Analysis of cardiac magnetic resonance images: towards quantification in clinical practice
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Analysis of Cardiac Magnetic Resonance Images –
Towards Quantification in Clinical Practice

PROEFSCHRIFT

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Technische Universiteit Eindhoven, op gezag van de
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commissie aangewezen door het College voor
Promoties in het openbaar te verdedigen
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doors

Guillaume Leopold Theodorus Frederik Hautvast

geboren te Heerlen
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prof.dr.ir. M. Breeuwer

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prof.dr.ir. B.M. ter Haar Romeny

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Abstract

Analysis of Cardiac Magnetic Resonance Images - Towards Quantification in Clinical Practice

Cardiac magnetic resonance allows imaging with different protocols in various orientations to assess myocardial function, perfusion, and viability for the diagnosis of cardiac disease. Although such diagnosis is primarily based on visual assessment in clinical routine, there is a trend towards quantitative assessments to enable more reproducible, evidence-based diagnosis. Unfortunately, the image processing involved in quantitative assessment of cardiac magnetic resonance images requires more time than visual assessment, thus driving the need for automation. This thesis presents the validation results of several image processing techniques that facilitate fast and reproducible quantitative assessment of cardiac magnetic resonance images.

For the analysis of short-axis functional cardiac magnetic resonance images, a semi-automatic approach based on contour propagation using active contours is presented. This method is initialized with a deformable template to provide fully automatic segmentation of the left ventricle at all phases. The clinical performance of this approach was measured on 1555 participants of the Framing Heart Study. In combination with image registration, contour propagation is also used to propagate contours from one stress level to another in dobutamine stress magnetic resonance exams.

Quantitative assessment of short-axis perfusion cardiac magnetic resonance images relies on even more elaborate image processing. The acquired images need to be corrected for respiratory motion, after which delineation of the left ventricular contours in all dynamics enables sampling of signal intensity curves that allow for true quantification of myocardial perfusion by means of deconvolution. An automated approach that employs techniques such as maximization of joint correlation between consecutive dynamics, deformable template segmentation on a temporal maximum intensity projection and deconvolution using a exponential approximation basis is shown to be reproducible and efficient. In addition, this thesis presents a novel visualization and quantification method of transmural gradients in contrast uptake that may enable better diagnosis of several myocardial pathologies.

Finally, this thesis presents an outlook on further studies to be executed to validate new image processing methods applicable to other cardiac magnetic resonance images. This includes methods for the delineation and quantification of myocardial viability and $T_2^*$, as well as methods that enable combined analysis of long- and short-axis functional cardiac magnetic resonance images. Preliminary results indicate that these methods may allow faster and more reproducible quantitative assessment of cardiac magnetic resonance images.
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<td>ANOVA</td>
<td>analysis of variances</td>
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<tr>
<td>AAM</td>
<td>active appearance model</td>
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<td>AAMM</td>
<td>active appearance motion model</td>
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<td>ACM</td>
<td>active contour model</td>
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<td>AIF</td>
<td>arterial input function</td>
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<td>ARMA</td>
<td>auto-regressive moving average</td>
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<td>ANOVA</td>
<td>analysis of variances</td>
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<td>ASM</td>
<td>active shape model</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<td>CE</td>
<td>contrast-enhanced</td>
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<td>CMR</td>
<td>cardiac magnetic resonance</td>
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<td>CNR</td>
<td>contrast-to-noise ratio</td>
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<tr>
<td>CO</td>
<td>cardiac output</td>
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<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>DSMR</td>
<td>dobutamine stress magnetic resonance</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<td>ED</td>
<td>end diastolic</td>
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<td>EDV</td>
<td>end-diastolic volume</td>
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<td>EF</td>
<td>ejection fraction</td>
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<td>ES</td>
<td>end systolic</td>
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<td>ESV</td>
<td>end-systolic volume</td>
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<td>ICA</td>
<td>independent component analysis</td>
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<td>IR</td>
<td>inversion recovery</td>
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<td>LA</td>
<td>long axis</td>
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<thead>
<tr>
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<td>late enhancement</td>
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<td>LV</td>
<td>left ventricle/ventricular</td>
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<td>MBF</td>
<td>myocardial blood flow</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>MIP</td>
<td>maximum intensity projection</td>
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<td>mIP</td>
<td>minimum intensity projection</td>
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<td>MPRI</td>
<td>myocardial perfusion reserve index</td>
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<td>MR</td>
<td>magnetic resonance</td>
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<td>NICM</td>
<td>non-ischemic cardiomyopathy</td>
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<td>PSIR</td>
<td>phase sensitive inversion recovery</td>
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<td>RAA</td>
<td>repeated averaging algorithm</td>
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<td>RMS</td>
<td>root-mean-square</td>
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<td>ROI</td>
<td>region of interest</td>
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<td>RV</td>
<td>right ventricle/ventricular</td>
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<td>SA</td>
<td>short axis</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>SNR</td>
<td>signal-to-noise ratio</td>
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<td>SI</td>
<td>signal intensity</td>
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<td>SVD</td>
<td>singular value decomposition</td>
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<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<td>SSFP</td>
<td>steady-state free precession</td>
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<td>SV</td>
<td>stroke volume</td>
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<td>WMSI</td>
<td>wall motion score index</td>
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<td>2CH</td>
<td>two chamber</td>
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<td>3CH</td>
<td>three chamber</td>
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<td>4CH</td>
<td>four chamber</td>
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1 Introduction

1.1 Background

In the western world, between 30 and 35% of all deaths are due to cardiovascular diseases \cite{5,4,6}. About half of these deaths are caused by coronary artery disease (CAD) \cite{5,4}. Consequently, CAD by itself is the most common cause of death in both men and women. Consequently, approximately every 25 seconds, an American will suffer a coronary event, and approximately every minute, someone will die of one \cite{5}.

In the UK, CAD costs the health care system about £3.2 billion per year, which represents a cost per capita of just over £50.- \cite{4}. The cost of hospital care for patients with CAD accounts for 73% of these costs \cite{4}. In the USA, the average Medicare payment per hospital discharge linked with a principal diagnosis of cardiovascular disease was $10,201 \cite{5}.

1.2 The Human Heart

Located just beneath the breastbone, the human heart is about the size of a clenched fist and made up mostly of cardiac muscle tissue (myocardium). The human heart has four chambers. The upper chambers are called the left and right atria, and the lower chambers are called the left and right ventricles. The two atria have relatively thin walls and function as collection chambers for blood returning to the heart, pumping blood to the ventricles only. The ventricles have thicker walls, as they need to provide the force that propels the blood through the circulation system. Especially the left ventricle, which pumps blood through the peripheral circulation, has a wall that is 3-6 times thicker to deliver a 5-6 times greater workload than that of the right ventricle, which pumps blood through the pulmonary circulation.

To do so, the left ventricular muscle tissue is supplied with oxygen- and nutrient-rich blood through the coronary circulation system. The anatomy of the coronary circulation system varies considerably from person to person,

\footnote{The clinical image data presented this chapter was kindly provided by Deutsches Herzzentrum Berlin, Germany, and King’s College London, UK.}
CHAPTER 1. INTRODUCTION

but in general there are two main coronary arteries, the left and right. Both these arteries originate from the beginning of the aorta (aortic root).

In CAD, the coronary arteries are affected by atherosclerosis which causes a narrowing of the vessel. As the degree of CAD progresses, this narrowing might trigger a cascade of pathologic symptoms known as the “ischemic cascade” [3]. This cascade initiates with pathologic symptoms of the left ventricle, including the presence perfusion deficits, wall motion abnormalities, diastolic and systolic dysfunction, but may ultimately trigger more systemic symptoms including electrocardiogram (ECG) changes as well as angina, or chest pain. The right ventricle is less affected, and thus less interesting for the diagnosis of CAD.

1.3 Cardiac Magnetic Resonance

Magnetic Resonance Imaging (MRI) is a medical imaging technology capable of visualizing the internal structure and function of bodily organs. When applied to the heart using rapid imaging techniques with ECG and respiratory gating, so-called cardiac MRI, or cardiac magnetic resonance (CMR), allows for the non-invasive assessment of the function, perfusion and viability of the left ventricle. To do so, a typical CMR exam consists of 10-30 acquisitions obtained from different views, as well as using different sequences [2]. For an assessment of left ventricular function, perfusion and viability the heart is usually imaged in three standardized orthogonal views, known as the short axis (SA) view, the long axis (LA) two chamber (2CH) and the LA four chamber view four chamber (4CH). The SA view images are acquired perpendicular to the long axis of the left ventricle, which runs from the apex through the center of the mitral valve. In these images, the left ventricle appears like a more or less circular structure, next to which the right ventricle is also visible, see figure 1.1. Parallel to the long axis, both the LA 2CH and LA 4CH views cover the left ventricle from apex to the mitral valve. In addition, the LA 2CH images show the left atrium, whereas the LA 4CH images also visualize the right ventricle and right atrium, see figure 1.1.

Next to images from different views, a typical CMR exam also contains images acquired using different protocols to assess various aspects of the left ventricular myocardium. In so-called functional, or cine, CMR imaging, ECG triggering is used to acquire images from different phases (time moments) in the cardiac cycle. Together, the resulting images form movies in which the contractile function of the left ventricular myocardium is visualized, see figure 1.2. Quantification of these images can be used obtain global functional parameters such as the ejection fraction or the cardiac output, as well as local contraction measures such as wall thickening and wall motion.

For the assessment of myocardial perfusion a different protocol is used in
1.3. CARDIAC MAGNETIC RESONANCE

Figure 1.1: Schematic images of the short axis view, the LA 2CH view and the LA 4CH view.
CHAPTER 1. INTRODUCTION

Figure 1.2: Functional CMR images in SA view (a), LA 2CH view (b) and LA 4CH view (c).

Figure 1.3: Examples of perfusion CMR images showing the contrast agent transit.

which imaging is performed during the first passage of a gadolinium contrast bolus through the myocardium, see figure 1.3. ECG triggering is again used, but now to acquire images of the same cardiac phase throughout the contrast bolus passage. As such, these sequences do not reveal the contractile function of the heart but may contain some respiratory motion. Quantification of these images traditionally involved semi-quantitative characterization of the contrast uptake curves based on the maximum upslopes, but more recently deconvolution analysis was introduced to obtain true-quantitative flow values in ml min\(^{-1}\) g\(^{-1}\) [24].

To assess myocardial viability, T1 weighted CMR imaging is performed between 10 and 20 minutes after the administration of gadolinium. During this period, the contrast agent has been cleared from the viable myocardium, but is still present in scar tissue, which therefore appears hyper-enhanced in these images. Due to this delayed contrast mechanism, these images are also known as late enhancement, late gadolinium enhancement, or delayed enhancement images. Quantitative analysis of these images allows measurements of scar volumes and mass. See figure 1.4 for example images.
1.4 Motivation of this thesis

In clinical practice, the analysis and reporting of CMR images is performed mainly based on visual assessment [1]. Despite the promise of more reproducible and objective evidence based decision criteria to be obtained from quantitative analyses, full quantitative analyses of CMR exams are not yet performed in clinical practice as they are simply too time consuming. Hence, the primary motivation for this work was to develop faster, highly automated analysis techniques to enable the use of quantification in clinical practice. In this work, the focus lies on developing and validating registration, segmentation, and quantification methods specifically for various types of CMR images. However, several ideas were inspired by applications in other fields of medical imaging, and may therefore also be extendable to other medical imaging applications.

1.5 Structure of this thesis

This thesis is a collection of contributions that have been, or will be, published in international scientific journals, conference proceedings or patent applications. Although the independent contributions have been adapted for the purpose of this thesis, differences in writing and formatting styles may occur. This thesis is organized in three parts. The first and second part describe new methods for the quantitative analysis of functional and perfusion CMR images, which are the main contributions of this thesis. The third part describes future work on the analysis of other CMR images in sections that contain preliminary results collected from several conference contributions.

In part I, quantitative analysis for functional CMR images is discussed. Chapter 2 provides an overview of the state of the art. In the past 10-15 years, numerous papers have been published that address automatic delin-
CHAPTER 1. INTRODUCTION

eation of SA functional CMR images, which has been the most eminent image processing problem in CMR analysis. Consequently, this survey mainly reviews the numerous solutions that have been proposed to reduce the burden of manual delineation of the heart in all phases and all slices of SA functional CMR images.

In chapter 3 we present a semi-automatic approach towards delineation of SA functional CMR images, by enabling a propagation of manually defined end diastolic myocardial contours to the remaining phases in the cardiac cycle. This approach based on active contours has been published in IEEE Transactions on Medical Imaging [7], and is partially protected by patent WO 2007/036887 A1 [20].

In chapter 4, we present the results of a large scale clinical evaluation on 1555 cases in which our automatic contouring methods have been used, including fully automated delineation of the left ventricle at end diastole, propagation of the myocardial contours as presented in chapter 3, and so-called dual propagation for efficiently correcting contour positioning errors. This work is published in Magnetic Resonance in Medicine [9].

Chapter 5 presents another semi-automatic approach towards delineation of SA functional CMR images, specifically in the context of dobutamine stress magnetic resonance (DSMR) exams. The approach of chapter 2 was extended to enable propagation from one stress level to another by incorporating an affine registration method and a novel contour averaging scheme. This work is submitted for publication in the International Journal of Cardiovascular Imaging [11]. In addition, this approach is protected by patent WO2008/135882 A2 [21].

Part II addresses quantitative analysis techniques used for perfusion CMR images, starting in chapter 6 with a review of the techniques that have been published. As quantitative analysis of perfusion CMR images requires respiratory motion correction, myocardial contour detection and dedicated quantification algorithms, this review covers a wide range of techniques including image registration and segmentation, as well as various deconvolution methods.

Chapter 7 presents our approach towards automated perfusion CMR analysis, which includes automatic region of interest detection, automatic respiratory motion correction, and automatic myocardial contour detection followed by both semi- and true-quantitative quantification methods. This work has been submitted for publication in IEEE Transactions on Biomedical Engineering [10].

In chapter 8 we present a novel approach towards visualization and characterization of transmural gradients in myocardial perfusion. This approach is based on analysis of a so-called "gradientogram", which visualizes the evolution of transmural gradients in myocardial contrast uptake over time. A methodology paper on this approach has been published in Magnetic Resonance in Medicine [8]. Moreover patents on the gradientogram analysis [22]
and volumetric perfusogram visualizations [23] have been filed.

Finally, part III discusses quantitative analysis techniques for other CMR image types. This part contains a single chapter with three sections, each containing materials collected from one or more conference contributions that present preliminary results obtained using newly developed image processing methods.

Section 9.2 presents ongoing research towards automated analysis of viability CMR images, which includes the use of the myocardial contours as defined on SA functional CMR images as prior information to delineate SA viability CMR images, as well as an automated scar classification approach. Initial results obtained using these methods have been published independently in [12, 18, 19, 13, 16, 17].

In section 9.3 we discuss automated quantification of $T_2^*$ from multi-echo CMR images, together with preliminary results presented in [14].

Finally, section 9.4 discusses simultaneous analysis of functional CMR images from different views. This topic is particularly important because of the significant impact of slice selection errors on volume quantification by SA functional CMR. The results presented in this chapter are collected from various conference contributions [15].

1.6 References


CHAPTER 1. INTRODUCTION


1.6. REFERENCES


Part I

Analysis of Functional CMR Images
2.1 Introduction

Visual assessment of global and regional ventricular function with cardiac magnetic resonance (CMR) is well established and used routinely in clinical practice [1]. Cine CMR images consisting of multiple slices and phases are routinely obtained in standardized cardiac orientations, or views, known as the long axis (LA) two chamber (2CH) view, the LA four chamber (4CH) view and the short axis (SA) view, see figure 2.1 for examples. The images are acquired using steady-state free precession (SSFP) protocols, of which the basic physical principles and potential image artefacts are well understood [33]. Moreover, $k$-$t$ accelerated protocols can be used to further increase temporal or spatial resolution [27].

![Figure 2.1: Functional CMR images in SA view (a), LA 2CH view (b) and LA 4CH view (c).](image)

Quantitative analysis of functional CMR images consists of calculation of global ventricular functional parameters, such as stroke volume (SV), ejection fraction (EF) and cardiac output (CO). Furthermore, regional and local parameters such as wall thickening and wall motion can be determined. Quantification of these parameters requires a delineation of the left ventricle (LV) endocardial and epicardial contours.

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The clinical image data presented in this chapter was kindly provided by Deutsches Herzzentrum Berlin, Germany.
This chapter provides a literature survey of image processing methods that can be applied to achieve fast and reproducible quantification of left ventricular function. While such quantification can be performed from LA views, this survey will focus on methods that are applicable to SA images. Moreover, this survey does not provide an exhaustive list of automatic delineation methods for SA functional CMR images, but is intended to explain the problem and highlight some popular solutions. A more exhaustive list of automatic delineation methods for SA functional CMR images is given in [58].

2.2 Delineation

Quantification of global and regional ventricular functional parameters requires a delineation of the LV contours, see figure 2.2 for an example. A typical SA functional CMR image contains 160-750 images (8-15 slices, 20-50 phases), about 80% of which cover the left ventricle, requiring a delineation in support of quantification. Thus, the total number of contours in a complete LV delineation is 250-1200 (LV endocardium and epicardium together).

Automatic delineation of the LV contours in SA cine CMR images has proven to be a challenging problem, which has been addressed in numerous publications over the past 15 years.

Challenges

The main challenges in the LV segmentation problem are a lack of local image features across the boundaries of interest and respiratory induced slice misalignment, variability of appearance from base to apex, as well as between patients, and variability of appearance and quality between scanners.

The lack of local image features across the boundaries of interest occurs near several anatomical structures. This includes the transition between the myocardial wall and the papillary muscles. The papillary muscles should be segmented as part of the blood pool to enable quantification of LV wall thickness. As both structures consist of myocardial muscle tissue there are no local image features present to guide image driven segmentation methods. In similar fashion, but less challenging, the LV epicardium contour has to cross the right ventricle (RV) inflection points. More challenging is the
2.2. DELINEATION

lack of contrast between the myocardium and the lungs in subjects without pericardial fat.

Respiratory induced slice misalignment originates from the fact that SA functional CMR images are acquired slice-by-slice in different breathholds. This approach may introduce substantial movement from slice to slice, prohibiting the use of strong 3D constraints.

Furthermore, the appearance of the LV and surrounding structures is very distinct from apex to base. At the apical level, the lungs and RV are usually not visible. These structures do surround the LV in mid-ventricular slices, but change considerably in shape when approaching the base. In the basal slices, a complex combination of through plane motion and structural challenges of the LV outflow tract and mitral valve hamper the delineation.

Finally, the vast amount of parameters and protocols that can be used to acquire functional CMR images introduce considerable variability in image quality, as well as image appearance. As a result, absolute grey levels cannot be integrated in the delineation methods.

Solutions

In reply to the above challenges, numerous methods for automatic delineation of SA functional CMR images have been developed. Solutions have been formulated based on several image processing algorithms, see table 2.1 for an overview.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Methods Papers</th>
<th>Application Papers</th>
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<tr>
<td>Basic morphology</td>
<td>[40]</td>
<td></td>
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<tr>
<td>Graph cuts</td>
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Table 2.1: Application of major image processing methods to SA functional CMR images.

As most of the early approaches failed to position the LV contours correctly, in particular with respect to the papillary muscles, solutions including manual initialization on the end diastolic (ED) phase were proposed. This reduced the complexity of the contour detection problem as the given myocardial contours can be used as a prior for delineation of the remainder of phases. In such contour propagation methods, the myocardial contours are repositioned in each phase in order to maintain a similar position with respect to neighbouring, moving anatomy of the heart. This can be achieved
by maximizing the similarity between the grey values in the contour neighbourhood in successive phases, which can be implemented based on active contours [5, 55, 19, 23], level sets [29, 12, 28], or registration methods [15].

For optimal performance in terms of contour positioning accuracy in SA functional CMR images, the basic image processing methods listed in Table 2.1 have been combined and adapted in various ways. Initially, solutions using better suited feature images were proposed. Most notably in this context were the introductions of gradient vector flow [44] and fuzzy connectivity [45]. While the use of gradient vector flow proved to be counterproductive as it drives LV endocardium contours into the papillary muscles [44, 52], fuzzy connectivity with respect to a seed in the LV blood pool was used in several papers dealing with delineation of SA functional CMR images [34, 9, 2, 36, 24]. To combine the advantages of the various approaches, so-called hybrid approaches have been developed [26, 6]. Furthermore, to obtain temporally consistent delineations, the basic image processing methods have been extended to the time dimension, including the formulation spatio-temporal statistic models of shape [21] and appearance [11]. Finally, further improvement was sought in combining image information from SA and LA views [30, 16, 39].

The aforementioned technologies all require an initialization of the LV contours that is reasonably close to their final position. Therefore, systems that apply these technologies start by locating a region of interest (ROI) that contains both ventricles and (ideally) no other structures. As the contracting motion of the heart is the only movement present in the images, the ventricles can be localized using the grey-value variation over time. This was implemented by computing an image depicting the variance [8, 37], the standard deviation [40] or the first harmonic [31, 17] over time. Further localization of the LV center is often performed based on the approximately circular shape of the LV [31, 37]. The LV center can also be located using the intersection of the SA images with the LA 2CH and 4CH images [36]. The latter approach is simple and almost flawless, but may fail in particular in apical slices when patients have difficulties in taking consistent breathhold positions.

Despite the extensive and ongoing research efforts in this field, there is still no solution capable of positioning all myocardial contours such that no manual corrections are necessary. As such, the problem of LV delineation in SA functional CMR images is still open. Nevertheless, commercially available software packages for the analysis of LV function from SA cine CMR images do provide automated methods for LV delineation [19, 55, 56, 17, 24, 21, 4], which do require manual corrections, but also greatly reduce the processing time [59].
2.3 Quantification

After delineating the functional CMR images, several global, regional and local parameters of myocardial function can be calculated. The global parameters include results derived from measurements of the left ventricular volume, whereas the regional and local parameters quantify the contracting motion.

Ventricular volumes can be computed from SA functional CMR images by summing the areas of the endocardial contours on each slice using Simpson’s Rule. This approach is considered to be the golden standard for ventricular volume measurements. Nevertheless, this method suffers from considerable inter-observer variations due to differences in the selection of the basal slice [60, 61]. Therefore, quantification of LV volumes may also be performed based on radial LA views [38] have been proposed to eliminate difficulties related to the valve plane definition on the volume measurements. Contrary to the acquisition of single plane LA 2CH and 4CH views, acquiring such radial LA images has not yet been accepted in clinical routine. Commercially available analysis packages are therefore usually limited to provide LV volume quantification based on single or bi-planar area-length computations [62, 63], which can be applied to CMR functional images [7].

By measuring the LV volume in all acquired phases a volume-time curve is obtained. Given this curve, see example in figure 2.3, several systolic and diastolic parameters can be obtained. The systolic parameters include the end-diastolic volume, the end-systolic volume, the stroke volume, the ejection fraction and the cardiac output. The diastolic parameters include early and late peak filling rates. These diastolic parameters are early indicators for heart failure [66].

Additionally, SA functional CMR enable quantification of regional and local parameters to assess local myocardial contractile function. Given the myocardial contours in all phases, time series of local wall thickness and wall motion, i.e. the displacement of the endocardium, can be obtained. Similar to volume-time curves, such time-series can be processed to obtain various parameters, including e.g. wall thickening and end systolic (ES) wall motion can be obtained. These parameters are usually presented to the clinical user in bulls eye plots 2.4. By averaging such localized measurements within myocardial segments, regional parameters may also be derived and displayed in bulls eye plots 2.4b.

2.4 Validation

The introduction of automated image processing procedures for use in clinical routine requires an extensive validation effort to verify whether automatically provided solutions are accurate and help executing clinical tasks.
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Figure 2.3: An example of an LV volume curve and a brief explanation of key functional parameters.

<table>
<thead>
<tr>
<th>Systolic Functional Parameters</th>
<th>Diastolic Functional Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-diastolic volume (EDV)</strong></td>
<td><strong>Early peak filling rate</strong></td>
</tr>
<tr>
<td>$V(t_{ED})$</td>
<td>$\frac{dV}{dt}(t_{PF1})$</td>
</tr>
<tr>
<td><strong>End-systolic volume (ESV)</strong></td>
<td><strong>Atrial peak filling rate</strong></td>
</tr>
<tr>
<td>$V(t_{ES})$</td>
<td>$\frac{dV}{dt}(t_{PF2})$</td>
</tr>
<tr>
<td><strong>Stroke volume (SV)</strong></td>
<td><strong>Early filling volume</strong></td>
</tr>
<tr>
<td>$V(t_{ED}) - V(t_{ES})$</td>
<td>$V(t_{ED}) - V(t_{AF})$</td>
</tr>
<tr>
<td><strong>Ejection fraction (EF)</strong></td>
<td><strong>Atrial filling volume</strong></td>
</tr>
<tr>
<td>$\frac{V(t_{ED}) - V(t_{ES})}{V(t_{ED})}$</td>
<td>$V(t_{AF}) - V(t_{ES})$</td>
</tr>
<tr>
<td><strong>Peak ejection rate</strong></td>
<td></td>
</tr>
<tr>
<td>$\frac{dV}{dt}(t_{PE})$</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.3: An example of an LV volume curve and a brief explanation of key functional parameters.
2.4. VALIDATION

Figure 2.4: Examples of bulls eye plots showing local LV wall thickening (a) and LV ES wall motion (b).

in less time. As a result, the large number of automatic methods for the delineation of SA cine CMR images has been evaluated in an equally large number of validation experiments.

Unfortunately, the results of these validation experiments are difficult to compare because of differences in the validation methodology. This includes differences in the performance metrics that are used, as well as differences in patient populations, in acquisition protocols, in reference contouring.

Nearly all studies include measurements of positioning errors with respect to a golden standard of manually defined reference contours to assess the accuracy of automatically determined contours. To quantify such positioning errors, one needs to establish corresponding points at both contours (or surfaces) along which the distances can be measured. Distances may be calculated between pairs of closest points (a so-called closest-point correspondence). Another approach is to perform a radial resampling if both contours about a common centroid, such that distances can be measured along the spokes radiating from the centroid. As can be seen in figure 2.5, these methods may over- or under-estimate distance in certain situations. Therefore, a centerline correspondence, in which distances are measured between pairs of points perpendicular to a centerline (or surface), is the preferred approach of quantification of positioning errors.

