PATIENT-SPECIFIC MULTI-PARAMETRIC MODEL OF THE HEART FROM MDCT IMAGES TO GUIDE VENTRICULAR TACHYCARDIA ABLATION PROCEDURES

Doctoral Dissertation of:
Sofia Antunes

Advisor:
Ing. Giovanna Rizzo
Prof. Sergio Cerutti

Tutor:
Prof. Paolo Ravazzani

The Chair of the Doctoral Program:
Prof. Andrea Aliverti

2014 – XXVI Cycle
Abstract

In the pre-procedural planning and guidance of ventricular tachycardia (VT) electro-anatomic mapping (EAM) and catheter ablation (CA) procedures, knowing the exact location and extent of myocardial scar is important. The objective is to decide a priori if the procedure will be epicardial or endocardial, as well as to reduce intervention time. Today, delayed enhanced magnetic resonance imaging (DE-MRI) is considered the imaging gold standard for the assessment of scar tissue and it is being used, integrated into the 3D EAM system, to guide ablation procedures. However, multi-detector computed tomography (MDCT) could be an interesting alternative. The main reasons are related to the reduced artefacts caused by the implantable cardioverter-defibrillator (ICD), the higher spatial resolution when compared to DE-MRI with which we can have detailed information about the anatomy of the heart (e.g. trabeculae and coronary arteries) as well as the reliability in visualizing epicardial fat distribution.

In the identification of re-entry circuits during an epicardial intervention the knowledge of the location and extent of epicardial fat is useful because it presents voltage characteristics similar to scar tissue and is often confused with them causing useless ablation. However, fat is often neglected in the ablation procedures because it needs a very time consuming manual segmentation. Moreover, the navigation of the catheter tip over the left ventricular epicardial surface might damage the coronary vessels, if its location is not known.

The purpose of this work was to construct a 3D multi-parametric model of the heart by segmenting automatically ventricular cavities, left myocardium, myocardial scar, epicardial fat and coronaries from MDCT images. For the anatomical segmentation a 3D level set algorithm based on a multi-scale directional stopping function was developed. The stopping function consists in decreasing the image scale space in two steps, letting the level set to expand at each step, preventing in this way over-segmentation.

We compared the proposed edge detector coupled in the curve evolution stopping function to the classical Gradient Magnitude and validated the segmentation framework on 21 MDCT volumes from healthy and pathologic subjects at the mid-diastole phase using manual segmentation performed by a team of expert radiologists as gold standard. Segmentation errors were assessed for each structure resulting in a mesh
surface-to-surface mean error below 0.5 mm and a percentage of surface voxels with errors less than 1 mm above 80% for the cavities and myocardium. Epicardial fat had an overlap agreement of 87% and the coronaries were qualitatively judged as good. The obtained results suggest that our approach is accurate and effective for the segmentation of ventricular cavities, myocardium, epicardial fat and the coronaries from MDCT images.

Myocardial scar was accessed by automatic segmentation of angiographic and/or DE MDCT scans. On the early scan, compromised zones are hypo-enhanced when compared to the normal myocardium or present myocardial wall thinning. The approach to detect scar on the delayed scan, contrary to the first case, consists in searching for hyper-enhanced zones of the myocardium. For this goal, a registration and a Gaussian model strategy were adopted. This framework was applied to 14 patients with recurrent VT undergoing angiographic and delayed MDCT before EAM and radiofrequency ablation. Hypo-enhanced zones were correctly detected in all subjects, and myocardial surface points with wall thinning locations (< 5 mm) had in average a classification of good− based on a qualitative classification performed by two radiologists. The best threshold to detect DE scar in our experiment was the formulation: \( \mu_{\text{scar}} + \frac{\mu_{\text{vascular}} - \mu_{\text{scar}}}{2} \), which best matched with the experts identification of hyper-enhanced zones.

Additionally, the accuracy of our model was assessed by comparing MDCT defined scar with the findings of EAM constructed by arrhythmologists previously to RF ablation. Fat presenting a thickness greater than 3mm was also assumed to be scar whenever an epicardial EAM was constructed. We obtained promising results in the identification of low unipolar voltages using MDCT defined scar (65% of unipolar low voltages lie under MDCT defined scar), suggesting MDCT as a potential alternative to DE MRI. Preliminary results suggest that our method could be integrated into the clinical surgery software system as an effective tool to assist the surgeon during the ablation procedure.
# Contents

1 Introduction .............................................................. 1
   1.1 Motivation .......................................................... 1
   1.2 Aim and Contributions ............................................ 2
   1.3 Organization ......................................................... 3
   1.4 Research Funding .................................................. 4

2 Radiofrequency Catheter Ablation in Ventricular Tachycardia 5
   2.1 RF Catheter Ablation Treatment ................................... 5
      2.1.1 Electroanatomical Mapping .................................. 6
      2.1.2 Clinical EAM Software ......................................... 8
   2.2 Image Guided VT RF CA ............................................. 8

3 Cardiac MDCT ............................................................... 13
   3.1 Introduction .......................................................... 13
   3.2 Image Segmentation ................................................ 14
      3.2.1 Parametric Models ............................................. 15
      3.2.2 Atlas Based Approaches ..................................... 16
      3.2.3 Deformable Models ........................................... 16

4 Cardiac Anatomy Segmentation from MDCT Images .................. 17
   4.1 Introduction .......................................................... 17
   4.2 Methods .............................................................. 18
      4.2.1 Anisotropic Diffusion filter .................................. 19
      4.2.2 Level Set ......................................................... 20
   4.3 Experiments .......................................................... 25
      4.3.1 Data Set ........................................................ 26
      4.3.2 Segmentation Accuracy ....................................... 27
   4.4 Results ............................................................... 28
      4.4.1 Comparison with Classical Gradient Magnitude ............... 28
      4.4.2 Validation ...................................................... 29
   4.5 Discussion ........................................................... 35
List of Figures

2.1 Example of an EAM .................................................. 7
2.2 Imaging artefacts caused by ICD ................................... 10
3.1 Early and delayed MDCT scan ..................................... 15
4.1 Schema of the segmentation approach ........................... 19
4.2 Anisotropic filter result ............................................. 20
4.3 Tuning of the parameters .......................................... 22
4.4 Proposed edge detector ............................................ 23
4.5 Heart cavities localization steps .................................. 24
4.6 Initial rough segmentation ........................................ 25
4.7 LVepi initialization .................................................. 26
4.8 Segmentation steps of the epicardial fat ........................ 27
4.9 Segmentation steps of the coronaries ............................ 27
4.10 Segmentation result of all cardiac structures of interest .... 29
4.11 RV segmentation results ......................................... 30
4.12 LV segmentation results .......................................... 31
4.13 Myocardium segmentation results ............................... 32
4.14 Epicardial fat segmentation results ............................. 34
4.15 Coronaries segmentation results ................................. 34
5.1 Misalignment between MDCT scans ............................. 39
5.2 Hypo-enhanced scar detection .................................... 42
5.3 alpha shape variation ............................................. 43
5.4 Myocardial thickness measurement .............................. 44
5.5 Different thresholds for DE scar detection ...................... 45
5.6 Results of DE scar extraction .................................... 48
6.1 Myocardial map ..................................................... 53
6.2 Epicardial fat measurement ....................................... 53
6.3 EAM superimposed to MDCT image .............................. 55
### List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4</td>
<td>Comparison of EAM with MDCT scar</td>
<td>55</td>
</tr>
<tr>
<td>6.5</td>
<td>Comparison between bipolar EAM and MDCT defined scar</td>
<td>56</td>
</tr>
<tr>
<td>6.6</td>
<td>Comparison between unipolar EAM and MDCT defined scar</td>
<td>57</td>
</tr>
<tr>
<td>6.7</td>
<td>EAM scar percentage under MDCT defined scar</td>
<td>57</td>
</tr>
<tr>
<td>6.8</td>
<td>Bipolar vs Unipolar findings</td>
<td>58</td>
</tr>
</tbody>
</table>
List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Optimal Parameters Setting of 3D GAC</td>
<td>22</td>
</tr>
<tr>
<td>4.2</td>
<td>Comparison with Classical Edge Detector</td>
<td>28</td>
</tr>
<tr>
<td>4.3</td>
<td>Results of the Proposed Segmentation Method</td>
<td>33</td>
</tr>
<tr>
<td>4.4</td>
<td>DSC Results of the Proposed Segmentation Method</td>
<td>33</td>
</tr>
<tr>
<td>4.5</td>
<td>State-of-art Results</td>
<td>36</td>
</tr>
<tr>
<td>5.1</td>
<td>Quality grade classification</td>
<td>46</td>
</tr>
<tr>
<td>5.2</td>
<td>SNR of MDCT scans</td>
<td>47</td>
</tr>
<tr>
<td>5.3</td>
<td>Performance of different thresholds in DE scar</td>
<td>47</td>
</tr>
<tr>
<td>6.1</td>
<td>Distance from EAM to MDCT defined scar</td>
<td>56</td>
</tr>
</tbody>
</table>
CHAPTER 1

Introduction

1.1 Motivation

Ventricular tachycardia (VT) is a life-threatening arrhythmia that is common to all forms of heart disease and represents an important cause of sudden death. Ventricular scars from infarction or replacement fibrosis in structural cardiomyopathies provide a substrate for re-entry that is a usual cause of VT. Patients with scar-related VT are subject to frequent arrhythmia recurrences and antiarrhythmic drug therapy is inadequate due to poor efficacy and side effects [64]. Patients receiving multiple implantable cardioverter-defibrillator (ICD) shocks because of VT have impaired quality of life. In this setting, radio-frequency (RF) catheter ablation (CA) is frequently the therapy of choice [76].

In the last few years electro-anatomical mapping (EAM) has become the most used method to map the substrate of VT and to guide the RF catheter ablation. Unfortunately, this important therapeutic approach has variable and sub-optimal results (success rate ranging from 45% to 75% for endocardial VT ablation [11]) and remains a very time consuming and challenging procedure. These suboptimal results are probably dependent on several technical limitations [11]. First of all, the electro-anatomic reconstruction of the cardiac chamber surface is based on the recording of the spatial position of several points obtained by the contact of the catheter tip with the myocardial surface. A good spatial resolution with low automatic interpolation in the reconstruction of cardiac chambers anatomy, crucial for correct definition of scar area, requires the registration of a great number of points and therefore is a very time consuming procedure; moreover, the opportunity to reach all the parts of the ventricle endocardium or/and epicardium in order to obtain high fidelity representation of myocardial surface is strictly related to the operator experience.
Chapter 1. Introduction

The second issue is related to the patient specific anatomy that can complicate the proper mapping. In an endocardial intervention, the imperfect representation of the irregular and trabeculated internal surface of the left ventricle, with which the catheter tip may cause poor contact and may induce erroneous recording of low voltage, leads to a definition of a wrong scar area followed by useless RF applications. In the same way, during an epicardial intervention, the presence of a thick epicardial fat layer may cause also recording of false low voltage information. Moreover, the localization of the epicardial vessels relative to the myocardial anatomy and scar is extremely important in order to avoid damage due to RF energy. The third problem is posed by the complete absence of information about the 3D spatial resolution of the scar lesions and such about the distribution and transmurality of scar that may be endocardial, epicardial, intramural or transmural [15].

As we will discuss later, recent literature tries to overcome these problems by integrating image-based cardiac anatomy and scar information to plan and guide EAM and subsequent VT ablation, upon which the operator may navigate, having precise anatomical and functional cardiac information. This is achieved using gadolinium-delayed-enhancement cardiac magnetic resonance imaging (DE-CMR), which is the gold standard to assess scar. However, these approaches are manual or semi-automatic and consequently very time consuming and operator dependent, and additional CMR sequences would be needed to visualize epicardial fat and vessels. Moreover, 75% of the patients that suffer from VT have an ICD and therefore cannot undergo MRI. Recent improvements in Multi Detector Computed Tomography (MDCT) [19] let us think that, for this specific application, MDCT cardiac imaging could be an interesting alternative to the gold standard, not only in the identification of the patient specific anatomy [72], but also in the determination of myocardial scar.

1.2 Aim and Contributions

The object of this thesis is the development and validation of clinically feasible strategies for the integration of patient specific anatomical and functional cardiac information from MDCT in the clinical 3D EAM system. In particular, we worked on the development of automatic approaches, aiming at accurate and robust automatic strategies for planning and guiding VT RF CA procedures.

This work makes the following contributions:

- **Cardiac Anatomy Segmentation**: an automatic segmentation framework able to extract ventricles, myocardium, epicardial fat and coronary tree from early contrast MDCT scan. For this purpose, a new multiscale directional filter was proposed to stop curve propagation at the real cardiac boundaries. We evaluated the method on healthy and pathologic subjects.

- **Myocardial Scar Segmentation**: development of a pipeline for the extraction of scar from early and delayed MDCT scans. The performance of the method was evaluated on patients suffering from VT.

- **Construction of a Multiparametric Myocardial Map**: designation of the feasibility of the integration into the clinical 3D EAM system of a patient specific
1.3 Organization

This thesis is divided into two main parts. The first part comprises chapters 2 and chapter 3 and faces theoretical issues on the clinical problem, deals with the general principles of cardiac MDCT and, finally, gives a review on cardiac MDCT and cardiac image segmentation methods. The second part consists of chapters 4-7 and presents a detailed analysis of the segmentation methods applied on pre-procedural MDCT data. The work is organized as follows:

- Chapter 2 presents the base concept of VT RF CA treatment, looking at the current state of art. We will describe in particular EAM and the clinical software used today to construct these 3D maps. The main clinical issues in the current settings of CA strategies will be regarded, underlining the ones addressed in the present work (related to the pre-procedural imaging guidance).

- Chapter 3 introduces the advances in MDCT imaging, as well as its clinical applicability and current limitations in the context of VT RF CA, tracing the path for the technical motivation beyond this thesis. A brief review of the state-of-art 3D cardiac segmentation methods will be also given, discussing advantages and drawbacks of existent automatic methods.

- Chapter 4 investigates the use of a multiscale directional filter to improve boundary detection. We propose a segmentation method for this purpose and validated the method against manual segmentation. The experiments show that the segmentations computed using our stopping function outperform the classical gradient magnitude edge detector. Moreover, we compare the performance of our algorithm against state-of-art approaches. The research concerning this chapter has been published in one conference proceedings [3] and submitted to one journal [5].

- Chapter 5 addresses the problem of accurate and robust segmentation of the non-viable myocardium (areas of scar) in early and delayed enhancement MDCT. A pipeline for the myocardial scar extraction is proposed, using a registration method and a Gaussian model that defines the segmentation threshold. We provide first experimental results that confirm the applicability of the proposed pipeline to automatize the scar identification process, its relative strengths and weaknesses. The research concerning this chapter has been published in one conference proceedings [7].

