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MR image analysis for the investigation of myocardial contractility

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Declaration

I herewith certify that this thesis presents original work of the titled author and all material in this dissertation which is not the author's own work has been properly acknowledged.

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Christina Koutsoumpa

Abstract

The aim of this work is to provide novel methods, tools and the theoretical background of an image analysis framework for the generation of consistent and detailed myocardial contractility maps, which have the potential to contribute to an early and accurate diagnosis and prognosis of cardiac disease. The image analysis framework is tailored to Tissue Velocity Mapping (TVM) images. 3D deformation measures from the field of tissue mechanics are examined and their consistency in myocardial studies is investigated; an original theoretical analysis of different strain formulas reveals significant discrepancies. A novel framework for the improvement of consistency in LV segmental contractility analysis is introduced and new interactive tools for the accurate detection of the LV anatomical landmarks and delineation of the myocardium are developed as part of it. A new automatic method for the correction of myocardial segmentation is proposed and improves further the consistency of the segmental maps. Plots of segmental maps are suggested for the intuitive clinical intra- and inter-subject assessment, and the segmental velocity patterns over TVM datasets lead to the newly introduced concept of motion symmetry. A new total-variation based restoration method is introduced which alleviates TVM image noise while preserving the underlying complex and possibly discontinuous myocardial motion; the proposed method improves considerably the consistency of the regional velocity maps, it is robust and less computationally expensive than its homologous methods. Deformational velocity maps are proposed as an alternative to the currently established strain maps for the assessment of contractility. A novel, analytical and fast method for the computation of translational motion is proposed considering two models of left-ventricular symmetry and shows high efficiency on synthetic and in vivo data. The rigid body motion is computed and subtracted from the TVM measurements; the velocity residuals constitute the suggested deformational velocity maps.

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*As you set out for Ithaca
hope the voyage is a long one,
full of adventure, full of discovery..*

Ithaca gave you the marvelous journey..

*Wise as you will have become, so full of experience,
you will have understood, by then, what these Ithacas mean.*

Ithaca, C.P. Cavafy

to my family

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Acronyms

AHA American Heart Association.

AI Anterior Interventricular groove.

AV Atrio-Ventricular node.

AVDP AV Plane Descent.

BSA Body Surface Area.

bSSFP balanced SSFP.

CAI Computer Assisted Intervention.

CAmyl Cardiac Amyloidosis.

CI Confidence Interval.

CMR Cardiovascular Magnetic Resonance.

CO Cardiac Output.

CT Computed Tomography.

CVD Cardiovascular Disease.

DCM Dilated Cardiomyopathy.

DENSE Displacement ENcoding with Stimulated Echoes.

DL Deep Learning.

EBCT Electron beam CT.

ECG Electrocardiography.

ECG Electrocardiogram.

ECV ExtraCellular Volume.

EDV End-Diastolic Volume.

EF Ejection Fraction.

ESV End-Systolic Volume.

FEM Finite Element Model.

FFE Fast Field Echo.

FID Free Induction Decay.

FLASH Fast Low-Angle SHot.

FOV Field Of View.

FSE Fast Spin Echo.

GRAPPA GeneRalized Autocalibrating Partially Parallel Acquisitions.

GRE Gradient Recalled-Echo.

HARP HARmonic Phase.

HCM Hypertrophic Cardiomyopathy.

HR Hear Rate.

IV Interventricular grooves.

LGE Late Gadolinium Enhancement.

LL Look Locker.

LV Left Ventricle.

M Myocardial Mass.

M-AHA mean Magnitude of velocity AHA.

MDCT Multidetector spiral row CT.

ML Machine Learning.

MMRN Modified MRN.

MOLLI Modified LL Inversion recovery.

MPRN Modified PRN.

MRI Magnetic Resonance Imaging.

MRN Mode of Removed Noise.

NL Non-Local means.

PC-MRI Phase-Contrast MRI.

PET Positron Emission Tomography.

PFR Peak Filling Rate.

PI Posterior Interventricular groove.

PRN Percentage Removed Noise.

PSNR Peak SNR.

PVR Percentage Variance Reduction.

RCL Radial-Circumferential-Longitudinal.

RCM Restrictive Cardiomyopathy.

ROI Region Of Integration.

RV Right Ventricle.

SA Sinoatrial node.

SASHA SATuration recovery single SHot Acquisition.

SD-AHA Standard Deviation of the magnitude of velocity AHA.

SENC Strain-ENCoded MRI.

SENSE SENSitivity Encoding.

SMC Sequential Monte Carlo.

SNR Signal-to-Noise Ratio.

SPAMM SPAtial Modulation of Magnetisation.

SPECT Single Photon Emission CT.

SSFP Steady-State Free Precession.

STE Speckle Tracking Echocardiography.

SV Stroke Volume.

TDI Tissue Doppler Imaging.

TSE Turbo Spin Echo.

TV Total Variation.

TVM Tissue Velocity Mapping.

V_{enc} maximum ENCoded Velocity.

1. Introduction

Cardiac disease is a main cause of mortality and morbidity worldwide urging the need for accurate and early diagnosis. Indicatively, Cardiovascular Disease (CVD) accounted for 31.5% of the global [1] and 45% of the European mortality [2] in 2013, as well as 26% of all deaths in the UK in 2018. The latest statistics by the British Heart Foundation in 2018 [3] state additionally, that over half a million of the current British population has been diagnosed with heart failure and 1 in 500 people in the UK suffer from hypertrophic cardiomyopathy. The recent report by the American Heart Association (AHA) in 2017 [4] states that 43.9% of the US adult population is expected to have some form of CVD by 2030, and cardiac disease, in particular, is currently diagnosed in 16.5 out of 92.1 million American adults, reflecting further its severity.

Cardiac disease and conditions like cardiomyopathies, myocardial ischemia, infarction and arrhythmias affect primarily the LV, which is the chamber of the heart that undertakes most of the cardiac work load. Diagnosis can be performed with a range of medical examinations and imaging modalities like echocardiography, cardiac Computed Tomography (CT), X-ray imaging, nuclear imaging, among which Cardiovascular Magnetic Resonance (CMR) imaging is advantageous not only because of its safe non-invasive acquisition, but also because it provides detailed information from any tomographic plane or volume in the heart. Depending on the CMR sequence programmed in the MRI scanner, the operator can select from a vast variety of CMR techniques, each one depicting specific attributes in the heart, several of which can be analysed to study the motion and contractility of the myocardium.

Contractility is the innate ability of the myocardium to actively contract and constitutes an intrinsic property of the heart. It is usually altered in the presence of myocardial pathologies and, thus, can be employed as a diagnostic indicator. Early-stage myocardial pathologies are associated with small-scale contractility distortions, which are commonly compensated by

the preeminent mechanisms of the heart and, thus, they may not affect the global cardiac indices making their detection a challenging task; such regional contractility distortions have shown to be possibly discernible in detailed maps of the regional cardiac indices. It is believed that the generation of detailed and consistent regional myocardial contractility maps for each patient will pave the way to a better understanding of the left-ventricular myocardial function and the accurate early diagnosis and prognosis of cardiac disease.

Detailed myocardial contractility maps are expected to extend the benefits of CMR in terms of clinical impact, patient management and healthcare cost [5]. They are anticipated to contribute to the accuracy of cardiac disease diagnosis and, in particular, the differentiation of the rare infiltrative diseases like amyloidosis and sarcoidosis from the common diseases like hypertrophic and dilate cardiomyopathy. The ability to detect non-contractile regions across the myocardium will improve the assessment of myocardial viability and consequently the associated therapeutic planning. For instance, if the lateral myocardium is shown non viable, the patient may not be referred for cardiac resynchronisation therapy, which would probably be inappropriate and ineffective in this case. Currently this happens in one third of these therapy cases. Moreover, the pathological nuances revealed by the maps will enable more effective monitoring of cardiac disease progression and treatment, provide important information for a prompt clinical intervention and, along these lines, favor the more appropriate planning of a cardiac transplantation which is of critical importance. From the above, it is implied that correct diagnosis anticipates a reduction in unsuitable treatments, additional testings and recurrent hospital admissions. Overall, the patient's life will improve, mortality rates will reduce but also patient care will benefit in a cost effective manner.

Regional myocardial contractility can be described as myocardial deformation and, thus, quantified with measures from tissue kinematics. The direct measurement of myocardial deformation is a challenging task, hence, often the total myocardial motion is measured and then used to derive the deformation. Among the existing CMR techniques for measuring regional myocardial motion, Phase-Contrast MRI (PC-MRI) shows a significant potential as it enables the direct depiction of pixel-wise velocity maps, in the three orthogonal directions, with high spatiotemporal resolution and non-

decreasing quality during acquisition, from which the three-dimensional deformation can be easily computed. Although PC-MRI has been successfully applied to image the blood flow, its applicability to myocardial TVM has been hindered by the low signal-to-noise ratio, complicated form of noise and other inevitable artefacts, which impact the consistency of the velocity measurements the establishment of a clinically suitable TVM analysis framework. As a result, the practicality of TVM is currently restricted to the computation of less accurate or coarser contractility maps and its translation to clinical practice is yet hampered. To enable the clinical applicability of TVM, it is necessary to establish an image analysis framework for the construction of accurate, detailed and consistent contractility maps from PC-MRI and the current thesis achieves a number of contributions towards this direction.

The first contribution of this thesis resides in the theoretical investigation of the meaningful myocardial contractility quantification measures, presented in *Chapter 3*. 3D deformation measures from the field of continuum kinematics are presented and given intuitive interpretations tailored to the needs of myocardial analysis. Prior to this, the behaviour of the myocardium as a continuum and its properties are investigated with a critical approach to the literature in order to examine the applicability of the continuum kinematics principles to myocardial contractility analysis. Although strain is a meaningful quantitative measure of tissue deformation and it has been already particularly popular in myocardial contractility studies, we observe that it introduces a certain degree of analysis inconsistency. Our critical approach to the literature and continuum kinematics theory shows that 3D strain is non-univocally defined and it occurs that different cardiac studies employ different strain formulas and parameters often without clarifying them. The main original contribution of this chapter is the theoretical analysis of the discrepancy between different reported strain formulas; accurate quantification of this discrepancy is provided with numerical studies and an easily computed approximation is proposed and proved. The discrepancy analysis is applied to myocardial strain values from the literature in order to investigate the statistical significance of the myocardial strain results from unreported strain formulas and thus examine the consistency and comparison compatibility across the myocardial strain studies.

One of the original technical contributions of this thesis is the proposal of a novel framework for the improvement of segmental myocardial contractility analysis consistency along with the necessary newly developed tools, presented in *Chapter 4*. Segmental analysis with the established 17-segment AHA model [6] has been quite broadly applied for the construction of contractility maps from the LV, but the myocardial segment division methodology that each study employs remains obscure and probably contains inaccuracies. We claim that the myocardial segment division plays an important role in the consistency of the AHA maps and, to support this claim, we investigate the variation of the involved reference points across the slices and frames of the TVM stacks as well as the impact of myocardial segmentation errors on the AHA maps. Accordingly, we develop and present new interactive tools for the accelerated accurate detection of the reference points and delineation of the myocardial contours and a novel automatic method for the correction of the myocardial segmentation tailored to the TVM image characteristics and segmental analysis requirements. We also suggest plots of AHA maps that provide a clinically meaningful spatiotemporal overview of the left ventricular contractility and are suitable for inter-subject assessment and intra-subject comparison. We also introduce the concept of motion symmetry in the LV supporting the results from the proposed segmental analysis framework.

Chapter 5 proposes a new TV based method (TV restoration) for the alleviation of TVM noise and the construction of consistent regional velocity maps. TV restoration is a previously suggested concept [7] for image denoising and simultaneous preservation of image discontinuities. Potential motion discontinuities, discussed in Chapter 3, are addressed in Chapter 5 and the TV restoration concept shows to respect them. The TV restoration concept is treated as an optimisation problem that was previously solved with complex numerical methods. The main contribution of this work is the suggestion of an estimate for the key parameter involved in the optimisation problem and this simplifies considerably the numerical solution, ensures convergence as well as accuracy of the restoration method. The proposed TV restoration method is applied to 10 datasets that were acquired for this purpose in the Royal Brompton Hospital with the latest developed TVM sequence; consistent regional velocity maps from the latest TVM data are presented and this is another contribution of this chapter.

Another contribution of the current thesis is the novel translational velocity estimation method presented in *Chapter 6*. The proposed method estimates effectively the translational motion from the left ventricular TVM measurements based on the assumption of left ventricular motion symmetry. We introduce the new concept of left ventricular motion symmetry, based on the observation of motion analysis results from the literature. We suggest and investigate two models of symmetry. The efficacy of the proposed method is proved mathematically, its performance and robustness are evaluated on synthetic and semi-synthetic datasets and the method is applied to the TVM datasets to generate the deformational 2D and 3D myocardial velocity fields. A novel idea is the use of the deformational velocity field as an alternative myocardial contractility map that provides an intuition into the myocardial deformation without the challenges of strain and strain rate analysis.

The thesis also includes preliminary new work on the automatic segmentation of the LV and myocardial tissue characterisation with T-1 mapping, included in the *Appendix*. We suggest that motion, shape and tissue information can potentially be combined in a common framework for the diagnosis and differentiation among a wide range of myocardial diseases, which is an interesting topic for future investigation.

A part of the work presented in this thesis appears also in the following two peer-reviewed publications and one arXiv paper. Further papers are in preparation.

- Peer-reviewed

1. Koutsoumpa, C., Simpson, R., Keegan, J., Firmin, D., and Yang, G. Z. Restoration of Phase-Contrast Cardiovascular MRI for the Construction of Cardiac Contractility Atlases. *In International Workshop on Statistical Atlases and Computational Models of the Heart*, pp. 275-283, Springer, Cham., 2014
2. C. Koutsoumpa, Y. Wang, and G.-Z. Yang, "T1-Mapping for Differential Diagnosis of Cardiac Amyloidosis and Hypertrophic Cardiomyopathy based on Intensity and Texture, 38th Annual International Conference of the IEEE Engineering in Medicine

and Biology Society (EMBC' 16), Orlando, 2016. (short paper)
<https://events.infovaya.com/presentation?id=26730>

- Non peer-reviewed

Koutsoumpa, C., Keegan, J., Firmin, D., Yang, G. Z., and Gillies, D. Translational Motion Compensation for Soft Tissue Velocity Images. *arXiv*, 2018.

2. Imaging the Myocardium

2.1. The heart and the left ventricle

2.1.1. The heart

The heart is a vital organ for the body and its main role is to pump oxygenated blood to the body through the systemic circulation and pump the de-oxygenated blood to the lungs through the pulmonary circulation for re-oxygenation. The pumping activity of the heart is accomplished by systematic contraction and relaxation of the cardiac muscle or myocardium. The systematic contraction of the myocardium is explained by its complex multilevel anatomical structure and the conductive system of the heart.

Cardiac anatomy and blood flow

- **Cardiac anatomy.**

The main anatomy of the heart consists of four chambers, four valves and the great vessels. The four *chambers* are the right and left ventricle, the right and left atrium. The atria are the upper chambers of the heart, thin-walled and their main role is to receive the blood that returns to the heart. The ventricles are the lower chambers of the heart, they are thicker and their main role is to expel the blood to the pulmonary and systemic circulation. The *great vessels* are the aorta, the superior and inferior vena cava, the pulmonary arteries and veins and their main role is to transfer the blood to and from the four chambers. The four *valves* are the mitral valve, the aortic valve, the tricuspid valve and the pulmonary valve; the valves lie between the same-sided chambers and between the ventricles and the great arteries and their role is to control passively the one way blood circulation. The valves are anchored via the *chordae tendineae* (collagenous fibres) to the *papillary muscles* that are extensions of the inner ventricular walls. Another secondary but critical component of the cardiac anatomy is the

coronary arteries that branch from the aorta near the LV and their main role is to supply blood to the myocardium and other components of the heart.

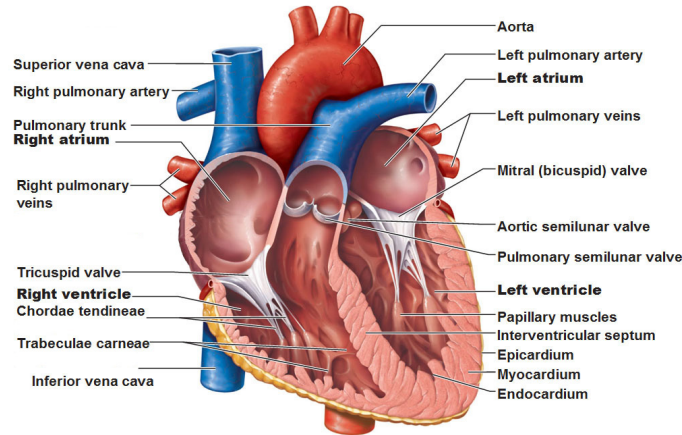


Figure 2.1.: Cardiac anatomy [8].

- **Cardiac wall.**

The cardiac chambers are formed between the cardiac wall. The cardiac wall comprises of three main layers from inside outwards; these are the endocardium, the myocardium and the epicardium. The *endocardium* is the thin inner layer of the cardiac wall consisting of a simple squamous epithelium and loose connective tissue; it lines the cardiac chambers and structures projecting into them i.e. valves and trabeculae carneae. The endocardium does not have the ability to actively contract but it plays a regulatory role in the contraction of the cardiac muscle. The *myocardium* is the thick middle layer of the cardiac wall consisting of striated cardiac muscle fibres embedded in collagen; The myocardium has the ability to actively contract endowing the heart with the pumping function; it is the muscle of the heart. The inner side of the ventricular myocardium forms irregular ridges known as *trabeculae carneae*, whose main role is to prevent suction of the inner surface of the ventricles during contraction. The *epicardium* is the thin outer layer of the cardiac wall composed of loose connective tissue, adipose tissue and a simple squamous epithelium; it covers and lubricates the heart by secreting a small amount of fluid into the pericardial cavity.

The pericardial cavity is formed between the epicardium also called visceral pericardium and the parietal pericardium which is further embraced by the fibrous pericardium. The *pericardium* is thus a double walled sack with a small amount of serous lubricating fluid that includes and protects the heart. Although the pericardium and endocardium do not contract, they support cardiac motion by protecting the heart from friction and stabilising the heart's position in the chest.

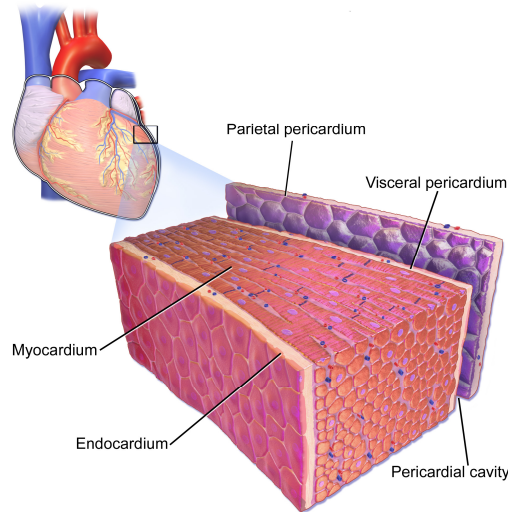


Figure 2.2.: Cardiac wall [9].

- **Blood flow.**

Coordination of the contractile and non-contractile anatomical components of the heart regulates blood flow in the heart and circulation in the body as follows. The de-oxygenated blood is directed by the superior and inferior vena cavae to the right atrium, from where it passes through the tricuspid valve to the Right Ventricle (RV). From the right ventricle, the blood moves through the pulmonary valve to the pulmonary artery and, then, it proceeds to the lungs for re-oxygenation. The oxygenated blood returns through the pulmonary vein to the heart and specifically the left atrium. From the left atrium the blood is pushed through the mitral valve to the LV. The LV pumps the blood through the aortic valve to the aorta and the rest of the body.

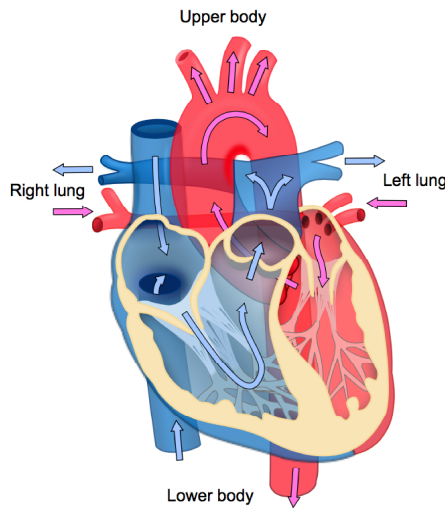


Figure 2.3.: Cardiac blood flow [10].

Cardiac conduction

The heart combines mechanical and electrical activity resembling an electro-mechanical pump. Successful pumping requires systematic and coordinated contraction of the cardiac chambers, which is triggered by the heart's electrical activity. Cardiac electrical activity is regulated by the cardiac conduction system that consists of the Sinoatrial node (SA), the Atrio-Ventricular node (AV) node, the bundle of His, the left and right bundle branches and the Purkinje fibres. The *sinoatrial* node is the natural pacemaker of the heart, as it initiates the electrical impulses without neural stimulation. The SA node is located in the upper wall of the right atrium near the superior vena cava and consists of nodal tissue. The nodal tissue has a twofold nature, it contracts similarly to the muscle tissue and generates electrical impulses similar to the nervous tissue. Electrical impulses travel through the cardiac conduction system and spread across the myocardial wall, causing depolarisation and, thus, contraction of the cardiac muscle cells known as *cardiac myocytes*.

The electrical impulses are generated at the SA node rhythmically and, then, they spread fast through the myocardial wall across the atria causing them to contract. When the electrical impulses reach the AV node, which is located at the bottom of the right atrium in the interatrial septum, they are delayed for about a tenth of second and re-distributed towards the ventricles;

this delay allows time to the atria to contract and propel blood to the ventricles, before the ventricles contract in turn. The electrical impulses are propagated fast along the septum through the bundle of His, which splits into the left and right bundle branches. The electrical impulses are conducted through the left and right bundle branches to each side of the septum and, from there, through the Purkinje fibers, they spread fast across the ventricular walls causing their contraction¹.

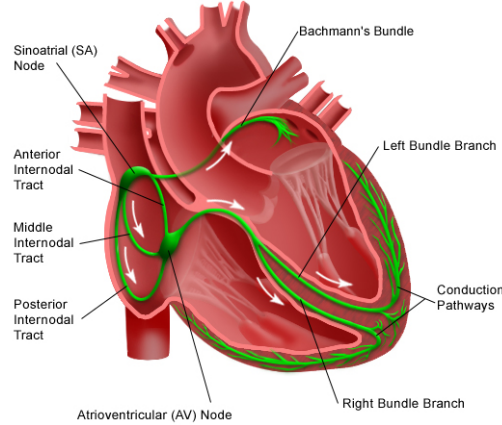


Figure 2.4.: Cardiac conduction system [11].

The normal heart rate is between 60 and 100 bpm (beats per minute) for a healthy adult at rest. The heart rate is controlled by the SA node, which is regulated under normal conditions by autonomic nerves of the peripheral nervous system. The SA is also regulated by the parasympathetic and sympathetic autonomic nerves which either accelerate or decelerate the heart rate (via the SA node) depending on the need.

Cardiac cycle

The cardiac cycle is a periodic sequence of coordinated events that occur during a heartbeat; these events refer to the cardiac electrical activity, the myocardial dynamics and blood pressure in the cardiac chambers. With regard to myocardial dynamics, we can distinguish two main phases that are the *diastole* and *systole*, which signify *contraction* and *relaxation* of the

¹The electrical impulses in the ventricles travel from the apex to the base and from the epicardium to the endocardium.