After establishing a suitable point-to-point correspondence it is possible to measure distances at many locations along a contour. For reporting, these measurements are summarized per contour, or alternatively per case. Usually, this is done using the mean distance, the root-mean-square (RMS) distance or the maximum distance. Then, averages and standard deviations for these results are computed to characterize the accuracy of the method.
Figure 2.5: Different point-to-point correspondences between discrete contours. Discrete closest-point correspondence (a) and radial correspondence (b) overestimate local distances where a centerline correspondence (c) is more accurate at estimating the local distance.
on a particular population.

Alternatively, some authors quantify delineation accuracy using overlap measures such as the dice metric [64], as has been used in the MICCAI 2009 CMR LV segmentation challenge. Unfortunately, the outcome of such measures correlates with the size of the objects to be segmented, thus compromising comparisons between subjects.

Next to these differences in assessing delineation accuracies, there are various differences in the experimental setup that further hamper comparison between the methods. This includes differences in size and nature of patient populations. Differences in acquisition protocols, which may affect the outcome LV volume quantification [65]. Differences in golden standard generation include different schools of myocardium contouring, as well as the use of single or multiple export to delineate images. Finally, the study design with a separation between training and evaluation data, or using a leave-on-out approach.

To enable direct comparison between various methods, benchmarking studies, such as [57] and the MICCAI 2009 CMR LV segmentation challenge, can be conducted. Such benchmarking studies enable direct comparisons because all methods are evaluated using the same approach on the same clinical image data. Unfortunately, up till now, such studies have been conducted in a single center fashion, using a single scanner and a single expert as golden standard. As such, the results of those benchmarking studies may not translate well to clinical routine.

2.5 References


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3

Automatic Contour Propagation in Cine Cardiac Magnetic Resonance Images

3.1 Introduction

Modern cardiac MRI examinations consist of several image acquisitions, using various MRI pulse sequences and imaging planes. For an assessment of ventricular function and morphology, cine MR acquisitions of the heart are made in three orthogonal views of the heart. In the cine protocol, ECG triggering is used to acquire images at several phases in the heart cycle, resulting in series of up to 50 phases. Perpendicular to the long axis of the heart, a stack of 3-14 short axis (SA) images is acquired for each phase. Additionally, often two orthogonal images per phase are obtained for the long axis (LA) two chamber (2CH) view and LA four chamber (4CH) view. These images are used to determine several physiological parameters for assessment of ventricular function and morphology. Quantification of relevant physiological parameters, such as wall motion, wall thickness, wall thickening and ventricular volume, requires delineation of the left ventricular (LV) endocardium and epicardium contours. Other structures of interest are the right ventricular (RV) endocardium contour in SA images and the valve plane in LA images. The RV myocardium is usually too thin to allow delineation of the RV epicardium contour.

Delineation of all images may involve up to 2400 contours per patient. Because complete manual delineation is prohibitively time consuming in clinical practice, computer assistance is essential. Many fully automatic methods fail to produce accurate myocardial contours, specifically near the papillary muscles and trabeculae. Although no local image feature can be used to distinguish the papillary muscles and trabeculae from the myocardium, these are required to be surrounded by the myocardial contour.

This chapter has been adapted from: G.L.T.F. Hautvast, S. Lobregt, M. Breeuwer, and F.A. Gerritsen, Automatic contour propagation in cine cardiac magnetic resonance images, IEEE Transactions on Medical Imaging, vol. 25, no. 11, pp. 1472-1482, 2006.

Author contributions: GH developed the method, designed and conducted experiments, and wrote the paper; SL conceived the contour model; SL, MB and FG supervised the project.
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to allow for accurate measurement of wall thickness, wall thickening and wall motion. Incorrect contours “leak” into the papillary muscles, requiring elaborate user interaction before such measurements can be performed. Our goal is to reduce the total user interaction time by developing an algorithm for the propagation of cardiac contours based on active contours [20, 10]. The user interaction is reduced to drawing an initial end diastolic (ED) myocardium delineation, which is thereafter automatically propagated through the data set. The resulting contours should reflect the preferences of the user by maintaining a constant position with respect to neighboring anatomical structures. For example, if a user decides to include the papillary muscles at ED, the contours are propagated such that the papillary muscles maintain included throughout the complete heart cycle.

3.2 Background

After their introduction in 1988, active contours or snakes [20, 10] quickly became a popular segmentation method in (medical) imaging science. The active contour deforms its shape to balance internal and external forces. The internal part causes the contour to become smooth, whereas the external part leads the contour towards the object to be segmented in the image. Over the years, many variations and extensions of the original algorithm emerged. In [17], a comprehensive survey of these approaches and their medical application is given. We present an adapted version of the popular active contour model published in [19]. The adapted version is specifically designed for contour propagation.

The potential use of active contours for contour propagation or motion tracking was demonstrated by [20, 10]. In [25], several early solutions for tracking using active models are shown, including [26], which uses an active contour to track the mitral valves in ultrasound images. Other early works on the usage of active contours for motion tracking include [29]. However, in these early works local image features, e.g. the gradient magnitude, were used to define the external energy and tracking only involved initialization of the active contour model using the segmentation result of the previous frame. Such approaches fail to provide correct contours if a user intends to segment a contour that does not coincide with local image features. Propagation of such contours based on local image features, discards deliberate user input and drives the contour towards incorrect locations, related to local image features. In the case of cine cardiac MR sequences, this effect may cause the endocardial contour to “leak” into the papillary muscles and trabeculae, despite user defined initializations that surround the papillary muscles and trabeculae.

In order to try to preserve the preferences of the user and to overcome the lack of local image features along the contour, gray value matching of the
3.2. BACKGROUND

contour environment was proposed to drive a contour to the best matching position in the target frame. In 1995, [4] proposed an initial repositioning of the contour vertices by selecting the best matching position along gray value profiles in consecutive images, which was followed by smoothing and repositioning using active contours. Later works extended this idea by defining a complete energy distribution based on gray value matching. In [2] and [8], such an external energy distribution is computed using gray value differences from profiles, radiating from a centroid. Furthermore, [2] [8] introduced an elastic coupling between the LV endocardium and epicardium contours to prevent the LV endocardium contour from leaking into the papillary muscles.

The gray value matching approach has been embedded in a dynamic programming framework and applied to SA cine MR images in [5]. Within such a dynamic programming framework, [12] defined an external energy by combining motion estimation and correlation coefficients for tracking in non-medical images. In [28], motion estimation based on optic flow was incorporated for an active contour model used on cardiac ultrasound. Both [12] and [28] use block matching instead of profile matching for the estimation of motion. Furthermore, [30, 31, 32] designed an active contour model, capable of radical topology changes such as merging and splitting of contours over time, common to many non-medical applications.

Level sets have been introduced by [18] and [18] as an alternative for active contour models, in which implicit contours deform according to curve evolution theory [16]. Over the years, both fields remained closely related. Consequently, motion tracking or contour propagation tasks have also been solved using level sets. Generic approaches have been proposed in [14], [13] and [22] and are applied to SA cardiac MR in [15] and [14].

Our new method also competes with fully automatic methods for cardiac MR segmentation. Many published approaches are based on Active Shape Models [23] or Active Appearance Models [11]. Both methods exploit prior statistical knowledge gained by Procrustes Analysis and Principal Component Analysis. A review of the usage of Active Shape Models in cardiac imaging is given in [9]. Numerous publications by the authors of [3] and [1] report on 3D and 4D extensions of Active Appearance Models for cardiac MR segmentation. Active Shape Models and Active Appearance models were combined in a hybrid approach by [6]. Furthermore, [7] proposed an interesting combined segmentation approach for the orthogonal views in cardiac MR using a multiview Active Appearance Model. However, in general these statistical models cannot deal with the large patient variation present in a clinical context. In semi-automatic approaches, the user deals with this patient variation by providing expert knowledge about the desired segmentation. Incorporating a statistical model in a semi-automatic approach is not beneficial, since such an approach would discard that expert knowledge in favor of the statistical model. In [33], efforts have been made to solve this issue by magnifying the influence of the manual delineation on the statis-
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tical model. This approach has shown to be beneficial for echocardiography images, but has not yet been applied to cine cardiac MR images.

3.3 Theory

The new active contour model for contour propagation is based on the discrete dynamic contour model, originally described in [19]. This publication explained the basic structure for an active contour model and introduced an internal force definition based on the local contour curvature. Furthermore, a mechanism for contour resampling was described. The new active contour model follows the approach of a curvature dependent internal force. However, for the definition of the external force we use a contour environment in terms of perpendicular profiles, which is kept constant by using an energy distribution based on profile matching, similar to [4, 2, 8]. The required structural changes also allow image processing and deformation to be performed in a local coordinate system, which provides computational efficiency.

3.3.1 Structure

The basic structure of the active contour model is a set of connected vertices. In a Cartesian coordinate system, the position of each vertex $V_i$ is represented by a vector $p_i$. Furthermore, in each vertex a set of vectors related to the local topology is defined. The connecting straight line segments are represented by a vector $d_i$, which is calculated using (3.1). Local tangential and radial directions, represented by the unit vectors $\hat{t}_i$ and $\hat{r}_i$, are calculated according to (3.2) and (3.3) (see figure 3.1). These directions define a local coordinate system in each vertex.

$$d_i = p_{i+1} - p_i \quad (3.1)$$

$$\hat{t}_i = \frac{\hat{d}_i + \hat{d}_{i-1}}{\|\hat{d}_i + \hat{d}_{i-1}\|} \quad (3.2)$$

$$\hat{r}_i = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} \hat{t}_i \quad (3.3)$$

The original active contour model [19] used the local $\hat{r}$-$\hat{t}$ coordinate system only to limit the movement of the vertices in the direction perpendicular to the contour. In the newly developed active contour model, the local coordinate system is used more intensively. The contour environment is defined and filtered in the local coordinate system. Furthermore, the Newtonian deformation process is calculated in the local coordinate system. Consequently, all vertex properties related to this process, i.e. internal force $f_{in,i}$,
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Figure 3.1: Computation of the local \( \hat{r} \)-\( \hat{t} \) coordinate system.

Figure 3.2: Computation of the curvature.

The internal force of the active contour model is related to the local contour curvature. To be able to define an internal force depending on the local contour curvature, we need a proper definition of the local contour curvature at the vertex positions. Although the contour curvature at these locations is not defined due to a first-order discontinuity, [19] gives a satisfactory solution to this problem. The local contour curvature in each vertex is represented by a vector \( \mathbf{c}_i \). This vector is calculated using the unit vectors \( \hat{\mathbf{d}}_i \), (see figure 3.2, equation (3.4)). Note that \( \mathbf{c}_i \) points either in the same direction as \( \hat{\mathbf{r}}_i \) or in the opposite direction of \( \hat{\mathbf{r}}_i \).

\[ \mathbf{c}_i = \hat{\mathbf{d}}_i - \hat{\mathbf{d}}_{i-1} \quad (3.4) \]

The internal force can now be calculated using (3.5) and (3.6). This definition for the internal force \( f_{in,i} \) is a discrete, signed scalar function suitable for the calculation of the deformation process in the local \( \hat{r} \)-\( \hat{t} \) coordinate system. The convolution with the discrete filter \( k_i \) prevents the contour from...
imploding into a single point. For the complete reasoning behind the introduction of this filter, together with a thorough analysis of the behavior of an active contour model using an internal force defined by the inner product $c_i \cdot \hat{r}_i$ alone, we refer to [19].

$$k_i = (0 \ldots 0 -\frac{1}{2} 1 -\frac{1}{2} 0 \ldots 0)$$ (3.5)

$$f_{in,i} = (c_i \cdot \hat{r}_i) \otimes k_i$$ (3.6)

### 3.3.3 External Force

Our new active contour model exploits the assumption that the initial, manual contour is positioned correctly with respect to neighboring structures by the expert user. This relation between contour and neighboring structures should be maintained during propagation. Therefore, the new active contour model is designed to maintain a constant contour environment in terms of perpendicular gray-value profiles. This is achieved by a profile matching scheme, which consists of four steps. First perpendicular profiles are sampled. The profiles are filtered, after which they are matched to compute an external energy distribution. Finally, the external force is derived from the external energy distribution.

**Sampling contour environments**

For a contour propagation from a reference image $I^0$ to a target image $I^1$, the profiles $P^0_i$ and $P^1_i$ are sampled from the images $I^0$ and $I^1$ at $n_p$ regularly spaced intervals of length $d s_p$ along the $\hat{r}_i$ direction using a bilinear interpolation scheme (see figure 3.3 and equations 3.7 and 3.8, where $n = \lfloor \frac{n_p}{2} \rfloor$).

Together, all profiles $P^0_i$ form a profile image $P^0$, representing the contour environment in the local $\hat{r}$-$\hat{t}$ coordinate system. We compute independent perpendicular profiles for each contour, instead of radial profiles from a centroid for both (coupled) LV contours together, as proposed by [2, 8].

$$P^0_i(j) = \begin{cases} I^0(p_i + j \cdot d s_p \cdot \hat{r}_i) & \in -n \leq j \leq n \\ 0 & \notin -n \leq j \leq n \end{cases}$$ (3.7)

$$P^1_i(j) = \begin{cases} I^1(p_i + j \cdot d s_p \cdot \hat{r}_i) & \in -n \leq j \leq n \\ 0 & \notin -n \leq j \leq n \end{cases}$$ (3.8)

**Filtering contour environments**

To reduce the influence of noise, we apply filtering before matching the profiles from consecutive images. We have found a satisfactory, computational efficient solution by filtering the profile images using 1D convolutions with
an appropriate Gaussian kernel of width $\sigma$ in the $\hat{t}_i$ direction, as proposed in [21]. Such a filter diffuses gray values along the object boundary to remove noise while preserving features across the boundary. This relates to the geometry driven diffusion filter described in [27], in which a diffusion flow is directed along the image edge feature.

**Matching contour environment**

For a contour propagation from image $I^0$ to image $I^1$, an external energy distribution $E_i$ for each vertex $V_i$ is calculated by matching the profile $P^0_i$ from image $I^0$ with the profile $P^1_i$, at the same positions as $P^0_i$, but in $I^1$. This is done using equations 3.9, 3.10 and 3.11, where $n = \left\lfloor \frac{n_p}{2} \right\rfloor$ again.

$$w(j) = \begin{cases} \frac{n_p}{n_p - 2|j|} & \text{if } j \in [-n,n] \\ 0 & \text{if } j \notin [-n,n] \end{cases}$$ (3.9)

$$d_i(j,k) = \begin{cases} |P^0_i(j) - P^1_i(k)| & \text{if } j \in [-n,n] \\ 0 & \text{if } j \notin [-n,n] \end{cases}$$ (3.10)

$$E_i(j) = \begin{cases} w(j) \sum_{k=-n}^{n} d(k, j + k) & \text{if } j \in [-n,n] \\ 0 & \text{if } j \notin [-n,n] \end{cases}$$ (3.11)

This external energy distribution is best described by the name normalized cumulative absolute gray value differences. The term $w(j)$ defined in equation 3.9 normalizes the sum of the absolute gray value differences for the number of pixels involved. This normalization allows computation of the external energy distribution from profiles at identical positions in $I^0$ and $I^1$, i.e. the length of the actually match portion of the profile varies. Other propagation methods did not include such a normalization. Without this normalization, profiles samples from the target image should be longer, such
that the quantification of the match always involves the entire length of the reference profile as described in [4]. The actual match in the approach of [4] is computed using a combination of correlation coefficients and normalized root mean square errors, which is computationally less efficient compared with our method. Furthermore, this distribution was only used to initialize the active contour in the next frame by selecting the best matching position, whereas the result of our matching scheme will serve as external energy distribution throughout the deformation process of the active contour model.

Sampling the external force

Finally, the external force $f_{ex,i}$ is calculated by sampling the derivative of $E_i(j)$ in the $\hat{r}_i$ direction using a linear interpolation scheme, according to (3.12). Consequently, the external force attempts to drive each vertex into local minima of the external energy distribution. For the model as a whole, this means that it will end up following a path of low energy through the external energy distribution.

$$f_{ex,i} = \frac{-\partial E_i}{\partial \hat{r}_i}(p_i)$$  \hspace{1cm} (3.12)

3.3.4 Deformation

The deformation process is implemented as a Newtonian process in which the vertices $V_i$ accelerate according to the total force $f_{total,i}$ acting on a vertex. The total force acting on a vertex is calculated using a weighted sum of the internal force $f_{in,i}$ and the external force $f_{ex,i}$ according to 3.13, in which $\alpha$ determines the weighting of the forces $f_{in,i}$ and $f_{ex,i}$.

$$f_{total,i} = \alpha f_{in,i} + (1 - \alpha)f_{ex,i}$$  \hspace{1cm} (3.13)

During deformation, the complete state of the contour is calculated at discrete positions in time $t$, which is given by the position $p_i(t)$, velocity $v_i(t)$ and acceleration $a_i(t)$. The complete deformation process is calculated in the $\hat{r}$-$\hat{t}$ coordinate system using the incremental difference scheme defined by equations (3.14) - (3.16) in which $\beta$ is the damping ratio and $\Delta t$ is the discrete time increment.

$$a_i(t + \Delta t) = \frac{1}{m_i} f_{total,i}(t + \Delta t)$$  \hspace{1cm} (3.14)

$$v_i(t + \Delta t) = \beta(v_i(t) + a_i(t + \Delta t))$$  \hspace{1cm} (3.15)

$$p_i(t + \Delta t) = p_i(t) + v_i(t + \Delta t)$$  \hspace{1cm} (3.16)
3.4. OPTIMIZATION

Each iteration is ended by using (3.17) to calculate the new $p_i(t)$, which is required for the calculation of the internal force in the next iteration. The entire deformation process can be stopped, either by detecting convergence or by exceeding a fixed, maximum number of iterations.

$$p_i(t + \Delta t) = p_i(t) + ds_p \cdot v_i(t + \Delta t) \cdot \hat{r}_i$$  \hspace{1cm} (3.17)

3.4 Optimization

The accuracy of the contours resulting from our propagation algorithm is influenced by several parameters. Finding an optimal, most accurate, parameter setting is a delicate task (common to many active contour algorithms). Often, the parameters interact in a complex manner, which is difficult to express in terms of parameter settings. Additionally, the parameter optimization is a returning task, since the optimal parameter setting is application dependent. Therefore, a methodical approach towards parameter optimization is preferred to empirical experiments.

Fortunately, the optimization of a certain response, i.e. contour accuracy, with respect to several factors, i.e. algorithm parameters, is present in many domains of engineering. The required methodology is studied extensively in the field of experimental design. As a result, the related complex, multidimensional analysis techniques are well established and implemented in numerous commercial software products, providing essential numerical tools for experimenters. In the remainder of this section, we will explain how we have used the methodology of experimental design to optimize our method by describing the response to be optimized, the relevant factors, the experimental design and the analysis of the results.

3.4.1 Response

The response to be optimized in our optimization experiment is the accuracy of the resulting contours. Contour accuracy can be expressed by contour positioning errors with respect to a golden standard, i.e. the intended contour location. Such contour positioning errors are commonly defined by distance measures between two contours, such as the mean absolute distance $\varepsilon_{\text{mean}}$, the RMS distance $\varepsilon_{\text{rms}}$ or the maximum absolute distance $\varepsilon_{\text{max}}$. Given two contours A and B, these positioning errors are defined by (3.18)-(3.20).

$$\varepsilon_{\text{mean}} = \frac{1}{N} \sum_{i=0}^{N} |p_i^B - p_i^A|$$  \hspace{1cm} (3.18)

$$\varepsilon_{\text{rms}} = \sqrt{\frac{1}{N} \sum_{i=0}^{N} |p_i^B - p_i^A|^2}$$  \hspace{1cm} (3.19)
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\[ \varepsilon_{\text{max}} = \max_{i=0}^{N} |p^B_i - p^A_i| \]  

Measuring positioning errors between discrete contours, such as (3.18)-(3.20), requires a definition of pairs of corresponding points \( p^A_i \) and \( p^B_i \) on both contours. These corresponding pairs define the location and orientation of the chords along which distances are measured. Consequently, different methods of establishing correspondence result in different values for the defined positioning errors.

A closest-point correspondence is established by pairing the vertices on one contour with the closest vertex on another contour. If both contours are sampled dense enough, the resulting pairs define chords which underestimate the distance between contours near strong bulges. Consequently, the contour positioning error would penalize insufficiently for an incorrect leakage of a contour into the papillary muscles. On the other hand, if the sampling distance between points at both contours is larger than the distance between both contours, overestimation occurs.

A radial correspondence defines pairs of corresponding points by the intersection of both contours with radial lines from a common centroid. This causes an overestimation for less circular shapes. Furthermore, radial correspondence requires closed, star shaped contours, which are intersected once by each radial line from the common centroid.

To reduce the error caused by incorrectly established correspondence by radial and closest-point correspondence we have used the Repeated Averaging Algorithm (RAA) described in [24]. This algorithm iteratively refines an initial correspondence by intersecting the original contours with chords perpendicular to an average contour calculated from corresponding pairs of the previous iteration. We have chosen this particular method for its ability to define correct chords near papillary muscles and at less circular sections of the cardiac contours.

3.4.2 Factors

The factors in our experiment are the profile length \( n_p \), the sampling distance on the profile \( d_{sp} \), the sampling distance along the contour \( d_{sc} \), the force balance \( \alpha \), the number of deformations \( n_d \) and the scale of the tangential filtering \( \sigma \). The main effect of each factor is defined as the change in response produced by a change in the level of the factor. If the difference in response between the levels of one factor is not the same at all levels of another factor, there is an interaction between factors. Next to the parameters of our method, there may be several other factors influence the accuracy of the resulting contours. Properties of the acquired images (i.e. the spatial resolution, the temporal resolution, the signal-to-noise ratio, etc) or the presence of certain pathologies (i.e. wall motion artifacts) may
have significant main effects and interactions between these factors and the parameters of our method can be expected. For instance, a significant interaction between temporal resolution, profile length $n_p$, sampling distance at the profile $d_s p$ is expected because accurate propagation of contours in data of relatively low temporal resolution requires profiles of larger length to capture the contracting motion of the heart. Unfortunately, the variation of these factors within our training data is too small to establish significant influences. Consequently, these factors have been excluded from our full factorial experiments.

3.4.3 Experimental Design

To optimize a response, in our case the accuracy of our method, with respect to several factors, or parameters, full factorial experiments should be performed. Full factorial experiments are known for their unique ability to discover factor interactions. In full factorial experiments, all possible combinations of a fixed number of levels of the factors are investigated. For each combination a response, i.e. the contour positioning error, on each replicate is calculated.

3.4.4 Analysis

The result of a full factorial experiment is a multidimensional vector space, which can be analyzed using the technique of Analysis of Variances (ANOVA), which uses a decomposition of the total variability of the observations to calculate the significance of each term of a linear statistical model describing the observations. This linear statistical model contains the main effects and interactions of the factors. ANOVA is considered to be one of the primary tools for statistical data analysis. Consequently, many books on applied statistics, such as [34], provide a detailed description of the method. Furthermore, several commercial software packages provide the complex multidimensional implementation as a numerical tool to the experimenter. These software packages present the results of ANOVA in standardized tables, called ANOVA tables. Based on the p-values in such ANOVA tables, one can visualize the significant relations in the multidimensional vector space using response graphs. These graphs provide essential knowledge required to select an optimal setting for the relevant factors.

3.5 Application

The contour propagation method is used within a clinical analysis application for cine cardiac MR sequences. This application introduces several issues, specific to the application to cine cardiac MR images. These issues
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will be briefly addressed in section 3.5.1. For accurate results, we have optimized the propagation of each contour in the SA, LA 2CH and LA 4CH view according the methodology. In section 3.5.2, we will describe the results of the optimization experiment. Next, in section 3.5.3, will discuss the results of an extensive validation performed to test the clinical relevance of our method.

3.5.1 Implementation Details

For the analysis of SA data, three contours need to be propagated over all phases. The contours of interest are the LV endocardium, the LV epicardium and RV endocardium. Both left ventricular contours are closed, whereas the RV endocardium contour is an open contour that should be attached to the LV epicardium contour. This is achieved by computing the intersection between both contours after each propagation from phase to phase. In the LA data, both left ventricular contours are open contours. These contours are closed by the valve plane, which is modelled by a straight line through the mitral valves (between the left atrium and ventricle). This straight line is also propagated using our new contour propagation method. After each propagation from one phase to the next, a straight line is fitted through the curved propagation result. The accuracy of the resulting straight line cannot be measured using the contour positioning errors defined in section 3.4.1. Instead, we have measured the angle between the resulting valve plane and the actual valve plane.

Our new method can propagate a contour from one image to another. The cine cardiac MR data consist of series of images. Within the cardiac analysis application a starting point for the propagation through the image sequence should be selected. The heart cycle contains two physiologically defined, easily identifiable phases suitable for initialization. These phases are known as end diastole (ED), when the myocardium is fully relaxed, and end systole (ES), when the myocardium is fully contracted. Because the inter-observer variability between the 6 expert segmentations at the ED phase is less than at the ES phase, we have chosen the ED phase to initialize our method providing better reproducibility.

Furthermore, if retrospective ECG triggering is used, the image sequence can be considered cyclic, such that also a propagation direction needs to be selected. The initial contours can be propagated either forward or backward in time until all images are segmented. During propagation, the positioning errors of the contours will gradually increase. Therefore we have chosen to propagate in both directions, such that each image requires a minimal number of propagation steps to be segmented. To maintain a time continuous segmentation results, contours are gradually merged near their meeting point using a weighted version of the RAA [24]. Note that optimization is performed for the propagation of contour from one phase to the next only.
3.5. APPLICATION

Table 3.1: Acquisition details for the data in the training set.

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>LA 2CH</th>
<th>LA 4CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of scans</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nr. of phases per scan</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Nr. of slices per scan</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>1.5-1.6</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Repetition time (ms)</td>
<td>3.1-3.2</td>
<td>2.9-3.1</td>
<td>2.7-2.8</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>8-10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Slice separation (mm)</td>
<td>18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>350^2-410^2</td>
<td>370^2-380^2</td>
<td>370^2-380^2</td>
</tr>
<tr>
<td>Image dimensions</td>
<td>256^2</td>
<td>256^2</td>
<td>256^2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75-110</td>
<td>75-96</td>
<td>73-113</td>
</tr>
<tr>
<td>Flip angle</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Consequently, each phase in the training data provides a replicate in the optimization experiment.

