = 1_N^T \tilde{\mathbf{t}} = 0 \quad \text{and} \quad \sum_{i=1}^N \mathbf{p}_i^T = 1_N^T \mathbf{C} = \mathbf{0}_3^T.
\]

(8.4)

Note that to satisfy (8.4), we can remove the average of electrodes’ ATs from all the considered ATs, such that the average of ATs of the electrodes becomes zero; and similarly, we can shift all the locations, such that the origin becomes the center point
of the catheter. Therefore, the assumptions in (8.4) do not restrict the generality of the considered problem.

We assume that vectors \( \mathbf{n}_t \sim \mathcal{N}(0_N, \sigma_t^2 \mathbf{I}_N) \) and \( \mathbf{n}_{p_k} \sim \mathcal{N}(0_3, \sigma_p^2 \mathbf{I}_3) \) for \( k = 1, \cdots, N \) are independent. Therefore, considering (8.3), the probability density function (pdf) of \( \tilde{\mathbf{t}} \) is

\[
f(\tilde{\mathbf{t}}|v, t_d) = \frac{\exp \left( -\|\tilde{\mathbf{t}} - \mathbf{P} \frac{v}{\|v\|^2} - t_d \mathbf{1}_N \|^2 / (\sigma_t^2 + \frac{\sigma_p^2}{\|v\|^2}) \right)}{\left(2\pi(\sigma_t^2 + \frac{\sigma_p^2}{\|v\|^2})\right)^{\frac{N}{2}}}.
\] (8.5)

Note that, in (8.5), the variance of the Gaussian random vector \( \tilde{\mathbf{t}} \) depends on unknown \( \|v\| \). In the following subsection, we assume that the catheter localization error is negligible and estimate the unknown vector \( \mathbf{\theta} \equiv [\frac{\mathbf{v}^T}{\|v\|}, t_d]^T \). Later, we estimate \( \mathbf{\theta} \) in a more general case by considering the catheter electrodes localization, as well as AT estimation, errors.

### 8.3.1 CCVV When Catheter Localization Error Is Negligible

When the catheter localization error is negligible, i.e., \( \sigma_p^2 \ll \sigma_t^2 \|v\|^2 \), the problem of the velocity estimation becomes easy to solve. In this condition, the presented model in (8.3) becomes the Gaussian linear model [92], in which the additive noise covariance matrix is no longer a function of the unknown VV. Thus, according to [92], the ML estimate of the unknown vector \( \mathbf{\theta} \) is \( (\mathbf{A}^T \mathbf{A})^{-1} \mathbf{A}^T \tilde{\mathbf{t}} \) where
\[ \mathbf{A} = [\mathbf{C} - \mathbf{1}_N \mathbf{p}_d^T, \mathbf{1}_N] \]. The inverse of \( \mathbf{A}^T \mathbf{A} \) can be written as [117] [118, sec. 3.2.6]

\[
(\mathbf{A}^T \mathbf{A})^{-1} = \begin{bmatrix}
\mathbf{x}^T (\mathbf{C}^T \mathbf{C})^{-1} \\
\mathbf{x}^T (\mathbf{C}^T \mathbf{C} + N \mathbf{p}_d \mathbf{p}_d^T)^{-1} \\
\mathbf{x}
\end{bmatrix},
\]

(8.6)

where \( \kappa = N - N^2 \mathbf{p}_d^T (\mathbf{C}^T \mathbf{C} + N \mathbf{p}_d \mathbf{p}_d^T)^{-1} \mathbf{p}_d \).

Using (8.4) and (8.6), the ML estimate of \( \mathbf{\theta} \) is

\[
\hat{\mathbf{\theta}} = (\mathbf{A}^T \mathbf{A})^{-1} \mathbf{A}^T \hat{\mathbf{t}} = \begin{bmatrix}
(\mathbf{C}^T \mathbf{C})^{-1} \mathbf{C}^T \hat{\mathbf{t}} \\
\mathbf{x} \\
\mathbf{p}_d^T (\mathbf{C}^T \mathbf{C})^{-1} \mathbf{C}^T \hat{\mathbf{t}}
\end{bmatrix},
\]

(8.7)

where we used the Sherman-Morrison formula [118]

\[
(\mathbf{C}^T \mathbf{C} + N \mathbf{p}_d \mathbf{p}_d^T)^{-1} = (\mathbf{C}^T \mathbf{C})^{-1} - \frac{N (\mathbf{C}^T \mathbf{C})^{-1} \mathbf{p}_d \mathbf{p}_d^T (\mathbf{C}^T \mathbf{C})^{-1}}{1 + N \mathbf{p}_d^T (\mathbf{C}^T \mathbf{C})^{-1} \mathbf{p}_d},
\]

to derive (8.8) from (8.7). The first 3 elements of \( \hat{\mathbf{\theta}} \), i.e., \( [\hat{\mathbf{\theta}}]_{1:3} \), is the unbiased ML estimate of \( \frac{\mathbf{v}}{\|\mathbf{v}\|^2} \) with the covariance matrix of

\[
\text{Cov}([\hat{\mathbf{\theta}}]_{1:3}) = \text{Cov}(\frac{\mathbf{v}}{\|\mathbf{v}\|^2}) = \sigma_v^2 (\mathbf{C}^T \mathbf{C})^{-1}.
\]

(8.9)

This equation shows that the covariance of estimated \( \mathbf{v}/\|\mathbf{v}\|^2 \) depends on the catheter shape and variance of the AT estimation error, and, as we expected, it is independent of \( \mathbf{p}_d \), the desired location for the velocity estimation. Note that when the localization error is negligible, the ML estimate of \( \mathbf{\theta} \) is the same as its least squared (LS) estimate [92], and (8.8) is consistent with the reported results in [112].
The fourth element of \( \theta \), denoted by \( [\hat{\theta}]_4 \), is the unbiased ML estimate of \( t_d \), and the variance of it can be expressed as

\[
\text{Var}([\hat{\theta}]_4) = \frac{\sigma_t^2}{N} + \sigma_t^2 p_d^T (C^T C)^{-1} p_d.
\] (8.10)

The first term in (8.10) is independent of the desired location for the AT estimation (\( p_d \)), and it decreases as the number of catheter electrodes increases; whereas, the second term depends on \( p_d \) and can be interpreted as the results of the estimation error in the velocity. Among all the desired \( p_d \) with given length \( \| p_d \|^2 = c \), the largest variance of \( [\hat{\theta}]_4 \) occurs when \( p_d \) is in the direction of the dominant eigenvector of \( (C^T C)^{-1} \), as we have

\[
\max_{p_d} \text{Var}([\hat{\theta}]_4) = \frac{\sigma_t^2}{N} + \frac{c \sigma_t^2}{\lambda_{\min}(C^T C)}.
\] (8.11)

s.t. \( \| p_d \|^2 = c \)

Note that the dominant eigenvector (eigenvector that corresponds to the largest eigenvalue) of \( (C^T C)^{-1} \), denoted by \( q_{\max}((C^T C)^{-1}) \), is the eigenvector that corresponds to \( \lambda_{\min}(C^T C) \) which is the smallest eigenvalue of \( C^T C \).

### 8.3.2 CCVV in the Presence of the Catheter Localization Error

When the catheter localization error is not negligible, the variance of the additive Gaussian noise in the linear model (8.3) depends on the unknown VV norm. In this condition, the pdf of the measured ATs is given in (8.5) and the log-likelihood (LL)
of it can be expressed as

\[
    \ln f(\tilde{t}|v, t_d) \propto -\frac{N}{2} \ln(\sigma_i^2 + \frac{\sigma_p^2}{\|v\|^2}) - \frac{\|\tilde{t} - P\frac{v}{\|v\|^2} - t_d1_N\|^2}{\sigma_i^2 + \frac{\sigma_p^2}{\|v\|^2}}. \tag{8.12}
\]

To obtain the ML estimate of \(t_d\), we set the derivative of the LL with respect to \(t_d\) equal to zero, i.e., \(\partial \ln f(\tilde{t}|v, t_d)/\partial t_d = 0\), which leads to \(1_N^T(\tilde{t} - P\frac{v}{\|v\|^2} - t_d1_N) = 0\). Thus, we have

\[
    \hat{t}_d = \frac{1}{N}1_N^T(\tilde{t} - P\frac{v}{\|v\|^2}). \tag{8.13}
\]

Substituting (8.13) in (8.12), we obtain

\[
    \ln f(\tilde{t}|v, \hat{t}_d) \propto -\frac{N}{2} \ln(\sigma_i^2 + \frac{\sigma_p^2}{\|v\|^2}) - \frac{\|\tilde{t} - P\frac{v}{\|v\|^2} - \frac{1}{N}1_N^T(\tilde{t} - P\frac{v}{\|v\|^2})1_N\|^2}{\sigma_i^2 + \frac{\sigma_p^2}{\|v\|^2}}. \tag{8.14}
\]

To obtain the wavefront VV, we set the derivative of above equation with respect to vector \(v\) equal to zero vector, i.e., \(\partial \ln f(\tilde{t}|v, t_d)/\partial v = 0\), which leads to

\[
    \frac{\sigma_p^2}{\|v\|^2}(N - 2\frac{\|\tilde{t} - C\frac{v}{\|v\|^2}\|^2}{\sigma_i^2 + \frac{\sigma_p^2}{\|v\|^2}})v - C^TCv + 4\frac{\tilde{t}^TCv}{\|v\|^4}v + 2C^T\tilde{t} - 4\frac{\tilde{t}^TCv}{\|v\|^2}v = 0, \tag{8.15}
\]
It is not hard to check that if $\sigma_p^2 = 0$, $v/\|v\|^2 = (C^TC)^{-1}C^T\tilde{t}$ satisfies (8.15), which is consistent with our results in subsection 8.3.1. We rewrite (8.15) as

$$
(C^TC + \lambda(v)I_3) \frac{v}{\|v\|^2} = C^T\tilde{t},
$$

(8.16)

where

$$
\lambda(v) = \sigma_p^2 \left( \frac{\|\tilde{t} - Cv/\|v\|^2\|^2}{\sigma_t^2 + \sigma_p^2/\|v\|^2} - \frac{N}{2} \right) - \frac{2v^TC^T Cv}{\|v\|^2} + 2\tilde{t}^TCv.
$$

(8.17)

Finally, considering (8.16), we propose the following pseudocode for the CCVV ($v^{(opt)}$) estimation.

**Input:** The electrodes’ location matrix ($C$) and AT vector ($\tilde{t}$), the minimum CCVV ($\|v_{min}\|$), grid search size ($\delta$) for 1-D optimization of $\lambda$, and the variances of the location and AT estimation error ($\sigma_p^2$ and $\sigma_t^2$).