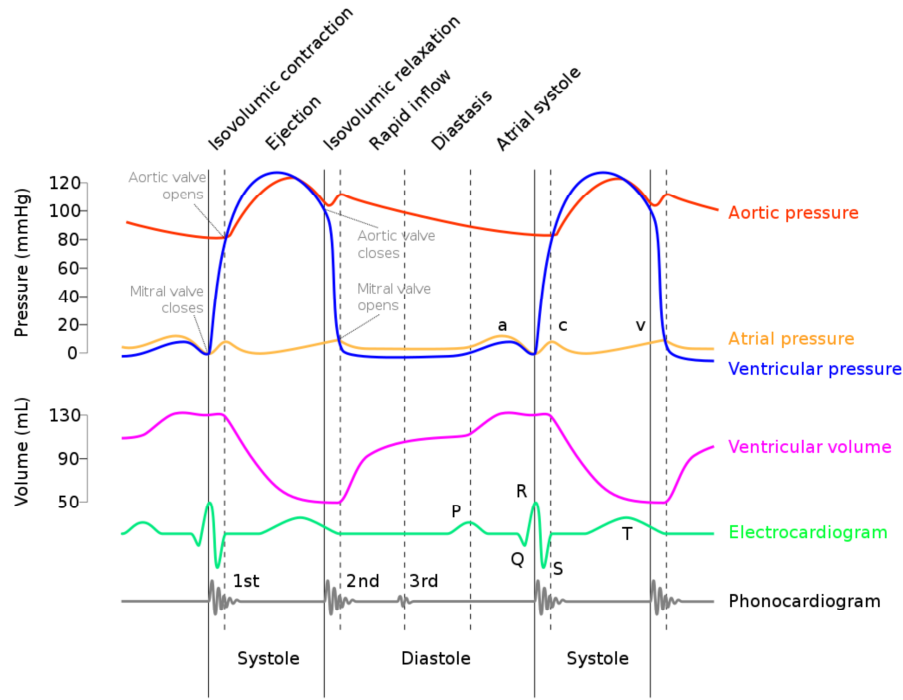


Figure 2.5.: Cardiac cycle: Synchronised curves for blood pressure, volume, ECG and Phonogram from the heart [12].

ventricles. The cardiac cycle is subdivided further into shorter intervals with respect to the activity in each cardiac chamber and the opening-closing of the valves. We have already described the events of the cardiac cycle with regard to blood flow and cardiac electrical activity. Here, we will associate these events with the events of ventricular contraction, relaxation, blood pressure and the ECG waveform.

Electrocardiography (ECG) is the most popular and simple clinical means to record the cardiac cycle and examine the heart rhythm. The ECG measures the cardiac electrical activity by detecting and amplifying the electrical signals or electrical impulses or action potentials from the synchronized depolarization and repolarisation of the myocytes in the atria and ventricles. Another simple means to examine the heart's rhythm is *phonocardiography*, which records the sounds made by the heart and specifically the closing of the valves as seen in Figure 2.5.

The ECG waveform starts with a P wave. The P wave denotes depolarization of the atria and the beginning of the *atrial systolic phase*. During

this phase, the atria contract causing the atrial pressure to rise and the blood to leave the atria and enter the ventricles.

The ECG diagram continues with the QRS complex, which denotes depolarization of the ventricles and the beginning of the *ventricular systolic phase*. The ventricular systolic phase consists of the isovolumetric contraction and ejection intervals. During ventricular systole, the ventricles contract causing increase of the ventricular pressure. Initially the ventricular pressure is high enough to close the mitral and tricuspid valves but still too low to open the aortic and pulmonary valves; as a result the ventricles perform *isovolumetric contraction* for some time. During isovolumetric contraction the ventricular pressure rises fast and once it reaches the aortic pressure, the aortic and pulmonary valves open. This signifies the start of the *ejection* interval, during which the blood is propelled from the ventricles to the aorta and pulmonary artery. Near the end of the ejection phase, the T wave of the ECG diagram is generated from the ventricular repolarization, hence relaxation of the ventricles begins. Ventricular relaxation results in fast decrease of the ventricular pressure and rate of blood ejection. When pressure falls sufficiently, the aortic and pulmonary valves close, denoting the end of the ventricular systolic phase and the beginning of the ventricular diastolic phase.

The *ventricular diastolic phase* starts with all valves closed and the ventricles performing *isovolumetric relaxation*; during this interval the ventricular pressure decreases fast because of the relaxation of the ventricles. When ventricular pressure drops, the mitral and tricuspid valves re-open and blood starts to flow from the atria to the ventricles relatively rapidly. The *rapid inflow* is followed by *diastasis*, during which the ventricles remain relaxed and receive blood from the atria at a slower rate than earlier; the ventricular pressure does not increase. Diastasis ends with the P wave of the ECG and the beginning of a new atrial systole. The ventricular diastolic phase is composed of the isovolumetric relaxation, rapid inflow, diastasis intervals and the atria depolarization phase.

In cardiac imaging and studies, the cardiac cycle is measured by R-R intervals meaning that the beginning of the cardiac cycle is set at the time of the R wave and the start of ventricular isovolumetric contraction. This has been established because the R wave is the most prominent component of the ECG waveform and, thus, it is convenient to be used as a reference

for the start of each cardiac cycle.

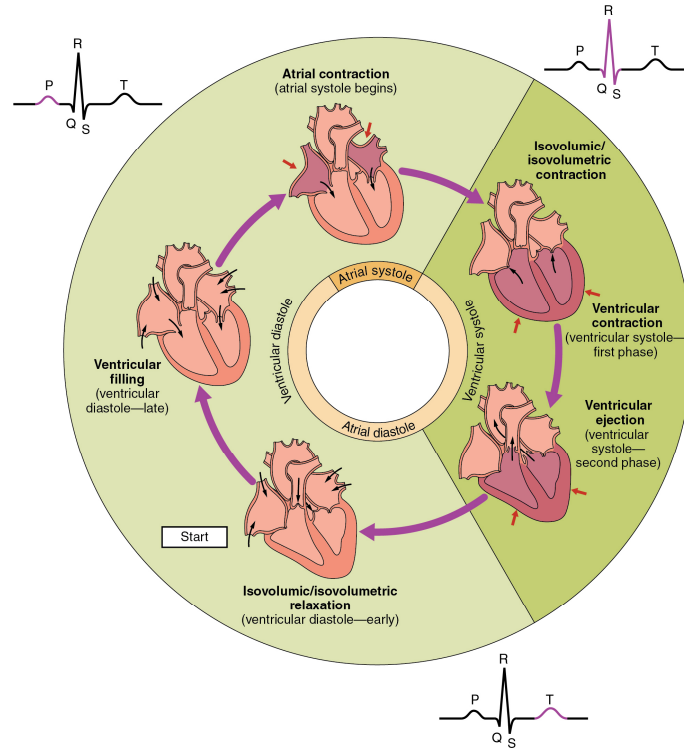


Figure 2.6.: Cardiac cycle: Phases of the cardiac cycle with respect to cardiac chamber dynamics and ECG waveform [13].

2.1.2. The left ventricle

The role of the LV is critical for blood pumping and circulation, as it pumps the high-pressure oxygenated blood to the aorta and the systemic circulation. The pressure of the oxygenated blood in the aorta is significantly higher than the pressure of the de-oxygenated blood in the pulmonary artery reaching a peak of about 15kPa versus 3kPa during normal heart beating. This means that the LV sustains considerably higher blood pressure compared to the RV as well as the atria. The *LV*, thus, undertakes most of the work output of the heart and this explains its size, thickness, shape and susceptibility to cardiac disease.

Ventricular myocardial anatomy

The LV has thicker walls compared to the other cardiac chambers and its shape approximates a truncated ellipsoid with annular and almost circular cross section; this left-ventricular structure facilitates contraction in high force. On the contrary, the *RV* propels blood towards the lungs in lower pressure and, thus, it produces a lower work output; for this reason, the right ventricular wall is thinner. The shape of the RV forms a shallow *U* that wraps around the LV in a crescent-like fashion. The part of the cardiac wall that separates the two ventricles is the *interventricular septum* and its two regions of connection between the left and right ventricle are known as the *Interventricular grooves (IV)*.

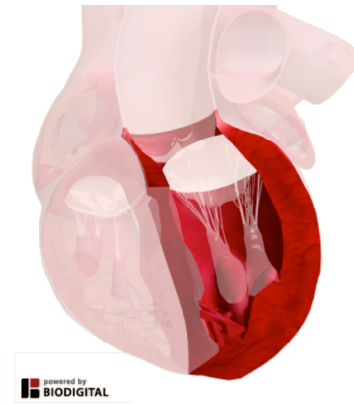


Figure 2.7.: The left ventricle [14]

Left ventricular orientations and segments.

Studies of the LV have adopted a consensus and common nomenclature for the different anatomical orientations, segments and deformational orientations within the LV. Nomenclature is tailored to the shape of the LV, which appears ellipsoidal or almost conical in the long axis cross sections and annular approximately circular in the short-axis cross sections; the motion of the LV is also considered.

The *long axis* of the LV is defined along the larger dimension of the LV and connects its lower tip with the mitral valve. The term *short-axis* denotes a direction that lies perpendicular to the long axis and parallel to

the mitral valve; this term is used to characterise the cross-sectional planes of the LV that are parallel to the mitral valve rather than an axis itself. The upper and wider part of the LV that is proximal to the mitral valve is the *base*, whereas the lower and narrower part of the LV is the *apex*. Short-axis cross sections are viewed from the apex towards the base. On the circumference of the left-ventricular short-axis cross section, we define the *anterior*, *septal*, *inferior* and *lateral* anatomical orientations. Referring to the location within the body, the anterior wall lies higher and near the front chest, whereas the inferior wall lies lower, towards the spinal cord and next to the liver. The septal wall is the part of the LV belonging to the interventricular septum, whereas the lateral wall is the free wall near the left lung.

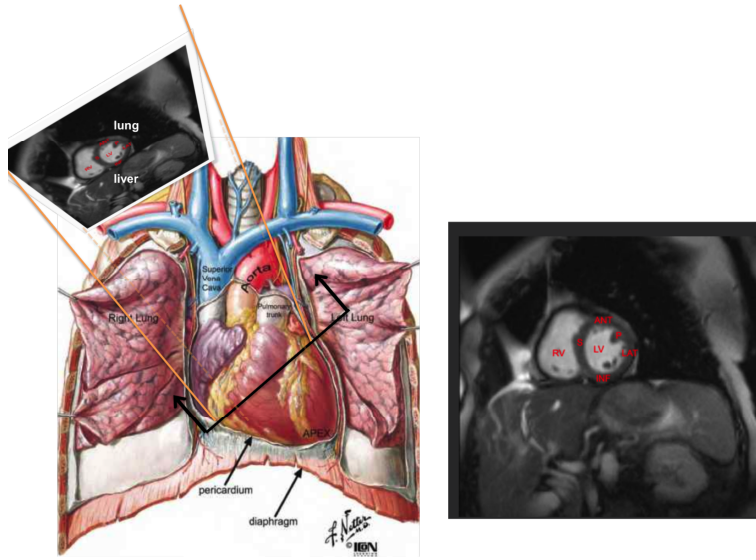


Figure 2.8.: Anatomical orientations in the LV.

The AHA [6, 15] has established a consensus for the division of the LV into distinct segments. The segment limits are defined along the long axis and across the short-axis plane, with regard to the shape of the LV at end-diastole. Along the long axis, the LV is divided into three equal thirds that give the *base*, *mid-cavity* or *mid-wall* and *apex*. The base is extended from the mitral valve to the tips of papillary muscles; the mid-cavity includes the entire length of papillary muscles and the apex covers from the area beyond the papillary muscles to just before the cavity ends. The remaining part of

the myocardium that is beyond the end of the left ventricular cavity up to the tip of the LV is called *true apex* or *apical cap*.

According to the 17-segment AHA model [6], each left ventricular cross section is further divided into (equiangular) wedges or segments, using the positions of the IV as reference. The basal and mid-wall are divided into six segments that are the *anterior*, *anteroseptal*, *inferoseptal*, *inferior*, *infero-lateral* and *anterolateral* segments. The apex is divided into four segments that are the *anterior*, *septal*, *inferior* and *lateral* segments. The apical cap is in the whole the 17th segment of the AHA model.

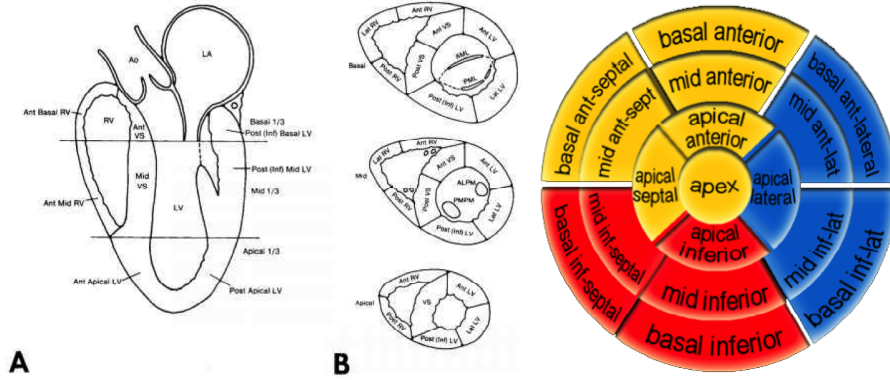


Figure 2.9.: Segments of the LV divided along the long axis(left) and across the short-axis plane(right) according to the AHA [6, 16].

For the description of motion and deformation in the LV, the Radial-Circumferential-Longitudinal (RCL) coordinate system is more convenient than the spatial Cartesian coordinate system. The RCL system is a local orthogonal coordinate system defined such that the longitudinal orientation is aligned with the long axis of the LV, the radial and circumferential orientations are given by the polar coordinates at each point. The longitudinal direction is defined positive from the base to the apex, the radial direction is defined positive inwards towards the centre of the LV and the circumferential direction is considered positive in the clockwise direction, as viewed from the apical tip [17].

2.1.3. Left ventricular myocardial motion

The LV motion/deformation comprises of six functional events of the cardiac muscle that are in-pair complementary; these are *narrowing- widening*,

twisting-uncoiling and shortening-lengthening. The combination of these functional events results in a complex left ventricular myocardial motion, which varies not only across the cardiac cycle but also across the different segments in the LV.

Description

Before describing the left ventricular myocardial motion, we will clarify the nomenclature for the different types of motion, the phases and main time points of the cardiac cycle that are commonly used in left ventricular myocardial motion studies. When studying intra-slice (short axis) motion, it is convenient to use the terms *contraction-expansion* and *clockwise- anticlockwise rotation* to indicate motion in the radial and circumferential directions, while maintaining the terms *shortening-lengthening* for the longitudinal direction. When studying motion across different short-axis slices (vertical segments), rotation should not be confused with twisting and torsion. In that case, *rotation* implies global rotation of the LV in space, whereas *torsion* or *twisting* describe the relative rotation between two different vertical segments, for example apex and base, and they are mostly used in deformation analysis.

Studies on left ventricular function use the aforementioned nomenclature, and additionally, isovolumetric *contraction-ejection-isovolumetric relaxation-rapid inflow-diastasis* for the description of each interval of the cardiac cycle. Studies on left ventricular motion use also the terms *end-diastole*, *mid-diastole*, *end-systole* and *mid-systole* to indicate correspondingly the time points right before systole, in the middle of systolic ejection, right before diastole and in the middle of diastolic diastasis [17].

- **Macroscopic description.**

Macroscopic observation of the cardiac motion gives the following descriptions for each interval of the cardiac cycle [18]. During *isovolumetric contraction*, the LV lengthens and the left ventricular cavity narrows. Global anticlockwise rotation and perhaps twisting also occur during this interval; studies present variability regarding the observed rotation or twisting of the LV during isovolumetric contraction, which could be attributed to the imaging differences or normal functional variations due to age for instance [19]. During *systolic ejection*, the heart wall thickens, the left ventricular cavity

narrows and shortens. Torsion between the base and the apex is prominent, with the apex rotating counterclockwise and the base rotating clockwise. In *isovolumetric relaxation*, the left ventricular cavity widens, lengthens and the LV rotates globally clockwise to compensate the previous movements so that the LV can slowly return to its initial shape and prepare for filling. During *rapid filling*, the LV continues lengthening, widening and the apex rotates further clockwise causing uncoiling. In the last interval of diastole, all motions have slowed down and the heart is relaxed and filling with blood.

Sengupta [20] claims that during isovolumetric phases, lengthening and shortening of the myocardium coexist. For example in isovolumetric contraction the inner subendocardial fibres in the anterior wall shorten whereas the outer subepicardial fibres stretch. This simultaneous shortening-stretching or myocardial fibres results in coexistence of regional contraction-relaxation in regions lying transmurally or along the longitudinal direction of the LV and another result is the increase in myocardial stiffness. For this it is difficult to assign the terms systole or diastole in these intervals and for this the terms pre- and post-ejection isovolumetric intervals have been suggested.

- **Detailed(regional) description: myocardial velocities and torsion.**

Analysis of the left ventricular myocardial velocity from Magnetic Resonance Imaging (MRI) has given a better insight into the motion patterns across the LV [17,19,21–30]. Mean global RCL velocity time courses in the three different vertical segments of the LV reveal the following.

Radial velocities point inwards during systole and outwards during diastole evolving in a similar fashion for all three vertical segments [21,23]. They show a positive peak near the beginning of the ejection phase and a higher negative peak near the beginning of rapid inflow. An indicative range for radial velocities is between -5.1 and 2.9 cm/s [21].

Circumferential velocities start anticlockwise for all three vertical segments meaning the heart rotates anticlockwise. They reach a peak at the beginning of rapid ejection. After that, velocity patterns show considerable differences between the base, the mid wall and the apex. Overall the apex seems to continue rotating slowly anticlockwise, while the base and the mid wall reverse their rotational motion reaching a clockwise peak at the end-systole. The different circumferential motion patterns between the

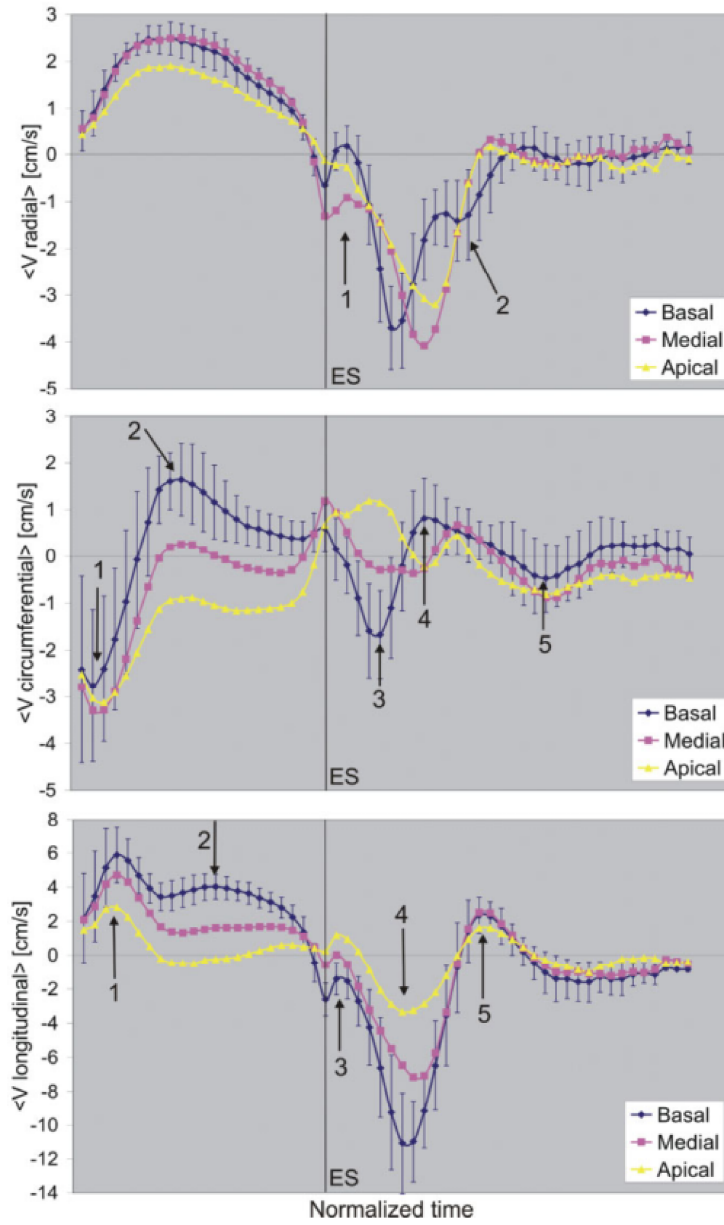


Figure 2.10.: Time courses of mean global radial, circumferential and longitudinal left-ventricular myocardial velocities [29].

base, mid-wall and apex result in torsion, which assists the ejection of the blood from the ventricles. The recorded patterns vary among the different studies, for example showing the apex to rotate clearly anticlockwise [23,31] or remain less mobile and maybe switch its rotation to clockwise for some

time [21]; such variations could be due to age differences among the cohorts [26]. In diastole, the circumferential velocity time courses show a complex motion and they vary further across studies. The highest peak is the peak at the beginning of the rapid ejection. An indicative range for radial velocities is between -3.8 and 2.7cm/s [21].

Longitudinal velocities begin with a similar pattern for all three vertical segments indicating global displacement of the LV towards the apex. However velocities are higher for the base than the mid-wall and a bit lower for the apex. Velocities reach a local peak during the first half of rapid ejection and then the movement decreases to a plateau for the base and the mid-wall while the apex changes direction and moves slowly towards the base [17]. Shortly before the end-systole the base and the mid-wall also change direction and start moving upwards with the base moving faster. The upward movement of all segments continues during isovolumetric relaxation and during ventricular filling it drops. Overall longitudinal velocities are higher in diastole than systole and the global peak is detected at the end of the isovolumetric relaxation. The base shows the greatest displacement along the longitudinal direction, whereas the apex moves a little. The septal segments show lower peak values compared to the other AHA segments [17]. Longitudinal velocities are considerably higher than radial and circumferential velocities with an indicative range between -11.7 and 7.2cm/s [21].

Torsion seems to reach its peak value near the end of systole and appears more prominent between the base and mid-wall (than between the mid-wall and apex or the base and apex). Also it seems to vary transmurally such that the endocardium twists more than the epicardium [32].

Interpretations

The above studies enlighten global and segmental motion in the LV. However there is motion on a smaller scale as well and the underline mechanisms of muscle contraction still remain obscure to some extent. There have been attempts to better understand myocardial motion by relating myocardial function to the anatomical structure of the cardiac muscle, the architecture of the myocardial fibres and, particularly, their arrangement in laminae sheets. Cardiac mechanical models have been proposed to simulate the mechanical properties of the myocardium and interpret myocardial motion as

a response to stresses, forces or pressure. Electromechanical models have also been suggested to model motion as a response to cardiac electrical activity [33,34], taking into consideration the electromechanical properties of the heart. It is worth mentioning that no single model simulates completely the cardiac function, but different models together provide a comprehensive scheme towards its description and interpretation.

- **The helical heart model.**

The most widely adopted model for the anatomical structure of the ventricles has been the *helical heart* proposed by Torrent-Guasp [36,37], who used a simple hand dissection to reveal a dominant cardiac pathway without defining individual fibre tracks across the ventricular myocardium. Torrent-Guasp showed that the ventricular myocardium comprises of a single long muscular band with a flattened rope appearance that is wound like a rope in a helical configuration to form the left and the right ventricles as shown in Figure 2.11. The single helical muscle band explains the propagation of electrical activation across the ventricular myocardium, the different thickness of the RV and LV, the dynamics and deformation of the ventricles during the cardiac cycle. Specifically, electrical pulses travel across the myocardial band causing a wave of contraction across the band from the pulmonary artery to the aorta. This results in the sequential contraction of the RV, the base and then the apex of the LV. In more detail, the wave of contraction explains the success of functional events in the LV that are *narrowing-shortening-lengthening-widening* overlapping with *twisting* and *untwisting* of the LV. With regard to the ventricular anatomy, the augmented thick-

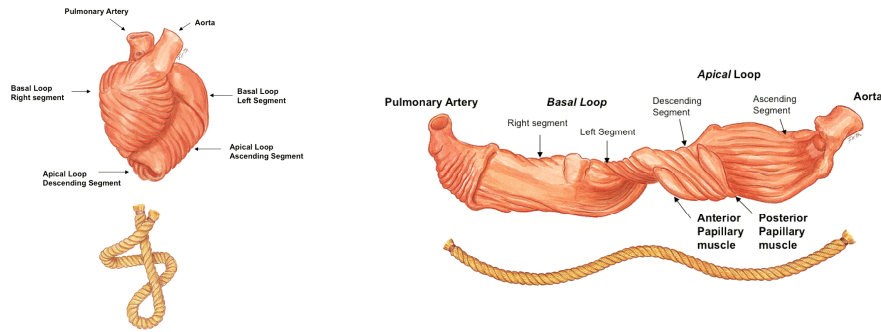


Figure 2.11.: The helical heart model [35] proposed by Torrent-Guasp.

ness of the myocardial wall of the LV compared to the RV is explained by the finding that the LV is formed by two windings of the muscle band embraced by a single winding section that creates the free wall of the RV. Subsequent studies have been based markedly on the Torrent-Guasp helical heart model to interpret the myocardial structure and function as well as their relation [18, 20].

