Development of a Method for Registering Surface of Left Atrium determined by LGE-MRI to Electroanatomical Maps

by

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A thesis submitted to the
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in partial fulfillment of the requirements for the degree of

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Abstract

Abnormal electrical conduction and excitability associated with fibrosis in the left atrium (LA) may serve as a substrate for atrial fibrillation (AF). Electroanatomical voltage mapping systems (EAMs) have become a dominant facilitator to treat AF with surgical ablation assisted by additional diagnostic imaging modalities. Importantly, AF has been associated with structural changes to the extracellular matrix of the myocardium, including increased collagen deposition - a process known as fibrosis. Late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) may aid in guiding AF cardiac ablation therapy by determination of fibrosis in the LA. To locate fibrosis for cardiac ablation, however, precise registration between EAMs and LGE-MRI data is crucial. The purpose of this thesis was to develop a method for registering EAMs with late gadolinium-enhanced magnetic resonance image (LGE-MR) images. Twenty patients with persistent AF, who underwent magnetic resonance imaging scanning and EAMs prior to first-time catheter ablation, participated in the study. An experienced radiologist manually segmented the boundaries of the LA on LGE-MR images. In our registration pipeline, the first step involved manual alignment of the LGE-MR images to the left atrial surface on EAMs. The iterative closest point (ICP) algorithm was then applied to deform the left atrial surface determined using LGE-MRI to that of EAMs in an affine manner. We then applied a non-rigid

ICP (NICP) algorithm to correct for non-linear deformations. The results demonstrate that NICP provided a substantial reduction in target registration error when compared to the use of affine ICP alone.

Dedication

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Abbreviation and Acronyms

AF Atrial fibrillation

CPD Coherent point drift

CT Computed tomography

DOF Degree of freedom

EAMs Electroanatomical voltage mapping system

ECG Electrocardiography

ED Euclidean distance

EGM Electrocardiograms

FN False negatives

FP False positives

FWHM Full width half maximum

Gd Gadolinium

ICP Iterative closest point

k-d tree k-dimensional tree

LA Left atrium

LGE Late gadolinium enhancement

LGE-MR Late gadolinium enhancement magnetic resonance

LGE-MRI Late gadolinium enhancement magnetic resonance imaging

LIPV Left inferior pulmonary vein

LSPV Left superior pulmonary vein

LV Left ventricle

MR Magnetic resonance

MRI Magnetic resonance imaging

NED Normalized Euclidean distance

NI Normalized intensity

NICP Non-rigid iterative closest point

PV Pulmonary vein

PVs Pulmonary veins

RA Right atrium

RF Radio frequency

RIPV Right inferior pulmonary vein

ROI Region of interest

ROIs Regions of interest

RSPV Right superior pulmonary vein

SD Standard deviation

STRM Signal threshold versus reference mean

TN True negatives

TP True positives

TRE Target registration error

2D Two dimensional

3D Three dimensional

Chapter 1

Introduction

1.1 Research Motivation and Problem Statement

Atrial Fibrillation (AF) is a heart rhythm disorder of the left atrium (LA) that is associated with an increased risk of stroke and death. A 2010 study estimated that 2.7 to 6.1 million people in the United States suffer from AF, and this number is expected to increase to 12.1 million in 2030 [8]. AF can be classified as paroxysmal, persistent, and longstanding persistent (also known as 'permanent' AF) [9]. While paroxysmal AF can be managed with pharmacological therapy, the conventional treatment for persistent and longstanding persistent AF is catheter ablation [10]. Despite advancements in catheter ablation technology, its success rate remains as low as 45 – 50 % after treatment [11]. This considerably low success rate has motivated a number of experimental studies, including some that explored the correlation between the extent of fibrillation burden and the degree of fibrosis in the LA [12, 13]. Importantly, AF has been associated with structural changes to the extracellular matrix of the myocardium, including increased collagen deposition-a process known as fibrosis. For

example, Verma et al. (2005) [14] showed that patients with evidence of fibrosis in the LA at the time of ablation resulted in nearly half the success rate of those without (43 vs. 81 %).

Electroanatomical voltage mapping systems (EAMs) can precisely identify the presence, location, and extent of fibrosis in the LA by detection of low voltage regions [15]. These systems enable operators to position the catheters without fluoroscopic guidance [16]. Slow conduction pathways ('low bipolar voltage regions') from fibrotic tissue in the LA and its surrounding areas are considered as potential targets for ablation [17]. Catheter ablation is an invasive procedure in which radio frequency (RF) energy is delivered through a catheter to deliberately destroy the small regions of heart tissue that are responsible for creating abnormal electrical signals. For example, pulmonary vein (PV) isolation is a common procedure, where the tissue bordering the pulmonary veins (PVs) is targeted for ablation in order to prevent abnormal wave propagation to the rest of myocardium. When EAMs is fused with other imaging sources, such as magnetic resonance (MR) Imaging or Computed Tomography (CT), it may provide crucial information for guiding catheter ablation by locating fibrosis.

Together with EAMs, pre-procedural MRI can provide a detailed depiction of the chamber of the LA and the PVs [18]. Late gadolinium enhancement (LGE)-MR is also playing an increasingly important role in the characterization of myocardial fibrosis [19] and can provide potentially relevant information prior to ablation. In late gadolinium-enhanced magnetic resonance imaging (LGE-MRI), images are acquired 10 to 20 minutes following a bolus injection of a gadolinium (Gd)-based contrast agent, which allows the contrast to distribute to the extravascular-extracellular spaces, including areas of fibrosis. As the use of LGE-MRI increases in pre-ablation planning, there is an urgent need for registration techniques that will enable us to compare the

spatial extent of low bipolar voltage areas on EAMs with hyper-enhanced regions on late gadolinium-enhanced magnetic resonance (LGE-MR) images. Several studies have demonstrated that fibrosis regions of the LA detected using LGE-MRI prior to ablation can assist in predicting ablation outcome [20–22]. Leonardi et al. (2014) [21] reported that an accurate morphological three-dimensional (3D) left atrial model produced by MRI can improve the cardiac ablation strategy. Romero et al. (2013) [22] described the clinical impact of incorporating LGE-MRI data to EAMs, specifically that regions of LGE-MR enhancement may assist in visualizing the fibrosis border zone in the LA.

Although others have reported significant correlations between EAMs and LGE-MRI with respect to the total burden of fibrosis in the LA [23, 24], the spatial correlation between regions of low bipolar voltage on EAMs and regions of hyperenhancement on LGE-MRI depends on the precise alignment of data acquired by these two disparate image modalities (i.e., registration). To our knowledge, registration methods for integration of LGE-MRI and EAMS have not been fully evaluated [25–27]. Furthermore, it remains unclear whether advanced registration methods have not been widely evaluated in clinical settings. Therefore, we propose a computational registration and evaluation strategy, which can be ultimately validated using clinical data acquired from a prospective study of patients with persistent AF.

1.2 Research Objectives

The two objectives of this thesis are;

1. To develop and validate a registration method for aligning the surface of the LA

determined from LGE-MRI to the left atrial surface depicted by EAMs, and

2. To evaluate the spatial relationship between fibrosis depicted in LGE-MRI determined by several segmentation algorithms and regions of low bipolar voltage on EAMs.

1.3 Research Contributions

The main contributions of this thesis are;

1. Development and validation a registration method

Previous studies have shown that integration of the LA determined by LGE-MRI to the left atrial surface of EAMs was performed with the aid of registration methods [27–30]. However, adequate attention has not been focused on the registration of surfaces determined by LGE-MRI to EAMs. Consequently, their resultant registration influences the association level of fibrosis regions on LGE-MRI and low bipolar voltage regions on EAMs. The contribution of this thesis is the development and evaluation of advanced registration methods for aligning EAMs and LGE-MRI in clinical patients with AF. In this thesis, computational registration methods were developed and evaluated to improve accurate integration of both modalities (i.e., EAMs and LGE-MRI). Further, the development of registration and evaluation methods that can be utilized to compare EAMs to data obtained from cross-sectional imaging modalities such as magnetic resonance imaging (MRI) or CT.

2. Evaluation of the spatial relationship between LGE-MRI fibrosis determined by several fibrosis segmentation methods and regions of low

bipolar voltage on EAMs

It was found that there is a substantial correlation between low bipolar voltage regions on EAMs and fibrosis regions on LGE-MRI [23, 24], but the extent of this correlation is influenced by the choice of image segmentation method for fibrosis and chosen thresholds. Consequently, the degree of the spatial relationship varies, and yet, no optimal segmentation method has been introduced. In this thesis, we computed seven automatic fibrosis segmentation methods that are commonly used in clinical settings to compare the spatial correlation of hyperenhancement on LGE-MRI and low bipolar voltage on EAMs.

Chapter 2

Background

2.1 Clinical Problem: Atrial Fibrillation

As one of the most common cardiac arrhythmias, AF is characterized as uncoordinated electric activity resulting in both irregular and rapid beating of the atria, which can result in palpitations, fainting, shortness of breath, and a host of other symptoms [8, 31, 32]. Patients with AF are also at increased risk of ischemic heart disease, heart failure, and stroke [18]. Figure 2.1 shows the contrast between healthy and AF hearts with the respect to electrical conduction.

Figure 2.1: Comparison between normal heart rhythm and atrial fibrillation. Ref. [/www.mayoclinic.org](http://www.mayoclinic.org)

In healthy hearts, electrical impulses are generated by the sinoatrial node in the right atrium (RA), also known as the natural pace-maker, and the electrical activity spreads throughout the walls of the atria resulting in contraction. Atrioventricular nodes serve to direct the electrical signals to the ventricles. This pathway propagates to the His-Purkinje fibre system to stimulate the myocardium. In AF, normal heart rhythms are overwhelmed by rapid electrical discharge.

When an irregular heart rhythm consistent with AF is suspected, the diagnosis can be either confirmed or excluded using an electrocardiogram (ECG). The ECG records the electrical activities of the heart for a certain period of time using electrodes placed on the skin in certain fixed locations. Figure 2.2 (a) illustrates how the pattern of ECG recording is associated with the polarization of the electro-physiological magnitude change. The morphology, duration, and intervals in ECG recording relate to the diagnosis of the abnormality for heart depolarization by a cardiologist.

2.1.1 Types of AF

In addition to the frequency and duration of AF, an ECG also plays a role in AF classification. A 2006 task force comprised of both American and European cardiovascular societies provided guidelines for classifying AF [8]:

- Paroxysmal,
- Persistent, and
- Permanent or longstanding persistent AF.

The ECG records show a termination of spontaneous recurrent within 7 days of monitoring a patient with paroxysmal AF. If AF lasts for more than 7 days, the patient is regarded to have persistent AF. Evidence of continuous, uncoordinated heart rhythm lasting for more than 12 months is considered 'permanent' or 'longstanding persistent' AF. Figure 2.2 (b) and (c) contrast sample ECG recordings obtained from both a healthy subject and a patient with AF.

(a) QRS complex pattern in ECG

(b) Normal sinus rhythm

(c) Atrial Fibrillation

Figure 2.2: (a) One heart beat electrical event consists of waveform components [1]. *P* wave indicates the atria is contracting (depolarization), *PR* interval is a transition time between sinus node to the ventricles, *PR* segment indicates the time delay between atrial and ventricular activation, *QRS* complex (i.e., *QRS* interval) represents ventricular contraction (depolarization), *ST* segment is zero potential between ventricular depolarization and repolarization, *T* wave indicates ventricular repolarization, *ST* interval indicates an interval between *S* and *T* waves, *QT* interval represents an interval between *Q* and *T* waves, and *U* wave represents papillary muscle repolarization, (b) Normal sinus rhythm. Ref. Harvard medical school (www.health.harvard.edu), (c) AF rhythm. Ref. Harvard medical school (www.health.harvard.edu). The ECG recordings for AF show "absolutely" irregular inter-beat/beat-to-beat (*RR*) intervals, no distinct *P* waves, and invariable atrial cycle length < 200 ms.

Along with diagnosis the type of AF in ECG, the cause of AF has been hypothesized by many researchers. We will describe the mechanism of AF in the next section.

2.1.2 Mechanism of AF

Proposed mechanisms for AF can be summarized as follows:

1. Multiple random propagating wavelets [33],
2. Focal electrical discharge [34, 35], and
3. Localized reentrant activity with fibrillatory conduction [36, 37].

Until the 1980s, the predominant hypothesis was that AF was caused by multiple random propagating wavelets. This proposed mechanism was not supported by either clinical or experimental research; a study performed in a canine model of AF suggested that the length of AF cycle appears to be shorter in the LA than the RA, and random propagating wavelets may occur only in some cases [38]. Rather, the location of ectopic foci was found at the orifices of the left or right PVs, and myocardial sleeves into the PVs [39–41]. More recent work has suggested that fibrillatory conduction arises from the heterogeneous AF substrate converted to high frequency reentrant AF circuits [33, 34, 36, 42–44].