- Chapter 6 extends the work presented in Chapter 5 and compares the non-viable myocardial segmentations from MDCT with the findings of EAM created by the arrhythmologist before RF CA. Each myocardial scar scenario is compared to unipolar and bipolar voltages. The research concerning this chapter has been published in one conference proceeding [4].
Chapter 1. Introduction

- Chapter 7 sums up results obtained in this work. Future improvements will be also examined.

1.4 Research Funding

The research was funded by the Portuguese Foundation for Science and Technology (FCT) through the grant SFRH/BD/69488/2010 and the Italian Ministry of Health GR-2009-1594705.

The work was developed at the Institute of Bioimaging and Molecular Physiology - National Research Council (IBFM-CNR) in Milan (Italy) in collaboration with the Radiology and Arrhythmology Departments of San Raffaele Hospital (OSR), and involved a multidisciplinary group of engineers and physicians.
CHAPTER 2

Radiofrequency Catheter Ablation in Ventricular Tachycardia

CA of VT is a very technically challenging procedure: traditionally, the arrhythmia is mapped by assessing the timing of electrical activation at various locations in the heart (endocardial, epicardial, or both) under fluoroscopic guidance. The physicians interpret the observed timing data, and the potential sites of ablation are in this way targeted. Recently, CA was transformed to the therapy of choice thanks to the introduction of computer-based 3D mapping systems. Furthermore, the introduction of anatomical information to the procedures is being widely studied in order to increase surgical success and to reduce the procedure time. In this chapter, a brief description of VT CA is presented, as well as a description of the electroanatomic mapping (EAM), which is the gold standard to detect ablation sites. Moreover, a brief description of the pre-procedural imaging used in this context to detect scar is presented.

2.1 RF Catheter Ablation Treatment

Ventricular scars from infarction or replacement fibrosis in structural cardiomyopathies provide a substrate, characterized by diminished cell coupling and interstitial fibrosis promoting slow or blocked conduction, for reentry that is a common cause of VT. Patients with scar-related VT are subject to frequent arrhythmia recurrences and antiarrhythmic drug therapy is inadequate due to poor efficacy and side effects. ICD is frequently chosen as life-preserver device, however patients receiving multiple ICD shocks because of VT have impaired quality of life. In this setting, RF CA is frequently the therapy of choice in a wide population of patients with advanced cardiac disease, with and without ICD.
Scar-related reentry circuits commonly depend on delayed conduction in scarred myocardial areas. These areas usually contain regions of dense, inexcitable fibrosis that act as conduction barriers and regions of surviving myocardium that create the reentry. Therefore, these areas need to be ablated. Ablation should primarily target the exit site of the critical isthmus that gives rise to the QRS complex, (border zone of low voltage) leaving only the electrical pathways that generate normal cardiac function. This procedure can be performed either endocardially or epicardially, in fact, the reentry circuit needs to be understood as a complex 3D structure, that can involve endocardium, mid-myocardium, or epicardium [76]. The latter procedure could be indicated in patients with ischemic cardiomyopathy and in patients with nonischemic cardiomyopathy with extension of the scar areas larger in the epicardial surface.

It consists in the delivery of RF energy to the endocardium or epicardium through electrode catheters, at a frequency of 300 to 1000 kHz, and selectively cauterize (turning the tissue to a necrotic state). RF current is most commonly delivered in the unipolar mode (preferred to bipolar mode), causing local myocardial destruction of the specific regions critical for abnormal impulse generation or propagation. The RF current is silencing the foci responsible for the abnormal rhythm or interruption of the reentry circuits.

Besides the known helpfulness of electrocardiographic (ECG) recordings, and in order to facilitate catheter manipulation, the procedure is performed with X-ray fluoroscopic imaging guidance to have cardiac radiographic anatomy, because it is easy to use, it provides real-time information, catheters are easily visualized, electrical interference with recording systems is minimal and virtually no time is required to set up the system. However, the images obtained are only two-dimensional (2D) representations of three-dimensional (3D) structures and only the cardiac silhouette can be seen.

There are a few limitations in the current settings of this procedure, being exploited. The first is related to the catheter contact force on the tissue to be ablated that is only inferred when the catheter movement becomes restricted and not earlier. This limitation has led to the development of non-fluoroscopic 3D mapping systems. Today, substrate-based ablations rely on detailed electroanatomic mapping (EAM) that will be discussed in the following section. The second limitation is related to the criteria used for choosing an endocardial or an epicardial approach; currently, the criteria are the type of cardiomyopathy and the ECG characteristics, which can suggest an epicardial origin. However this information has a poor specificity and frequently the epicardial ablation is chosen only after a failed endocardial approach [76]. This limit is being addressed studying pre-procedural imaging, in order to better plan the intervention (see Section 2.2).

2.1.1 Electroanatomical Mapping

In electrophysiology, computerized 3D EAM refers to the identification of temporal and spatial distributions of myocardial electrical activation (endocardial, epicardial, or both), important to assist in the definition of the tachycardia mechanism [70] [76]. In the last few years 3D EAM has become the most used method to map the substrate of VT and to guide the RF CA. The mapping catheter is moved sequentially in the endocardial or epicardial surface under fluoroscopic guidance to sample electrical activation and spatial location of the catheter tip from various points of interest. After
2.1. RF Catheter Ablation Treatment

A 3D reconstruction of the ventricular anatomy (thanks to the spatial position coordinates of the catheter), the local activation time of the moving catheter is compared to an anatomically stable and electrically well-defined reference electrogram, which in VT is often a surface lead, and the voltage maps are such generated. The 3D geometry of the mapped surface is reconstructed in real time and analyzed to assess the mechanism of arrhythmia and to identify sites of conduction to serve as a target for CA. EAM of the myocardium is a fundamental tool used today to identify discrete sites that need to be ablated, in order to eliminate tachycardia [70]. For this purpose, bipolar and unipolar electric activation are used. The former is obtained by the difference between two electrodes near the cardiac area of interest, and the latter is the voltage difference recorded between an intracardiac electrode and a reference electrode free of cardiac signal [81].

There are some advantages and drawbacks in each of the two measurements: bipolar recordings provide an improved signal-to-noise ratio when compared to unipolar; nevertheless, the precision of local activation is less defined. However, unipolar recordings can provide a more accurate measure of the timing of local activation. Due to these considerations, differences in both unipolar and bipolar recordings are used to assess scar areas during EAM. An example of a EAM with bipolar and unipolar information is shown in Figure 2.1.

Figure 2.1: Example of an EAM, showing Bipolar and Unipolar voltages of the same endocardium.

Bipolar voltages, with its narrower field of view, are accurate in identifying local depolarization in abnormal areas (infarction or scar), however in the presence of viable endocardial tissue (e.g. intramural or epicardial), the sensitivity of scar detection may be compromised. Unipolar recordings on the contrary, due to its far field signal, incorporate a larger region of myocardial electrical activity, however, they cause confusion between distant and local activity. For this reason, despite the limitations of bipolar recordings, these voltages are always being considered at first to detect scar areas. Unipolar recordings are used to supplement the information obtained from bipolar recordings or, in the case of a normal endocardial bipolar voltage map, unipolar voltage may identify abnormal epicardial substrate. Conventionally, bipolar amplitude between 0.5 mV and 1.5 mV represents the border zone of the scar and < 0.5mV is a region of
Chapter 2. Radiofrequency Catheter Ablation in Ventricular Tachycardia

dense scar. Similarly, unipolar amplitude between 4 mV and 8 mV is considered border zone and < 4 mV is a region of dense scar. Sites of the reentrant circuit are located in the border zone of low voltage area. One common issue during the construction of an EAM is the insufficient or excessive contact force with tissue, which can lead to a wrong point anatomy and electrical measurement. Besides, if scar is located intramural it can be difficult to detect such areas. In the case of an epicardial mapping, additional difficulties arise, related to the increase of false low voltages, due to areas of a thick fat layer. Although VT CA based on EAM represents a very important therapeutic approach, it has variable and sub-optimal results [70]. It is limited by the need for a minimum degree of ventricular mapping accuracy and relies on the advanced operator skill with catheter manipulation and capability of recognition of the mapping sites of interest from the morphology of the tachycardia. The accuracy of EAM of arrhythmia diagnosis depends on its spatial resolution and temporal stability. Higher point numbers reduce anatomical interpolation and allow for a precise anatomical resolution, with the drawback of making the electronatomical reconstruction of scar time consuming and consequently expose patient and operators to increased levels of radiation from the extended fluoroscopy time. Moreover, the acquisition of false low voltages due to the patient specific anatomy is a very recurrent error. The poor contact of the catheter tip with the myocardial surface in zones of trabeculae or in an area of thick epicardial fat (during an epicardial procedure) may cause erroneous recording of bipolar voltage lower than 0.5 mV leading to the definition of a wrong scar area followed by useless RF applications. Another important limitation of EAM in scar related VT is related to the complete absence of information about the volumetric myocardial distribution of the scar lesions and epicardial vessels position relative to the scar. The former information would allow increasing accuracy and efficiency of EAM and the latter is important to avoid any damage due to RF energy. As final remark, it is important to note that due to surface indentation and potentially missed areas during mapping, the acquired EAM does not represent the perfect anatomy of the cardiac chamber.

2.1.2 Clinical EAM Software

In the Center for arrhythmia research Ospedale San Raffaele, the CARTO mapping system (Biosense Webster, Inc.) is currently used for this procedure. The system uses magnetic technology to determine the location and orientation of the catheter, and continuously calculates the position of the catheter in relation to the anatomical reference, solving the problem of possible motion artifacts [8]. It is also possible to integrate pre-acquired computed tomography (CT) or magnetic resonance imaging (MRI) scan in the clinical software, useful to guide real-time EAM and CA by using the detailed cardiac anatomy.

2.2 Image Guided VT RF CA

Considering all previously reported limitations of VT RF ablation, guided only by EAM, it is clear the need to provide to the arrhythmologists an imaging-based 3D high resolution myocardial map together with information about myocardial tissues viability, that fused with EAM can have an important impact in the ablation procedure. For
2.2. Image Guided VT RF CA

This role, pre-procedural cardiac magnetic resonance imaging (MRI) and multi-detector computed tomography (MDCT) are available:

- **Cardiac MRI** is well recognized as the gold standard for the non-invasive detailed myocardial characterization. In particular, the technique of gadolinium delayed enhancement (DE) MRI allows identifying and locating myocardial scars with high sensitivity, allowing the differentiation of transmural and non-transmural infarction as well as dense and border zone, thanks to its high spatial and temporal resolution and the capacity of nulling the healthy myocardium (improving the visualization of infarcted zones). However, this technique is contraindicated in patients with pacemaker or ICD. The main reasons are related to safety issues, such as heating of the tissue near the lead electrodes, mechanical forces, induction of arrhythmias, and alteration of device function, in patients with ICD [33]. Despite safety concerns, MRI is used in such patients in research protocols, however prevalent imaging artifacts obscures image integrity (see Figure 2.2). Two types of artifact can occur: intravoxel dephasing (dark signal void) or hyperintensity artefact, which causes improper inversion of the signal. Recently, Stevens *et al.* [69] proposed a wideband LGE MRI technique for the hyperintensity image artifacts reduction, but still more research needs to be done in this direction.

- **Cardiac CT** had in the last years a technological and knowledge progress which enabled the reduction of the gap with MRI in terms of myocardial characterization. In fact, the technique of delayed-enhancement was transferred from CMR and fitted to MDCT in order to obtain a similar detection and quantification of scar. CMR has an unquestionable advantage in terms of contrast resolution, but on the other hand the MDCT provides images with higher spatial resolution (and consequently less partial volume effect) and higher anatomic coverage. Moreover, it can depict the anatomic course of epicardial coronary vessels very easily and with high spatial resolution. Another crucial advantage of MDCT in this setting is the absence of interaction with ICD. In fact, the large ICD diffusion occurred in the last few years to prevent sudden cardiac death in patients resuscitated from a life-threatening arrhythmia. Treating VT with antitachycardia pacing caused a vast majority of patients submitted to catheter ablation to have an ICD making then CMR analysis unfeasible.

In this context, image registration and segmentation algorithms offer a huge potential to be exploited, due to the great interest and potential in using pre-procedural data to plan and guide RF ablation. Our focus will be on the image segmentation, but before, a brief review of the registration process used in the integration process is given.

The integration of MRI and/or CT volumes is being recently studied as an useful complement for precise and reproducible RF CA guidance, facilitating the mapping of complex arrhythmias and decreasing fluoroscopic exposure while potentially reducing the procedure duration and risk. Integrating EAM data with the spatial information contained in the CT or MRI requires the alignment of the 3D pre-procedural CT or MRI surface reconstruction with the real-time EAMs created by the mapping system. The assumption made is that the anatomy of the organ being registered has not changed. The preferred algorithms used are landmark registration and, in order to complement
Chapter 2. Radiofrequency Catheter Ablation in Ventricular Tachycardia

Figure 2.2: Imaging artefacts caused by the ICD in MRI and MDCT images.

and improve this data, surface registration. The former aligns the 3D CT/MRI image reconstruction with the corresponding EAM through corresponding fiducial points. Under the guidance of fluoroscopy, at least three noncollinear endocardial landmark points are sampled by real-time catheter tip locations on the mapping system being used for registration. These points are then marked on the estimated locations on the 3D CT/MRI image reconstructions. Using more landmark points increases the accuracy of the registration process. Surface registration searches for the endocardial points that are closest to the CT/MRI surface, until it reaches the best fit of the two sets of images by minimizing the average distance between the landmarks, and the distance from multiple endocardial locations, to the surface of 3-D CT/MRI image reconstructions.

In the context of growing interest in the integration of imaging based anatomy in the ablation system, various state-of-art works attempt to describe the feasibility and utility of such process, depreciating the great effort needed to accurately segment such large 3D volumes. Desjardins et al. [21], Andreu et al. [2], Tian et al. [22] focused on scar characterization by means of DE-CMR, differentiating the scar components in core scar and border zone, and their integration into the CARTO system; Cochet et al. [14] showed the feasibility and usefulness of merging DE-MRI and MDCT data to guide mapping and ablation, providing MDCT anatomical details such as myocardial wall thickness that together with DE-MRI provide complementary information on VT substrate; Abbara et al. [14], Piers et al. [62] and van Huls van Taxis [72] manually segmented endocardial, epicardial and pericardial contours from MDCT to calculate epicardial fat thickness and imported it into the CARTO system to evaluate epicardial procedures. In non ischemic cardiomyopathy, the authors in [62] found that cutoff values of 1.81 mV and 7.95 mV for bipolar and unipolar voltages respectively best differentiate between presence and absence of scar in areas without fat. Moreover, unipolar voltages could not differentiate between presence or absence of scar in areas covered by a fat layer greater than 2.8mm. The previously described studies use mainly manual segmentations to extract the cardiac structures of interest. However, in order to decrease analysis and processing time threshold methods are often used in this context today to differentiate between the blood pool (high in contrast) and the endocardium, given although poor results.
2.2. Image Guided VT RF CA

In DE-MRI, manually segmented scar is commonly thresholded based on an adjustable percentage of the maximum voxel signal intensity of the scar region, in order to differentiate between dense and border zone \cite{24}.