However, the helical heart model has been a subject of controversy [38]. Its main opponents query the claim that the myocardial fibres are aligned to the unraveled band by questioning the objectivity of Torrent-Guasp's dissection technique and pointing out the lack of histologic evidence for this alignment or embryonic explanation of the myocardial band development. Moreover, the helical heart model does not explicate several aspects of the myocardial function like the wall thickening or the propagation of the electrical activation from the endocardium to the epicardium and the apex to the base. Austin [38] concludes that the helical heart model can serve as a first simplified approximation of the ventricular contraction and relaxation. The other aspects of the myocardial structure and function may be addressed by different heart models emerging from different dissection and observation techniques [39].

- **Myofibre architecture.**

Histological studies have shown that the myocardium consists of striated cardiac myocytes organised in myofibers, whose arrangement has an important impact on the electromechanical function of the heart [40]. Most studies have considered the myocardium as a continuum consisting of individual myofibres that are arranged in a right-handed helix in the subendocardium gradually changing into a left-handed helix in the subepicardium [41]. The helical arrangement of fibres has proven energetically efficient and important for the uniform distribution of stresses and strain in the heart and it has explained myocardial dynamics and motion to some degree. However, several functions like the thickening of the myocardium are not interpreted by the contraction of myofibres in the described orientations and, besides, myocardial motion has been reported in different directions from the myofibre angles [42].

A better understanding of the relation between myofibre architecture and myocardial function has been achieved, since Le Grice [43] discovered the

higher level of myofibre organisation in laminar sheets. *Laminae* are distinct layers of four to six cells thick that are formed by adjacent myofibres tightly bound together with endomysial collagen. Neighbouring laminae are loosely coupled together with perimysial collagen, and are able to slide over each other. Laminar sheets lie almost perpendicular to the myocardial walls and they seem to follow the angle of the containing myofibres [44]. The arrangement, relative motion and deformation of laminar sheets has explained myocardial thickening; laminar sheets contribute to myocardial wall thickening via their sheet extension, thickening and shearing, as stated in the combined analysis of diffusion tensor and strain MRI imaging [45]. On the other hand, fibre shortening and shearing make a minor contribution in myocardial thickening.

- **Mechanical models.**

Cardiac mechanical models simulate myocardial motion taking into consideration the mechanical properties of the tissue, the myofibre architecture and electrical propagation across the myocardium [46]. Mechanical models of the passive myocardium evolved from considering the myocardium an incompressible, homogeneous, hyperelastic, transversely isotropic material [47], to an incompressible, non-homogeneous, non-linearly elastic, orthotropic, material [48–50] or an orthotropic, viscoelastic material [51] or a material with variant compressibility (incompressible in volume increase, but compressible in volume reduction) [52].

2.1.4. Myocardial disease and conditions

- **Statistics.**

CVD is the most common cause of morbidity and mortality worldwide, for instance, in 2013 it accounted for 31.5% of global deaths [1, 2] and 45% of deaths in Europe [2]. According to the latest statistics published by the British Heart Foundation in 2018 [3], 26% of all deaths in the UK are due to CVD, while over half a million people have been diagnosed with heart failure and 1 in 500 people suffer from Hypertrophic Cardiomyopathy (HCM). The latest report by the American Heart Association in 2017 [4] states that 43.9% of the adult population in the US is projected to have some form of CVD by 2030.

Also according to their latest statistics [4], heart disease is currently diagnosed in 16.5 out of 92.1 million American adults, of which 7.9 million have had a heart attack and 6.5 million are suffering from heart failure. Among all cases of cardiac disease, ischaemic heart disease is the first cause of death. These statistics highlight the severity of heart disease and the necessity for early diagnosis and prevention.

Diseases of the myocardium are an important category of CVD. They may lead to heart failure that is the insufficient function of the heart to meet the body's needs in blood. Diseases of the myocardium affect primarily the LV, as this chamber undertakes most of the work output of the heart, and are associated with several myocardial conditions. Diseases and conditions of the myocardium often interfere with the proper function of the LV [53]. As a result, contractility across the myocardium deteriorates and this is manifested by altered myocardial motion and deformation patterns [54]. Motion and deformation abnormalities may be present in small myocardial regions, while global cardiac function is still normal; this happens because the heart employs compensatory mechanisms to preserve its global normal function. Thus, regional myocardial motion and deformation have been proposed as prognostic and early diagnostic indicators for myocardial disease. The most common diseases and conditions of the myocardium are described below.

Cardiomyopathies

Cardiomyopathies are a heterogeneous group of diseases of the myocardium that are associated with anatomical and functional abnormalities [53–56]. Cardiomyopathies are classified as primary or secondary. Primary cardiomyopathies are disorders confined in the myocardium, whereas secondary cardiomyopathies are disorders that arise as a secondary consequence from other conditions like myocardial ischaemia, hypertension, valvular disease, tachycardia, infection and affect the myocardium. Primary cardiomyopathies are further classified according to their phenotype into five groups named as *hypertrophic*, *dilated*, *restrictive*, *arrhythmogenic* and *unclassified cardiomyopathy*.

- **Hypertrophic cardiomyopathy.**

HCM has a prevalence of 2 in 1000 individuals and accounts for one third of sudden cardiac deaths in athletes. The main characteristic of HCM is the asymmetric hypertrophy of ventricular wall unrelated to chronic blood pressure. Its etiology is genetic; it is associated with mutations in genes that encode proteins of the cardiac sarcomere, a component of the cardiac myocytes. It is clinically high heterogeneous and its main symptoms are angina, fatigue, dyspnoea and palpitations. Fibrosis is commonly present in HCM and forms patchy sub-endocardial or mid-wall patterns that are usually located near the IV [57]. In HCM, full relaxation is impeded due to increased stiffness of the myocardium, this means impaired diastolic function while systolic function is preserved. Also, isovolumetric relaxation is prolonged in HCM.

- **Dilated cardiomyopathy.**

Dilated Cardiomyopathy (DCM) is the most common cardiomyopathy worldwide with a prevalence of 1 in 2500 adults, and its main characteristic is the dilated and weak ventricular myocardium. The etiology of DCM can be genetic, inflammatory i.e. viral myocarditis, or idiopathic and the most common symptoms are fatigue, dyspnoea and weakness. Fibrosis in the case of non-ischemic DCM is detected in the mid-wall of the interventricular septum. DCM shows impaired systolic function and insufficient myocardial contraction.

- **Restrictive cardiomyopathy.**

Restrictive Cardiomyopathy (RCM) have a prevalence from 5% among children and they are an important cause of death in South and Central America, Africa, India and Asia. Common symptoms are swelling of the extremities and general fatigue. The main characteristics of RCM are impaired ventricular filling, reduced diastolic volume and they are mostly associated with hemodynamic abnormalities in the heart. Infiltrative fibrosis and calcification are fundamentally manifested in RCM, with fibrotic patterns appearing homogeneous across the myocardium. Abnormal filling of the ventricles is caused by the insufficient relaxation of the myocardium and this results in impaired diastolic function. On the other hand, myocardial systolic function and morphology are usually preserved. RCM can be classified as primary or secondary. The origin of secondary RCM can be an infiltrative disease

such as amyloidosis, sarcoidosis, Hurler disease, fatty infiltration or a storage disease such as hemochromatosis, Fabry disease, Gaucher disease and glycogen storage disorder.

- **Amyloidosis.**

Amyloidosis is a rare but fatal group of diseases caused by the abnormal deposition of amyloid protein in the tissue [58]. Cardiac amyloidosis usually goes underdiagnosed, because its clinical symptoms and morphological alterations resemble those of other more common cardiomyopathies. Infiltrative fibrosis accompanies amyloidosis [59], in contrast to the replacement fibrosis appearing in the aforementioned cardiomyopathies and infarction; infiltrative fibrosis is uniformly distributed in the tissue [57, 59]. Cardiac amyloidosis has shown to be associated with impaired diastolic function indicated by abnormal radial and longitudinal strain, whereas ejection fraction and thus global systolic function are preserved [60]. Deformation analysis of the LV is probably a sensitive tool for the characterisation of myocardial dysfunction in cardiac amyloidosis. Cardiac amyloidosis and diagnosis is further analysed in Chapter F.5.

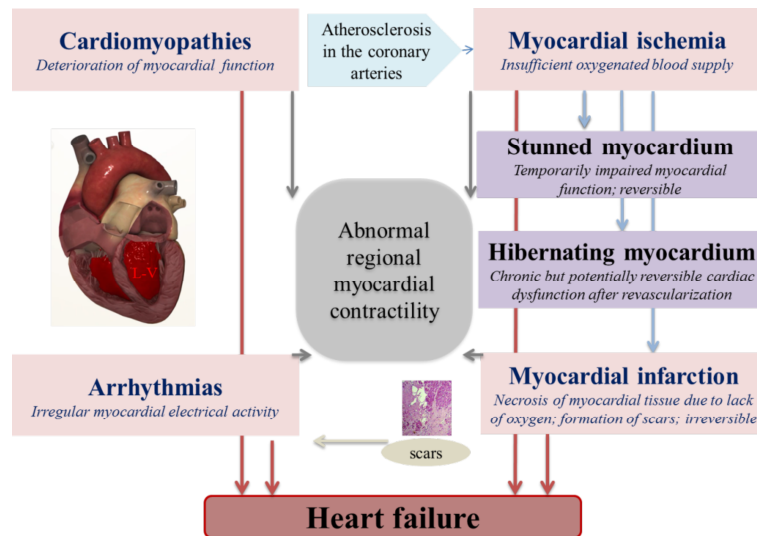


Figure 2.12.: Myocardial Disease and regional myocardial contractility.

Myocardial conditions: ischaemia, infarction, arrhythmia

Common myocardial conditions are myocardial ischaemia, myocardial infarction and arrhythmia and they are often associated with cardiomyopathies.

- **Myocardial ischaemia.**

Myocardial ischaemia is the condition of insufficient blood supply to the myocardial tissue, which is translated into inadequate oxygenation, nutrient supply and removal of metabolic end-products from the myocardium. Its prevalence is rather high as, for instance, its acute manifestation accounts for 1 out of 6 deaths in the US. The main cause of myocardial ischaemia is a reduction in coronary blood flow due to atherosclerotic coronary artery disease and, specifically, the embolism or thrombosis of atherosclerotic coronary arteries. Since the subendocardium is the last part accessed by the coronary arteries and yet the most contractile part of the myocardium, it is rather susceptible to ischaemia. For this reason, myocardial ischaemia affects the subendocardium first and propagates gradually towards the subepicardium. Insufficient oxygenation of the ischaemic myocardium affects its contractility, meaning that areas of reduced motion and deformation appear. In infarcted, stunned and hibernating myocardium motion and deformation patterns change and regional strain can be used to differentiate between viable and non-viable myocardial tissue [61,62].

In such areas, normal myocardial tissue may transform into stunned, hibernating or necrotic tissue [63]. *Stunned* myocardium consists of viable myocardial tissue with temporarily deteriorated contractility. Stunning emerges after a discrete episode of severe ischaemia, related to exercise for instance, followed by re-perfusion; contractility is retained reduced for a period of time after re-perfusion and it reverts to normal gradually. *Hibernating* myocardium is also viable yet less contractile. Hibernation occurs during ischaemia and usually results from severe coronary artery stenosis even under resting conditions. Hibernation lasts as long as the cause applies and it reverses quickly if the cause is removed, for example after revascularisation. Revascularisation is the restoration of myocardial perfusion usually performed with surgery. Prolonged cessation of blood supply to the myocardium poses a risk of myocardial tissue *necrosis* that is the case of *infarction*.

- **Myocardial infarction.**

Myocardial infarction is the necrosis of myocardial tissue and this is an irreversible state even after myocardial re-perfusion. The prevalence of myocardial infarction is particularly high with 30% of patients having atypical symptoms. The main cause of myocardial infarction is myocardial ischaemia, it might follow myocardial stunning or hibernation and, similarly, it progresses from the subendocardium to the subepicardium. When myocardial infarction occurs, previously viable contractile myocardial tissue is replaced by fibrotic non-contractile tissue forming scars [57]. Therefore, myocardial infarction is accompanied by irreversible loss of contractility, which appears as areas of permanently reduced motion and deformation [61]. The acute form of myocardial infarction commonly known as *heart attack* is a life-threatening urgent condition and the main cause of sudden cardiac death; in that case severe necrosis of the myocardium occurs suddenly, usually due to blockage of blood supply by a blood clot. In acute and chronic myocardial infarction deformation patterns change and regional strain can differentiate between myocardial segments that are likely to become infarcted and the stunned or hibernating segments that are likely to recover [61].

- **Arrhythmia.**

Arrhythmia describes the condition of irregular heart rhythm and it is related to abnormal cardiac electrical activity and, thus, the cardiac conduction system [5]. Dysfunction of the cardiac conduction system is detected either at the stage of electric impulse formation in the SA node or the propagation of the electric impulses. Arrhythmia may manifest as tachyarrhythmia or bradyarrhythmia, which indicate fast or slow heart rate respectively. Ventricular bradyarrhythmia is more common, while ventricular tachyarrhythmia is more severe, because it can lead to ventricular fibrillation that is the rapid uncoordinated contraction of myofibres; ventricular bradyarrhythmia may result in sudden cardiac death in the absence of treatment.

While cardiac electrical activity regulates myocardial contraction, myocardial contractility in turn affects the propagation of electrical signals across the myocardium; in other words, altered myocardial mechanics can initiate electrophysiological changes that lead to arrhythmia and this

excitation-contraction coupling in the myocardium is described as mechano-electrical feedback [64]. Besides, ischaemic or infarcted areas are electrically unexcitable and can block electrical impulses. Abnormal myocardial deformation across the myocardium and over time is associated with the presence of arrhythmia.

Modesto and Sengupta [54] review the changes in myocardial mechanics in the presence of each cardiomyopathy, as observed by a list of studies that correlate motion and deformation indices with the morphological phenotypes of cardiomyopathies. The studies agree that global and regional longitudinal, circumferential, radial and twist mechanics are associated with the presence of HCM, RCM, DCM, cardiac amyloidosis and other cardiomyopathies. Overall, cardiomyopathies with mainly diastolic dysfunction like HCM and RCM are primarily associated with impaired longitudinal mechanics and affect mostly the subendocardium, whereas transmural diseases like DCM with predominant systolic dysfunction present impaired circumferential and twist mechanics and affect mostly the mid-wall and the subepicardium.

Analysis of myocardial motion and deformation with imaging indicates that myocardial velocity, strain and torsion show different regional patterns, time courses and peak values between healthy volunteers and patients diagnosed with HCM [29, 65], DCM [26, 66], RCM, ischaemia [30, 67–69], infarction [30, 67, 68, 70, 71], heart failure [27, 67, 72], dyssynchrony [27, 66, 70] and other heart disease and conditions [67, 73–75]. Therefore myocardial motion and deformation analysis can be used for the early detection of myocardial abnormalities, the differentiation between viable and non-viable myocardium, the differentiation between conditions at an early stage and the prognosis and early diagnosis of myocardial disease.

2.2. CMR assessment of myocardial contractility

The myocardium is subjective to diseases and conditions that affect its normal function and, in particular, its contractility. Contractility is the innate ability of the myocardium to contract and propel the blood successfully through the heart to and from the rest of the body. Contractility can be described and quantified with measures from tissue mechanics. When the

focus is confined in the result (kinematics) rather than the cause (dynamics) of cardiac contraction or the tissue mechanical properties (constitutive relations), contractility is described as the deformation of the myocardial tissue. The deformation of myocardial tissue and the rigid body motion of the heart constitute the total motion of the myocardium. Direct measurement of myocardial deformation is difficult and, for this, myocardial contractility is usually assessed by measuring the total myocardial motion instead. Myocardial motion and deformation are measured directly as velocity, displacement and strain, which are considered the functional features, or they are estimated from tracking the anatomical features over the cardiac cycle. These quantities have been studied in a global, segmental and regional scale, with the latter offering the advantage of capturing fine abnormalities that are masked in the global scale. Anatomical and functional features are captured non-invasively with cardiac imaging modalities, among which CMR offers important advantages and a number of techniques. Image processing tailored to each imaging technique enables the estimation of global, segmental and regional parameters for the description of myocardial motion and deformation, thus, the quantification of myocardial contractility and assessment of myocardial function.

Cardiac anatomy shown with tissue intensity images, commonly supplies adequate information for the estimation of global contractility parameters. For example, measurement of the area of the blood pool in systole and diastole gives the ejection fraction, which is an important indicator for cardiomyopathy, ischaemia and infarction. The thickness of the myocardial wall is another global parameter associated with myocardial dysfunction and it is readily measured from short-axis slices. For the estimation of global parameters, conventional cine CMR² is considered as a reference method, because it provides clear anatomical images thanks to its high contrast, sharpness and low SNR. Cine CMR is therefore suitable for the detection of myocardial boundaries and, thus, the estimation of masses, volumes and ejection fraction.

Segmental and regional contractility parameters have been also estimated from conventional cine CMR by tracking distinct anatomical features. Delineation and tracking of the epicardial and endocardial contours across time frames, for instance, is a common strategy to extract information about

²acquired with Gradient Recalled-Echo (GRE) or balanced SSFP (bSSFP) sequences

motion around the myocardial boundaries and it performs well along the radial direction. As for mid-wall motion, its estimation from conventional cine CMR is particularly challenging, especially along the circumferential paths, because the myocardial mid-wall appears almost homogeneous and, therefore, intramural points cannot be directly identified and tracked. To address the challenge of intramural motion estimation, fitting of a Finite Element Model (FEM) to the myocardial contours over time has been suggested [76]. The FEM analysis requires input of the myocardial material properties which are generally unknown. As another solution, non-rigid image registration between different frames has been proposed; registration-based methods result in a spatially continuous non-rigid transformation that spans over the homogeneous areas too, giving an estimate for regional intramural motion. Although conventional cine CMR is suitable for the estimation of global contractility parameters and regional contractility parameters near tissue boundaries and along the radial direction, estimation of intramural motion from conventional cine CMR is of high uncertainty, particularly in the circumferential direction.

For more accurate estimation of regional myocardial motion and contractility, conventional CMR was modified to yield CMR techniques that are able to capture intramural motion. Up to this date, regional myocardial contractility has been studied with CMR Tagging, PC-MRI or TVM, Displacement ENcoding with Stimulated Echoes (DENSE) and Strain-ENCoded MRI (SENC) [77–86] with CMR Tagging and TVM being the most widely used techniques (for techniques see *Appendix C.3*). In contrast to conventional cine CMR, which reflects the different magnetic properties of tissues revealing the anatomy, the four aforementioned CMR techniques involve a preparation pulse that modulates the image contrast in response to a kinematics quantity i.e. velocity, displacement, strain, independently from the type of the tissue, or superimposes dark bands that follow the tissue movements.

2.2.1. CMR Tagging

Technique

CMR Tagging was introduced three decades ago by Zerhouni [87] as an imaging technique for tracking tissue motion. CMR Tagging employs a tag-

ging preparation pulse (see *Appendix section C.3.5*) followed by a standard cine image acquisition. The tagging pulse causes sinusoidal spatial modulation of the magnetisation across the tissues, such that the points of nearly zero magnetisation form non-selective parallel equidistant bands that lie perpendicular to the image plane. On the image plane, the bands appear as non-selective dark tags superimposed on the anatomy. Tags fade with time due to T_1 -relaxation of magnetisation, as discussed in *Appendix section C.1.3*, which occurs slowly enough to permit persistence of tags for almost an entire cardiac cycle. Tags follow the tissue during the cardiac cycle providing an intuitive visualisation of myocardial tissue motion. Myocardial tissue motion can be quantified with analysis of the tags' motion and regional myocardial contractility parameters like strain and torsion can be calculated from the tags deformation. In contrast to cine CMR, CMR Tagging captures motion information also from the mid-wall of the myocardium, wherever tags traverse, and this enhances the reliability of regional deformation analysis.

The most popular CMR Tagging sequence is the SPAtial Modulation of Magnetisation (SPAMM) and was developed by Axel [88] based on a different idea to Zerhouni, who introduced CMR Tagging earlier [87]. In its simplest version 1-1 GRE, the tagging pulse consists of two 90° non-selective tagging pulses separated by a magnetic gradient oriented parallel to the image plane and perpendicular to the desired tag lines, followed by a spoiler gradient to eliminate the remaining transverse magnetisation (see *Appendix C.3*). The tagging pulse results in the sinusoidal modulation of the longitudinal magnetisation and is succeeded by a standard cine image acquisition performed with a GRE, an EPI or most commonly a bSSFP host sequence. Since the invention of GRE, many different and more sophisticated CMR Tagging sequences and techniques have been developed, which achieve improved spatiotemporal image resolution, higher SNR, lower scan time, better anatomical coverage and tagging quality.

Tagging is extended from one dimension (parallel lines pattern) to two and three dimensions (grid pattern), with repetition of the tagging pulse in the second and third spatial orientation. Compared to parallel lines, the grid pattern includes intersections of the tags, which are identifiable features in CMR Tagging analysis. Myocardial motion analysis in 3D is also performed with the combination of short and long-axis 2D CMR-Tagged images. Polar

pattern of tags has also been employed [89], which is in accordance with the RCL coordinate system of the LV and ensures better resolution of tags in the radial direction. Another variation of the CMR Tagging technique allows localised tagging with variable density of tags, resulting in better quality of tags in the region of interest and shorter image acquisition time. A limitation of CMR Tagging is the fact that a slice covers a slightly different part of the myocardium across different frames, which impacts the motion analysis from CMR Tagging, and this arises from the longitudinal motion of the heart in combination with the non-selective tagging of the tissue. To overcome this limitation, slice-following was achieved with either a pair of saturated slices adjacent to the selected slice that also follow the tissue or with slice-selective tagging.

Image analysis

Analysis of MR-Tagged images depends on the quality and density of the tags. The increase in tags' quality and density has been the main aim of GRE sequence advancements. Higher order GRE sequences that employ a binominal combination of multiple RF pulses instead of the two RF pulses yield sharper tags. DANTE sequence [90] uses a train of RF pulses, which offers the flexibility to regulate the spacing and thickness of tags by varying the interpulse delay. The biggest disadvantage of GRE is the fading of tags especially in the later frames of the cardiac cycle, which causes gradual degradation of motion analysis reliability from early systole to late diastole. To reduce the effect of fading and, simultaneously, improve the contrast of tags, the CSPAMM technique has been developed. CSPAMM includes a double image acquisition, where one image is acquired with a conventional GRE and the other image is acquired with a modified GRE of two 90° RF pulses. The two sequences modulate tags with 180° phase difference or in other words complementary tags. Subtraction of the two images yields an MR-Tagging image with enhanced tags, reduced tag fading and limited anatomical information, which facilitate the image analysis.

CMR Tagging provides an intuitive visualisation of tissue deformation allowing for immediate qualitative assessment of myocardial motion and image analysis is performed for quantitative assessment. Numerous image analysis methods have been developed for either the image domain or the

frequency domain. Image analysis methods for the *image domain* can be classified in two categories. Methods of the first category rely on the explicit tracking of tagging features which may be the tag lines, tag intersections, tag planes along with the myocardial contours; tracking has been performed with active contours, snakes or edge-based detection algorithms. Popular tag tracking algorithms are the FindTags [91] and SPAMMVU [92], which identify tag lines and tag intersections, respectively, and find their most probable locations across successive frames. Myocardial motion and deformation is estimated from the tag locations and quantified, for instance, as displacement or strain tensor fields. Motion of points between the tags is interpolated from the adjacent tags using, for example, FEM, B-splines or regularisation. The tagging features and myocardial contours can be used to drive the fitting of deformable models. Tracking methods require the prior extraction of tagging features which is usually a challenging task while their accuracy depends on the quality of images and tag resolution.