Others have proposed that AF is predominantly driven via PV focal firing. Although this putative mechanism has not been fully explored, Ehrlich et al. (2003) [45] and Chen et al. (2009) [46] showed that the conduction system in the myocardial muscle sleeves extended from the LA into all PVs have distinctive ion channel and action potential properties in canine and rabbit models of AF. This is the rationale for

'PV isolation', which is a common treatment for AF whereby the PVs are effectively disconnected electrically from the body of the LA via ablation [47].

These hypotheses are related to the anatomy of the LA and its electrophysiology. In the next section, we will further explore the relationship between the structure and function of the LA in the context of AF.

2.1.3 Anatomy of the LA and Its Relation to AF

The physical structure and the internal tissue of the LA are shown in Figure 2.3. By convention, the LA itself can be further subdivided into anterior, superior, lateral, septal, and posterior walls. Histological studies [48, 49] have shown that there are considerable regional differences in the thickness of the left atrial wall, ranging from approximately 1.3 *mm* in the left PVs vestibule plane to 2.7 *mm* in the anterior wall [50]. Due to the higher prevalence of fibrosis substrate on the left atrial posterior wall, the posterior wall of the LA is one of the primary targets for catheter ablation in AF [51].

Figure 2.3: The anatomy and structure of the LA [2]. a and b are longitudinal sections of the LA of two healthy patients' hearts, and a short vestibule or funnel-like vein for both left PVs. c and d are transverse sections of the roof of the LA and the entrance of the PVs of two healthy patients' hearts. The blue dotted line is called the left atrial isthmus and the blue arrow indicates a vestibule. *CS* coronary sinus, *LAA* left atrial appendage, *LIPV* left inferior pulmonary vein, *LLR* left lateral ridge, *LSPV* left superior pulmonary vein, *MV* mitral valve, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

In addition, the PV area shows structural features related to AF. Histological studies [48, 52] were able to show two structural features in PVs without heart disease. First, the muscular sleeves are composed of fibrosis and the gaps in between create discontinuities among myocytes due to absence of ganglia [48]. Figure 2.4 shows the composition of muscular sleeves without heart disease. Second, a mesh-like arrangement of muscular fascicles within the muscular sleeves leads to the anisotropic conduction between bundles, which can act as a focal trigger for AF [2].

Figure 2.4: The anatomy and structure of the muscular sleeves without heart disease [2]. a. The left atrial wall becomes thinner at the entrance of the PVs to form the muscular sleeves, b. The circumference of the left PVs shows variation in its wall thickness, d. The presence of the gap between myocardial fibers (red arrows). *LS* left superior pulmonary vein, *LI* left inferior pulmonary vein

Along with PVs and the left atrial wall, the left lateral ridge is also considered as potential candidate locations for ablation. Anatomically, the width of the superior wall is narrower than its inferior wall, and in one of eight cases in AF patients, the superior wall can be obliterated by fibrosis [53].

It is clear from histological and clinical studies that there are substantial intra-atrial variations in myocardial wall thickness as well as tissue composition, and that these differences must be considered prior to invasive catheter ablation or surgical treatment for AF.

2.1.4 Current Treatment for AF

AF can be treated in three ways: pharmacological, surgical, or catheter ablation. Treatment decision making depends on a number of factors, including the classification of AF, clinical considerations, and patient preference.

Pharmacological cardioversion is typically preferred for patients who have paroxysmal AF, and this treatment has a success rate between 60 – 80 % [54]. The advantages of this approach include its convenience and simplicity. However, pharmacological treatment can be ineffective for patients with either persistent, permanent, or longstanding persistent AF, and it may have potential side-effects.

Surgical cardioversion has a success rate between 80–90 %. The advantages of surgical options include the ability to completely isolate the PVs, as well as the detection and treatment of the precise location of the fibrosis regions [55]. However, the open heart surgery option (i.e., Cox maze III procedure) has not been widely adopted as it relies on the availability of surgeons with highly specialized expertise in this technique. As an alternative, Wolf et al. (2005) [56] introduced a minimally invasive video-assisted thoracoscopic technique that provides complete isolation of the PVs by ablating the ganglia on the left atrial surface and removing the left atrial appendage. Despite its high success rate, the drawbacks of this treatment relate to aspiration risk, pain, skin burning, pulmonary oedema, pacemaker malfunction, patient anxiety, and adverse cardiac effects such as sinus arrest and ventricular fibrillation [57, 58].

More commonly, the conventional treatment for patients with persistent AF is direct electric current, catheter ablation. Catheter ablation is an invasive procedure directed at burning (i.e., ablating) pathological atrial tissue. In this procedure, RF energy is delivered via catheter to deliberately destroy the small areas of heart tissue that

are responsible for creating abnormal electrical signals. Heat is produced when the catheter makes contact with tissues leading to coagulation and cellular necrosis.

Despite advancements in the procedure, the recurrence rate of AF is 20 % or higher [59] for patients with persistent AF undergoing first-time ablation return for a second ablation procedure. There are several potential explanations for recurrence of AF post-ablation. First, the sites targeted during ablation are not always completely identified, for example, arrhythmic foci areas can be missed. Second, the recurrence of AF can be caused by incomplete isolation of PVs. Additionally, the stability of the LA may be otherwise deteriorated through aging, heart failure, or the presence of other diseases (i.e., comorbidities). Moreover, successful cardiac ablation requires specialized electro-physiology training and expertise.

There are a few potential side-effects associated with cardiac ablation. Although the complete linear ablations of the left atrial isthmus leads a high success rate in treatment for patients with persistent AF, the creation of deliberate fibrosis may be associated with significant complications. Moreover, the wall of the left atrial appendage is thin ($\leq 0.5\text{ mm}$) making it vulnerable to perforation [60].

Until recently, X-ray fluoroscopy was the predominant imaging tool for guiding cardiac ablation. In fact, ablation is still often guided by X-ray fluoroscopy at many centres. Fluoroscopy is a real-time X-ray imaging technique that allows clinicians to guide the progression of the catheter with an injection of a contrast agent. Despite its role with respect to visualizing the anatomy of the LA and its associated vasculature, it is unable to provide information about the heart muscle tissue in the wall of the LA.

In the next section, we explore an alternative hypothesis for the low success rate of cardiac ablation.

2.1.5 Fibrosis Hypothesis

One of the hypotheses for the low success rate of cardiac ablation in AF is that the burden of fibrosis may be increased in some patients. Although numerous studies [2, 10] have addressed the mechanism of AF, the ability to predict recurrence of AF following electrical cardioversion and anti-arrhythmic therapy is still difficult.

To this question, Verma et al. (2005) [14] investigated the impact of fibrosis in the LA on patient outcomes following first-time ablation. The major finding of the study was that the left atrial scarring caused by cardiac ablation is associated not only with excessive ablation damage in the abnormal atrium, but also with the larger size of the LA, lower ejection fraction, and elevated level of C-reactive protein and B-type natriuretic peptide. Kazui et al. (2015) [13] found that left ventricular function was associated with AF. In a porcine model of AF, the authors reported that both the structure and the function of the LA and left ventricle (LV) change as soon as six weeks following ablation: both increased fibrosis in the LA, as well as increased left atrial and left ventricular chamber size, and decreased left atrial cardiac output function. Pyotr et al. (2011) [12] found evidence of an association between the extent of fibrosis in the left atrial wall and atrial conduction pathways of AF. Additionally, they found the presence of AF or its severity wasn't associated with the structural changes in the atria or age-related changes.

Exploring the candidate mechanisms of AF has also informed innovations in treatment technique. We will describe a mapping technique, an embedding system of the catheter, and an aid from cross-sectional imaging modality in the next section.

2.1.6 Improvements for Current Treatment

Several methods have been proposed for improving the current method and its associated success rate in ablation treatment. First, a new mapping technique may lead to improve localization for RF ablation lesion formation. The ability to measure pressure with the catheter tip may improve the correlation with lesion formation, which in turn may lead a high success rate in surgical ablation. Second, the introduction of a cooling system in the catheter tip may enable more efficient energy delivery to fibrotic tissue. During cardiac ablation, it is crucial to deliver a precise amount of RF energy and ensure a quick contact with the surface of the endocardial is crucial to distribute a reproducible degree of fibrosis for each application. A delivery system consisting of multiple RF sources per catheter could potentially simplify and improve the efficiency of ablation. Reddy et al. (2004), Andreu et al. (2011), and Ling et al. (2015) [25, 61, 62] reported that EAMs-guided cardiac ablation used in conjunction with reference cross-sectional imaging modalities, e.g., MRI or CT, increase the success rate in ablation and reduce radiation exposure to patients and clinicians.

2.2 Electroanatomical Voltage Mapping System

2.2.1 EAMs Application

EAMs such as CARTO (Biosense Webster Inc., Irvine, California, USA) and NavX (St.Jude Medical, St. Paul, Minnesota, USA) have become integral to the delivery of cardiac ablation for the treatment of AF. The key distinction between CARTO and NavX systems is that the former uses contact mapping whereas the latter uses a

non-contact mapping system. For the purposes of this chapter, we will focus on the functionality of CARTO as it is the mapping system used for acquiring the EAMs data described in this thesis.

The configuration of CARTO is shown in Figure 2.5. The low magnetic field (5×10^{-6} to 5×10^{-5} Tesla) consists of three separate coils (C1, C2, and C3) integrated into a locator pad that is positioned under the patient. The magnetic field is detected by the location sensor at the tip of a catheter that consists of small magnets. The catheter is composed of electrodes, and its role is to deliver RF energy for ablation. Using this system, the tip builds a 3D geometric shell of the LA at each contact from a specialized mapping catheter. The strength of the magnetic field of the catheter and its measurement contacted by the catheter is calculated with the value of distance (D1, D2, and D3).

The reconstruction of the cardiac chambers with EAMs results in a depiction of anatomical structures that are adjacent to the heart, such as the oesophagus, parasympathetic ganglia, and the phrenic nerve. These structures are potentially vulnerable to unintentional damage during catheter ablation due to their proximity to the PVs.

Figure 2.5: A representative figure of EAMs [3]. A. An EAMs catheter embedded of location sensor and ring electrode. B. A locator pad with three separate coils (C1, C2, and C3). The distance (D1, D2, and D3) are generated from the coils and determined by the catheter tip location in 3D space (S).

In order to acquire a valid activation map, proper timing windows are required. With EAMs, an appropriate timing reference and window for arrhythmia mapping are guided using the activation of either intra-cardiac electrocardiograms (EGM) or surface ECG leads. The timing reference represents the activation of the arrhythmic origin on the endocardial surface of the LA. Normally, EGM is selected as the timing reference for arrhythmia mapping due to its precision. The timing windows represents the range of activation time surrounding the EGM [16]. Based on the accurate determination of parameters, a propagation map can be generated throughout the endocardial surface of the LA during arrhythmia.

Ablation procedures performed under EAMs guidance presents many advantages. First, EAMs facilitates fibrosis mapping including identification of low endocardial voltage regions, i.e., targets for ablation. The recorded amplitude of the local voltage can be represented as the region of fibrosis. In addition, the system can characterize its degree of fibrosis, e.g., dense fibrosis, fibrosis border zone, or normal myocardium. Secondly, EAMs identifies the presence, location, and extent of fibrosis by detection of low voltage regions [15]. Additionally, the recording of intra-cardiac electrical activation and the locations of arrhythmia origin allow operators to position the catheters without fluoroscopic guidance [16]. EAMs is also well suited for performing PV isolation procedures for patients with complex anatomy. Lastly, the use of EAMs alone or with fluoroscopy reduces the radiation exposure to patients and clinicians during catheter ablation procedure.

Despite these advantages, mapping systems are not without drawbacks, which we outline below. During voltage mapping, the contact-based sequential acquisition of endocardial signals corrupted by sporadic arrhythmias. Consequently, reconstruction of a completely new map of the endocardial surface may be required. The construction of 3D EAMs data is a time consuming process, requiring 190 minutes for atrial tachycardia procedures, and 161 minutes for atrial flutter procedures, even in the hands of highly-trained and experienced electro-physiologists [63]. The sequential mapping and data reconstruction and subsequent identification of the endocardial region of interest (ROI) is an operator-dependent process, relying heavily on the expertise of the electro-physiologist. Finally, given the regions of fibrosis can occur within the left atrial wall itself, rather than at the surface of the left atrial endocardium, it may not be possible for the mapping system to access or interrogate certain substrates of arrhythmia foci. This may impact the success rate of cardiac ablation, resulting in

patients returning for repeated ablation surgeries.