In this thesis we will address the cardiac image segmentation paradigm.
CHAPTER 3

Cardiac MDCT

MDCT is being widely studied as an interesting alternative to MRI, the clinical gold standard for assessment of myocardial scar, in the pre-procedural settings of VT [45]. As referred in the previous Chapter, the main reason is due to the fact that the majority of patients referred for VT ablation (up to 75%) have an ICD. However, recently promising works in myocardial viability quantification using MDCT has opened new paths in the study of this technique, as we will address in this Chapter.

3.1 Introduction

The availability of MDCT with a high number of simultaneously acquired slices has enabled whole heart coverage within a single heart beat with isotropic spatial resolution of submillimeter resolution, and without partial volume effects that are commonly in MRI. Problems related to patient motion are thereby minimized, providing detailed information about cavities, surrounding papillary muscles and trabeculae, myocardium and vessels. Besides, the usefulness of cardiac CT for assessing coronary artery disease, it is increasingly becoming a well-established imaging modality for myocardial function, perfusion, and viability studies [1]. The functional and volumetric assessment of the ventricles (with retrospective gating) remains essential for the diagnosis and follow-up of cardiac diseases, such as quantitative global function, local motion and deformation, being ejection fraction the most important descriptors. Moreover, the introduction of prospective ECG-gated MDCT has enabled the reduction of the radiation dose by scanning only when cardiac motion is at a minimum (mid-diastole phase). This specific phase is used to evaluate cardiac anatomy. The detailed knowledge of the cardiac structures is essential not only to perform increasingly accurate ventricular cardiac measurements but also to plan and guide electrophysiological interventions. As
Chapter 3. Cardiac MDCT

discussed in the previous chapter, pre-procedural imaging can provide valuable patient-specific anatomical information and the integration with EAM improve the procedure efficacy and efficiency, minimizing intra-operative radiation and reducing intervention failures [14, 62, 72].

In recent years, research on DE has become a focus of MDCT. The reduction in radiation dose and the higher contrast for DE has made possible the assessment of myocardial viability and the evaluation of transmural extent of myocardial necrosis. This is possible making the same assumptions of DE-MRI and using similar contrast kinetics: LE-MDCT acquisition after iodinated contrast administration shows myocardial infarction as a late (5 to 10 min after injection) increased attenuation (hyperattenuation) when compared to normal myocardium. Recent studies proved the reliability and good correlation of this technique in comparison with MRI and SPECT [29]. However, the effects of image noise are more pronounced in DE MDCT imaging when compared to MRI,
as well as the contrast-to-noise ratio, that is lower on MDCT, due to the restricted dynamic attenuation range.

In this thesis, we will address two MDCT scans: angiographic (early) scan and the delayed enhanced scan (DE). Each of these scans can identify different aspects of myocardial viability [1]. Imaging the myocardium during the arterial phase is a rising tool. It allows not only the visualization of the coronary artery tree, the cardiac function and anatomy, the epicardial fat, but recently also the study of early myocardial perfusion defects. The areas of decreased myocardial blood flow (deficit of contrast) are seen as hypo-attenuated areas of the myocardium (infarction). Moreover, the measurement of the end-diastolic wall thickness is a parameter of myocardial viability, since scar formation occurs with myocardial thinning. As CT can achieve a submillimeter 3D reconstruction, wall thickness measurements using this technology may be more accurate than CMR [77]. Delayed myocardial contrast enhancement is assessed from a second CT scan, 5-15 minutes after the first-pass arterial phase. Late phase visualizes residual perfusion defects in infarct core and delayed myocardial contrast enhancement (Figure 3.1).

Zhao et al [77] showed that DE MDCT has comparable diagnostic accuracy to that of late gadolinium enhancement CMR, in qualitatively detecting MDE and quantitatively delineating dense scar. Figure 3.1 shows the example of an early and delayed MDCT scan.

Though the promising advances in MDCT, there is not yet an agreement of the protocol for the DE scan due to contrast administration and scan delay variables. Today, it is not performed in the clinical practice despite its important contribution in patients with ICD.

3.2 Image Segmentation

Segmentation is a fundamental problem in cardiac imaging. Within the current clinical setting, an accurate segmentation of the cardiac structures of interest is an essential requirement in order to be able to quantify in the most complete way cardiac anatomy and function. However, visual and manual analysis has been hampered by the huge amount of data involved (up to 350 slices for each cardiac phase) [1] and an accurate
3.2. Image Segmentation

Figure 3.1: Early and delayed MDCT scan.

Automatic segmentation is highly demanded without tedious and time-consuming analysis. Specifically, the segmentation of the ventricles and LV myocardium is essential to perform routine measurements. The main challenge in extracting the cardiac cavities include large shape variability within cardiac cycles and between patients and weak edges. State-of-art methods involve methods that make no assumption on the geometric properties of the region of interest [34] and model based ones that make some a priori assumptions on the allowed solution space [25, 36, 60, 78, 80]. Despite the latter have been established as one of the most successful methods for clinical assessment of the global parameters (such as cavity volumes and myocardial mass), they still lack in giving an accurate segmentation of the patient specific anatomical boundary of the cardiac structures. In the next paragraphs, current methodologies used in cardiac MDCT segmentation will be briefly described, although hybrid approaches are actually preferred.

3.2.1 Parametric Models

Parametric shape models can be trained from a set of example data and the deformation allowed are confined to the shape space where the heart models are embedded. The best known methods are the active shape models [17] that build a statistical shape model from a set of trained points using the principal component analysis. The idea was extended in active appearance models [16], incorporating the intensity information of the object;

These methods have the drawback that they can only account for variations observed in the training set, additionally, segmentation based on templates requires training data and an intensive learning process. It is difficult to capture (new) heavy ventricle wall variations mostly present in pathological subjects, because the resulting surface cannot account for great variations on his adaptation towards image boundaries, being limited by the model shape. For this reason, Zheng et al [78] used a statistical shape model to enforce shape constrains in the model fitting approach. Moreover, they used marginal space learning to localize the heart, and nonrigid deformation estimation with control
Chapter 3. Cardiac MDCT

point constrains. Steerable features were used to estimate an initial nonrigid shape and finally active shape models to guide the shape deformation.

3.2.2 Atlas Based Approaches

This category treats segmentation as a registration problem. It uses shape information implicitly by directly registering pre segmented atlas image to the target image. This can be performed using linear and nonlinear transformations. Kirisli et al [36] used a decision fusion algorithm to combine a multi-atlas strategy into a single solution. Even with nonlinear registration methods, finding accurate segmentations of complex structures is difficult due to anatomical variability. One method that helps model anatomical variability is to derive a probabilistic atlas of possible variations. For example Lapp et al [41] developed a statistical atlas-based method combining an active appearance model with a statistical deformation model.

3.2.3 Deformable Models

For cardiac image segmentation, surface deformable models have been extensively used, represented either as deformable templates [25, 59] or level sets [52, 52, 61, 79]. Using these approaches cardiac surfaces are deformed by the minimization of an internal energy that controls the surface regularity that, in the case of using a prior knowledge concerning the appearance of the object, keeps the surface close to the expected shape [50], and of an external energy that deforms the surface based on image characteristics such as edge or region properties. In the case of deformable templates, the surface is usually represented as a mesh. Initially, the mesh is registered to the image volume; then, the external energy locally deforms (attracts) the mesh vertices to the boundaries of interest based on a stopping function that best matches the boundary criterion [25, 59]. In fact, such models currently seem to be the most successful fully automatic cardiac segmentation algorithms in MDCT, robust to significant variations in morphology, contrast and noise [13]. Deformable surfaces based on level set evolution may have some advantages over deformable templates, in terms, for example, of easy topology change and the fact that there is no need to remesh [43]. Thanks to these properties, level sets are a popular alternative choice for cardiac image segmentation. However, the major difficulty in surface deformation with both deformable templates and level sets is mainly related to the definition of the stopping criterion that is the external energy that drives the surface propagation to stop at the real cardiac boundaries. For the segmentation of cardiac images, the external energy was proposed based on a variety of edge-detectors such as gradient operator [47], gradient vector flow [56], modified canny edge detector [44], and gradient magnitude [12] or gradient orientation [35]. Furthermore, more complex models, such as intensity gradient calculators and texture gradients [68], as well as phase symmetry filters [6] were studied. All these approaches, however, present an important limitation related to the sensitivity to inhomogeneities, noise and weak boundaries, and precise stopping at the correct edges continues to represent a significant challenge in cardiac image segmentation [34].

16
CHAPTER 4

Cardiac Anatomy Segmentation from MDCT Images

Image-guided VT EAM and RF CA allows the navigation of the catheter tip over the cardiac structures of interest within a high resolution anatomical map. For this intent, the accurate segmentation of the patient specific cardiac anatomy of interest is a fundamental effort. The cardiac structures of interest include both ventricular cavities (including their trabeculae) and left ventricular (LV) myocardium. Of great importance in any epicardial intervention is epicardial fat tissue, as explained previously, it may be confused with myocardial scar causing useless ablation. Moreover, the anatomical course of the main coronary vessels may help in optimizing epicardial interventions, reducing potential damage of such structures. In this Chapter we propose an automatic method for the segmentation of the left and right ventricle cavities, left ventricular myocardium, epicardial fat and coronary vessels in angiographic MDCT.

4.1 Introduction

For the left ventricle (LV), including LV endocardium (LVendo) and epicardium (LVepi), the problem of accurate automatic segmentation was addressed since long time ago, due to the importance of this structure in detecting cardiac anomalies. Acceptable results have been already published using different segmentation approaches; a complete review is shown in [34] and [61].

Segmentation of the right ventricle (RV), contrary to the LV, is still an unsolved problem due to its complex, irregular shape and the high variation among subjects [30]. Such difficulties still remain even with contrast enhanced CT data, mainly due to the irregular distribution of the contrast on the blood pool of the right cavity. For this reason, it was only addressed using heart templates, which are fitted to the new
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

volume, without taking in consideration the trabeculae [74]. However, using model based segmentation it could be difficult to capture (new) heavy right ventricle variations mostly present in pathological subjects, because the resulting surface cannot account for great variations on its adaptation towards image boundaries, being limited by the model shape.

A less studied topic is epicardial fat segmentation. Despite the great potential of epicardial fat quantification, no reliable automatic methods are available for such purpose. The main reason is related to its high variation in shape and dimension among subjects. In [72], epicardial fat was manually segmented and integrated into the EAM software system to study its impact on epicardial ablation interventions. However, the manual segmentation is almost impracticable due to the time required to accomplish it. Semi-automatic methods were proposed, based on the attenuation characteristics of fat tissue in MDCT. Park et al [57] manually delineated the pericardium and used a threshold in the range of -200 to -30 hounsfield units (HU) to isolate fat tissue. In Coppini et al [18] a level set was proposed which included a term based on a Gaussian mixture model, after analyzing the intensity distribution of fat.

Last, addressing the coronary tree, a prerequisite for its successful segmentation is high and consistent vascular enhancement within the vessel lumen. Without homogeneous enhancement, threshold-based visualization techniques may systematically fail. A wide literature is available in the tracking of the coronaries [51]. Between the best succeeding approaches are the shortest path [27], 2D cross sectional analysis such as medialness measurements, as well as intensity distribution models in the vessel [42].

Here we propose a new automatic 3D segmentation method, based on a multiscale directional edge detector and a level set algorithm, to segment cardiac ventricles and the LV myocardium. A surface deformation scheme was used which, after initializing the surface with a region growing approach, evolves as a classical level set with a directional filter in a rough scale; furthermore, and since we are approaching the boundary of interest, a refinement was applied, adding an advection term to the level set and simultaneously reducing the scale-space of the edge detection filter. Using this method in the reduced scale only, and using the fat attenuation values as a priori information, we were able to segment epicardial fat. The coronary vessels were segmented using a threshold approach after isolating the pericardium. Our segmentation framework was evaluated on MDCT volumes of both normal and pathologic subjects to assess its accuracy.

4.2 Methods

A complete scheme of our level set segmentation method for RVendo, LVendo, LVepi and epicardial fat is shown in Figure 4.1. Firstly, the heart volume was re-sliced into the short axis view and preprocessed using an anisotropic diffusion filter to improve signal to noise ratio (SNR) (Section 4.2.1). Starting from a rough initial segmentation of the structure of interest, a 3D level set including our multiscale directional edge detector was applied. The proposed segmentation method was implemented using in-house developed software written in Python with the C++ ITK library (www.itk.org).
4.2. Methods

4.2.1 Anisotropic Diffusion filter

In MDCT volumes, signal-to-noise ratio (SNR) can present great variation across studies due to differences among subjects in terms of weight and heart rate. As our segmentation approach uses only low level information, we applied a nonlinear anisotropic diffusion filter in order to enhance the local properties in those volumes. Noise in regions of homogeneous physical properties was thereby removed, thus increasing SNR and at the same time minimizing information loss of boundaries and fine detail. The nonlinear anisotropic diffusion filter, first proposed by Perona et al. [58], has subsequently been optimized to be less sensitive to contrast and to increase SNR in few iterations [75] resulting in the diffusion function:

\[
\frac{\partial I}{\partial t} = |\nabla I| \nabla \cdot \left( c(|\nabla I|) \frac{\nabla I}{|\nabla I|} \right)
\] (4.1)

where \( c \) is the conductance parameter responsible for strengthening the diffusion. Here \( c \) was set to a value of 3 according to the best performance range found in previous research. SNR measurements of the MDCT volumes were used as an index for choosing the number of iterations of the anisotropic diffusion filter in 4.1. SNR was measured as the ratio between mean value and standard deviation of the voxel intensity in a region of interest placed in the aorta in the middle slice of the heart volume on three randomly selected subjects: 1 healthy subject and 2 subjects with ischemic heart disease. Iterations were increased until image quality was considered good by a trained observer. In our experiment, the number of iterations was chosen to be 20. An example of the image pre and post filtering is shown in Figure 4.2.
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

Figure 4.2: Original image and image after application of the anisotropic filter.