3.5.2 Optimization

Data

The data used for optimization was obtained from two patients; scans were made before and after administering adenosine, to stimulate the heart rhythm. The data was acquired using ECG gated cine MRI with a Philips MR Gyroscan Intera 1.5T. All images were acquired using the steady state free precession protocol (SSFP). Further details on the acquisition parameters are listed in table 3.1.

Golden Standard

To generate a golden standard, sufficiently accurate for optimization of the parameter setting of our algorithm, three experts manually segmented all phases in each data set twice. The resulting six manual segmentations have been averaged using the repeated averaging approach described in [24]. These average contours reflect the common intentions of the experts and were used as golden standard. Example images, including golden standard segmentations are shown in fig. 3.4. In table 3.2, we have listed the variance of the manual segmentations in terms of the positioning errors with respect to the golden standard.
Table 3.2: Variance of manual segmentations over all phases.

<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{mean}$ (mm)</th>
<th>$\varepsilon_{rms}$ (mm)</th>
<th>$\varepsilon_{max}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA LV Endocardium</td>
<td>0.89 ± 0.54</td>
<td>1.07 ± 0.61</td>
<td>2.15 ± 1.10</td>
</tr>
<tr>
<td>SA LV Epicardium</td>
<td>0.60 ± 0.24</td>
<td>0.75 ± 0.30</td>
<td>1.71 ± 0.72</td>
</tr>
<tr>
<td>SA RV Endocardium</td>
<td>1.32 ± 0.77</td>
<td>1.58 ± 0.93</td>
<td>3.63 ± 2.68</td>
</tr>
<tr>
<td>LA 4CH LV Endocardium</td>
<td>1.10 ± 0.29</td>
<td>1.32 ± 0.34</td>
<td>2.79 ± 0.96</td>
</tr>
<tr>
<td>LA 4CH LV Epicardium</td>
<td>0.92 ± 0.19</td>
<td>1.12 ± 0.19</td>
<td>2.38 ± 0.45</td>
</tr>
<tr>
<td>LA 2CH LV Endocardium</td>
<td>1.24 ± 0.31</td>
<td>1.51 ± 0.37</td>
<td>3.72 ± 1.51</td>
</tr>
<tr>
<td>LA 2CH LV Epicardium</td>
<td>0.97 ± 0.23</td>
<td>1.19 ± 0.22</td>
<td>2.79 ± 0.87</td>
</tr>
</tbody>
</table>

Figure 3.4: Example of ED golden standard segmentations for SA (a), LA 2CH (b) and LA 4CH (c) cine MR data and ES golden standard segmentations for SA (d), LA 2CH (e) and LA 4CH (f) cine MR data.
3.5. APPLICATION

Results

For each cardiac contour in each view, a full factorial experiment that tests over 2500 parameter settings is performed. The resulting multidimensional spaces are analysed using ANOVA, generating six ANOVA tables. The p-values from these ANOVA tables are listed in table 3.3 and table 3.4. A p-value below the $\alpha = 0.05$ level of significance indicates that a source of variation has a statistically significant effect. The optimal parameter setting is determined by selecting the optima in the response graphs of the significant main effects and interactions. To determine the correct optimum, the response graphs of the significant interactions are reviewed first. After determining the optimal settings for interacting factors, the optimal setting of the remaining factors can be selected from the response graphs of their main effect. Note that significant interactions influence the response graphs of the main effects of the factors involved, such that the optima in those response graphs have little meaning. Unfortunately, space limitations prohibit us from publishing all relevant graphs. Therefore we will give a detailed discussion on the results in table 3.3 and table 3.4.

Before performing the final full factorial experiments, several explorative full factorials are performed to determine correct ranges for the parameters in our full factorial experiment. These experiments showed that the active contour model can be deformed until convergence to provide the most accurate result. This confirms the correctness of our choice for the external energy. Optima for $n_d$ imply that the contour is driven past or away from the intended contour location. Because the active contour model can be deformed until convergence, we have omitted $n_d$ to reduce the size of the full factorial experiment. Furthermore, these initial experiments indicated no interactions between more than two factors, which allowed us to use a simplified linear model for the multidimensional ANOVA.

For the LV endocardium contour in the SA view, we found significant effects from the interactions $n_p \ast d_{sp}$, $d_{sp} \ast \alpha$ and $d_{sc} \ast \alpha$. The $n_p \ast d_{sp}$ interaction determines the length of the profiles and thus the amount of information included. Furthermore, the $d_{sc} \ast \alpha$ interaction is related to the shape and flexibility of the contours. Although the importance of the $n_p \ast d_{sp}$ and $d_{sc} \ast \alpha$ interaction can be understood from reasoning based on the theory of the active contour model, the response graphs from our full factorial experiment provide additional quantitative data on the amplitude of their effect and allow for selection of an optimal setting. Although the effect of the $d_{sp} \ast \alpha$ interaction is significant, its amplitude is relatively small with respect to both other significant interactions. The $d_{sp} \ast \alpha$ interaction can therefore be ignored. The response graph of the main effect for the remaining factor $\sigma$ shows a clear optimum, which relates to a filtering scale that blurs trabeculae and papillary muscles substantially without affecting the contour accuracy in other locations, such as near the septum.
Table 3.3: P-values of algorithm parameters of SA Contours.

<table>
<thead>
<tr>
<th>Parameter Combination</th>
<th>LV Endocardium</th>
<th>LV Epicardium</th>
<th>RV Endocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_p$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$ds_p$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$ds_c$</td>
<td>0.005</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.000</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>$n_p \times ds_p$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.123</td>
</tr>
<tr>
<td>$n_p \times ds_c$</td>
<td>0.999</td>
<td>0.735</td>
<td>1.000</td>
</tr>
<tr>
<td>$n_p \times \alpha$</td>
<td>0.999</td>
<td>0.999</td>
<td>0.977</td>
</tr>
<tr>
<td>$n_p \times \sigma$</td>
<td>1.000</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>$ds_p \times ds_c$</td>
<td>0.923</td>
<td>0.000</td>
<td>0.625</td>
</tr>
<tr>
<td>$ds_p \times \alpha$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.258</td>
</tr>
<tr>
<td>$ds_p \times \sigma$</td>
<td>1.000</td>
<td>0.748</td>
<td>-</td>
</tr>
<tr>
<td>$ds_c \times \alpha$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.303</td>
</tr>
<tr>
<td>$ds_c \times \sigma$</td>
<td>1.000</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha \times \sigma$</td>
<td>0.999</td>
<td>0.029</td>
<td>-</td>
</tr>
</tbody>
</table>

For the LV epicardium contour in the SA view we found similar relations. However, for the LV epicardium contour we have found additional $ds_c \times \sigma$ and $\alpha \times \sigma$ interactions. Although the amplitude of the effect of these interactions is relatively small, this does confirm prior theoretical assumptions. Larger filtering scales generate smoother external forces which make the contour less flexible. The differences regarding the significance of these interactions can be explained by the size of the anatomical structures in the contour environment. For the LV epicardium contour, the lung and the RV are large with respect to the filtering scale, whereas for the LV endocardium contour, papillary muscles and trabeculae are small with respect to the filtering scale.

For the RV endocardium contour, the explorative experiments indicated that tangential filtering is not beneficial for the contour accuracy, which is why $\sigma$ was omitted from the full factorial experiment. Even more surprisingly, our results showed no significant interactions between the parameters for the propagation of the RV endocardium contour. We believe that the variance introduced by appearance differences of the RV in our training data exceeds the variance related to the factors in our experiment, which therefore turn out to be non-significant. From slice to slice, differences in size and neighboring anatomy are large. Furthermore, RV myocardium is hardly visible at ED due to its thickness of only one pixel, whereas at ES the RV myocardium is thick enough to define a clear distinction between endocardium and epicardium.
In both LA views, we have found no significant differences between contour propagation in the LA 2CH view and contour propagation in the LA 4CH view. Therefore, we consider the propagation of contours in the LA view as a single application with a single optimal setting. The results of the full factorial experiments show that the parameters for the propagation of cardiac contours relate differently in the LA view. These differences are caused by the different shape of the heart in the LA view. Specifically near the apex, both cardiac contours exhibit a strong curvature, such that the propagation of cardiac contours in the LA view requires a more flexible parameter setting. Intuitively, this can be achieved by lowering $ds_c$, $\alpha$ and $\sigma$. However, lowering $ds_c$ decreases the magnitude of $f_{in,i}$, as direction changes decrease when the vertices $V_i$ are closer to each other. Furthermore, the physical width of the tangential filter is influenced because profiles are located closer to each other. These relations cause larger amplitudes for the effects of the interactions $ds_c \ast \sigma$ and $ds_c \ast \alpha$. The implementation and validation of the valve plane propagation is different, such that the result from the full factorial experiment for the valve plane cannot be compared to the results of the other cardiac contours. Nevertheless, the full factorial experiment allowed us to select an optimal parameter setting using the response graphs for the significant sources of variation, $ds_p \ast \alpha$ and $\alpha$.

The extensive golden standard available on the training data allows for a thorough investigation of the behavior of the contour propagation algorithm

### Table 3.4: P-values of algorithm parameters of LA contours.

<table>
<thead>
<tr>
<th></th>
<th>LV Endocardium</th>
<th>LV Epicardium</th>
<th>Valve Plane</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_p$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.248</td>
</tr>
<tr>
<td>$ds_p$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$ds_c$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.481</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.000</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>$n_p \ast ds_p$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$n_p \ast ds_c$</td>
<td>0.999</td>
<td>0.000</td>
<td>0.994</td>
</tr>
<tr>
<td>$n_p \ast \alpha$</td>
<td>1.000</td>
<td>0.316</td>
<td>0.998</td>
</tr>
<tr>
<td>$n_p \ast \sigma$</td>
<td>0.903</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>$ds_p \ast ds_c$</td>
<td>0.219</td>
<td>0.000</td>
<td>0.696</td>
</tr>
<tr>
<td>$ds_p \ast \alpha$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>$ds_p \ast \sigma$</td>
<td>0.000</td>
<td>0.854</td>
<td>-</td>
</tr>
<tr>
<td>$ds_c \ast \alpha$</td>
<td>0.000</td>
<td>0.000</td>
<td>0.995</td>
</tr>
<tr>
<td>$ds_c \ast \sigma$</td>
<td>0.000</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha \ast \sigma$</td>
<td>0.934</td>
<td>0.000</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 3.5: Variance of the resulting segmentations over all phases.

<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{\text{mean}}$ (mm)</th>
<th>$\varepsilon_{\text{rms}}$ (mm)</th>
<th>$\varepsilon_{\text{max}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA LV Endocardium</td>
<td>1.16 ± 0.83</td>
<td>1.33 ± 0.89</td>
<td>2.38 ± 1.42</td>
</tr>
<tr>
<td>SA LV Epicardium</td>
<td>0.69 ± 0.44</td>
<td>0.83 ± 0.51</td>
<td>1.75 ± 0.97</td>
</tr>
<tr>
<td>SA RV Endocardium</td>
<td>0.81 ± 0.55</td>
<td>1.05 ± 0.74</td>
<td>2.67 ± 2.04</td>
</tr>
<tr>
<td>LA LV Endocardium</td>
<td>0.98 ± 0.55</td>
<td>1.19 ± 0.68</td>
<td>2.57 ± 1.57</td>
</tr>
<tr>
<td>LA LV Epicardium</td>
<td>0.70 ± 0.30</td>
<td>0.84 ± 0.34</td>
<td>1.72 ± 0.68</td>
</tr>
</tbody>
</table>

over time. Fig. 3.5 shows the development of the positioning error over all phases using this scheme. By averaging positioning errors over all phases, a summary of the propagation is given, see table 3.5. Averaging the angular error of the valve plane over all phases results in $5.6 \pm 6.7$ degrees deviation between the golden standard valve plane and the propagated valve plane. Selected phases of an example result for each orthogonal view are given in figure 3.6. In the optimal parameter setting, our method can be considered to be fast. On a single core desktop computer (2.8 GHz), the propagation of all contours in a slice can be calculated within one second, such that the total time required for delineation is reduced to the time required for manual delineation of the first phase only, if no corrections are required.

3.5.3 Validation

To test the clinical performance of our optimized contour propagation algorithm, a more extensive validation on a larger number of data sets is required. The following sections will described the experiments performed for this validation.

Data

Our contour propagation algorithm is validated on data sets from 69 patients. These patients underwent a complete cardiac MR exam. Each exam started with a couple of scout scans, followed by several scans required for diagnostics such as cine, late enhancement and perfusion scans. For each patient, a SA cine acquisition was made. In most cases, the LA images were acquired during the scan planning stage of the exam. Consequently, the image quality of the LA images was often insufficient for reliable diagnostics. Unfortunately, for 20 patients, only the SA cine acquisitions were preserved. All together, the contour propagation was validated on 69 SA acquisitions and 38 LA acquisitions. Like the training date, these data were acquired using the SSFP protocol on a Philips MR Gyroscan Intera 1.5T. More acquisition details on the validation data are given in table 3.6.
Figure 3.5: RMS positioning error and standard deviation of propagated golden standard segmentation validated against the golden standard (a-f).
Figure 3.6: Examples of ED initializations for SA (a), LA 2CH (b) and LA 4CH (c) view and propagation results for SA (d,g,j,m), LA 2CH (e,h,k,n) and LA 4CH (f,i,l,o) view.
Table 3.6: Acquisition details for the data in the validation set.

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of scans</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Nr. of phases per scan</td>
<td>15-50</td>
<td>15-25</td>
</tr>
<tr>
<td>Nr. of slices per scan</td>
<td>9-14</td>
<td>1</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>1.40-1.72</td>
<td>1.36-1.75</td>
</tr>
<tr>
<td>Repetition time (ms)</td>
<td>3.1-3.2</td>
<td>2.87-4.0</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Slice separation (mm)</td>
<td>7.9-10</td>
<td>-</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>350^2-480^2</td>
<td>350^2-460^2</td>
</tr>
<tr>
<td>Image dimensions</td>
<td>256^2</td>
<td>256^2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>46-100</td>
<td>47-94</td>
</tr>
<tr>
<td>Flip angle</td>
<td>45-55</td>
<td>45-55</td>
</tr>
</tbody>
</table>

**Golden Standard**

Unfortunately, the task of complete, manual segmentation of all images in the validation data cannot be completed within a reasonable amount of time. Therefore, the golden standard in the validation data sets consists of manual segmentations at the ED and ES phase only. For the SA data, this was done by a cardiologist, who was not involved in the generation of the golden standard for the training data. The SA data contains 753 time series (slices), of which 511 contained all 3 cardiac contours at both end diastole and end systole allowing for propagation and validation. For the LA data, the three experts involved in drawing the golden standard for the training data also segmented the validation data. The 38 LA acquisitions segmented by all three experts have been used in the validation experiment.

**Results**

First our method is validated using positioning errors. Each ED segmentation is propagated to ES and validated using the manual ES segmentation as golden standard. The results are given in table 3.7. Again, the valve plane was validated by calculating the angular error, which was 4.50 ± 3.13 degrees. Note that the average positioning errors are close to the peak values in the graphs in figure 3.5, indicating that our method is robust to the significant variation in image quality within the validation data.

In clinical practice, the cardiac contours are used to determine the cardiac function by calculating ventricular volumes, such as the End Diastolic Volume (EDV) and the End Systolic Volume (ESV), and derived properties such as the Stroke Volume (SV) and the Ejection Fraction (EF). Therefore we have evaluated the influence of the use of our propagation algorithm on
Table 3.7: Average contour positioning errors at ES.

<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{\text{mean}}$ (mm)</th>
<th>$\varepsilon_{\text{rms}}$ (mm)</th>
<th>$\varepsilon_{\text{max}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA LV Endocardium</td>
<td>2.23 ± 1.10</td>
<td>2.64 ± 1.30</td>
<td>5.00 ± 2.72</td>
</tr>
<tr>
<td>SA LV Epicardium</td>
<td>1.84 ± 1.04</td>
<td>2.27 ± 1.35</td>
<td>4.70 ± 3.63</td>
</tr>
<tr>
<td>SA RV Endocardium</td>
<td>2.02 ± 1.21</td>
<td>2.63 ± 1.77</td>
<td>7.87 ± 8.11</td>
</tr>
<tr>
<td>LA LV Endocardium</td>
<td>1.82 ± 0.61</td>
<td>2.31 ± 0.87</td>
<td>5.76 ± 2.62</td>
</tr>
<tr>
<td>LA LV Epicardium</td>
<td>0.92 ± 0.42</td>
<td>1.12 ± 0.61</td>
<td>2.38 ± 2.41</td>
</tr>
</tbody>
</table>

Table 3.8: Results of physiological measurements based on contours provided by the cardiac contour propagation algorithm.

<table>
<thead>
<tr>
<th>Property</th>
<th>Unit</th>
<th>Error</th>
<th>Fit</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA view</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESV</td>
<td>ml</td>
<td>-0.8 ± 5.5</td>
<td>1.03$x - 2.08$</td>
<td>0.98</td>
</tr>
<tr>
<td>SV</td>
<td>ml</td>
<td>0.8 ± 5.5</td>
<td>0.78$x + 9.74$</td>
<td>0.71</td>
</tr>
<tr>
<td>EF</td>
<td>%</td>
<td>1.7 ± 6.8</td>
<td>0.99$x + 2.08$</td>
<td>0.78</td>
</tr>
<tr>
<td>LA view</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESV</td>
<td>ml</td>
<td>-11.06 ± 9.03</td>
<td>0.92$x + 13.72$</td>
<td>0.93</td>
</tr>
<tr>
<td>SV</td>
<td>ml</td>
<td>11.06 ± 9.03</td>
<td>0.61$x + 11.19$</td>
<td>0.68</td>
</tr>
<tr>
<td>EF</td>
<td>%</td>
<td>12.32 ± 10.44</td>
<td>0.59$x + 12.43$</td>
<td>0.76</td>
</tr>
</tbody>
</table>

the resulting physiological properties. In both views we have calculated LV volumes by summing areas according to Simpson’s Rule. In the SA view, endocardial contour areas are used. In the LA view, we used the areas of circular discs, having a diameter determined by the length of normals to the long axis. We have compared the results for ESV, SV and EF based on the reference contours and the propagated contours. This resulted in table 3.8 and figure 3.7.

Our results show that contour propagation in the LA view is more accurate than contour propagation in the SA view. However, in terms of the accuracy of the derived physiological properties, the results in the LA view are significantly less accurate. This difference is caused by the contribution of inaccurate valve plane positions. In the SA view, the validation does not include such errors because the user defines the valve plane implicitly as the image slice (without contours) above the basal segmentation. In the LA view, the valve plane propagation is not yet as robust as the propagation of the other contours. Consequently, the correlation between physiological properties derived from propagated segmentations and reference contours is lower. Note that in the SA view, the maximum error due to incorrect valve plane definition is equal to the contribution to the LV volume of the basal
Figure 3.7: Measured versus reference ESV (a,b), SV (c,d) and EF (e,f) from 69 SA series (a,c,e) and from 38 LA series (b,d,f) acquired using cine cardiac MR.
CHAPTER 3. CONTOUR PROPAGATION IN CINE CMR

slice. Unfortunately this is usually the slice with the largest contribution. In our 69 SA data sets, this contribution is on average 9.6 ml (24.3%).

In general, the propagation of the valve plane seems to be less robust because the contour neighborhood provides fewer image features. We believe this has three important causes. One is the lack of temporal resolution of data. Opening and closing happens between two phases, which results in too much difference in contour environment to be useful for tracking. Another important factor is the planning of the LA scans. Sometimes, the valve plane ends in the outflow tract, providing no transition near the end point of the contour. Finally, the spatial resolution is in some cases insufficient, given the dimensions of the valves.

3.6 Conclusion

We have developed a method for automatic contour propagation in cine cardiac magnetic resonance images based on active contours. The method can be used to reduce user interaction time by propagating initial, manual segmentations over time in image sequences. The accuracy of the resulting contours from our method depends on 6 parameters. We have described a methodical approach towards parameter optimization. This approach has been used to define an optimal parameter setting for cardiac cine MR images from three orthogonal views. In the optimal parameter setting, our propagation method proved to be robust and accurate. The resulting cardiac contours are positioned within the inter-observer ranges of manual segmentation. Consequently, the resulting contours can be used to accurately determine the end-systolic volume (ESV), the stroke volume and the ejection fraction.

3.7 References


3.7. REFERENCES


CHAPTER 3. CONTOUR PROPAGATION IN CINE CMR


3.7. REFERENCES


4

Accurate Computer-Aided Quantification of Left Ventricular Parameters: Experience in 1555 CMR Studies from the Framingham Heart Study

4.1 Introduction

Quantitative analyses of short-axis (SA) functional cardiac magnetic resonance (CMR) images over the entire cardiac cycle require a complete delineation of the myocardium. Such a complete delineation typically consists of the left ventricular (LV) endocardial and epicardial contours on 8-12 slices and 20-50 phases/slice, altogether involving up to 1200 (12x50x2) myocardial contours. Consequently, manual delineation is too time-consuming to be performed in clinical routine and therefore automatic delineation tools are essential.

The problem of automatic delineation of the myocardium in SA functional CMR images has proven to be exceptionally challenging. The papillary muscles are particularly difficult to delineate automatically. These need to be excluded from the myocardium wall to enable measurements of wall thickness, although there are often no image features separating the papillary muscles from the myocardium wall. Consequently, the problem has attracted much attention in the image processing community. The presented solutions include methods based on active contour models [13, 6, 7], active shape models [10, 8], active appearance models [4, 2, 9], level sets [5, 3],


Author contributions: GH implemented the contour detection method and performed the analysis of collected data (contours, results and log files). CS performed image analysis on all participants. MC performed image analysis on the reproducibility cases (including manual analysis) and assisted in interpretation of the resulting data. GH prepared the manuscript. MB arranged funding for the project. MB and WM supervised the project.

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CHAPTER 4. COMPUTER-AIDED ANALYSIS OF SA CINE CMR

graph cuts [22, 21], fuzzy connectivity [23, 24] and combinations of those approaches [11, 1]. While these methods perform reasonably well in validation studies comparing quantification results obtained from manually and automatically defined contours on medium-sized populations, none provide perfect contours on a case-by-case basis, as shown in the recent review by Petitjean and Dacher [26]. Consequently, effective deployment of automatic delineation methods into clinical practice still requires human-operator interaction to enable correction of imperfect contours. In addition, little is known about the effect of manual contour correction on the quantitative analysis results.

In this study we sought to assess the accuracy, time-efficiency, and reproducibility of a computer-aided analysis system incorporating an automatic delineation method [16] together with several (semi-automatic) contour correction mechanisms [13, 15]. We deployed our system to analyze CMR SA-image data from the Framingham Heart Study (FHS) using computer-aided contouring methods with a specific step-by-step strategy and monitored the evolution of the quantitative results following each of these steps. Moreover, extensive logging of user interactions provided additional insights into the effectiveness of computer-aided analysis of SA functional CMR images.

4.2 Methods

4.2.1 Study Population

The study design and selection criteria for the FHS Offspring study have been described previously [18]. Briefly, the FHS Offspring cohort participants are the children of the original FHS cohort and the spouses of those children. The Offspring cohort was initiated in 1971 and participants have undergone comprehensive examinations and interval histories every 3-4 years. Offspring were excluded prospectively if there were potential contraindications to CMR imaging, including pacemaker, implanted cardioverter-defibrillator, metallic intraocular or intracranial clips, and history of foreign ocular bodies or severe claustrophobia. Participants with known permanent atrial fibrillation were also excluded. A total of 1837 Offspring underwent CMR imaging. The study was approved by human study committees of both the Boston University School of Medicine and Beth Israel Deaconess Medical Center (Boston, MA). Written informed consent for CMR scanning was obtained from all participants.

4.2.2 Imaging

CMR imaging was performed with subjects positioned supine in a 1.5-T scanner (Gyroscan NT, Philips Healthcare, Best, The Netherlands) using a 5-element cardiac array coil for radiofrequency signal detection. Following
scout images to determine the position and orientation of the heart within the thorax, images were acquired using an electrocardiogram (ECG)-gated steady-state free precession (SSFP) cine sequence [19]. A stack of 10-mm thick contiguous SA slices encompassing the LV from base to apex was acquired during a series of end-tidal breath-holds. Imaging parameters included the following: repetition time = 3.2 ms, echo time = 1.6 ms, flip angle = 60°, 208x256 matrix with 400-mm FOV, temporal resolution of 30-40 ms.

4.2.3 Image Analysis

All image analyses were performed by a single expert observer (CJS), with 12 years of CMR analysis experience and >4000 cases previously analyzed, blinded to participant characteristics and clinical history, using a commercially available workstation (Extended MR Workspace 2009, Philips Healthcare). The analysis software provides automatic contour detection in a task guided application in which the user needs to indicate the slice range (i.e. from apex to base) deemed suitable for automatic analysis. To account for through-plane (long-axis) motion over the cardiac cycle, slice-extent for automated analysis was determined by the operator at end-systole (ES). The apical limit was selected as the most apical slice for which blood pool could be seen at ES. The basal limit was selected as the most basal slice at ES for which there was myocardium encompassing at least 75% (270°) of the circumference. The 75% criterion was selected as that which consistently yielded visually identical contours by automated contouring as would be obtained by manual tracing. This was determined empirically by CJS and MLC based on experience with a “operator training” dataset that was analyzed prior to performing the analyses included in this report. The training dataset comprised 20 healthy volunteers who had been scanned contemporaneously with the Offspring and using the same CMR protocol, but who were not part of the Offspring cohort. Contour detection was then performed without the need for operator-identification of the LV blood pool, or any other features, in the image.