If $\sigma_t^2 \gg \sigma_p^2/\|v_{min}\|$, estimate $v$ using (8.8).

Else $e_{min} = 10^{10}$ and $\lambda = \lambda_{low}$,

While $\lambda < \lambda_{up}$, $\frac{\hat{v}}{\|\hat{v}\|^2} = (C^TC + \lambda I_3)^{-1}C^T\tilde{t}$; calculate $\lambda(\hat{v})$ using (8.17), and $e = |\lambda(\hat{v}) - \lambda|$.

If $e < e_{min}$, $e_{min} \leftarrow e$ and $\frac{v^{(opt)}}{\|v^{(opt)}\|^2} \leftarrow \frac{\hat{v}}{\|\hat{v}\|^2}$, End

$\lambda \leftarrow \lambda + \delta$, End

End
8.4 Simulation Results

In this section, we assume that the recording catheter and the cardiac shell surface are in the $x-y$ plane, and the $z$-component of the VV is zero. In this case, the VV can be presented as a complex value $V = |V|e^{j\phi}$, where its real and imaginary parts show the $x$ and $y$ components of the velocity, respectively, and $|V| = \|v\|$. In our simulation, we assume that the cardiac speed can vary between 40-200 cm/s. We consider 360 different values for the phase of the VV ($\phi = 1^\circ, 2^\circ, \cdots, 360^\circ$) and for each velocity phase, we generate 100 different VVs with their $|V|$s randomly selected from [40-200]cm/s. For each VV, we synthesize the ATs of the recording catheter. The ATs and electrodes’ locations that are contaminated with white Gaussian noise are then used for the VV estimation. Any point on the plotted curves with a “Sample Estimate” label is the result of the averaging over 36000 VVs.

We consider two different types of catheters: 1) a circular catheter with $N$ bipolar electrodes (electrodes are uniformly distributed on a circle with radius of 1.25cm); 2) a spiral catheter as shown in Figure 8.1(a). In all the simulations, the desired locations $p_d$s are either 180 or 90 points uniformly distributed on the circle with a radius of 2cm, which has the same center point as the catheter, e.g., Figure 8.1(a) shows the desired locations on the circle around the spiral catheter.

For the 1st simulation, the catheter localization error is negligible ($\sigma_p = 0$); thus, we use the equations in subsection 8.3.1 to obtain the ML estimate of $\theta$. Figure 8.1(b) shows the polar plot with the radius of the $\text{Var}([\hat{\theta}]_d)$ (variance of the estimated $t_d$) and the angle of the phase of $p_d$, when $\sigma_t = 4$ms and the spiral catheter is used. The
Figure 8.1: Left: The spiral catheter and 180 desired points $p_d$s uniformly distributed on the circle with radius 2cm with the same center point as the catheter. Right: Polar plot with the radius of the variance of the estimated $t_d$, and the angle of the phase of $p_d$ when $\sigma_t = 4$ms and $\sigma_p = 0$. The directions $p_d$s associated with the maximum and minimum possible variances of the estimated AT are shown with blue and green arrays, respectively.

directions of the eigenvectors of $C^T C$ (see (8.11)), which are accurately aligned with the extremum variances of ($\hat{\theta}_4$), are also shown in this figure.

The impact of the AT noise variance on the accuracy of the AT estimation is studied in Figure 8.2. This figure shows the polar plot with the radius of the variance of estimated $t_d$ in dB, and the angle of the phase of $p_d$ for the spiral or circular catheter ($N = 10$) and for various $\sigma_t$s when $\sigma_p = 0$.

The effect of the number of the electrodes of the circular catheter ($N$) on the variance of the estimated $t_d$ is investigated in the next simulation. Figure 8.3 shows
8.4. SIMULATION RESULTS

Figure 8.2: Polar plot with the radius of the variance of the estimated $t_d$ in dB, and the angle of the phase of $p_d$ for various $\sigma_t$ when $\sigma_p = 0$

the polar plot of the variance of the estimated $t_d$, when $\sigma_t = 5$ms.

Figures 8.1-8.3 show that the “Sample Estimate” curves, which are the results of the averaging over many independent simulation runs, perfectly match the derived equations in Section 10.3.

Finally, in the last simulation, we compare the performance of the ML velocity estimator (8.8) and the proposed ML estimator in the presence of the localization error. Figure 8.4 shows the average of the normalized velocity estimation error $|V - \hat{V}|^2/|V|^2$, as a function of $\sigma_p$ for various $\sigma_t$, where $\hat{V}$ denotes the estimated velocity. The ML estimator that is the solution of (8.16) and is robust to the localization error is labeled as the “Robust ML” (RML) in this figure. We use $\lambda_{up} = -\lambda_{low} = 10\sigma_p^2$ and $\delta = 0.002$ in the proposed pseudocode in Section 8.3.2 to obtain the RML.
From the outer loop to the inner one $N = 4, 6, \cdots, 12$

Figure 8.3: Polar plot with the radius of the $\text{Var}([\hat{\theta}]_4)$, and the angle of the phase of $p_d$ for $\sigma_t = 5\text{ms}$ and the circular catheter with $N$ electrodes

...̂\theta}_4)$, and the angle of the phase of $p_d$ for $\sigma_t = 5\text{ms}$ and the circular catheter with $N$ electrodes

...̂\theta}_4)$, and the angle of the phase of $p_d$ for $\sigma_t = 5\text{ms}$ and the circular catheter with $N$ electrodes

8.5 Conclusion

In this chapter, we studied the problem of wavefront velocity estimation using the IEGMs. Assuming that the ATs and locations of the catheter’s electrodes are
Figure 8.4: The average of the normalized velocity estimation error as a function of $\sigma_p$ (in cm) for various $\sigma_t$ when the spiral catheter is used contaminated with white Gaussian noise with known variances, we derived the ML estimates of the VV of the planar wavefront and the activation time that the wavefront reaches a desired location. We also derived the covariance matrix of the error of the estimated VV and AT. We showed that when the AT noise variance is significantly larger than the variance of the localization error divided by the norm of the minimum velocity ($\sigma_t^2 \gg \sigma_p^2/\|v_{\text{min}}\|^2$), the performance of the LS estimator and the ML estimator becomes similar. However, when this condition is not valid, the ML velocity estimator provides better accuracy. Our simulation results for the circular and spiral catheters showed the accuracy of our proposed cardiac velocity estimators and confirmed the validity of our results.
Chapter 9

Cardiac Conduction Velocity Estimation from Sequential Mapping Assuming Known Gaussian Distribution for Activation Time Estimation Error

9.1 Abstract

In this chapter, we study the problem of the cardiac conduction velocity (CCV) estimation for the sequential intracardiac mapping. We assume that the intracardiac electrograms of several cardiac sites are sequentially recorded, their activation times (ATs) are extracted, and the corresponding wavefronts are specified. The locations of the mapping catheter’s electrodes and the ATs of the wavefronts are used here for the wavefront velocity estimation. We assume that the extracted ATs include some estimation errors, which we model with zero-mean white Gaussian noise values with known variances. Assuming stable planar wavefront propagation, we derive the maximum likelihood CCV estimator, when the synchronization times between
various recording sites are unknown. We analytically evaluate the performance of the CCV estimator and provide its mean square estimation error. Our simulation results confirm the accuracy of the proposed method and the error analysis of the proposed CCV estimator.

9.2 Introduction

The intracardiac mapping systems provide a platform for three-dimensional visualization of the cardiac electrical activities [13]. They are deployed to collect the intracardiac electrograms (IEGMs) from chambers of interest and track the catheters’ movements in real-time without the use of the fluoroscopy [113–115]. Common cardiac mapping systems that are currently used can be categorized into various types: continuous, sequential, contact, and non-contact systems [33].

In continuous mapping, a large catheter with a sizable number of electrodes collects the IEGMs and the cardiac map can be created quickly after analysing a few wavefronts [40]. In sequential mapping, however, a small catheter with a high density of electrodes is used to collect the IEGMs from several sites sequentially. The sequential mapping with small catheters is the most common mapping approach for the ablation therapy procedure mainly because the small catheters are easier to control (easier to land them on the intracardiac surface) and are less expensive [34] (see Section 1.5 for more details).

In this chapter, we consider the problem of the cardiac conduction velocity (CCV) estimation [67, 68, 108, 109, and references therein] using sequential recording. More
specifically, we assume that the IEGMs of several sites are sequentially recorded and the ATs of the electrograms are estimated \([3, 68, 78]\). We model the ATs estimation error with independent identically distributed (i.i.d.) zero-mean Gaussian noise with known variance that depends on the location of the IEGM recording site. We derive the maximum likelihood (ML) CCV estimation for the planar wavefront when the time synchronization values between sequential recordings are also unknown. Furthermore, we derive the mean square estimation error (MSE) of the proposed wavefront velocity estimator. Finally, using our simulation results, we show that the proposed method can estimate the CCV accurately and also that the error analysis of the proposed method is precise.

9.3 Sequential CCV Estimation

In this chapter, we assume that electrical activities of the heart are sequentially recorded from \(C\) sites, and our goal is to use the recordings from these locations to estimate the CCV at a close desired location. Here, we consider an isotropic cardiac medium and assume that the direction and speed of the planar wavefront propagation does not change throughout our recording duration within the recording sites. We further assume that the desired location and recording sites are in a plane. Suppose that the catheter is located at the \(c\)th recording site and during measuring \(W_c\) wavefronts \(N_c\) of its electrodes are in contact with the cardiac shell. We assume that for \(c = 1, \cdots, C\), the \(w\)th planar wavefront with CCV \(\mathbf{v}\) hits the catheter such that it passes the area under its \(i\)th electrode located at \(\mathbf{p}'_{c,i} \in \mathbb{R}^{3 \times 1}\) at time \(t'_{c,w,i}\). Our aim is to find the AT and velocity (\(\mathbf{v}\)) at a desired location \(\mathbf{q}'\).
9.3. SEQUENTIAL CCV ESTIMATION

Figure 9.1: The ATs of $C = 2$ sites are collected sequentially using the spiral catheter. At the 1st (2nd) location, the ATs of $N_1 = 4$ ($N_2 = 3$) electrodes during the propagation of $W_1 = 3$ ($W_2 = 2$) wavefronts are recorded.

Figure 10.1 shows an example of our considered scenario, where the IEGMs of two sites are recorded using a spiral catheter. At each site, IEGMs of some of the electrodes are used to estimate the velocity at $q'$. At the first (second) recording site, four (three) of the catheter’s bipolar electrodes, which are close to the desired site, are
in contact with the cardiac shell, and their IEGMs are used for the CCV estimation. The ATs of the IEGMs are extracted, and the wavefronts are specified. Three (two) wavefronts are recorded at the first (second) catheter site. Thus, for this example, we have $C = 2, N_1 = 4, W_1 = 3, N_2 = 3$ and $W_2 = 2$.