The second category of methods do not require prior extraction of tagging features and they use total image information to generate a deformation field i.e. velocity or strain field. Two main directions are distinguished and these are based on optical flow or image registration. *Optical flow* techniques track image pixels based on their intensity to estimate 2D motion. The fundamental assumption is that each pixel maintains constant intensity between successive frames, but since slow brightness variations are common between frames, optical flow is often based on looser assumptions like constant gradient of intensity. In CMR Tagging, the assumption of constant intensity is not satisfied, because tags fade during the cardiac cycle and, for this, optical flow techniques adjusted to the variable brightness of tags or pre-processing with a spatial filter i.e. Laplacian have been suggested. *Non-rigid image registration* computes implicitly the transformation matrix between successive frames to estimate rigid and deformational motion across the imaged area. CMR Tagging image registration yields directly the displacement field on a per pixel basis, without the need for prior extraction of tagging features [93]. It uses information from both the tags and the anatomical structures in the registering images, but it is mostly driven by the tags as a result of their high contrast.

HARmonic Phase (HARP) introduced by Osman [94] is a fast and popular CMR Tagging analysis method in the *frequency domain* for tissue mo-

tion estimation. HARP relies on the spatial sinusoidal periodicity of tags, which is translated into pairs of off-centre peaks in the k-space. If one of these spectral peaks is isolated with a bandpass filter or a bank of filters i.e. Gabor and the inverse Fourier transform is applied, a complex image is generated whose phase reveals discontinuities (of the initial CMR-tagged image) that are attributed to tagging and are located at approximately the same positions as the tags. The harmonic phase, as called, of the tags is determined at the tagging formation and is preserved upon tissue deformation. Tags motion analysis is therefore possible by tracking pixels of constant intensity in the harmonic phase image. Feature based tracking and optical flow algorithms show significantly higher efficiency on the harmonic phase image compared to the CMR-tagged image, because of the lack of fading and elimination of anatomical information. Tracking the pixels of constant phase across the cardiac cycle enables the computation of the Lagrangian strain, while the Eulerian strain is calculated directly from the spatial gradient of the harmonic phase image. A major advantage of HARP is the fast processing with no need for extraction of tagging features; HARP analysis is typically 10 times faster than feature based tracking methods. Since HARP analysis makes use only of the off-centre spectral peaks, k-space sampling can be limited to small regions around the symmetric peaks reducing the acquisition time significantly. On the other hand, HARP is affected by phase wrapping in the case of large motion and by anatomical contours that contain frequencies near the spectral peaks of tags. Also since HARP analysis yields only in-planar motion, extension to 3D requires both short and long axis CMR-tagged images. Sine-wave modeling (Sinmod) is [95] a CMR Tagging analysis method performed partially in the frequency and image domain, according to which a narrow bandpass filter is applied around the first harmonic frequency of the tag pattern to accentuate the sinusoidal waveform of tagging, on which a sine wave of several directions in the slice plane is subsequently fitted [95].

Advantages, weaknesses and applications

CMR Tagging has been the most studied and validated CMR technique for the quantification of myocardial contractility. Segmental parameters of myocardial deformation such as normal strain and strain rate in the radial,

circumferential and longitudinal direction as well as shear strain and torsion [96–99] have been estimated from CMR Tagged images. CMR Tagging is considered the gold standard in the investigation of myocardial function, thus far, also because it provides a direct intuitive visualisation of myocardial deformation. It has been applied for the assessment of several myocardial diseases and conditions such as HCM, DCM, myocardial ischaemia, myocardial infarction, inter-ventricular synchrony, coronary artery disease and other cardiac diseases [84, 100]. However, its current role in clinical practice is rather assistive and the main hindrances against the broader clinical application of this technique are the complicated post-processing analysis, long acquisition time, fading of tags during the cardiac cycle and sparse information only from the tagging lines.

2.2.2. SENC

Technique

Strain-ENCoDeD MRI (SENC) was introduced by Osman in 2001 [101] for the direct measurement of tissue strain. The SENC acquisition technique is similar to the CMR Tagging acquisition technique, as it also employs a tagging preparation pulse followed by a standard cine image acquisition (see Section C.3). The key difference between SENC and CMR Tagging is in the orientation of the spatial modulation of magnetisation, which occurs along the longitudinal direction in the case of SENC. As a result, SENC creates tag planes that lie parallel to the image plane instead of perpendicular, which is the case in conventional CMR Tagging. The frequency of spatial modulation is high enough to allow the fitting of several tag planes within the slice thickness. The modulated GRE sequence is applied twice with two different modulation frequencies and the corresponding images are subtracted to yield a SENC image. Through-plane stretching or compression causes the through-plane spatial frequency of tags to differ from the initial modulation frequency and this difference encodes the regional tissue deformation. The intensities in the resulting SENC image are directly proportional to the regional Eulerian through-plane strain.

Advantages, weaknesses and applications

Contrary to CMR Tagging where exhaustive processing is required for the extraction of strain, SENC needs limited image processing because it encodes strain directly and this is its main and major advantage. Furthermore, SENC measurements are performed at a pixel level, which means SENC has higher spatial resolution compared to CMR Tagging.

Like CMR Tagging, a weakness of SENC technique is the tag fading during the cardiac cycle due to T_1 relaxation of magnetisation. Shorter acquisition time can significantly improve the quality of SENC images in the later frames of the cardiac cycle. Fast-SENC has achieved reduction of the acquisition time to one breath-hold by combining localised SENC, interleaved tuning and spiral imaging. As in CMR Tagging, slice-following has been applied to correct for the through-plane motion. Composite SENC (C-SENC) is another variation of SENC that includes the acquisition of three images after tagging at three modulation frequencies along with the administration of late-gadolinium based contrast agent and it results in capturing of both strain and myocardial viability.

Another disadvantage of SENC is the one-dimensional nature of deformation measurements that is the through-plane normal strain. Longitudinal strain is encoded in short-axis SENC, circumferential strain is encoded in long-axis SENC while radial strain cannot be captured by SENC. Short-axis SENC can act complementary to CMR Tagging, which is primarily applied for the estimation of in-planar strain. Considering this, Sampath has proposed the combination of short axis SENC and HARP for the estimation of 3D myocardial strain from short axis images [102]. Along these lines, SENC has also been combined with DENSE for the estimation of 3D myocardial strain [103].

Stretching or compression of the tagged tissue along the through plane direction changes the spatial frequency of tags along this direction resulting in a positive or negative value of SENC measurement. Apart from the case of deformation, the spatial frequency of tags seems to change along the through plane direction in the case of rigid body rotation. As a result, an apparent through-plane strain component contributes to the SENC measurements and it is attributed to tilting, which reduces the reliability of the strain measurements. It has been shown that the heart's tilting does not exceed

15° and, therefore, the apparent strain is not considered significant. Another weakness of SENC CMR imaging is the low SNR.

SENC is a relatively new technique and it has not been studied as widely as the other CMR techniques for the assessment of regional myocardial deformation yet. SENC has been employed for the assessment of coronary artery disease, myocardial infarction, myocardial ischemia and coronary stenosis. Specifically, Neizel [104] measured the segmental longitudinal and circumferential strain in the myocardium with SENC in healthy volunteers and patients with acute myocardial infarction; they evaluated the strain measurements with CMR Tagging, assessed the degree of infarction in each segment and compared it to the results from Late Gadolinium Enhancement (LGE). Korosoglou [105] measured the segmental myocardial circumferential strain and strain rate with SENC in healthy volunteers and patients with coronary stenosis and stress induced ischemia and evaluated the technique with coronary angiography. In another study, Korosoglou [106] applied fast-SENC to measure the circumferential segmental strain in healthy volunteers and patients with heart failure and compared the technique to CMR Tagging. Oyama-Manabe [107] measured the peak longitudinal and circumferential myocardial strain with fast-SENC in patients with ischemic heart disease to identify the infarcted myocardial segments and compared the results to LGE results. In a more recent study, they applied SENC for the assessment of the right ventricular function [108]. Nonetheless, SENC CMR has not entered the clinical practice yet.

2.2.3. DENSE

Technique

Displacement ENcoding with Stimulated Echoes (DENSE) was first developed by Aletras in 1999 [109] for the direct measurement of regional myocardial tissue displacement. The traditional DENSE sequence is a stimulated echo acquisition mode sequence (see paragraph *Technique* below), which includes a triad of RF pulses (90_x° - 90_y° - 90_y°), and two gradients: the displacement *encoding gradient* interleaves the first and second RF pulse and the *rewinding gradient* follows after the third RF pulse. The time between the second and third pulse is the *mixing time*, during which large tissue displacements are allowed to accrue. The first block of the displacement

encoding pulse is same as the 1-1 GRE tagging pulse in CMR Tagging and, accordingly, it modulates the longitudinal magnetization along the encoding direction. The third RF pulse flips the modulated magnetisation to the transverse plane such that the phase dispersion from the encoding gradient reappears, and, then, the rewinding gradient causes the reverse phase dispersion. Spins in tissue that has remained stationary during the mixing time experience equal positive and negative phase shifts, whereas spins in moving tissue accumulate a total net phase shift that is proportional to the tissue displacement. This way, displacement maps with a per pixel resolution can be acquired from the phase of the measured MR signal.

Displacement Encoding with Stimulated Echoes (DENSE) can be applied along in-planar directions as well as the through-plane direction of the same slice with selection of the suitable encoding and rewinding gradients. It is, therefore, possible to measure regional tissue displacement in all three orthogonal directions, which is an important advantage of DENSE technique. DENSE acquisitions commonly consist of three displacement encoded datasets in the three encoding directions and a reference dataset. DENSE has been extended from a single-frame to cine, after its acceleration enabled the completion of a slice within one breath-hold [110]. This has permitted the study of tissue motion almost during the entire cardiac cycle. Acceleration techniques such as parallel imaging, spiral trajectories i.e. SENSitivity Encoding (SENSE), as well as slice-following techniques have also been adjusted and incorporated to DENSE.

- **STEAM.**

STEAM [111] is an imaging sequence that employs stimulated echoes. Stimulated echoes (STE) is a variation of the spin echo type of sequence, which involves a triad of RF pulses $(90_x^o-90_y^o-90_y^o)^3$ instead of a pair of $90_x^o-90_x^o$ RF pulses. The first RF pulse flips the magnetisation to the transverse plane, where the magnetisation fully dephases to a 360^o "fan" of magnetic moments after $TE/2$ time (TE is the echo time). The second pulse flips the 'fan' to the yz plane. This arrangement of magnetic moments results in a smaller impact of precession onto their initial longitudinal magnitude and phase and, this way, they are preserved longer. The time between the second and the third pulse is called mixing time and can be relatively long,

³the index x or y denotes the axis around which the magnetisation is forced to rotate

according to the above. The third RF pulse flips the magnetic moments back to the xy plane, where the STE echo is created after $TE/2$ time. The third pulse can be repeated at several time moments to read different T1 contrasts. STEAM allows the acquisition of a sequence of differently T1-weighted images with high contrast.

Image analysis

Strain is easily derived from the displacement field by tracking the pixels in the DENSE phase image across the time frames. For each pixel in each frame, the final position is known and DENSE measurement gives the distance travelled up to this point, therefore, the earlier positions of the pixel are easily estimated. Quadrilateral or hexahedron elements of neighbouring elements can be considered and their earlier configurations can be estimated this way [110]; from the current and earlier configurations the Lagrangian 2D or 3D strains are computed. Therefore, all three normal and shear RCL strains as well as myocardial torsion and twist are relatively easy to derive from DENSE [112–114]. As mentioned earlier, DENSE has also been combined with SENC for the estimation of 3D strain [103] and strain analysis with DENSE has been validated against CMR Tagging with good agreement [113,115].

The main challenge in the analysis of DENSE images is the alleviation of image artefacts that interfere with the displacement field and, thus, impact the tracking methods i.e. image wrapping and noise. Image wrapping is a particularly important phase-encoding-related artefact and it is potentiated by higher encoding gradients that are employed to increase the motion sensitivity of DENSE. Considering this, Spottiswoode et al. [112] proposed a spatiotemporal phase unwrapping algorithm to improve the quality of DENSE images and, then, they computed spatial trajectories of selected pixels, from which the corresponding radial and circumferential strain was derived. The algorithm was then adapted for motion-guided segmentation of the myocardium [116], a principle that was adopted by several preceding studies. One of these uses the segmented volumes to estimate the left ventricular volumes, mass, and ejection fraction [117].

It is observed that DENSE and CMR Tagging have similar k-spaces [118], as they both include three distinct echoes arranged horizontally in k_{enc}

distance from each other, where k_{enc} depends on the tagging frequency. The three echoes are: the stimulated echo, the T1 recovery echo and the stimulated anti-echo. The difference between the two techniques in terms of k-space is that the triad of echoes in DENSE is shifted by k_{enc} to the right, as compared to CMR Tagging. The displacement encoded information is contained in the stimulated echo, whereas the other two echoes may cause unwanted artefacts. Taking this into account, an approach to improve the quality of the displacement field is to isolate the stimulated echo with image analysis in the frequency domain, similarly to HARP analysis.

Advantages, weaknesses and applications

DENSE combines tissue tagging and phase encoding principles and, therefore, it contains advantages and weakness from both techniques. Like PC-MRI, DENSE allows direct encoding of regional motion at a per pixel level and along the three orthogonal directions from the same slice acquisition. As a phase-encoding method, it inherits artefacts such as phase wrapping, magnetic field inhomogeneities, eddy current related artefacts and high noise. An advantage of DENSE to PC-MRI is the fact that stimulated echoes allow motion measurements over a long period of time, which means that large displacements can be measured with gradients of lower strength than in PC-MRI. A weakness of DENSE is the signal loss caused by tissue deformation, rotation and perfusion, which becomes more severe in higher gradients. Like CMR Tagging, DENSE suffers from fading due to T1-relaxation, which impacts the quality of images towards the end of the cardiac cycle. Compared to CMR Tagging, DENSE provides motion information at a pixel level, thus higher spatial resolution, and it has simpler and quicker post-processing as it encodes tissue displacement directly, from which strain and strain rate can be easily computed.

As mentioned, DENSE has been employed for the estimation of 2D and 3D Lagrangian normal, shear and principle strains, torsion and twisting. DENSE imaging technique has not entered the clinical practice yet, but has been used in several cardiac studies e.g. for the investigation of myocardial strain in non-ischaemic DCM [113] and myocardial infarction [112], as well as, the assessment ventricular dyssynchrony [119] and cardiac resynchronisation therapy in heart failure [120]. DENSE has also been utilised

as a reference technique for the evaluation myocardial infarction with T_2 -weighted imaging [121].

2.2.4. PC-MRI

Technique

Phase-Contrast MRI (PC-MRI) was introduced in 1984 with two separate studies by Bryant [122] and van Dijk [123] for the measurement of velocities in the heart. PC-MRI was initially applied to image the blood flow through the heart and cardiac vessels [124, 125], a technique known as *flow velocity mapping*. Since then, numerous cardiac studies have been conducted with flow velocity mapping, which is, currently, a standard clinical technique for the assessment of blood flow dynamics and related cardiac conditions [85, 126–128]. Although Bryant had already mentioned the potential value of PC-MRI in myocardial motion imaging, PC-MRI was confined to flow velocity mapping for about a decade, before it was translated to *myocardial tissue velocity mapping* [129], a technique also mentioned as *Tissue Phase Velocity Mapping (TPVM)*, *Tissue Phase Mapping (TPM)* or *Tissue Velocity Mapping (TVM)*.

PC-MRI measures regional tissue⁴ velocity by encoding the velocity in the phase of the MR signal. The PC-MRI basic sequence consists of a velocity encoding pulse, which is a bipolar gradient in the encoding direction, commonly followed by a GRE host-sequence like bSSFP. The first lobe of the gradient causes phase accumulation that varies with the position of spins along the encoding direction. The second gradient lobe is of equal strength and opposite polarity to the first one, hence it causes the reverse phase accumulation. The two encoding gradient lobes last for a short time δ , during which the tissue is considered stationary, and they are separated by a longer time interval Δ , during which the moving tissue changes position along the encoding direction. Spins in tissue that has remained stationary between the two lobes of the encoding gradient experience equal clockwise and anti-clockwise velocity encoding phase shifts, whereas spins in moving

⁴here solid tissue as well as blood is implied - blood is considered as a type of liquid connective tissue

tissue experience different phase shifts at the initial and final location and this phase shift difference is proportional to the velocity of the tissue during Δ .

The phase shift difference in tissue moving with velocity v in the encoding direction caused by a bipolar encoding gradient $G_{enc}(r(t), t)$ of strength G_{enc} , duration δ per lobe and distance Δ between lobes is given by the formula

$$\Delta\phi = \gamma v G_{enc} \delta \Delta \quad (2.1)$$

(see proof below).

• **Proof.**

The angular velocity $\omega = \frac{d\phi}{dt}$ of a precessing spin is the Larmor angular frequency $\omega = \gamma B$ (Equation C.1), where ϕ is the phase of a spin's magnetic moment. The velocity encoding gradient G_{enc} contributes to the magnetic field B with the addend $G_{enc}(t) * r_1$ during the time interval $(0, \delta)$ and the addend $-G_{enc}(t - \Delta) * r_2$ during the time interval $(\Delta, \Delta + \delta)$, where r_1 and r_2 are the locations of the spin in the encoding direction during the first and second time intervals accordingly. The duration δ is short enough to assume that the spin does not change position during each time interval, but it can move considerably in the time between the two lobes, let's say with mean velocity $v = \frac{(r_1 - r_2)}{\Delta}$. According to the above, the contribution of the bipolar gradient to the phase of the spin is

$$\begin{aligned} \Delta\phi = \phi^+ + \phi^- &= \int_0^\delta \gamma G_{enc} * r_1 dt - \int_\Delta^{\Delta+\delta} \gamma G_{enc} * r_2 dt = \\ &= \gamma \int_0^\delta G_{enc} * (r_1 - r_2) dt \end{aligned}$$

Assuming that the gradient pulses are (approximated as) rectangular pulses with respect to time, the above equation yields

$$\Delta\phi = \gamma v G_{enc} \delta \Delta$$

which is the fundamental equation in phase velocity encoding and PC-MRI technique.

For a 3D velocity vector field reconstruction, phase velocity encoding is repeated along the three orthogonal directions with appropriate selection of the encoding gradients. In addition to the velocity encoding acquisitions, a *reference* (non velocity encoding) acquisition is performed. The reference phase image is subtracted from each velocity encoded phase image to cancel common phase shifts, which do not originate from the velocity encoding gradients, and the resulting image is the PC-MRI phase image commonly delivered from the scanner. Nayler [124] extended PC-MRI from a single-frame to a cine technique, allowing the imaging of tissue and blood velocities

over time. PC-MRI cine datasets normally comprise of six images per time frame: three phase images independently acquired for the three velocity encoded orthogonal directions, and the corresponding magnitude images.

Since its emergence, PC-MRI has improved significantly in terms of sensitivity, image quality and spatiotemporal resolution thanks to advances in CMR hardware and PC-MRI pulse sequences. Acceleration techniques mentioned in section C.3 such as parallel imaging with SENSE [130] and Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) [131], radial [132] and spiral [133, 134] (non-Cartesian) k-space trajectories have been integrated into the PC-MRI technique. Shorter acquisition time allowed further improvement of PC-MRI in terms of image resolution and motion induced artefacts. Respiratory motion artefacts, in particular, were eliminated with prospective respiratory gating navigator echoes [31] and retrospective respiratory gating on breath-hold acquisitions [135]. Black blood preparation pulse was also incorporated into the PC-MRI sequence to suppress the blood flow signal and allow the measurement of low tissue velocities [136, 137] enabling, this way, myocardial Tissue Velocity Mapping (TVM). Along these lines, Simpson [134] has developed a spiral PC-MRI sequence for TVM with retrospective gating, parallel imaging with SENSE reconstruction and blood suppression, which achieves acquisition of a slice dataset during one breath hold (of 14 ms duration) with $1.7 \text{ mm} \times 1.7 \text{ mm}$ spatial resolution (reconstructed to $0.85 \text{ mm} \times 0.85 \text{ mm}$) and 24 ms temporal resolution. This is the PC-MRI sequence used for TVM in the current work.

Image analysis

Studies in myocardial motion and deformation analysis employ velocity, strain rate, strain and torsion analysis. PC-MRI technique provides directly a dense three dimensional velocity field in the three directions, from which strain rate can be easily calculated by taking the spatial derivatives of velocity at each pixel. With integration of velocities over time, the corresponding displacements are calculated and, thus, positions and trajectories are estimated for each pixel. With spatial derivation of the displacements, regional strain is estimated accordingly. Motion and deformation analysis are commonly performed in the RCL rather than the Cartesian coordinate

system, as described in section 2.1.2.

- **Velocity analysis.**

As mentioned, velocity analysis shows the myocardial motion rather than the deformation and the ideal goal is to enable the assessment of myocardial velocities on a regional level at pixel resolution; this is hindered by the PC-MRI image artefacts that degrade the quality of velocity measurements. Because of this and in order to facilitate inter- and intra-subject comparison, velocity analysis has been mostly performed on a segmental and global scale rather than a regional scale. Segmental velocity analysis involves dividing the myocardium into segments and assigning a velocity value per segment. Global analysis, in turn, is performed with averaging the velocities across the entire myocardial area. The established model for segmental analysis is the 17-segment AHA model [6], as elaborated in section 2.1.2, and it is visualised with a standardised bull’s eye plot. Finer segmental maps or plots have been employed by several studies for more detailed motion analysis. Visualisation of regional velocities is usually provided with 2D vector or colour coded maps.

One of the first studies on myocardial velocity analysis with PC-MRI was performed by Karwatowski [138], who divided myocardial slices from healthy subjects into 16 segments and showed the time courses for each segmental longitudinal velocity. Then they extended the velocity analysis to patients with ischaemic heart disease in the presence and absence of myocardial infarction [30].

Soon after, Hennig’s pivotal publication [68] established a framework for myocardial velocity analysis, which was followed by several other studies; they first analysed the in-planar myocardial velocities and, furthermore, they introduced the RCL system, a velocity correction scheme for global cardiac motion and the colour coded maps for the visualisation of regional myocardial velocities. Along these lines, Markl [69] studied the radial and circumferential in-planar velocities and suggested vector plots besides colour coded maps for the visualisation of regional myocardial motion; they analysed PC-MRI images from normal subjects as well as patients with myocardial infarction and ischaemia, which showed that myocardial defects can be indicated by disturbances in the regional myocardial velocity maps.

A similar framework was followed by Jung [28] in order to investigate

the myocardial motion patterns in healthy volunteers; they analysed the regional and global RCL myocardial velocities and illustrated the results in vector and colour coded maps. They also extended the analysis to patients with LV hypertrophy [29] and evaluated their results with Tissue Doppler Imaging (TDI). In the same study, they divided the myocardial slices into 24 segments and described the myocardial motion patterns as time courses of the segmental RCL velocities. In a separate study [42] they investigated the link between myocardial tissue motion and fibre orientation, mentioning that they do not necessarily coincide, as explained later by the effect of myocardial shearing. A few years later and after the establishment of the 17-segment AHA model [6], they compared the regional, segmental and global velocity patterns among mice, rabbits and humans showing the results in vector plots, AHA plots and colour coded maps [24]. The same year, DallArmellina [139] presented the global and segmental RCL velocity patterns in mice.

Föll [26] combined the 24-segment plots introduced by Jung from several slices to construct a bull's eye plot that is similar, though finer, to the 17-segment AHA plot. They performed segmental myocardial velocity analysis on 58 healthy volunteers and a patient with DCM to show the alterations in the segmental maps. In another study [19], they investigated the differences between segmental velocity maps from the two genders and from different age groups; the segmental maps used in this study result from subdividing the 17-segments of the AHA plot into an epicardial and endocardial part. Föll [140] extended the segmental velocity analysis to the study of LV dyssynchrony. In the meantime, Delfino [27] validated the consistency of PC-MRI with a moving phantom and measured myocardial velocities in healthy volunteers and patients with ventricular dyssynchrony.

Codreanu [141] presented a segmental and global analysis for the longitudinal and circumferential myocardial velocities in healthy volunteers, showing the time courses of segmental velocity for each segment. Then, they extended this analysis [22] to estimate the normal values for segmental and global RCL velocities, torsion and longitudinal strain rate in two age groups of healthy volunteers.