Recently, a feature has been introduced on the CARTO EAMs workstation ("CARTO merge"), which facilitates the superposition of the EAMs constructed 3D geometric chamber of the interest with cross-sectional CT or MR images acquired pre-procedure. The CT or MR images supply anatomic information to inform cardiac mapping and, ultimately, ablation. Malcome-Lawes et al. (2013), Romero et al. (2013), and Leonardi et al. (2014) [21, 22, 64] have reported the benefits of using this image-integration technique. In this thesis, we will restrict our focus on the relationship between EAMs and LGE-MRI. In order to find a relation between EAMs and LGE-MRI, we first need to address how we define fibrosis thresholds using EAMs.

2.2.2 Identifying Fibrosis with EAMs

With respect to RF energy sources for catheter ablation, there are many options for ablation. However, we will limit our scope to two technologies;

- Unipolar RF ablation, and
- Bipolar RF ablation (dry and irrigated).

For unipolar recordings, a negative electrode is connected to the remote electrode as a reference, which is positioned far away from the heart. As a depolarization of the wavefront propagation towards the main electrode, it generates a positive deflection [5]. A RS complex (as in three deflection (QRS complex) seen on ECG) is generated when the wavefront reaches the exploring electrode, and when the propagation is away from the electrode, the deflection sweeps negatively. The signal pattern for unipolar

recording is described in Figure 2.6.

Unipolar RF ablation provides an evenly distributed heat source to create fibrosis, and it can map local electrical activity more accurate than bipolar recordings. However, the major disadvantage of unipolar recordings is that the recorded signal near fibrosis is relatively small, consequently, it can be difficult to detect areas of fibrosis. Furthermore, the quality of the signals can be vulnerable to electromagnetic interference from the equipment in the catheterization laboratory [65]. For these reasons, the unipolar method is considered less desirable than the bipolar method.

Two electrodes are used for bipolar recordings, with the recorded signal in a remote distance similar to the exploring electrode (Figure 2.6). Bipolar RF ablation provides more efficiency and safety by achieving transmural lesions than the unipolar approach. The jaw-clamp structure provides a real-time assessment of the impedance measurement from the transmural lesions by clamping atrial tissue and heating until irreversible protein denaturation occurs [59]. Thus, bipolar recordings facilitate the identification of local depolarization in the areas of fibrosis.

Figure 2.6: Unipolar and bipolar electrograms [4, 5]. A. A diagram of unipolar recording. The excitation of the tissue proceeds from left to right. The lighter grey zone indicates depolarized tissue. From left to right of the depolarized tissue, *QRS* complex is created. B. A diagram of bipolar recording. *Uni-1* is a positive input of amplifier, and *Uni-2* is a negative input of the second electrode. The summation of these two signals generate the bipolar signal (*Bi 1-2*). C. Setup for unipolar recording. It can be used either Wilson central terminal or a catheter in inferior vena cava (IVC). *RA* right arm, *LA* left arm, *LL* left leg.

Using bipolar RF ablation, regions of low voltage are labeled as fibrosis using the following thresholds;

- 1.90 ± 1.45 mV is for sinus rhythm [65],
- 1.45 ± 1.66 mV is for tachycardia [66], and
- 0.5 mV is used for atrial tachycardia [67].

In this thesis, we defined regions of fibrosis as those with bipolar voltage below 0.5 mV

for the LA.

In the next section, we will describe LGE-MRI, introducing its functionality and strategies for identifying the relationship between low voltage areas on EAMs with regions of late gadolinium enhancement on MRI.

2.3 Late Gadolinium Enhancement Magnetic Resonance Imaging

2.3.1 Imaging Technique

Since Felix Bloch and Edward Mills Purcell discovered the magnetic resonance phenomenon in 1946 and Paul Lauterbur created an image from MRI in 1973, MRI has been prominently used as a safe diagnostic medicine and research imaging tool. In MRI, images are generated using a strong magnetic field and radio waves. Unlike X-ray, CT, or nuclear medicine imaging, MRI does not require ionizing radiation. In most clinical and experimental applications, MR images reflect both the abundance and behavior of hydrogen nuclei (protons). In order to generate a measurable signal, RF is applied at a particular frequency (the 'Larmor frequency') to perturb the net magnetization from its equilibrium orientation with the strong magnetic field. Once disrupted from equilibrium, the protons revert to their previous low-energy states. This process of returning to equilibrium manifests in a signal that can be measured by external RF receiver coils. With the help of three low-amplitude (mT), but time varying magnetic fields ("gradients"), the signals received by the RF coils can be localized within the body (slice) and, in turn, within each slice (xy location). For a

given slice or volume, the raw signal data is stored in so-called 'k space' or spatial frequency space; images are reconstructed from these data by applying an inverse Fourier transform. Compared to CT imaging, for example, patients who have medical implants or non-removable metals inside their body may not be able to undergo MRI safely. Additionally, some patients may feel discomfort or anxiety due to the narrow imaging bore of the MRI machine.

MRI is a noninvasive medical imaging modality that is particularly well suited for the assessment of soft tissues. Together with ECG gating and rapid imaging techniques, MRI has become useful and valuable tool for the assessment of cardiovascular structure and function due to its potential for achieving fine spatial resolution and its ability to characterize myocardial tissue [68]. LGE-MRI is particularly useful for distinguishing between healthy myocardium and fibrotic tissue.

In fact, LGE-MRI is considered the gold standard non-invasive technique for the assessment as well as quantification of myocardial fibrosis, particularly in the settings of cardiomyopathy and infiltrative disorders like myocarditis [69]. LGE imaging involves acquisition of T_1 -weighted images approximately 10 minutes after injection of gadolinium-based contrast media.

Gadolinium-based contrast media are the most common clinical MRI contrast agents. Gadolinium is a lanthanide metal element and is paramagnetic. Gadolinium-based contrast agents coordinate with neighboring water molecules, indirectly shortening the longitudinal relaxation time of tissues (T_1). In its free form, Gd^{3+} is highly toxic, therefore, it has to be complexed to a ligand or chelate from the potentially toxic effects of free Gd^{3+} before injection [69]. The chelator moiety also governs the distribution or kinetics of the contrast media. Characteristically, clinical Gd-based

contrast media can only distribute to the extravascular and extracellular spaces and will not permeate healthy (intact) cell membranes. Therefore, the loss of membrane integrity in injured tissue (i.e., fibrosis of AF) allows the distribution of the contrast media into its formerly intracellular space.

In the context of fibrosis or irreversible injury, the contrast media can occupy these formerly intracellular spaces and cause T_1 shortening. A dynamic process, contrast media is cleared from the body by glomerular filtration, decreasing in concentration exponentially. Conventionally, imaging is timed to occur at a point when contrast is no longer concentrated in the blood and maximally distributed to the extravascular or extracellular spaces (10 - 20 minutes post intravenous injection).

The goal of LGE is to exploit the difference in T_1 between healthy and fibrotic myocardium. LGE-MR sequences begin by applying a volume inversion preparation pulse, i.e., a RF pulse that inverts the initial longitudinal magnetization (M_z) 180° to the opposite direction of the main magnetic field (B_0). Following inversion, the signal from normal myocardium will pass through the $M_z = 0$ ('null point') later than the signal from fibrotic tissue. If images are collected at a time=TI (inversion time) when healthy myocardium is nulled, then areas of fibrosis will appear bright by comparison. Figure 2.7 depicts the difference of recovery time between healthy myocardium and fibrosis.

(a)

(b)

Figure 2.7: (a) a The blue arrow indicates an initial magnetization, and it is aligned in the z direction. b The magnetization vector was flipped to the opposite direction of the initial magnetization after applying inversion recovery with 180° RF pulse. c The flipped magnetization vector slowly recovers to the original equilibrium. d The magnetization vector slowly recovers to the original magnetization direction. (b) After applying inverted pulse sequence, each component (tissue, fat, and fluid) shows different recovery time. M_z is the initial longitudinal magnetization, T_1 is a relaxation time, and TR is a repetition time. Ref. <http://www.revisemri.com>

If, however, images are collected when $TI < \text{null point}$, fibrotic myocardium will appear darker than normal tissue; conversely, when $TI > \text{null point}$, normal myocardium

will appear grey.

In the context of AF, the assessment of fibrosis in the left atrial wall on LGE-MRI poses a much greater challenge due to its thin wall. Nevertheless, others have shown that the extent of LGE-MRI determined fibrosis can predict the likelihood of post-ablation AF recurrence [23].

Left Atrial Fibrosis

In conventional LGE imaging for identifying fibrosis in the LV, 8 - 10 two-dimensional (2D) slices are acquired sequentially, while the patient holds his/her breath for $\sim 6-12$ seconds. This approach is well suited for obtaining high signal-to-noise ratio images of the LV, where the myocardial wall is approximately 8 *mm* thick. Figure 2.8 highlights the difference between LGE-MR images acquired to identify fibrosis of LA and LV.

Figure 2.8: Examples of the LA (A), LV (B) and their adjacent anatomy, e.g., RA, aorta (Ao) on LGE-MRI, in three patients. The fibrosis of the LA is displayed as bright grey color in the left atrial wall whereas the wall of the LV is displayed as black color.

Unlike LV, the thickness of left atrial wall is $1 - 3 \text{ mm}$ (i.e., 3 mm on average), therefore, the signal available is inherently weaker. Obtaining images of the left atrial wall requires longer acquisition times to collect sufficient signal from the thin walled myocardium; more than can be achieved with sequential 8 - 12 seconds breath-hold acquisitions. To address the difficulty in holding breath for patients during MR image acquisition, free breathing (respiratory navigated) acquisition enables collection of 3D LA LGE data over approximately 5 - 10 minutes to achieve the sub- mm resolution required to resolve fibrosis in the LA.

Correspondingly, a crude surface ECG signal is required for LGE-MRI studies, in order to synchronize or 'gate' the collection of image data during the same phase of the cardiac cycle. Typically, MR data acquisition begins after the detection of the first

R -wave in the ECG rhythm and completes before the next R -wave (R - R interval). Therefore, the repetition time (TR) sequence is set prospectively with a multiple of the average R - R interval for image acquisition process. In addition to ECG gating, 3D segmented inversion-recovery gradient echo, shallow flip-angle readout (e.g., $< 20^\circ$), inversion pulse triggered every heartbeat ~ 20 contiguous sections acquired in the z direction, often with the aid of zero-filling and interpolation.

Similar to EAMs, hyper-enhanced regions on LGE-MR images will be defined by several segmentation techniques in this thesis. Therefore, the segmentation of fibrosis on LGE-MRI is described in the next section.

2.3.2 Fibrosis Segmentation

Before we can evaluate the spatial correlation between EAMs and LGE-MRI, we first need to identify and isolate the fibrotic regions of interest (ROIs) on each imaging data set. More generally, image segmentation aims to extract a precise boundary of an object or image. This task is highly challenging and complex due to inter/intra-artifacts from the results of imaging procedure and methodology. Despite the fact that manual segmentation can be considered as a gold standard, it is a tedious task and its results are highly operator-dependent. Therefore, (semi) automatic segmentation methods have emerged that identify salient tissue patterns with minimal operator input.

Many computational approaches have been proposed [70–73], however, there is not yet a consensus on the "optimal" method for fibrosis quantification. At present, a precise classification of fibrosis from healthy myocardium on LGE-MRI has been only indirectly validated against electro-anatomic voltage mapping (i.e., regions of low

bipolar voltage on EAMs). Recall from section 2.3.1 that 'fibrosis' distinguished from healthy myocardial tissue by its relative image signal intensity. Given that LGE-MR image signal intensity is generally expressed in 'arbitrary units', it is not surprising that the intensity threshold corresponding to fibrosis is also relative or expressed with respect to the intensity of 'normal' myocardium. Importantly, the signal intensity of LGE-MR image obtained of the left atrial wall will necessarily depend on a number of factors: surface coil proximity, contrast dose, inversion time, slice thickness, the delay between contrast injection and image acquisition, and patient characteristics (e.g., body mass index) [74].

The following describes fibrosis segmentation strategies, including those focused on quantifying fibrosis:

1. Thresholding between one to six standard deviation (SD) above the mean intensity of healthy myocardium (STRM1, 2, 3, 4, 5, 6) [75, 76],
2. Thresholding fibrosis signal intensity greater than 50 % of hyper-enhanced myocardium (FWHM) [76],
3. Normalized intensity (NI) [77],
4. Clustering [78–80], and
5. Advanced methods, e.g., region growing, active contour models, level sets, graph-cut

The first two thresholding techniques have been widely used due to their simplicity [79]. Schmidt et al. (2007) [81] found 2 SD above the mean of remote (i.e., presumed to be 'healthy' myocardium) overestimated the infarct size of the LA, and Karim et

al. (2013) [82] showed that FWHM method is a reasonable segmentation technique for high fibrosis contrast. However, these thresholding techniques produce outcomes that depend on the characteristics of the chamber being imaged (e.g., LA, LV), as well as the associated wash in/out characteristics. Giannakidis et al. (2015) [77] attempted to account for inter-subject differences in contrast clearance by selecting NI thresholds on LGE-MRI that were visually correlated with EAMs areas of low bipolar voltage (by consensus of multiple expert observers). In this thesis, we used STRM1, STRM2, FWHM, NI techniques and their results will be demonstrated in section 4.