If $s_{c,w}'$ shows the AT at $q'$ due to the $w$th wavefront at the $c$th site, and $n'_{c,w,i}$ shows the estimation error of $t'_{c,w,i}$, for $c = 1, \ldots, C, w = 1, \ldots, W_c$, and $i = 1, \ldots, N_c$, we have

$$t'_{c,w,i} = s'_{c,w} + (p'_{c,i} - q')^T v/\|v\|^2 + n'_{c,w,i}.$$  

(9.1)

We assume that the AT noise components $n'_{c,w,i}$ in (10.1) for different values of $c, w$, and $i$ are i.i.d. zero-mean Gaussian variables with $n'_{c,w,i} \sim N(0, \sigma_c^2)$. Note that $\mathbb{E}\{n'_{c,w,i}n'_{c',w',j}\} = \sigma_c^2 \delta_{c-c'}\delta_{w-w'}\delta_{i-j}$, where we assumed that variance of $n'_{c,w,i}$ only depends on the location of the catheter and is the same for all the electrodes and wavefronts at that recording site.

The following theorem provides the ML estimates of $v/\|v\|^2$ and $s'_{c,w}$ for $c = 1, \ldots, C$ and $w = 1, \ldots, W_c$.

**Theorem 2.** The ML estimation of $v/\|v\|^2$ is

$$\hat{v}/\|v\|^2 = \left(\sum_{i=1}^C W_i C_i^T C_i\right)^{-1} \sum_{c=1}^C (1_{W_c}^T \otimes C_c^T) t_c,$$

(9.2)

and the covariance matrix of this estimate is

$$\text{Cov}(\hat{v}/\|v\|^2) = \left(\sum_{i=1}^C W_i C_i^T C_i\right)^{-1},$$

(9.3)
where \( t_c \) for \( c = 1, \ldots, C \) is created as follows

\[
\begin{align*}
t'_{c,w} &= \left[ t'_{c,w,1}, \ldots, t'_{c,w,N_c} \right]^T \in \mathbb{R}^{N_c \times 1}, \\
t_{c,w} &= \frac{t'_{c,w}}{\sigma_c} - 1_{N_c}^T t'_{c,w}/(\sigma_c N_c) \in \mathbb{R}^{N_c \times 1}, \\
t_c &= \left[ t_{c,1}^T, \ldots, t_{c,W_c}^T \right]^T \in \mathbb{R}^{W_c \times N_c \times 1}.
\end{align*}
\]

and \( C_c \) for \( c = 1, \ldots, C \) is

\[
\begin{align*}
C'_c &= \left[ p'_{c,1}, \ldots, p'_{c,N_c} \right]^T \in \mathbb{R}^{N_c \times 3}, \\
C_c &= \frac{C'_c}{\sigma_c} - 1_{N_c}^T C'/\sigma_c - 1_{N_c}^T C'/(\sigma_c N_c) \in \mathbb{R}^{N_c \times 3}.
\end{align*}
\]

The ML estimate of \( s'_{c,w} \) for \( c = 1, \ldots, C, w = 1, \ldots, W_c \) is

\[
\hat{s}'_{c,w} = 1_{N_c}^T t'_{c,w}/N_c + q_c^T \sqrt{v}/\|v\|^2, \quad (9.4)
\]

where \( q_c = q' - C'_c 1_{N_c}/N_c \) and \( \sqrt{v}/\|v\|^2 \) is given in (9.2).

**Proof:** See Appendix A.

Note that similarly scaling all the AT estimation noise variances (multiplying \( \sigma_1, \ldots, \sigma_C \) to a constant) does not change the proposed estimator in (9.2). Thus, only the relative quality of the AT estimation is required to calculate (9.2). Here, we assume this information is available. In [119] an iterative approach is used to estimate the CCV when the variance of the AT estimation error is unknown. In practice, the variance of the AT estimation error closely relates to the powers and durations of the active zones (AZs) of the electrogram. It also depends on the IEGMs’ isoelectric
baseline power, in addition to the AT estimation method. More specifically, the AT estimation noise variance is a decreasing function of the power of the electrograms’ AZs and is an increasing function of the IEGM’s isoelectric baseline power, as well as the duration and fractionation complexity of the AZs. Therefore, the relative qualities of the AT estimation noise variances can be estimated by analysing the IEGMs at different sites; however, this is beyond the scope of the current chapter.

From (9.3), it is clear that if the variance of the AT estimation noise and the locations of the collecting electrodes are known, the CCV estimation performance can be estimated before collecting the electrograms. It also shows that the CCV estimation error is a decreasing function of the number of the IEGM recording sites and the number of wavefronts. Consequently, we can decrease the estimation error by collecting the longer IEGMs or collecting the IEGMs from more sites, where the attained improvement depends on the variance of the AT estimation at each site and the positions of the recording electrodes. We can also determine the number of wavefronts that are required to reach the specific CCV estimation accuracy. Thus, (9.3) can be used to analyse the quality of the IEGMs at each recording site, and it also shows the impact of the collected IEGMs from the specific site on the CCV estimation error reduction.

9.4 Simulation Results

In this section, we assume that the recording catheter and the cardiac shell surface are in the $xy$ plane. Thus, the $z$-component of the CCV is zero, and it is presented by a complex $V = |V|e^{j\phi}$, where its imaginary and real parts, respectively, show the $y$
and $x$ components of the velocity. For each simulation run, we generate a CCV with its $|V|$ and $\phi$ randomly chosen from $[40-200]$cm/sec and $[0−2\pi]$Rad, respectively [36], i.e., $|V| \sim U(40, 200)$ and $\phi \sim U(0, 2\pi)$, where $x \sim U(a, b)$ means that the random variable $x$ has the uniform distribution between $a$ and $b$. We assume the IEGMs of $C = 4$ sites are sequentially collected using a spiral catheter with ten bipolar electrodes; where, for each simulation run, the center of the randomly rotated catheter is located at $(\pm2 \pm j2)$cm for the measurement of the 4 sites. At the $c$th location, $N_c$ electrodes of the catheter are randomly selected, and their electrogram during the propagation of the $W_c$ planar wavefronts with the CCV $V$ are used in the proposed estimator. In this simulation, we assume that $N_1 = 3, N_2 = 2, N_3 = 3, N_4 = 5$ and $W_1 = 1, W_2 = 3, W_3 = 2, W_4 = 2$.

Figure 9.1, shows the catheter positions during two independent simulation runs. Also, it shows the average of the normalized error (ANE) of the CCV estimation for various $\sigma$ when $\sigma_1 = 0.5\sigma, \sigma_2 = 0.8\sigma, \sigma_3 = \sigma, \sigma_4 = 0.8\sigma$, where $\text{ANE} = \mathbb{E}\{|V|^2(V/|V|)^2 - \hat{V}/|\hat{V}|^2\}$, in which $\hat{V}$ is the ML CCV estimation. The ANE during the recording of the eight wavefronts is calculated by averaging over 50000 independent simulation runs. Considering (9.3), the ANE can be approximated as $|V|^2\text{tr}((\sum_{i=1}^C W_iC_i^T C_i)^{-1})$, where considering the distribution of $|V|$, we have $|V|^2 = \mathbb{E}\{|V|^2\} = 16533$. It is clear from Figure 9.1 that as the number of the wavefronts that are used for the CCV estimation increases, the ANE decreases. The amount of the improvement achieved by including the specific wavefront in our analysis depends on the quality of the AT estimation at the corresponding recording site, and the number and locations of the electrodes that are used for the CCV estimation. This figure also confirms the accuracy of the derived formula for the covariance of the CCV estimation.
9.4. SIMULATION RESULTS

Figure 9.1: Top: Examples of the positions of the spiral catheter during two independent simulation runs when $N_1 = 3$, $N_2 = 2$, $N_3 = 3$, and $N_4 = 5$; Bottom: $\text{ANE} = \mathbb{E}\{|V|^2(V/|V|^2 - \hat{V}/|\hat{V}|^2)^2\}$ averaged over 50000 independent runs. Eight wavefronts are collected ($W_1 = 1, W_2 = 3, W_3 = 2, W_4 = 2$) when $\sigma_1 = 0.5\sigma, \sigma_2 = 0.8\sigma, \sigma_3 = \sigma$, and $\sigma_4 = 0.8\sigma$. 

\[
\sigma_1 = 0.5\sigma, \sigma_2 = 0.8\sigma, \sigma_3 = \sigma, \sigma_4 = 0.8\sigma 
\]
9.5 Conclusion

In this chapter, we studied the problem of the CCV estimation in the sequential mapping when the time alignment references between the sequential recordings are unknown. Assuming that the AT estimation errors at various sites have the zero-mean Gaussian distribution with known variances, we derived the ML CCV estimation for the stable planar wavefront in a two-dimensional scenario. We derived the MSE of the proposed estimator and showed that we can decrease the estimation error by using the longer IEGMs or collecting the IEGMs from more sites. We showed that the improvement attained by including a wavefront for the CCV estimation depends on the variance of the AT estimation at that site and also the number and the positions of the recording electrodes.