Lutz [66] performed global and segmental velocity analysis of the RCL velocities as well as strain and torsion analysis in healthy volunteers and patients who were referred for cardiac resynchronization therapy. They

employed multi-slice acquisitions with many slices that produced fine segmental maps. Simpson [23] showed the reproducibility of the global and segmental motion analysis on PC-MR images that were acquired with their newer PC-MRI sequence [134] applied on 10 healthy volunteers. Lin [142] also investigated the reliability and reproducibility of segmental analysis on healthy subjects. Chang [73] investigated the myocardial motion in the case of repaired tetralogy of Fallot with the analysis of segmental velocities and twisting, and similarly, Gimpel [143] investigated the case of children with chronic kidney disease. In a recent study, Menza [21] extended the segmental and global velocity analysis from the LV to the RV.

The studies by Codreanu [22], Simpson [23], Jung [28, 29] and Petersen [144] can possibly serve as reference studies for comparison of myocardial velocity analysis.

- **Strain rate, strain and torsion analysis.**

Strain, strain rate and torsion analysis are performed for the quantification of myocardial deformation, which is a better descriptor of myocardial contractility. Strain rate analysis from TVM images involves spatial derivation of the measured velocity field and, further, strain analysis is commonly performed with temporal integration of the derived strain rate. Upon derivation and integration, velocity errors may enhance and accumulate, which impacts the accuracy of the derived regional deformation maps. While velocity errors limit regional velocity analysis to some extent, they seriously affect the regional strain and strain rate analysis, particularly at a pixel level. For this reason, myocardial strain and strain rate have been analysed at a segmental level instead. Although strain and strain rate are suitable measures for the quantification of myocardial contractility, there are a couple of points that should be taken into consideration when examining the literature and comparing studies. Unlike velocity, which is a vector measure, strain and strain rate are tensor measures represented by a 3x3 matrix in the three dimensions and, furthermore, the strain tensor is defined with multiple formulas as elaborated in the next chapter. Strain and strain rate tensors are often represented by one or more scalars or vectors which are often selected among the normal strain, principal strain, principal directions of strain, shear strain, norm or invariants of the strain tensor. The selection of the representative quantity as well as its visualisation varies across stud-

ies. The inconsistency of strain and strain rate formulas and visualisation across studies makes their comparison challenging. We suggest the studies by Moody [96], [145], Wu [98], Yingchoncharoen [146], Augustine [147], Petitjean [99] and Moore [148] as potential reference studies for the evaluation of strain and strain rate analysis.

One of the primary studies in myocardial deformation analysis with TVM was published by Beache [149], who calculated the in-planar *strain rate* as the symmetric part of the velocity gradient tensor and showed the potential of strain rate measure in the detection of myocardial abnormalities in HCM. They suggested visualisation of the 2D strain tensor with pixel-centred 2D ellipses. Moreover, they proposed representation of the 2D strain rate tensor by its second invariant, which, as a scalar, was easily visualised with colour coded maps. Selskog [150] extended the above strain rate computation and visualisation from two to three dimensions and studied the principal directions of the strain rate tensor; they showed that the principal direction varies with time, the circumferential direction is more prominent and the principal direction does not necessarily coincide with the main motion direction. Delfino [151] studied in particular the radial strain rate from TVM and compared it to the radial strain rate from cine CMR. They computed the segmental radial strain rate with derivation of the radial velocities and the corresponding strain with temporal integration of the strain rate. They claimed that regional strain rate is a more sensitive descriptor of myocardial contractility than strain.

For regional motion analysis Arai [152] presented a velocity correction method that estimates and subtracts the rigid body motion from the velocity measurements, which is equivalent to the transformation of in planar velocities from the imaging plane to the heart's coordinate system. Rigid body velocity was estimated with linear regression on the velocity measurements and the residual velocities described the myocardial deformation. The in-planar velocity correction was validated with a rotating agar phantom. For myocardial deformation analysis, they computed the segmental radial strain rate and showed how this alters across the myocardium and in the presence of myocardial ischaemia. It is worth noting that strain rate is theoretically not affected by rigid body motion, but in fact a deviation can be observed in strain rate analysis under the presence of rigid body motion, which is attributed to errors introduced in image processing computations.

We will show later that rigid body motion affects the radial strain rate, for instance.

Zhu [153] calculated regional myocardial displacement with temporal integration of the velocity measurements and then computed the *strain* from the estimated trajectories. To reduce the accumulating velocity errors they applied repetitive forward and backward tracking. The forward and backward tracking technique was extended to the Fourier tracking technique in a separate study [154], which takes advantage of the periodicity in normal cardiac motion to model myocardial motion with its first Fourier harmonics. Again, from successive velocity images, they estimated the position of each pixel, drew their trajectories and computed the regional strain. Zhu and Pelc [155, 156] proposed the fitting of a dynamic finite element mesh onto the TVM data in order to model simultaneously the spatial and temporal behaviour of the myocardium taking also into account velocity information from the entire myocardial area rather than each pixel separately; the DMESH framework, as called, ensures periodicity of the myocardial motion by using the Fourier modelling and they address the effect of velocity errors with the condition of strain smoothness. Likewise in an earlier study, Meyer [157] superimposed a deforming mesh onto the TVM images and tracked the deformation of the whole mesh instead of each pixel across the time frames; they used the spatial constraint of the epicardial and endocardial boundaries and applied a Kalman filter to reconcile the noisy velocity field with a smoothly deforming cyclic mesh that represents the myocardium.

Inspired by the CMR tagging and deforming meshes, Masood suggested the virtual tagging framework [158] for the estimation of regional strain at a CMR tagging-like resolution from TVM data. In the virtual tagging framework, an arbitrary tagging grid is superimposed onto the myocardial images and deforms according to the TVM measurements. The tags deformation is the solution to the problem of error minimisation between the predicted velocity of tags and the actual TVM measurements regulated by the incompressibility constraint, which smooths the virtual tags while correcting for noise induced deformational errors. The resulting deformed tags are used to extract the in-planar Lagrangian strain tensor in the myocardial area. Virtual tagging was validated on a computational velocity dataset, a deforming phantom and was compared to CMR tagging with good agree-

ment. Lee [159] proposed a technique for the refinement of the previously estimated coarse virtual tagging grid, which basically improves the convergence towards the global rather local minima.

For myocardial strain analysis, Reese [160] proposed a novel image acquisition and processing technique, which relies on the processing of adjacent slices that are velocity encoded by a single pair of velocity encoding gradients. They visualised the 3D strain tensors as eigensystems, which are rectangular boxes oriented and sized lengthened according to the eigenvectors and eigenvalues of the strain tensor. They also suggested HSB color maps to encode the strain tensor shape, norm and anatomical information from the magnitude image into the hue, saturation and brightness of each pixel.

Lutz [161] presented preliminary results in displacement and strain analysis for the radial and circumferential direction in a patient with asynchrony, a patient with DCM and a patient with Left bundle branch block; they showed reduced twisting in patients with DCM. In a more analytical study, Chitiboi [32] estimated the myocardial *torsion* with PC-MRI across the myocardium and compared the torsion time courses between patients with non-ischemic cardiomyopathy and healthy volunteers stating that torsion can be considered as a sensitive measure for the detection of myocardial abnormalities.

As implied, the main challenge in the motion and deformation analysis with TVM is the alleviation of image artefacts that interfere with the captured velocity field. Noise and other artefacts of high spatial frequency affect the smoothness of the velocity field on the regional scale, but they may go unobserved in the global and segmental velocity analysis providing they average to zero. On the other hand, they amplify upon velocity derivation; hence they significantly affect the derived strain rate and strain maps. Slowly spatially varying artefacts, in turn, such as the background phase shifts analysed below, diminish upon spatial derivation and so does their impact on the strain and strain rate maps. They distort the velocity field by adding an apparent velocity that is almost constant or slowly varying across the myocardial slice and thus affect the velocity analysis on a regional, segmental and global scale. Overall, while strain and strain analysis provide more meaningful measures for the quantification of myocardial contractil-

ity, velocity analysis with PC-MRI is often preferred because the measured velocities are more accurate than the derived parameters and require less processing.

PC-MRI specific artefacts

Apart from the CMR artefacts elucidated in section C.4, PC-MRI is corrupted by phase encoding specific artefacts that distort the phase images and, thus, the measured velocities. These errors may be small when examined individually but they can reach the order of 10% of the true velocity values or more [128,162], when combined together. Analysis of velocities for the computation of deformation or motion parameters often involve tracking, spatial or temporal derivation, which amplify or accrue the velocity errors. For this reason, even small velocity inaccuracies can affect significantly the derived contractility maps and parameters i.e. myocardial strain and strain rate. Minimisation or correction of phase artefacts in PC-MRI is essential for further processing of the measured velocities and can be achieved with suitable hardware and sequence modifications as well as image processing methods. Although progress has been made in this direction, there is still enough room for improvement of the PC-MRI image quality, especially in TVM, which is also one of the goals tackled in the current thesis.

- **Phase aliasing.**

One of the main phase encoding related artefacts is the *phase aliasing* or *wrapping* artefact, which arises from the inherent bounded range of phase that can be measured. The maximum range of phase determines the maximum range of velocity that can be measured without ambiguity. Specifically, phase measurements can take values between $-\pi$ and π , and this sets the minimum and maximum encoded velocity to $-V_{enc}$ and V_{enc} , where

$$V_{enc} = \pi / \gamma G_{enc} \delta \Delta \quad (2.2)$$

is the *aliasing velocity*. Velocities that fall within the interval $(-V_{enc}, V_{enc})$ can be phase-encoded without ambiguity according to Equation 2.2.4. On the other hand, velocities that exceed this interval are erroneously mapped to velocities within the range $-V_{enc}$ and V_{enc} and this causes the *aliasing* or

phase wrapping artefact. Phase aliasing happens because a velocity v greater than V_{enc} (in absolute value) causes phase accumulation $\kappa\pi + \phi$, $\kappa \in \mathbb{N}^*$, which is read as the apparent phase ϕ and decoded to the wrapped velocity $v_{wrapped} = \phi/\gamma G_{enc}\delta\Delta$ instead of the real velocity $v = (\kappa\pi + \phi)/\gamma G_{enc}\delta\Delta$ (in absolute value), such that the $v_{wrapped}$ is in the range $-V_{enc}$ and V_{enc} and by $\kappa\pi/\gamma G_{enc}\delta\Delta$ lower than v .

The aliasing velocity V_{enc} is a critical parameter in phase encoding and phase aliasing and can be tuned via the encoding gradient. V_{enc} depends on the encoding gradient, such that the lower the strength or duration of the encoding gradient, the higher the V_{enc} (see Equation 2.2.4); this means that phase aliasing can be avoided with lower and shorter phase encoding gradients. However, the encoding gradient cannot be set arbitrarily low, and equally V_{enc} arbitrarily high, because this would result in low sensitivity and SNR in the velocity measurements. The SNR_ϕ of the phase difference image is proportional to the SNR_m of the magnitude image multiplied by the factor v/V_{enc} ($SNR_\phi = SNR_m \frac{v}{V_{enc}}$) [128]. Therefore, a trade-off between phase wrapping, measurement sensitivity and noise need to be considered when setting the aliasing velocity parameter V_{enc} . Optimum V_{enc} can be identified with repetition of a sample image acquisition starting with low V_{enc} and increasing it incrementally until the peak measured velocity is free of aliasing or the SNR and sensitivity limits are met. Phase aliasing can be corrected with phase unwrapping image processing methods [163]. Phase aliasing artefact affects the flow velocity mapping in particular, as blood flow can reach velocities up to 120 cm/s in the aorta [164]. Tissue velocities, on the other hand, do not exceed the 10cm/s in-plane and 15cm/s through-plane (see section 2.1.3) and, therefore, a V_{enc} of 20cm/s in-plane and 30cm/s through-plane is sufficient to avoid phase aliasing in TVM [134].

- **Background phase shifts.**

An important artefact in TVM is the *residual phase errors* or *background phase shifts* that incur at the subtraction of the encoded and reference phase images and source from MRI artefacts that affect the encoded and reference phase images differently. Background phase shifts are identified as non-zero phase shifts in areas of stationary tissue and affect also areas of moving tissue. They vary spatially and increase gradually from the isocentre of the MR image to its periphery, and the increase is super-linear with distance.

Background phase shifts are hardware dependent (different across different scanners), temperature dependent [165], may vary unpredictably with slice orientation, thickness and slice selection but they are stable over all frames of a retrospective gated cine [166] facilitating image processing, but not of a prospective gated cine. Phase shifts are typically small, but their effect is considerable when the velocity processing involves summation over an area or across frames. For example in flow velocity mapping [166], phase shifts are of the order of 1-2cm/s, which is only 1% of the $V_{enc} = 150\text{cm/s}$ but enough to affect considerably the computation of shunt flow⁵ and Cardiac Output (CO) from velocity summation over a cross sectional area. In TVM the effect of phase shifts is expected to be higher, as tissue velocities are 10 times lower on average than blood velocities and velocity processing often involves summation and derivation.

The known sources of background phase shifts are concomitant field terms, gradient field distortions and eddy currents (see section with artefacts and correct names) and they are partly corrected with existing techniques [166]. The *concomitant or Maxwell gradients* are unavoidable distortions of the main magnetic field resulting from its interaction with the magnetic field gradients [167], as explained by the principles of fundamental electromagnetism and their effect is more significant in acquisitions with low main magnetic field or high strength gradients. They include quadratic spatial terms, depend on the gradients' amplitude and are independent from the hardware as they express a fundamental physics effect [167]. Concomitant field terms are, thus, calculated analytically and often corrected precisely and automatically by the scanner's software. Correction can be performed at the acquisition stage with adjustment of the magnetic gradients or at the reconstruction process by the scanner's software [167], which is the widely adopted way by most commercial scanners [168].

The other known source of background phase shifts is the *eddy currents* induced by varying magnetic fields like the encoding gradients and their computation and correction is more challenging. Unlike the concomitant gradient terms, gradient eddy currents are associated with the gradient slewing and are hardware dependent, which means that they cannot be calculated analytically and precisely [166,167]. They normally have linear and constant spatial dependence [169] and a computational way to correct them

⁵irregular patterns of flow in the heart

is by fitting a surface to control points in the areas of identified stationary tissue [166,169]. Another way is calibration of the acquisition with respect to a background area, which is selected from within a region of stationary tissue adjacent to the moving region of interest [168]. Such baseline corrections of phase shifts are not easily applicable when there is insufficient stationary tissue or its image is highly corrupted by noise. In such cases, a baseline phantom correction is adopted, for which, the acquisition is repeated on a static phantom with identical slice and pulse sequence parameters and the generated dataset is subtracted from the homologous in-vivo dataset to correct for the background phase shifts [166,168]. Subtraction is usually performed with an average phantom image over the cine dataset rather than on a frame-by-frame basis [168]. Phantom correction has proved effective and precise in the reduction of background phase shifts also in cases where their distribution is not linear (for example when concomitant terms are included), and this correction technique is preferred despite it being time consuming. Baseline phantom correction is applied in the present study too.

Another way to minimise background offsets is the pre-calibrated compensation of eddy currents with appropriate adjustment of the gradient waveforms, a technique controlled by the scanner's software and known as pre-emphasis. Pre-emphasis seems to be efficient in acquisitions performed on static phantoms, but its reliability with in-vivo acquisitions is questionable and in any case residual phase shifts seem not to be negligible. In flow velocity mapping [166], residual phase shifts after concomitant current and pre-emphasis corrections have been reported to exceed the limit of 0.6 cm/s for a V_{enc} of 150cm/s, thus image processing correction is required. In TVM, where the velocities of interest are 10 times smaller than in flow velocity mapping, the residual phase shifts are likely to be more significant⁶. A question to this is whether eddy current gradients depend on the tissue motion which makes them different in the in-vivo dataset. Smaller V_{enc} does not always guarantee reduced background velocity offsets [128]. A simple strategy to obtain initially small background phase shifts is positioning the region of interest at the iso-centre of the image.

Sources of MRI artefacts like the external magnetic field inhomogeneity either hardware or patient specific, RF inhomogeneity and distortion of the

⁶Impact of V_{enc} to be considered.

localisation gradient fields affect the velocity phase encoded and reference image in the same way and, thus, they are cancelled out at their subtraction [170,171]. Hence, the delivered PC-MRI phase image does not include them.

- **Blood flow artefacts.**

In PC-MRI, unless the velocity encoded signal originating from the blood flow is selectively suppressed, it masks the ten times weaker signal from the moving myocardial tissue. Thus, while the blood flow signal is the target measurement in flow velocity mapping, it is considered a crucial artefact in TVM and its alleviation is a pre-requisite. Apart from the erroneous phase shifts in phase velocity encoding, unsuppressed blood flow induces phase shifts also in phase encoding for localisation, accounting for signal misregistration too. Blood signal suppression is, therefore, necessary in TVM and it has been achieved with the addition of a dark or black blood preparation pulse [68, 134, 136] as described in *Appendix C.3*. Acquisition acceleration has also aided the reduction of blood induced phase shifts. Despite blood signal suppression, blood flow still introduces phase shifts in the presence of several cardiac pathologies, where it becomes more complex and turbulent [170]. Such phase shifts can cause phase dispersion and loss of signal.

- **Noise.**

Noise in PC-MRI has the same behaviour as noise in the magnitude and phase MR image, as elucidated in *Appendix section C.4.4*. Because tissue velocities are considerably lower than blood flow velocities, noise appears to have a significantly greater impact on TVM than flow velocity mapping. The alleviation of noise from TVM images is currently the greatest challenge in the improvement of this technique. The noise alleviation problem has been addressed both in the acquisition as well as the image analysis stage of TVM, with the latter being the main focus of the current thesis.

Advantages, weaknesses and applications

Research studies have performed TVM with PC-MRI for the investigation of the myocardial motion and deformation in healthy volunteers [23,27,134] both males and females [27, 66] of a younger age [22, 141], an older age [21, 32] or over different age groups [19, 22, 26] in cohort sizes ranging from

one-subject [150, 154, 155] to large number of subjects [19, 144]. Similar studies have been conducted on patients with HCM [149], DCM [26, 161], LV hypertrophy [29], myocardial infarction [69], myocardial ischemia [69, 138, 152], ventricular dyssynchrony [27, 140, 161], non-ischaemic cardiomyopathy [32] and heart failure [27]. TVM has also been studied on patients referred for cardiac resynchronisation therapy [66], patients with repaired tetralogy of Fallot [73], left bundle branch block [161] and children with chronic kidney disease [143].

PC-MRI like CMR Tagging is one of the widely used techniques for measuring myocardial motion and deformation by virtue of its significant advantages. PC-MRI provides direct measurements of velocities, thus TVM images require little or no processing to quantify motion and deformation, unlike CMR tagging. Furthermore, the velocity measurements are acquired on a per pixel basis setting the grounds for a more detailed regional analysis than CMR Tagging. Unlike SENC and like DENSE, PC-MRI captures motion in all three orthogonal directions during a single slice acquisition. An important advantage of PC-MRI to all three CMR Tagging, SENC and DENSE, is the lack of fading which allows constant quality of images from the entire cardiac cycle and, accordingly, constant quality of image analysis both from early systole and late diastole. Unlike tagging techniques, large through plane motion does not bring the encoded motion information out of the image plane. PC-MRI measures velocity at each instance while DENSE measures the total travelled distance of each voxel with respect to its position in the initial frame, for this reason it could be claimed that PC-MRI measurements are more accurate. On the other hand, DENSE allows the measurement of larger scale motion with low encoding gradients because of the long time interval between the encoding lobes; lower encoding gradients means also lower risk for phase alignment and other related image artefacts.

However, TVM with PC-MRI has not entered the clinical practice yet, although PC-MRI has been clinically available for blood flow imaging [127]. A major hindrance to that is the fact that the tissue velocities are low enough to be masked by the high noise and other PC-MRI artefacts like the phase aliasing, background phase shifts and blood flow artefacts. Another reason is the long acquisition time of PC-MRI particularly because the encoding of the three orthogonal velocity components requires four image acquisitions per slice. Furthermore, despite the amount of research on TVM analysis,

there does not exist an established and widely accepted software for TVM analysis and visualisation. To sum up, TVM has the potential to become an important clinical tool for cardiac disease diagnosis providing several challenges are met before it becomes clinically available.

2.2.5. Visualisation

Visualisation of myocardial motion and deformation is essential for an intuitive comprehension and interpretation. Regional myocardial velocity has been represented with vector fields and color-coded pixel-wise maps [28, 29, 31, 69]. A recent suggestion for regional motion visualisation is the 3D superquadric glyphs [172], which encode the direction of myocardial motion into their shape. Segmental myocardial motion has been visualised with bull's eye plots, which are compact representations of the 3D arrangement of segments in the left ventricle. Variations of the segmental plots were suggested by a recent study [173]; these are the 2D arrow glyph, warped segment, pin, warped line, combination of warped line and pin plots that encode simultaneously the in-planar and through plane motion, as well as the opacity-encoded plots that provide a more intuitive visualisation of the essential information. Global motion is shown mostly with time courses over the cardiac cycle.

The visualisation of regional strain and strain rate is more challenging. A tagging-like deformable grid [174] is an intuitive visualisation of deformation and it was also adopted by Masood in the virtual tagging framework [158]. Reduction of the tensor information to one, two or three representative scalars allows the visualisation of strain and strain rate with colour coded maps [150]. Each colour map can encode one scalar or three scalars, one in each channel of the colour coded RGB or HSB maps; likewise, Reese [160] combined deformational and anatomical parameters in HSB maps, as explained above. Colour coded images have been extended to surfaces [175, 176] that incorporate the shape information. Colour coded meshes, combination of colour coded meshes and surfaces [177, 178] and point clouds are similar illustrations of regional myocardial deformation [159, 179].

2D/3D ellipses [150] and eigensystems [160] have shown to provide a more intuitive representation of the strain and strain rate tensors, particularly with regard to the main direction of deformation. Wunsche [178, 180, 181]

suggested hyperstreamlines and line integral convolution for the visualisation of the spatial as well as the temporal information of deformation in a single plot rather than a sequence of plots; hyperstreamlines, for instance, are tangential trajectories to one eigenvector, they are coloured after the corresponding eigenvalue and their ellipsoidal cross section encodes the other two eigenvectors and eigenvalues.

2.2.6. Validation

As with any imaging and image processing methods, the performance of CMR imaging techniques and image analysis for myocardial motion may have an important effect on the diagnostic procedure where included. Validation and evaluation of each method can serve as a useful feedback for their improvement and are necessary for the translation of the method into clinical practice. As much as validation of medical image processing methods is important, it remains a difficult problem mainly due to the intrinsic difficulty in obtaining the absolute ground truth, that is myocardial motion in this case, as well as the complexity and variability of medical images. As a result, each published work employs a different in-house performance evaluation method applied on different datasets and compared to proprietary ground truth. For this reason direct and objective assessment of published works on medical image processing and comparison of published image processing methods is challenging.

Validation and evaluation of image processing methods for myocardial motion analysis is commonly performed on computational cardiac models or cardiac phantoms that simulate the cardiac motion.

Left-ventricular phantoms

Left ventricular phantoms for CMR motion analysis are often moving or deformable silicon gel phantoms in the form of a cylindrical annulus. In the early years of cardiac motion analysis with CMR, Young [182] built such a phantom for validation of strain analysis from CMR-tagging and a decade later Masood replicated this phantom in order to evaluate the virtual tagging framework from PC-MRI [158]. Khan's [183] cylindrical dynamic deformable cardiac phantom incorporates pseudorespiratory motion and blood flow. Swailes [184] integrated cardiac and respiratory motion

as well as blood circulation in a thorax phantom for validation of motion artefacts in MRI for endovascular procedures. Dierigens [185] built a more realistic deformable phantom of the LV with tunable tissue and blood flow properties for the simulation of both healthy and pathological myocardium and used it for the correction of motion artefacts in MRI assisting catheter tracking; their phantom was tested with CINE and PC-MRI images with respect to structural, mechanical, magnetic resonance and flow properties.

More recently Manzke [186] developed a polyvinyl alcohol (PVA)-based dynamic cardiac phantom of the LV for cross evaluation of CMR-tagging and PC-MR sequences in a 3T scanner. An air-pressure actuator manipulates the hollow cylinder-shaped phantom, generates the ECG signals sent to the MR scanner and optionally adds translational respiratory motion to the system. Manzke's phantom was also used for comparison between k-t Broad use of Linear Acquisition Speed-up Technique (BLAST) [187] and SENSE techniques in terms of consistency at different acceleration rates [188]. It was extended later by Eder and Rasche [189] to a new dynamic phantom with adjustable pulse, and respiratory rate and optimised user interface for evaluation of self-gated imaging sequences and motion artefacts. For comparison between strain analysis with echocardiography and CMR, Werys and Cygan [190, 191] built a deformable PVA phantom of the left ventricle. Stanton [192] constructed a PVA dynamic phantom of the LV with realistic anatomy and control over the respiratory and cardiac motion for the evaluation of bSSFP imaging.