The automatic contour detection starts by locating the myocardium using a fast and robust ring detection method. This ring detection method uses a variant of the Hough transform tailored to detect circular shapes, which is computed efficiently in the Fourier domain using an analytic Hankel transformation. Thereafter, the precise delineation of the endocardial and epicardial contours at end diastole (ED) is obtained by deforming a geometric template in a coarse-to-fine approach. This geometric template models the myocardium as a ribbon structure consisting of a centerline and a variable width, both described by interpolating splines controlled by as few nodes as possible. The position and width of those nodes is optimized using a greedy algorithm to minimize an energy criterion that includes: 1) circularity and regularity terms to favor smooth circular shapes, 2) bound-
CHAPTER 4. COMPUTER-AIDED ANALYSIS OF SA CINE CMR

Analysis procedure

1. Select slice range requiring contours at all phases.
2. Detect contours automatically.
3. Verify contours at end diastole:
   - When necessary: correct and propagate corrections.
4. Verify contours at other phases:
   - When necessary: correct and propagate from phase with maximum error.
5. Add apical/basal slices at end diastole.

Figure 4.1: Analysis procedure as used throughout this study.

ary terms based on edge and ridge features to drive the contours to an appropriate location and 3) regional terms forcing the template to segment homogenous regions, so that the papillary muscles are considered part of the LV cavity volume, in accordance with commonly used manual contour delineation conventions. The resulting ED contours are then propagated to the remainder of phases by optimizing the match of grey values along profiles in consecutive images perpendicular to the contour [13].

If manual contour correction is necessary, semi-automatic contour propagation allows efficient correction across all phases. Computer-aided contouring was performed using a strict protocol, including automatic contour detection [16] on all slices in which the complete circumference of the LV cavity was surrounded by myocardial tissue in all phases. The resulting contours were reviewed at end-diastole and necessary corrections were propagated to the remainder of phases [13]. Successive review and correction of the remainder of phases was performed by correcting contours at the phase where contour positioning was worst, followed by a dual (forward and backward) propagation [15, 20] to guarantee temporal consistency. Finally, if needed, additional basal and apical slices at end-diastole (ED) were drawn manually to enable accurate volume quantification at ED. This complete analysis procedure is summarized in Figure 4.1. The most common modification was addition of at least one additional basal slice at ED. The most basal slice was selected as that containing an arc of $\geq 180^\circ$ of myocardium, as shown in Figure 4.2. During the analyses, all user interactions were recorded in log files. Furthermore, the analysis software was augmented with automatic result-export and logging functionality for the purpose of this study.

Quantification included global volumetric parameters, as well as contractile parameters determined in 16 segments of the standard AHA model [17] (the apical segment cannot be reliably assessed from SA functional CMR images). LV volumes were computed in all phases using Simpsons rule for slice summation. The resulting volume vs. time curve was processed to obtain the ED volume (EDV), end systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and cardiac output (CO). In addition, LV mass (LVM) was
4.2. METHODS

![Image](image.jpg)

Figure 4.2: Examples of manual end diastolic delineations of the basal slices in the short axis stack.

determined from the ED datasets. For segmental measurements, wall thickness and wall motion (i.e. the displacement of the endocardium contour) were quantified in all phases. The resulting segmental thickness vs. time and motion vs. time curves were processed to obtain several parameters.

Inter- and intraobserver reproducibility was assessed from 48 cases that were randomly selected from equal strata of sex and Framingham Risk Score. The second observer (MLC), for interobserver reproducibility, had 17 years of CMR experience and >1000 cases analyzed.

Finally, we sought to verify that our methodology of automated contouring followed by manual correction would yield results comparable to fully manual contours. One observer (MJC) analyzed the 48 randomly selected cases without the help of automation by manually drawing LV endocardial contours on ED and ES and LV epicardial contours at ED only, which is sufficient to enable quantification of global volumetric parameters. These manual analyses were performed en bloc over two days at a time point widely separated from other analyses without reference to prior contours and results.

4.2.4 Statistical Analysis

The time spent to perform each task in the analysis protocol was derived from the log files that were stored by the analysis workstation. This analysis included the time spent to select the appropriate slice, to perform automatic contour detection, to correct the automatic contours, to add the additional slices at ED, and to export the quantitative results. The resulting times were found to be non-Gaussian in distribution. Therefore, we use the median and the interquartile range to summarize these results. The accuracy of automatically determined myocardial contours was assessed by measuring the distance between the automatically detected contours and final, i.e. after editing, contours. We have measured the mean, root-mean-square (RMS), and maximum distance after establishing a point-to-point correspondence perpendicular to a centerline obtained using the repeated averaging algo-
These results are summarized using the mean and the standard deviation. The quantitative parameters obtained from the automatically detected contours were compared with the final quantification results after editing, to assess the impact of manual adjustments made to the contours. Moreover, to assess the impact of adding the additional slices alone, quantification was also performed based on delineations that include the additional slices, but did not contain the detailed adjustments made to the automatically detected contours. The differences were reported by mean and standard deviation of the signed difference. In addition, scatter plots were generated including the results of linear regression analysis. The close correspondence between the quantification results after adding the additional slices at ED and final quantification results also allowed for the generation of Bland Altman plots [25], in which the difference between two measurements is plotted against their mean to visualize the agreement between both measurements.

4.3 Results

We allocated 6 months for the image analysis, during which the images of 1,555 participants were transferred to the workstation and analyzed by a single observer (CJS). The median ± interquartile of the total analysis time was 9.1 ± 3.8 minutes/case. Timing results for the individual steps in the analysis protocol are listed in table 4.1. Note that exporting all the contours and results to text files was performed for research purposes and is not mandatory in clinical practice. These text files were exported immediately after automatic contour detection and after manual correction. This added a median 85 seconds (i.e. 42 seconds immediately after contour detection and 43 seconds after all corrections) to our analysis protocol, which was 16% of the total time spent to analyze the cases. Excluding the export time, the total analysis time for a single case was 7.6 ± 1.7 minutes.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Required time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selecting slices</td>
<td>32 ± 12</td>
</tr>
<tr>
<td>Automatic detection and result export</td>
<td>42 ± 27</td>
</tr>
<tr>
<td>Reviewing and correcting</td>
<td>292 ± 97</td>
</tr>
<tr>
<td>Adding additional contours</td>
<td>177 ± 61</td>
</tr>
<tr>
<td>Defining segments</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>Result export</td>
<td>43 ± 26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>546 ± 229</strong></td>
</tr>
</tbody>
</table>

Table 4.1: Distribution time of activities involved in analysis (median ± interquartile range).

Automatic contour detection was performed at 8148 slices and success-
4.3. RESULTS

fully located the LV in 8072 slices (99% success rate). All automatically detected contours (323,202) were reviewed and corrected where necessary. Overall, 16,378 contours (5%) required manual modifications, which were propagated using the dual propagation mechanism. This included 3,157 modifications to endocardial contours (2% of all endocardial contours), and 12,948 modifications to epicardial contours (8% of all epicardial contours). The size of these manual corrections was assessed by measuring the mean, RMS, and maximum distance between the automatically detected and corrected contours, as reported in table 4.2. Moreover, figure 4.3 shows the cumulative percentage of edits versus the contour displacement. Overall, visual contour verification and manual adjustment (as needed) required 292 ± 97 seconds/case.

The accuracy of the automatically detected myocardial contours was assessed by measuring the mean, RMS and maximum distance with respect to the final contours after manual editing (table 4.2), which lists the contour positioning errors for the LV endocardial and epicardial contours at ED only. Table 4.2 shows the accumulated positioning errors across all 323,202 automatically-detected myocardial contours (i.e. all slices and all phases) versus the final, manually-corrected contours. Figure 4.4 shows scatter plots of the time between the first and last export of results vs. the mean, RMS and maximum contour positioning error for all cases. The intercepts of the trend lines in these plots, 254s, 245s, and 243s for the mean, RMS and maximum contour positioning errors respectively, indicate the time that would be expected for an analysis with perfect automatic contouring. Note that these times exclude the time spent on slice selection, but include the time spent on reviewing automatically defined contours, adding additional slices, and defining myocardial segments, as well as the time spent on exporting the results once. Moreover, the slope of the trend lines, 437 s mm$^{-1}$, 338 s mm$^{-1}$,
CHAPTER 4. COMPUTER-AIDED ANALYSIS OF SA CINE CMR

### Table 4.2: Mean, root-mean-square (RMS), and maximum distances (mean ± SD) between automatically detected contours and the final, manually corrected contours averaged across the manually corrected contours, across end-diastolic contours, and across all contours. LV = left ventricular.

<table>
<thead>
<tr>
<th></th>
<th>Mean Distance (mm)</th>
<th>RMS Distance (mm)</th>
<th>Max. Distance (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manually corrected contours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Endocardium (n=3157)</td>
<td>0.91 ± 0.75</td>
<td>1.36 ± 0.87</td>
<td>3.21 ± 1.76</td>
</tr>
<tr>
<td>LV Epicardium (n=12948)</td>
<td>1.37 ± 0.98</td>
<td>1.90 ± 1.15</td>
<td>4.13 ± 2.15</td>
</tr>
<tr>
<td><strong>End diastolic contours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Endocardium (n=8072)</td>
<td>0.02 ± 0.18</td>
<td>0.03 ± 0.26</td>
<td>0.09 ± 0.65</td>
</tr>
<tr>
<td>LV Epicardium (n=8072)</td>
<td>0.25 ± 0.51</td>
<td>0.43 ± 0.79</td>
<td>1.11 ± 1.90</td>
</tr>
<tr>
<td><strong>All contours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Endocardium (n=161601)</td>
<td>0.19 ± 0.42</td>
<td>0.25 ± 0.55</td>
<td>0.54 ± 1.16</td>
</tr>
<tr>
<td>LV Epicardium (n=161601)</td>
<td>0.87 ± 0.84</td>
<td>1.18 ± 1.07</td>
<td>2.46 ± 2.16</td>
</tr>
</tbody>
</table>

160 s mm$^{-1}$ for the mean, RMS and maximum contour positioning errors respectively, indicate the crucial impact of the accuracy of the automatically generated contours on the total analysis time. An average 0.1 mm improvement in contour detection accuracy assessed by the mean contour positioning error is expected to result in a 44 s time gain.

Image quality affects the time spent during analysis. The images of 89 cases (5.7%) contained significant artifacts at one of the slices. In these artifact-afflicted cases, the RMS distance between the automatically detected and final contours at all phases was 0.49 ± 0.92 mm and 1.38 ± 1.26 mm for the LV endocardium and LV epicardium respectively. The total time spent to correct the automatically detected contours and export the final results for these artifact cases was 551 ± 227 s, vs. 464 ± 222 s for the cases without artifacts (p < 0.001).

The final step in our analysis protocol was to add myocardial contours to the basal, and occasionally apical, slice(s) at ED, which were not included for automatic contour detection as these slices did not cover the LV at ES. To assess the importance of this step, we quantified the volumetric parameters before and after adding these slices to the automatically generated contours and compared the results to the final quantification results. Note that the latter (automatically-detected contours + manually-added basal slice(s)) dataset was obtained by reconstructing contour sets from a previously saved version, as the addition of ED slices was performed after detailed adjustments of all contours. The reconstructed contour sets only included correction for the 1% of slices in which the automatically detected
4.3. RESULTS

Figure 4.4: Time between first and last result export vs. average mean (a), RMS (b) and maximum (c) contour displacement in all 1555 participants. The lines define the resulting fit from linear regression analysis. RMS = root-mean-square.
contours did not surround the LV. In total 4,320 slices were added, which on average equals to 2.78 ± 0.92 slices per case. The results for the EDV, ESV, SV and EF are shown in scatter plots with linear regression results in figure 4.5, while table 4.3 lists the mean ± SD differences and the $r^2$ for all volumetric results. Moreover, the close correlation between the results from reconstructed data and the final data are suitable for visualization in Bland-Altman plots, as shown in figure 4.4.

<table>
<thead>
<tr>
<th></th>
<th>Automatic</th>
<th>Including ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Volume (ml)</td>
<td>($-43.0 \pm 18.1$)</td>
<td>($0.4 \pm 4.1$)</td>
</tr>
<tr>
<td>ES Volume (ml)</td>
<td>($-0.1 \pm 5.5$)</td>
<td>($-0.3 \pm 2.9$)</td>
</tr>
<tr>
<td>Stroke Volume (ml)</td>
<td>($-42.9 \pm 17.0$)</td>
<td>($0.7 \pm 3.1$)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>($-13.3 \pm 5.1$)</td>
<td>($0.3 \pm 1.8$)</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>($-2.7 \pm 1.1$)</td>
<td>($0.0 \pm 0.2$)</td>
</tr>
<tr>
<td>LV Mass (g)</td>
<td>($-27.2 \pm 14.1$)</td>
<td>($0.3 \pm 6.8$)</td>
</tr>
</tbody>
</table>

Table 4.3: Difference of volumetric parameters before and after adding additional slices at ED with respect to final contours (mean ± SD) $r^2$. CO = cardiac output; EF = ejection fraction.

Due to the time-consuming nature of hand-tracing ventricular contours, fully manual analysis is usually performed by drawing contours at the ED and ES phases only. This requires manual selection of the ES phase blinded from volume quantification results. Automatic contour detection provides myocardial contours at all phases. Consequently, the ES phase can be automatically selected afterwards, rather than manually selected beforehand, which may save additional time (and potentially leading to more accurate volume parameters). While the automatically detected ES phase could be overridden (explicitly selected manually), this proved to rarely be necessary. As the ES phase is also redetected after modifying the myocardial contours, only small changes in ES phase were observed. The mean difference between the automatically detected and final ES time was 0.2 ± 3.0 ms, with a 0.994 correlation coefficient ($r^2$), indicating excellent agreement between user-determined and automatically-identified ES time.

Functional CMR can be used for quantitative assessments of local myocardial contractile. Thus, we also measured LV wall thickness and wall motion in 16 AHA segments from the automatically generated contours and the final contours (table 4.4). Note the lower correlation coefficients for the thickness-based measurements, which indicate the need for more accurate contours to accurately quantify these measures. This result is also affected by the lower accuracy of epicardial contours with respect to endocardial contours, as shown in table 4.2.

Compared to volumetric measurements, such measures of local myocar-
4.3. RESULTS

Figure 4.5: Scatter plots for end-diastolic (ED) volume (a,b), end-systolic (ES) volume (c,d), left ventricular ejection fraction (e,f) and stroke volume (g,h) measured using only automatic contour detection (a,c,e,g) and after adding slices at ED (b,d,f,h) compared to the final results (Reference) obtained after reviewing and correcting all contours. The lines depict the resulting fit from linear regression analysis. The fit parameters are given in the upper left corner, together with $r^2$. 

![Scatter plots for end-diastolic (ED) volume (a,b), end-systolic (ES) volume (c,d), left ventricular ejection fraction (e,f) and stroke volume (g,h) measured using only automatic contour detection (a,c,e,g) and after adding slices at ED (b,d,f,h) compared to the final results (Reference) obtained after reviewing and correcting all contours. The lines depict the resulting fit from linear regression analysis. The fit parameters are given in the upper left corner, together with $r^2$.](image-url)
Figure 4.6: Bland-Altman plots for resulting ED volume (a), ES volume (b), left ventricular ejection fraction (c) and stroke volume (d) measured after adding slices at ED (related to figure 3 b,d,f,h) compared to the final results obtained after reviewing and correcting all contours.

dial contractility require more accurate contours, associated with additional correction time. Our results indicate that this is particularly important for measurements based on wall thickness. In general, this can be explained as it requires both the endocardial and epicardial contours to be accurate on a point-by-point basis (whereas small local errors may cancel out when assessing only global parameters such as overall LV volume). However, this result is also affected by the lower accuracy of epicardial contours with respect to endocardial contours, as shown in table 4.2.

Intra- and interobserver variability was determined both by measuring distances between the contours of both observations (table 4.5), as well as by comparing the volumetric parameters obtained in both observations (table 4.6). Note that the distances reported in table 5 are comparable to the distances reported for all contours in table 4.2. Moreover, the intra- and interobserver variability for the volumetric parameters (table 4.6), is comparable to the differences between the results derived from the reconstructed and final data (table 4.6). The intra- and interobserver variability for volumetric parameters derived from the reconstructed data sets (automatically-detected contours + manually-added basal slice(s)) was comparable to the intra- and interobserver variability after all corrections have been applied (table 4.6). As the contours between two observations in the latter ap-
4.3. RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Difference (mean ± SD)</th>
<th>Correlation Coefficient ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thickness-based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.20 ± 0.80</td>
<td>0.87</td>
</tr>
<tr>
<td>ES Thickness (mm)</td>
<td>1.30 ± 1.64</td>
<td>0.70</td>
</tr>
<tr>
<td>Wall Thickening (%)</td>
<td>19 ± 31</td>
<td>0.78</td>
</tr>
<tr>
<td>Maximum Thickness (mm)</td>
<td>1.26 ± 1.55</td>
<td>0.72</td>
</tr>
<tr>
<td>Time of Maximum Thickness (ms)</td>
<td>−2.6 ± 37.05</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Motion-based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES Motion (mm)</td>
<td>0.09 ± 0.72</td>
<td>0.92</td>
</tr>
<tr>
<td>Maximum Motion (mm)</td>
<td>0.09 ± 0.72</td>
<td>0.92</td>
</tr>
<tr>
<td>Time of Maximum Motion (ms)</td>
<td>−0.10 ± 21.85</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Table 4.4: Difference of segmental parameters derived from automatically detected contours with respect to final contours.

The approach are only different at a few ED slices, average values for the mean, RMS and maximum distance between the contours of both observations are all <0.1mm.

<table>
<thead>
<tr>
<th></th>
<th>Mean Distance (mm)</th>
<th>RMS Distance (mm)</th>
<th>Max. Distance (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-observer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Endocardium</td>
<td>0.22 ± 0.42</td>
<td>0.30 ± 0.54</td>
<td>0.63 ± 1.12</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>0.42 ± 0.58</td>
<td>0.53 ± 0.68</td>
<td>1.11 ± 1.29</td>
</tr>
<tr>
<td><strong>Inter-observer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Endocardium</td>
<td>0.26 ± 0.43</td>
<td>0.34 ± 0.56</td>
<td>0.73 ± 1.15</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>0.72 ± 0.65</td>
<td>0.90 ± 0.76</td>
<td>1.84 ± 1.48</td>
</tr>
</tbody>
</table>

Table 4.5: Intra- and inter-observer variability of myocardial contours assessed by measuring the distance between contours from two observations (mean ± SD).

To enable a comparison with other works, the accuracy of the automatically detected myocardial contours was also assessed with respect to the contours from the fully manual analyses (Table 4.7). Moreover, the volumetric parameters as obtained before and after detailed corrections were compared to the volumetric parameters obtained from fully manual analysis (Table 4.8). The analysis time for manual segmentation of LV endocardial contours at ED and ES, and epicardial contours at ED, was 361 ± 11 seconds (median ± interquartile range).
CHAPTER 4. COMPUTER-AIDED ANALYSIS OF SA CINE CMR

Intra-observer Inter-observer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete analyses</th>
<th>Intra-observer</th>
<th>Complete analyses</th>
<th>Inter-observer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Volume (ml)</td>
<td>(0.45 ± 2.37)</td>
<td>0.996</td>
<td>(−0.49 ± 3.82)</td>
<td>0.989</td>
</tr>
<tr>
<td>ES Volume (ml)</td>
<td>(0.55 ± 2.46)</td>
<td>0.978</td>
<td>(−1.09 ± 2.92)</td>
<td>0.969</td>
</tr>
<tr>
<td>Stroke Volume (ml)</td>
<td>(−0.10 ± 2.77)</td>
<td>0.987</td>
<td>(0.59 ± 3.90)</td>
<td>0.976</td>
</tr>
<tr>
<td>EF (%)</td>
<td>(−0.31 ± 1.72)</td>
<td>0.937</td>
<td>(0.61 ± 2.02)</td>
<td>0.911</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>(0.00 ± 0.19)</td>
<td>0.982</td>
<td>(0.03 ± 0.25)</td>
<td>0.968</td>
</tr>
<tr>
<td>LV Mass (g)</td>
<td>(−0.31 ± 3.60)</td>
<td>0.982</td>
<td>(−0.37 ± 4.19)</td>
<td>0.975</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reconstructed analyses</th>
<th>Intra-observer</th>
<th>Reconstructed analyses</th>
<th>Inter-observer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Volume (ml)</td>
<td>(0.00 ± 2.48)</td>
<td>0.996</td>
<td>(0.69 ± 4.03)</td>
<td>0.988</td>
</tr>
<tr>
<td>ES Volume (ml)</td>
<td>(−0.06 ± 1.82)</td>
<td>0.990</td>
<td>(2.81 ± 6.64)</td>
<td>0.863</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>(0.06 ± 2.31)</td>
<td>0.963</td>
<td>(−2.11 ± 6.89)</td>
<td>0.934</td>
</tr>
<tr>
<td>EF (%)</td>
<td>(0.10 ± 1.30)</td>
<td>0.991</td>
<td>(1.63 ± 3.27)</td>
<td>0.784</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>(0.01 ± 0.15)</td>
<td>0.988</td>
<td>(−0.11 ± 0.36)</td>
<td>0.936</td>
</tr>
<tr>
<td>LV Mass (g)</td>
<td>(−0.85 ± 4.37)</td>
<td>0.975</td>
<td>(−1.70 ± 3.92)</td>
<td>0.979</td>
</tr>
</tbody>
</table>

Table 4.6: Intra- and inter-observer variability for the LV volumetric parameters using the complete analysis (with final corrected contours) and the reconstructed analyses (with automatically detected contours plus additional slice) reported by (mean ± SD) $r^2$.

4.4 Discussion

Quantitative analysis of SA functional CMR images across the cardiac cycle requires a complete delineation of the LV myocardium, which cannot be obtained manually within the time constraints of clinical routine. Therefore, clinical software for the analysis of SA functional CMR images should provide automated contouring tools. To date, such automated methods are helpful, but require manual interventions by the user to obtain visually satisfactory LV contours. In this study, we assessed the accuracy and time-effectiveness of a clinical application for the analysis of SA functional CMR images, which contains a combination of automatic and semi-automatic contouring algorithms.

We further have assessed the impact of manual contour corrections on the final outcome of clinical measurements. The addition of basal and apical slices at the ED phase caused a significant increase in the EDV, while not affecting the ESV. Consequently the derived SV and EF both increased significantly. This result confirms the known importance of correct slice selection for the outcome of volume measurements in SA functional CMR.

While the reviewing and correcting the automatically proposed contours doubles the analysis time (Table 4.1), Table 4.3 and Figure 4.6 highlight the limited impact of detailed, manual contour corrections on the outcome.
4.4. DISCUSSION

<table>
<thead>
<tr>
<th>Contour</th>
<th>Mean Error (mm)</th>
<th>RMS Error (mm)</th>
<th>Maximum Error (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED LV Endocardium (n=308)</td>
<td>1.16 ± 0.81</td>
<td>1.36 ± 0.85</td>
<td>2.58 ± 1.37</td>
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<tr>
<td>ED LV Epicardium (n=308)</td>
<td>1.28 ± 0.59</td>
<td>1.54 ± 0.67</td>
<td>3.08 ± 1.30</td>
</tr>
<tr>
<td>ES LV Endocardium (n=299)</td>
<td>1.58 ± 0.71</td>
<td>1.87 ± 0.81</td>
<td>3.43 ± 1.49</td>
</tr>
</tbody>
</table>

Table 4.7: Mean, root-mean-square (RMS), and maximum distances (mean±SD) between automatically detected contours and manual contours. LV = left ventricular; ED = end diastolic; ES = end systolic.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reconstructed Analyses</th>
<th>Complete Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Volume (ml)</td>
<td>(1.90 ± 5.20) 0.980</td>
<td>(1.41 ± 4.37) 0.985</td>
</tr>
<tr>
<td>ES Volume (ml)</td>
<td>(1.90 ± 6.63) 0.864</td>
<td>(0.20 ± 2.10) 0.985</td>
</tr>
<tr>
<td>Stroke Volume (ml)</td>
<td>(0.00 ± 5.64) 0.952</td>
<td>(1.21 ± 4.22) 0.970</td>
</tr>
<tr>
<td>EF (%)</td>
<td>(−0.65 ± 2.99) 0.803</td>
<td>(0.28 ± 1.75) 0.936</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>(0.00 ± 0.31) 0.948</td>
<td>(0.07 ± 0.29) 0.957</td>
</tr>
<tr>
<td>LV Mass (g)</td>
<td>(−6.53 ± 7.74) 0.935</td>
<td>(−4.29 ± 7.83) 0.924</td>
</tr>
</tbody>
</table>

Table 4.8: Difference of volumetric parameters before and after detailed corrections with respect to fully manual analysis (mean±SD) R2. CO = cardiac output; EF = ejection fraction.

of global volume measurements in SA functional CMR. Our results also indicate that such detailed corrections are required for quantification of local myocardial contractility (Table 4.4). In particular, measurements based on wall thickness require both the endocardial and epicardial contours to be accurate on a point-by-point basis (whereas small local errors may cancel out when assessing only global parameters such as overall LV volume).

Finally we have assessed the accuracy of the automatically detected contours with respect to fully manually drawn contours (Table 4.7), as well as the accuracy of the global volumetric results before and after correction with respect to the global volumetric results obtained from fully manual analysis (Table 4.8). Both experiments revealed equivalent accuracy with respect to our previous experiments [13, 15, 14], and with respect to many other methods [26].

The overall accuracy of automated segmentation followed by manual correction as needed was high compared with results obtained from fully manual contouring, with excellent correlation between the two methods (Table 4.8). Limits of agreement were tight and comparable to those of inter-observer variation between two fully manual observations from the literature [27]. LV mass was slightly but significantly underestimated, by approximately 5%,
CHAPTER 4. COMPUTER-AIDED ANALYSIS OF SA CINE CMR

by the automated method versus fully manual analysis. Although EDV was significantly overestimated in the statistical sense, the difference (1.0% of mean EDV) is unlikely to be of clinical relevance. LV ESV, SV and perhaps most importantly EF did not differ between automated and fully manual analyses.

4.5 Limitations

The timing results reported in this paper are taken from analyses by a single user. It remains to be investigated how these timing results translate to other users, with different levels of experience, in other environments. In clinical practice, a typical weekly case load might be 10-20 CMR cases, as compared to the 50-100 studies/week performed by this user during this study. Consequently, clinical users may be less experienced with respect to manipulating contours, but also be less fatigued from repetitive analyses. Moreover, in clinical practice, users will be more focused on time-efficiency versus absolute accuracy of each contour for purposes of generating reference values. Thus the mean analysis times reported here may not be fully generalizable to any given clinical practice for reasons noted above.