Appendix A: Proof of Theorem 1

The equations in (10.1) can be expressed in a matrix format by collecting the ATs of all the catheter’s electrodes as

\[ t_{c,w}' = [C_c' - 1_{N_c}q_{T}^{T}, 1_{N_c}][v^{T}/\|v\|^{2}, s_{c,w}']^{T} + n_{c,w}', \]  

(9.5)
for \( c = 1, \cdots, C \), and \( w = 1, \cdots, W_c \), where

\[
C'_c = [p'_{c,1}, \cdots, p'_{c,N_c}]^T \in \mathbb{R}^{N_c \times 3},
\]

\[
t'_{c,w} = [t'_{c,w,1}, \cdots, t'_{c,w,N_c}]^T \in \mathbb{R}^{N_c \times 1},
\]

\[
n'_{c,w} = [n'_{c,w,1}, \cdots, n'_{c,w,N_c}]^T \in \mathbb{R}^{N_c \times 1}.
\]

Consider the following parameters

\[
t_{c,w} \overset{\text{def}}{=} t'_{c,w}/\sigma_c - 1_{N_c}1^T_{N_c}t'_{c,w}/(\sigma_c N_c), \quad (9.6a)
\]

\[
C_c \overset{\text{def}}{=} C'_{c}/\sigma_c - 1_{N_c}1^T_{N_c}C'_{c}/(\sigma_c N_c), \quad (9.6b)
\]

\[
s_{c,w} \overset{\text{def}}{=} s'_{c,w}/\sigma_c - 1_{N_c}1^T_{N_c}s'_{c,w}/(\sigma_c N_c), \quad (9.6c)
\]

\[
q_c \overset{\text{def}}{=} q'/\sigma_c - C'^T_{c}1_{N_c}/(\sigma_c N_c), \quad (9.6d)
\]

\[
n_{c,w} \overset{\text{def}}{=} n'_{c,w}/\sigma_c, \quad (9.6e)
\]

for which we have \( \mathbb{E}\{n_{c,w}n^T_{c,w}\} = I_{N_c} \),

\[
1^T_{N_c}t_{c,w} = 0, \quad \text{and} \quad C'^T_{c}1_{N_c} = 0_3. \quad (9.7)
\]

Using (9.6), for \( c = 1, \cdots, C \), \( w = 1, \cdots, W_c \), (9.5) becomes

\[
t_{c,w} = [C_c - 1_{N_c}q'^T_{c}, 1_{N_c}][v^T/\|v\|^2, s_{c,w}]^T + n_{c,w}, \quad (9.8)
\]

We combine all the equations in (10.2) for \( w = 1, \cdots, W_c \) as

\[
t_c = [1_{W_c} \otimes (C_c - 1_{N_c}q'^T_{c}), I_{W_c} \otimes 1_{N_c}][v^T/\|v\|^2, s'^T_c]^T + n_c. \quad (9.9)
\]
for $c = 1, \cdots, C$, where $s_c \overset{\text{def}}{=} [s^c_{1,1}, \cdots, s^c_{c,W_c}]^T \in \mathbb{R}^{W_c \times 1}$,

\[
\mathbf{t}_c \overset{\text{def}}{=} [\mathbf{t}^T_{c,1}, \cdots, \mathbf{t}^T_{c,W_c}]^T \in \mathbb{R}^{W_c \times N_c \times 1},
\]

\[
\mathbf{n}_c \overset{\text{def}}{=} [\mathbf{n}^T_{c,1}, \cdots, \mathbf{n}^T_{c,W_c}]^T \in \mathbb{R}^{W_c \times N_c \times 1}.
\]

We can express all the equations in (9.9) for $c = 1, \cdots, C$ as

\[
\mathbf{t} = \mathbf{A} \mathbf{\theta} + \mathbf{n}, \quad (9.10)
\]

where

\[
\mathbf{t} \overset{\text{def}}{=} [\mathbf{t}^T_1, \cdots, \mathbf{t}^T_C]^T \in \mathbb{R}^{M \times 1},
\]

\[
\mathbf{n} \overset{\text{def}}{=} [\mathbf{n}^T_1, \cdots, \mathbf{n}^T_C]^T \in \mathbb{R}^{M \times 1},
\]

\[
\mathbf{s} \overset{\text{def}}{=} [\mathbf{s}^T_1, \cdots, \mathbf{s}^T_C]^T \in \mathbb{R}^{L \times 1},
\]

\[
\mathbf{\theta} \overset{\text{def}}{=} [\mathbf{v}^T/\|\mathbf{v}\|, \mathbf{s}^T]^T \in \mathbb{R}^{3+L \times 1},
\]

in which $L \overset{\text{def}}{=} \sum_{c=1}^C W_c$ and $M \overset{\text{def}}{=} \sum_{c=1}^C W_c N_c$; and $\mathbf{A}$ is an $M \times 3 + L$ dimensional matrix defined in (9.11). Equation (9.10), in which $\text{E}\{\mathbf{nn}^T\} = \mathbf{I}_M$, represents the linear Gaussian model, and the ML estimation of $\mathbf{\theta}$, which is an unbiased estimator
for it, is given as [120]

\[
\hat{\theta} = (A^T A)^{-1} \hat{A}^T t_z,
\]

(9.12)

and the covariance matrix of this estimate is

\[
\text{Cov}(\hat{\theta}) = E\{(\hat{\theta} - \theta)(\hat{\theta} - \theta)^T\} = (A^T A)^{-1}.
\]

(9.13)

Using (10.3), 3 + \(L\)-dimensional vector \(z \overset{\text{def}}{=} A^T t\) is \(z = [\sum_{c=1}^{C} t_c^T (1_{W_c} \otimes C_c), 0_L^T]^T\).

Since the last \(L\) elements of the vector \(z\) are zero, we only need to obtain the first three columns of \((A^T A)^{-1}\) to be able to calculate \(\theta\) in (9.12). Only the top left \(3 \times 3\) block matrix of \((A^T A)^{-1}\) is required to find the CCV. Using \(a^T \otimes b = ba^T\), which is valid for any vector \(a\) and \(b\), and also using \((F \otimes G)(H \otimes K) = (FH \otimes GK)\), which is valid for the arbitrary matrices \(F, G, H, K\) with compatible dimensions, we can simplify \(A^T A\) as

\[
(A^T A) = \begin{bmatrix}
E & QD \\
DQ^T & D
\end{bmatrix},
\]

(9.14)

where

\[
E \overset{\text{def}}{=} \sum_{c=1}^{C} W_c(C_c^T C_c + N_c q_c q_c^T),
\]

\[
D \overset{\text{def}}{=} \text{diag}(N_1 I_{W_1}, \ldots, N_C I_{W_C}),
\]

\[
Q \overset{\text{def}}{=} -[q_1 1_{W_1}^T, \ldots, q_{W_C} 1_{W_C}^T].
\]
We can further simplify \((A^T A)^{-1}\) using the formula for the inverse of a block matrix [118, Section 9.1.3] as

\[
(A^T A)^{-1} = \begin{bmatrix}
F & -FQ \\
-Q^T F & D^{-1} + Q^T FQ
\end{bmatrix},
\]

where \(F \overset{\text{def}}{=} (E - QDQ^T)^{-1} = (\sum_{c=1}^C W_c C_c^T C_c)^{-1}\). Therefore, the ML estimation of \(v/\|v\|^2\) or \([\hat{\theta}]_{1:3}\) can be written as (9.2); and considering (9.13), the covariance matrix of \([\hat{\theta}]_{1:3}\) becomes (9.3). The ML estimate of \(s_{c,w}\) for \(c = 1, \ldots, C\) and \(w = 1, \ldots, W_c\) becomes \(q^T [\hat{\theta}]_{1:3}\); and using (9.6c), the ML estimate of \(s'_{c,w}\) can be written as (9.4).
Chapter 10

Maximum Likelihood Cardiac Conduction Velocity Estimation from Sequential Mapping in the Presence of Activation Time Noise With Unknown Variances

10.1 Abstract

The cardiac conduction velocity can be estimated by analysing the activation times (ATs) and the locations of the electrodes that are used for the intracardiac electrogram (IEGM) recording. Here, we study the problem of the conduction velocity (CV) estimation in sequential mapping without using any independent electrogram as a time alignment reference. We assume that the IEGMs are sequentially recorded from several sites, where at each site, at least two of the catheter’s electrodes are in contact with the cardiac tissue. We consider the planar wavefront with stable CV that propagates within the recording sites throughout our data collection period.
Assuming the zero-mean Gaussian AT estimation error, we derive the maximum likelihood estimations of the CV and AT at a desired location on the cardiac shell. The CV is estimated when the variance of the AT estimation error and the time delay between the sequential recordings are unknown variables. Our simulation results show that the proposed method can precisely estimate the CV of the planar wavefront.

10.2 Introduction

Cardiac mapping provides critical diagnostic information about the various types of complex arrhythmias, such as atrial fibrillation and ventricular tachycardia [13]. For instance, the cardiac isochrone and conduction velocity (CV) maps can be used to identify and eliminate problematic regions in the ablation therapy procedure [11, 13, 33].

The cardiac mapping techniques can be categorized into two types: 1) continuous mapping which requires a large catheter, e.g., the basket catheter (Constellation, Boston Scientific), 2) sequential mapping that is done by using a small catheter, such as the Reflexion spiral catheter (St. Jude Medical) [33]. In this chapter, we study the wavefront velocity vector (VV) estimation using the latter mapping approach.

The cardiac CV can be estimated by analysing the intracardiac electrograms (IEGMs), i.e., the activation times (ATs) and locations of the catheter’s electrodes can be used to estimate the VV [68, 105, 107, 108, and references therein]. In this chapter, we assume that electrical activities of the heart are sequentially recorded from several cardiac sites. Our goal is to use these local recordings to estimate the
CV at a desired location which is close to the recording sites. Here, we consider a locally isotropic cardiac medium and assume that the direction and speed of the planar wavefront propagation does not change throughout our recording duration and within the recording sites.

Note that in the currently available mapping systems, to create the propagation or isochrone maps from the sequential recordings, the time alignment/synchronization of each recorded site is calculated relative to a reference electrogram which serves as a fiducial point [121]. Because of the stability of the catheter placed in the coronary sinus, one of the recorded IEGM from the coronary sinus is usually used as a fiducial point [121], and this time alignment reference is used to transform the sequential recordings to the continuous one. In contrast, in this chapter, without having any fiducial point, we consider the time synchronization between the sequential recordings as unknown variables and estimate those variables as well as the velocity.

In this chapter, we assume that the IEGMs are sequentially recorded from several sites where at each site at least two of the electrodes are in contact with the cardiac shell. One or more wavefronts pass the area under each catheter at each measurement site, and our goal is to estimate the cardiac CV and the AT at a desired location on the heart shell. We assume that the ATs of the IEGMs are estimated [1, 4, 68, 78], and their errors have the zero-mean Gaussian distribution. In [122], the problem of the CV estimation is investigated when the AT estimation error statistics are known. Here, on the other hand, we assume that the variances of the AT error at the recording sites are unknown, and we derive the maximum likelihood (ML) estimates of all the parameters including the CV.
10.3 Sequential Mapping and the CV Estimation

We start this section by describing the sequential IEGM recording that is considered in this chapter. Suppose that we sequentially collect the IEGMs of \( C \) cardiac sites. At the \( c \)th site \((c = 1, \cdots, C)\), \( N_c \) of the catheter’s electrodes, which are close to the desired location \( p' \), are in contact with the intracardiac surface. The catheter remains fixed at the \( c \)th site during measuring \( W_c \) wavefronts. Then, the ATs of the collected IEGMs from various sites are estimated, and the corresponding wavefronts are specified. The estimated ATs of the wavefronts along with the locations of the catheter’s electrodes are used for the CV estimation.

The estimated ATs include some errors which are modeled here with white Gaussian noise, i.e., we assume that the AT estimation error has the zero-mean Gaussian distribution with unknown variance. We further assume that the variance of the AT noise only depends on the location of the recording site.