Clustering classifies data in a specific group; data in the similar group have similar features whereas those in the different group have dissimilar features. Among clustering techniques, Fuzzy and K -mean clusterings are the most commonly used methods. In Fuzzy clustering, the fibrosis pixels/voxels will be clustered based on the similarity measure upon their signal intensities. Unlike hard clustering, Fuzzy clustering (i.e., soft clustering) may quantify more than one clustering of fibrosis. K -mean clustering groups similar pixels/voxels by finding a centroid for each group based on a single mean vector. The Otsu thresholding technique [83] belongs to the class of clustering threshold techniques. This technique transforms the grey-scale image to a binary image, with which an optimum line is prescribed to divide the image to a bi-modal, e.g., background and foreground 'mask'.

Along with clinical fibrosis threshold techniques, more advanced fibrosis segmentation methods are briefly introduced here. Region growing [84] is a simple image segmentation method by selecting seed points with the involvement of operator. From the seed point, the ROI grows up to the boundary of the object by comparing the pixel

neighbor intensity. Active contour models, i.e., snake [85], is a more advanced alternative to region growing. While only the internal energy term is used for region growing, the active contour defines a more accurate segmentation by adding an external energy term. Edge detection [86] can be used with four different operators, e.g., Sobel, Prewitt, Canny, Laplacian, and their applications provide dynamic edge detection results. These algorithms delimit the detection and localization criteria for a class of edges.

Moreover, Level sets approach [87] was developed by Osher and Sethian. The propagation speed of this approach depends on the object curvature; the algorithm searches each level of the object boundary and proceeds by solving a "Hamilton-Jacobi" type equation. Finally, the Graph-cut method [88] is an energy-based approach to find a minimum cut between background and foreground to define the boundary of the object. Many more machine learning algorithms such as convolution neural networks, support vector machines, genetic algorithms have been evaluated, as they appear to offer less operator-dependent alternatives to manual segmentation.

Once hyper-enhanced regions on LGE-MRI and regions of low bipolar voltage on EAMs are determined, the registration process between the two imaging modalities can be discussed with respect to its relevance to previous work. The next section introduces a detailed explanation of the proposed registration approach, contrasting with prior work in this field.

2.4 Point Cloud Registration

Ever since the introduction of LGE-MRI, numerous studies have been published describing the gadolinium-enhancement characteristics of the myocardium in healthy and diseased states [21, 89–94]. Several studies have demonstrated that areas of hyperenhancement identified in the LA using LGE-MRI prior to ablation can assist in predicting ablation outcome [21, 22, 64]. For instance, Malcolme et al. (2013) [64] quantified fibrosis in the LA using a simple intensity-based threshold method (i.e., 2 - 4 SD) and found a significant correlation with endocardial voltage.

Prior to image registration, one needs to determine which image will be the static (i.e., target, fixed, stationary, or reference), and which image will be moving (i.e., source, floating, complementary, or test) object. This decision depends primarily on the goal of the registration. While the static data remains in the original spatial scene, the moving data moves toward the target image for alignment.

In image processing, registration involves aligning two or more objects into the same spatial scene [95]. The fundamental components in image registration can be divided into three: the nature of transformation, similarity measures, and optimization [96]. The generic registration pipeline is depicted in Figure 2.9.

Figure 2.9: Generic registration pipeline

Based on deformation, the nature of transformation can be categorized as either rigid, affine, or non-rigid (i.e., elastic, curved). Rigid deformation only includes global translations and rotations, whereas affine deformation also includes size and shear transformations. Non-rigid deformation includes global and local distortions. With respect to geometric transformations, three components are considered: no distortion, global distortion, and local distortion. Generally, objects with similar shapes require no distortion, particularly when the objects were acquired using the same diagnostic imaging modality. For global distortion, multiple transformations can be applied such as size, shear. In registration, similarity measures, e.g., distance measures, are used to find the distance between corresponding points. As the last component, more complex transformation, e.g., elastic, radial, is used for local distortion, which belongs to a class of non-rigid transformation. This type of transformation is shown in figure [2.10](#).

Figure 2.10: Examples of 2D transformation [6]. Different transformation (rigid, affine, projective, or curved) is applied to the images globally and locally.

In order to evaluate the alignment of two images in image registration, a similarity metric is necessary. The suitability of a given similarity measure depends on the registration problem. Commonly, mean-square difference and normalized cross-correlation are preferable for registration between images acquired using the same modalities. To maximize the similarity measure, an optimization algorithm is essential. The criteria of optimization is always locally defined and the deformation of object is constrained by a regularization term. Least-squares, Gauss-Newton, and Marquardt-Levenberg optimizers etc. are the most common optimization algorithms used in image registration [97–99]. Bainville et al. (1995) [100] found a local non-rigid deformation field with a regularization term to find the closest point of two models, and Szeliski and Lavalley (1996) [101] performed 3D non-rigid surface registration using pre-computed octree distance map.

Images can be described with respect to their fundamental building blocks, i.e., pixels (XY) or voxels (XYZ) in 2D or 3D space. The registration strategy can be determined by image signal intensity distributions, textures, or shapes contained within the image datasets. In this thesis, we used a point cloud to represent the left atrial geometry, as isolated from LGE-MR images and EAMs data. In this context, a point cloud is a collection of coordinate points, $XY(Z)$, in space, which can be converted to create a surface of the LA using Delaunay triangulation.

The most popular registration method for point cloud data is the iterative closest point (ICP) algorithm [102, 103]. In the standard ICP algorithm, adjacent points on each point cloud refine their distance at each iteration using translation and rotation transformation matrices. Refined transformation of the output results in minimization of the error metric, e.g., the root mean squared differences, between coordinate points from two point clouds. The termination of iteration occurs when the error metric falls below a user-defined threshold, $\tau > 0$. In this context, τ denotes a tolerance of the distance error. However, the standard ICP algorithms perform well for only two types of global transformation: translation and rotation [102, 103]. Furthermore, the initial interactive (i.e., manual) alignment can influence the accuracy of point cloud registration [103]. Many modified versions of ICP algorithm have been introduced to address these limitations [104–106]. Despite improvements, however, the transformed source does not necessarily fit into the structure of the target data. To compensate for some of the known limitations of ICP, many non-rigid iterative closest point (NICP) algorithms have been studied [107–109] because NICP provides more degrees of freedom in transformation and a deformation field to alter the shape of images considerably.

We introduce prior studies related to nonrigid registration methods. To form an initial correspondence field in NICP registration, Andresen et al. (2018) [110] applied a convolution to the nearest neighbor displacements. Although the introduced convolution algorithm created a deformation field to show useful anatomical landmarks of the image, they only performed well for areas where the topology remains fixed. Chui and Rangarajan (2003) [111] regularized points movement using thin-plate splines, and based on Laplacian coordinates, an implicit regularization term was proposed by Pauly et al. (2005) [112]. The proposed robust point matching algorithm outperformed to synthetic outliers compared to the classic ICP developed by Besl (1992), and modified by Chen and Medioni (1992) [102, 103]. However, the experimental method on point cloud set was computed as approximately 13 times smaller than our data set size, and its computational complexity is largely dependent on the implementation of the robust point matching algorithm. Furthermore, Amberg et al. (2007) [113] proposed a locally affine regularization term, and Mitra et al. (2004) [114] presented a space-time surface registration algorithm instead of points-based correspondence.

Solving optimization problem in NICP algorithm has been proposed by many studies [106, 111]. Fuzzy correspondences and expectation maximization ICP was proposed by Chui and Rangarajan (2003) [111] and a prior knowledge method was used by Munch et al. (2010) [106]. To find more efficient error metric to coordinate points, unit normals were introduced [106], nevertheless, a curvature criterion can be included in the future study. Amberg et al. (2007), Chui and Rangarajan (2003), and Munch et al. (2010) [106, 111, 113] altered the error minimization step in NICP algorithm. Normalized Euclidean distance (NED) measurement was used to check the accuracy of registration between two objects [106] for the purpose of assessment.

Chapter 3

Methodology

3.1 Overview

In AF, there is substantial clinical demand for integration of LGE-MRI with EAMs data to provide complementary information. Recall from Section 2.4, we introduced the spatial correlation of fibrosis regions determined from LGE-MRI to low bipolar voltage regions on EAMs. Therefore, in this chapter, we describe our registration method pipeline to explore the relationship between EAMs and LGE-MRI.

Our proposed registration pipeline is shown in Figure 3.1, which consists of manual, affine, and non-rigid alignments. In the original space (i.e., prior to registration), LGE-MR and EAMs data were located in the same scene of 3D space at a remote distance. In the manual registration step, translation and rotation transformation were applied to relocate the left atrial surface obtained from LGE-MRI closer to the EAMs, as guided by the anatomy of the LA. This was followed by application of an ICP algorithm, in which the left atrial surface determined by LGE-MRI was deformed

to that of EAMs in an affine manner. Finally, we applied a NICP algorithm to maximize the matching criteria by searching for the correct parameters in a deformation field.

Figure 3.1: Point cloud registration flow diagram. The top left image indicates EAMs data and the top right image indicates LGE-MRI data. Both LGE-MRI and EAMs data were preprocessed before registration was performed. The results of the registration were validated by both landmark-based and surface-based evaluation methods.

3.2 Study Subjects and Image Acquisition

Twenty patients (mean age: 64 years, age range: 45 - 76 years, see Appendix Table [A.1](#)) participated in this prospective study of persistent AF. The study was approved by the Institutional Human Research Ethics Board at the University of Ottawa Heart Institute, and a written consent was obtained from all participants. 3D LGE-MR images were acquired prior to first-time ablation (median duration: 57 days), and EAMs data were acquired immediately prior to ablation. The dates at which LGE-MRI and EAMs data were acquired are depicted in Figure Appendix [A.2](#).

All patients underwent MRI examination on a 1.5 Tesla clinical scanner (Siemens Aera, Siemens Medical Systems, Erlangen, Germany). LGE imaging was performed approximately 15 minutes after injection of 0.1 *mmol/kg* Gadobutrol (Gadovist, Bayer Healthcare, Canada) using a 3D inversion recovery prepared, ECG gated, respiratory navigated, gradient echo sequence. Images were acquired with an inversion time selected to null the signal from normal ventricular myocardium (typically between 340 – 360 *ms*). The 3D images were acquired axially with a voxel size of $1.25 \times 1.25 \times 2.5 \text{ mm}^3$, which was subsequently reconstructed to $0.63 \times 0.63 \times 1.25 \text{ mm}^3$.

Participants underwent voltage mapping prior to cardiac ablation. A mapping catheter and proximal electrodes accessed the left atrial chamber percutaneously for recording the unipolar and bipolar signal [\[3\]](#). Sequential contact along the left atrial endocardium of the mapping catheter was recorded with respect to its position (vertex), the distance from location sensors to three coil magnetic fields beneath the patient triangulated in the space (face), and the magnitude of the local peak voltage at each vertex (uni/bipolar voltage). The CARTO (Biosense Webster Inc., Irvine,

California, USA) workstation progressively displays reconstruction of the left atrial chamber in 3D space with color encoded in sequential activation time, wherein purple-to-green denotes healthy myocardium, yellow the border zone, and red fibrosis on the basis of voltage as shown in Figure 3.2 [7].

Figure 3.2: Examples of EAMs images obtained from representative patients with persistent AF, displayed in gradient color (patients A (left), B (middle), and C (right)). The gradient color bar on the top right corner shows the geometric voltage values for each LA; purple-to-green indicates healthy myocardium, whereas red and yellow indicate areas of fibrosis and border-zone, respectively [7]. The red dots adjacent to PVs indicate the recommended locations for ablation ('PV isolation'). Images displayed in the top row correspond to the posterior view of the LA, those in the middle row correspond to the anterior view of the LA, and those on the bottom row correspond to the inferior view of the LA. The images were captured by CARTO XP system viewer version 1.0.0.4.