Currently commercially available is the MR and CT-compatible dynamic phantom of the right and left ventricle provided by Shelley Medical Imaging Technologies incorporation [193]. It replicates realistic left and right ventricular anatomy with coronary arteries, myocardial and respiratory motion allowing heart rate control. It is suitable for validation of CMR (e.g. motion artifacts), image analysis (e.g. segmentation, visualization, strain analysis) and navigation of interventional devices. The developed phantoms, their characteristics and availability are summarised in Table 2.1.

Simulated datasets

The construction of a cardiac phantom is expensive, time-consuming, furthermore, its deformation is likely to deviate considerably from the realistic

2.2. CMR ASSESSMENT OF MYOCARDIAL CONTRACTILITY

Table 2.1.: Phantom validation in cardiac motion analysis with CMR

Author/ Company	Year, Citation	Phantom structure, main specifications	Simulated features	Validation target	CMR type	Availability
A. Young	1993 [182]	Deformable Silicone gel Cylinder (LV)	Myocardial deformation	Strain analysis	MR tagging (SPAMM)	NA
S. Masood	2003 [158]	Deformable Silicone gel Cylinder (LV)	Myocardial deformation	Virtual tagging framework	PC-MRI	Not available
S. Khan	2003 [183]	Deformable Silicone gel Cylinder Flow pump (LV)	Myocardial deformation Respiratory motion Blood flow	MR scanner performance: Spatial resolution and ghosting artifacts	Cine	Not available
N. Swailes	2011 [184]	Hydraulic system (heart) Respirator (lungs) Flow pump (blood) (2-chamber heart, lungs, valves, vessels)	Respiratory motion Cardiac motion Circulatory system	Endovascular catheter tracking Motion artefacts	Cine (FGRE gated/non gated, SPGR)	NA
M. Dieringer	2012 [185]	Deformable Silicone gel Truncated cone Flow pump (LV)	Myocardial deformation Respiratory motion Blood flow Myocardial edema Volume and wall thickness		Cine (SSFP, FGRE) PC-MRI	NA
R. Mancke	2010 [186]	Deformable PVA Cylindrical Pneumatic control ECG generator (LV)	Myocardial deformation Respiratory motion ECG 60bpm	MR-Tagging and PC-MRI at 3T		Available
Lutz	2011 [188]			kt-BLAST and SENSE	PC-MRI	
M. Eder and V. Rashce (latest version)	2014 [189]	User-friendly interface Improved respiratory motion	Adjustable cardiac pulse and respiratory rate	Motion artefacts	MR Tagging (CSPAMM, sGRE) PC-MRI	
K. Werys	2012 [190]	Deformable PVA criogel Truncated ellipsoid	Myocardial deformation Left-ventricular shape, size, volume	Strain analysis Ultrasonography and CMR	Cine (True-FISP) MR Tagging (SPAMM)	Data Available
S. Cygan	2014 [191]	Hydraulic pump ECG generator (LV)				
D. Stanton	2011 [192]	Deformable PVA Realistic shape Pneumatic control (LV, RV)	Myocardial deformation Respiratory motion Accurate ventricular shape, size, volume	CMR Data	Cine (SSFP)	NA
Shelley	2008 [193]	Deformable PVA Realistic shape Pneumatic control Coronary arteries (LV, RV)	Myocardial deformation Respiratory motion Accurate ventricular shape, size, volume Blood flow Coronary arteries Arrhythmias	CMR and CT Segmentation Visualisation Registration Motion artefacts Strain analysis Navigation		Commercially available

deformation of the heart, which is innately complex. For this, simulated datasets are often preferred especially at early stages of development and evaluation of an image processing method. Young [194], for instance, generated images of a two surface prolate shape that deforms mimicking the normal left ventricle and used them to evaluate motion analysis with CMR-tagging. Masood [83] validated the virtual tagging framework for strain estimation from PC-MRI, first, on a simulated dataset defined by parametric velocity functions in the RCL directions satisfying also the incompressibility constraint and, subsequently, proceeded with phantom validation. Hunchach [175] mentions the computation of a deforming hexahedral solid mesh morphologically similar to the LV that simulated contraction, shortening and torsion.

2.2.7. Direct image analysis with machine learning or deep learning.

With the increase in hardware capabilities and evolution of Machine Learning (ML) and Deep Learning (DL) algorithms, new strategies have recently emerged for contractility analysis from CMR images like the *direct image analysis* [195–200]. This strategy and terminology has been adopted by a group of researchers to emphasize that the suggested image analysis frameworks lack or require reduced intermediate processing steps like segmentation, registration and tracking and rely on ML and DL techniques to model the direct relationship between CMR image intensities and clinical indices from a big number of datasets. Direct image analysis has been developed primarily for bSSFP images because of their presence in clinical practice, abundance and quality. Although direct image analysis has shown promising results towards the estimation of global contractility measures, its effectiveness in regional contractility analysis has not been shown yet and it possesses several drawbacks; like any ML-based methods, a plethora of training data, high computational time and complexity are required. What is more, some initialisation and labeling from the user are still needed, despite the term *direct*.

2.3. Conclusions and Overview

This review chapter has provided a detailed background of the heart's complex structure and function with emphasis on the tissue's motion and deformation during the cardiac cycle, as well as the different models for its complex contraction. Myocardial diseases and conditions cause alterations not only in the anatomy and histology of the myocardium, but also in its contractile activity, increasing further the complexity of the cardiac function. Low scale contractility changes can serve as prognostic and early diagnostic indicators in the diagnosis of cardiac disease.

Cardiac X-ray, CT, radionuclide imaging and CMR imaging modalities are clinically available for cardiac disease diagnosis and their types, advantages, limitations and applications have been elucidated in the chapter. For this study, CMR has been selected, because of its significant advantages and versatility. This review provides an exhaustive description of the CMR modality including the MRI physics from a nuclear level, the CMR imaging principles, the various CMR sequences and image types, the numerous techniques for the improvement of image quality and acceleration of acquisition as well as the sources and patterns of CMR image artefacts.

CMR offers unique techniques for imaging the regional motion and deformation within the myocardium, each one presenting advantages and disadvantages. Image processing algorithms tailored to each technique aim at the quantification of regional myocardial contractility from the CMR images or the improvement of the CMR image quality prior to image analysis. This chapter provides a thorough elaboration on CMR Tagging, SENC, DENSE and PC-MRI including a description of each imaging technique and its advancements, a review of their existing image analysis methods, outcomes, visualisation and validation, as well as a discussion on their advantages, weaknesses and clinical applications. PC-MRI is considered to offer significant advantages and TVM can potentially increase the diagnostic accuracy when translated into clinical practice. For its clinical translation, the TVM technique necessitates a standardised TVM image analysis framework, and in particular, effective processing for the alleviation of the persisting image artefacts. TVM with PC-MRI has, therefore, been selected for the current study.

Cardiac image analysis is a multidisciplinary field of study in the intersec-

tion of medicine, physics and computing. We believe that a deep and clear understanding of the triple nature of cardiac image analysis is essential for the development of successful, meaningful and clinically useful image analysis algorithms. It is important for the analyst researcher to understand the imaged properties and features, in order to be able to identify and distinguish innate imaging artefacts or image processing outcomes from the intrinsic cardiac features and pathologies; this is important for the development of successful cardiac image analysis methods. The current review chapter aims at this deep understanding of the cardiac image analysis field and its studied area; this review can offer guidance also in future research.

3. Myocardial Mechanics and Contractility

3.1. Introduction

This chapter presents the theoretical background of myocardial tissue mechanics and contractility, the most representative measures and an analysis of the relation between the different strain definitions. The chapter starts with the definition of myocardial contractility and the global and regional myocardial contractility measures that are commonly encountered in CMR studies. The second part of this chapter is devoted to the principles of myocardial tissue mechanics and the description of myocardial deformation measures adopted from the field of deformable continuum kinematics. The continuum and the incompressibility property of the myocardial tissue are reviewed and discussed, in particular. The third part of this chapter performs a comparative theoretical analysis of the strain formulas and will show how the selected formula affects the strain analysis results.

3.2. Myocardial Contractility

3.2.1. Definition

Contractility is the innate ability of the myocardium to contract independently of preload or afterload. It is an important descriptor of the myocardial function, as described in the previous chapter. Contractility is an ambiguous property of the myocardium rather than a well-defined quantity and it is described with relations and measures from tissue dynamics, kinematics or constitutive relations; tissue dynamics focuses on tissue forces and stresses, tissue kinematics is confined on motion and deformation and, lastly, constitutive relations model the tissue behaviour under several conditions. The current study approaches contractility from the aspect of tissue

kinematics describing it as myocardial motion and deformation.

3.2.2. Quantification: global and regional measures

Left ventricular myocardial contractility has been quantified with global and regional measures.

- **Global contractility measures.**

Global contractility measures are either computed from anatomical indices or by averaging the regional measures across the myocardial volume or area. Popular global indices of the first category are the left ventricular *Stroke Volume (SV)*, *Ejection Fraction (EF)* and *Cardiac Output (CO)* and these are calculated from the anatomical indices *End-Diastolic Volume (EDV)*, *End-Systolic Volume (ESV)* and *Myocardial Mass (M)* [82]. Papillary muscles are usually included in the mass measurement but excluded from the volumes. Stroke Volume (SV) is the volume of blood pumped from the LV to the aorta at each heart beat and it is calculated as the difference between ESV and EDV,

$$SV = EDV - ESV$$

Ejection Fraction (EF) is the most widely used global index for LV systolic function and it is defined as the fraction of blood ejected to the aorta with respect to the EDV. EF is calculated accordingly as the ratio

$$EF = \frac{SV}{EDV}$$

CO gives the blood pumped into the aorta per minute and it is computed as the stroke volume times the Hear Rate (HR),

$$CO = SV \times HR$$

Additional indices are mentioned in the Maceira's study [201] like the *AV Plane Descent (AVDP)* and *Peak Filling Rate (PFR)*. The AVDP is confined in the longitudinal direction and is calculated as the ratio of left ventricular length between end-dystole and end-diastole. The PFR refers to the diastolic phase and is defined as the maximum derivative of the time-volume curve; it is also used normalised with respect to End-Diastolic Volume (EDV).

To account for different body sizes, the above indices Myocardial Mass (M), End-Systolic Volume (ESV), EDV, SV, EF, AVDP, PFR were normalised to the *Body Surface Area (BSA)* to yield the MI, ESVI, EDVI, SVI, EFI, AVDPI, PFRI respectively. BSA is given by the Mosteller formula as

$$BSA = \frac{\sqrt{HW}}{6}$$

where H is the person's height (m) and W the person's mass (Kg). Maiceira [201] proposed reference values for each of the above indices for different age groups and gender based on a study on 120 subjects; they claim that most of the above LV clinical indices are significantly and independently influenced by age, gender and BSA.

- **Regional contractility measures.**

Although global indexes are sufficient clinical indicators for the diagnosis of an advanced cardiac disease or condition, they lack sensitivity in small scale abnormalities that occur at the initial stages of the disease or condition. As mentioned in the previous chapter, this happens because the cardiac compensatory mechanisms tend to preserve the global function of the heart against small scale alterations in the heart. As an example, 30-40% of patients with systolic heart failure have reported retained normal EF [202]. To detect regional abnormalities at early stages of a disease as well as to localise precisely those abnormalities across the myocardium, contractility needs to be quantified with regional myocardial measures. Regional contractility analysis is often more challenging compared to global contractility analysis. The most common regional contractility measures are the regional myocardial *wall thickness*, *strain*, *strain rate*, *torsion*, *displacement*, *velocity* and *peak velocity* [79, 82, 203].

Most regional contractility measures have been reviewed in section 2.2.3, As discussed in particular in subsection 2.2.4, regional strain and strain rate are good descriptors of regional myocardial contractility; however strain analysis presents several challenges, one of which is the non-univocal definition of the strain tensor and non-consistent selection of the scalar quantity/-ies for the strain representation across studies. As Petitjean [99] pertinently describes, the three normal strains across the R,C,L directions are either

calculated from the strain rate tensor equations in the RCL system or with transformation of the Cartesian strain tensor to directional strain across the R,C,L directions with the aid of a unit vector in the desired direction. A simplified but less accurate estimation of normal strain values is by computing the relative change in length of material segments across the desired directions [98] or, similarly, the relative change in the squared length of the material segments (ϵ_v). As seen later, the 3D strain tensor is defined either in the reference or the local coordinate system, where in both cases it has multiple definitions. The Seth hill generalised strain tensor summarises a group of those definitions. For infinitesimal deformation the aforementioned definitions coincide (excluding ϵ_v) and ϵ_v is the double quantity. However, this is not the case of finite deformations as those observed in the myocardium. In terms of representative scalars, the most commonly used quantities are the principal, the shear, the normal strain, the norm of the strain tensor, the strain tensor invariants and the Von-Mises' strain [177].

Many studies employ different formulas and representative quantities for the strain and strain rate measures. For example, left-ventricular deformation studies have adopted the 3D Lagrangian strain tensor [158, 177, 204] mapped to the scalar Von-Mises' strain [177] or its first invariant [150], the infinitesimal 3D strain tensor expressed by its principal components [205], the axial Engineering strain [98, 206], the axial True strain [206], the 3D rate of deformation tensor [150] in place of the 3D strain rate tensor and the radial derivative of the radial velocity [152] as a measure of scalar strain rate. In addition, we have noticed misalignment of definitions for the Lagrangian, Eulerian and Engineering strain between certain studies [79, 98, 206] and the bibliography [207, 208], while we have also encountered unclarified computation of the Lagrangian strain from the TVM field [158], which has Eulerian expression. What is more, we have observed that other studies dismiss completely the formulas they employ for the strain analysis [96, 147, 209]. The following section aims at the clarification of tissue mechanics, deformation measures and 3D strain formulas, in particular, tailored to the specifications of the myocardial tissue.

3.3. Myocardial tissue mechanics: principles and incompressibility property

3.3.1. Motion models and deformation

In tissue mechanics [207] three main types of models are employed to emulate the motion of an object: the *particle model*, the *rigid object model* and the *deformable continuum model*. These three models are going to be considered in this study to emulate the motion of the left-ventricular myocardium. The selection of the model type depends on the type of motion that is predominant or selected to be studied in each case. We distinguish three types of motion: the *translational*, *rotational* and *deformational* motion. According to this, the complex motion of an object can, at any time, be decomposed into a pure translational, rotational and deformational component.

In pure *translational* motion all points of an object move with the same velocity vector, at an instant of time. In such case, the object is sufficiently represented by a point that is located at the centre of mass of the object and moves with velocity equal to the translational velocity of the object; this simplified representation of the object's motion is the *particle model*.

If all points of the object do not move with the same velocity vector, but their velocity at an instant is proportional to their distance from one single fixed axis or in other words their pathlines form circles about centres belonging to a straight line, the object performs pure *rotational motion*. Rotational motion (pure or combined with translational motion) is emulated by the *rigid body model*, whose any pair of points maintains a fixed distance over time.

Lastly, if there is relative motion between any two material points of the object meaning the distance between the points changes over time, then the object performs also deformational motion and the object's motion is emulated by the *deformable continuum model*. The following analysis focuses mainly on the deformational motion or simply *deformation*, which is the type of motion associated with myocardial contractility.

3.3.2. The deformable continuum model and the myocardium

The *deformable continuum model* is employed to model myocardial tissue on the grounds that myocardial tissue behaves macroscopically like a continuum. Tissue is considered to behave like a continuum in a specific scale of study, if it appears continuously distributed such that its infinitesimal elements adopt the properties of the bulk tissue. In CMR imaging the smallest distinguished element of matter is in the size of a voxel, which is significantly larger than a myocardial myocyte. Speaking in numbers, if the voxel is of dimensions $0.7 \times 0.7 \times 8 \text{ mm}^3$ and the mean healthy myocyte is about $100 \mu\text{m}$ in length and $10 - 25 \mu\text{m}$ in diameter [210], each voxel depicts tens of thousands of myocytes together setting each myocyte indiscernible from each other. Based on this fact myocardial matter has assumed to appear continuous in the CMR scale and myocardial tissue to be regarded a continuum.

Although this assumption of myocardial tissue continuity has been generally adopted in CMR imaging, it dismisses consideration of higher levels of myocardial microstructure that may impact the macroscopic mechanical behavior of the muscle. In fact, it has been shown that myocardial myocytes form a three-dimensional arrangement that influences the mechanical (and electrical) function of the heart, known as laminar sheets or laminae [43]. Laminae are of about 4 myocytes or $48 \mu\text{m}$ thick, they are loosely interconnected with perimysial collagen in the normal-sheet axis and they form branches that can be in 1-2mm distance from each other [44]. This distance is comparable to a voxel's dimensions and it could potentially account for discontinuities in the myocardial continuum that are visible by CMR. Despite indications for such discontinuities, their existence or visibility by CMR has not been proven yet.

In this thesis for myocardial contractility analysis, the myocardium will be considered as a continuum that is potentially disrupted sparsely by discontinuities. The potential discontinuities in the otherwise continuous myocardial velocity field will be respected by the restoration method for myocardial velocities presented in Chapter 5. The results of TV restoration will show discontinuities in the myocardial velocity field that are distributed sparsely, with a distance from each other that is significantly larger than 1-2mm or in

other words larger than the distance between the laminar interconnections. If these velocity discontinuities are caused by intrinsic discontinuities in the myocardial matter and not imaging artefacts, they indicate that several of the laminar interconnections are considerably loose. In this case, discontinuities would be expected to appear along the sheet direction, which means almost radially aligned to the centre of the LV [43]. The existence of velocity discontinuities and their orientation would be interesting topics for further research.

In this work, myocardial contractility analysis will be based on relations evolving from deformable continuum mechanics. To solve a problem in deformable continuum mechanics, classes of relations are considered such as *kinematics*, which deal for instance with velocity and strain, *forces*, which involve tractions and stresses, *conservation laws* listing the conservation of mass, momentum and energy and *constitutive relations*, which describe the material behaviour i.e deformation resulting from stress. Since TVM provides tissue velocity data rather than any information about forces in the myocardial tissue, myocardial mechanics will be studied mainly from the aspect of deformable continuum kinematics. In the computation of kinematics quantities, several studies on myocardial contractility with CMR and TVM engage the incompressibility constraint linked to the conservation of mass law; for this reason, the conservation laws from the aspect of continuum mechanics will be presented briefly and myocardial incompressibility will be discussed in detail. Constitutive equations related to myocardial tissue behaviour will also be mentioned for completeness.

3.3.3. Lagrangian and Eulerian specifications

Before proceeding with the quantities and relations in tissue mechanics, it is legit to define the Lagrangian and Eulerian specifications. In deformable continuum mechanics, quantities, i.e. velocity, strain, density, temperature, vary not only with time but also from material particle to material particle and, in turn, material particles change generally their location in space with time. The quantities are usually expressed either with respect to a specific material particle as this moves in space, or with respect to a specific location in space as this is crossed by various material particles. The choice between

these two types of references defines the Lagrangian specification or Eulerian specification, in which each quantity and equation are expressed.

In the *Lagrangian* or *material* specification, the observer follows a material particle, initially positioned at $\vec{X}_0$, as this changes position $\vec{x}(\vec{X}_0, t)$ with time t . In the *Eulerian* or *spatial* specification the observer is fixed at a spatial point $\vec{x}_0$ observing the material particles $\vec{X}(\vec{x}_0, t)$ that pass through $\vec{x}_0$ with time t . In deformable solid mechanics and, thus, myocardial tissue contractility the Lagrangian specification is more suitable, in contrast to fluid mechanics i.e. blood flow analysis where the Eulerian specification is more popular.

PC-MRI measures the instantaneous velocity at each tissue voxel, as explained in section 2.2.4. The position in space of each tissue voxel is captured at the time of the measurement, and therefore the PC-MRI velocity measurements refer to the Eulerian specification as also stated by Simpson [79]. The origin of each tissue voxel is estimated indirectly with temporal integration of velocity. DENSE, on the other hand, measures displacement of each voxel with respect to its position at the beginning of the image acquisition and therefore DENSE displacement measurements are in the Lagrangian specification.

The expressions of a quantity in the Lagrangian and Eulerian specifications are bridged via the material derivative formula. The material derivative is the rate of change of the property $\frac{D}{Dt}$ in the Lagrangian specification and it is related to the rate of change of the property $\frac{\partial}{\partial t}$ in the Eulerian specification with the formula $\frac{D}{Dt} = \frac{\partial}{\partial t} + \vec{u} \nabla \cdot$, where $\vec{u} = \vec{u}(\vec{x}, t) = \vec{u}(\vec{X}(\vec{x}_0, t), t)$ is the velocity of the material particle at position x and time t , which is the regional tissue velocity for our study. For now, the following equations are expressed in Eulerian specification, unless stated otherwise.

3.3.4. Conservation laws

In the myocardial continuum, like in any continuum, the fundamental *conservation laws of mass, momentum and energy* apply (along with myocardial-tissue-specific *constitutive relations*). Each conservation law states that for any system the total quantity of *momentum*, *energy*, or *mass* is conserved in time unless an external agent intervenes. A stronger form of a conservation law is the corresponding continuity equation, which ensures the local preser-

vation of the quantity on top of its global preservation stated by the law. The conservation of mass is important in myocardial tissue kinematics as it is related to the much debatable myocardial (in)compressibility property.

Conservation of momentum and Cauchy laws of motion

The conservation of momentum states that the total (linear and angular) momentum of an object remains constant unless forces or stresses are applied or exchange of matter occurs. The local conservation of momentum in a deformable continuum is expressed by the Cauchy momentum equations. Cauchy's momentum equation for the local preservation of linear momentum or Cauchy's 1st law of motion is

$$\rho \frac{\partial \vec{u}}{\partial t} + \nabla \vec{u} \vec{u}^T - \nabla \boldsymbol{\sigma} - \rho \vec{g} = 0 \quad (3.1)$$

where $\vec{u}$ is the regional (tissue) velocity at a point of the continuum and $\vec{g}$ is the external body forces per unit mass simplified to only gravitational force for our analysis. Providing the incompressibility constrain, Cauchy's 1st law of motion becomes

$$\rho \frac{\partial \vec{u}}{\partial t} = \nabla \boldsymbol{\sigma} + \rho \vec{g} \quad (3.2)$$

which states that the temporal change in momentum per unit volume at a fixed point equals the total stress force per unit volume plus the gravitational force per unit volume. Cauchy's momentum equation for the local preservation of angular momentum or Cauchy's 2nd law of motion is

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^T \quad (3.3)$$

where $\boldsymbol{\sigma}$ is the (Cauchy) stress tensor at a point of the continuum. This equation ensures symmetry of the stress tensor which means that the stress tensor can be diagonalized or in other words one can find an appropriately oriented coordinate system in which only normal stresses occur. The conservation of momentum constrain is related to the stresses applied on tissue. The study of stresses is out of the scope of the current study and will not be analysed further.

Conservation of energy and heat equation

The conservation of energy states that the total energy in a closed system remains constant or that the total energy in an object equals the rate of energy flux into the body. In continuum mechanics the total energy of an object is analysed into the kinetic energy $K = \frac{1}{2} \iiint_V \rho \vec{u} \vec{u} dV$ and internal energy U which groups all other forms of energy such as heat, chemical or electromagnetic energy etc. of an object. The energy flux occurs with direct flow of heat into the body and mechanical power delivered by surface tractions (forces) of forces acting at a distance like gravity, electromagnetic force etc. The local conservation of energy equation or heat equation is

$$\rho \frac{\partial \epsilon}{\partial t} = \boldsymbol{\sigma} : (\nabla \vec{u}) - \nabla \vec{q} + \rho r \quad (3.4)$$

where ϵ is the specific internal energy (energy per unit mass), q is the heat flux vector (rate of heat per unit area transferred into the object) and r is the internal source of heat per unit mass at a point and symbol $:$ denotes the double tensor contraction operator ¹. The heat equation states that the temporal change of the specific internal energy of an object multiplied by its local density equals the sum of stress power minus the divergence of the heat flux plus the internal heat generation at a point. The heat equation describes the heat conduction in an object. *Heat conduction and energy transformation is out of the scope of the current study and the heat equation is mentioned rather for completeness.*

Conservation of mass and continuity equation.