In this chapter, we assume that the cardiac propagation wave within our recording sites is stable with planar wavefront. We assume that at the \( c \)th recording site \((c = 1, \cdots, C)\), the \( w \)th planar wavefront passes the area under the catheter’s \( i \)th electrode located at \( p'_{c,i} \in \mathbb{R}^{3\times 1} \) at time \( t'_{c,w,i} \). Our aim is to find the AT and CV at a desired location \( q' \). For example, Figure 10.1 shows a spiral mapping catheter located at the \( c \)th recording site where \( N_c = 3 \) of its electrodes that are close to the desired location are considered for the CV estimation. The IEGMs of the selected electrodes and the estimated ATs of \( W_c = 2 \) wavefronts are also shown in this figure.

If \( s'_{c,w,q} \) shows the AT at \( q' \) due to the \( w \)th wavefront at the \( c \)th recording site,
Figure 10.1: The spiral catheter is located at the $c$th recording site, and $N_c = 3$ of its electrodes are used for the VV estimation. The IEGMs and ATs of the selected electrodes for $W_c = 2$ wavefronts are shown. The isochrone lines corresponding to the first wavefront are also plotted with dashed lines; the earliest (latest) activation is shown with red (violet). The direction of the VV is specified with a brown arrow which is perpendicular to the isochrone lines.

for $c = 1, \cdots, C$, $w = 1, \cdots, W_c$, and $i = 1, \cdots, N_c$, we have

$$t'_{c,w,i} = s'_{c,w,q'} + (p'_{c,i} - q')^T v / \| v \|^2 + n_{c,w,i},$$

(10.1)

where $v$ is the VV and $n_{c,w,i}$ shows the AT estimation error of $t'_{c,w,i}$. We assume that
10.3. SEQUENTIAL MAPPING AND THE CV ESTIMATION

Table 10.1: Descriptions of the variables used in (10.2)

<table>
<thead>
<tr>
<th>Description</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mathbf{p}_{c,i}' \in \mathbb{R}^{3 \times 1} ): location of the ( i )th electrode at the ( c )th recording site;</td>
<td>( \mathbf{C}'<em>c = [\mathbf{p}'</em>{c,1}, \cdots, \mathbf{p}'_{c,N_c}]^T \in \mathbb{R}^{N_c \times 3}; \quad \mathbf{C}<em>c = \mathbf{C}'<em>c - \mathbf{1}</em>{N_c} \mathbf{1}</em>{N_c}^T \mathbf{C}'_c / N_c )</td>
</tr>
<tr>
<td>( \mathbf{q}' \in \mathbb{R}^{3 \times 1} ): location of the desired point;</td>
<td>( \mathbf{q}_c = \mathbf{q}' - \mathbf{C}'<em>c \mathbf{1}</em>{N_c} / N_c )</td>
</tr>
<tr>
<td>( \mathbf{t}'<em>{c,w,i} ): the estimated AT at ( \mathbf{p}</em>{c,i}' ) due to the ( w )th wavefront;</td>
<td>( \mathbf{t}'<em>{c,w} = [\mathbf{t}'</em>{c,w,1}, \cdots, \mathbf{t}'_{c,w,N_c}]^T \in \mathbb{R}^{N_c \times 1} )</td>
</tr>
<tr>
<td>( \mathbf{s}'_{c,w,\mathbf{q}'} ): the AT at ( \mathbf{q}' ) due to the ( w )th wavefront recorded at the ( c )th recording site;</td>
<td>( \mathbf{s}<em>{c,w,\mathbf{q}'} = \mathbf{s}'</em>{c,w,\mathbf{q}'} - \mathbf{1}<em>{N_c} \mathbf{1}</em>{N_c}^T \mathbf{t}'_{c,w} / N_c )</td>
</tr>
<tr>
<td>( \mathbf{n}<em>{c,w,i} ): the AT estimation error at ( \mathbf{p}</em>{c,i}' ) due to the ( w )th wavefront;</td>
<td>( \mathbf{n}<em>{c,w} = [\mathbf{n}</em>{c,w,1}, \cdots, \mathbf{n}_{c,w,N_c}]^T \in \mathbb{R}^{N_c \times 1} )</td>
</tr>
</tbody>
</table>

\( n_{c,w,i} \) for different values of \( c, w, \) and \( i \) are independent identically distributed zero-mean Gaussian variables with the variance of \( \sigma_c^2 \), i.e., \( \text{E}\{n_{c,w,i}n_{c',w',j}\} = \sigma_c^2\delta_{c-c'}\delta_{w-w'}\delta_{i-j} \), where \( \delta \) denotes the Kronecker delta. Combining all the equations in (10.1) for \( i = 1, \cdots, N_c \), we can express (10.1) for \( c = 1, \cdots, C, \) and \( w = 1, \cdots, W_c \) as

\[
\mathbf{t}_{c,w} = \left[ \mathbf{C}_c - \mathbf{1}_{N_c} \mathbf{q}_c^T, \mathbf{1}_{N_c} \right] \left[ \mathbf{v}^T / \| \mathbf{v} \|^2, \mathbf{s}_{c,w,\mathbf{q}'} \right]^T + \mathbf{n}_{c,w},
\]

(10.2)

where parameters in (10.2) are defined in Table 10.1. Note that for the AT estimation error \( \mathbf{n}_{c,w}, \) we have \( \text{E}\{\mathbf{n}_{c,w}\mathbf{n}_{c,w}^T\} = \sigma_c^2 \mathbf{I}_{N_c}, \) and also considering \( \mathbf{C}_c \) and \( \mathbf{t}_{c,w} \) defined in
Table 10.1, we have

\[ 1^T_{N_c} t_{c,w} = 0, \quad \text{and} \quad C_c^T 1_{N_c} = 0. \] (10.3)

The probability density function (pdf) of all the ATs collected in

\[ t = [t_{1,1}^T, \ldots, t_{1,W_1}^T, \ldots, t_{C,1}^T, \ldots, t_{C,W_C}^T]^T \]

is

\[
f(t|v, \sigma, s) = \exp \left( \sum_{c=1}^{C} \sum_{w=1}^{W_c} \frac{\|t_{c,w} - (C_c - 1_{N_c} q_c^T)v\| - 1_{N_c} s_{c,w,q'}^2}{-2\sigma_c^2} \right) \prod_{k=1}^{C} \left(2\pi \sigma_k^2\right)^{N_k W_k/2} \] (10.4)

where \( s = [s_{1,1}, \ldots, s_{1,W_1}, \ldots, s_{C,1}, \ldots, s_{C,W_C}]^T \) and \( \sigma = [\sigma_1, \ldots, \sigma_C]^T \). From (10.4), the log-likelihood (LL) becomes

\[
\ln f(t|v, \sigma, s) = \sum_{i=1}^{C} \sum_{m=1}^{W_i} \frac{\|t_{i,m} - (C_i - 1_{N_i} q_i^T)v - 1_{N_i} s_{i,m}\|^2}{-2\sigma_i^2} - \sum_{k=1}^{C} N_k W_k / 2 \ln(2\pi \sigma_k^2) \] (10.5)

To find the optimum \( s_{c,w,q'} \) that maximizes the LL, we find the root of \( \partial \ln f(t|v, \sigma, s)/\partial s_{c,w,q'} \)

which leads to

\[ 1^T_{N_c} (t_{c,w} - (C_c - 1_{N_c} q_c^T)v/\|v\|^2 - 1_{N_c} \hat{s}_{c,w}) = 0. \] (10.6)
Using (10.3), the ML estimate of $s_{c,w,q}$ becomes

$$\hat{s}_{c,w} = q^T_c v / \|v\|^2. \quad (10.7)$$

Substituting $\hat{s}_{c,w}$ in the LL (10.5), we obtain

$$\ln f(t|v, \sigma, \hat{s}) = \sum_{i=1}^{C} \sum_{m=1}^{W_i} \frac{\|t_{i,m} - \frac{C_i v}{\|v\|^2}\|^2}{-2\sigma^2_i} - \frac{C}{2} \sum_{k=1}^{N_k} W_k \ln(2\pi \sigma_k^2). \quad (10.8)$$

The ML estimate of the $\sigma^2_c$ can be found as

$$\hat{\sigma}^2_c = 1/(N_c W_c) \sum_{m=1}^{W_c} \|t_{c,m} - C_c v / \|v\|^2\|^2 \quad (10.9)$$

which is obtained by solving $\partial \ln f(t|v, \sigma, \hat{s}) / \partial \sigma^2_c = 0$. Using $\hat{\sigma}^2_c$ in (10.8) and eliminating all the constants that are independent of $v$, we obtain

$$\ln f(t|v, \hat{\sigma}, \hat{s}) \propto - \sum_{c=1}^{C} N_c W_c \ln \left( \sum_{w=1}^{W_c} \|t_{c,w} - \frac{C_c v}{\|v\|^2}\|^2 \right). \quad (10.10)$$

Thus, the ML estimate of $v$ can be found from

$$\hat{v} = \arg \min_v I(v), \quad (10.11)$$

where

$$I(v) = \sum_{c=1}^{C} N_c W_c \ln \left( W_c v^T C_c^T C_c v / \|v\|^4 + \sum_{w=1}^{W_c} \|t_{c,w}\|^2 - 2v^T C_c^T \hat{t}_c / \|v\|^2 \right). \quad (10.12)$$
\[ \nabla(v_k) = - \sum_{c=1}^{C} 2N_c W_c \frac{-2W_c v_k^T C_c v_k}{\|v_k\|^4} v_k + \frac{W_c}{\|v_k\|^2} C_c^T C_c v_k + \frac{2v_k^T C_c^T \tilde{t}_c}{\|v_k\|^2} v_k - C_c^T t_c \tag{10.13} \]

and \( \tilde{t}_c \) defined as \( \sum_{w=1}^{W_c} t_{c,w} \). In the next section, we describe the gradient descent (GD) algorithm to estimate the VV.

### 10.4 Solving (10.11) Using the GD Algorithm

Here, we use the GD algorithm [91] to solve the optimization problem (10.11). The GD gets an initial estimate of the velocity \( (v_k \text{ for } k = 0) \) as input and, by taking steps in the direction of the negative of the gradient, minimizes \( I \). Thus, the CV is obtained iteratively from the following steps: calculate the gradient of the \( I \) at the current available velocity using \( \nabla(v_k) \) presented in (10.13). Find the optimum step size for each iteration by solving the following 1-D optimization using, for instance, the Nelder–Mead method [123]

\[ \alpha_o = \arg \min_{\alpha} I(v_k - \alpha \nabla(v_k)) \tag{10.14} \]

Repeat the similar steps for the following new velocity until the convergence conditions are satisfied

\[ v_{k+1} = v_k - \alpha_o \nabla(v_k). \tag{10.15} \]
10.4. SOLVING (10.11) USING THE GD ALGORITHM

The performance of the GD highly depends on the accuracy of the initial velocity vector \( v_0 \). In the following subsection we introduce a proper initial solution for the GD.