4.2.2 Level Set

A 3D level set algorithm was used, implementing the geodesic active contour (GAC) formulation. GAC consists in integrating the curve evolution approaches with classical energy minimization problems, finding a geodesic curve in a Riemannian space derived from characteristics of the image. The classical energy based active contour is given by:

$$E(C) = \alpha \int_0^1 |C'(q)|^2 dq + \beta \int_0^1 |C''(q)|^2 dq - \gamma \int_0^1 |\nabla I(C(q))| dq$$

(4.2)

with $C(q), q \in [0, 1]$ a parameterized planar curve and $I$ a given image in which we want to detect the objects boundaries. The first two terms correspond to the internal energy and impose a piecewise smoothness constraint. The third term pushes the contour toward image features. $\alpha, \beta$ and $\gamma$ are constants acting as weights. In GAC, the contour energy is used without the second order term and its minimization is equivalent to finding a minimal length geodesic curve $C(q)$, a differentiable parameterized curve, weighted by a strictly decreasing function $g$ in a Riemannian space:

$$\min \int_0^1 g(|\nabla I(C(q))|)|C'(q)| dq$$

(4.3)

To find this minimal curve, we searched for the correspondent gradient descent direction and computed the correspondent Euler-Lagrange equation solution

$$\frac{\partial C(t)}{\partial t} = g(I)\kappa \vec{N} - (\nabla g \cdot \vec{N}) \vec{N}$$

(4.4)

where $\kappa$ is the Euclidean curvature and $\vec{N}$ is the unit inward normal. Starting from an initial curve, the geodesic flow deforming the contour (evolving) toward the minimum is given by a steady state solution $C_t = 0$. This flow can be embedded in a
4.2. Methods

level-set formulation, representing the surface $C$ by the zero level set of a function $\phi(t, x, y, z)$, i.e., $C(t) = \{(x, y, z) | (t, x, y, z) = 0\}$, handling the surface indirectly by manipulating the level set function. The use of this implicit, higher dimensional surface representation provides good measurements of curvature (as the curve is represented implicitly as the zero level set) with sub-pixel resolution. The level set function to be minimized is usually selected to be a signed distance function (SDF), with zero value on the surface, negative in the interior and positive in the exterior of the zero level set. SDF was computed on the initial segmentation of each structure of interest (Section 4.2.2) and used as our level set initialization $\phi$, integrating the GAC evolution in the level set function formulated by the following partial differential equation:

$$\phi_t = g(I)K |\nabla \phi| + pg(I) |\nabla \phi| + a \nabla g \cdot \nabla \phi$$  

where $K$ is the curvature of the closed surface $\phi$ and $g$ is the stopping function, which depends on the input image $I$, being responsible for stopping the surface evolution on the boundaries. The first and second terms on the right-hand side guide the propagation, containing the mean curvature flow and the motion in the normal direction, where the term with the propagation constant $p$ speeds up the evolution. The third term on the right-hand side, the so called advection flow, weighted by the constant value, is bilateral and depends on the current position of the surface, preventing crossover edges by locking the surface to the neighboring borders. The solution of the segmentation is given by the steady state $\phi_t = 0$.

The level set evolution in 4.5 was applied twice:

$$\phi^n_t = g_n(I)K |\nabla \phi| + p_n g_n(I) |\nabla \phi| + a_n \nabla g_n \cdot \nabla \phi$$

with $n = 1, 2$; $g_n$ is the curve stopping function, dependent on image features, that will be described in detail in the next section. The stopping function $g_1$ was updated after the convergence of the evolution $\phi_1$ to $g_2$, the reduced scale space of the stopping function, until the level set $\phi_2$ converged again. For $\phi_1$ we ignored the advection term due to its attraction properties to nearby boundaries; thus 4.6 was reduced to:

$$\phi^1_t = g_1(I)K |\nabla \phi| + p_1 g_1(I) |\nabla \phi|$$

which corresponds to the classical level set approach proposed in [10,47], weighting the propagation term by the constant $p_1$ to obtain a rapid propagation to the boundaries of interest. In the second evolution $\phi_2$, we were already near to the boundaries of interest and therefore exploited the additional advection term from the geodesic formulation in 4.6 to attract the surface to the nearby encountered edges. The three parameters $p_1$, $p_2$ and $a_2$ were tuned experimentally, performing a quantitative evaluation on 3 randomly selected subjects. Figure 4.3 shows the tuning of the RV, LVendo, LVepi and Fat based on the Dice similarity coefficient; Table 4.1 summarized the chosen parameters.

Stopping Function: Multiscale and Directionality

The heart presents structures at multiple scales, where the right ventricle (RV) can be considered a larger structure when compared to the left ventricle (LV), which, with its pronounced trabeculae and papillary muscles, can be very slim. Additionally, the LV myocardium can present different wall thicknesses, resulting in a very thin wall in
Figure 4.3: Tuning of the parameters of the first curve evolution $p_1$ and the final segmentation step with parameters $p_2$ and $a_2$ of the 3D GAC for each of the cardiac structures of interest based on the Dice similarity coefficient.

Table 4.1: Optimal parameters setting for $p_1$, $p_2$ and $a_2$ of both 3D GAC for the cardiac structures of interest.

<table>
<thead>
<tr>
<th></th>
<th>RVendo</th>
<th>LVendo</th>
<th>LVepi</th>
<th>EpiFat</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_1$</td>
<td>4</td>
<td>10</td>
<td>1.2</td>
<td>4.5</td>
</tr>
<tr>
<td>$p_2$</td>
<td>0</td>
<td>3.5</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>$a_2$</td>
<td>0.6</td>
<td>4</td>
<td>6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

pathological subjects. Therefore, image representation at different scales could be desirable in order to better capture the information contained within it. For this purpose a 3D edge detector was built, based on the work presented by Varma and Zisserman [73], which examines image volume over a range of orientations and scales decomposing the original image into several filtered images with limited spectral information. The kernel of our detector is an even symmetric 2D second derivative Gaussian filter. A method to obtain such a directional filter is to construct, firstly, an optimal one dimensional filter in the direction perpendicular to the edge, multiplying it by a projection function in the direction parallel to the edge. Our even symmetric 2D filter $f$ has the following form:

$$f(x, y) = \frac{\partial^2}{\partial y^2} G(x, y) = \frac{y^2 - \sigma_y^2}{2\pi \sigma_x \sigma_y^5} e^{-\frac{1}{2} \left(\frac{x^2}{\sigma_x^2} + \frac{y^2}{\sigma_y^2}\right)}$$

(4.8)

where $x$ is the direction parallel and $y$ the direction perpendicular to the edge. The filter $f$ is characterized by $\sigma_x$ and $\sigma_y$ which are the standard deviations of the Gaussian along $x$ and $y$ respectively, elongated by a ratio of 3:1 along the edge direction $x$. Starting from the formulation in [4,8] directionality in the 2D filter component is applied using the rotational matrix $R(\theta)$ with $\theta \in \Theta = \{0, \frac{\pi}{6}, \frac{\pi}{3}, \frac{\pi}{2}, \frac{2\pi}{3}, \frac{5\pi}{6}\}$:

$$f^\theta(x, y) = R(\theta) f(x, y), \text{ with } \theta \in \Theta$$

(4.9)
4.2. Methods

where \( f^\theta(x, y) \) is the battery of 6 directional filters. For a given image volume \( I(x, y, z) \) the filters on each slice \( I_z(x, y) \) were applied, obtaining 6 output images \( j^\theta_z(x, y) \), one for each angle \( \theta \):

\[
j^\theta_z(x, y) = I_z(x, y)^\theta(x, y) \forall z
\] (4.10)

An image \( J_z(x, y) \), containing in each point \( (x, y) \) the maximum value in that position among the 6 images \( j^\theta_z(x, y) \) was then composed. In the same way, we derived \( J_y(x, z) \) and \( J_x(y, z) \) which are the maximum response values of the directional filters applied to the remaining 2 orthogonal planes along the directions \( y \) and \( x \) respectively. Finally, extending the maximum response value search in each position to the 3 orthogonal planes, the 3D edge detector \( H(x, y, z) \) was built:

\[
H(x, y, z) := \max(J_z(x, y), J_y(x, z), J_x(y, z))
\] (4.11)

Taking the maximum response of the second derivative, will yield the stopping map slightly after the edge occurrence, this will allow our level set to stop exactly above the real edge. Multiscale was obtained by modifying the standard deviation values \( (\sigma_x, \sigma_y) \) of the Gaussian in Equation 4.8. \( H(x, y, z) \) was computed in two different scales: \( H_1 \), a coarse level \( (\sigma_x, \sigma_y = 9, 3) \) and \( H_2 \), a finer level \( (\sigma_x, \sigma_y = 3, 1) \). The MDCT volume was filtered using 4.11 in the case of the cavities (RVendo and LVendo), and in the case of the LVepi, 4.11 was applied after inverting the grayscale values of the MDCT volume, as we were attempting to identify the boundaries of bright areas. In Figure 4.4 a result of applying the edge detector at the two different scales is shown for the cavities on an exemplificative cardiac MDCT slice.

![Figure 4.4](image)

**Figure 4.4:** A slice in the short axis view after the application of the edge detector with the first scale \( H_1 \), obtaining a high smooth level, accentuating the principal edges and with the reduced scale \( H_2 \), obtaining detailed information about the edges.

Recalling 4.6 the stopping function \( g_n \), which presents the general form:

\[
g_n = \frac{1}{(1 + e^{\frac{B_n - L_n}{\alpha n}})}
\] (4.12)
contains our two edge detectors $H_1$ and $H_2$. The constant values were set as follows: $eta_1 = 0.1$, $\alpha_1 = 0.1$, $\beta_2 = 0.05$ and $\alpha_2 = 0.01$.

Initialization

For each cardiac structure of interest segmented using the proposed level set, an initial 3D rough segmentation was constructed. For LVendo and RVendo the approach starts by searching for coordinates on two slices. In the cases of LVepi and epicardial fat the initial segmentation is based on the 3D final segmentations of the previously mentioned structures, as described in the following.

- **LVendo and RVendo**: Initially, the input image was simplified to emphasize heart detection and to suppress surrounding structures. Since CT images have calibrated gray values defined on the Hounsfield scale, the rough initial segmentation was constructed using image features calculated from the original gray values. The image was thresholded at +50 Hounsfield units to separate the heart from the surrounding tissues. The largest connected component was chosen after a morphological opening to get a mask with the heart structures of interest for the following operations (Figure 4.5).

![Figure 4.5: An apical and a middle slice of two different subjects showing the processing steps performed for the heart cavities localization. (a) original image (b) thresholded image (c) morphological open operation and (d) the largest volume after filling holes](image)

A 3D connected confidence region growing algorithm was applied: a voxel $I(x, y, z)$ should be included in the region if its intensity satisfies the following condition:

$$I(x, y, z) \in [m - r\sigma, m + r\sigma]$$  \hfill (4.13)

where $m$ and $\sigma$ are the mean and standard deviations of the intensity in the region, multiplied by a constant value $r$ that controls the capture range. To find seeds for this region growing algorithm, an automated coordinate search to identify a set of voxels within the cavities was performed on two slices, at 25 and 50 percent of the heart volume (on an apical and a medial ventricular slice). On both
4.3. Experiments

slices, the standard Fuzzy C Mean algorithm [9] was applied (computing a fuzzy membership function with a weighting exponent of 2) to segment each slice into 5 tissue classes: LVendo, RVendo, myocardium, adipose tissue and background (see Figure 4.6). As the location of the cavities was known (thanks to the previously created mask), the LVendo structure was identified as the largest area from the brightest class; this is true for most of all MDCT protocols, that use a contrast agent to enhance the blood pool. RVendo was obtained by selecting the 2 brightest classes (LVendo, RVendo) and subtracting the dilated LVendo. Skeletonization of the resulting structures was computed and three of the skeletonization intersection points extracted. The points were used as seeds for the 3D connected confidence region growing algorithm on the masked volume. The LVendo initial segmentation was obtained using \( r = 2.5 \). The image volume was then further processed to obtain the initial segmentation of RVendo applying an alpha concave hull to the resulting region growing with \( r = 1.5 \).

![Figure 4.6: An apical and a middle slice of two different subjects showing the intermediate steps necessary to obtain the initial rough segmentation of the RVendo and LVendo: (from left to right) original slice, 5 labels resulting from the fuzzy c mean overlapped with the extracted RV and LV structures, skeletonization of the extracted structures overlapped with three intersection points, 3D region growing result obtained using the intersection points and final LVendo segmentation and final RVendo segmentation after application of the concave hull.](image)

- **LVepi:** From the final LVendo segmentation, the initial rough segmentation of LVepi was obtained, by applying an expansion with a convex hull and a morphologic dilation (see Figure 4.7).

- **Epicardial Fat:** The initial rough segmentation of the epicardial fat was obtained by adding in the same structure the final RVendo and LVepi segmentation and applying the convex hull method to this structure.

4.3 Experiments

We used the multiscale level set evolution method to segment the RVendo, LVendo and LVepi. To extract the epicardial fat, due to its small dimension, the 3D level set was
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

Figure 4.7: Original image on the left and LVendo segmentation result (red contour) and LVepi initialization (green contour) on the right

applied only on its reduced scale \((\sigma_x, \sigma_y = 3, 1)\) to extract the pericardium. After the curve evolution, the extracted structure was multiplied by the adipose tissue typical Hounsfield values range (threshold between -190 and -30HU) and RVendo and LVepi subtracted. The procedure is described in Figure 4.8. The segmentation of the coronary tree was obtained after subtraction of the LVendo and RVendo from the thresholded bright areas within the pericardial limitation (obtain from the epicardial fat segmentation). An exemplary description is given in Figure 4.9.

4.3.1 Data Set

Our dataset consists in twenty-one randomly selected studies collected for the clinical diagnosis and follow-up of patients with suspected cardiac problems that have been acquired with a 64-slice cardiac-MDCT scanner (Philips Brilliance 64). All subjects signed the informed consent form approved by the Institutional Review Board. This data set consisted of 9 normal subjects and 12 subjects with ischemic heart disease. In subjects with heart rate lower than 65bpm, prospective gating step-and-shoot protocol with subsequent axial scans prospectively-triggered in the mid-diastolic phase (75\% of R - R interval) was applied. In subjects with heart rate higher than 65bpm, after the administration, when indicated, of \(\beta\)-blockers, a retrospective gating helical scan with ECG-controlled tube dose modulation was applied (maximum 700 mAs between 40\% and 80\% of R - R interval, maximum 300 mAs during the other phases of the ECG cycle). An angiographic scan was performed (18 prospective and 3 retrospective) during the intravenous injection of a high concentration non-ionic contrast (Iomeron 400, Bracco) at a rate of 5.6 ml/second (120 ml of 370 - 400mg I/ml). The data set has an isotropic voxel size ranging from 0.3mm to 0.5mm, and SNR that ranged from 10 to 45. From these twenty-one volumes, three were used as training set, whenever parameter tuning was needed.
4.3. Experiments

Figure 4.8: Segmentation steps of the epicardial fat: in white the initialization and blue the curve evolution result (top); the red contour corresponds to the convex hull of the curve evolution resulted structure (top right); HU defined threshold (bottom left) and segmentation result (bottom right).