3.3 Dataset Pre-processing

A cardiothoracic radiologist with 7 years of experience manually segmented the left atrial blood-pool and wall on LGE-MR images using the Cardiac MRI Toolkit Slicer extension in 3D Slicer (CARMA Center, University of Utah, UT, USA). For the left atrial blood-pool segmentation, the left atrial appendage and PVs (and their respective ostia) were identified by the operator who then defined five walls (septal, posterior, anterior, inferior, and roof) of the LA. Subsequently, the axial dilate function (Cardiac MRI toolkit) was applied to the left atrial blood-pool volume. In particular, this function performs a four-pixel radius binary dilation (in-plane) for each 2D axial slice. A first approximation of the left atrial wall contours was then created by subtracting left atrial blood-pool segmentation from the dilated result; contours were subsequently refined manually by the radiologist (i.e., thinning or thickening the wall as appropriate). We utilized the segmented myocardium of the LA as the ROI for the purpose of registration to EAMs, and for delineation of fibrosis.

We built a polygonal mesh representing the LA composed of vertices and faces from the label map using the Marching cube algorithm [115]. Developed in 1987 by Lorensen and Cline, the algorithm constructs a surface intersected cube composed of eight vertices. We also constructed a left atrial surface composed of multiple polygons derived from vertices and faces that were transferred from voltage map. The coordinates (vertices) were formatted as a matrix, and the triangulation connectivity (faces) was labeled for identifying specific vertices using the triangulation. The preprocessing for both data was performed in MATLAB 2017b (The Mathworks, Inc. Natick, Massachusetts, USA).

During the creation of multiple polygons for EAMs and LGE-MRI data, we discovered that the number of vertices of MR is typically denser than those in EAMs (see Appendix Table A.3). Each vertex consisted of xyz coordinates in 3D space for its geometric representation. The relationship between vertices and faces to formulate triangulation connectivity was followed by Euler’s polyhedron formula;

$$V - E + F = 2 \quad (3.1)$$

where V is the number of vertices, E is the number of edges, and F is the number of faces.

In our registration process, we used EAMs as our target and the left atrial point cloud from LGE-MRI as the source, which was ultimately deformed to match the target. We determined EAMs as the target due to its primary role in ablation as well as the goal of the registration. In this thesis, LGE-MRI is the cross-sectional imaging modality to find the spatial correlation with low bipolar voltage regions on EAMs. The point cloud for the source (s) is a set of vertices $v^s = (v_1, \dots, v_i) \in \mathbb{R}^3$ and faces $f^s = (f_1, \dots, f_l) \in \mathbb{R}^3$, and the point cloud for the target (t) is a set of vertices $v^t = (v_1, \dots, v_j) \in \mathbb{R}^3$ and faces $f^t = (f_1, \dots, f_m) \in \mathbb{R}^3$.

3.4 Point Cloud Registration

3.4.1 Manual Alignment

We manually aligned the left atrial surfaces determined by MR to those of EAMs first to provide a good initialization for the ICP algorithm by observing the resultant

shortest distance between corresponding landmarks. The source was aligned to the target manually while considering the structure of the LA (e.g., left superior pulmonary vein(LSPV), left inferior pulmonary vein (LIPV), right superior pulmonary vein (RSPV), right inferior pulmonary vein (RIPV), and the mitral valve). Figure 3.3 depicts the results of manual alignment. In this step, only translations and rotations were applied where six degrees of freedom (DOF) were allowed (3 rotations + 3 translations) for this registration.

Figure 3.3: Example of the left atrial surface from EAMs and MR obtained from manual alignment. EAMs is represented as purple and MR is represented as blue. A posterior view, B inferior view, and C anterior view. *L* denotes left and *R* denotes right, respectively.

DOF is a freedom of movement of independent parameters in 2D or 3D space. The rotation transformation is consisted of tilting left or right on the X axis, tilting forward or backward along the Y axis, and turning left or right on the Z axis. Similar to rotation, translation transformation includes moving forward or backward along the X axis, moving left or right on the Y axis, and moving up or down along the Z axis. Both transformations have three independent parameters, therefore, the total DOF is 6. The mathematical form of translation and rotation matrix are followed by;

$$\begin{pmatrix} x_2 \\ y_2 \\ z_2 \end{pmatrix} = R \begin{pmatrix} x_1 \\ y_1 \\ z_1 \end{pmatrix} + \begin{pmatrix} T_{x1} \\ T_{y1} \\ T_{z1} \end{pmatrix} \quad (3.2)$$

where T_{x1} , T_{y1} , and T_{z1} denote translations in x , y , and z directions, x_2 , y_2 , and z_2 indicate manually aligned point coordinates, x_1 , y_1 , and z_1 denote the original point coordinates, and $R = R_x \times R_y \times R_z$ denotes rotation matrix. In this context, we only introduced R_x matrix format in the xy -plane counterclockwise through an angle (θ) due to its similarity to R_y and R_z , followed by;

$$R_x = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos\theta & -\sin\theta \\ 0 & \sin\theta & \cos\theta \end{pmatrix} \quad (3.3)$$

where θ is a rotation angle.

3.4.2 Affine ICP Registration

Recall from 2.4, the standard ICP algorithm includes rotation and translation matrices. In contrast to the standard ICP algorithm, we applied affine ICP with 12 DOF (3 rotations + 3 translations + 3 scales + 3 shears) to the manually aligned point cloud due to the dissimilar appearance of the source and target, which is computed

as follows:

$$\begin{pmatrix} x_3 \\ y_3 \\ z_3 \end{pmatrix} = TF \begin{pmatrix} x_2 \\ y_2 \\ z_2 \end{pmatrix} + \begin{pmatrix} T_{x2} \\ T_{y2} \\ T_{z2} \end{pmatrix} \quad (3.4)$$

where T_{x2} , T_{y2} , and T_{z2} denote translations in x , y , and z directions, x_2 , y_2 , and z_2 indicate manually aligned point coordinates, x_3 , y_3 , and z_3 denote the point coordinates after affine ICP is applied, $TF(a; v_i^s)$ represents a transformation where a is a parameter vector including rotation (R), scale (S), and shear (Sh). v_i^s denotes a set of vertices for target, and S denotes a scale transformation followed by;

$$S = \begin{pmatrix} S_x & 0 & 0 \\ 0 & S_y & 0 \\ 0 & 0 & S_z \end{pmatrix} \quad (3.5)$$

where S_x , S_y , and S_z denote scale in x , y , and z directions. Sh denotes a shear transformation followed by;

$$Sh = \begin{pmatrix} 1 & sh_x^y & sh_x^z \\ sh_y^x & 1 & sh_y^z \\ sh_z^x & sh_z^y & 1 \end{pmatrix} \quad (3.6)$$

where sh_{yx} , sh_{zx} , sh_{xy} , sh_{zy} , sh_{xz} , and sh_{yz} denote shear in x , y , and z directions.

Figure 3.4 depicts the results of manual alignment.

Figure 3.4: Example of the left atrial surface from EAMs and MR obtained from affine ICP algorithm. EAMs is represented as purple and MR is represented as blue. A posterior view, B inferior view, and C anterior view. *L* denotes left and *R* denotes right, respectively.

The affine ICP algorithm created uniform grids of target vertices by sorting the points into local groups to speed up the distance measurement process. The source points were then calculated by the radius of each point from the uniform grid. For point correspondence between the two surfaces, the nearest source point from the target grids was found using k -dimensional tree method (k-d tree) [116], which is a computationally efficient algorithm to find the nearest point on the other surface. This approach is initiated by calculating the distance of correspondences from the target to source followed by a selection of those with the shortest distance.

The error function associated with affine ICP can be written as:

$$E(a) = \sum_{j=1}^{N_{vt}} w_i (\min_j (\epsilon^2 (|v_j^t - TF(a; v_i^s)|))) \quad (3.7)$$

where N_{vt} is a number of vertex for target, w_i is a weight, $\min_j$ is part of minimization process of the distance between target and source, v_i^s is a set of vertices for source, $a \in \mathbb{R}^{12}$ are parameter vectors of TF , and ϵ^2 is an error function for alignment

measurement defined as;

$$\epsilon^2 (\|x\|) = \|x\|^2 \quad (3.8)$$

where $x \in \mathbb{R}^3$ is manually aligned vertices of source. We set w_i as zero for vertices where no finding for the corresponding vertex, and one otherwise. During point cloud registration, only vertices were registered in the registration procedure.

At each iteration, a least squares method was used to reduce the average distance between corresponding points, and distance of each point will be reduced individually. The mean-square error $d_k = e_k$ converges monotonically to a minimum value followed by:

$$d_k = e_k = \frac{1}{N_{vt}} \sum_{j=1}^{N_{vt}} \|\vec{y}_{jk} - \vec{v}_{jk}^t\|^2 \quad (3.9)$$

where N_{vt} denotes a number of points of target, $\vec{y}_{jk}$ is a set of closest vertices from target to source, $\vec{v}_{jk}^t$ is a set of vertices of target, and the initial k is the number of iteration. The distance error ($d_k = e_k$) decreases at each iteration in finding a set of the closest points, therefore, eventually it reaches to a minimum value until the threshold $\tau > 0$ specified by $d_k - d_{k+1} < \tau$.

Considering the large number of vertices (mean v^s : 40358, mean v^t : 27684), we used memory efficient optimizers supported by Quasi-Newton, BroydenFletcherGoldfarb-Shanno [117–120], and followed by Davidon-Fletcher-Powell [121, 122]. Quasi-Newton

analyzes successive gradient vectors, $\nabla_{v_i^s} F = g(v_i^s)$ where $F(v_i^s)$ is a minimizing function, by updating Hessian matrix;

$$\text{Hessian } H^* = H - \frac{Hyy^T H}{y^T H y} + \frac{s^T}{sy^T} \quad (3.10)$$

where H is an approximation to the inverse Hessian [123], $s = v_i^{s*} - v_i^s$ and $y = g^* - g$ are the changes in v_i^s and g made at each iteration, T denotes transpose, $*$ denotes an appropriate value to the next iteration.

Using a Quasi-Newton optimizer, the local minimum and maximum can be found by approaching the value of the function tolerance by minimizing distance error. Broyden-Fletcher-Goldfarb-Shanno formula [117–120] is used here;

$$B^* = (I - \frac{ys^T}{sy^T})B(I - 1) + \frac{yy^T}{sy^T} \quad (3.11)$$

where I is an approximate Hessian matrix, and B is a positive definite Hessian matrix. In this context, vector s^T and y must satisfy the curvature condition:

$$s^T y = s^T B s > 0 \quad (3.12)$$

3.4.3 NICP Registration

As the deformation of the heart muscle is nonlinear, we also applied a non-rigid registration of EAMs to the MR point cloud. We used a NICP algorithm that is similar to the one described by Amberg et al. (2007) [113]. We retained a locally

affine regularization, smooth translation, and set the number of iterations for all datasets to 160 based on the previous study [113].

In our implementation of NICP, we used the quadratic cost function [124] for the minimization of distances between the deformed source and the target. This can lead us to solve the minimization problem directly and exactly due to more than three parameters per vertex in the deformation field. The affine 3×4 transformation matrix X_p is predefined for each vertex of the source, and the error function in NICP is;

$$E_d(X) \approx \sum_{v_i \in s} w_p (\text{dist}^2(T, X_p v_i^s)) \quad (3.13)$$

where $X = [X_1 \cdots X_p]^T$ is an affine matrix, X describes a set of displaced source vertices, $v_i = [x, y, z, 1]^T$ in homogeneous coordinates, s denotes source, w_p is a weight, T is a target, and $\text{dist}(T, v)$ denotes a distance between a source point v_i^s and its closest point on the target surface. We set w_p as zero for vertices where no finding for the corresponding vertex, and w_p as one for other vertices.

We included an additional regularization function [124] by penalizing the adjacent vertices of the source to be mapped to the disparate vertices of the target in transformation. The error function is used;

$$E_r(X) \approx \sum_{v_i^s, v_j^t \in E^t} \| (X_j - X_i) G \|^2_F \quad (3.14)$$

where E^t denotes edges of target, X_j and X_i are affine transformation matrix for target and source, G is a weighting matrix by $G = \text{diag}(1, 1, 1, \gamma)$, γ used as differences in weighting in rotational deformation, set to one here, and was scaled into the $[-1, 1]^3$

cube. $\|\bullet\|_F$ is Frobenius norm.

The complete objective function (E) for cost function is the weighted sum of the two-error functions by;

$$E(X) \approx E_d(X) + \alpha E_r(X) \quad (3.15)$$

where the initial $\alpha = 1$, $\alpha^q > \alpha^{q+1}$, is a weight for smoothness of source and it was lowered when two successive iterations (i.e., q) were smaller than a threshold.

3.5 Image Intensity Normalization

Image intensity normalization is a pre image processing method in order to correct image intensity variation caused by inter-subject differences in image acquisition [125]. MR image intensity is impacted by a number of factors: patient anatomy, inhomogeneity of magnetic static field, the variation of the RF receiver coil sensitivities. The image intensity variation may not be a crucial factor from a clinical perspective, however, it can impact image processing. Image intensity normalization is a vital step that can impact virtually any step downstream in the analysis pipeline.