10.4.1 Initial velocity for the GD algorithm

Here, we obtain the optimum VV when the AT noise variances in different measurement sites are equal, i.e., we assume that \( \sigma_1 = \cdots = \sigma_C = \sigma \). Following the same procedure as in Section 10.3, we first solve \( \partial \ln f(t|v, \sigma, s)/\partial s_{c,w,q'} = 0 \), which leads to (10.7). After that, we replace \( \hat{s}_{c,w} \) in the pdf and solve \( \partial \ln f(t|v, \sigma, \hat{s})/\partial \sigma^2 = 0 \) which leads to

\[
\hat{\sigma}^2 = \sum_{i=1}^{C} \sum_{w=1}^{W_c} \| t_{c,w} - C_c v / \| v \|^2 \|^2 / ( \sum_{i=1}^{C} W_i N_i ). \tag{10.16}
\]

Considering the estimated \( \hat{\sigma}^2 \) and \( \hat{s}_{c,w} \), maximizing \( \ln f(t|v, \hat{\sigma}, \hat{s}) \) over \( v \) leads to

\[
\min_v \sum_{i=1}^{C} \sum_{w=1}^{W_c} \| t_{c,w} - C_c v / \| v \|^2 \|^2, \tag{10.17}
\]

and the velocity can be estimated from

\[
\hat{v} = \arg \min_v v^T \sum_{c=1}^{C} W_c C_c^T C_c v / \| v \|^4 - 2v^T \sum_{c=1}^{C} C_c^T \tilde{t}_c / \| v \|^2. \tag{10.18}
\]
Finally, by setting the derivative of the objective function in (10.18) with respect to \( \mathbf{v} \) equal to zero, we can obtain the \( \mathbf{VV} \) as

\[
\hat{\mathbf{v}} = \frac{\mathbf{a}}{\|\mathbf{a}\|^2}, \quad \text{where} \quad \mathbf{a} = \left( \sum_{c=1}^{C} W_c C_c^T C_c \right)^{-1} \sum_{c=1}^{C} C_c^T \tilde{t}_c.
\]  \hspace{1cm} (10.19)

The proposed GD is summarized as

**Input:** Available electrodes’ locations \( (p_{c,k}') \) and ATs \( (t_{c,w,k}) \); the maximum GD iteration number \( (M) \), the minimum \( (\epsilon) \) and maximum \( (\Psi) \) changes in each step for the GD.

**Initialization:** \( k = 0, \alpha_o = 100 \) and \( \mathbf{v}_0 \) is given in (10.19).

**While** \( k < M \) and \( \|\alpha_o \nabla(\mathbf{v}_k)\| > \epsilon \),

Calculate \( \nabla(\mathbf{v}_k) \) using (10.13) and obtain \( \alpha_o \) from (10.14)

**If** \( \|\alpha_o \nabla(\mathbf{v}_k)\| > \Psi \),

\[
\mathbf{v}_{k+1} = \mathbf{v}_k - \alpha_o \nabla(\mathbf{v}_k) \Psi / \|\alpha \nabla(\mathbf{v}_k)\|,
\]

**Else** \( \mathbf{v}_{k+1} = \mathbf{v}_k - \alpha_o \nabla(\mathbf{v}_k) \) **End.** \( k = k + 1 \)

**End.**

### 10.5 Simulation Results

In this section, we assume that all the recording sites, the desired location, and the cardiac shell are located on the \( xy \) plane. Consequently, the \( z \)-component of all the locations and the CV are zero, and we can represent the locations/CV with complex
10.5. SIMULATION RESULTS

Scalars where their real and imaginary parts show the $x$ and $y$ components of the locations/CV, respectively. Thus, the CV can be represented by $V = |V| \exp(j\phi)$, where we assume that $40 \leq |V| \leq 200\text{cm/sec}$ [36]. We assume that the spiral catheter with 10 bipolar electrodes, shown in Figure 10.1, is used to sequentially record the IEGMs of $C = 4$ sites. The center of the catheter for the $c = 1, 2, 3, \text{and } 4$ are located at $-2 - 2j, -2 + 2j, 2 + 2j, \text{and } 2 - 2j \text{ (all in cm)}$, respectively. At the $c$th site, $N_c$ of the 10 available electrodes of the catheter are randomly selected as the electrodes that are in contact with the cardiac shell. For each simulation run, we generate a CV with $|V| \sim U(40, 200)\text{cm/sec}$ and $\phi \sim U(0, 2\pi)\text{Rad}$. After that we specify the ATs of the selected electrodes at each location for all the measured wavefronts. We assume that the IEGMs of six wavefronts are collected at each site ($W_1 = \cdots = W_4 = 6$). Then, the zero-mean Gaussian noises are added to the ATs to model the AT estimation error. We consider different AT noise levels for various sites as $\sigma_1 = 0.5\sigma, \sigma_2 = \sigma, \sigma_3 = 0.6\sigma, \text{and } \sigma_4 = 0.8\sigma$. The resulting contaminated ATs are used for the CV estimation. All the curves plotted in this section are results of averaging over $10^5$ independent simulation runs.

Figure 10.1 shows the normalized mean squared error (NMSE) of the CV estimation ($E\{|V - \hat{V}|^2/|V|^2\}$, where $\hat{V}$ is the estimated CV) as a function of the $\sigma$, when the number of the electrodes that are used to collect the IEGMs at four sites are $N_1 = 4, N_2 = 3, N_3 = 2, N_4 = 5$. The performance of the proposed method is compared with two CV estimators; in one $\sigma_1, \cdots, \sigma_C$ are known [122], and in the other one, it is incorrectly assumed that $\sigma_1 = \cdots = \sigma_C$ which leads to the estimator in (10.19). Note that at the $c$th measuring site, all the ATs of the IEGMs of sites 1 to $c$ are used in (10.19) to estimate the initial CV, and this initial CV is used in the
proposed GD in Subsection 10.4.1. For $c = 1$, since the AT error variances of all the collected IEGMs are equal to $\sigma_1^2$, the proposed method and the one with the known variances become equal to the estimator in (10.19). Thus, the performance of all the considered CV estimators are similar when $c = 1$. Figure 10.1, shows that our initial estimated CV is close to the optimum solution; the proposed method can accurately estimate the CV, and its estimation error is very close to the estimator that knows $\sigma_1, \cdots, \sigma_4$.

If the normalized CV estimation error ($|V - \hat{V}|^2/|V|^2$) of any of the methods becomes larger than 40%, we consider that estimated CV as a diverged solution and do not include that in calculating the NMSE. Figure 10.2, shows the probability of observing NMSE larger than 40% in our simulations, as a function of the location of the IEGM collection. This figure confirms that when the AT estimation noise is large, the chance of having a diverged solution is higher, and this probability decreases by using the IEGMs of other sites.

10.6 Conclusions

In this chapter, we proposed the ML CV estimator for sequential mapping when the variances of AT Gaussian noise at different IEGM collection sites are unknown variables. We assumed that the IEGMs are sequentially recorded from various sites, where at each site, the IEGMs of more than one electrode are collected. Assuming stable planar wavefronts on the 2-D cardiac surface and also assuming the zero-mean Gaussian AT estimation error (with unknown variance), we proposed the ML cardiac CV estimator. Without using any IEGM as a time alignment reference, in this
10.6. CONCLUSIONS

Figure 10.1: The NMSE (E{|V - \hat{V}|^2/|V|^2}, where \( \hat{V} \) is the estimated CV) as a function of the \( \sigma \), when \( N_1 = 4, N_2 = 3, N_3 = 2, N_4 = 5, W_1 = \cdots = W_4 = 6 \), and \( \sigma_1 = 0.5\sigma, \sigma_2 = \sigma, \sigma_3 = 0.6\sigma, \sigma_4 = 0.8\sigma \).

chapter, we assumed that the time synchronization between the sequential recordings are unknown. We proposed the GD algorithm to find the CV estimator and derived a proper initial CV estimate. Our simulation results showed that the proposed method can accurately estimate the CV, and its estimation error is very close to the estimator that knows the AT noise variances.
10.6. CONCLUSIONS

Figure 10.2: The probability of the NMSE being larger than 40% as a function of the location of the IEGM collection, when $N_1 = 4, N_2 = 3, N_3 = 2, N_4 = 5$, $W_1 = \cdots = W_4 = 6$, and $\sigma_1 = 0.5\sigma, \sigma_2 = \sigma, \sigma_3 = 0.6\sigma, \sigma_4 = 0.8\sigma$. 

$\Pr(\text{NMSE}>0.4)$

<table>
<thead>
<tr>
<th>Location</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Divergence Threshold for NMSE $40\%$, Num Diverged/ Total

Assuming $\sigma_1 = \cdots = \sigma_4$

Known $\sigma_1, \cdots, \sigma_4$

Proposed

$\sigma = 7\text{ms}$

$\sigma = 5\text{ms}$

$\sigma = 3\text{ms}$

$\sigma = 1\text{ms}$
Chapter 11

Regional Dominant Frequency: A New Tool for Wave Break Identification During Atrial Fibrillation

11.1 Abstract

Study of the intracardiac electrograms (IEGMs) during atrial fibrillation (AF) can provide clinically significant information that can potentially be deployed in the ablation therapy. Feature analyses of IEGMs that are currently used in cardiac mapping systems are based on the time/frequency processes of the recorded signals from individual bipolar/unipolar electrodes of a mapping catheter. Since the collected signals of each electrode is processed independent of other simultaneously recorded adjacent electrodes, these approaches fail to investigate the interrelationship between simultaneously recorded channels of the mapping catheter, and thus, do not provide
any information about the wavefront propagation during AF. In this chapter, we introduce a new measure which encompasses the relationship between simultaneously recorded channels and, therefore, reflects the dominant frequency (DF) components of a region rather than just one single electrode. We refer to this new measure as regional dominant frequency (RDF), and we show that it can be used to identify and characterize variation and disorganization in wavefront propagation or wave breaks (WBs) at each recording site. Our results suggest that the WB analysis based on the RDF can provide insightful information that potentially can be used in catheter ablation therapy.

### 11.2 Introduction

Atrial fibrillation (AF) is characterized by complex spatiotemporal wavefront propagation that results in complex signal formation and fragmentation [13, 124]. Intracardiac electrograms (IEGMs) collected from both atria can be used in the ablation therapy procedures; e.g., complex fractionated electrogram (CFE) [125, 126] and the dominant frequency (DF) [127] parameters extracted from IEGMs, in conjunction with anatomical locations, are commonly used to guide catheter ablation [13, 98]. However, electrogram and anatomical-guided ablation is not a satisfactory treatment for persistent AF [46].