It bears mention that our study was conducted on image data obtained from Framingham Offspring cohort participants, the majority of whom were free from clinical cardiovascular disease at the time of CMR study. In clinical practice, analysis of SA functional CMR images is performed for a wide variety of clinical indications. Although similar performance can be expected for many conditions, lower contour accuracy may occur in cases with morphologically deformed ventricles, which may consequently require more analysis time.

The results reported in this paper are obtained using a particular clinical software application for the analysis of SA functional CMR images, which combines automatic and semi-automatic contouring algorithms with graphics editing tools to enable efficient analysis. Thus, it remains to be investigated how timing results are affected by using different contouring algorithms or other editing paradigms. Similarly, all image data used in this study were acquired with a single CMR scanner. Thus, the time-efficiency of our methods may vary when applied to data from other scanners. That said, the accuracy of automatic contouring in this study was comparable to earlier published results [13, 15, 14] obtained on image data from other medical centers.

Finally, we did not determine the time required to load images for analysis. Although this can be important to clinical workflow, the generalizability of such data are extremely limited and depend strongly on local factors such as whether the analysis software operates on a stand-alone workstation or shares resources with other applications, e.g. a PACS, and of course on
the specific hardware configuration. Since any report of data-loading times would apply only to our specific site, and would not provide information of general interest, these data were not obtained.

4.6 Conclusion

We have assessed the accuracy, time-effectiveness, and reproducibility of a clinical application for the analysis of SA functional CMR images, including several automatic and semi-automatic contouring methods. For LV volume quantification, the use of the automatic contouring in a strict protocol enables complete analysis, including generation of LV time-volume curves, within 3-4 minutes, while quantitative analysis of local myocardial contractile function requires additional time to obtain sufficiently accurate contours for reproducible analysis.

4.7 References


CHAPTER 4. COMPUTER-AIDED ANALYSIS OF SA CINE CMR


5

Segmentation of Short Axis Dobutamine Stress Magnetic Resonance Images

5.1 Introduction

Stress induced wall motion abnormalities are early indicators of myocardial ischemia in coronary artery disease (CAD) that can be identified using pharmacologic stress testing with echocardiography or cardiac magnetic resonance (CMR) imaging. For CMR stress testing, a standardized dobutamine stress magnetic resonance (DSMR) exam [15] prescribes cine CMR imaging during dobutamine induced cardiac stress. Throughout such an exam, dobutamine is administered in increments of 10 µg per kg body weight per minute until the target heart rate ($0.85 \times (220 - \text{age})$) is reached. If the heart rate response is poor, additional doses of atropine may be administered. During each increment, or stress level, cine CMR imaging is performed in 3 short axis (SA) imaging planes (basal, mid, and apical slices) and 3 long axis (LA) imaging planes (LA two chamber (2CH), LA three chamber (3CH), and LA four chamber (4CH) views). The test is stopped when wall motion abnormalities are induced, when serious side effects occur, or when the target heart rate is reached, typically resulting in 3-6 stress levels.

The three SA slices contain 25-50 phases in the heart cycle, see figure 5.1 for examples. Altogether, up to 900 SA images may be acquired, which in clinical practice are reviewed in a synchronized fashion. A quantitative assessment requires delineation of the left ventricular LV endocardial and epicardial contours in all images. In addition, although currently of lesser clinical importance, right ventricular RV endocardial delineations may be drawn. Delineation of the RV epicardial contour is currently not feasible as the RV myocardium usually appears too thin in the MR images to be indicated with two contours. Nevertheless, the complete delineation involves up

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This chapter has been adapted from: G.L.T.F. Hautvast, T. Tangcharoen, M. Breeuwer, and E. Nagel, *Segmentation of Short Axis Dobutamine Stress Magnetic Resonance Images*, Submitted to the International Journal of Cardiovascular Imaging, 2011.

Author contributions: GH implemented the contour detection methods, analysed the resulting data, and prepared the manuscript. TT collected image data and performed the analysis. MB and EN supervised the project.
to 2700 contours in a single DSMR exam. Consequently, manual delineation is prohibitively time-consuming for clinical practice and computer assistance is a necessity.

Fortunately, automatic algorithms for segmentation of SA cine CMR acquisitions have been investigated extensively to enable time-efficient analysis of regular 10-15 slice cine acquisitions performed at rest. These methods can be applied to SA DSMR images without any modification. However, to the best of our knowledge, studies investigating the accuracy at increased heart rates have not been published.

In this study, we will evaluate the accuracy of a semi-automatic delineation method [30] that was developed and validated for regular SA cine CMR images on SA DSMR images. This evaluation reveals a reduced accuracy for myocardial contour detection at increasing levels of stress. Therefore, we also propose a new automated method for delineation of SA DSMR images that exploits the close relation between the separate stress levels to increase contour detection accuracy and ultimately reduce user interaction time. The new method combines the contour propagation method with a registration algorithm and a contour averaging algorithm to enable the propagation of cardiac contours to higher stress levels. We will present results
from optimization and validation experiments using image data acquired from 47 patients. In the experiments we assessed the performance of our method by quantification of contour positioning accuracy, analysis time and wall motion measurements.

5.2 Background

Pharmacological stress testing emerged as an alternative to physical exercise for the detection of inducible myocardial ischemia. Cardiac stress was routinely induced using adenosine or dobutamine and stress echocardiography quickly became a well established method for the detection of wall motion abnormalities. The use of DSMR was first reported in 1992 [14]. DSMR yields a significantly higher diagnostic accuracy for the detection of wall motion abnormalities than dobutamine stress echocardiography [12] and is capable of detecting wall motion abnormalities in patients not suited for stress echocardiography [11]. The use of dobutamine is superior to adenosine for the induction of wall motion abnormalities in patients with significant CAD [13] and has a similar safety profile to other methodologies using dobutamine infusions [10]. A more extensive review of the development of the DSMR in the past two decades is given by Charoenpanichkit and Hundley [18].

Automatic delineation of the SA cine CMR images has been studied extensively. This problem has proven to be exceptionally challenging, in particular because of the presence of papillary muscles that need to be excluded from the myocardium wall to enable measurements of wall thickness, although there are often no image features separating the papillary muscles from the myocardium wall. Consequently, solutions have been proposed based on many image processing algorithms, including methods based on active contour models [30, 24, 25], active shape models [28, 26], active appearance models [22, 20, 27], level sets [23, 21], graph cuts [32, 31], fuzzy connectivity [33, 34] and combinations of those approaches [29, 19]. While these methods perform reasonably well in validation studies comparing quantification results obtained from manually and automatically defined contours on medium-sized populations, none provide perfect contours on a case-by-case basis, as was concluded in the recent review by Petitjean and Dacher [35].

Our new method is, to our best knowledge, the first to be developed specifically to overcome the segmentation difficulties present in DSMR images. This includes small displacements of the heart from one stress level to another, as the images are acquired in different breath holds. In our method, we correct for these deformations using an affine transform that is estimated by means of image registration. A review of the most important existing registration techniques is given in [1, 2]. Furthermore, a review of the use of image registration in cardiac imaging is given in [3]. The registration
techniques used in our method are based on descriptions given in [1].

Unfortunately, such affine transformations are not sufficient to describe the deformations from one stress level to another. Therefore we use active contours [5, 7] for accurate repositioning of the myocardial contours after image registration and successive contour transformation. We have used an active contour model that was developed for accurate myocardial contour propagation over the phases in SA cine CMR acquisition [30]. This active contour model deforms its shape to balance an internal force that retains contour smoothness with an external force that is intended to maintain a constant contour neighborhood through matching of perpendicular gray value profiles.

Finally, our new method combines information from neighbouring phases and stress levels using a weighted sum of contours resulting from different propagations. To achieve this, we have developed a weighted version of the repeated averaging algorithm (RAA) [6]. Moreover, we use the RAA for establishing a point-to-point correspondence that is suitable for validating the resulting contours.

5.3 Methods

5.3.1 DSMR Imaging

We have evaluated our method using DSMR exams from 47 patients. Cine CMR imaging with retrospective ECG triggering was used to obtain 25-50 phases at 3-6 levels of cardiac stress. All images were 256x256 in size and covered a field of view of 350x350 - 480x480mm. The images were acquired using echo time 1.5 - 1.8 ms, repetition time 3.1 - 3.6 ms, and flip angle 60 degrees. Three SA slices were acquired with slice thickness 8 mm and 6-13 mm spacing in between at approximately basal, mid and apical position. Ten of these cases were used for the initial evaluation and optimization of our method, while the remainder was used for a more extensive validation to prove that our new method is robust for variations as present in larger patient populations.

5.3.2 Image Analysis

All images were transferred to a commercially available workstation (ViewForum 5.1, Philips Healthcare) that is equipped with a functional analysis package that enables propagation of the cardiac contours from end diastolic (ED) to the remainder of phases in SA cine CMR images. This is implemented using an active contour model that tries to maintain a constant contour environment by matching gray values in profiles perpendicular to the contour [30], as described in chapter 3. Consequently, the contours should maintain a constant position with respect to neighbouring anatom-
5.3. METHODS

ical structures, such that the resulting contours reflect the preferences of the user, which is particularly important in cine CMR images because local image features do not describe the desired contours near the papillary muscles.

For the purpose of this study, the workstation was also equipped with a prototype dedicated analysis application for SA DSMR exams, incorporating our new method for cardiac contour propagation from lower to higher stress levels. The new, dedicated method for segmentation of SA DSMR images combines an image registration algorithm, an active contour model and the RAA to delineate the images of a particular stress level, given the images and contours of the previous stress level. This approach exploits the close relation between the images of different stress levels and phases in a DSMR exam, as well as valuable user input provided throughout the segmentation procedure. By using the corrected contours as prior for delineation of remaining stress levels, we prevent repetition of the same error in these stress levels.

Our new method includes an image registration step to cope with displacements of the heart in DSMR exams that are caused by different breath hold positions. This image registration is performed between ED images only, relying on successful ECG triggering to prevent inaccuracies from temporal misalignment. To capture the non-rigid and mixed motions of the heart [3], we estimate an affine transformation, i.e. including translation, rotation, scaling, and skewing, between the coordinate systems of the ED images from different stress levels. The 3 SA slices are registered independently by maximizing the correlation coefficient using a gradient descent approach. We choose to use the correlation coefficient because it is known to be the optimal similarity measures for registering images with linearly related gray values [9], which is the case in DSMR as the same acquisition protocol is repeated at each stress level.

Because an affine transformation is not sufficient to describe the deformations from one stress level to another, we use an active contour model that enables myocardial contour propagation from one stress level to another while taking into account the estimated affine transform. Therefore we have adapted the active contour model that we developed specifically for the propagation of myocardial contours over the phases in cine CMR images [30]. While adhering to the same general structure for computation of the deformation process given internal and external forces, we have modified the sampling scheme of the gray value profiles, see figure 5.2. These are now sampled perpendicular to the initial contour in the reference image, and perpendicular to the transformed contour in the target image. The contour is then deformed in a Newtonian process that balances an external force based on gray value matching along the profiles [30] and an internal force that favours smooth contours [4].

When performing this propagation over stress levels in all phases inde-
CHAPTER 5. ANALYSIS OF DSMR IMAGES

Figure 5.2: The active contour model samples profiles perpendicular to the reference contour and the transformed contour. After computing an external energy distribution based on the matching of gray values, the final position in the image is calculated using a newtonian process.

...pendently, the resulting delineation becomes less smooth over the phases with increasing stress levels as relevant temporal information is ignored. Therefore, we balance the information from prior stress levels and neighbouring phases by combining the new propagation method with the existing method. Next to propagating myocardial contours over the stress level in all phases, we also propagate the ED contours (obtained with stress propagation) over the phases. To enable control over the relative contribution of propagation over the phases and the stress levels, we incorporated a weighted averaging using the RAA to compute the final resulting contour. We established an initial correspondence using radial resampling for both LV contours and a closest-point method for the RV contour and refined this correspondence in an iterative approach that typically converges within 5 iterations.

Finally, our new method can be deployed in two usage modes: semi-automatic or fully automatic. In semi-automatic deployment, the clinical user may correct contours locally where necessary. Those corrections will then be propagated to the next stress level. In fully automatic deployment, the myocardial contours are propagated over all stress level in an unsupervised way.
5.3. METHODS

5.3.3 Optimization

Our new method for segmentation of DSMR images has several parameters that affect the accuracy of the resulting cardiac contours. Finding the optimal parameter configuration for optimal accuracy is a very delicate task due to the complex parameter interactions that may exist, which is especially true for methods in which several complex algorithms are combined. To optimize the accuracy of our method, we have used full factorial experiments, which are known for their unique ability to discover factor interactions [8]. In these full factorial experiments, we compute the contour position error for each possible combinations of a fixed number of levels for each parameter. To prevent an otherwise excessive computation time, we divided the parameter space hierarchically into smaller sub-problems. By decomposing the total variability in the resulting parameter spaces using analysis of variances (ANOVA), we identify the significance of each parameter using a linear statistical model. The optimal parameter setting is then concluded using the response plots of the significant parameters only.

5.3.4 Evaluation Methods

We have assessed the accuracy of the resulting contours using contour positioning errors with respect to a golden standard. For the purpose of optimization, we used a golden standard defined by two experts that each made two delineations using the existing, commercially available contour detection methods. The resulting four delineations have been averaged using the RAA to obtain the golden standard contours. Furthermore, this allows us to compute the variance of the expert delineations at all stress levels. Repeating this procedure for the purpose of validation in the remaining 37 cases was too time consuming. Therefore, a single expert analysed those cases using the new method, with the specific instruction to meticulously correct all delineations for the purpose of validation.

Contour positioning errors are quantified as the mean absolute distance \( \varepsilon_{\text{mean}} \), the RMS distance \( \varepsilon_{\text{rms}} \) and the maximum absolute distance \( \varepsilon_{\text{max}} \), as defined by equations 5.1-5.3, in which \( p_i \) and \( \hat{p}_i \) refer to corresponding pairs of points on the resulting and reference contours respectively. This point-to-point correspondence was obtained using the RAA, which was chosen for its ability to establish correspondence such that distances are computed perpendicular to the centerline, even in close proximity to the papillary muscles [30].

\[
\varepsilon_{\text{mean}} = \frac{1}{N} \sum_{i=0}^{N} |p_i - \hat{p}_i| \quad (5.1)
\]
These contour positioning errors are quantified for the fully automatic version after propagating the golden standard contours at rest to all stress levels, whereas the contour positioning errors for the semi-automatic version were quantified after propagating the golden standard contours at any stress level one level up (simulating that the user corrects all contours meticulously before further propagation).

In addition to contour positioning errors, we have assessed the clinical value of the contour detection methods, by assessing the impact on time efficiency and derived quantitative parameters. To assess the time-efficiency of each method we measured the time spend to analyse each SA cine CMR series. For this purpose, the analysis software was equipped with logging functionality. Mean ± standard deviation (SD) analysis times per stress level are reported. Finally, to assess the impact on derived quantitative parameters, we quantified contractile parameters in 16 segments of the standard AHA model [16] (the apical segment is not imaged in SA DSMR images). This included measurements of end systolic (ES) wall motion, i.e. the displacement of the endocardium contour from ED to ES measured in mm, and of wall thickening, i.e. the difference in ED and ES wall thickness in mm. Scatter plots of these measurements were generated including the results of linear regression analysis. In addition, differences were reported as mean and standard deviation of the signed difference.

5.4 Results

The four expert delineations were averaged, after which observer variability for myocardial contour delineation was assessed by measuring the mean, root-mean-square (RMS) and maximum distance between the individual expert delineations and the golden standard, resulting in table 5.1. Moreover, we have measured the user interaction time, or correction time and correction sizes (measured using the RMS positioning error) during the generation of the golden standard. The resulting mean ± SD correction size and correction time has been plotted against the stress level in figure 5.3. Student-t tests confirm that it takes significantly larger corrections and more time to obtain a satisfactory delineation at higher stress levels, versus at rest.

After defining the optimal parameter setting from the full factorial experiments, we performed an initial assessment of contouring accuracy using our new method on the 10 cases used for optimizing the parameter settings.
5.4. RESULTS

<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{\text{mean}}$ (mm)</th>
<th>$\varepsilon_{\text{rms}}$ (mm)</th>
<th>$\varepsilon_{\text{max}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Endocardium</td>
<td>$0.83 \pm 0.48$</td>
<td>$0.98 \pm 0.57$</td>
<td>$1.82 \pm 1.06$</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>$0.91 \pm 0.40$</td>
<td>$1.06 \pm 0.44$</td>
<td>$2.05 \pm 0.86$</td>
</tr>
<tr>
<td>RV Endocardium</td>
<td>$1.12 \pm 0.73$</td>
<td>$1.29 \pm 0.87$</td>
<td>$2.33 \pm 1.68$</td>
</tr>
</tbody>
</table>

Table 5.1: Variance of the expert delineations.

We measured the mean, RMS, and maximum contour positioning error for all myocardial contours obtained using semi-automatic and fully automatic deployment of our new method. We listed the results after each stage of our method in table 5.2. For comparison to the initial situation, the mean, RMS, and maximum distance between golden standard contours from one stress level to another was $3.85 \pm 3.14$mm, $4.36 \pm 3.40$mm, and $7.12 \pm 5.11$ mm respectively. The final results were split for the LV endocardial contour, the LV epicardial contour and the RV endocardial contour in table 5.3. Examples of segmentation results at the ED images and ES images in a DSMR exam are given in figure 5.4.

To assess the time-efficiency of our new method, both experts have repeated their contour drawing effort, this time aided by our new optimally configured method. Again, we have measured the mean $\pm$ SD correction size and interaction time on each stress level resulting in figure 5.5. Furthermore, we computed the mean, RMS, and maximum contour positioning errors of the resulting contours throughout the analysis of the validation cases, resulting in table 5.4. Finally, we quantified ES wall motion and wall thickening in 16 AHA segments after using new method in fully automatic and semi-automatic deployment, and compared the results to the final quantification results obtained after correcting contours, resulting in figure 5.6.
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<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{\text{mean}}$ (mm)</th>
<th>$\varepsilon_{\text{rms}}$ (mm)</th>
<th>$\varepsilon_{\text{max}}$ (mm)</th>
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</thead>
<tbody>
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<td>Automatic Registration</td>
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<td>2.76 ± 1.97</td>
<td>4.61 ± 2.87</td>
</tr>
<tr>
<td>Stress Propagation</td>
<td>1.18 ± 0.88</td>
<td>1.42 ± 0.91</td>
<td>2.73 ± 1.70</td>
</tr>
<tr>
<td>Temporal Propagation</td>
<td>1.11 ± 0.77</td>
<td>1.34 ± 0.92</td>
<td>2.56 ± 1.72</td>
</tr>
<tr>
<td>Semi-automatic Registration</td>
<td>1.60 ± 1.14</td>
<td>1.85 ± 1.24</td>
<td>3.29 ± 2.01</td>
</tr>
<tr>
<td>Stress Propagation</td>
<td>1.02 ± 0.63</td>
<td>1.23 ± 0.78</td>
<td>2.43 ± 1.53</td>
</tr>
<tr>
<td>Temporal Propagation</td>
<td>0.99 ± 0.62</td>
<td>1.20 ± 0.75</td>
<td>2.35 ± 1.51</td>
</tr>
</tbody>
</table>

Table 5.2: Positioning errors after each stage of our method with respect to the golden standard in the 10 cases used for parameter optimization.

<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{\text{mean}}$ (mm)</th>
<th>$\varepsilon_{\text{rms}}$ (mm)</th>
<th>$\varepsilon_{\text{max}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatic LV Endocardium</td>
<td>1.20 ± 0.82</td>
<td>1.43 ± 0.97</td>
<td>2.63 ± 1.74</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>0.76 ± 0.39</td>
<td>0.94 ± 0.47</td>
<td>1.95 ± 0.99</td>
</tr>
<tr>
<td>RV Endocardium</td>
<td>1.39 ± 0.87</td>
<td>1.65 ± 1.07</td>
<td>3.11 ± 2.06</td>
</tr>
<tr>
<td>Semi-automatic LV Endocardium</td>
<td>1.03 ± 0.65</td>
<td>1.24 ± 0.77</td>
<td>2.33 ± 1.41</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>0.78 ± 0.41</td>
<td>0.97 ± 0.49</td>
<td>2.02 ± 1.04</td>
</tr>
<tr>
<td>RV Endocardium</td>
<td>1.15 ± 0.69</td>
<td>1.38 ± 0.87</td>
<td>2.69 ± 1.90</td>
</tr>
</tbody>
</table>

Table 5.3: Positioning errors of the detected contours with respect to the golden standard in the 10 cases used for parameter optimization.

<table>
<thead>
<tr>
<th>Contour</th>
<th>$\varepsilon_{\text{mean}}$ (mm)</th>
<th>$\varepsilon_{\text{rms}}$ (mm)</th>
<th>$\varepsilon_{\text{max}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatic LV Endocardium</td>
<td>1.69 ± 1.37</td>
<td>1.96 ± 1.61</td>
<td>3.41 ± 2.78</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>1.38 ± 0.99</td>
<td>1.68 ± 1.19</td>
<td>3.31 ± 2.26</td>
</tr>
<tr>
<td>RV Endocardium</td>
<td>1.57 ± 1.36</td>
<td>1.92 ± 1.69</td>
<td>3.95 ± 3.45</td>
</tr>
<tr>
<td>Semi-automatic LV Endocardium</td>
<td>1.07 ± 1.15</td>
<td>1.25 ± 1.32</td>
<td>2.21 ± 2.26</td>
</tr>
<tr>
<td>LV Epicardium</td>
<td>0.86 ± 0.86</td>
<td>1.05 ± 1.02</td>
<td>2.12 ± 1.98</td>
</tr>
<tr>
<td>RV Endocardium</td>
<td>1.11 ± 1.26</td>
<td>1.37 ± 1.57</td>
<td>2.77 ± 3.16</td>
</tr>
</tbody>
</table>

Table 5.4: Positioning errors of the detected contours with respect to the golden standard in the 37 cases used for validation.
Figure 5.4: Resulting segmentations of DSMR images at ED (a) and ES (b), different slices from one stress level from top to bottom, the same slice at increasing stress levels from left to right.
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Figure 5.5: Correction size (a) and correction time (b) required to obtain delineations in a DSMR exam using our new method.

Figure 5.6: Quantification of ES wall motion (a,b) and wall thickening (c,d) in AHA segments using the semi-automatic (a,c) and fully automatic (b,d) propagation across stress levels.
5.5 Discussion

By recording all user interactions, we were able to gain valuable information on the accuracy of myocardial contour propagation, as described in chapter 3, on increased levels of cardiac stress. We believe that the significant decrease in contour positioning accuracy (and related increase in analysis time) is caused by the variability in myocardial contraction patterns at increased heart rates for this patient population.

The reported contour positioning errors after each stage of the algorithm (table 5.2) clearly show that merely applying an affine transformation obtained using an optimally configured registration algorithm results in inaccurate positioning of myocardial contours on successive stress levels. While the accuracy of the resulting contours improves after each step of the algorithm, the impact of the final temporal propagation and averaging seems to be limited despite a clear improvement in temporal consistency of the resulting contours.

Using our new method in semi-automatic deployment, we achieved a significant reduction in correction size and correction time. Note that the experts needed on average 53 seconds to review a perfect segmentation. Furthermore, the accuracy of the contours resulting from our new method does not decrease with increasing heart rate. A comparison of figures 5.3 and 5.5 reveals that the experts needed about 200 seconds less to obtain the desired LV and RV segmentations at a stress level using our new method. This may amount to a time gain of about 17 minutes (1000s) for analysing a DSMR exam including a rest scan and 5 stress levels.

Comparing tables 5.3 and 5.4, we conclude that our semi-automatic approach is robust for variations as present in larger patient populations and translates well to clinical practice without significant loss of contour positioning accuracy. However, the accuracy of resulting contours in fully automatic deployment decreases, which seems to be the result of the larger variability in contour positioning from the step-wise propagation. Nevertheless, the resulting delineations can be perceived as highly accurate with contour positioning errors close to the pixel dimensions [35]. The difference between the results obtained from semi-automatic and fully automatic deployment, can also be interpreted as the difference between users that never perform corrections, and diligent users that correct until perfection.

The lower accuracy of contours obtained in fully automatic deployment clearly results in less accurate quantification of regional ES wall motion and wall thickness, as compared to semi-automatic deployment. The correlation between quantification results before and after correction in semi-automatic deployment are comparable to the results presented in chapter 4, and thus confirm the notion that quantification of regional contractile function still requires manual contour corrections. Furthermore, as quantification of absolute wall thickening requires both the endocardial and epicardial contours...
to be accurate on a point-by-point basis it is less accurately quantified compared to ES wall motion, which depends on endocardial contours only.

5.6 Limitations

For the 37 validation cases, we have assessed the accuracy of the resulting contours obtained using our new method against a golden standard that was obtained by correcting those resulting contours. This approach has been used extensively in the validation of automatic myocardial contour delineation in regular 10-15 slice SA cine CMR acquisitions [17], but cannot be compared to comparisons of resulting contours to fully manual analysis. Nevertheless, this approach enables the inclusion of more contour data within the same amount of time and arguably provides a more realistic impression of clinical use, as clinical users will ignore minor contour positioning errors and correct only contours that affect quantification too much [17].

5.7 Conclusion

We have developed a new method for delineation of cardiac contours in SA cine CMR data from DSMR exams that is specifically designed to exploit the close relation between the images at the various stress levels. The method uses registration, contour propagation and contour averaging to position the cardiac contours in the stress series given the cardiac contours at rest. We have obtained optimal parameter settings for all algorithms using a factorial experimental design. The optimally configured method is capable of propagating contours from one stress level to another with sub-pixel precision. Consequently, our new dedicated method allows experts to obtain all cardiac contours in a DSMR exam in significantly less time than required for independent analysis of all series in the stress exam. Furthermore, we have shown that our new method is robust for variations as present in larger patient populations.