The conservation of mass states that the mass of a continuum object remains constant over time, despite changes in shape, regional velocity, density and volume of the object. The continuity equation is

$$\frac{\partial}{\partial t} \iiint_V \rho dV + \oint_S \rho \vec{u} d\vec{S} = 0 \quad (3.5)$$

in the integral form and

$$\frac{\partial \rho}{\partial t} + \nabla(\rho \vec{u}) = 0 \quad (3.6)$$

¹ $A : B = \sum_i \sum_j A_{ij} B_{ij}$

in the differential form, where ρ is the density of the continuum material or myocardial tissue in this study, V is the studied volume of the tissue i.e. the left-ventricular volume, $\vec{u}$ the regional velocity of the continuum or regional tissue velocity in this study, S is the surface that encloses the volume V and ∇ is the divergence operator at a point of the continuum. The continuity equation states that the rate at which the mass enters a tissue area equals the rate at which the mass leaves the tissue area plus the accumulation of mass in the area. It also implies that in order for the velocity field to converge to a sink or diverge from a source point, the corresponding point must absorb or expel mass by changing its density over time.

- **Incompressibility property.**

If such temporal change in density does not apply ($\frac{\partial \rho}{\partial t} = 0$), which is the general case in tissue mechanics, then the continuity equation converts to the incompressibility equation that is

$$\nabla \cdot \vec{u} = 0 \quad (3.7)$$

The incompressibility property implies a divergence-free, besides continuous tissue velocity field. The incompressibility property is related to the tissue deformation and, thus, strain and strain-rate.

3.3.5. Myocardial (in)compressibility

Myocardial incompressibility is a much debatable property of the myocardial tissue and it is discussed below along with the related literature. Most soft tissues in the human body consist of water some of which is mobile causing small fluid shifts that behave like small density changes in the tissue continuum [211]. Because these fluid shifts are generally small, the majority of studies in tissue mechanics either regard the tissue slightly compressible [212, 213] or neglect the fluid shifts by regarding the tissue incompressible.

The incompressible behaviour of the unperfused passive myocardium was first supported by Vossoughi in 1980², who showed experimentally that the bulk change in volume is in the order of 10^5 bigger than the shear changes in volume. The incompressibility of the unperfused myocardium is explained

²Publication not available

by the fact that the fluids in the myocardial tissue excluding vasculature are not particularly mobile.

On the other hand, Yin [214] suggested in 1996 that the perfused myocardium behaves like a compressible continuum due to the vasculature that grids it. The vasculature constitutes 10-20% of the total myocardial volume and contains highly mobile blood, which causes larger blood shifts in the perfused myocardium than in other kinds of soft tissue. Yin showed that blood volume in the myocardial vasculature can fluctuate between 20-40% during myocardial contraction (or passive stretching of the myocardium), which is explained by the fact that during active contraction the vasculature is squeezed by the surrounding muscle extruding the contained blood. Since vasculature is part of the myocardial continuum, the blood volume fluctuations appear as density fluctuations of the myocardial continuum around the vasculature and, thus, Yin claimed that the perfused myocardium is compressible.

In computational modelling of the passive myocardium, the assumptions about its compressibility vary between regarding the myocardium incompressible and slightly compressible (quasi-incompressibility), with quasi-incompressibility to be often simplified to incompressibility in order to facilitate computations. Considering Vossoughi's statement of myocardial incompressibility, Guccione [47] published a study in 1991 on the canine left ventricle, where the passive myocardium was modelled as an incompressible, homogeneous, hyperelastic, transversely isotropic material. Similarly, two decades later Holzapfel and Ogden [48] modelled the passive myocardium also as an incompressible and non-homogeneous, orthotropic, non-linearly elastic material. Holzapfel and Ogden's model was integrated into a finite element formulation by Göktepe [49]; to avoid complications in the finite element analysis, Göktepe first regarded the myocardium strictly incompressible and then extended the finite element formulation for the case of quasi-incompressibility with tuneable compressibility level in order to take into consideration Yin's statement. Likewise, Gültekin [51] applied a similar simplification of myocardial quasi-incompressibility when modelling the passive myocardium as an orthotropic, viscoelastic material.

The variant compressibility of the (active and passive) myocardium was recently modelled by Soares [52] according to the observation that the myocardium is nearly incompressible in volume increase, but compressible

in volume reduction when active contraction occurs. Attributing quasi-incompressibility to the myocardium in active contraction, results showed that the otherwise underestimation of volume strain and overestimation of myocardial thickness and stress were avoided.

With regards to CMR image analysis, Bistoquet [215] claimed that myocardial deformation attributed to the blood volume fluctuations explained by Yin, are indiscernible with conventional CMR imaging. To the support of this claim, they pointed out that blood volume fluctuations are small relatively to the myocardial volume and, besides, distributed in all three orthogonal directions. Given the maximum thickness of the normal left ventricular myocardium at $14mm$, they pointed out that the myocardial continuum does not expand or contract by more than 2% in any direction, which is no more than $0.28mm$ in absolute value; this length is smaller than a voxel's smaller dimension in CMR imaging that is in the order of $1mm$, and thus smaller than the smallest deformation that can be captured by CINE MRI. Based on this Bistoquet supported that the myocardium appears incompressible in cine MRI, so they made use of the incompressibility constraint to recover the velocity field in the left ventricle from cine MRI data. Likewise, the incompressibility constraint had already been used by Song [216] in 1991 to reconstruct the velocity field in the heart from cine CT images³. Later Masood [158] applied the incompressibility constraint to restrict the deformation of virtual tags computed from TVM under a physically meaningful deformation boundary.

While in conventional CMR imaging the use of the incompressibility constraint has been adequately advocated, its applicability to TVM images can possibly be questioned. The incremental displacement that can be captured with TVM is approximately⁴

$$\Delta l_{min} = \frac{V_{enc}}{N_{\phi}} \Delta t = \frac{V_{enc}}{N_{\phi}} \frac{1}{N_f HR} \quad (3.8)$$

where V_{enc} is the maximum ENCodeD Velocity (V_{enc}), Δt is the time resolution, N_{ϕ} is the number of phase steps, N_f is the number of time frames and HR is the heart rate. Replacing parameters with the specifications of the TVM datasets acquired in this work, which are $V_{enc} = \pm 20cm/s$, $N_{\phi} =$

³Nowadays spatial resolution in CT can be as little as 0.5mm

⁴Velocity is assumed constant between frames.

$2047 \times 2 + 1, N_f = 50$ and average normal $HR = 68bpm$ [217], the incremental displacement depicted with TVM results $\Delta l_{min} \approx 0.0017mm$. This displacement is significantly smaller than the incremental displacement captured by cine imaging ($\sim 1mm$) and smaller than the mean regional displacement attributed to blood fluctuations between successive frames ($\sim 0.28mm \times \frac{2}{\pi} = 0.1783mm$)(See Proof A.2 in Appendix)

This means that myocardial motion can be measured in a significantly higher resolution with TVM than with conventional CMR setting blood volume fluctuations probably discernible. By applying the incompressibility constraint, there is a risk that myocardial deformation is underestimated when actual volume changes happen. On the other hand, TVM analysis benefits from the incompressibility constraint by means of penalising large unrealistic deformations [158], which likely originate from noise and other artefacts that are known to corrupt significantly the TVM measurements [170, 218]. In TVM imaging analysis there is, therefore, a trade-off in the applicability of the incompressibility constraint balancing between deformation errors due to volume changes underestimation and errors due to tissue velocity imaging artefacts, which needs further investigation.

3.3.6. Constitutive relations and tensor quantities

While the conservation laws apply on any tissue continuum independently from the tissue's mechanical properties, the constitutive relations are specific to each tissue and describe the tissue's characteristic behaviour under several conditions. The most popular constitutive equation is the equation for the general stress

$$\sigma = F/A$$

where F is the perpendicular force to the area A , the definition of the axial strain

$$\epsilon = \Delta L/L$$

as the relative change in length (L) of the tissue along the studied direction and the equation for the general elastic modulus

$$E_{mod} = \sigma/\epsilon$$

that relates the applied stress σ to the resulting strain ϵ . Expanding the latest equation to the three dimensions, it yields the strain-stress constitutive relation

$$\epsilon = cs$$

where c is the stiffness matrix. More constitutive relations can be found in [207, 208].

In three dimensions there are several combinations of strain and stress elements and, therefore, many types of elastic moduli can be defined including the three principal types that are the Young's modulus, the Shear modulus and the Bulk modulus. The Young's modulus (E) is defined along one axis and describes the tensile elasticity or the tendency of an object to deform along an axis when opposing forces are applied along that axis. The shear modulus or modulus of rigidity (G) describes an object's tendency to shear (change shape at a constant volume) when a shear stress is applied to it and it is the ratio of a shear strain over the corresponding shear stress. The bulk modulus (K) describes the object's volumetric elasticity, or the tendency of an object to deform in all directions when forces are applied uniformly in all directions, it is defined as the volumetric stress over volumetric strain and is the inverse of compressibility.

- **Strain, stress and stiffness tensors.**

In three dimensions, stress and strain are represented by second-order tensors that are 3×3 matrices. Tensor quantities have the advantage of being independent from the coordinate system where they are observed, but they may have different mathematical expression in each coordinate system. Second-order tensors describe the two-point measurements mentioned by [203]. One-point measurements like velocity, acceleration and force are described by the first-order tensors known as vectors, while mass and inertia are zero-order tensors or scalars. Stiffness c is a higher order tensor i.e. a four-order in the above case or equally a $3 \times 3 \times 3 \times 3$ matrix of 81 elements.

The strain tensor $\epsilon(x, y, z)$ describes the relative deformation in a neighbourhood of the pixel (x, y, z) and the stress tensor $\sigma(x, y, z)$ describes the forces per area applied in the same neighbourhood at an instance. The three diagonal elements are the *normal* strain or stress elements and express the relative deformation or force per area along the three axes; in this case

opposite forces cause deformation along the axis they are aligned to. The off-diagonal elements are the *shear* strain or stress elements; in this case opposite forces cause deformation along a different axis to the axis aligned with the forces. Shear stress and strain occurs in solid tissue but not fluids.

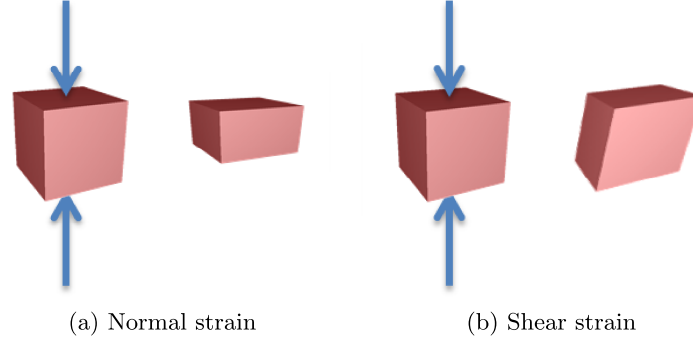


Figure 3.1.: Normal and shear strain.

Unlike strain and stress, the stiffness tensor (c) is a property of the material and depends on physical state variables such as temperature, pressure, microstructure. Due to inherent symmetry, the strain and stress tensors have at most 6 independent elements while the stiffness tensor has at most 21 independent elements out of the 81 elements.

- **Invariants.**

While the strain tensor has different expressions in the Cartesian and RCL coordinate system, its invariants are independent from the coordinate system and remain constant under transformation. The first invariant I_A is the trace of the strain tensor and always equals the sum of its eigenvalues

$$I_A = \sum_i \lambda_i$$

The eigenvalues are also called principal strains and quantify the relative deformation along the direction defined by the corresponding eigenvector. The third invariant of the strain tensor is defined as the product of its eigenvalues

$$III_A = \prod_i \lambda_i$$

For symmetric tensors like the strain tensor, the following invariant also applies

$$I_2 = \sum_{i \neq j} \lambda_i \lambda_j$$

and it is different from the second invariant II_A . The invariants I_A, II_A, III_A are the coefficients of the characteristic polynomial of the strain tensor.

- **Transformation of coordinate system.**

Coordinate transformation of a second-order tensor takes place with a double multiplication of the tensor with the transformation matrix and its transpose $\epsilon' = T\epsilon T'$. This multiplication is analogous to the $v' = Tv$ transformation for first-order tensors i.e. vectors v . For fourth-order tensors like the stiffness tensor, coordinate transformation takes place with the quadruple multiplication $c' = TTcT'T'$.

Any transformation of Cartesian coordinate system decomposes into a translation and rotation of the basis vectors. Rotation leaves the eigenvalues and thus invariants of the strain tensor unaffected but the tensor elements change in principle. Similarly, translation does not affect the eigenvalues and invariants of a tensor and in the case of strain tensor, in particular, translation does not affect the tensor elements either.

3.4. Deformable Continuum Kinematics: 3D deformation measures

In deformable continuum kinematics, motion refers to the movement of the material particles in space as well as the relative change of their positions within the continuum body with time. This motion, as explained earlier, can be decomposed into a translational, a rotational and a deformational component. The combination of the translational and rotational components constitutes the *rigid body* motion. Rigid body motion involves changes in the location and/or orientation of the body while the distance between any pair of points is maintained. For this, in rigid body motion the knowledge of 6 parameters, which usually are $[v_x, v_y, v_z, \omega_x, \omega_y, \omega_z]$, is sufficient to define the new locations of all points in the body. On the other hand, *deformation* implies changes in shape and/or size of the body and it occurs if and only if the distance between any pair of points changes. In this case, only

6 parameters are not enough to describe the new positions of all points in the deformable continuum body and, instead, a kinematics quantity defined per point is required.

Common kinematics quantities for the description of deformation are the *mapping function*, *displacement field*, *deformation gradient tensor*, *strain and strain rate tensors*; these quantities vary in terms of the motion components they carry, their computability and practicality as elaborated below.

Deformation measures

3.4.1. Mapping function

Assume a deformable continuum body i.e. the left-ventricular myocardium, consisting of an infinite number of material particles⁵. Each material particle of the body is located at a point in space⁶. The term *material* implies that each particle follows the motion of the body such that it changes location in *space* with time. Fixing the material particles of the body at points in space at an instance t yields a *configuration*⁷ Ω_t , such that the motion of the body can be seen as a sequence of configurations over time $\{\Omega_t\}$.

Assume a *reference configuration* Ω_0 and a *deformed configuration* Ω_t at an instance t ; the choice of reference configuration is arbitrary and, in this case, the initial configuration ($t = 0$) is selected. Let $\vec{X}$ denote the position of a material particle P in Ω_0 , and $\vec{x} = \vec{x}(t)$ the new position of P in Ω_t . The position vector $\vec{X}$ in $\{\Omega_0\}$ is an identifier of the material particle P or the so called *material point*. The sequence of configurations $\{\Omega_t\}$ can be described by the parametrised mapping function

$$\mathcal{X} : \Omega_0 \rightarrow \Omega_t, \text{ with } \vec{x} = \mathcal{X}(\vec{X}, t) = \vec{x}(\vec{X}, t), \forall X \in \Omega_0.$$

which associates each material point in Ω_0 to a spatial point in Ω_t at an instance t (see Figure 3.2). The position $\vec{X}$ of each material point in Ω_0 and

⁵Here a particle denotes a small portion of continuous matter rather than the Newtonian particle where mass is concentrated at a point.

⁶One should distinguish the two different notions of *body* and *space*

⁷ A configuration is strictly described by the set of material points within a body and their arrangement. Hereafter the arrangement of points within the body will be neglected in the mathematical usage of the term *configuration* Ω_t for simplicity. *Configuration* will be used to denote, instead, the finite set of points occupied by a body's material particles, which means $\Omega = \{\vec{x}^i\} \subset \mathbb{R}^3$.

the position $\vec{x}$ of each spatial point in Ω_t are expressed in reference to two generally different coordinate systems (fixed or convective as seen later); that are the *material* or *spatial coordinate* system. Notice the position vectors of the material and spatial points and thus the mapping function $\mathcal{X}$ depend on the coordinate system selected and specifically its origin.

If $\{O, \hat{E}_i\}_{i=1,2,3}$ describes the material coordinate system, then each material point is denoted as $\vec{X} = X_1\hat{E}_1 + X_2\hat{E}_2 + X_3\hat{E}_3$ and (X_1, X_2, X_3) are called the *material coordinates* of P . Analogously, if $\{o, \hat{e}_i\}_{i=1,2,3}$ describes the spatial coordinate system, then each spatial point is denoted as $\vec{x} = x_1\hat{e}_1 + x_2\hat{e}_2 + x_3\hat{e}_3$ and (x_1, x_2, x_3) are known as the *spatial coordinates* of the material particle P at time t . The material coordinate system is convenient in the Lagrangian specification wherein quantities are expressed at material points, whereas the spatial coordinate system is convenient in the Eulerian specification wherein quantities are expressed at spatial points. However, the notions *specification* and *coordinate system* are independent and do not necessarily imply each other, which means that any cross combination is possible.

To sum up the mapping function $\mathcal{X}$ carries the complete information for all three components of motion in the body (translational, rotational and deformational) and, thus, it provides a complete description of transformation between configurations. However, $\mathcal{X}$ depends on the coordinate system and specifically the placement of its origin and that hinders its usage as a measure of deformation. Driven by the need for a kinematics quantity that is invariant to the coordinate system where it is expressed, the following quantities have been introduced.

3.4.2. Displacement field

The vector that connects each material point in the reference configuration to the corresponding spatial point in the deformed configuration at time t is the displacement vector of the associated material particle. The vector field of all the displacements of all material particles in the body constitutes the displacement field of the body.

Assume the material and spatial coordinate systems as described above with the material coordinate system attached to the reference configuration Ω_0 and the spatial coordinate system attached to the deformed configuration

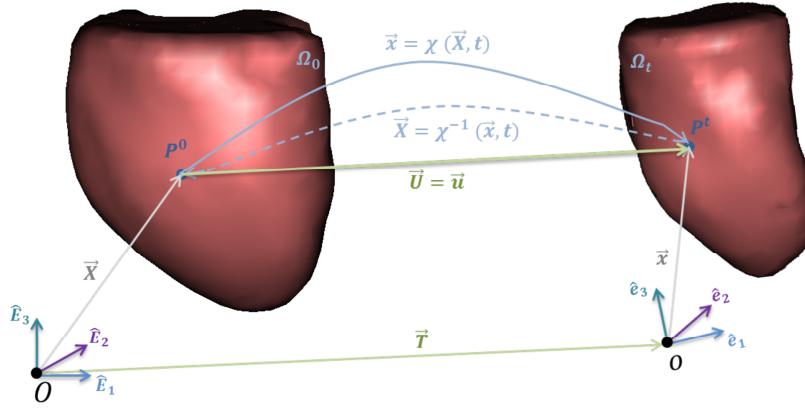


Figure 3.2.: Left ventricular myocardial surface reconstructed from a point cloud $\{P^i\}$ that has been extracted from a short-axis cardiac CT stack of images representing the myocardial volume. The material point $\vec{X}$ in the reference configuration Ω_0 is mapped to the spatial point $\vec{x}$ in the deformed configuration Ω_t via the mapping function χ .

Ω_t such that the latter follows the rigid body motion. If translational motion exists, the displacement vector $\vec{T}$ is the same for all material points and equals the distance of the origins O and o at each time t that is $\vec{T}(t) = \vec{O}o$. The displacement vector for each material particle is equal to $\vec{X} - \vec{x} + \vec{T}$ (see Figure 3.2) can be expressed in the Lagrangian or Eulerian specification and in the material or spatial coordinate system.

In the Lagrangian specification, recall that quantities are expressed at material points $\vec{X}$, so each material point $\vec{X}$ in Ω_0 moves to the spatial position $\vec{x} = \vec{x}(\vec{X}, t)$ in Ω_t and the associated displacement vector is

$$\vec{U}(\vec{X}, t) = \vec{x}(\vec{X}, t) - \vec{X} + \vec{T}(t) \quad (3.9)$$

which is expressed as $\vec{U}(\vec{X}, t) = \sum_{i=1}^3 U_i \hat{E}_i$ in the material coordinate system.

In the Eulerian specification, recall that quantities are expressed at spatial points, hence, a material particle located at the spatial point $\vec{x}$ in Ω_t comes

from the material point $\vec{X} = \vec{X}(\vec{x}, t)$ in Ω_0 . The associated displacement vector in this case is

$$\vec{u}(\vec{x}, t) = \vec{x} - \vec{X}(\vec{x}, t) + \vec{T}(t) \quad (3.10)$$

which is expressed as $\vec{u}(\vec{x}, t) = \sum_{i=1}^3 u_i \hat{e}_i$ in the spatial coordinate system.

The displacement vector and, thus, the displacement field are independent of the coordinate system or specification where they are expressed, which means that $\vec{U}(\vec{X}, t) = \vec{u}(\vec{x}, t)$ for every point and instance, and with this equality the above two relations are associated. However, the displacement field is not commonly used to describe tissue deformation because it interlaces deformational motion with rigid body motion and, besides, it provides motion information at each point disassociated from its neighbourhood rather than motion information in a region around each point, or as called here *regional* or *local* motion. For this reason, the *deformation gradient tensor* and its derived quantities have been established.

3.4.3. Deformation gradient tensor

The deformation gradient tensor quantifies regional motion in a deformable continuum body. The regional attribute comes from the fact that the tensor, unlike a vector field, allows for the description of motion in a small three-dimensional region around each point, as explained subsequently.

The deformation gradient tensor is mathematically derived from the equations for the displacement field and, accordingly, it is expressed in the Lagrangian or Eulerian specification. Taking the partial derivative of the displacement field with respect to the material coordinates, relation 3.9 yields

$$\nabla_{\vec{X}} \vec{U}(\vec{X}, t) = \nabla_{\vec{X}} \vec{x}(\vec{X}, t) - \mathbf{I} = \mathbf{F} - \mathbf{I} \quad (3.11)$$

where

$$\mathbf{H} = \nabla_{\vec{X}} \vec{U}(\vec{X}, t) \quad (3.12)$$

is the *material displacement gradient tensor* and

$$\mathbf{F} = \mathbf{F}(\vec{X}, t) = \nabla_{\vec{X}} \vec{x}(\vec{X}, t) \quad (3.13)$$

is the *material deformation gradient tensor* at a material point $\vec{X}$ at an

instance t . Similarly taking the partial derivative of the displacement field with respect to the spatial coordinates, relation 3.10 yields

$$\nabla_{\vec{x}} \vec{u}(\vec{x}, t) = \mathbf{I} - \mathbf{F}^{-1} \quad (3.14)$$

where

$$\mathbf{h} = \nabla_{\vec{x}} \vec{u}(\vec{x}, t) \quad (3.15)$$

is the *spatial displacement gradient tensor* and

$$\mathbf{F}^{-1} = \mathbf{F}^{-1}(\vec{x}, t) = \nabla_{\vec{x}} \vec{X}(\vec{x}, t) \quad (3.16)$$

is the *spatial deformation gradient tensor* at a spatial point $\vec{x}$ at an instance t . Since the Lagrangian specification is more popular in elastic solid mechanics, we will primarily focus on the Lagrangian expressions of quantities. With regards to the rigid body displacement, $\vec{T}$ is eliminated after differentiation of relations 3.9 and 3.10 to 3.11 and 3.14 respectively, that is to say the deformation gradient tensor remains unaffected by rigid body translation. For this reason and without loss of generality, translational motion will be dismissed in the following analysis. Furthermore, in the continuous regions of the myocardial field, the compatibility condition applies $\nabla \times \mathbf{F} = \mathbf{0}$.

For the intuitive interpretation of the deformation gradient tensor, two graphical descriptions based on differential line elements and infinitesimal hexahedron material elements, as well as a mathematical consideration are provided below.

Consideration of differential line elements.