Feature analyses of IEGMs are based on the time and frequency analysis of the recorded signals from individual bipolar/unipolar electrodes of a conventional multi-electrode recording catheter (mapping catheter); e.g., the IEGM of each electrode is processed and used to estimate the CFE or DF. After processing the recorded IEGM,
a CFE or DF value is assigned to each electrode at the XYZ coordinate location. The assigned values are further processed, interpolated and color-coded to generate an anatomical map of the cardiac chamber to aid targeting of catheter ablation therapy and thus improve procedural efficacy [44,125,128]. Since the IEGM of each electrode is processed independently of other simultaneously recorded adjacent electrodes, these approaches fail to investigate the interrelationship between simultaneously recorded channels of the mapping catheter and, thus, do not provide any information about the wavefront propagation during AF.

In this chapter, instead of assigning a DF to each electrode of the catheter, we introduce a new measure which encompasses the relationship between simultaneously recorded channels and, therefore, reflects the dominant frequency components of a region rather than just one single electrode. We refer to this new measure as regional dominant frequency (RDF) to distinguish from electrode DF (EDF) extracted from single electrodes. The relative delays between the activation times (ATs) of the catheter’s electrodes affect the RDF; and as a result, the RDF provides insightful information regarding the wavefront propagation at the recording site. For instance, it can be used to identify regions with slow conduction and rapidly identify change in wavefront propagation. This is done without directly identifying the ATs, as an accurate local AT estimation is challenging during AF. We use the novel RDF feature to evaluate variation in wavefront propagation or wave breaks (WBs) at each recording site. The proposed method can be used to identify and characterize wavefronts with long/fractionated/non-discrete activations and without clear isoelectric lines between the wavefronts. The unorganized activations during WBs are the result of rotating waves, local conduction block, and wavefront collision [124,129–131]; quantifying the
WB characteristics at each atrial site might inform AF mechanism and perpetuation [129]. Our goal was to develop a computationally efficient algorithm to identify and quantify regional wavefront discontinuities or WBs.

11.3 Methods

Data were collected from patients attending for diagnostic electrophysiologic studies with catheter ablation for AF. The study was approved by the institutional ethics committee of Queen’s University. Data were collected during AF prior to ablation. Antiarrhythmic drugs (other than Amiodarone) were held 5 half lives prior to the study. Data were collected after the administration of Ibutilide 1mg. The left atrium was mapped using the NavX Velocity system and a high definition catheter (Reflexion™ HD or Spiral, St. Jude Medical). Data from 15 patients (average age 60.7±8.9 years; persistent AF durations of 20.6±8.6 months; 13 male; 5 paroxysmal; 10 persistent) were collected with sampling frequency of 2034.5 and used offline in the MATLAB (Mathworks, Natick, MA) environment. The Reflexion™ HD or Spiral (St. Jude Medical) catheter that has 20 electrodes with 1mm width was used in these patients to record for 29.9±9.8 seconds at 24.4±7 locations per patient (the bipolar pair electrodes spacing for Reflexion™ HD and Spiral are 2mm and 1mm, respectively). Herein, we describe the methods employed to identify WB within this cohort and validation thereof.
11.3. METHODS

11.3.1 Regional and Electrode Dominant Frequency

The EDF of each electrode of the catheter is extracted from the frequency analysis of the preprocessed IEGM of that electrode independent of the rest of the catheter’s electrodes; to estimate the EDF, we first apply the preprocessing in [78] to the IEGM recorded from each electrode, remove the mean amplitude of the resulting signal, and estimate the EDF from the extracted power spectrum. To obtain the power spectrum, short time Fourier transform (STFT) of the signal is calculated. For this aim, the signal is divided into segments with \( T \) second duration and 95\% overlap; the Hanning window is applied on each segment and the power spectrum is estimated using the fast Fourier transform (FFT). Finally, the EDF of the \( i \)th electrode is calculated using

\[
\text{EDF}_i(t, T) = \arg \max_f P_i(f, t, T),
\]  

where \( P_i(f, t, T) \) is the power spectrum obtained from \( i \)th electrode of the catheter.

To obtain the RDF, first, the IEGM of each electrode of the catheter is preprocessed to generate a smooth train of pulses on the active intervals of the electrogram. Then, the preprocessed signals of all the catheter electrodes are averaged to produce one signal; this is smoothed by a lowpass filter, and the mean amplitude is subtracted. Finally, the power spectrum of the resulting signal is used to estimate the RDF. The upper quartile of the RDF (UQRDF) is also extracted from the generated power spectrum. Figure 11.1, shows the flowchart of the proposed processing approach which includes sample output at each stage explained in more detail below.

Similar to the EDF calculation, in the first stage of the RDF calculation, the
Figure 11.1: Block diagram of the proposed method for the regional dominant frequency (RDF) analysis and sample output of each stage.

The proposed method in [78] is applied to the IEGM recorded from each electrode of the catheter (sampling frequency of IEGM collection is 2034.5 Hz). This preprocessing step replaces the complex morphologies of the IEGMs with smooth pulses. The AT of each bipolar electrode can be obtained by threshold crossing the associated preprocessed signal. However, here, we use the processed signal as an indicator of IEGM active intervals without trying to extract local ATs of electrodes which are prone to error (see Part II of this thesis). The preprocessed signals of all the electrodes are then averaged. The following two-sided exponential finite impulse response (FIR) filter \( h \) with the length of 180 is then used to further smooth the processed signal and allow estimation of WBs:

\[
h_n^* = \exp(-| - 1 + \frac{n - 1}{90} |), \quad h_n = \frac{h_n^*}{\sum_{n=1}^{180} h_n}, \quad \text{for} \quad n = 1, \ldots, 180. \quad (11.2)
\]
The mean amplitude of the resulting signal is removed and in the next stage, the STFT of the signal is calculated in a similar manner to the EDF to obtain its power spectrum, i.e., the signal is divided into segments with $T$ second duration and 95% overlap; the Hanning window is applied on each segment and the power spectrum of the signal is estimated using the FFT. The RDF and UQRDF are calculated from the extracted power spectrum, i.e.,

$$\text{RDF}(t, T) = \arg \max_f P(f, t, T),$$  \hspace{1cm} (11.3)
$$\text{UQRDF}(D, T) = \text{upper quartile } \{ \text{RDF}(t, T) \}_{t \in [0, D]},$$  \hspace{1cm} (11.4)

where "$T$" is the duration of the segments used in the STFT, "$D$" is the duration of the IEGM segment, and $P(f, t, T)$ is the power spectrum of the output of the 2-sided exponential lowpass filter which depends on time, frequency and $T$.

We select the time window length $T$ in the STFT to be equal to one second; this value is smaller than the common value that is used for EDF calculation \[43,132\]. The small value for $T$ increases time resolution of the extracted RDF and enables us to identify WBs. Increasing $T$, however, increases the frequency resolution and degrades the time resolution thus obscuring transient WB events. We define the WB as any drop in the RDF which is more than 3Hz below the UQRDF (or below 0.5Hz) and lasts longer than 100ms. The duration of a clinically significant WB was empirically chosen at 100msec. Finally, the number of the WBs per second or the wave break rate (WBR) is proposed as a feature/measure to quantify the quality of the wavefront propagation at each site.
11.3.2 Example of RDF-Based Wave Break Identification

Figure 11.2 shows sample IEGMs recorded using Reflexion™ Spiral (St. Jude Medical) catheter from the roof of the left atrium of a patient with persistent AF; the outputs of various stages of proposed processing are also plotted for this segment. For the regions where a clear wavefront is present, the peaks of the preprocessed signals of all the electrodes occur very close to each other; therefore, the averaged signal generates a large peak for each wavefront; see Figure 2(A). However, for the areas/time intervals where a WB occurs due to slow conduction velocity, the delays between the ATs of the electrodes increase and, consequently, the peaks of the preprocessed signals occur during a longer time interval. In this case, averaging the preprocessed signals generates several small peaks resulting in a segment with high frequency. This high frequency component of the signal attenuated significantly by the two-sided exponential lowpass filter leading to a drop in the RDF; see Figure 2(B). This example shows how changes in RDF can be used to study the wavefront variation and identify WBs. Three WBs are present in this IEGM segment (at around Time=12s and 24s), and the WBR for this segment is estimated as 0.1 WB/sec.
11.3. METHODS

Figure 11.2: Bipolar intracardiac electrograms (IEGMs) collected using the Reflexion™ Spiral (St. Jude Medical) catheter from a patient with persistent AF. From top to bottom, axes 1 to 10, show the bipolar IEGMs. The average of the preprocessed signals and the low-passed version of that are plotted on the 11th axis, and the 12th axis shows the dominant frequency (DF) of the lowpassed signal. Subfigure (A) shows the IEGM segment with clear wavefronts; the normalized preprocessed signals (with the maximum amplitude of one) are also plotted in this sub-figure. The output of the lowpassed filter has a large peak for each wavefront and the DF for this subfigure varies between 4.9 to 5.5 Hz. Subfigure (B) shows another segment of the IEGM with a wave break in which there are no distinguishable wavefronts at the beginning of the segment. Here, the average of the preprocessed signal has multiple small peaks that are not present in the lowpassed version of it, and there is a significant drop in the regional DF (RDF) at this time.
Figure 11.3 demonstrates 10 EDF functions of the segment shown in Figure 11.2; the average of all the EDFs of the catheter is shown below (blue line) compared with RDF. Note that the RDF in Figure 11.2 is different from the average of the EDF of the electrodes of the catheter exposing WBs not shown by average EDF as this does not account for relative delays in the AT between neighboring electrodes.

Figure 11.3: The electrode dominant frequency (EDF) and the regional dominant frequency (RDF) of the IEGM shown in Figure 11.2 when T=1s. The average of the EDF of all the electrodes (shown in blue) does not drop at the same time as the RDF, identifying different wave break (WB) instances. Green boxes mark WB instances obtained using RDF.
11.3.3 Minimum Required Segment Duration for Accurate UQRDF Estimation

We defined the WB as a significant drop in the UQRDF of the studied IEGM segment. Here, we aim to find the minimum segment duration that is required for an accurate and robust estimation of the UQRDF. We assume that the feature obtained using the 30-second segment is accurate/gold standard, e.g., UQRDF(30s,1s) is an accurate estimate of the segment UQRDF. We aim to find the segment duration such that the Pearson correlation between the desired feature obtained from that segment and the gold standard is higher than 85%. We selected IEGMs of the patients with durations longer than 30 seconds (201 segments were selected from 15 patients) and calculated the UQRDF(30s,1s) for them. We also calculated the UQRDF using shorter segment durations “D” and compared the results. Figure 11.4 shows the Pearson correlation between the UQRDF(D,1s) and the UQRDF(30s,1s) for various Ds; the upper and lower bounds of the confidence interval (CI) of the correlation are also plotted with red and blue, respectively. From this figure, we conclude that the UQRDF obtained using the IEGM segment longer than four seconds is an accurate estimate of the UQRDF(30s,1s), as the correlation of the UQRDF(4s,1s) and UQRDF(30s,1s) is 90%.