5.8 References


5.8. REFERENCES


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5.8. REFERENCES


Part II

Analysis of Perfusion CMR
Myocardial perfusion imaging by dynamic contrast-enhanced (CE) cardiac magnetic resonance (CMR) was introduced in 1990, when Atkinson et al. [30] first imaged the contrast agent transit through the cardiac chambers and myocardium after injection of a bolus of Gadolinium. Subsequently, the technique has undergone continuous development in the areas of MR hardware, pulse sequence design, new contrast agents, and perfusion analysis methods. Nowadays, rapid imaging during the first pass of a Gadolinium contrast bolus is still the most robust method to image myocardial perfusion with CMR [25]. Electrocardiogram (ECG) triggering is used to acquire images from the same phase of the cardiac cycle to eliminate the contracting motion of the left ventricle (LV). However, breathing motion is usually present in perfusion CMR series, as the contrast agent transit often lasts too long for patients to hold their breath. A typical perfusion CMR series consists of approximately 40-60 dynamics for each slice location.

Quantitative analysis of myocardial perfusion using CMR images consists of the computation of various parameters derived from signal intensity (SI) curves, that represent the intensity vs. time extracted from a single voxel or region in the perfusion CMR images. These SI curves should represent intensity from exactly the same positions(s) in the myocardium in all dynamics, which is complicated by the presence of breathing motion. Therefore, if a regional analysis is performed it is necessary to adapt myocardial segment

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The clinical image data presented in this chapter was kindly provided by King’s College London, UK.

Figure 6.1: Delineated short axis (SA) perfusion CMR images.
delineations accordingly in all dynamics. Optionally, this process may be simplified by the use of breathing motion correction. However, for voxel based analysis such breathing motion correction is a necessity to obtain the required voxel-to-voxel correspondence over all dynamics. Hence, the analysis of perfusion CMR images should include motion correction and LV delineation as essential pre-processing steps before the quantitative analysis.

6.1 Motion Correction

In early publications on the analysis of perfusion CMR images, respiratory motion correction was performed manually by aligning each image to a reference [20, 13]. Fortunately, this time-consuming procedure can now be performed automatically using image registration algorithms. These algorithms are capable of estimating transformations between images in order to align the anatomical structures that are present. Image registration algorithms have been used for many applications and are well described in [35], however, because of the non-rigid and mixed motions of the heart and the thorax structures, cardiac image registration is still considered to be complex problem. Hence, cardiac image registration techniques have been reviewed separately in [1].

Image registration is performed between pairs of images. In perfusion CMR images this can be done by registering all dynamics to a single reference [27], or by registering each consecutive pair of dynamics [8, 15, 19]. Alternatively, [28] proposed to combine both approaches in a weighted sum.

Despite the non-rigid and mixed motion of the heart, most published approaches for respiratory motion correction in perfusion CMR only correct for in-plane translations [18, 7, 19, 2, 5, 31]. Such methods are said to have two degrees of freedom. Other authors also included an additional degree of freedom by including rotations [9, 8, 27, 15, 28, 3, 26].

Image registration methods estimate a transformation by maximizing the similarity between two images, as can be quantified by various similarity measures. For respiratory motion correction in perfusion CMR, the mean squared difference has been used in [9, 27, 2], the correlation coefficient was used in [8, 15], [19] used cross correlation and [31] used normalized mutual information, as introduced in [34].

In [4] the image registration approach was extended by relating the diaphragm motion to the resulting transformation. This patient specific motion model is obtained from 40% of all dynamics and can be applied to the remainder of dynamics, thus eliminating the need for image registration for those dynamics.

Alternatively, it is also possible to estimate transformations between the dynamics in perfusion CMR series based on its delineation. This approach is used in [16, 7] after propagating an initial contour through all dynam-
6.2. Delineation

In the absence of perfect motion correction, tracing the endo- and epicardial LV contours on each image is a tedious and time-consuming process, which remains the primary bottleneck of the analysis [25]. Moreover, manual tracing is difficult due to the poor contrast between the myocardium and blood in the dynamics before contrast arrival in the LV, as well as in the last dynamics of the first contrast passage. If motion correction is successfully applied, a single tracing for the endocardial and epicardial contours suffices to delineate the LV in all dynamics, thus greatly simplifying the delineation task.

The first attempt towards automatic delineation of perfusion CMR images has been in [13], in which a fuzzy C-means algorithm is applied to manually registered functional and perfusion CMR images. The clustering is used to decompose the perfusion CMR images into specific feature images denoting the background, the myocardium and the blood pool. Such a decomposition may also be computed using a regularized factor analysis, as shown in [29]. In subsequent papers by Breeuwer and Spreeuwers, several other features images have been used in combination with a active contour model (ACM), among which the temporal maximum intensity projection (MIP) [15, 8], a combination of temporal MIPs and selected dynamics, [32] and an upslope map [15]. Such upslope maps have also been used to support visual assessments [17]. In [22], a stochastic level set segmentation scheme is used to delineate perfusion CMR images. Finally, the use of AAM, as proposed in [26, 14], perfusion CMR sequences are simultaneously registered and delineated, as the myocardial borders are an integral part of AAMs.

6.3. Quantification

After registering and delineating a perfusion CMR series, signal intensity curves that depict the variation of the SI over time can be obtained, either for each voxel, or for regions. Quantification from perfusion CMR images involves processing of such SI curves to obtain either a direct estimate or semi-quantitative indicators of the myocardial blood flow. An earlier, more extensive review of these approaches is given in [25].

In semi-quantitative analysis, the myocardial blood flow is assessed by quantifying several parameters of SI curves, for which the relationship to the
CHAPTER 6. PERFUSION CMR ANALYSIS: STATE OF THE ART

Figure 6.2: Examples of SI curves derived from perfusion CMR images and key semi-quantitative parameters explained.
6.4. VALIDATION

tissue blood flow is based on empirical observations only. The parameters most commonly used to assess myocardial perfusion semi-quantitatively include the peak SI, the time to peak SI, the peak up-slope, the mean transit time and the area under the SI curve, as indicated in figure 6.2.

In true quantitative analysis, the myocardial blood flow (MBF), expressed in ml min\(^{-1}\) g\(^{-1}\), is estimated based on the central volume principle [36], see eq. 7.1, which relates the tracer concentration in a tissue region \(C_T(t)\) to the convolution of the tracer concentration at the arterial input \(C_{AIF}(t)\) with an unknown impulse response \(K(t)\). As perfusion CMR allows extraction of SI-curves proportional to \(C_T(t)\) and \(C_{AIF}(t)\), this relation needs to be reversed, or deconvolved, to estimate the impulse response \(K(t)\) and quantify MBF according MBF = \(K(0)\).

\[
C_T(t) = \int_0^t K(t-s)C_{AIF}(s)ds = \text{MBF} \int_0^t (C_{AIF}(s) - C_{out}(s))ds \tag{6.1}
\]

Using linear algebra, deconvolution can be formulated as solving a simple linear system \(Ax = B\), in which \(B\) holds \(N\) samples of the output, \(A\) is a \(N \times N\) lower triangular Toeplitz matrix holding the arterial input function (AIF), and \(x\) is the impulse response \(K(t)\). Unfortunately, this linear system is known to be "ill-posed", such that many mathematically admissible solutions have to be dismissed as physiologically unrealistic. To cope with these numerical problems, several approaches have been proposed to constrain or regularize the deconvolution to obtain physiologically plausible solutions in which the tissue impulse response is smooth and decreasing [21], as well as spatially coherent [23]. The solution to the deconvolution problem can be constrained using a Fermi function [10, 33]. In unconstrained, regularized methods the tissue impulse response is modelled using splines [21], or using auto-regressive moving average (ARMA) models [12, 11, 23].

6.4 Validation

The validation of breathing motion correction methods has been performed in various approaches, without providing a single best practice. Most studies include an experiment in which the motion of one or more markers in all dynamics is measured before and after registration [4, 24, 3, 28, 2, 31], which unfortunately has little value for various reasons. Direct comparisons are often impossible because different studies use different markers. Moreover, the number of anatomical markers per dynamic is usually very small, i.e. up to 3 in [4]. Consequently, the markers do not span the entire LV and therefore do not provide information on other myocardial regions. Moreover, the markers are positioned at well defined anatomical locations with high contrast, which may be better aligned than other myocardial regions. Most
importantly, if too few markers are used, it is impossible to discriminate possible benefits from adding more degrees of freedom to the registration method, simply because a single point cannot prescribe an affine transform. Therefore, measuring contour displacements including many markers, as done in [26], should be considered as primary method.

Because of the limitations of measuring marker motion to validate motion correction, many studies include an additional experiment in which the quality of the derived SI-curves before and after registration are compared. Again, this provides limited information for direct comparisons. With respect to SI-curves obtained from non-aligned perfusion CMR images, any reasonable method will provide significant improvements in signal-to-noise ratio (SNR). However, with respect to each other, the differences are very small and probably insignificant. This is in particular likely to occur because the SI-curves are extracted for segments, rather than voxel-based. In this context, comparing voxel-based SI-curves acquired after registration to SI curves acquired from an optimally registered, ground truth perfusion CMR sequence may be a better alternative. However, this does not solve another important limitation of comparing SI curves (and derived perfusion parameters), namely the fact that these will also be influenced by the delineation.

Until now, the technical validation of the automatic contour detection methods has been limited. However, measuring distances between golden standard and automatically determined contours, as done in [26] should be the method of choice. Measuring distances between golden standard contours at consecutive dynamics may serve as a criterion for image registration quality, whereas measuring distance between golden standard and automatically determined contours may serve as a criterion for contour delineation quality.

The goal of the analysis of perfusion CMR images is quantification of the myocardial blood flow via semi-quantitative, or ultimately truly quantitative methods. Little is known about the dependency of these quantification methods on the pre-processing methods used for motion correction and contour delineation, as the focus for validation has been clinical, rather than technical. The clinical validation have been performed by comparing the diagnostic performance of perfusion CMR analysis with other diagnostic tests.

6.5 References


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6.5. REFERENCES


7

Myocardial blood flow quantification from MRI by deconvolution using an exponential approximation basis

7.1 Introduction

In perfusion cardiac magnetic resonance (CMR), rapid imaging is used to visualize the first pass of a Gadolinium contrast bolus through the cardiac chambers and myocardium (figure 7.1). Visual and semi-quantitative analysis of such images are well accepted methods for the diagnostic assessment of myocardial perfusion [10, 11, 6]. Moreover, perfusion CMR images can be used to estimate the myocardial blood flow (MBF) by means of deconvolution analysis. However, the post-processing procedure for MBF quantification is time consuming and requires substantial technical expertise, including detailed knowledge about acquisition parameters and their relation to the assumptions used in the quantification algorithms. For these reasons, analysis software packages are expected to retain the flavor of research tools [18].

Deconvolution analysis requires the extraction of an arterial input function (AIF) and one or more tissue signal intensity (SI) curves, which represent the intensity over time in a single voxel or region. To facilitate the extraction of these SI curves, it is essential to remove the respiratory motion present in perfusion CMR images and to delineate the myocardium of the left ventricle (LV) in all dynamics. In addition, the deconvolution analysis procedure includes automatic inhomogeneity correction and requires the

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Author contributions: GH implemented the pre-processing methods, the deconvolution method and the simulation experiment, designed and conducted evaluation on patient data and prepared the manuscript; AC developed the phantom experiments and acquired and analysed the patient data; NZ performed the analysis of the simulation and phantom experiments; AS analysed the patient data. MB and EN arranged funding and supervised the project.
user to define, or verify, several parameters, including time of contrast arrival in the AIF and tissue SI curves.

To enable the translation of MBF quantification from clinical research to clinical routine, we aim to simplify and shorten the post-processing workflow by introducing a robust deconvolution method together with extensive automation. In this work, we propose to quantify MBF by deconvolution using an exponential approximation basis [19]. We have integrated our solution in a post-processing framework that performs automatic respiratory motion correction and myocardial delineation. Altogether, we will show that the quantification of MBF based on perfusion CMR images can be an accurate, efficient and reproducible procedure.

7.2 Background

Quantification of MBF in ml min⁻¹ g⁻¹ myocardial tissue using perfusion CMR is based on the central volume principle [20], see equation 7.1. The right-hand side of this equation is a statement of mass balance, also known as Fick’s principle, that states that the accumulated tracer in a tissue region is given by the difference of concentrations of tracer inflow $C_{in}(s) = C_{AIF}(s)$ and outflow $C_{out}(s)$, multiplied by the MBF. Essentially, the central volume principle also relates the tracer concentration in a tissue region $C_T(t)$ to the convolution of the tracer concentration at the arterial input $C_{AIF}(t)$ with an unknown impulse response $K(t)$. As perfusion CMR allows extraction of SI curves proportional to $C_T(t)$ and $C_{AIF}(t)$, this relation needs to be reversed, or deconvolved, to estimate the impulse response $K(t)$ and quantify MBF according MBF = $K(0)$.

$$C_T(t) = \int_0^t K(t-s)C_{AIF}(s)ds = \text{MBF} \int_0^t (C_{AIF}(s) - C_{out}(s))ds \quad (7.1)$$

Deconvolution can be formulated as solving a linear system $Ax = B$, in which $B$ holds $N$ samples of the output, $A$ is a $N \times N$ lower triangular Toeplitz matrix holding the AIF, and $x$ contains $N$ samples of the impulse response $K(t)$. This linear system is unfortunately known to be *ill-posed*,
meaning that there is no unique solution. Many mathematically admissible solutions need to be dismissed as physiologically unrealistic. To solve these numerical problems, the impulse response $K(t)$ has been modelled using a Fermi function [2, 9], pharmacokinetic models [23, 5], auto-regressive moving average (ARMA) modelling [4, 3], or splines [7]. These approaches reduce the size and complexity of the linear system, and constrain or drive the solution towards physiologically realistic impulse responses.

To enable accurate MBF quantification, SI curves need to be extracted from corresponding locations, or regions, in all dynamics. Therefore, it is essential to remove any respiratory motion present in perfusion CMR images. Respiratory motion correction of perfusion CMR images is nowadays performed using image registration techniques [1, 8] that are capable of dealing with the contrast variation during the bolus passage and the non-rigid motion of the heart.

Extraction of SI curves also requires the myocardial contours to be delineated in all dynamics. Manual delineation is difficult and time-consuming, in particular because the user needs to integrate information from several dynamics as the contrast across the myocardial boundaries varies during the bolus passage. Consequently, automation is highly desirable and should take into account features from all dynamics.

### 7.3 Methods

Our new automated analysis method towards quantification of MBF employs deconvolution using an exponential approximation basis to guarantee a physiologically feasible solution. The method starts by automatically determining a region of interest (ROI) containing the heart. Within the ROI, image registration is performed to correct for respiratory motion. Next, the myocardial contours are delineated automatically using a deformable template segmentation scheme on a temporal maximum intensity projection (MIP) obtained after respiratory motion correction. In the remainder of this section, each of these steps will be described in more detail.

#### 7.3.1 Region of interest

To enable faster and more accurate respiratory motion correction, we automatically determine a ROI based on the observation that both ventricles are the largest enhancing structures in the images. This is implemented by segmenting bright structures in a temporal MIP and dark structures in a temporal minimum intensity projection (mIP) using an automated thresholding method [24]. The temporal MIP and mIP are computed according equations 7.2 and 7.3 respectively, in which $I_{x,y,t}$ denotes the image intensity at position $(x, y)$ in dynamic $t$. The resulting binary segmentations are then processed using morphological operations to isolate the ventricles from the
rest of the image contents and subsequently join the ventricles in a single binary object. The final ROI is the bounding box surrounding this binary object.

\[
\text{MIP}_{x,y} = \max_t \{I_{x,y,t}\} \tag{7.2}
\]

\[
\text{mIP}_{x,y} = \min_t \{I_{x,y,t}\} \tag{7.3}
\]

### 7.3.2 Respiratory motion correction

Given the automatically determined ROI, we correct for the respiratory motion that is present in perfusion CMR sequences by applying image registration [13, 14] between consecutive dynamics (a cascading scheme). We estimate an in-plane, affine transformation by maximizing the joint correlation measure using a gradient descent method embedded in a hierarchical course-to-fine approach.

### 7.3.3 Myocardial contour delineation

After respiratory motion correction, we compute a single pair of LV endocardial and epicardial contours to delineate all dynamics using a deformable template segmentation method [16, 12]. The template models the myocardium using a ribbon-shape, i.e. a centerline with variable width, which is initially positioned using an LV center and radius obtained from a ring detector based on the Hankel transform. The template is deformed using a greedy optimization scheme in a coarse-to-fine approach to minimize an energy function \(E(T, I)\), in which \(T\) refers to the template and \(I\) refers to the feature image. Again, we use a temporal MIP as feature image \(I = \text{MIP}_{x,y}\). Examples of the feature image together with resulting contours are given in figure 7.3.

The geometric template \(T\) is defined by a set of \(N\) connected vertices defining the centerline contour \(C\). In each vertex \(V_i\), the position is represented by a vector \(p_i\) and the width is represented by a scalar \(w_i\). Fur-
7.3. METHODS

Figure 7.3: Examples of resulting myocardial contours at the apical, mid, and basal level displayed at the temporal MIP used during template deformation.

Figure 7.4: Structure of the geometric template.

Furthermore, we derive in each vertex a normal direction $\mathbf{n}_i$, and a curvature $\kappa_i$. Together, these properties are used to define the positions for the inner contour $C'$ and outer contour $C''$, for which we again compute normals represented by $\mathbf{n}'_i$ and $\mathbf{n}''_i$. Finally, these contours delineate the blood pool region $\Omega_b$ and myocardial region $\Omega_m$, holding $N_b$ and $N_m$ pixels respectively. The structure of the geometric template is presented in figure 7.4.

The energy function is a weighted sum of shape terms $E_s(T)$, boundary terms $E_b(T, I)$ and regional terms $E_r(T, I)$, as defined by equations 7.4-7.7, in which the constants $\gamma_0$ to $\gamma_5$ denote the weights that control the accuracy of our method by balancing the impact of each term. The shape terms $E_s(T)$ penalize variations in width $w$ and curvature $\kappa$, see equation 7.5, in which $\bar{w}$ and $\bar{\kappa}$ refer to the mean width and curvature. The boundary terms favour alignment of the normals of the endocardial and epicardial contours with the image gradient $\nabla I$, see equation 7.6. Finally, the regional terms penalize intensity variation within the blood pool region $\Omega_b$ and myocardium region $\Omega_m$, see equation 7.7, in which $\bar{I}_b$ and $\bar{I}_m$ refer to the mean grey value in the regions $\Omega_b$ and $\Omega_m$.

$$\min_T \left\{ E(T, I) = E_s(T) + E_b(T, I) + E_r(T, I) \right\}$$

$$E_s(T) = \frac{\gamma_0}{N} \sum_{i=1}^{N} |\kappa_i - \bar{\kappa}|^2 + \frac{\gamma_1}{N} \sum_{i=1}^{N} |w_i - \bar{w}|^2$$
\[ E_b(T, \vec{I}) = \frac{\gamma_2}{N} \sum_{i=1}^{N} n_i' \cdot \vec{v}_i - \frac{\gamma_3}{N} \sum_{i=1}^{N} n_i'' \cdot \vec{v}_i \] (7.6)

\[ E_r(T, \vec{I}) = \frac{\gamma_4}{N_b} \sum_{\Omega_b} |\vec{I} - \vec{I}_b|^2 + \frac{\gamma_5}{N_m} \sum_{\Omega_m} |\vec{I} - \vec{I}_m|^2 \] (7.7)

### 7.3.4 Quantification

Finally, SI curves are extracted to enable MBF quantification using deconvolution analysis. To deal with the ill-posedness of the inverse problem, we propose to use a constrained deconvolution algorithm using an exponential approximation basis, as previously applied to brain perfusion [19]. In this method, an \( N \times M \) exponential approximation basis matrix \( E_M \), as defined in equation 7.8, is used to modify the linear system \( Ax = B \) to \( AE_M \tilde{x}_M = B \), such that \( x \) is modelled using a sum of \( M \) exponential decays, as defined by \( x = E_M \tilde{x}_M \).

\[
E_M = \begin{pmatrix}
e_{1,1} & \cdots & e_{M,1} \\
\vdots & \ddots & \vdots \\
e_{1,N} & \cdots & e_{M,N}
\end{pmatrix}, \quad e_{i,j} = e^{-\frac{i(j-1)}{N}} \] (7.8)

To guarantee that we obtain physiologically feasible solutions, we solve this linear system under a number of linear constraints [21]. We require a physiologically feasible solution \( x \) to be positive and non-increasing, for which we use the conditions defined by equations 7.9 and 7.10 as introduced by Keeling et al. [19], in which \( \Delta_j^i = (\lambda_i - \lambda_j)^{-1} \) and \( \Lambda = \text{diag}(\lambda_1, \ldots, \lambda_M) \).

\[
\tilde{x}_M [\Lambda D_1^{-1} \cdots D_{M-1}^{-1}] \geq 0 \] (7.9)

\[
D_M = \begin{bmatrix}
\Delta_{m+1}^1 & 0 & \cdots & 0 \\
0 & \Delta_{m+1}^2 & \cdots & 0 \\
\vdots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & \Delta_{M-m}^{M-1} \\
0 & \cdots & \cdots & 1
\end{bmatrix} \] (7.10)
7.4 Experimental Setup

To validate our system for MBF quantification we performed experiments using simulated SI curves, phantom acquisitions, and clinical perfusion CMR data.

The simulation experiment allows for an assessment of the accuracy of MBF quantification using deconvolution, in isolation of other error sources. The computer simulation models the arterial input $C_{AIF}(t)$ using a gamma-variate function and the tissue impulse response $K(t)$ using an exponential decay function. We simulated 100 replicates of tissue SI curves at flow rates ranging from 0.5 to 5.0 ml min$^{-1}$ g$^{-1}$, all at a heart rate of 80 beats per minute. Furthermore, the contrast-to-noise ratio (CNR) was varied from 5.0 to 40.0.

To assess the accuracy of our deconvolution method under more realistic circumstances, we have developed an MR-compatible hardware phantom that allows reliable, reproducible and efficient simulation of myocardial first-pass MR perfusion [22]. This phantom resembles the anatomy of the heart and thoracic vessels of a 60 kg subject to progressively dilute the contrast bolus. Furthermore, the myocardium is modelled by two compartments made by arrays of parallel tubes through which perfusion can be controlled precisely. One of the myocardial compartments was operated at flow rates of 1.0, 2.0, 3.0 and 4.0 ml min$^{-1}$ g$^{-1}$ to assess the accuracy of MBF estimates across the physiological range of flow values, while the other myocardial compartment was operated at 5.0 ml min$^{-1}$ g$^{-1}$ to assess the reproducibility of the MBF estimates obtained using our method. During those experiments, 8 perfusion CMR scans were made using a 3.8 fold accelerated k-t SENSE sequence (TR = 3.0ms, TE = 1.0ms, flip angle 15°, in-plane resolution 1.2mm, slice thickness 10mm) during the first pass of a bolus of Gadolinium on a 3T MR scanner (Philips Achieva TX). The availability of references values for myocardial perfusion in the hardware phantom enables a direct comparison of resulting flow values obtained through deconvolution.

In addition, we optimized and validated our methods on 30 clinical perfusion CMR series, acquired with written consent of all patients. These images were acquired using a steady-state free precession (SSFP) protocol at a Philips Achieva 1.5T scanner (TR 2.4-2.6ms, TE 1.2-1.3ms; flip angle 60°, in-plane resolution 1.29 – 1.41mm), to assess reproducibility of MBF quantification. Five series were used to optimize respiratory motion correction and myocardial contour detection for maximum accuracy. The remaining 25 series are used to further validate our methods. These 25 series contained 3 slices with 49-90 dynamics, containing 4914 images altogether. The heart rate of the subjects during acquisition varied between 64 and 134 beats per minute. Two experts manually delineated all relevant dynamics using a standard analysis package (Philips ViewForum R6.1), to enable the generation of golden standard delineations by averaging both expert delineations.
CHAPTER 7. PERFUSION CARDIAC MR ANALYSIS

using the repeated averaging algorithm (RAA) algorithm [15].

Errors in MBF estimates were quantified by computing the mean and standard deviation (SD) difference between the estimated flow and the reference. The accuracy of respiratory motion correction was assessed by measuring the displacement of the myocardial centroid and the myocardial contours from consecutive dynamics. Errors in contour positioning were quantified computing mean, root-mean-square (RMS) and maximum contour positioning errors based on a point-to-point correspondence established by the RAA algorithm [15].

7.5 Results

In the simulation experiment, our deconvolution method proved to be accurate for the estimation MBF with a mean ± SD error of 0.08 ± 0.20 ml min⁻¹ g⁻¹. Moreover, the variability of MBF estimates increased with increasing flow rates and decreasing CNR, see figure 7.5.

![Figure 7.5: Error of the MBF estimates as function of the actual MBF (left) and CNR (right) in the simulation experiment.](image)

Eight perfusion CMR scans of the phantom were obtained, see figure 7.6 for example dynamics. We obtained SI curves with CNR ranging between 11.4 and 100.5, see figure 7.7. From the SI curves of the right myocardium compartment we obtained MBF with a mean ± SD error of −0.02 ± 0.35 ml min⁻¹ g⁻¹ (r² = 0.91) across the physiological range of flow values, see figure 7.8. Moreover, the mean ± SD MBF estimate in the left myocardium compartment was 4.97±0.29 ml min⁻¹ g⁻¹, indicating excellent reproducibility of MBF estimation using our method.

Manual delineation of a perfusion CMR series took on average 13 ± 6 min. Averaging both expert delineations resulted in 2913 delineated images, in which the average mean, RMS and maximum positioning error of the individual manual delineations with respect to the golden standard was measured, see table 7.1. This golden standard was used to quantify the accuracy of automatic respiratory motion correction by measuring the displacement of the myocardial contours and their centroid for each consecutive
7.5. RESULTS

Figure 7.6: Example dynamics from the phantom experiment, with delineated ascending aorta (yellow), left myocardium compartment (red), and right myocardium compartment (green).

pair of delineated dynamics (n=2815), as summarized in table 7.2. Moreover, the golden standard was used to quantify the accuracy of the automatic myocardial contour detection by measuring contour positioning errors in all dynamics used for quantification (n=1267), see table 7.3.