In the current thesis, the variation in image intensity acquired from the LGE-MR images relates to the retainment of gadolinium contrast agent in the extracellular spaces of the myocardium. LGE-MRI image intensity within the left atrial wall can manifest in specific image intensity profiles (histograms) for each patient. Figure 3.5 depicts the histogram of the left atrial wall image intensity. This variability is owed in large part to inter-subject differences in contrast wash-in and wash-out (biological clearance), as well as to differences in imaging time post-injection [69].

Figure 3.5: A histogram of left atrial wall image intensity before normalization process. The image intensity for hyperenhancement region in the left atrial wall under LGE-MRI differs in the range of its value (bins, x axis) and the number of counts (y axis). The legend on the right indicates each patient ID. Before normalization process, a universal threshold of all patients data for fibrotic tissue cannot be drawn.

Several studies have proposed methods for correcting or normalizing the image intensity in LGE-MRI [96, 125, 126]. Madabhushi et al. (2005) [125] investigated the effect of correcting MR image intensity inhomogeneity followed by normalization. They applied four different MR protocols to evaluate their impact on LGE-MR image quality. Although authors did not find a significant improvement in MR image quality, the study demonstrated that normalization for non-uniform intensity was the best sequence in terms of image quality and computational efficiency. Bagci et al. (2010) [96] extended their research for the role of image intensity normalization on image registration. They found that accurate image intensity normalization improves image registration for not only geometric similarity but also intensity similarity.

In this thesis, we applied the image intensity normalization method advanced by Giannakidis et al. (2015) [77]. We normalized the image intensity of the voxels

within the left atrial wall contours by that of the left atrial blood pool [77] using the following;

$$NI(h) = [I(h) - \mu_{bp}] / \sigma_{bp} \quad (3.16)$$

where $NI(h)$ is normalized left atrial wall intensity, μ_{bp} is the mean value of the left atrial blood pool signal, I , σ_{bp} is the SD value of left atrial blood signal, I , and $I(h)$ is left atrial wall intensity for each voxel, h . Both μ_{bp} and σ_{bp} were computed from the image intensity histograms corresponding to the left atrial blood pool (Fiji open source software, National Institutes of Health, MD, USA).

After the foregoing normalization of image intensity, we aligned all histograms as depicted in Figure 3.6. Although the data associated with patient # 6 demonstrated a broader dispersion of normalized image intensity values compared other patients, overall, the normalization process provided a standard threshold for fibrosis delineation on LGE-MRI.

Figure 3.6: A histogram of the left atrial wall image intensity after normalization. The normalized image intensity of hyperenhancement region in the left atrial wall was aligned to the threshold for fibrotic tissue (red line). The range of the normalized image intensity value is bins, i.e., x axis, the number of counts is y axis, and the legend on the right side of the figure indicates patient ID.

3.5.1 Segmentation of Fibrosis in LGE-MRI

We applied seven different methods for identifying voxels in left atrial wall as "fibrosis" for the purpose of finding a spatial correlation with low bipolar voltage regions on EAMs. The FWHM method labels voxels with normalized signal intensity greater than half the maximum signal intensity within a hyper-enhanced region as fibrosis. The voxels with signal intensity greater than the mean + 1 standard deviation intensity of the left atrial wall are defined as fibrotic in STRM1, and the voxels with signal intensity greater than the mean + 2 standard deviation intensities of the left atrial wall are defined as fibrotic in STRM2. For NI methods, the cut-off threshold for hyperenhancement region was marked out for lower boundaries of fibrosis, and the number of NI was incremented by 0.5 starting from 1 and up to 2.5. Above NI

2.5, there was not enough fibrotic signal intensity to quantify the voxel values.

3.6 Spatial correlation of fibrosis determined by LGE-MRI to low bipolar voltage regions on EAMs

We projected vertices labeled as fibrosis in the left atrial wall determined from LGE-MR, created using intensity-threshold-based techniques, on EAMs to evaluate their spatial correlation. Figure 3.7 depicts the projection of LGE-MR areas of fibrosis onto regions of low bipolar voltage on EAMs. We used the k-d tree method [116] based on the Euclidean distance (ED) metric to locate the closest point on the target surface. In the Euclidean space, the minimum distance between two points is drawing a straight line. During k-d tree search, each vertex of fibrosis in the left atrial wall was regarded as a query point and unlabeled points (vertices in the registered left atrial endocardial surface of LGE-MR) were classified to query points under the ED metric. Subsequently, we limited our assessment of fibrosis in the LA on MR to the registered left atrial endocardial point cloud delineated by the ROI, i.e., to the exclusion of tissue directly adjacent to the PVs. Next, we determined the cut-off value (below 0.5 *mV* [66, 127]) for the regions of low bipolar voltage on EAMs for the purpose of discovering a spatial relationship with LGE-MR. Accordingly, each vertex corresponding to the seven fibrosis thresholds on LGE-MR (FWHM, STRM1, STRM2, NI 1, NI 1.5, NI 2, and NI 2.5) was projected to the regions of low bipolar voltage on EAMs. The resultant LGE-MR-to-EAMs projections were displaying using ParaView open source software (Kitware Inc., New York, NY, USA).

Figure 3.7: Projection flow diagram. Both LGE-MRI and EAMs data were preprocessed before projection was performed. Regions of LGE-MR fibrosis were identified using seven threshold-based approaches and their correspondence with regions of low bipolar voltage (EAMs) was assessed. In the example of the spatial correlation result, A denotes posterior view, B denotes anterior view, C denotes inferior view, and *L* denotes left, *R* denotes right. The registered LA was depicted in purple, blue depicts the regions of low bipolar voltage on EAMs, and yellow depicts the distributed gadolinium on LGE-MRI.

We identified areas of potential spatial correlation between LGE-MRI and EAMs by searching for LGE-MR fibrotic vertices that were located within a 3 mm radius of the EAMs low bipolar voltage vertices based on the NED measurement. The NED defines the squared distance between two point sets with uniformed scale form [128].

3.7 Comparison of our method to an alternative technique

We compared results of our method to the coherent point drifts (CPD) [129], which is an alternative to the NICP algorithm. The CPD algorithm considers the alignment of target and source datasets as a probability density estimation problem and coherently re-parameterizes Gaussian mixture model centroid locations with rigid parameters using maximization step of the Expectation-Maximization algorithm. The CPD algorithm followed the same procedure for registration up to affine ICP. No more than 50 iterations were set for convergence due to its demands on memory.

3.8 Evaluation of our Registration Approach

We used a landmark-based evaluation method by measuring the distance between corresponding landmark points on the two surfaces in ParaView. Figure 3.8 shows the location of the eight chosen landmarks. To choose distinctive features in the LA, two vertices in the diagonal direction at each PV were selected under careful visual inspection. For left PVs, in the middle of a short vestibule or funnel-like common vein between LSPV and LIPV, the adjacent edges of the posterior and anterior wall were chosen as landmarks. Similarly, in the middle of a long vestibule between RSPV and RIPV, the edges on the right PV areas were selected as landmarks.

Figure 3.8: Example of the location of the landmarks in the LA with three points of view, displayed in white square dots (patients A (left), B (right)). (1) Posterior view, (2) Anterior view, (3) Inferior view. A total of eight landmarks were selected, and two points at each PV are located at a diagonal direction in the middle of a short (or long) vestibule or funnel-like common vein in PVs. R and L denote a right and left, respectively.

We did not use the mitral valve as a landmark due to the obscurity of its position on EAMs. As the target object, the landmarks on EAMs are static whereas the corresponding point on MR was selected one by one manually for each registration step. We used target registration error (TRE)

$$TRE(v^t, v^s) = \sqrt{\frac{1}{8} \sum_{k=1}^8 (v_k^t - v_k^s)^2} \quad (3.17)$$

as the metric for evaluating the registration method, where k is the number of landmarks.

We also validated our registration method by computing the alignment of the entire surface of point pair correspondence. We computed the distance from all vertices in EAMs to those in MR based on the ED metric, and vice versa. Then, the median value (M) of the results at each coordinate was selected as the distance between EAMs and LGE-MRI. The evaluation results are presented as medians and interquartile ranges due to the non-Gaussian distribution of the ED measurement. The distance computation of surface-based evaluation was followed by;

$$d(v^t, v^s) = M \sqrt{(v^t - v^s)^2} \quad (3.18)$$

All statistical analyses were conducted using the SAS environment (SAS Institute Inc., Cary, NC, USA). Differences in the ED measurement (surface-based evaluation) from the manual-alignment to affine ICP, and finally to NICP were assessed using a non-parametric repeated measure (Friedman) test. Post-hoc Wilcoxon paired tests were performed to assess pair-wise differences between manual-alignment and affine ICP, manual-alignment and NICP, and affine ICP and NICP, and NICP and CPD with respect to TRE (landmark-based evaluation). Afterward, we validated the performance of CPD with our evaluation methods. The mean number of iterations and running time for affine ICP, NICP, and CPD were also compared. A p - value < 0.05 was considered statistically significant.

The spatial correlation of fibrosis on LGE-MRI with low bipolar voltage regions on EAMs was evaluated by deriving the following from a 2×2 contingency table;

- Sensitivity = $TP / (TP + FN)$,
- Specificity = $TN / (TN + FP)$,
- Precision = $TP / (TP + FP)$, and
- Accuracy = $(TP + TN) / (TP + FP + TN + FN)$.

where TP represents the number of true positives, i.e., the fibrosis vertices for source within 3 *mm* of NED of the low bipolar voltage vertices for target, FP represents the number of false positives, i.e., the non-fibrosis vertices for source within 3 *mm* of NED of the low bipolar voltage vertices for target, TN represents the number of true negatives, i.e., the non-fibrosis vertices for source within 3 *mm* of NED of the high bipolar voltage (> 0.5 *mV*) vertices for target, and FN represents the number of false negatives, i.e., the non-fibrosis vertices for source within 3 *mm* of NED of the low bipolar voltage vertices for target. We arbitrarily set the range (3 *mm*) to search close vertices from target to source to achieve the goal of the study. The statistical values shown above will be described in Section 4.2, and the number of TP, FP, TN, FN with seven fibrosis segmentation methods determined by LGE-MRI and low bipolar voltage regions on EAMs is described in Appendix A.4.

Chapter 4

Results and Discussion

4.1 Registration Results

We developed and validated a method for registering the left atrial surface on LGE-MRI to that of EAMs based on three integrated steps. We aligned the left atrial surface of LGE-MRI to EAMs manually using translation and rotation transformation matrices with careful observation of the structure of the LA. Then, we applied affine ICP algorithm to rescale the left atrial shape on LGE-MRI to match that of EAMs. The results of our registration pipeline were validated by two evaluation methods; landmark-based and surface-based. Moreover, we added an experimental algorithm (CPD) as an alternative method for comparison of the results to our method.

We summarized the results of our landmark-based TRE for our method and the alternative method (CPD) in Table 4.1. Manual alignment reduced the TRE from 368.94 *mm* to 25.06 *mm*, which was decreased further to 20.97 *mm* after affine ICP (Wilcoxon paired test between manual alignment and affine ICP, $p < 0.05$). NICP

improved the TRE to 0.61 *mm* whereas CPD only improved the TRE to 1.8 *mm* (Wilcoxon paired test between NICP and CPD, $p < 0.01$). The TRE reduction associated with the NICP step was significantly greater than that which was achieved by affine ICP (A reduction of 0.61 *mm* for NICP vs. 20.97 *mm* for affine ICP, $p < 0.01$). The proposed registration outperformed the CPD algorithm in terms of TRE by three-fold, based on landmark evaluation.

Table 4.1: Evaluation results of the registration method based on landmarks using the ED measurement (*mm*). Q1 denotes 1st quartile, Q3 denotes 3rd quartile, IQR denotes interquartile, and SD denotes standard deviation.

Registration step/ (mm)	Mean	Median	Min	Max	IQR (Q1-Q3)	SD	Outliers (low)	Outliers (high)
Original	365.77	368.94	206.6	473.47	337.2 – 403.85	54.64	6	160
Manual	26.73	25.06	1.74	90.95	16.09 – 33.04	15.47	0	153
Affine ICP	21.99	20.97	1.99	104.55	16.67 – 31.44	11.00	0	157
NICP	0.86	0.61	0.05	8.02	0.41 – 1.26	0.9	0	151
CPD	2.25	1.80	0.26	8.67	1.10 – 3.14	1.59	0	155

The median ED measurements associated with each registration step are depicted in Figure 4.1. The range of the highest observation and Q3 reduced from 57.92 *mm* to 34.37 *mm* after affine ICP, and further decreased to 6.76 *mm* in NICP. CPD resulted in a similar reduction in ED to NICP. Moreover, the range of the lowest observation and Q1 resulted in fourteen-fold improvement in TRE (14.68 *mm* in affine ICP vs. 0.36 *mm* in NICP, $p < 0.01$).