11.3.4 Minimum Required Segment Duration for Accurate WBR Estimation

Having established the use of 4 second segments provides accurate estimation of the UQRDF, our aim in this section is to find the minimum required segment duration
11.3. METHODS

Figure 11.4: The Pearson correlation of the UQRDF$(D,1s)$ and UQRDF$(30s,1s)$ and also the upper and lower bounds of the confidence interval of the correlation as a function of segment duration $D$.

for reliable WBR estimation. We expected that much longer segment duration is required for WBR estimation. Thus, we followed the same procedure as the one we described in the previous section. Segments with duration $D$ longer than 50s (37 segments) were selected from two patients, and for each segment, the WBR was obtained using the first 50 seconds of each segment. The Pearson correlation (and the 95% CI bounds) of the WBRs estimated from $D$-second segments and 50-second segments are plotted in Figure 11.5. Based on this figure, we conclude that IEGM segments longer than 25s are required for reliable estimation of the WBRs.

Segments longer than 25s were selected from 15 patients (258 segments). The first 25s of each segment was used for the UQRDF and, consequently, the WBR estimation.
Figure 11.5: The Pearson correlation between the wave break rate (WBR) obtained using the \( D \)-second segment and the one obtained from the 50s segment. The 95\% confidence interval (CI) bounds of the correlation are also plotted.

The UQRDF of the segments was 5.5±0.85 Hz (median 5.38Hz; range, 2.86 to 7.66Hz), and the WBR of them was 0.17±0.13 WB/sec (median 0.16 WB/sec; range, 0 to 0.63 WB/sec). The WBR for five paroxysmal patients was 0.24±0.14 (median 0.23; range, 0 to 0.63WB/sec); the UQRDF for them was 5.99±0.8 (median 5.94; range, 3.47 to 7.66Hz). For ten persistent patients, the WBR was 0.14±0.11 (median 0.13; range, 0 to 0.47) and the UQRDF for them was 5.29±0.78 (median 5.23; range, 2.86 to 7.03Hz).

Figure 11.6 shows the scatter plot of the estimated WBR and UQRDF, in which circles and triangles are used to mark the estimated values from the patients with persistent and paroxysmal AF, respectively. The histograms of the WBR (in WB/sec)
and UQRDF (in Hz) are also shown in this figure.

Figure 11.7 shows the estimated values for the WBR and UQRDF in different left atrial sites for all the segments collected from the patients. As we discussed earlier, study of the spatial distribution of the WBR and the UQRDF might provide clinically important insight regarding putative sources of the AF. The WBR is proposed as a feature/measure to quantify the quality of the wavefront propagation at each site; it can be color-coded and shown on cardiac mapping systems and be used as an insightful map to characterize and differentiate signal complexity leading to a more informed choice of ablation target when combined with RDF or other features.
Figure 11.7: The estimated values for the wave break rate (WBR) in WB/sec and the upper quartile regional dominant frequency (UQRDF) in Hz in different left atrial sites. RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, LAA: left atrial appendage, RAnt: right antrum, LAnt: left antrum, PostW: posterior wall, Sept: septum, AntW: anterior wall, MitIs: Mitral Isthmus.
Figure 11.8 shows an example of color-coded atrial maps of a patient with persistent AF. The color-coding is based on the UQRDF and WBR which are extracted from processing 19 segments with durations longer than 25s. Regions with high RDF and with a small number of WBs might be critical for AF perpetuation. One of these regions is identified in this patient, and four bipolar IEGMs of the catheter at a site with high UQRDF and low WBR are also shown. This site can potentially be a putative driving source of AF and, therefore, might be a good candidate site for the ablation.

Further work is needed to characterize a WB and establish its relationship to the DF and ablation outcomes. Moreover, in this study, IEGMs were collected exclusively from the left atrium, and the right atrium during AF is not represented in these data.

11.4 Conclusion

The discontinuity of wavefront propagation during WBs in AF patients might be the results of rotating waves, local conduction block, or wavefront collision. We introduced the novel RDF concept and showed that it can be used to identify and quantify unorganized activations that represent discontinuities in wavefront activation and, thus, provide insightful information that potentially can be used for catheter ablation therapy.
Figure 11.8: Example of 3-dimensional atrial maps color-coded based on the upper quartile regional dominant frequency (UQRDF) and wave break rate (WBR). Four bipolar IEGMs of the catheter at a site with the high UQRDF (7 Hz) and low WBR (no WB observed in 25s) are shown.
Contributions and Future Plans

11.5 Contributions and Future Plans

Throughout this thesis, we proposed several computationally efficient methods to extract insightful clinical information for the AF ablation therapy. The main contributions of this thesis are categorized into three parts:

1. Active Interval Extraction


2. Localizing Spiral Rotor Sources


3. Wavefront Dynamics


In the following, I briefly overview some of our main contributions and our future plans.

**Active Interval Extraction**

Based on sequential hypothesis tests, we proposed several computationally efficient methods to extract the onset and duration of active intervals (AIs) of the intracardiac electrograms (IEGMs). In the proposed methods, the variances of small IEGM segments are compared with the variances of their surrounding segments. Consequently, the proposed methods are able to identify fractionated AIs with small amplitudes. We
showed that the extracted AIs have a high level of consistency with manual annotations and can be implemented efficiently to be used during atrial fibrillation ablation procedures.

The proposed methods do not rely on regular cardiac activations (like those present in atrial tachycardia), and they do not use any independent reference IEGM for time synchronization. In the proposed methods, we only used the local recorded IEGMs because in complex arrhythmias, such as AF, the cardiac electrical activations are temporarily and spatially heterogeneous, and usually, there is no single stable wavefront propagation.

Although the maximum negative slope of the unipolar electrogram provides an accurate estimate of the activation time (AT), the sensitivity of the unipolar recording to noise contamination and remote activations restricts their clinical application. On the other hand, the bipolar recordings, which are commonly used, only reflect the local activations and were the focus throughout this thesis. However, morphologies of the activations from bipolar recordings are influenced by the wavefront orientation with respect to the interpolar axis and also interpolar distance; furthermore, the exact spatial location of the measurement of bipolar recordings is not clear [13,68,90]. Our proposed methods extract the onset and duration of the AIs and provide a possible time window for AT, which enables us to benefit from the unipolar recording for accurate AT estimation (as described in [79,89]), and compensates the aforementioned drawbacks of processing bipolar recordings. Our contribution to AI extraction leads to improvements of other methods which use local activation times, e.g., cardiac conduction velocity estimators can directly benefit from our proposed AT estimation.
approaches.

In short, based on our reported results in Chapter 3, we found the Eq method had the highest similarity to manual annotation (with a similarity index of $91.1 \pm 3.1\%$), making it a desirable AI extractor for real-time use in a procedural context. Success of catheter ablation in persistent AF is suboptimal, and research is focused on targeting AF sources [13]. This method affords the ability to rapidly extract electrogram activation during AF procedures. These data are critical to identification of perpetuating sources of activation, wavefront dynamics and propagation, and are fundamental to techniques under investigation for characterization of putative AF sources. The proposed methods can provide the estimation of onset and duration of AIs during an irregular rhythm with an acceptable level of accuracy, and they may be combined with unipolar activation techniques as described earlier.

**Localizing Spiral Rotor Sources**

The latest studies using optical mapping in animals and mathematical models suggest that rotors and focal sources sustain AF [133,134]. In addition, recent IEGM analysis using basket catheters suggests the existence of several spiral rotors in both the left and right atria during AF [35,35,135,136]. While large catheters can create atrial activation maps quickly, their limitations are incomplete endocardial coverage of the atrium, especially in appendage, and the risk of systemic thromboembolism during mapping in the left atrium [41]. Thus, in this thesis, we studied the problem of spiral tip localization using small catheters. Though deploying small mapping catheters requires more time to collect data from several sites in the atria, these
catheters are easier to control and are less expensive. We proposed two computationally efficient methods to extract the location of the core of Archimedean spiral rotors. The accuracies of these methods were evaluated using synthetic data. We showed that both methods are able to accurately identify the location of the core/tip of the rotors. The proposed method in Chapter 4 can also be used when more than one rotor is present. Further validation of the proposed methods for rotor localization can be done by analysing the optical mapping and large basket catheter, and these are among our future plans.

**Wavefront Dynamics**

The last six chapters of this thesis were devoted to the study of wavefront dynamics during AF. We started by investigating the conduction velocity (CV) at various sites. Several methods were proposed and their accuracies were analysed. For example, in Chapter 10, we studied the CV estimation in sequential mapping, where the electrical activities of several atrial sites are recorded one after another. Assuming local stable planar wavefront and Gaussian AT estimation errors with unknown variances, we derived the maximum likelihood CV estimator when the synchronization times between various recording sites were also unknown.

Feature analyses of IEGMs, like the complex fractionated electrogram (CFE) and dominant frequency (DF), are based on the time/frequency processing of the recorded signals from individual electrodes of a catheter. Since the IEGM of each electrode is processed independently, these approaches fail to provide any information regarding the wavefront propagation. In the last chapter, we introduced the regional dominant
frequency (RDF), which reflects the DF components of a region rather than just one single electrode. We showed that RDF can be used to identify disorganized wavefront propagation or wave breaks (WBs). Our results suggest that the WB analysis based on the RDF can potentially be used in the ablation therapy procedure. For instance, sites with high RDF and low WBR can be a putative driving source of AF and, consequently, might be a good candidate for ablation.

Further work is needed to characterize WB and establish its relationship to the ablation outcomes. Depending on the achieved result, a pilot clinical trial for feasibility and efficacy analysis of ablation of sites with high RDF and low WBR is among our future plans. We are also planning to use optical mapping models (collaboration with Dr. J. Jalife, Center Arrhythmia Research, University of Michigan) and continuous mapping using a basket catheter to further validate the proposed method for WB identification.
Bibliography


[108] M. H. Shariat, S. Gazor, and D. Redfearn, “Maximum likelihood cardiac conduction velocity estimation in the presence of ambiguities in the locations and
activation times of the recording points,” in *IEEE 29th Canadian Conference on Electrical and Computer Engineering (CCECE 2016)*, 2016.


[122] M. H. Shariat, S. Gazor, and D. Redfearn, “Cardiac conduction velocity estimation from sequential mapping assuming known Gaussian distribution for