Figure 4.9: Segmentation steps of the coronaries

4.3.2 Segmentation Accuracy

We compared our proposed edge detector to the classical Gradient Magnitude on 8 subjects (4 healthy and 4 pathologic) using the presented surface evolution scheme.

After this, we validated the proposed method on the cavities, myocardium and epicardial fat segmentation of eighteen MDCT volumes. Thirty equally spaced slices (in the short axis view) were extracted for each heart volume and the RVendo, LVendo and LVepi were manually outlined by an expert radiologist using the free software 3DSlicer
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

(http://www.slicer.org/), and the segmentation was additionally controlled by two other experts. Using the same manual segmentation approach, the epicardial fat was segmented on ten equally spaced slices. In this latter case, a labeled image with the typical fat tissue Hounsfield Units was used to help the physicians in the segmentation. These manual drawn binary images were used as ground truth to estimate segmentation accuracy of the correspondent structures. The same slices were extracted on the segmentation results of our proposed method after having binarized the final SDF at $\phi = 0$. From both manual and automatic binarized images, an isosurface of each structure was generated by triangular approximation of the interfaces between slices, without smoothing constraints, to perform a surface to surface comparison. The segmentation performance of our method was assessed comparing our automatically obtained surface against the manual ground truth in terms of average symmetric surface-distance (ASD), maximum surface distance (MSD) and percentage of surface voxels with errors of less than 1 mm. Additionally, the Dice similarity coefficient (DSC) and the relative volume difference between the manual (M) and automatic (A) segmented sets of voxels expressed as: $100(\frac{|A| - |M|}{|M|})$ was measured. One-way ANOVA with Tukey’s post hoc test [40] were used to determine statistical differences between segmentation performance after the first curve evolution and after the final evolution of the proposed method, relative to the ground truth. In the case of the coronary tree, segmentation was evaluated on each volume qualitatively by an expert radiologist. The qualitative evaluation consists in the visualisation of the 3D coronary tree reconstruction and assigning one of the following 5-points classification: 1-excellent, 2 - good, 3 - satisfactory, 4 - poor and 5 - unsatisfactory.

4.4 Results

4.4.1 Comparison with Classical Gradient Magnitude

The proposed edge detector showed better results in all similarity metrics when compared to the classical edge detector, as can be seen in Table 4.2.

Table 4.2: Results obtained in the comparison between proposed edge detector and classical gradient magnitude in the curve evolution segmentation approach.

<table>
<thead>
<tr>
<th>Edge Detector</th>
<th>Structure</th>
<th>DSC</th>
<th>ASD (mm)</th>
<th>MSD (mm)</th>
<th>dist &lt; 1mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed</td>
<td>RVendo</td>
<td>0.94 ± 0.02</td>
<td>0.34 ± 0.18</td>
<td>7.04 ± 2.77</td>
<td>89.51</td>
</tr>
<tr>
<td>Multiscale Directional</td>
<td>LVendo</td>
<td>0.92 ± 0.01</td>
<td>0.49 ± 0.14</td>
<td>10.33 ± 3.73</td>
<td>84.81</td>
</tr>
<tr>
<td>Directional</td>
<td>LVepi</td>
<td>0.96 ± 0.01</td>
<td>0.47 ± 0.13</td>
<td>6.47 ± 2.39</td>
<td>82.47</td>
</tr>
<tr>
<td>Gradient Magnitude</td>
<td>RVendo</td>
<td>0.83 ± 0.05</td>
<td>1.24 ± 0.56</td>
<td>9.80 ± 4.01</td>
<td>58.23</td>
</tr>
<tr>
<td></td>
<td>LVendo</td>
<td>0.88 ± 0.04</td>
<td>0.82 ± 0.35</td>
<td>10.47 ± 4.95</td>
<td>71.07</td>
</tr>
<tr>
<td></td>
<td>LVepi</td>
<td>0.92 ± 0.05</td>
<td>1.12 ± 0.60</td>
<td>8.59 ± 2.78</td>
<td>60.86</td>
</tr>
</tbody>
</table>
4.4. Results

4.4.2 Validation

The segmentation accuracy was found to be similar for both normal and pathologic subjects with no significant differences. An exemplary qualitative view of our outcome is shown in Figure 4.10. Results for each structure of interest are presented separately in the following sections.

![Figure 4.10: Two views of the segmentation result of all cardiac structures of interest: RV in yellow, LVendo in blue, LVepi in green, epicardial fat in pink and coronaries in red.](image)

**RVendo**

RVendo shows good correspondence between manual and automatic segmentation, as can be observed qualitatively in Figure 4.11 for the apical, medial and basal zones of the cavity. These good results were confirmed quantitatively, as shown in Table 4.3 and Table 4.4, with DSC value higher than 94% , and 90% of the voxels presenting a distance error less than 1mm relative to the manual segmentation. The average and maximum surface distance errors were 0.33mm and 7.13mm respectively. Further, the relative volume difference is below 7%. For this structure, the application of the second surface evolution with the reduced scale of the stopping function does not increase segmentation performance.

**LVendo**

Examples for qualitative evaluation of the apical, medial and basal zones of the cavity are reported in Figure 4.12. In the case of the LVendo, better correspondence with the manual drawn segmentation was obtained when using both evolutions (see Table 4.3)
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

Figure 4.11: RV apex, medial and basal segmentation examples of three different healthy and pathologic subjects. Green corresponds to the manual segmentation and red to the proposed approach.

and Table 4.4). Specifically, in this last case DSC shows a value of 91%, and 84% of the voxels presents distance error less than 1mm relative to the manual segmentation; these values are significantly improved relative to the first evolution. The average and maximum surface distance errors are 0.48mm and 8.39mm respectively. Further, the relative volume difference between manual and automatic segmentation is 10.72%.
4.4. Results

Figure 4.12: LVendo apex, medial and basal segmentation examples of three different healthy and pathologic subjects. Green corresponds to the manual segmentation and red to the proposed approach.

LVepi

Figure 4.13 shows examples of the LVepi segmentation in the apical, medial and basal zones of the heart, and Table 4.3 and Table 4.4 summarized the quantitative results. For this structure, after the subtraction of RVendo from the final segmentation, 96% of the volume is in concordance with the manual segmentation and 84% of the voxels present a surface distance error less than 1mm. Average and maximum surface distance errors are 0.45mm and 7.16mm respectively. Further, the relative volume difference is about 3%. All metrics excluding MSD show significant improvements between the
application of $\phi_1$ only and $\phi_1$ and $\phi_2$ (see Table 4.3).

**Figure 4.13:** LVepi apex, medial and basal segmentation examples of three different healthy and pathologic subjects. Green corresponds to the manual segmentation and red to the proposed approach.
4.4. Results

Table 4.3: Results for the proposed method for the segmentation of the RVendo, LVendo and LVepi reported as mean and standard deviation.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Curve Evolution</th>
<th>ASD (mm)</th>
<th>MSD (mm)</th>
<th>dist &lt; 1mm (%)</th>
<th>Volume Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVendo</td>
<td>$\phi_1$</td>
<td>0.33 ± 0.15</td>
<td>7.15 ± 2.72</td>
<td>89.99 ± 4.69</td>
<td>6.66 ± 4.16</td>
</tr>
<tr>
<td></td>
<td>$\phi_2$</td>
<td>0.33 ± 0.15</td>
<td>7.13 ± 2.72</td>
<td>90.00 ± 4.69</td>
<td>6.63 ± 4.17</td>
</tr>
<tr>
<td>LVendo</td>
<td>$\phi_1$</td>
<td>0.66 ± 0.26</td>
<td>9.74 ± 4.3</td>
<td>77.02 ± 10.21$^{\phi_2}$</td>
<td>17.98 ± 8.79$^{\phi_2}$</td>
</tr>
<tr>
<td></td>
<td>$\phi_2$</td>
<td>0.48 ± 0.16</td>
<td>8.39 ± 3.11</td>
<td>84.43 ± 6.26$^{\phi_1}$</td>
<td>10.72 ± 6.25$^{\phi_1}$</td>
</tr>
<tr>
<td>LVepi</td>
<td>$\phi_1$</td>
<td>1.15 ± 0.40$^{\phi_2,\phi_3}$</td>
<td>6.73 ±1.47</td>
<td>55.50 ± 8.52$^{\phi_2,\phi_3}$</td>
<td>13.68 ± 5.44$^{\phi_2,\phi_3}$</td>
</tr>
<tr>
<td></td>
<td>$\phi_2$</td>
<td>0.53 ± 0.17$^{\phi_1}$</td>
<td>6.62 ± 2.0</td>
<td>80.68 ± 5.62</td>
<td>5.06 ± 3.98$^{\phi_1}$</td>
</tr>
<tr>
<td></td>
<td>$\phi_3$</td>
<td>0.45 ± 0.16$^{\phi_1}$</td>
<td>7.16 ± 1.66</td>
<td>83.91 ± 5.87$^{\phi_1}$</td>
<td>3.07 ± 2.54$^{\phi_1}$</td>
</tr>
</tbody>
</table>

$^{\phi_1}$ - significant difference at p-value < 0.05 relative to the segmentation using the first surface evolution; $^{\phi_2}$ - significant difference at p-value < 0.05 relative to the final segmentation; $^{\phi_3}$ - significant difference at p-value < 0.05 relative to the segmentation using the final LVepi segmentation subtracted by the RVendo.

Table 4.4: DSC results for the proposed method for the segmentation of the RVendo, LVendo, LVepi and epicardial fat reported as mean and standard deviation.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Curve Evolution</th>
<th>DSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVendo</td>
<td>$\phi_1$</td>
<td>0.94 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>$\phi_2$</td>
<td>0.94 ± 0.02</td>
</tr>
<tr>
<td>LVendo</td>
<td>$\phi_1$</td>
<td>0.89 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>$\phi_2$</td>
<td>0.91 ± 0.03$^{\phi_1}$</td>
</tr>
<tr>
<td>LVepi</td>
<td>$\phi_1$</td>
<td>0.92 ± 0.03$^{\phi_3}$</td>
</tr>
<tr>
<td></td>
<td>$\phi_2$</td>
<td>0.96 ± 0.01$^{\phi_1}$</td>
</tr>
<tr>
<td></td>
<td>$\phi_3$</td>
<td>0.96 ± 0.01$^{\phi_1}$</td>
</tr>
<tr>
<td>EpiFat</td>
<td>$\phi_1$</td>
<td>0.87 ± 0.05</td>
</tr>
</tbody>
</table>

$^{\phi_1}$ - significant difference at p-value < 0.05 relative to the segmentation using the first surface evolution; $^{\phi_2}$ - significant difference at p-value < 0.05 relative to the final segmentation; $^{\phi_3}$ - significant difference at p-value < 0.05 relative to the segmentation using the final LVepi segmentation subtracted by the RVendo.
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

Epicardial Fat

Satisfactory results were achieved in the epicardial fat tissue segmentation, as shown in Table 4.4. Figure 4.14 show some qualitative results in the segmentation of this structure.

![Epicardial Fat Segmentation Examples](image)

**Figure 4.14:** Epicardial fat segmentation examples of different subjects. Green corresponds to the manual segmentation and red to the proposed approach (yellow the overlap of both).

Coronary Tree

The segmentation of the coronaries was, in average, defined as good. The satisfactory classification was chosen by the experts whenever additional structures were included (poor subtraction of the surrounding structures). Some qualitative 3D results are presented in Figure 4.15.

![Coronary Tree Segmentation Examples](image)

**Figure 4.15:** Examples of the coronary segmentation obtained in three different subjects.
4.5 Discussion

In this chapter we addressed the segmentation of different cardiac structures of interest. A new segmentation method was proposed, based on a directional multiscale edge detector, for the segmentation of RV, LVendo, LVepi and epicardial fat. The edge detector is based on a second derivative Gaussian filter in 6 directions and coupled with a 2-step surface evolution method using 2 different scales in order to capture the fine cardiac boundaries. Despite the initial segmentation (initialization of the surface evolution method) was guided by intensity information of the volume, a pre-adapted shape template could be used for this purpose. It was found that for RV the first evolution process is sufficient to obtain an accurate segmentation, with ASD of 0.33mm and a volume difference of 6.7%, and that the second step, with the reduced scale space, is not necessary. However, the second evolution step is fundamental in LVendo and LVepi in order to perform an accurate segmentation, being the segmentation performance between first and final evolution significantly different for most similarity metrics. Volume error improved from 18.0% to 10.7% and 13.7% to 5.1% respectively, while surface points below 1mm distance increased from 77.0 to 84.4 and 55.5% to 80.7% respectively. This fact could be due to the dimensions of the structures: the RVendo is larger than LVendo and LVepi and the first scale space is therefore able to capture the boundaries in an optimal way. On the other hand, in order to be accurately detected, the pronounced papillary muscles and trabeculae of the LVendo required a decreased scale space, as well as the surface evolution through the myocardium wall until LVepi, which, with its small thickness, is properly detected after the second, reduced scale space. The expanding evolution process of the structures reduces false edge detection, especially for the LVepi border, where wall thinning in the pathologic process can be better captured as shown in the example in Figure 4.13. The accuracy of the segmentation method seems comparable to that of recently published works on LVendo, LVepi and RV segmentation of MDCT volumes (see Table 4.5). In particular, our approach presents better values for all structures of interest in common (LVendo, LVepi and RVendo) in terms of both ASD and percentage voxels with distance error less than 1 mm. It was not possible to compare the other metrics included in our evolution such as MSD, DSC and volume difference, as they have not been analyzed in previous works.

Despite epicardial fat does not achieve the performance of the previous discussed structures, today this structure is segmented manually. In the case of the epicardial fat, as we are dealing with a slight layer only the reduced scale was used to properly identify the pericardium border. However, the segmentation performance in this case was slight lower than the previously referred structures. The main reasons are due to the non visible pericardium border at some locations and the high variability in the fat layer thickness between subjects.

The segmentation accuracy of the coronaries remains however strictly related to the contrast medium at the time of the scan acquisition.

However, a direct comparison of segmentation accuracy between our approach and previous works is cumbersome, especially regarding conceptual differences in the choice of ground truth used for the validation process. In fact, due to the considerable effort required to manually segment a great number of 3D volumes, model-based methods have been evaluated using a manual correction of the automatic segmentation
Chapter 4. Cardiac Anatomy Segmentation from MDCT Images

Table 4.5: Results obtained for previously proposed segmentation methods for MDCT volumes.