Figure 4.1: Median and interquartile ranges for the ED are depicted for manual, affine ICP, NICP, and CPD registration.

The surface-based evaluation of registration are presented in Figure 4.2 and Figure 4.3 as examples of six patients. Recall from section 3.8, the ED metric was used to express the distance between MR and EAMs and the median ED values are depicted graphically using 'distance maps.' The distance metric in a gradient color bar was ranged from 0 to 2 mm and the resultant LA surface demonstrated < 0.5 mm mostly on the exclusion of PVs in NICP. In contrast, the distance of the entire LA surface including PVs ranged from 0.5 mm to 1.5 mm in CPD. The farthest distance between the left atrial surface on MR to that of EAMs in NICP mainly located in the ostia of the PVs whilst CPD demonstrated < 0.5 mm in small regions of the LA. A non-parametric Friedman test of differences among repeated measures was conducted and was significant $p < 0.01$. Despite the superior performance of our registration method, two patients demonstrated results that were not considerably better than

those achieved by CPD, which is shown in Figure 4.4. Compared to the CPD results, NICP demonstrated wider regions for < 0.5 mm.

Figure 4.2: Representative distance maps depicting the results of NICP registration method (top) and CPD registration method (bottom) based on surface evaluation using the entire vertices on LGE-MRI and those on EAMs for patients A (left), B (middle), and C (right). (1) Posterior view, (2) Inferior view, (3) Anterior view. The distance maps were depicted in a gradient color bar at the top right ranged from 0 to 2 *mm*. *L* denotes left and *R* denotes right. All measurements are depicted in *mm*.

Figure 4.3: Representative distance maps depicting the results of NICP registration method (top) and CPD registration method (bottom) based on surface evaluation using the entire vertices on LGE-MRI and those on EAMs for patients A (left), B (middle), and C (right). (1) Posterior view, (2) Inferior view, (3) Anterior view. The distance maps were depicted in a gradient color bar at the top right ranged from 0 to 2 *mm*. *L* denotes left and *R* denotes right. All measurements are depicted in *mm*.

Figure 4.4: Representative distance maps depicting the results of NICP registration method (top) and CPD registration method (bottom) based on surface evaluation using the entire vertices on LGE-MRI and those on EAMs for patients A (left), B (right). (1) Posterior view, (2) Inferior view, (3) Anterior view. The distance maps were depicted in a gradient color bar at the top right ranged from 0 to 2 *mm*. *L* denotes left and *R* denotes right. All measurements are depicted in *mm*.

Similar to the results of landmark-based evaluation, the proposed evaluation method resulted in a three-fold improvement in registration accuracy for NICP based on surface evaluation compared to the CPD algorithm. NICP method improved the surface error to 0.58 *mm* whereas CPD only improved the surface error to 1.68 *mm* ($p < 0.05$). The lowest observation to Q1 in NICP also showed lower range (0.4–0.48) than 1.12 – 1.36 in CPD. Similarly, while the outliers in NICP reached only up to 1.06 *mm*, those in CPD extended to 3 *mm*. The median ED measurements associated

with NICP and CPD registration methods are depicted in Figure 4.5.

Figure 4.5: Median and interquartile ranges for the ED are depicted for NICP and CPD registration.

Table 4.2 shows the number of iterations and computational time required to perform affine ICP, NICP, and CPD registration methods. The number of iterations varied due to the convergence threshold configuration ($\tau > 0$) for affine ICP whereas NICP and CPD were set as static value due to complete utilization of vertices for the source. Affine ICP ($0.39 \pm 0.24 \text{ min}$) demonstrated a fast execution time, particularly relative to the running time required for our NICP registration steps ($79 \pm 16.73 \text{ min}$), using a workstation with an Intel *i7* processor and a memory of 12 GB. In a similar fashion, the CPD algorithm considerably increased the computational time ($21 \text{ hrs } 27 \text{ min} \pm 19 \text{ hrs } 44 \text{ min}$), an increase of sixteen-fold compared to NICP.

Table 4.2: The number of iterations and computation time required for affine ICP, NICIP, and CPD. CT denotes computational time in seconds.

Registration	Affine ICP	Affine ICP	NICIP	NICIP	CPD	CPD
iteration/CT	iteration	CT (sec)	iteration	CT (sec)	iteration	CT (sec)
Mean	33	23.1	160	4739.6	50	77265.3
Median	15	2.0	160	1557.4	50	1190.0

Our registration methods validated by landmark-based and surface-based evaluations and compared by an experimental algorithm presented more reliable outcomes that can be applied in finding accurate spatial relationship of fibrosis on LGE-MRI and low bipolar voltage on EAMs.

4.2 Correlation Results between EAMs and LGE-MRI

Our evaluation of the spatial correlation between the regions of hyperenhancement on LGE-MRI and the regions of low bipolar voltage on EAMs was predominantly focused on the posterior and anterior wall of the LA and the left atrial appendage due to the exclusion of PVs. In this thesis, the fibrosis segmentation methods on LGE-MRI included the following strategies:

1. FWHM, STRM1, STRM2, and

2. NI 1, NI 1.5, NI 2, NI 2.5

Figure 4.6 depicts the spatial correlation between two surfaces in a qualitative manner for FWHM, STRM1, and STRM2. Recall from section 2.2.2, low bipolar voltage regions on EAMs are static (< 0.5 mV) whereas hyper-enhanced regions on LGE-MRI float depending upon fibrosis segmentation method. In general, the regions of low bipolar voltage on EAMs are denser and clustered than the regions of hyperenhancement on LGE-MRI. STRM1 demonstrated the most density of fibrosis on LGE-MRI, and followed by FWHM and STRM2.

Figure 4.6: Representative results from two patients (top, bottom) depicting the spatial correlation between regions of low bipolar voltage on EAMs and regions of hyperenhancement on LGE-MRI using each of the three thresholds for left atrial fibrosis. The regions of low voltage on EAMs is stationary whereas fibrosis on LGE-MRI differs due to fibrosis thresholds. (1) Posterior view, (2) Anterior view, (3) Inferior view; (A) FWHM, (B) STRM1, (C) STRM2. Regions depicting low bipolar voltage on EAMs are shown in blue, while regions of hyper-enhancement on LGE-MR are shown in yellow.

Table 4.3 summarizes the extent of spatial correlation between regions of hyperenhancement delineated by LGE-MRI and low bipolar voltage regions on EAMs based on FWHM, STRM1, and STRM2. Overall, all methods for fibrosis thresholds demonstrated over 80 % in accuracy, and over 90 % in specificity. STRM1 showed the highest value in sensitivity (41.31 %) and precision (90.6 %) whereas FWHM and STRM2 showed low value in sensitivity (7.6 % and 2.78 %) and relatively low value in precision (69.27 % and 78.68 %).

Table 4.3: Results of a relationship between the regions of fibrosis on LGE-MRI and the regions of low bipolar voltage on EAMs.

Method	Sensitivity (%)	Specificity (%)	Precision (%)	Accuracy (%)
FWHM	7.6	99.9	69.27	83.21
STRM1	41.31	99.33	90.6	85.05
STRM2	2.78	99.92	78.68	84.05

For NI threshold techniques, the range of normalized image intensity threshold for left atrial fibrosis was arbitrarily set, and its computation was followed by equation 3.16 in section 3.5. Figure 4.7 depicts the spatial correlation between two surfaces in a qualitative manner. Gradually, the amount of fibrosis on LGE-MRI decreases as the threshold cut off value increases. Similar to FWHM, STRM1, and STRM2, the regions of low voltage on EAMs is stationary whereas fibrosis on LGE-MRI differs.

Figure 4.7: Representative results from two patients (top, bottom) depicting the spatial correlation between regions of low bipolar voltage on EAMs and regions of hyper-enhancement on LGE-MRI using each of the four thresholds for left atrial fibrosis. The regions of low voltage on EAMs is stationary whereas fibrosis on LGE-MRI differs due to fibrosis thresholds. (1) Posterior view, (2) Anterior view, (3) Inferior view; (A) NI 1, (B) NI 1.5, (C) NI 2, (D) NI 2.5. Regions depicting low bipolar voltage on EAMs are shown in blue, while regions of hyper-enhancement on LGE-MR are shown in yellow.

Table 4.4 summarized the extent of spatial correlation between regions of hyperenhancement delineated by LGE-MRI and low bipolar voltage regions on EAMs. On the whole, as the range of normalized signal intensity increases, all parameters decreased with minor adjustment. All parameters showed over 86 % in accuracy and over 96 % in specificity, which are higher values than FWHM, STRM1, or STRM2. Contrast to prior threshold techniques (FWHM, STRM1, STRM2), NI demonstrated more consistent results in all parameters.

Table 4.4: Results of a relationship between the region of fibrosis on LGE-MRI and the region of low bipolar voltage on EAMs.

Method	Sensitivity (%)	Specificity (%)	Precision (%)	Accuracy (%)
NI 1	49.31	99.4	95.05	87.88
NI 1.5	48.48	99.33	94.35	87.55
NI 2	46.98	98.65	88.61	87.31
NI 2.5	44.86	96.9	81.9	86.3

4.3 Discussion

In summary, the registration results demonstrated that there was incremental but significant improvement with each step in the proposed pipeline over the steps (i.e., from manual alignment to affine ICP, and to NICP). Particularly, the median result of registration showed the most improvement from affine ICP to NICP by thirty-four-fold, based on landmark evaluation. However, the primary contribution of affine ICP to the overall registration outcome was to resize or scale the left atrial surface of MR to match that of EAMs. Furthermore, the computational time required by affine ICP was 205 times faster than NICP. With respect to surface-based evaluation results of the registration methods, their outcome exhibited similar values as those on landmark-based evaluation.

Our presumption in this thesis is based on the evidence of fibrosis in the LA defined by any of the foregoing segmentation threshold methods from the attainment

of gadolinium in the extravascular/extracellular spaces. Accordingly, we evaluated the extent of correspondence between areas of hyperenhancement (as identified by each of the scar thresholds) to an in vivo reference standard for fibrosis (i.e., areas of low bipolar voltage on EAMs). Recall from section 2.3, there is extensive research demonstrating an association between gadolinium enhancement and left ventricular fibrosis [130] whereas there are minimal to no histopathology studies to support this connection for the LA. At present, EAMs can provide as the closest vivo non-invasive gold standard for fibrosis in the LA. Therefore, we presumed the integration of the left atrial surface of LGE-MRI to that of EAMs will establish the spatial correlation between low bipolar voltage and gadolinium enhancement.

The spatial correlation rate between low bipolar voltage regions on EAMs and hyper-enhanced regions on LGE-MRI can depend on the fibrosis segmentation method. With respect to sensitivity, relatively similar value was resulted in NI and STRM1 thresholds whereas FWHM and STRM2 were both low. For FWHM, the number of FP was greater than the number of TP in four patients due to the extensive amount of hyperenhancement on MR. On the contrary, STRM2 identified a smaller region of hyperenhancement on MR that its number of FN was greater than its number of TP in most patients. In specificity, all fibrosis segmentation methods demonstrated almost comparable results because most patients resulted in either a small number of FP or a large number of TN. The proposed fibrosis segmentation methods can be replaced by more advanced segmentation algorithms [131] to increase the accuracy of the segmentation results, which will influence to the rate of spatial relationship between fibrosis on LGE-MRI and low bipolar voltage on EAMs.

Chapter 5

Conclusions and Future Research

5.1 Conclusions

The objective of this thesis was to develop a method for registering the left atrial surface from EAMs to the one determined from LGE-MR images. Such a method would enable merging of complementing information from both LGE-MRI with EAMs, and potentially improve cardiac ablation outcomes for patients with persistent AF. We described a registration pipeline based on the ICP algorithm, which was evaluated by measuring distance between manually picked anatomical landmarks in left atrial surface obtained from both EAMs and LGE-MRI. In our approach, the ICP algorithm was used to deform the left atrial surface determined using LGE-MRI to that of EAMs by an affine transformation; we then applied a NICP to deform the left atrial surface by non-rigid deformations. The results demonstrated that NICP can provide considerable incremental improvement in TRE over the use of affine ICP alone (median 20.97 *mm* in affine ICP vs. 0.61 *mm* in NICP). Moreover, NICP outperformed the TRE reported in previous studies (mean distance for LV: 3.41 – 3.8 *mm* [25, 26],

LA: $> 5 \text{ mm}$ [62]) in terms of the accuracy of registration assessed by points-based methods.