<table>
<thead>
<tr>
<th>Interobserver variability</th>
<th>Endocardium</th>
<th>Epicardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Error (mm)</td>
<td>1.10 ± 0.61</td>
<td>1.24 ± 0.55</td>
</tr>
<tr>
<td>RMS Error (mm)</td>
<td>1.31 ± 0.71</td>
<td>1.47 ± 0.61</td>
</tr>
<tr>
<td>Maximum Error (mm)</td>
<td>2.50 ± 1.28</td>
<td>2.81 ± 1.07</td>
</tr>
</tbody>
</table>

Table 7.1: Interobserver variability assessed by measuring myocardial contour positioning errors from expert delineations with respect to the golden standard for the endocardium and epicardium contours.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centroid Displacement (mm)</td>
<td>1.17 ± 1.51</td>
<td>0.40 ± 0.62</td>
</tr>
<tr>
<td>Mean Displacement (mm)</td>
<td>0.76 ± 0.98</td>
<td>0.30 ± 0.45</td>
</tr>
<tr>
<td>RMS Displacement (mm)</td>
<td>0.84 ± 1.08</td>
<td>0.36 ± 0.53</td>
</tr>
<tr>
<td>Maximum Displacement (mm)</td>
<td>1.27 ± 1.60</td>
<td>0.66 ± 0.95</td>
</tr>
</tbody>
</table>

Table 7.2: Mean ± SD for myocardial centroid and contour displacement between consecutive dynamics before and after respiratory motion correction.

To assess the sensitivity of MBF quantification with respect to contour positioning errors, we quantified the MBF from transmurally averaged SI curves after displacing the golden standard delineations in the inward (negative) or outward direction [26], resulting in figure 7.9. This revealed that MBF quantification requires more accurate endocardial contours than epicardial contours.
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Figure 7.7: SI curves for the AIF (a), left myocardium compartment (b) and right myocardium compartment (c).
7.6. DISCUSSION AND LIMITATIONS

Figure 7.8: The estimated MBF versus reference MBF in the phantom experiment.

<table>
<thead>
<tr>
<th>Error</th>
<th>Endocardium</th>
<th>Epicardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Error (mm)</td>
<td>1.45 ± 0.73</td>
<td>2.32 ± 1.47</td>
</tr>
<tr>
<td>RMS Error (mm)</td>
<td>1.79 ± 0.98</td>
<td>2.81 ± 1.67</td>
</tr>
<tr>
<td>Maximum Error (mm)</td>
<td>3.72 ± 2.37</td>
<td>5.44 ± 2.92</td>
</tr>
</tbody>
</table>

Table 7.3: Myocardial contour positioning errors from automatic delineations with respect to the golden standard for the endocardium and epicardium contours.

In addition, we have quantified MBF based on 330 regional SI curves (CNR was 27.7 ± 29.5 extracted from 16 standardized myocardial segments [17] (the apex is not imaged), given automatic and golden standard contours. A comparison including linear regression analysis is given in figure 7.10. Overall, we found a mean ± SD difference of 0.09 ± 0.57 ml min$^{-1}$ g$^{-1}$ for the MBF. Between both manual analyses, we found comparable differences of 0.12 ± 0.57 ml min$^{-1}$ g$^{-1}$ in MBF estimation. Unfortunately, this analysis was performed excluding 3 cases (48 segments) because of severe MRI signal saturation in the AIF. Therefore, clinical implementation of our methods should rely on full saturation recovery imaging, preferably using dual bolus contrast administration [27], to avoid saturation effects that violate the assumed signal linearity.

7.6 Discussion and Limitations

In this study we aimed to simplify and shorten the post-processing workflow by combining a robust deconvolution method with extensive automation. For deconvolution we have used an exponential approximation basis. We have tested this method in isolation using simulated SI curves and phantom acquisitions, in which reference flow values are available for validation. In these experiments we obtained accurate and reproducible MBF using the deconvolution method.
CHAPTER 7. PERFUSION CARDIAC MR ANALYSIS

Figure 7.9: Sensitivity of MBF quantification for contour positioning errors of the endocardial (left) and epicardial contours (right).

Figure 7.10: Scatter plot of MBF estimates based on automatic contours vs MBF estimates based on manual contours.

Furthermore, we have evaluated the deconvolution method in combination with automated pre-processing methods in clinical image data. Although the automatic positioning of epicardial contours was less accurate as compared to endocardial contours, MBF estimates were found to be less affected by such contour positioning errors in epicardial contours.

Throughout this study we have assumed that the SI in perfusion CMR images is linearly dependent on the contrast concentration. Unfortunately, this relation is increasingly non-linear with increasing contrast concentrations [25]. Therefore, future studies using our method should include correction for signal saturation [25], or prevent saturation by using a dual bolus approach [27].

Furthermore, our method has been tested on clinical image data from a single scanner, using a single protocol. Whether reported efficiency and reproducibility are also applicable for different imaging sequences or contrast administration schemes remains to be investigated as part of larger scale...
validation studies.

7.7 Conclusion

We have evaluated the use of deconvolution using an exponential approximation basis for the quantification of MBF from perfusion CMR. Our experiments based on simulated SI curves, phantom acquisitions and clinical image data indicate that exponential deconvolution allows for accurate quantification of MBF. Together with automated respiratory motion correction myocardial contour delineation, the exponential deconvolution may enable efficient and reproducible quantification of MBF in clinical routine.
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7.8 References


7.8. REFERENCES


CHAPTER 7. PERFUSION CARDIAC MR ANALYSIS


Quantitative analysis of transmural gradients in perfusion CMR images

8.1 Introduction

Rapid cardiac magnetic resonance (CMR) imaging during the first pass of a gadolinium contrast bolus, as introduced in Atkinson et al. [14], is a well-accepted diagnostic method to image myocardial perfusion with CMR [16, 17, 10]. Quantitative analysis of the acquired dynamic data consists of processing signal intensity (SI) curves that represent SI vs. time extracted from a myocardial region. Once the images are corrected for respiratory motion and delineated, the SI curves are extracted to enable quantification of various semi-quantitative parameters, including the time to contrast arrival, the peak enhancement, and the maximum upslope. Of these, the maximum upslope has proven to be a robust method for the diagnosis of coronary artery disease coronary artery disease (CAD) [10] when used in a rest-stress study including normalization for contrast bolus differences. More recently, the use of deconvolution methods [15, 11, 4] enabling true quantification of the coronary blood flow has gained popularity. A more in-depth review of both semi-quantitative and true quantitative analysis methods is given in chapter 6.

Both semi- and true-quantitative analysis assess the temporal relation between the arterial input function (AIF) and the myocardial SI curves, while ignoring the spatial characteristics of perfusion deficits. However, it is well known that due to the higher cardiac workload in the sub-endocardial layer, myocardial blood flow is highly heterogeneous even in healthy subjects, with distinct differences between sub-endocardial and sub-epicardial

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This chapter has been adapted from: G.L.T.F. Hautvast, A. Chiribiri, T. Lockie, M. Breeuwer, E. Nagel, and S. Plein, Quantitative analysis of transmural gradients in perfusion CMR images, Magnetic Resonance in Medicine, 66(5):1477–1487, 2011.

Author contributions: GH, AC, SP, and EN jointly conceived gradient quantification; GH and AC developed gradient quantification; GH and MB developed image processing framework; GH created software implementation; AC conducted evaluation experiments; GH prepared the manuscript; TL acquired image data; MB, EN and SP supervised the project.
layers. In disease states such as myocardial ischaemia, left ventricle (LV) hypertrophy or metabolic disease, these differences are further accentuated [7, 3, 2, 1]. Epicardial coronary stenosis affects predominantly the sub-endocardial layers, but many factors including the severity of the lesion, microvascular function and collateralization determine the extent and persistence of perfusion defects. The high spatial resolution achievable with modern CMR perfusion imaging permits detailed interrogation of the regional distribution of myocardial blood over time, but the depiction and graphical representation of these complex dynamic changes is challenging.

In this paper, we describe a new approach for characterization and visualization of regional and dynamic differences in myocardial contrast uptake. Based on the myocardial SI curves in the epicardial- and endocardial layers, we calculate the transmural gradient in SI in each dynamic, thus obtaining gradient curves. These gradient curves can be displayed in a new two dimensional representation that allows for direct quantification of the gradient amplitude, the temporal persistence and circumferential extent of myocardial perfusion defects.

8.2 Methods

Method development

The implementation of accurate voxel-based SI analysis in this work required respiratory motion correction and myocardial contour delineation. We developed an automated approach based on [20, 21], in which respiratory motion is removed using affine image registration by maximization of the joint correlation between consecutive dynamics within an automatically determined region of interest. Then, a temporal maximum intensity projection is calculated to serve as a feature image for an automatic contour delineation method based on active contour models. More details on this method are given in 7.

Following motion correction and contour delineation, SI curves are extracted at a grid of 60 angular positions and 10 transmural positions, or layers, see figure 8.1. The transmural positions are located on chords perpendicular to the myocardial centreline obtained by applying the repeated averaging algorithm (RAA) [19] to the endocardial and epicardial LV contours. We used bi-linear interpolation in the spatial domain to extract SI curves of satisfactory quality at these positions, as lower order interpolators are not sufficient for extracting high quality SI curves, while the added value of higher order interpolators is unclear.

Conventionally, SI curves are displayed in charts, but the number of SI curves that can be differentiated in a single chart is limited. Moreover, the spatial relation between the SI curves in such charts is lost. An alternative approach for visualising SI curves are perfusograms [22], which are two
8.2. METHODS

Figure 8.1: Examples of the sampling grid used to acquire perfusogram layers from registered SA perfusion CMR series.

Figure 8.2: Examples of perfusograms for an endocardial layer (a), mid-myocardial layer (b) and a epicardial layer (c). Note the endocardial perfusion defect indicated by the arrow.

dimensional images in which each line corresponds to a SI curve at an angular position in a particular slice, see figure 8.2. Thus, the vertical axis of the perfusogram relates to the angular posititon and the horizontal axis corresponds to the temporal position. The SI values themselves are shown in grey-levels (as in the original images) or colours. In our new method, we acquire SI curves in a grid of angular and transmural positions, allowing for the construction of a perfusogram for each transmural layer. Altogether, this results in a stack of perfusograms. In these, perfusion defects affecting only the sub-endocardial layers will be seen only in the endocardial perfusograms, as shown in figure 8.2. This can also be seen in figure 8.3, which shows the sub-endocardial and sub-epicardial SI curves at the angular location of the perfusion deficit.

To enable direct quantification of such endocardial perfusion deficits, we calculate gradient curves based on sub-endocardial and sub-epicardial SI curves. The sub-endocardial and sub-epicardial SI curves are obtained by averaging the three innermost and outermost layers, thus ignoring the 4 mid-
myocardial layers to be more sensitive to transmural gradients in contrast uptake. The resulting average sub-endocardial SI curves are subtracted from the sub-epicardial SI curves to calculate the gradient curves. This is expressed in equation 8.1, in which $G_{a}[t]$ denotes a gradient in the transmural direction at time $t$ and an angular position $a$ and $I_{a,l}[t]$ denotes the intensity at time $t$, angular position $a$, and transmural position $l$.

$$G_{a}[t] = \frac{1}{3}(\sum_{l=0}^{2} I_{a,l}[t] - \sum_{l=7}^{9} I_{a,l}[t])$$  \hspace{1cm} (8.1)

The resulting gradient curves represent the evolution of transmural gradients in contrast uptake over time and can be calculated at all angular positions. As the transmural gradient is defined at each temporal and angular position, gradient curves can be represented in a spatio-temporal display, similar to perfusograms, which we refer to as gradientograms, see figure 8.4. The gradientogram thus summarizes the stack of perfusograms acquired from transmural layers into a single two dimensional representation. The amplitude of the endocardial to epicardial SI gradient encodes the grey (or colour) value of the gradientogram. In our current implementation we encoded increasing endocardial to epicardial gradients with a darkening grey level, so that an endocardial perfusion defect would generate a dark area in the gradientogram.
The acquired perfusion CMR series are subject to B1 inhomogeneities and can contain substantial amounts of noise. Therefore, it is essential to pre-process the SI curves to allow for visualization and characterization of transmural gradients in contrast uptake as described above. To cope with noise present in the perfusion CMR series, the voxel-based SI curves are filtered in both the spatial and temporal domain using a binomial filter \[18\]. These filtered voxel-based SI curves are used to calculate the gradient curves, which are then also less noisy. In a second pre-processing step, the gradient curves are normalized to be robust against the inhomogeneities that are present in perfusion CMR series. We chose to normalize the transmural gradient by dividing it by the mean transmural signal intensity, as expressed in equation 8.2, in which \( N_a[t] \) denotes the normalized gradient. By multiplying the resulting ratio with 100% we express the gradient amplitude as a percentage of the transmural signal intensity. Although this approach does not completely correct SI curves for the signal variation due to B1 inhomogeneities, this relative quantity is less affected, and is thus more homogenous across myocardial regions

\[
N_a[t] = \frac{G_a[t]}{\frac{1}{10} \sum_{i=0}^{9} I_{a,i}[t]} \quad (8.2)
\]

Similar to the analysis of SI curves in conventional semi-quantitative analysis, temporal analysis of the normalized gradient curves can be performed. For each normalized gradient curve, the mean gradient amplitude \( N_a^{mean} \), the peak gradient amplitude \( N_a^{peak} \) and the cumulative gradient amplitude \( N_a^{sum} \) over time, i.e. along the horizontal axis of the gradientogram, are calculated, see equations 8.3, 8.4, and 8.5 in which \( t_{AIF} \) and \( t_{2nd} \) refer to the time of contrast arrival for the first and second bolus passage measured in the LV blood pool.

\[
N_a^{peak} = \max_{t_{2nd}} - t_{AIF} N_a[t] \quad (8.3)
\]

\[
N_a^{sum} = \sum_{t=t_{AIF}}^{t_{2nd}} N_a[t] \quad (8.4)
\]

\[
N_a^{mean} = \frac{N_a^{sum}}{t_{2nd} - t_{AIF}} \quad (8.5)
\]

As shown in figure 8.4 and expressed in equations 8.3, 8.4, 8.5, these measures are based on the gradients caused during the first pass only. The results of this analysis are defined for each angular position and can therefore be displayed in bull’s eye plots, see figures 8.6ghi and 8.7ghi for examples.

From the gradient curves and the specific appearance of an endocardial perfusion deficit in the gradientogram representation several measures can
CHAPTER 8. TRANSMURAL GRADIENTS IN PERFUSION CMR

Temporal Persistence
Circumferential Extent
AIF
Gradient
Area
Peak
Gradient
Cumulative Gradient
Circulation Period
Mean Gradient = Temporal Position / Angular Position / Intensity /
t_{AIF} t_{2nd}

Figure 8.4: The newly defined quantitative measures for assessing the severity of perfusion deficits based on the segmented gradientogram and gradient curves.
be derived that characterize and quantify perfusion deficits. In visual assessments, the severity of endocardial perfusion deficits is usually characterized from three aspects; the amplitude of the transmural difference in contrast uptake, the time this transmural difference persists and the circumferential extent of the perfusion defect. The gradientogram captures all these aspects, see figure 8.4. An endocardial perfusion deficit appears like a dark region, in which the intensity is related to the amplitude of the transmural gradient in contrast uptake. The persistence of a transmural gradient in contrast uptake can be estimated from the width of the dark region in the gradientogram. Finally, the circumferential extent of the perfusion deficit can be estimated from the height of the dark region in the gradientogram.

To translate these aspects into quantitative measurements, the perfusion deficit needs to be segmented. This can be done by means of a simple thresholding of the gradientogram, after which quantitative characterization of perfusion deficits can be performed based on the dimensions of the resulting segmentation, as well as based on the intensity values within the resulting segmentation. As the severity of perfusion deficits is visually assessed from the combination of the amplitude, the persistence and the circumferential extent of the transmural difference in contrast uptake, we also developed quantification of compound measures, aiming to summarize these aspects in a single quantitative property. The area of the obtained binary segmentation can be used to report on the circumferential extent and temporal persistence and may be linked to the severity of the perfusion deficit. Similarly, the average amplitude of the transmural gradient within the deficit may be of interest. As the significance of a coronary occlusion relates to the size of its downstream territories, we also propose to normalize the average amplitude by the circumferential extent of a perfusion deficit. We refer to the resulting ratio as the strength of the perfusion deficit. The newly defined quantitative measures for assessing the severity of perfusion deficits are explained in figure 8.4 and listed in table 8.1 including appropriate units.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unit</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum intensity</td>
<td>%</td>
<td>Maximum transmural gradient</td>
</tr>
<tr>
<td>Mean intensity</td>
<td>%</td>
<td>Mean transmural gradient</td>
</tr>
<tr>
<td>Maximum width</td>
<td>s</td>
<td>Persistence of deficit</td>
</tr>
<tr>
<td>Maximum height</td>
<td>°</td>
<td>Circumferential extent of deficit</td>
</tr>
<tr>
<td>Area</td>
<td>°s</td>
<td>Severity of deficit</td>
</tr>
<tr>
<td>Strength</td>
<td>%°s⁻¹</td>
<td>Severity of deficit</td>
</tr>
</tbody>
</table>

Table 8.1: New quantitative parameters that are derived from segmented gradientograms.
CHAPTER 8. TRANSMURAL GRADIENTS IN PERFUSION CMR

Method evaluation

The new method was tested in a total of 8 patients suspected of having CAD. All patients had undergone first pass myocardial perfusion imaging on a 3T CMR scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a high spatial resolution $k$-$t$ SENSE accelerated perfusion method in combination with a saturation recovery gradient-echo pulse sequence (repetition time msec/echo time msec, 3.0/1.0; flip angle, 15°; non-selective saturation pulse with saturation prepulse delay 120 msec in all slices; partial Fourier sampling; acquisition window, 120 msec; matrix 256 x 256, spatial resolution 1.3 x 1.3 x 10 mm; $k$-$t$ factor of five with 11 $k$-$t$ interleaved training profiles; effective acceleration, 3.8) [5, 9, 8, 6]. Three slices were acquired at every heart beat for 40 dynamics in apical, equatorial and basal short-axis positions. After 4 minutes of intravenous infusion of the vasodilator adenosine (at 140mcg/kg/min), stress perfusion images were acquired with bolus injection of 0.05mmol/kg Gd-DTPA, administered at a rate of 5 ml/s by a power injector and followed by a flush of 20ml normal saline.

The first 2 patients were chosen to test the new method in a normal and an abnormal case. Moreover, these cases were used to assess the impact of respiratory motion correction and filtering the SI curves by quantification of the contrast-to-noise ratio (CNR), which was calculated by dividing the peak enhancement by the standard deviation of the SI curves in the pre-contrast dynamics.

A further 6 patients were randomly selected from our clinical case pool to test the methods variability. To assess intra-observer variability, one observer (AC) analysed all cases twice. For inter-observer variability all cases were also analysed by another observer (SP). Both observers rated the gradientogram appearance in each coronary artery territory as positive or negative. To establish the presence of pericardial coronary artery stenosis by coronary artery territory, these 6 patients underwent subsequent coronary angiography.

8.3 Results

Automatic respiratory motion correction and myocardial contour detection was performed. If necessary, the automatically detected myocardial contours were manually corrected. Care was taken in the placement of endocardial contours to exclude any endocardial dark rim artefacts. Without respiratory motion correction and filtering, the resulting SI curves obtained from all slices of the first two cases after respiratory motion correction had a CNR of 4.32 - 11.92. With respiratory motion correction, the resulting SI curves had a CNR of 7.22 - 12.89 before filtering and 14.41 - 27.12 after filtering. To further illustrate the impact of these pre-processing methods figure 8.5 shows sub-epicardial perfusograms before registration, before filtering, and after...
filtering. Thus, by employing respiratory motion correction and filtering in both the temporal and spatial domain we achieved voxel-based SI curves of sufficient quality for accurate analysis, which in practice requires SI curves with CNR values higher than 10.0 [12]. Altogether, a single analysis took between 2 and 3 minutes to be performed.

Figure 8.6 shows the results obtained from the first case in our evaluation. In this case, no perfusion deficit was visible in the acquired high resolution perfusion CMR images, see figure 8.6abc. Consequently, no transmural gradients in myocardial contrast uptake occur, as can be seen from the uniform bright appearance in the gradientograms, see figure 8.6def. The results of quantification of the mean, peak and cumulative gradient amplitude is displayed in bulls eye plots, see figure 8.6ghi. The uniform appearance of the bulls eye plots for the mean gradient (figure 8.6g), peak gradient (figure 8.6h) and integral gradient (figure 8.6i) further exclude the presence of transmural gradients in myocardial contrast uptake.

The results obtained for the second case in our evaluation are shown in figure 8.7. In this case, visual assessment of the acquired high resolution perfusion CMR images (figure 8.7abc) revealed a clear sub-endocardial perfusion deficit in the inferoseptal and inferior segments at the mid and basal level. The dark areas in the gradientograms obtained in this case (see figure 8.7def) clearly reveal the presence of strong and persistent transmural gradients in myocardial contrast uptake, as is consistent with the presence of sub-endocardial perfusion defects. The presence of transmural gradients in myocardial contrast uptake is further confirmed by the bulls eye plots for the mean gradient (figure 8.7g), peak gradient (figure 8.7h) and cumulative gradient (figure 8.7i), as can be concluded from the yellow to bright colour in the inferoseptal and inferior segments at the mid and basal level. Note that the bulls eye plots from both cases for the mean gradient (figure 8.6g and 8.7g), peak gradient (figure 8.6h and 8.7h) and integral gradient (figure 8.6i and 8.7i) are generated using identical colour scales.

For the second case we continued our quantitative analysis by segment-
CHAPTER 8. TRANSMURAL GRADIENTS IN PERFUSION CMR

Figure 8.6: Results for a patient with normal perfusion, including the original high resolution CMR perfusion images at apical (a), mid (b) and basal (c) position, gradientograms for the apical (d), mid (e) and basal (f) position, and bulls eye plots for the mean gradient (g), peak gradient (h) and integral gradient (i); bright (yellow) is worse.
8.3. RESULTS

Figure 8.7: Results for a patient with abnormal perfusion, including the original high resolution CMR perfusion images at apical (a), mid (b) and basal (c) position, gradientograms for the apical (d), mid (e) and basal (f) position, and bulls eye plots for the mean gradient (g), peak gradient (h) and integral gradient (i); bright (yellow) is worse.
CHAPTER 8. TRANSMURAL GRADIENTS IN PERFUSION CMR

Figure 8.8: Segmented perfusion deficit in the gradientograms of the apical (a), mid (b) and basal (c) slices of the positive example case (as shown in figure 8.7).

ing the gradientograms, see figure 8.8. This segmentation was obtained by selecting the largest object after thresholding the gradientogram at the 15% level. Based on these segmentations, we quantified the parameters listed in table 8.1 for the segmented defects in the apical, mid and basal gradientogram resulting in table 8.2. Note that these results cannot be computed for the first case, as there are no perfusion deficits to be segmented. This quantitative assessment confirms differences in circumferential extent, temporal persistence, and amplitude of the transmural gradients in myocardial contrast uptake over the slices that can be seen from the gradientograms (figure 8.6def). Moreover, table 8.2 shows that compound measures such as the area and strength of the segmented deficit are capable of capturing the more subtle difference in defect severity between the mid and basal slices, which is not apparent from maximum intensity, the mean intensity, the maximum width, or the maximum height alone.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apical</th>
<th>Mid</th>
<th>Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum intensity (%)</td>
<td>30.71</td>
<td>62.90</td>
<td>58.88</td>
</tr>
<tr>
<td>Mean intensity (%)</td>
<td>22.01</td>
<td>29.56</td>
<td>32.93</td>
</tr>
<tr>
<td>Persistence (s)</td>
<td>2.86</td>
<td>14.29</td>
<td>14.29</td>
</tr>
<tr>
<td>Circ. Extent (°)</td>
<td>24.00</td>
<td>162.00</td>
<td>174.00</td>
</tr>
<tr>
<td>Area (°s)</td>
<td>68.57</td>
<td>1457.14</td>
<td>2078.57</td>
</tr>
<tr>
<td>Strength (%° s⁻¹)</td>
<td>14.68</td>
<td>62.04</td>
<td>91.78</td>
</tr>
</tbody>
</table>

Table 8.2: Results of quantitative assessment of transmural gradients in myocardial contrast uptake in the positive case.

The remaining 6 cases were analysed to provide a preliminary assessment of inter- and intra-observer variability of the new method. To assess intra-observer variability, one observer (AC) analysed all cases twice. For
inter-observer variability all cases were also analysed by another observer (SP). Both observers rated the gradientogram appearance in each coronary artery territory as positive or negative. Table 8.3 lists the results of these observations by coronary artery territory including a comparison with coronary angiography. In the positive coronary artery territories, the gradientogram was segmented and quantitatively assessed. The mean ± SD of the difference between the observations was quantified resulting in table 8.4. This preliminary evaluation on six cases revealed a promising correspondence between gradientogram analysis and coronary angiography, as well as good reproducibility for the derived measurements from gradientogram analysis.

<table>
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<tr>
<th>Patient</th>
<th>Vessel</th>
<th>Cath. Lab</th>
<th>Operator 1 (1st)</th>
<th>Operator 1 (2nd)</th>
<th>Operator 2</th>
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Table 8.3: Comparison of coronary angiography results to gradient quantification.
### CHAPTER 8. TRANSMURAL GRADIENTS IN PERFUSION CMR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intra-observer</th>
<th>Inter-observer</th>
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<tr>
<td>Maximum intensity (%)</td>
<td>1.26 ± 12.37</td>
<td>5.14 ± 7.79</td>
</tr>
<tr>
<td>Mean intensity (%)</td>
<td>1.11 ± 7.75</td>
<td>3.75 ± 8.28</td>
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<tr>
<td>Maximum width (s)</td>
<td>0.84 ± 3.42</td>
<td>−0.19 ± 2.66</td>
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<tr>
<td>Maximum height (°)</td>
<td>−2.33 ± 23.30</td>
<td>12.00 ± 32.01</td>
</tr>
<tr>
<td>Area (°s)</td>
<td>3.07 ± 166.2</td>
<td>3.75 ± 8.28</td>
</tr>
<tr>
<td>Strength (%° s⁻¹)</td>
<td>4.34 ± 14.24</td>
<td>−0.03 ± 5.43</td>
</tr>
</tbody>
</table>

Table 8.4: Intra and inter-observer variability assessed by measuring the mean SD difference in the quantitative parameters derived from a segmented gradient.