<table>
<thead>
<tr>
<th>Method</th>
<th>MDCT dataset structure</th>
<th>ASD (mm)</th>
<th>dist &lt; 1mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al [60]</td>
<td>67 volumes from 33 subjects</td>
<td>LVendo 0.76 ± 0.88, LVepi 0.68 ± 0.62</td>
<td>77, 79.1</td>
</tr>
<tr>
<td>Peters et al [59]</td>
<td>28 volumes from 13 subjects</td>
<td>RVendo 0.84 ± 0.94, LVendo 0.98 ± 1.32, LVepi 0.82 ± 1.07</td>
<td>72.9, 54.5, 74.2</td>
</tr>
<tr>
<td>Ecobert et al [25]</td>
<td>37 volumes from 17 subjects</td>
<td>RVendo 0.63 ± 0.66, LVendo 0.77 ± 1.14, LVepi 0.68 ± 0.96</td>
<td>87.9, 76.4, 80.5</td>
</tr>
<tr>
<td>Zhu et al [79]</td>
<td>34 subjects</td>
<td>LVendo 0.88 ± 0.96, LVepi 1.07 ± 1.16</td>
<td></td>
</tr>
</tbody>
</table>

State of the art results using different Gold Standards.

as ground truth [25, 59, 60]; however it should be noted that this choice can typically result in a slight underestimation of the segmentation error, as pointed out by the authors [25]. Moreover, different ground truths can be defined, depending on the inclusion or exclusion of trabeculae and papillary muscles of the cavities under study, leading to significant volume differences, as can be seen in most pathological cases, where the heart tends to present increased papillary muscles and trabeculae areas in both RVendo and LVendo [28]. In previous works, the manual delineation of cardiac cavities has been often simplified by including both papillary muscles and trabeculae in the blood pool, thus obtaining a smoother surface. On the contrary, in our work, the physicians excluded papillary muscles and trabeculae whenever possible, with the purpose of obtaining a true patient specific anatomy of the ventricle cavities, more suitable for surgical interventions such as catheter ablations, where it is important to know the precise location of those structures. We have demonstrated the accuracy of our method in the precise identification of RVendo, LVendo and LVepi, excluding trabeculae and papillary muscles, obtaining a patient specific heart segmentation. In our work, the test dataset (10 pathological and 8 healthy subjects) has a dimension comparable to those of previous studies, where 13 [60], 17 [59], 33 [25] and 34 [79] subjects were analyzed. The main difference of our framework relative to these studies consists in the cardiac phase, which has been taken into account. In fact, while most previous works have considered dynamic MDCT studies and evaluated the performance of the segmentation in various phases of the cardiac cycle, our work focused only on the image volumes corresponding to the mid-diastole. This specific cardiac phase is the most important for anatomical studies and guided electrophysiology procedures. The only step that requires operator interaction in the proposed method is the reslice of the original MDCT volumes into the short axis view. This view is largely used in the clinical practice, and is useful in our study to decrease processing time (we are only interested in the ventricles) and to facilitate the automatical separation of ventricles and atriums.

We would like to emphasise that, despite the use of a region growing approach for the surface evolution approach, the proposed edge detector can be used coupled to any curve evolution approach.
CHAPTER 5

Myocardial Scar Extraction from MDCT

There are three different approaches to detect non-viable myocardium including perfusion defects in MDCT; two approaches are on the early angiographic scan and one on the delayed scan (see Chapter 3). On the early scan compromised zones are hypoenhanced when compared to the normal myocardium or present myocardial wall thinning. The approach to detect scar on the delayed scan, contrary to the first case, consists in searching for hyperenhanced zones of the myocardium. As myocardial perfusion and viability assessment using MDCT imaging is a relatively new technique, there is not yet clear the best way to automatically quantify the information on such images. Today, manual and semi-automatic segmentation is used for this purpose [46], remaining however, a very time consuming approach and operator expertise dependent. First efforts in automate such task on DE MDCT was presented by Mahnken et al [72]. In this chapter we present the different automatic approaches used to segment myocardial scar areas in the three possible scenarios using co-registration of the scans and automatic segmentation.

5.1 Introduction

To obtain accurate scar identification, the most important requirement is the reliable segmentation of the LV myocardium, within which perfusion and viability defects can be further evaluated. In the literature, this is accomplished by manual segmentation of the LVendo and LVepi on the delayed MDCT scan [2,15,24,62,71,72,77]. Subsequently to this step, a variety of threshold methods have been proposed for segmenting the myocardial scar.

The performance of threshold-based methods in the delayed MDCT scan is however hampered by high image noise and beam-hardening artifacts, which makes diffi-
cult the success of such algorithms [65]. Additionally, contrast administration protocol and the delayed scan acquisition timing are two factors that may cause high variability between patients and lead to the failure of reliable and automated segmentation methods. Ruzsics et al. [66] developed a semi-automatic algorithm to quantify infarct size; MI was defined as HU attenuation value of 2 SD above the mean healthy myocardium value. In [72], they analyzed the late phase images with two different approaches. The methods are initialized by a live-wire semi-automatic method, followed in the first case by a 3SD threshold and in the second by a mixture model approach. The mixture model fits the histogram to two Gaussians to define the threshold values. They found that the threshold method alone had a bad performance, systematically overestimating the scar size, due to image noise and partial volume effects. The optimization of the signal to noise ratio (SNR) and improvement of contrast-to-noise ratio are important for the quantification of the scar area.

In the scenario of LV wall thinning (early scan), state-of-art considered scar tissue when the myocardial wall has a thickness less than 5 mm [23, 54] or less than 6 mm [32, 39]. This value was confirmed in MRI (thickness < 5.5 mm) for the prediction of non viability (transmural scar formation) [67].

In this work, a strategy was developed to extract scar from the previously segmented myocardium (Chapter 4) in the three possible cases: hypoenhanced myocardial tissue, wall thinning and delayed hyperenhanced tissue. For this goal, a registration and a Gaussian model threshold strategy were adopted.

### 5.2 Methods

We took the advantage of having the myocardium segmentation from the early scan (Chapter 4), where the myocardium boundary is clearly defined, to use as template for the scar identification.

#### 5.2.1 Registration of Angiographic and Delayed Scan

Although angiographic and DE scans were acquired with a few minutes distance, misalignment of the heart between both scans often occurred as seen in Figure 5.1. These errors occur due to movements related to the beating heart and patient positioning, which required registration in order to match LVendo and LVepi segmentation.

In this case, the image registration problem consist in finding the transformation of the different scans into the same geometric coordinate system in order to determine the correspondence between structures in the two scans. Given a reference $I(x, y, z)$ and a floating image $J(x, y, z)$, the goal is to optimize a transformation $T$ such that the floating equals the reference one:

$$T_{opt} = \arg\min_T C(I(x, y, z), J(T(x, y, z))).$$

(5.1)

where $(x, y, z)$ are the coordinates in the fixed (reference) image domain and $C$ is a cost function (similarity metric) that measures dissimilarity between both images and depends on the intensity values of both images. The problem is ill-posed and it may not have a unique and optimal solution $T_{opt}$. Moreover, different initializations or small changes of the input images can lead to completely different registration results.
5.2. Methods

Figure 5.1: Overlap of the two MDCT scans (angiographic and DE) before (left) and after registration (right).

The transformation $T$ defines the model with which we can deform the floating image to match the reference one. The goal is to improve $C$, which describes the goodness of the match between reference and transformed floating image, using a specific optimizer to solve the minimisation problem of Equation 5.1. The output transformation, estimated from the optimizer, is used to generate the warped image, with the help of an interpolation scheme. The interaction between these elements are described in the next sections.

First of all, to optimize the registration, both scans were cropped in order to exclude the circular reconstruction region, typical of CT scans, and the angiographic volume was used as the reference image. We used a coarse-to-fine strategy: building a pyramid of resampled images, the algorithm will depend always on new features until the resolution approaches the initial voxel size. The deformation approximated at each stage is used as input for the next (finer) stage. This approach reduces the risk of stopping at local minima at the highest resolutions. This down-sampling is combined with a Gaussian image filter, in order to enhance differences in the features at the diverse scales and reduce details at higher (coarser) levels.

Transformation Model

Registration methods can be divided into rigid and elastic transformations. The former are global transformations described by three parameters of translation and three parameters of rotation, preserving the distance between all points in the image (differing only by shift and rotation). Adding to these transformations scale and shear parameters give raise to the affine transformations (broader class). In this extended case, lengths and angles of lines are not preserved. In this work, where registration was performed using the same scanner and intra-patient, we excluded scale and shear parameters (affine transformation), because this type of transformations are useful only when it is necessary to compensate problems due to differences in the calibration between scanners or large-scale differences between subjects. Thus, our rigid problem can be written as:

$$T_{\text{rigid}}(\mathbf{x}|\lambda_r) = \mathbf{R} \cdot \mathbf{x} - \mathbf{T}$$

(5.2)
with $\lambda$, the six unknown parameters to estimate, $R$ the rotation matrix ($3 \times 3$), $x = [x, y, z]^T$ the voxel location in the reference image and $T = [t_x, t_y, t_z]^T$ the translation vector.

Since the heart cannot be seen as rigid body, we model the transformation as a sum of global rigid transformation (Equation 5.2) and a local elastic deformation (free-form deformations [46]) for the correction of the deformations that may occur due to anatomical motions:

$$T_{el}(x, y, z|\lambda_{el}) = \sum_{l,m,n=0}^{3} B_l(u)B_m(v)B_n(w)\phi_{i+l,j+m,k+n}$$  (5.3)

The idea is to associate the reference image coordinate space to a parametric hyper patch, parametrized by $(u, v, w)$. The hyper patch was defined as a trivariate cubic B-splines tensor product volume. Its deformations were controlled by a sparse, regular grid of $n_x \times n_y \times n_z$ points $\phi_{i,j,k}$, with resolution $\rho = [\rho_x, \rho_y, \rho_z]$ and weighted by cubic B-spline basis function $B_l$. We have $i = \lfloor x/\rho_x \rfloor$, $j = \lfloor y/\rho_y \rfloor$, $k = \lfloor z/\rho_z \rfloor$, $u = x/\rho_x - \lfloor x/\rho_x \rfloor$, $v = y/\rho_y - \lfloor y/\rho_y \rfloor$, $w = z/\rho_z - \lfloor z/\rho_z \rfloor$.

In this local deformation the unknown parameters $\lambda_{el}$ are the values of the control points $\phi_{i,j,k}$. It is clear that, the higher the number of control points, the higher the resolution of the searched transformation. However in the same way more computational time will be required.

The estimation of the local strain on the nodes of the grid and the deformation on the voxels of the image, which do not match with the control points, require a B-Spline interpolation [38]. B-spline functions are defined as polynomial basis functions of $n > 0$ degree. In particular, Free-Form Deformation methods use 1D cubic B-splines, which were used in our work as regularized interpolators, and to parameterize a vector field over the volume of interest. The B-spline coefficients are defined on control points, which lie on a grid that covers the region and the deformation field is a smooth interpolation of the coefficient value. The vector field is defined in terms of coefficients provided by a set of control points. A B-spline is a piecewise polynomial with uniform spacing between the control points $n_x, n_y, n_z$ (extended in 3D).

Cost Function

Despite the two MDCT volumes under study are from the same MDCT scanner, the late enhanced scan presents density information that does not coincide with the angiographic scan and depends on the contrast agent. To deal with this non-linear dependency, we used the mutual information (MI) as cost function to minimize [63]. MI assumes only a probabilistic relationship between the intensities. It is based on the computation of the entropies of the intensities distribution. MI can deal with different forms of intensity dependency, and is defined in terms of entropy ($H$):

$$MI(I(x, y, z), J(x, y, z)) = H_I(x,y,z) + H_J(x,y,z) - H_{I(x,y,z), J(x,y,z)},$$

with $H = - \sum_a (p_a \cdot \log(p_a))$  (5.4)
5.2. Methods

The probability densities $p_a$ need to be estimated from the images. Taking $N$ samples of intensity values and super-positioning a kernel function $K(\cdot)$ centered on the sampled elements ($S$):

$$p_a = \frac{1}{N} \sum_{s_j \in S} K(a - s_j)$$  \hspace{1cm} (5.5)

We used the implementation proposed in [48], which suggests the use of B-spline as smooth kernels, and is very stable to noise in the input images.

The metric reaches its maximum when the two images are aligned, requiring however normalization to exclude dependence from initial alignment.

Optimization Scheme

Detecting convergence and guaranteeing that the chosen stopping condition is always optimal for the considered images is a fundamental but rather complicated in translating these algorithms into the clinical practice.

To find the best transformation, we look for parameters that minimize the chosen cost function. The optimization problem becomes more complicated with the increase of the flexibility of the transformation. This means that there are more parameters to choose from compared to the rigid case. Moreover, in some cases, the algorithm converges to a solution, but this is not physically meaningful. Seeking the optimization of a parameter set is a problem solvable with standard methods. The optimizer chose in this work was the Limited-memory Broyden, Fletcher, Goldfarb and Shannon minimization (L-BFGS), due to its superiority in dealing with high dimensional problems [49]. Starting from an approximation of the inverse Hessian, it derives the optimisation variables by iteratively searching in the solution step. A backtracking lines search was employed to find the step size of movement in order to reach the minimum.

5.2.2 Segmentation

The segmentation approach used to extract scar areas makes use of a probability density function of the Hounsfield units: the Gaussian distribution. In this chapter, we assume that each type of structure or tissue of MDCT belongs to the same normal distribution [46]:

$$f(x_i | \mu, \sigma) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(x_i - \mu)^2}{2\sigma^2}}$$  \hspace{1cm} (5.6)

In patients with a metallic cardioverter, areas showing streak artifacts caused by the metallic equipment were excluded (they present highest signal intensity) before the further described analyses were performed. This was accomplished using a fixed threshold equal to $\frac{1}{5}$ of the high intensities.

Angiographic Scan

Imaging performed immediately after contrast injection will show hypo-enhanced areas corresponding to infarcted myocardium. The extraction of hypo-enhanced zones from the early scan is relative easy, because it can be clearly differentiated from normal myocardium, thanks to the lower CNR and high spatial resolution of this scan [55].
but it strongly depends on the contrast protocol, acquisition timing and cardiac output. Moreover, these hypo enhanced zones are in most cases correspondent to the same anatomical location of myocardial wall thinning and consequently excluding hypoenhanced zones from the myocardium and after this measuring the wall thickness implicitly integrates both scar detection methods.

Next, we present both methods of the extraction of non viable myocardium.

- **Hypoenhanced Extraction:** Given the MDCT image characteristics, with the myocardium densities measured in HU, we made the assumption that the distribution of the MDCT values of the myocardium can be described as two different Gaussians distributions, which represents normal and non viable (hypoenhanced) tissue [46]. However, myocardial scar is often minimal (or absent) when compared to the normal tissue, and estimating a mixture model with two Gaussians can be a very hard task on the angiographic scan. As it was not possible to estimate the distribution of the scared voxel, we calculated mean $\mu$ and variance $\sigma^2$ of the entire data:

$$
\mu = \frac{1}{N} \sum_{i} x_i, \sigma^2 = \frac{1}{N-1} \sum_{i} (x_i - \mu)^2
$$

and used as higher threshold $\mu - 3\sigma$ to identify the hypo-enhanced zones (low attenuation values). In this way, only values outside the normal distribution were considered. An illustrative example is shown in Figure 5.2.