Andreu et al. (2011) [25] included 12 patients in the study, co-registered the left ventricular surface of MRI to that of EAMs, and evaluated by three anatomical landmarks: the left ventricular apex, mitral annulus, and aortic annulus. Wijnmaalen et al. (2011) [26] integrated LV from the same number of patients as Andreu and validated by one landmark, the ostium of the left main stem. Ling et al. (2015) [62] reported registration of left atrial surface of CT to that of EAMs; however, location of the corresponding landmarks wasn't specified. In addition, the combined rigid and non-rigid approach was found to be superior to an independent non-rigid alternative (CPD) with respect to registration error. Although the CPD algorithm can provide an alternative for registration of MR images to EAMs, it was shown to be higher TRE than our proposed registration pipeline.

Our evaluation of a non-rigid algorithm for registration provides background information to clinical studies requiring the spatial correlation of fibrosis with low-voltage points on EAMs. Although several studies [25–27] have evaluated the correlation of two surfaces by computing a global assessment of fibrosis correlation (i.e., over the entire left atrial wall), there has been a dearth of studies focused on evaluating the potential algorithms for registration. The spatial correlation results of fibrosis determined by MRI to low bipolar voltages on EAMs based on our registration method demonstrated more consistent values in all parameters for NI thresholds techniques than FWHM, STRM1 or STRM2 fibrosis threshold selection. For FWHM, STRM1, and STRM2 techniques, some differences in sensitivity (7.6 % in FWHM vs. 41.31 % in STRM1 vs. 2.78 % in STRM2) were expected due to the amount of fibrosis identified by each threshold. However, the specificity of each threshold for identifying

EAMs-positive low-voltage regions was high (mean: 99.72 %). Importantly, selection of the NI threshold criteria resulted in superior accuracy compared to the FWHM, STRM1, or STRM2 (by an average of 3.16 %) despite the fact that sensitivity along with precision diminishes as the range of NI increases due to decrease of the hyper-enhanced regions (sensitivity: 49.31 % in NI 1, 48.48 % in NI 1.5, 46.98 % in NI 2, 44.86 % in NI 2.5, precision: 95.05 % in NI 1, 94.35 % in NI 1.5, 88.61 % in NI 2, 81.9 % in NI 2.5).

5.2 Limitations and Future Research

The work described in this thesis has several limitations. First, the cohort consisted of only 20 patients, which was relatively small. Despite the small number of patients, we demonstrated statistical significance using non-parametric repeated measure (Friedman and Wilcoxon paired tests). With respect to the spatial correlation between regions of low bipolar voltage on EAMs and hyper-enhanced regions on LGE-MRI, the resultant parameters, e.g., TP, FP, TN, FN, may change their outcome with a minor adjustment. However, this limitation is balanced by the fact that patients were recruited prospectively and met strict inclusion criteria, e.g., the participants have persistent AF and underwent the first-time ablation.

Since left atrial wall is very thin, the image resolution greatly influences the ability of the imaging technique in identifying the fibrotic regions. As we acquired contiguous 3D spatial data via multi-slice selection, this leads to anisotropic spatial resolution, especially in the z direction. In terms of the signal intensity, normally, acquired image contrast under LGE-MRI relies on the signal intensity difference between normal myocardium and myocardial fibrosis. Although LGE-MR images are designed

to delineate healthy from fibrotic myocardium, there is not always a clear differentiation between fibrosis and adjacent normal myocardium. In the same manner, the assessment of diffuse myocardial fibrosis can be ambiguous in terms of defining the threshold of fibrotic tissue. Moreover, the extent of hyperenhancement may differ depending on the signal intensity threshold selected by the operator or image analyst. Finally, irregular heart-rates or respiratory rates can heavily impact image quality.

As described in Section 2.4, ICP algorithm is considerably influenced by the initial alignment. Despite careful experiments on manual alignment, this factor can influence the outcome of the registration, and ultimately the degree (strength) of the spatial relationship between hyper-enhanced regions on LGE-MRI and low bipolar voltage regions on EAMs. Advanced refinement [105] on ICP algorithm, e.g., uniform sub-sampling of the available points, random sampling with different points at each iteration, a large number of normal among selected points, can be further studied to improve the accuracy of the registration. With respect to NICP, the computational time can be greatly reduced if a small number of iterations can provide similar results. To improve computational time of the registration method, faster program environment, e.g., C, or simplified structure of the registration algorithm can be alternative options.

With respect to dataset preprocessing, manual segmentation of the left atrial wall was a considerably time-intensive task, which is subject to high-observer variability. The application of automatic segmentation methods can be studied in the future to improve the computational time of registration further. For instance, principal component analysis can be performed on the left atrial shapes on LGE-MRI, and then align them based on eigenvectors to those of EAMs. Yang et al. (2013) [132] proposed a model-based method to segment LA with left atrial appendage and PV

trunks from CT images using marginal space learning, and obtained over 0.94 outcome based on Dice's coefficient evaluation. Veni et al. (2013) [71] presented a surface-detection method of segmenting LA by computing a-posterior estimate and obtained over 0.9 in Dice's coefficient.

Finally, due to the properties of EAMs, regions of hyperenhancement in the left atrial wall of LGE-MRI was projected to the constructed left atrial endocardium depicted in EAMs by finding the shortest path (straight line), where their corresponding point should be computed over the surface of the LA, i.e., geodesic distance. Although we used the ED measurement for its wide-usage and simplicity, another disadvantage with the ED is the largest-scaled features dominate the others if dataset clusters are not isolated or compacted [42]. An alternative metric can be proposed to refer to the shortest path between two vertices on a curved surface or sphere.

In this thesis, we registered the left atrial surface determined by LGE-MRI to that of EAMs, validated the registration outcome, and evaluated the spacial relationship between hyperenhancement regions on LGE-MRI and low bipolar voltage regions on EAMs. The results of our registration methods, and ultimately the spatial relationship can be further studied by improving described limitations.

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Appendix A

Figures and Tables

A.1 Patient Characteristics

The table describes sex and age information of the patients participated in this study.

Table A.1: Patient Characteristics

Patient ID.	Sex (Male/Female)	Age (yrs)
1	M	76
2	F	74
3	M	65
4	M	47
5	M	49
6	M	62
7	M	64
8	M	62
9	M	70
10	M	57
11	M	62
12	M	61
13	M	71
14	M	45
15	F	68
16	M	56
17	F	74
18	M	68
19	F	73
20	M	68

A.2 Acquired Dates on which EAMs and LGE-MRI

The figure describes the dates on which EAMs and LGE-MRI were acquired. All patients underwent LGE-MRI and first time ablation was performed under EAMs. x

axis indicates patient ID, y axis indicates the data acquisition time, blue dots denote LGE-MRI, and red dots denote EAMs.

A.3 The number of vertices and faces on LGE-MRI and those on EAMs for patient data

The table describes the number of vertices and faces on LGE-MRI and those on EAMs for patient data. The vertices and faces for LGE-MRI are denser than those on EAMs.

Patient ID	EAMs		LGE-MRI	
	Vertex	Face	Vertex	Face
1	11404	22806	11454	22080
2	19542	39088	47616	95228
3	25547	51695	58464	116924
4	32275	65375	33442	66024
5	29800	59948	28778	57556
6	39558	80064	37875	72984
7	11692	23436	41376	81576
8	11762	23528	42052	81236
9	40226	81434	45898	91792
10	33274	66824	41378	82752
11	34693	69855	55278	110552
12	23508	47654	41500	82996
13	36773	74032	47260	94520
14	26839	54774	34970	69932
15	23906	47824	31832	63644
16	27961	56412	38320	76636
17	33079	66681	37650	75296
18	33026	66514	44060	88100
19	30220	61182	45836	91660
20	28595	58260	41820	982556

A.4 The confusion matrix of LGE-MRI determined by fibrosis segmentation methods and EAMs low voltage regions for patient data

The table describes the confusion matrix of LGE-MRI determined by seven fibrosis segmentation methods and EAMs low bipolar voltage regions for patient data.

Patient ID	FWHM			
	TP	FP	TN	FN
1	0	4	9161	2120
2	793	3	9351	10191
3	514	22	19183	5979
4	0	3	30108	2040
5	N/A	N/A	N/A	N/A
6	0	165	32082	7464
7	N/A	N/A	N/A	N/A
8	46	6	11200	514
9	576	28	33244	6799
10	70	2	27896	5037
11	883	51	54242	54363
12	534	16	20874	2556
13	215	19	32957	3558
14	N/A	N/A	N/A	N/A
15	0	3	22875	793
16	335	20	27253	701
17	133	15	30941	2080
18	N/A	N/A	N/A	N/A
19	1048	58	25242	4608
20	N/A	N/A	N/A	N/A

Patient ID	STRM1			
	TP	FP	TN	FN
1	1349	78	9161	2120
2	6045	26	9351	10191
3	4815	327	19183	5979
4	2782	46	30093	2040
5	1120	0	24708	4899
6	1947	0	32082	7464
7	3511	372	11219	468
8	1486	140	11200	514
9	3973	45	33244	6799
10	2365	26	27896	5037
11	3541	240	52311	52491
12	2748	79	20874	2556
13	1850	20	32957	3558
14	N/A	N/A	N/A	N/A
15	0	3	22875	793
16	1724	156	27253	701
17	2203	0	30941	2080
18	N/A	N/A	N/A	N/A
19	2844	213	25242	4608
20	N/A	N/A	N/A	N/A

Patient ID	STRM2			
	TP	FP	TN	FN
1	59	47	9161	2120
2	270	0	9351	10191
3	230	14	19183	5979
4	5	0	30108	2040
5	4	0	24708	4899
6	96	0	32082	7464
7	137	46	11219	468
8	0	16	11200	514
9	33	2	33244	6799
10	7	0	27896	5037
11	704	30	54368	54499
12	17	1	20874	2556
13	206	8	32957	3558
14	81	9	23486	3251
15	0	3	22875	793
16	38	3	27253	701
17	23	25	30941	2080
18	N/A	N/A	N/A	N/A
19	8	2	25242	4608
20	N/A	N/A	N/A	N/A

Patient ID	NI 1			
	TP	FP	TN	FN
1	2110	74	9161	2120
2	10177	14	9351	10191
3	5978	121	19183	5979
4	2040	35	30108	2040
5	4362	598	24708	4899
6	7476	0	32082	7476
7	450	23	11219	468
8	514	37	11200	514
9	6798	53	33244	6799
10	4718	380	27896	5037
11	7648	0	26987	7648
12	2556	40	20874	2556
13	3558	258	32957	3558
14	3073	259	23486	3251
15	783	28	22875	793
16	628	81	27253	701
17	1887	251	30941	2080
18	4182	63	28253	4214
19	4511	266	25242	4608
20	2577	245	25773	2620

Patient ID	NI 1.5			
	TP	FP	TN	FN
1	2110	74	9161	2120
2	6065	26	9351	10191
3	5978	212	19183	5979
4	2036	39	30108	2040
5	4329	631	24708	4899
6	7476	0	32082	7476
7	450	23	11219	468
8	514	37	11200	514
9	6797	54	33244	6799
10	4718	380	27896	5037
11	7648	0	26987	7648
12	2556	40	20874	2556
13	3557	259	32957	3558
14	3008	324	23486	3251
15	776	35	22875	793
16	628	81	27253	701
17	1674	464	30941	2080
18	4181	64	28253	4214
19	4511	266	25242	4608
20	2575	247	25773	2620

Patient ID	NI 2			
	TP	FP	TN	FN
1	1712	472	9161	2120
2	10010	181	9351	10191
3	5975	215	19183	5979
4	1889	186	30108	2040
5	4269	691	24708	4899
6	7469	7	32082	7476
7	450	23	11219	468
8	514	37	11200	514
9	6797	54	33244	6799
10	4618	480	27896	5037
11	7460	8	26987	7648
12	2556	40	20874	2556
13	3557	259	32957	3558
14	2851	481	23486	3251
15	733	78	22875	793
16	626	83	27253	701
17	520	1618	30941	2080
18	4181	64	28253	4214
19	4360	417	25242	4608
20	2084	738	25773	2620

Patient ID	NI 2.5			
	TP	FP	TN	FN
1	1465	719	9161	2120
2	7488	2703	9351	10191
3	5973	217	19183	5979
4	1736	339	30108	2040
5	2863	2097	24708	4899
6	7075	401	32082	7476
7	450	23	11219	468
8	494	57	11200	514
9	6552	299	33244	6799
10	4273	825	27896	5037
11	7632	16	26987	7648
12	2380	216	20874	2556
13	3553	263	32957	3558
14	2834	498	23486	3251
15	549	262	22875	793
16	626	83	27253	701
17	396	1742	30941	2080
18	4180	65	28253	4214
19	4029	748	25242	4608
20	2081	741	25773	2620

Appendix B

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electrograms to guide catheter ablation. *Heart Rhythm*, 8(5):791-796, 2011.

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