### 8.4 Limitations

The evaluation of our method was limited to 8 patients with suspected CAD. Although our evaluation revealed a promising correspondence between coronary angiography and gradientogram analysis, future studies need to explore the correlation between the new parameters and the severity of epicardial coronary disease, microvascular function and collateralization in larger patient populations. As gradients in myocardial perfusion are also seen in left ventricular hypertrophy and microvascular disease, future studies should also investigate the use of our method in patients with these pathologies.

In patients with transmural infarcts, the absence of myocardial perfusion will limit contrast uptake such that no transmural gradients occur, causing a false negative result. Fortunately, such transmural infarcts are easy to distinguish from the original perfusion images, as well as from late gadolinium enhancement images that are usually acquired after performing first pass perfusion imaging. Consequently, the risk of missing such transmural defects is limited.

The use of a 0.05 mmol/kg Gd-DTPA bolus for perfusion imaging can cause susceptibility artefacts, potentially introducing false positive transmural gradients. The typical dark rim in this imaging artefact is one voxel wide and persists for one dynamic preceding contrast uptake stage in the myocardium. By using high spatial resolution perfusion imaging the width of the artefact is reduced. During post processing, false positive gradients can be avoided by excluding the dark rim using the endocardial contours or a different setting for the time of contrast arrival. Moreover, the gradientogram segmentation method is tailored to ignore defects that persist for a single dynamic.

Finally, the current implementation of our method incorporates a number of parameters that have been configured by trial-and-error to demonstrate the potential of our method. These parameters include the dimensions of the myocardial sampling grid, the number of sub-endocardial and sub-epicardial layers to be averaged in the computation for the transmural
8.5 DISCUSSION

gradient and the threshold value used for segmenting the perfusion deficit in the gradientogram. As our intention in this work is to explain and demonstrate our new method, we have not performed an extensive quantitative analysis on the influence of these parameters. While such an analysis might reveal better diagnostic performance using a different configuration, this would not alter the basic principles of our method.

8.5 Discussion

We presented a new method for the visualization and characterization of transmural myocardial perfusion distribution that reflects the severity of transmural perfusion gradients as well as their spatial and temporal evolution during contrast passage. Our method relies on high spatial resolution imaging and an integrated motion compensation algorithm to enable the extraction of SI curves in layers within the myocardium. The SI curves in each layer were visualized in a perfusogram, a two dimensional representation spanning the time and angular dimension. By subtracting the epicardial and endocardial perfusograms, we were able to visualize the temporal evolution of the transmural gradient in myocardial contrast uptake at each angular position in a similar two dimensional gradientogram. Within these gradientograms, the severity and extent of transmural gradients in myocardial contrast uptake and their evolution over time was visualised. In addition, we proposed several new quantitative measures that characterize the severity of perfusion defects.

Our preliminary evaluation revealed a clear distinction between patients with normal perfusion or inducible ischaemia. As the sub-endocardium is known to be more susceptible to ischaemia than the sub-epicardium, the newly proposed measurements may well be novel indicators of the severity of myocardial perfusion deficits. Future studies need to explore the correlation between these new parameters and the severity of epicardial coronary disease, microvascular function and collateralization in larger patient populations of suspected coronary artery disease, as well as other pathologies in which gradients in myocardial perfusion are seen.

The proposed method can be used to visualize and characterize transmural gradients in contrast uptake, which should not be confused with transmural gradients in myocardial perfusion itself, as assessed in [1]. Although transmural gradients in myocardial perfusion are the main cause of transmural gradients in myocardial contrast uptake, the appearance of transmural gradients in myocardial contrast uptake is also affected by the contrast administration protocol. Moreover, the transmural gradient in myocardial contrast uptake evolves over time. This temporal aspect also highlights the importance of clear and reproducible contrast administration protocols, which is particularly eminent for the interpretation of epicardial to endo-
Our method relies on the ability to extract accurate SI curves in layers within the myocardium, which requires high spatial resolution images. For the initial evaluation of the method we therefore used high spatial resolution \( k-t \) SENSE accelerated first pass perfusion imaging as presented in [5, 9, 8, 6], rather than conventional TFE or SSFP first pass perfusion imaging. As the requirements with respect to the in-plane resolution of images are related to the myocardial thickness, our new method may perform particularly well under circumstances with increased myocardial thickness such as LV hypertrophy. Moreover, it may be beneficial to perform imaging near end systole when the myocardium is at its maximum thickness. The use of conventional TFE or SSFP first pass perfusion imaging techniques [13] instead of high spatial resolution \( k-t \) SENSE accelerated first pass perfusion imaging in these situations of increased myocardial thickness may also be investigated.

To acquire high spatial resolution images, we have used \( k-t \) SENSE accelerated first pass perfusion imaging on a 3T CMR scanner. While 3T compared to 1.5T enables an increased acquisition speed and spatial resolution, it is also associated with stronger B1 variation which may reveal limitations in our gradient normalization scheme. Therefore, the use of a 1.5T CMR scanner, sacrificing resolution for signal homogeneity, may be considered. Furthermore, technologies that reduce the impact of B1 variation at 3T should be investigated, including adiabatic or multipulse saturation schemes, and multi-channel transmission.

In addition to sufficient spatial resolution, the extraction of accurate voxel-based SI curves requires anatomically consistent sampling positions in each dynamic. Therefore, we integrated a motion compensation method to reduce the respiratory motion that may be present in first pass perfusion images. Next to enabling accurate SI curve sampling, successful respiratory motion compensation enables tracing of the endocardial and epicardial contours in all dynamics by a single tracing. This greatly simplifies the delineation task, which is the primary bottleneck of perfusion analysis in the absence of respiratory motion correction [12]. While we have used a newly developed approach based on [20, 21], as presented in chapter 7, alternative approaches towards automatic respiratory motion correction and myocardial contour detection as reviewed in [23, 24] and chapter 6 may also be applicable.

8.6 Conclusions

We have developed a new method for the visualization and characterization of transmural myocardial perfusion distribution based on the gradien-
togram representation, which permit simultaneous display and measurement of amplitude, extent and persistence of transmural gradients in myocardial contrast uptake. This representation, together with several newly defined measurements, revealed a clear distinction between normal perfusion and inducible ischaemia in application to clinical image data. In a small evaluation, the new methods have shown to be reproducible and their outcome corresponds well with that of coronary angiography. Thus, the new method may find application in the detection and characterization of epicardial coronary disease and microvascular disease states.

8.7 References


CHAPTER 8. TRANSMURAL GRADIENTS IN PERFUSION CMR


8.7. REFERENCES


Part III

Analysis of other CMR Images
9.1 Introduction

Quantitative analysis of cardiac magnetic resonance (CMR) images is not limited to the analysis of short axis (SA) functional and perfusion images as described in parts I and II, but may also involve images obtained using different protocols, or obtained from different views. Quantitative analysis of these additional images provides complementary information that may improve clinical decision making, but also increase the time required to perform the additional post-processing. As such, automation of the analysis of these images is desirable. This chapter reviews preliminary results obtained using automated image processing for viability CMR images (section 9.2), multi-echo CMR images for the assessment of myocardial $T_2^*$ (section 9.3), and a multi-view analysis for functional CMR images (section 9.4).

9.2 Viability Cardiac MR Analysis

Delayed, or late enhancement (LE) enhancement MR images are acquired 10-20 minutes after Gadolinium contrast injection, when the intensity differences between normal and injured myocardium are nearly 500% [5, 19], see figure 9.1. These images can be used to assess myocardial viability by performing scar size measurements that are known to agree closely with positron emission tomography (PET) in patients with severe ischemic cardiomyopathy [6] and are superior to single photon emission computed tomography (SPECT) in patients with small myocardial infarctions (MIs) [15]. In these patients, the presence and extend of myocardial infarction can be used to predict improvement in contractile function after revascularization [13, 18]. The image analysis for such scar quantification involves delineation of the myocardial boundaries, followed by a classification of the myocardial voxels as injured or viable using image intensity characteristics.

The clinical image data used in this section was kindly provided by Deutsches Herzzentrum Berlin, Germany, Leeds General Infirmary, UK, and Texas Heart, Houston, USA.
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Figure 9.1: Examples of SA (a), LA 2CH (b) and LA 4CH (c) viability CMR images revealing myocardial scar after myocardial infarction.

9.2.1 State of the Art

Delineation

Automatic delineation of the myocardium is challenging due to the lack of features between papillary muscles and myocardial wall, and between blood and scar tissue. Delineation is further complicated by differences in inversion times and contrast injection delays. To overcome these challenges the use of a shape prior obtained from functional CMR delineations was proposed [21, 4]. This approach has been implemented using 2D non-rigid registration of an automatically obtained shape prior [4], or using an explicit 3D shape prior for initialization of a dedicated deformable template [21].

Classification

After delineation of the myocardium, the myocardial voxels can be classified, which is usually done using simple thresholding schemes. The threshold value is determined manually [16] or (semi-) automatically from the image intensity characteristics. The semi-automatic approaches require the user to indicate a myocardial region to determine the mean and standard deviation (SD) intensity of non-enhanced myocardium. Then, hyperenhanced voxels with intensity values that exceed 2 SDs [5], or 3 SDs [20] above the mean intensity in healthy myocardium are classified as injured myocardium. More advanced approaches proposed the use of support vector machines to address partial volume effects [4, 2], and added additional post-processing of the resulting scar segmentation to handle microvascular obstruction and non-hyperenhancing scar as typically seen in patients with myocardial infarction due to coronary artery disease [12, 14]. These semi-automatic approaches have been compared to manual thresholding results, providing satisfactory results for clinical implementation [10]. Moreover, the direct relation between hyperenhanced areas and scar was confirmed in animals by a comparison of in-vivo CMR images with with ex-vivo pathology images

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with triphenyltetrazolium chloride (TTC) staining [5, 20, 12].

**Quantification**

Quantification in LE CMR images involves measurements of the scar volume, relative to the myocardial volume, and the scar transmurality. The clinical reproducibility of such LE CMR analysis for infarct volume determination compares favorably with that of routine clinical SPECT [11]. Moreover, segmental quantification of scar transmurality is predictive of recovery of regional contraction after revascularization [13, 18]. The accuracy of this prognosis can be further improved by measuring the thickness of the non-enhanced myocardium [7].

**9.2.2 Methods**

**Delineation**

To obtain a delineation of the left ventricle (LV) in viability CMR images, we applied an affine transformation to the corresponding LV contours from functional CMR. The affine transformation was automatically obtained through 2D image registration between functional and viability CMR images. To anticipate on gross patient motion, initial translations were estimated by localizing the myocardium using a ring detection method based on the Hankel transform. Then, image registration was performed by maximizing normalized mutual information in a coarse-to-fine approach using a conjugate gradient optimization scheme. The image registration was performed between the LE slices and neighboring slices (to address through-plane motion) and phases (for accurate contour interpolation) in the functional scan. Furthermore, image registration was constrained to a region of interest that was defined by the bounding box of the LV contours in the functional CMR images.

**Classification**

We classified myocardium voxels through estimating density distributions for healthy and injured myocardium from the histogram of myocardium voxels using a specifically tailored expectation maximization algorithm [43]. The estimated distributions, as parameterized by the mean and SD for each tissue, are used to generate a fuzzy map indicating the membership to scar tissue in every voxel. As simply thresholding this fuzzy map would result in false positive classifications of myocardial voxels, we have adapted the region competition algorithm [44] to obtain well-defined regions corresponding to pathological areas. In the basic region competition framework, images are segmented by balancing regularization terms, including terms based on image statistics as well as boundary curvature. While the curvature term
CHAPTER 9. FUTURE WORK

requires relatively slow iterative schemes to avoid instabilities and weight-
ing of regularizations terms is critical and difficult to configure, we propose
to use a fast region competition method, in which those limitations are
mitigated by expressing the unknown partition as the super-level set of a
smoothed function. Based on this key idea, an alternative regularization is
formulated resulting in an evolution equation enabling a very simple itera-
tive algorithm to perform a regularized binary segmentation with a single
intuitive smoothness parameter [22].

9.2.3 Results

Delineation

Our delineation method was validated on CMR images from 32 patients
acquired between 2004-2007. The functional scans consisted of 10-14 slices
and 20-25 phases, whereas the viability scans consisted of 10-12 slices. All
images were 256x256 and covered fields of view of 320-460mm (functional)
and 344-494mm (viability). All images were delineated by three experts and
golden standard contours were obtained by averaging. Inter-observer vari-
ability and contour accuracy were measured using root-mean-square (RMS)
positioning errors with respect to the golden standard.

In functional CMR, the inter-observer variability over all phases was
small, $0.80 \pm 0.43\text{mm}$ and $0.89 \pm 0.48\text{mm}$ for the endocardial and epicardial
contours respectively, as compared to viability CMR, $1.17 \pm 0.57\text{mm}$ and
$1.12 \pm 0.58\text{mm}$ (figure 9.2). Our automatic segmentation method provided
endocardial and epicardial contours with RMS errors of $2.20 \pm 1.15\text{mm}$ and
$2.08 \pm 1.02\text{mm}$ respectively, see figure 9.3. In 6/32 patients both scans were
acquired at identical positions, according to SCMR guidelines [23]. For those
images, we obtained endocardial and epicardial contours with RMS errors of
$1.35 \pm 0.65\text{mm}$ and $1.41 \pm 0.35\text{mm}$ respectively. For the remainder of images,
myocardial contours with RMS errors of $2.34 \pm 1.15\text{mm}$ and $2.18 \pm 1.05\text{mm}$
were obtained.

![LV Endocardium](image1.png) ![LV Epicardium](image2.png)

Figure 9.2: Inter-observer variability for contour positioning in functional and via-
bility CMR images. The gray ellipse visualizes variation in contour positioning as
well as trigger delay for viability CMR images.
9.2. VIABILITY CMR ANALYSIS

Figure 9.3: Examples of myocardial contour delineations obtained in SA LE CMR.

Classification

The classification method was tested on 112 slices from 11 short-axis viability CMR scans (Philips Intera scanner 1.5T, FFE sequence, TE=1.1ms, TR=3.8ms, flip angle=15°, slice thickness=10mm, pixel size ≈ 1.5mm). The automatically defined infarct areas are compared with manually defined infarct areas from an experienced operator based on three measurements: the percentage of infarct voxels, the transmural extent of the infarct and the circumferential extent of the infarct.

The difference in percentage, transmural extent and circumferential extent of infarct voxels between the manually and automatically defined infarct areas was 3.5%, 15.0%, and 6.7% respectively. This compared favorably to simple thresholding at 2 SD, or 3 SD, levels above the average healthy myocardium values. Moreover, our method always avoids false detections contrary to thresholding approaches.

9.2.4 Conclusions

We developed a new method for segmenting LE CMR images given delineated cine CMR images. Our new method provided very accurate contours for LE CMR images acquired according the recent SCMR guidelines [23], while maintaining reasonable accuracy in older, more difficult cases. Moreover, we presented a fast and robust method for detecting and quantifying the injured myocardium SA LE CMR images.

9.2.5 Outlook

Our new method has been tested for viability CMR images acquired using an inversion recovery [9] protocol and therefore still needs to be tested on images acquired using the newer phase sensitive inversion recovery [3] protocol.

More recently, [1, 8] defined voxels with image intensities between mean + 2 SDs and mean + 3 SDs as the gray zone, which is supposed to increase
susceptibility to ventricular arrhythmias in patients with prior myocardial infarction and LV dysfunction. Whether the image intensity distributions obtained from our expectation maximization methods can be used for such grey zone quantification remains a topic for further evaluation.

Finally, the use of our method in patients with various forms of non ischemic cardiomyopathy (NICM) related to specific hyperenhancement patterns [17], needs to be assessed. Especially, our fast region competition method is configured towards obtaining segmentations that are consistent with myocardial infarction, which may be counterproductive for other hyperenhancement patterns, e.g. sub-epicardial or patchy hyper-enhancement.

9.3 Myocardial $T_2^*$ Assessment by CMR

Thalassaemia major is an inherited disorder of haemoglobin (Haemoglobinopathy) that causes severe anemia, which has to be treated using regular blood transfusions. This transfusion regime causes iron overloading, as each blood unit contains 200-300mg iron that the human body cannot excrete. While the blood transfusions enable patients to survive, the excess iron gradually causes heart failure, which is the main cause of death in patients with thalassaemia major, and liver injury (cirrhosis) to develop in the first 2 decades of life. Therefore, patients with thalassaemia major retrieve iron chelation therapy (ICT) to excrete the excess iron introduced by regular blood transfusions.

To monitor the effect of ICT the hepatic and myocardial iron content is monitored on a regular basis. The use of $T_2^*$ quantification by CMR to monitor myocardial iron content, alongside other improvements in clinical care, improves survival in patients with thalassaemia major [25] and is therefore recommended on a yearly basis [24].

9.3.1 State of the Art

Quantification of the myocardial $T_2^*$ from multi-echo CMR images (see figure 9.4) is performed by fitting an exponential decay to the average intensity within a region of interest in the myocardial septum [26], see figure 9.5. As the acquisition of 4-8 echos can be performed within a single breathhold using electrocardiogram (ECG) triggering, there is usually no motion in the images, such that the region of interest can be copied over all echos. Automatic contour detection for multi-echo CMR images is not available.

The clinical image data in this section was kindly provided by Children’s Hospital Boston, MA, USA, and Bioiatriki, Athens, Greece.
9.3. MYOCARDIAL $T_2^*$ BY CMR

Figure 9.4: Example echoes from a multi-echo SA CMR acquisition.

Figure 9.5: Example segmentation and decay fit (b) for quantification of $T_2^*$ from multi-echo SA CMR.

9.3.2 Methods

To detect myocardial contours in multi-echo CMR images, we located the LV contours by detecting ring structures using the Hankel transform, followed by a greedy optimization of a deformable template [27] in a coarse-to-fine approach to obtain accurate myocardial contours. This method assumed a bright myocardium and a dark blood pool. Furthermore, contour detection was performed at the first echo only, after which the contours were copied to all other echos.

To fit the exponential decay curve we used the Ratio-Least-Squares algorithm [28], in which a weighted fit is computed using decreasing weights for later echos. Especially in patients with severe iron overload, this is important as the image intensity may decrease below noise levels due to a short $T_2^*$.

We used 28 black-blood multi-echo CMR scans from 10 patients to evaluate our method. Each scan consisted of 4-8 echos at TE 1.3-17ms and the isotropic image resolution was 0.94-1.45mm. Golden standard contours
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were defined manually on all images and contour quality was assessed by measuring RMS contour positioning errors the manual and automatically detect contours. In addition the resulting $T_2^*$ value from manual and automated analysis was compared by calculating the mean absolute difference and correlation coefficient between $T_2^*$ values obtained from the automatically detected contours and the golden standard contours.

9.3.3 Results

All images were delineated successfully (see examples in figure 9.6). We found RMS contour positioning errors of $1.42 \pm 0.61$mm for the LV endocardium, and $1.36 \pm 0.96$mm for the LV epicardium.

![Figure 9.6: Examples of resulting LV contours (red) and the golden standard (yellow).](image)

$T_2^*$ values derived using automatically obtained contours correlated very well ($r^2 = 0.99$) with $T_2^*$ values derived from manually defined contours (figure 9.7). The average difference in $T_2^*$ values was only 0.68ms and non-significant. Furthermore, the average difference in $T_2^*$ in iron overloaded patients ($T_2^* < 20$ms) was even lower (0.36ms).

![Figure 9.7: $T_2^*$ from detected contours versus $T_2^*$ from manual contours.](image)
9.3.4 Conclusions

We have developed and technically validated an automatic delineation algorithm for multi-echo CMR images. The resulting contours are accurate and allow for accurate $T_2^*$ quantification.

9.3.5 Outlook

More recent advances in decay fitting suggest that more accurate $T_2^*$ can be acquired by means of maximum likelihood estimation using the complex data available during image reconstruction. Such a reconstruction approach should be compared to our post-processing approach towards quantification.

9.4 MultiView Analysis of Functional CMR

Quantitative analysis of cardiac function requires delineation of the LV in functional CMR. Typically, this is done using SA images only, even though several long axis (LA) views are usually acquired. The latter are known to facilitate more accurate and reproducible volume quantification [41] by simplifying the selection of the basal slice, which is a major cause for inter-observer variability [29, 30]. Automation of this procedure may reduce analysis time and observer variability further.

![Functional CMR images](a), (b) and (c)

Figure 9.8: Functional CMR images in SA view (a), LA 2CH view (b) and LA 4CH view (c).

9.4.1 State of the Art

In order to exploit the complementary information provided by SA, LA 2CH and LA 4CH images (see figure 9.8), so-called MultiView applications have developed. The simplest of these approaches use the intersections of LA

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The clinical image data used in this section was kindly provided by Deutsches Herzzentrum Berlin, Germany, and University Medical Center Utrecht, Netherlands.
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Figure 9.9: Reconstruction of SA LV contours using partial elliptical interpolation based on local estimates of the major axis A and minor axis B of an ellipse.

Contours with the SA image plane to reconstruct SA contours [38]. More complex approaches using a single 3D model for segmentation of views have been proposed based on active shape model (ASM) [39, 32, 40] and active appearance model (AAM) [36, 37, 35]. Such a single model may also be positioned interactively, using a small number of guide points [42]. To eliminate the need for separate models per view, such approaches need to be capable of handling sparse and arbitrary oriented images [39]. Moreover, the SA and LA views are subject to respiratory induced misalignment between slices, which may be corrected using image registration [33, 34].

9.4.2 Methods

In an attempt to further reduce analysis time and variability we have developed two MultiView segmentation approaches.

In the first approach, we developed a registration method to align the independent views to correct for respiratory induced motion. Afterwards, the SA images are delineated by applying partial elliptical interpolation to the intersection points of the LA 2CH and 4CH contours with the SA image planes, see figure 9.9.

The second approach consisted of automatic delineation of the LV myocardium in LA image(s) followed by delineation of the SA myocardial contours, both using a deformable template method. We apply a deformable, ribbon-like template that is defined using very few nodes connected by splines. The template is deformed to optimize an energy criterion comprising shape, contrast, and region terms using greedy optimization framework [31] in a coarse-to-fine manner. The initial position of the LA template is derived from the intersections between the SA and LA images, while that for the SA was again determined using a partial elliptical interpolation scheme.
9.4.3 Results

The first approach was evaluated using 75 orthogonal image sets. These orthogonal image sets contained 3 LA 2CH series including 25 phases, and corresponding LA 4CH and SA images. The slice alignment reduces the distance between the intersection points of the long axis contours and a multiuser golden standard in the SA image plane from $2.00 \pm 1.50\text{mm}$ to $1.52 \pm 0.82\text{mm}$, which approximates the pixel dimensions. Given 4 golden standard contour points, the elliptical interpolation results in contours with average RMS positioning errors of $1.04 \pm 0.59\text{mm}$ for the endocardium and $0.90 \pm 0.39\text{mm}$ for the epicardium. The complete procedure results in contours with average RMS positioning errors of $1.99 \pm 0.66\text{mm}$ for the endocardium and $1.32 \pm 0.35\text{mm}$ for the epicardium.

The accuracy of the second approach was quantitatively assessed on a database of 35 function CMR scans acquired using an SSFP protocol (TE = 1.4-1.8ms, TR = 2.9-4.0ms, flip angle = 45-55°, slice thickness = 8mm, number of phases = 15-50). The SA scans consisted of 9-14 slices (325 slices in total). The LA scans consisted 1-2 views (40 slices in total). The resulting contours were validated at end diastolic (ED) only by calculating a mean positioning error with respect to expert golden standard delineations. In the LA images, the mean positioning error was $1.3 \pm 0.4\text{mm}$ for the endocardium and $1.1 \pm 0.4\text{mm}$ for the epicardium, relative to a 1.3-1.8mm pixel size. In the SA images, the mean positioning error was $1.3 \pm 0.5\text{mm}$ and $1.5 \pm 0.8\text{mm}$ for the endocardium and epicardium respectively, relative to 1.4-1.8mm pixel sizes. Both results are under one pixel accuracy and comparable with inter- and intra-observer variability. An excellent correlation was found between manual and automatic LV volumes ($r=0.98$, $p<0.001$), with mean difference $-2.5 \pm 7.6\text{ml}$ ($5.5 \pm 3.9\%$).

9.4.4 Conclusion

We presented automated methods for the fully automatic delineation of the myocardium contours in LA and SA functional CMR images. Our preliminary results show promising accuracy for the myocardial contours, as well as for derived volumetric parameters.

9.4.5 Outlook

Although automated MultiView delineation methods may help to reduce the analysis time and variability, the more fundamental problem of correct volume quantification from different views still needs to be addressed. The presented methods produce volume curves with discontinuities, when the geometric intersection computation selects a different basal slice to be included for volume quantification using Simpson’s rule. A smarter solution
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for obtaining volumes from multiple views should not result in such discontinuities, and potentially be more accurate than volume quantification from a single view to increase the clinical benefit of MultiView analysis.

9.5 Summary

In this chapter, three automated methods for the analysis of CMR images have been presented, including methods for processing viability CMR images (section 9.2), multi-echo CMR images (section 9.3), and for multi-view analysis of functional CMR images (section 9.4). The presented methods all aim to provide faster and more reproducible analysis through automating common post-processing tasks. For viability CMR images, this included an automatic contour detection method, capable of delineating the myocardial contours given delineated functional CMR images, and an automated classification method, capable of segmenting the myocardial scar tissue. The analysis of multi-echo CMR images for the purpose of $T_2^*$ assessments was simplified by providing a fully automatic contour detection method, enabling quick quantification of the $T_2^*$ in the ventricular septum. Finally, we presented a framework for relating LA and SA functional CMR images providing additional automation over the works presented in part I, but ultimately aimed at obtaining more accurate volume estimates that are robust for basal slice positioning in the SA stack. Altogether, the results obtained with these methods are promising and additional validation studies are warranted to further determine the clinical value of these methods.

9.6 References


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9.6. REFERENCES


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Curriculum Vitae

Gilion Hautvast was born on 06-06-1981 in Heerlen, the Netherlands. After finishing VWO in 1999 at Sophianum in Gulpen, the Netherlands, he studied Biomedical Engineering at the Eindhoven University of Technology in Eindhoven, the Netherlands. In 2005 he graduated within the Biomedical Image Analysis group on ”Segmentation of Short Axis Cardiac MR using Active Contours”. From 2008 he started a PhD project at the Eindhoven University of Technology at Eindhoven, the Netherlands, of which the results are presented in this dissertation. Since 2005 he is employed at Philips Healthcare.
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