![Figure 5.2](image.png)

**Figure 5.2:** A slice showing a hypoenhanced scar and the correspondent density distribution of the myocardium with its Gaussian fitting curve and the correspondent threshold value (green vertical line) to detect scar areas.

- **Wall Thinning:** In order to accurately measure myocardial wall thickness, the papillary muscles within the LVendo structure need to be excluded from the struc-
5.2. Methods

ture. However, due to the 3D bending geometry of the LV cavity, the convex hull is not a good choice to represent the area occupied by the papillary muscles. A typical error that may occur if using the convex hull to enclose the entire set of points is shown in Figure 5.3.

We used a more generalisation of the notion of convex hull: the alpha-hull \((\alpha - \text{hull})\) \[26\]. Varying the parameter \(\alpha\) leads to different shape types, not necessary convex, as it controls the shape estimator. Sufficient large \(\alpha\), the \(\alpha\)-shape equals the convex hull of the sample. Decreasing \(\alpha\), the shape shrinks until it is empty when \(\alpha\) approaches zero.

Concave hull, despite having not a precise definition such as convex hull (minimum perimeter and area convex enclosure of a given set of points), is flexible and allows to tune the parameter to the shape that best matches the papillary exclusion condition. Supposing that \(P\) is a set of points, if \(P\) is \(\alpha - \text{convex}\) the correspondent complement can be separated from \(P\) by means of an open ball with radius \(\alpha\) (in the case of the convex hull half-spaces were used to define the enclosed shape). Figure 5.3 shows an example of the use of different \(\alpha\) values in the exclusion of the papillary muscles from the LVendo surface. In order to preserve the 3D curvature of the LV (Figure 5.3 left) it is fundamental to use such a method instead of the convex hull.

![Figure 5.3](image)

**Figure 5.3**: Differences in using the convex hull (red), and two different values of \(\alpha\)-shape method (green: \(\alpha = 0.5\) and blue: \(\alpha = 0.3\)).

After the regularization step to exclude the trabecular and papillary muscles, and due to the fact that we are already dealing with a surface mesh (see Chapter 6), from each LVendo triangle vertex, a ray was casted outwards, and the distance to the nearest point on the LVepi surface was taken as the myocardium wall thickness. Points with distance less than 5 mm were considered scared areas according to \[54\] (Figure 5.4).

**DE Scan**

- **Hyper enhanced Extraction**: As mentioned in Chapter 3, the greatest drawback of the DE scan is its low resolution and high noise content. As the detection of
myocardial scar areas in the delayed scan consist in detecting high density values when compared to the normal myocardial tissue, we studied different relative thresholds to detect scar as similar as physicians would do. The detection of scar was much easier in the angiographic scan, because its high resolution and SNR enables a coherent non viable myocardium extraction, taking the scar voxel as being outside the myocardial Gaussian distribution.

In this case however, we made different assumptions to determine the best way to identify automatically areas of scar; the first one was that scar in DE MDCT has similar attenuation values than the blood pool. For this reason, using the LVendo segmentation from the early scan as template on the pre-registered delayed scan, we identified the parameters of the Gaussian distribution of the LV attenuation values \( (\mu_v, \sigma_v) \). In order to identify the best parameters to identify scar, we used as thresholds the following values: \( \mu_v, \mu_v - \sigma_v \) and \( \mu_v - 2\sigma_v \).

Looking to the myocardium, on the other hand, as it involves (if scar is present) a mixture of two tissue types (corresponding to two different histogram attenuation peaks), a Gaussian mixture model with two component densities was used to identify two clusters on the myocardial tissue \[46\]. It consists in a parametric probability density function described as a weighted sum of two Gaussian densities \( g(x|\mu_i, \sigma_i) \):

\[
p(x|\lambda) = \sum_{i=1}^{2} w_i g(x|\mu_i, \sigma_i)
\]

\[
= \sum_{i=1}^{2} w_i \frac{1}{(2\pi)^{D/2} |\sum_i^{-1}|^{1/2}} e^{-\frac{1}{2}(x-\mu)^t \sum_i^{-1}(x-\mu)}
\]
with $\lambda = (\mu_i, \sigma_i, w_i)$ the mixture weights (which satisfy $\sum_{i=1}^{2} w_i = 1$), $\mu_i$ the mean vector and $\sum_i$ the covariance matrix. Given this model, we estimate the parameters $\lambda$ which maximizes the likelihood iteratively using the Expectation Maximisation algorithm. It consists of, starting with an initial model $\lambda$ to estimate a new model $\lambda'$, such that $p(x|\lambda') \geq p(x|\lambda)$, and so on.

We obtained mean $\mu_i$ and variance $\sigma_i$ values of the two Gaussians (healthy myocardial tissue mean value $\mu_h$ and non viable myocardial tissue mean value $\mu_p$). To identify hyper-enhanced areas, the thresholds $\mu_p$ and $\mu_p + \frac{\mu_h - \mu_p}{2}$ were also experimented.

Before the application of the thresholds, and since the DE MDCT images come with a poor SNR, a Gaussian kernel was used to filter the delayed scan. This operation was fundamental to improve visualization of scared myocardium as it reduces noise, and to further avoid the inclusion of single speckle noise voxels into the segmentation result, as are typical when using thresholds in these type of images [46].

Figure 5.5 shows an example on the DE scar detection using the different experimented thresholds.

Figure 5.5: Different thresholds for DE scar detection: starting from the best performer ($\mu_p + \frac{\mu_h - \mu_p}{2}$) until the worst ($\mu_v - 2\sigma_v$).
heart rate above 65 beat/min were prepared with intravenous injection of beta-blockers (Atenolol from 1 to 15 mg), in absence of any major contraindications. In three patients the MDCT study was performed during continuous intravenous infusion of lidocaine hydrochloride to control ventricular arrhythmias.

All the MDCT cardiac studies included two scans:

1. Coronary computed tomography angiography (CCTA) during triphasic intravenous administration of high-iodine (370 - 400 mg iodine/ml) contrast agent (CA) (90 ml CA, 40 ml mixed solution 30% CA - 70% saline, 40 ml saline) at an injection rate of 5 - 6 ml/sec

2. Delayed enhanced computed tomography scan (CTDE) 10 minutes after the intravenous administration of 130 - 140 ml of high iodine CA, reached by a second injection of contrast media at the end of the CCTA.

Both CCTA and CTDE scans were acquired using prospective gating (collimation: 64 x 0.625 mm, rotation time 0.4 sec, pitch 0.32, thickness 0.8 mm with an overlap of 0.4 mm) in case of HR <65 beats/min and retrospective gating with ECG-based tube current modulation (collimation: 64 x 0.625 mm, rotation time 0.4 sec, pitch 0.2, thickness 0.67 mm with an overlap of 0.33 mm) in patients with an HR > 65 beats/min. All CCTA scans were performed at 120 kVp, while all CTDE studies at 80 kVp.

Effective radiation doses calculated by the product of the chest coefficient (0.014) and the dose-length product according to the European Working Group for Guidelines on Quality Criteria in CT (Bongartz G, Golding SJ, Jurik AG, et al. European Guidelines for Multislice Computed Tomography. Funded by the European Commission).

5.3.2 Validation

In this Chapter, as a great number of manually annotated structures would be additionally needed to perform a complete quantitative evaluation, which results very time consuming and not feasible for large 3D data, we performed for now a preliminary qualitative analysis. This quality analysis consists in visually inspecting the 3D volumes and assigning a grade consistent with the classification presented in Table 5.1 [37], having in some cases the addition of a + or − symbol to further detail the classification (+ slightly better and − slightly worse than the description).

Table 5.1: Scar segmentation quality grade classification.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (excellent)</td>
<td>Identified correctly</td>
</tr>
<tr>
<td>2 (good)</td>
<td>Most regions accurate detected, with few deviations</td>
</tr>
<tr>
<td>3 (satisfactory)</td>
<td>Most regions accurate detected, with many deviations</td>
</tr>
<tr>
<td>4 (poor)</td>
<td>A significant region (up to 50%) has been incorrectly segmented</td>
</tr>
<tr>
<td>5 (insatisfactory)</td>
<td>Segmentation failed</td>
</tr>
</tbody>
</table>

The adequacy of the registration results was qualitatively assessed by two expert radiologists [46]. It consists in the visualization of the angiographic scan subtracted
from the aligned DE scan in the long axis view, and classifying regionally the accuracy of the overlapped scans.

Segmentations of all defined scar regions were superimposed to the correspondent scan and, were evaluated for each patient, by the same radiologists. In this case, the classification is based in determining (see Table 5.1) if all regions of scar were detected without exclusions nor false inclusions.

5.4 Results

In the angiographic scan, SNR was higher when compared to the DE scan (see Table 5.2).

Table 5.2: SNR of the LV cavity of MDCT scans.

<table>
<thead>
<tr>
<th>Scan structure</th>
<th>SNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>angiographic MDCT LV cavity</td>
<td>11.85</td>
</tr>
<tr>
<td>DE MDCT LV cavity</td>
<td>10.25</td>
</tr>
</tbody>
</table>

Hypo-enhanced zones were correctly detected in all subjects, which represent non viable areas on the angiographic scan (8 out of 14 subjects had such areas). The wall thinning locations (< 5 mm) were in average good−.

The best threshold to detect DE scar in our experiment was the formulation: $\mu_p + \frac{\mu_v - \mu_p}{2}$, which best matched with the experts identification of hyper enhanced zones. A qualitative example is presented in Figure 5.5.

Using this threshold, it was possible to extract scar in agreement with the opinion of the physicians on the scar location. The average evaluation for this threshold was good+. The second best performance was obtained by $\mu_v$, followed by $\mu_p$. It was not possible to detect scar using the $\mu_v - 1\sigma_v$ and $\mu_v - 2\sigma_v$ values, due to its overestimation (inclusion of the total myocardium in the latter case). The qualitative analysis is summarized in Table 5.3.

Table 5.3: Performance of the different thresholds applied to DE scar detection.

<table>
<thead>
<tr>
<th>Grade</th>
<th>$\mu_p + \frac{\mu_v - \mu_p}{2}$</th>
<th>$\mu_p$</th>
<th>$\mu_v$</th>
<th>$\mu_v - 1\sigma_v$</th>
<th>$\mu_v - 2\sigma_v$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (excellent)</td>
<td>7%</td>
<td>14%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (good)</td>
<td>93%</td>
<td>36%</td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (satisfactory)</td>
<td>29%</td>
<td></td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (poor)</td>
<td>21%</td>
<td>36%</td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (insatisfactory)</td>
<td>57%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is important to note that this results do not consider the presence of the ICD nor imperfections due to the automatic myocardial segmentation, but only the threshold that best characterized scar in DE.

Taking the best performant method, we applied the myocardial mask to obtain the final segmentation. In this case the classification was in average satisfactory. Examples are shown in Figure 5.6.
Chapter 5. Myocardial Scar Extraction from MDCT

Figure 5.6: Results of DE scar extraction using $\mu_p + \frac{\mu_e-\mu_p}{2}$.

On 11 out of the 14 subjects that have an ICD, the percentage of analyzable myocardium was of 89% (due to the artefacts).

5.5 Discussion

Today, segmentation methods are widely used to segment cardiac structures. However, methods to segment scar, to the best of our knowledge, are not yet completely automatically, as proposed in this Chapter. The manual segmentation of non viable myocardium is not only a very time-consuming task, but also due to the poor resolution of the DE scan, it is also very challenge to properly identify the hyper-enhanced zones.

The calculation of the myocardial thickness is performed usually by measuring manually the LVendo to LVepi distance from 2D contours of the slice under study. This approach, besides being very time-consuming and increasing the difficulty in a proper myocardium analysis, can lead to an imprecise and coarse measure of the wall thickness due to the 3D anatomical shape of the myocardium.

In this Chapter we addressed these two challenges.

A fundamental step, in order to obtain accurate segmentation of the DE scar, is the registration between early and DE scan. Despite we did not validate the registration method, its performance was assessed visually and is implicitly reflected on the segmentation results. Consequently, the accurate segmentation of the DE scar is limited to the low DE resolution and the goodness of registration.

The qualitative evaluation takes into account the limited or inexistent segmentation near the ICD due to image artefacts that it generates. In particular, if some scar is near to the ICD it cannot be detected using pre-procedural imaging modalities. And this is a limitation in the present settings.

The best performance was obtained in the detection of hypo-enhanced zones from the angiographic scan. This was possible due to the high SNR and spatial resolution.
5.5. Discussion

The evaluation of the wall thinning was mostly based on the wrong thinning assignment on apical zones of the myocardium. In fact this region of the LV presented the greatest source of error.

Despite the great amount of noise that DE images present, satisfactory first results were obtained in the scar identification using the threshold $\mu_p + \frac{\mu_c-\mu_p}{2}$. While the other threshold methods present a high variability between segmentation accuracy (see Table 5.3), this threshold remains constantly high. It is however important to consider that the presence of ICD in almost all patients (11 out of 14) decreases the potentiality to reliably detect hyper-enhanced areas. The additional limitation of the low resolution of this scan further complicates the accurate, precise segmentation of scar, and only a location specific characterisation can be made, contrary to DE MRI, in which a differentiation between dense scar and border zones are usually made [2, 14, 22, 24, 62]. First effort in differentiating dense scar from border zones were studied by Zhao et al [77], showing comparable diagnostic accuracy between both modalities in quantitatively delineating dense scar, being however border zones more likely to be missed when using MDCT. In fact, we were not able to make a differentiation between dense and border scar in this study.
In this Chapter we face the myocardial map construction, using information from the automatically segmented cardiac structures of interest from Chapter 4 and Chapter 5, describing scar location and extent, as well as zones of thick fat layers. Further, this map was compared with the findings of EAM, created previously to the VT RF CA procedure.

6.1 Introduction

As was discussed in Chapter 2, CA RF has a very low success rate and the arrhythmologists have a critical need of highly detailed anatomical and functional information about the myocardium and the surrounding structures. Recent studies show that the knowledge of scar location from pre-procedural imaging can help in planning and guiding RF CA. Results in the comparison between EAM and 3D myocardial scars reconstructions from DE-CMR are already available \cite{2, 14, 21, 22, 24, 62}, which demonstrate the high correlation between scar from MRI and low bipolar and unipolar voltages. Desjardins et al. \cite{21} studied 14 patients with DE-CMR, comparing the findings with endocardial EAM, and showed that all sites identified at EAM were located within areas of DE at MR imaging (71% located at the core area of scar). The same group of authors \cite{31} has taken a further step suggesting that EAM and ablation procedure of VT should be guided by a DE-CMR based scars map, with another paper recently published. They studied 29 consecutive patients with non-ischemic cardiomyopathy, referred for catheter ablation of VT or premature ventricular complexes. In 14 patients a scar map was extracted from DE-CMR study and integrated into the mapping software system. Then they correlated the EAM data with the localization (sub-endocardial, intramural, sub-epicardial) of scar tissue, demonstrating that the localization of the scar,
as demonstrated with DE-CMR imaging, could be very effective to indicate the appropriate approach (endocardial vs epicardial) for EAM and ablation. In fact, they found that in 5 patients with evidence of predominantly sub-endocardial scar in DE-CMR, mapping and ablation of arrhythmias was effectively performed from the endocardium; in 2 patients with partial sub-endocardial scar extension associated also with intramural or sub-epicardial scars the endocardial EAM and ablation was only partially effective; in 2 patients with most of the scar tissues confined to the sub-epicardium according with DE-CMR imaging the EAM and ablation performed with epicardial approach identified and eliminated the epicardial origin of arrhythmia and, finally, the EAM and ablation was not effective in 5 patients with predominantly intramural scar at DE-CMR.

For MDCT on the other hand, this comparison lacks. First results in this direction were published by Maccabelli et al. [45]. In this Chapter we will face this subject. After constructing the myocardial map using the segmented structures, we compared scar location and extent from MDCT against the correspondent EAM findings. As thick fat layer may cause low voltages, in the construction of our map (making the assumption that thick fat layer is recognised as scar during EAM), we included these zones in the comparison with EAM whenever an epicardial intervention was needed.

6.2 Methods

To construct the mesh of the myocardium, containing information about the myocardial wall thickness, epicardial fat depth and myocardial scar areas (see Figure 6.1), we extracted a triangulation (surface mesh) for each segmented structure. The mesh data-structure is one of the most used techniques for rendering 3D objects. It is defined as a collection of vertices (points positioned in a virtual space), edges (connection between vertices) and faces (close set of edges). Commonly, triangular polygons are used to form the faces since this simplifies rendering. The LVendo, LVepi and epicardial fat, being segmented with a level-set formulation, are already a 3Dmesh. However, scar from hypoenhanced and hyperenhanced zones, being a binary volume, are represented as a discrete implicit surface, and we used the Marching Cubes algorithm to generate the triangulation from this discrete implicit surface. As in our case data presents a substantially high resolution, the resulting triangular mesh using Marching Cubes is a reasonable approximation [53].

6.2.1 Surface Distance Measurements

From each triangle vertex of the surface of interest, a ray was casted inwards (or outwards) until it reaches the nearest point of the second surface, using the signed distance field. The sign of the distance field stands for the position of the point with respect to the other mesh (inside, outside or on the surface). In this way we obtain a mesh with the distance information, for each point, to the nearest point in the surface under study.

- **Myocardial wall thinning** Using the distances from the LVepi to the LVendo surface, zones where the thickness was less than 5 mm were considered scar vertices (as explained in the previous Chapter).

- **Thick fat layer** For each triangle vertex of the LVepi mesh, the distance from
6.2. Methods

Figure 6.1: The myocardial map: yellow represents fat layer greater than 3 mm, red represents myocardial wall thinning (less than 5 mm) and violet represents scar from DE (right), and the correspondent epicardial EAM (left).

LVepi to the epicardial fat surface was computed (see Figure 6.2); points above 3 mm were considered myocardial scar.

Figure 6.2: LVepi (blu) and epicardial fat (yellow) surfaces. Red arrows represent nearest distance from LVepi surface to the epicardial fat surface.
Chapter 6. Myocardial Multi-Parametric Map

6.3 Experiments

6.3.1 Dataset

11 patients with recurrent VT and ICD underwent MDCT examinations with a 64-channel scanner (Philips Brilliance 64) before EAM and RF ablation (two scans as described in Section 5.3.1).

The decision of an endocardial or epicardial EAM and RF ablation approach was taken basing on the prevalent distribution of scars at CE-MDCT or during the failed endocardial procedure. In our study, a 3.5mm distal tip irrigated catheter was used for the construction of EAM. The value of 1.5 mV defined normal LVendo bipolar electrogram amplitude and a voltage < 0.5 mV defined dense scar. A value of 8 mV defined normal LV endocardial unipolar electrogram amplitude. Areas with < 5mV defined dense scar and intermediate values border zones.

9 patients have an ICD; 8 had only an endocardial and one only an epicardial intervention, and two patients had both an endocardial and epicardial intervention (and consequently an EAM).

6.3.2 Comparison between EAM and Myocardial Parametric Mesh

After the CA intervention, the created EAM mesh was exported from the commercial ablation software (CARTO system) and the correspondent surface was constructed using point by point information of the correspondent .txt file. The file has information not only about the spatial position but also unipolar, bipolar and latency values for each vertex. Using the reversed registration matrix and point coordinates, myocardial map and EAM were merged (see Figure 6.3).

In patients that underwent an epicardial intervention, points with epicardial fat thickness greater than 3 mm were added to the myocardial mesh to be considered as myocardial scar (due to the fact that fat > 3mm is seen as low voltage by the cathether [20]).

Bipolar and unipolar voltages were correlated with MDCT based scar using two different approaches. Firstly, the distance between each low voltage mapping point and MDCT defined scar was calculated (Figure 6.4 middle). Additionally, MDCT defined scar was projected over the EAM surface to study the correspondent voltage characteristics under the MDCT defined scar (Figure 6.4 right).

6.4 Results

A qualitative example of our results are shown in Figure 6.5 for the bipolar and Figure 6.6 for the unipolar voltage respectively.

In Table 6.1 are summarized the distances from the points with low voltages (from EAM) to the nearest MDCT defined scar. In these results we see that 54.1% of bipolar defined scar points had a distance less than 5mm to MDCT defined scar, and the percentage of points increases to 89.3% if we consider the distance 10 mm and to 97.7% with distance less than 20 mm.

In Figure 6.7 are shown the results of the percentage of EAM scar points (low voltages) which fall under the MDCT defined scar area. In this case, we compared each MDCT scar definition separately, as well as the union and intersection of all scar
6.4. Results

Figure 6.3: Unipolar EAM overlaid to MDCT image and correspondent color codes.

Figure 6.4: Methodologies used to compare EAM points with MDCT defined scar: distance between all EAM low voltages to the nearest MDCT defined scar point (middle) and identification of all EAM points that lie under MDCT defined scar (right).

indexes. 35.3% of bipolar points with the characteristic < 1.5mV of the EAM are within our defined scar area, and 64.72% of unipolar points < 8 mV are within our defined scar.

Within our definition of scar (the union of all scars shown in MDCT) we found a mean bipolar and unipolar voltage values of 3.65 mV and 8.74 mV respectively and intersection between more than one definition of scar of 2.29 mV and 6.02 mV for
Chapter 6. Myocardial Multi-Parametric Map

Figure 6.5: Comparison between bipolar EAM and MDCT defined scar in an endocardial and epicardial intervention.

Table 6.1: Percentage of the points defined as scar in EAM that have distance less than 5, 10 and 20 mm to MDCT defined scar.

<table>
<thead>
<tr>
<th>Voltage Type</th>
<th>Intervention</th>
<th>dist &lt; 5 mm</th>
<th>dist &lt; 10 mm</th>
<th>dist &lt; 20 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar</td>
<td>endocardial</td>
<td>55.69%</td>
<td>91.89%</td>
<td>99.49%</td>
</tr>
<tr>
<td></td>
<td>epicardial</td>
<td>52.47%</td>
<td>86.60%</td>
<td>95.87%</td>
</tr>
<tr>
<td>Unipolar</td>
<td>endocardial</td>
<td>52.34%</td>
<td>84.76%</td>
<td>98.89%</td>
</tr>
<tr>
<td></td>
<td>epicardial</td>
<td>45.22%</td>
<td>78.86%</td>
<td>90.34%</td>
</tr>
</tbody>
</table>

bipolar and unipolar voltages respectively.

Additionally, for these patients, we analyzed the percentage of myocardium analyzable due to the artifacts caused by ICD, obtaining a mean percentage of myocardium analyzability value of 90.4%.

6.5 Discussion

Today, DE-MRI has been widely studied as an effective way in detecting myocardial scar areas, in order to plan the strategy and to guide ventricular ablation procedures, which is universally recognized as the gold standard for this purpose. On the contrary, MDCT has been used for the definition of the anatomical landmark and for the identification of the epicardial fat, due to its higher spatial resolution during one breath-hold acquisition. In this work, we wanted to demonstrate that, besides the previously men-
6.5. Discussion

Figure 6.6: Comparison between unipolar EAM and MDCT defined scar in an endocardial and epicardial intervention.

Figure 6.7: Percentage of EAM scar under MDCT defined scar.

tioned advantages, MDCT is also a good predictor of scar localization.

Being bipolar voltage a local measure, it is able to detect only superficial scared areas, on the sampled points. Since our dataset have intramural and extended scars, these structures cannot be detected using bipolar voltages, and the value of 35.3% agreement found, reflected this. On the other hand, it was demonstrated in [62] that unipolar volt-
age best differentiates between the absence and presence of scar, having a larger field of view, which may allow detection of scar covered by fat and intramural scar. This fact is in good agreement with our findings, where MDCT defined scar had a quite high concordance value (64.72%) with low unipolar voltage measures. Additionally, the mean unipolar value under MDCT defined scar (6.02 mV) is well in concordance with the literature, that established 8 mV as the cut-off value.

The low agreement of bipolar findings with our results could be a reflection of the transmurality of most of these scars. In fact, looking to a patient with intramural scar (Figure 6.8), we see how unipolar voltage was able to detect the scar, which was not detectable within bipolar low voltage findings.

![Figure 6.8: Example showing an intramural scar, detected using unipolar voltages and not visible on Bipolar findings.](image)

Moreover, we found that 54.1% of the bipolar low voltage points and 48.8% of unipolar points with low voltage were within 5 mm of the MDCT defined scar. Although these values were not extremely high, we need to take in mind that the comparison is between a surface (EAM) and a 3D structure, which is the scar shown in MDCT images. The 3D scar structure may have extension of the whole myocardial wall and therefore distances may go far further than 5 mm or even 10 mm, considering that the myocardial wall thickness can go up to 12 or 13 mm. In fact, the literature has defined this range as being much larger than 5 mm [62].

Another critical point of this comparison is related to the cut off values, that are known to be patient dependent. We assumed the state of art values 1.5 mV and 8 mV for bipolar and unipolar respectively, but it could be a source of error.

Thanks to these preliminary but very satisfactory results, we are confident that this segmentation method and surface distance measurements (in order to construct the myocardial map) can be very important for the prediction of scar localization and consequently real low voltages predictor. In this way improving the EAM and ablation procedure of VT, defining the sites to be ablated reducing false low voltages and mapping time, as well as the damage of nearby healthy tissue.
CHAPTER 7

Conclusion

This thesis presented the research in MDCT image processing carried out during my PhD. The motivation of this work tries to improve further RF CA intervention procedures by integrating image-based, patient-specific information about myocardium anatomy and viability, epicardial fat, as well as coronary vessels into the mapping software system. We analyzed both technological issues connected to automatic MDCT image segmentation applicability and clinical feasibility of its integration for image guided EAM and RF ablation intervention.

We presented in Chapter 4 the segmentation of the anatomical structures of interest: ventricles, myocardium, epicardial fat and coronary tree. The segmentation is based on a new coarse to fine surface evolution approach that we proposed. This stopping function uses multi scale and directionality to proper stop propagation at the edges of interest. To our knowledge, this is the first published approach presenting decreasing scales of directional filters on a curve evolution segmentation, obtaining promising results from a low level based segmentation perspective. Using only the reduced scale allowed us to extract the pericardium boundary, to further segment epicardial fat. We compared the performance of this stopping function with the ones of the gradient magnitude edge detector (in the same initial conditions). The quantitative evaluation of the segmentation method was performed using different similarity metrics, and its superiority against results published by other state-of-art methods demonstrated. Having segmented and validated these structures, the coronaries were obtained using a threshold and excluding the previously mentioned cardiac structures. This multiscale, directional approach can be easily incorporated into other segmentation frameworks in order to be used as a stopping function. We are confident that, based on the presented results, our method could offer reliable performance in the field of cardiac segmentation.

We then addressed technological aspects connected with the problem of reliable de-
Chapter 7. Conclusion

tecting scar in the different MDCT scans (Chapter 5). The key condition here is having an accurate segmentation of the myocardium, which is the basis for the myocardium characterization. Having already such segmentations from the angiographic scan, a free-form B-spline method was chosen to deal with the local misalignments between the angiographic and DE scan, due to motions of the heart and patient positioning. Moreover, mutual information was applied as matching function to deal with the different attenuation values in MDCT and DE MDCT. The difference in the voxel intensities between acquisitions is related to the use of different energy (and consequently also different noise level) and the contrast agent. After re-alignment, we analyzed the myocardium histogram distribution of both scans, and studied different metrics to best identify scarred and/or non viable myocardium.

Beyond scar segmentation, we investigated in Chapter 5 and Chapter 6 the use of surface distance measurements to identify the precise location of wall thinning (in the case of the myocardium), as well as thick layers of fat (in the case of the pericardium). First qualitative results, consisting in the visualisation and assignment of a value based on a classification by two expert radiologists, demonstrated that it can meet the robustness and accuracy needed in the clinical environment.

As a second research line, we investigated the accuracy and feasibility of the use of a patient-specific myocardial map, containing information about the cardiac anatomy and myocardial viability integrated into the mapping software system. For this purpose, we fused this map with EAM created during the clinical procedure and compared scar definition from both modalities. The experimental results obtained with this system demonstrated that scar correspondence with unipolar voltages are good, strongly suggesting the potentiality of this myocardial map in the improvement of EAM; first of all in terms of effectiveness and secondly in terms of time of procedure and adverse events.

This work represents a step forward not only to the accomplishment of accurate patient-specific segmentation of cardiac structures, but primarily to the introduction of MDCT scar detection as a feasible and effective approach to plan EAM, aiming at improving CA RF and reducing intervention time.

7.1 Future Work

Important future developments could be speed up of the segmentation method through the use of a deformable model coupled to our stopping function, incorporating also other cardiac structures (the atria for example).

With respect to the non viable myocardium in MDCT, future work is needed to quantitatively access the accuracy of scar extraction from early and DE scans.

An interesting extension of this thesis would be to study if and how the EAM and ablation procedure success rate changes using this myocardial map for the planning and guidance.
Bibliography


Bibliography


Bibliography


[79] Liangjia Zhu, Yi Gao, Vikram Appia, Anthony Yezzi, Chesnal Arepalli, Tracy Faber, Arthur Stillman, and Allen Tannenbaum. A complete system for automatic extraction of left ventricular myocardium from ct images using shape segmentation and contour evolution.