The graphical interpretation of the deformation gradient tensor with the consideration of differential line elements is illustrated in Figure 3.3. Let an oriented differential line segment or *material vector* $d\vec{X}$ connecting two neighbouring material points at positions $\vec{X}$ and $\vec{X} + d\vec{X}$ in the reference configuration and $d\vec{x}$ the analogous vector connecting the corresponding spatial points at positions $\vec{x}$ and $\vec{x} + d\vec{x}$ in the deformed configuration; the term *material* again implies that the vectors travel along with the same set of material particles. The deformation gradient tensor $\mathbf{F}$ associates $d\vec{X}$ and

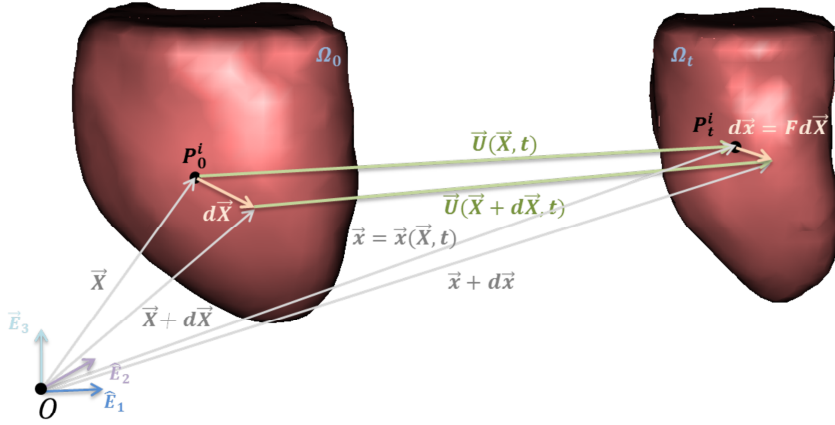


Figure 3.3.: The deformation gradient tensor $\mathbf{F}$ describes the reorientation and stretching of each differential line element from $d\vec{X}$ to $d\vec{x}$, while the continuum body is passing from the initial to the deformed configuration.

$d\vec{x}$ according to the relation

$$d\vec{x} = \mathbf{F}d\vec{X} \quad (3.17)$$

In other words, $\mathbf{F}$ describes the transformation of the differential material line segment $d\vec{X}$ emanating from $\vec{X}$ to the differential line segment $d\vec{x}$, while the continuum body is passing from the reference to the deformed configuration. Transformation of a material line segment implies its reorientation and/or elongation or shortening. (See Proof A.3 in Appendix A.)

Recalling relations 3.13 and A.1, $\mathbf{F} = \frac{\partial \vec{x}}{\partial \vec{X}} = \nabla_{\vec{X}} \vec{x}(\vec{X}, t)$. In the material coordinate system, this sets

$$\mathbf{F} = \begin{bmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{bmatrix} \quad (3.18)$$

If $d\vec{X} = dX_1\hat{E}_1 + dX_2\hat{E}_2 + dX_3\hat{E}_3$, relation 3.17 becomes

$$d\vec{x}_i = \frac{\partial x_i}{\partial X_1}dX_1\hat{E}_1 + \frac{\partial x_i}{\partial X_2}dX_2\hat{E}_2 + \frac{\partial x_i}{\partial X_3}dX_3\hat{E}_3, \text{ where } i = \{1, 2, 3\}$$

This means that $\mathbf{F}(\vec{X}, t)$ quantifies the relative length changes of the projections of the differential material line element $d\vec{X}$ onto the three axes of

the coordinate system, while the body is changing configuration from Ω_0 to Ω_t .

Consideration of the mapping function.

Relation 3.17 can be seen as a linear mapping of the material line element $d\vec{X}$ onto $d\vec{x}$. This is because for small changes $\mathbf{F}$ can be considered a linear vector-valued function, although $\mathbf{F}$ is non-linear in the general case. If $\mathbf{F}$ is linear, meaning that $\mathbf{F}$ is independent of $\vec{X}$ so each material vector is subject to the same transformation, then any material vector $\vec{M}$ emanating from $\vec{X}$ in Ω_0 is mapped to $\vec{m}$ in Ω_t via $\vec{m} = \mathbf{F}\vec{M}$. (See proof A.4 *Vector mapping* in Appendix A)

In the general case of non-linear mapping we have shown that $\mathbf{F} = \nabla_{\vec{X}}\vec{x}(\vec{X}, t)$ which is also the Jacobian matrix of the mapping function $\mathcal{X} : \Omega_0 \rightarrow \Omega_t, \vec{x} = \mathcal{X}(\vec{X}, t), \forall \vec{X} \in \Omega_0$. Due to the assumption of myocardial continuity, or piece-wise continuity meaning that cracks and voids do not open or close upon deformation, the Jacobian determinant is non-singular at all continuous points that is $\det(\mathbf{F}(\vec{X}, t)) \neq 0$ and, thus, at these points $\mathcal{X}$ has a differentiable inverse function $\mathcal{X}^{-1} : \Omega_t \rightarrow \Omega_0, \vec{x} = \mathcal{X}^{-1}(\vec{x}, t), \forall \vec{x} \in \Omega_t$, as illustrated in Figure 3.2. The Jacobian matrix of the inverse mapping function $\mathcal{X}^{-1}$ defined at the points of continuity is the spatial deformation gradient tensor $\mathbf{F}^{-1} = \nabla_{\vec{x}}\vec{X}(\vec{x}, t)$ as mentioned earlier (Equation 3.16). *From the properties of the Jacobian, many interesting properties of the deformation gradient tensor and derived measures evolve.*

Consideration of hexahedron material elements.

The graphical interpretation of the deformation gradient tensor with the consideration of hexahedron material elements is illustrated in Figure 3.4. Assume that the deformable continuum body is divided into infinitesimal material cubes in the initial configuration Ω_0 . Upon deformation, each material cube deforms into a generally non-cubic hexahedron in the deformed configuration Ω_t , as represented by Figure 3.4. The deformation gradient tensor $\mathbf{F}$ quantifies the deformation and rotation of each material cube in Ω_0 to its analogous hexahedron in Ω_t as this follows the body's motion.

Let each cube be unit and characterised by an orthonormal triad of material vectors $\{\hat{G}_1, \hat{G}_2, \hat{G}_3\}$ that form its edges. Following body motion, the

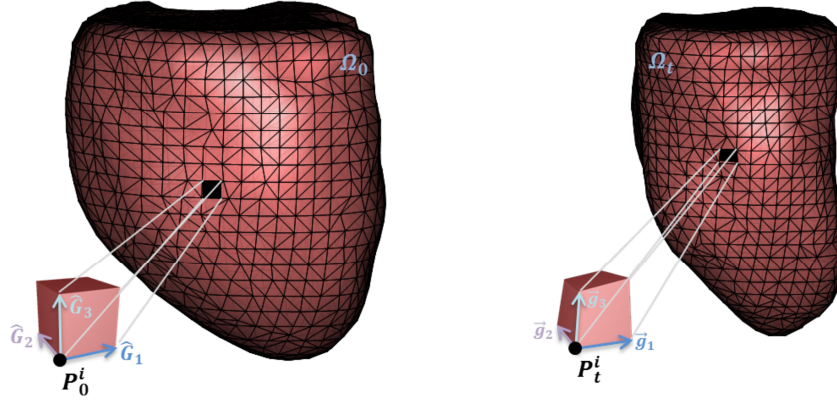


Figure 3.4.: The left ventricular myocardial tissue volume in Ω_0 is divided into infinitesimal (unit) material cubes following tissue deformation. The deformation gradient tensor $\mathbf{F}$ quantifies the change in shape and orientation of each infinitesimal material cube described by the orthonormal triad of vectors $\{\hat{G}_j\}_{j=1,2,3}$ to the analogous hexahedron with edge vectors $\{\vec{g}_j\}_{j=1,2,3}$, as a linear transformation of each $\hat{G}_j$ to the analogous $\vec{g}_j$, while the myocardium is changing configuration.

edge material vectors $\{\hat{G}_j\}_{j=1,2,3}$ transform to another triad of vectors $\{\vec{g}_j\}_{j=1,2,3}$ generally non-orthogonal and non-unit that form the edges of the analogous hexahedron in Ω_t . This transformation can be seen as a linear mapping of each material vector $\hat{G}_j$ to the analogous $\vec{g}_j$ such that the following relation applies

$$\vec{g}_j = \mathbf{F} * \hat{G}_j, \text{ where } j = \{1, 2, 3\} \quad (3.19)$$

This is equivalent to the change of basis between the orthonormal basis $\{\hat{G}_j\}_{j=1,2,3}$ to the basis $\{\vec{g}_j\}_{j=1,2,3}$. In this case the transformation gradient tensor $\mathbf{F}$ coincides with the related transformation matrix such that the j -th column of $\mathbf{F}$ is the vector of coordinates $\begin{bmatrix} g_{1j}, g_{2j}, g_{3j} \end{bmatrix}^T$ of $\vec{g}_j, j = 1, 2, 3$.

Therefore, the transformation gradient tensor $\mathbf{F}$ describes the transformation, meaning change in orientation and shape, of each infinitesimal material

cube comprising the deformable continuum body, while this is passing from the initial to the deformed configuration. (See proof A.4 in Appendix A.)

As the above interpretations illustrate, the deformation gradient tensor is a descriptor of regional motion in the deformable continuum. It quantifies the regional size, shape and orientation changes of the deformable continuum body between configurations, by means of encompassing the rotational and deformational components of motion in the body. With regard to translational motion, the deformation gradient tensor remains unaffected.

The deformation gradient tensor is a fundamental quantity from which other deformation measures i.e. strain and strain rate are derived. However, the deformation gradient tensor is not as commonly used as a measure of regional deformation in deformable continuum kinematics and, consequently, in myocardial tissue mechanics. The main reason is because it carries the information about deformation intertwined with rotation. Being generally not symmetric and two-point tensor, its mathematical manipulation is not as convenient either. To overcome the above hindrances, strain and strain rate tensors have been established to describe deformation, as elaborated hereinafter, and thus they have become popular in myocardial tissue mechanics and myocardial contractility studies.

Clarification on coordinate systems and specifications.

$\mathbf{F}$ is a two-point tensor because it associates two different coordinate systems (Equation A.10). In the definition and physical interpretation of deformation measures, we have mentioned four different coordinate systems so far that are summarised below.

1. $\{O, \hat{E}_i\}$ global Cartesian coordinate system defined with respect to the initial configuration, or *material coordinate system*.
2. $\{o, \hat{e}_i\}$ global Cartesian coordinate system defined with respect to the deformed configuration, or *spatial coordinate system*.

These two global coordinate systems can be selected to coincide. However, the spatial coordinate system (2) can be selected to follow rigid body motion such that the displacement vector $\vec{T}$ equals the rigid body translation and the axes follow the rigid body rotation. Global

Cartesian coordinate system (1) is usually selected in the Lagrangian specification, while global Cartesian coordinate system (2) is usually selected in the Eulerian specification. This is the origin of the terms *material coordinates* and *spatial coordinates*; accordingly, (1) and (2) will be called *material* and *spatial coordinate system* in this thesis. However Lagrangian or Eulerian specification do not necessarily mean material or spatial coordinate system!

3. $\{P_0^i, \hat{G}_i\}$ regional orthonormal coordinate system defined with respect to a material point in the initial configuration; its start is the material point P_0^i in the initial configuration and its axes are aligned to the edges $\hat{G}_i$ of the infinitesimal material cube around the material point. This is a regional coordinate system and while its start varies with material points, its axes can be selected to coincide with the global Cartesian coordinate systems (1).
4. $\{P_t^i, \vec{g}_i\}$ regional non-orthonormal coordinate system defined at the position of each material point in the deformed configuration with $\vec{g}_i$ being the mapping of the material edge vectors $\hat{G}_i$ onto the deformed configuration. It reflects material deformation in the Lagrangian specification, rather than being initially selected as a coordinate system. In the Eulerian specification this regional coordinate system is convenient to be selected such that its start is the spatial point P_t^i and $\vec{g}_i$ vectors set an orthonormal basis aligned to the global coordinate system (2). In this case the coupled coordinate system (3) is non-orthonormal with its axes following deformation.

3.4.4. Stretch tensor

As mentioned earlier, the deformation gradient tensor quantifies rigid body motion consisting of translation and rotation as well as deformational motion consisting of extension and shearing. The deformation gradient tensor is mathematically not easily manipulated as a non-symmetric, two-point tensor and, besides, it carries the information about deformation intertwined with rigid body translation. For these reasons, the deformation gradient tensor is not particularly used in deformable solid continuum kinematics and other quantities known as strain have been derived from it and established, instead, as described below.

Right and left stretch tensors.

At points of tissue continuity, where $\mathbf{F}$ is invertible with positive determinant $\det(\mathbf{F}) > 0$, the singular value polar decomposition theorem is fulfilled. This states that $\mathbf{F}$ can be decomposed into an orthogonal and a positive definite tensor that quantify rotation and deformation correspondingly. Decomposition can occur either with *right stretch* $\mathbf{U}$ first followed by rotation $\mathbf{R}$ or conversely with rotation $\mathbf{R}$ followed by *left stretch* $\mathbf{V}$ such that

$$\mathbf{F} = \mathbf{R}\mathbf{U} = \mathbf{V}\mathbf{R}$$

Both in *right* and *left polar decomposition*, the rotation tensor $\mathbf{R}$ is the same orthogonal tensor, meaning it has the properties $\det \mathbf{R} = 1$ and $\mathbf{R}^{-1} = \mathbf{R}^T$. The left and the right stretch tensors $\mathbf{U}$ and $\mathbf{V}$ are generally different from each other, both symmetric and unique as implied by the theorem.

Recall that $\mathbf{F} = \mathbf{F}(\vec{X}, t)$, is a function of material points $\vec{X}$ (Equation 3.13) and at the same time it associates the material and spatial coordinate systems like a two-point tensor. This means that, first of all, $\mathbf{R}$, $\mathbf{U}$ and $\mathbf{V}$ are also functions of $\vec{X}$. The attribute of $\mathbf{F}$ to associate two different coordinate systems is carried by $\mathbf{R}$ which is also a two-point tensor. On the contrary $\mathbf{U}$ and $\mathbf{V}$ are one-point tensors with $\mathbf{U}$ defined in the material coordinate system and $\mathbf{V}$ in the spatial coordinate system (while both defined at material points $\vec{X}$).

The stretch tensors notify the relative change in length of each infinitesimal material cube, which, in one dimension, would equal the ratio of the final to the initial length of a deformable material rod. The eigenvalues λ_i , where $i = 1, 2, 3$, of the stretch tensors are the maximum or *principal* stretches and they occur along the *principal directions* that are notified by the corresponding eigenvalues of the stretch tensors. Due to orthogonality of $\mathbf{R}$, $\mathbf{V} = \mathbf{R}\mathbf{U}\mathbf{R}^T$ and, thus, $\mathbf{U}$ and $\mathbf{V}$ have the same principal stretches but different principal directions, as expected from the fact that $\mathbf{U}$ and $\mathbf{V}$ are defined in different coordinate systems.

Cauchy-Green tensors.

Because polar decomposition can be a computationally complicated process, two other deformation tensors easily computed from $\mathbf{F}$ are derived using the

orthogonally property of the rotation vector $\mathbf{R}^T \mathbf{R} = \mathbf{R} \mathbf{R}^T = \mathbf{I}$. These are the *right* and *left Cauchy-Green* tensors defined as

$$\mathbf{C} = \mathbf{F}^T \mathbf{F} = \mathbf{U}^2$$

and

$$\mathbf{B} = \mathbf{F} \mathbf{F}^T = \mathbf{V}^2$$

correspondingly. In the Cartesian coordinate system their elements equal

$$C_{ij} = \sum_{k=1,2,3} \frac{\partial x_k}{\partial X_i} \frac{\partial x_k}{\partial X_j}$$

and

$$B_{ij} = \sum_{k=1,2,3} \frac{\partial x_i}{\partial X_k} \frac{\partial x_j}{\partial X_k}$$

respectively. As quadratics of $\mathbf{U}$ and $\mathbf{C}$, $\mathbf{B}$ and $\mathbf{C}$ are both rotation-free, symmetric, one-point tensors and functions of $\vec{X}$. $\mathbf{C}$ is defined in the material and $\mathbf{B}$ in the spatial coordinate system respectively.

For the physical interpretation of Cauchy-Green tensor, assume the material element $d\vec{x}$. The squared length of $d\vec{x}$ is

$$d\vec{x}^2 = d\vec{x}^T d\vec{x} = d\vec{X}^T \mathbf{C} d\vec{X}$$

which means that the right Cauchy-Green tensor $\mathbf{C}(\vec{X}, t)$ quantifies the square of length change of each material line element $d\vec{X}$ emanating from $\vec{X}$ and upon deformation. Since $\mathbf{C}$ and $\mathbf{B}$ are the quadratics of $\mathbf{U}$ and $\mathbf{V}$, their eigenvalues are the squares of the principal stretches λ_i that is λ_i^2 and, thus, they have the same invariants as $\mathbf{U}$ and $\mathbf{V}$.

Cauchy tensor.

Cauchy-Green tensors are quantities of the Lagrangian specification. The analogous of the left Cauchy-Green tensor $\mathbf{B} = \mathbf{F} \mathbf{F}^T = \mathbf{V}^2$ in the Eulerian specification could be considered the *Cauchy* tensor defined as

$$\mathbf{c} = \mathbf{F}^{-T} \mathbf{F}^{-1} = \mathbf{B}^{-1}$$

In the Cartesian coordinate system its elements are

$$c_{ij} = \sum_{k=1,2,3} \frac{\partial X_k}{\partial x_i} \frac{\partial X_k}{\partial x_j}$$

As implied by the derivation of the Cauchy tensor, it is defined at spatial points $\vec{x}$ expressed in the spatial coordinate system. As the inverse of $\mathbf{B}$, the eigenvalues of $\mathbf{c}$ are the inverse eigenvalues of $\mathbf{B}$ that is $1/\lambda_i^2$.

The stretch tensors $\mathbf{C}$, $\mathbf{B}$ and $\mathbf{c}$ are rotation-free. Furthermore, in the absence of motion they are equal to $\mathbf{I}$ and the same applies for the other stretch tensors as well as the deformation gradient tensor, as in $\mathbf{F} = \mathbf{U} = \mathbf{V} = \mathbf{B} = \mathbf{C} = \mathbf{I}$. A deformation measure that would null in the absence of motion would have a more intuitive interpretation. For this reason, strain has been introduced and established as the most popular quantity for the quantification of myocardial deformation.

3.4.5. Strain tensor

Like the stretch tensor, the strain tensor is not univocally defined. In theory a 3D strain tensor has infinite definitions, among which are the Lagrangian and Eulerian strain tensors.

The *Lagrangian* or *Green strain* tensor originates from the left Cauchy-Green stretch tensor, it is defined accordingly as

$$\mathbf{E} = \frac{1}{2}(\mathbf{C} - \mathbf{I}) \quad (3.20)$$

and it is expressed in the initial configuration.

The *Eulerian-Almansi* strain tensor originates from the right Cauchy stretch tensor, is defined as

$$\mathbf{e} = \frac{1}{2}(\mathbf{I} - \mathbf{B}^{-1}) = \frac{1}{2}(\mathbf{I} - \mathbf{c}) \quad (3.21)$$

and it is expressed in the current configuration respectively.

From equations 3.11 and 3.12, it applies $\mathbf{F} = \mathbf{I} + \mathbf{H}$, hence the Lagrangian strain tensor is equivalent to

$$\mathbf{E} = \frac{1}{2}(\mathbf{H} + \mathbf{H}^T + \mathbf{H}\mathbf{H}^T) \quad (3.22)$$

Likewise, from equations 3.14 and 3.15, $\mathbf{F}^{-1} = \mathbf{I} - \mathbf{h}$ and the Eulerian strain tensor becomes

$$\mathbf{e} = \frac{1}{2}(\mathbf{h} + \mathbf{h}^T - \mathbf{h}\mathbf{h}^T) \quad (3.23)$$

In Cartesian coordinates, the above equations are expressed as

$$E_{ij} = \frac{1}{2} \left(\frac{\partial U_i}{\partial X_j} + \frac{\partial U_j}{\partial X_i} + \sum_{k=1,2,3} \frac{\partial U_k}{\partial X_i} \frac{\partial U_k}{\partial X_j} \right)$$

$$e_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} - \sum_{k=1,2,3} \frac{\partial u_k}{\partial x_i} \frac{\partial u_k}{\partial x_j} \right)$$

Both the Langragian and Eulerian strain are one-point and symmetric tensors that are independent of rigid body motion null in the absence of motion. The Langragian strain tensor is expressed in the Langragian specification and the material (initial) coordinate system, whereas the Eulerian strain tensor is expressed in the Eulerian specification and the spatial (current) coordinate system. These quantities are particularly useful in TVM analysis.

Note that if the deformation and rigid body rotations are both small ($\mathbf{F} \approx \mathbf{I}$ and $\mathbf{R} \approx \mathbf{I}$), the second order terms in the above equation can be neglected without considerable error. In this case the Langragian and Eulerian strain tensors coincide and besides take the following linear form

$$\epsilon = \frac{1}{2}(\mathbf{F} + \mathbf{F}^T) - \mathbf{I} \approx \frac{1}{2}(\mathbf{H} + \mathbf{H}^T) \approx \frac{1}{2}(\mathbf{h} + \mathbf{h}^T)$$

expressed as

$$\epsilon_{ij} \approx \frac{1}{2} \left(\frac{\partial U_i}{\partial X_j} + \frac{\partial U_j}{\partial X_i} \right) \approx \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right)$$

in Cartesian coordinates. The strain tensor ϵ is called the *infinitesimal strain* tensor and it is also used as the linear approximation of the strain tensor in finite deformations. Unlike $\mathbf{E}$ and $\mathbf{e}$, ϵ is a two point tensor and contains rigid body rotational information and thus it does not follow the strict deformation of strain measure when applied in finite strain analysis. Other 3D strain tensors are the engineering or *Biot strain* tensor $\mathbf{E}_{eng} = \mathbf{U} - \mathbf{I}$, the logarithmic or *Henky strain* $\mathbf{E}_{log} = \ln \mathbf{U}$ and the *Almansi* strain tensor $\mathbf{E}_{alm} = \frac{1}{2}(\mathbf{I} - \mathbf{U}^{-2})$, which belong to the *Seth-Hill* family of 3D strain tensors described as $\mathbf{E}_m = \frac{1}{2m}(\mathbf{U}^{2m} - \mathbf{I})$ in the material coordinates.

3.4.6. Strain rate tensor

The strain rate tensor is directly computed from the deformation gradient tensor as

$$\dot{\mathbf{E}} = \frac{1}{2}(\dot{\mathbf{F}}_T \mathbf{F} + \mathbf{F}^T \dot{\mathbf{F}})$$

which is equivalent to

$$\dot{\mathbf{E}} = \mathbf{F}^T \mathbf{D} \mathbf{F}$$

where $\mathbf{D} = \frac{1}{2}(\mathbf{L}^T + \mathbf{L})$ is the rate of deformation and $\mathbf{L} = \nabla_{\vec{x}} \vec{V}$ is the velocity gradient tensor. The rate of deformation $\mathbf{D}$ is often used in place of the strain rate tensor in myocardial studies because it is easier to compute; however it does not possess the tensor properties i.e. it does not null in close deformation paths and may introduce errors in the analysis. However, it has been shown to be a convenient measure of deformation in several studies.

3.5. Analysis of discrepancy between strain definitions

The Seth-Hill generalised definition strain is a family of strain measures and hence, as mentioned, strain has multiple definitions. The Seth-Hill family includes the Lagrangian and Engineering strain which are often encountered in myocardial strain analysis; the selected strain definition is sometimes not clarified in myocardial studies, and this a possible source of discrepancy between different strain analysis studies [99, 146]. For small myocardial deformation this discrepancy is negligible, but for larger deformation like at mid systole and mid diastole, the discrepancy between the computed strain measures may be considerable and requires to be taken into consideration when assessing and comparing strain analysis results. The present section explores the discrepancy between the different strain measures of the Seth-Hill family and shows that discrepancy can be considerable. Analysis is performed for the axial strain and conclusions can be extended for the three dimensions.

3.5.1. The Seth-Hill family of axial strain

Axial strain describes the one dimensional fractional change in length of an object relative to its original length. Consider a homogeneous bar under-

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going one dimensional uniaxial length change δL from an initial length L_0 to a final length L . The Seth-Hill family of strain measures is a generalised definition of axial strain

$$\epsilon_\kappa = \begin{cases} \frac{\lambda^\kappa - 1}{\kappa}, & \kappa \in \mathbb{Z}^* \\ \ln \lambda, & \kappa \rightarrow 0 \end{cases}, \quad 0 < \lambda < \infty$$

The axial stretch λ is defined as the ratio of the deformed L to undeformed length L_0 that is $\lambda = \frac{L}{L_0} = 1 + \frac{\Delta L}{L_0} = 1 + g$, where $g = \frac{\Delta L}{L_0}$ is the displacement gradient [219, 220].

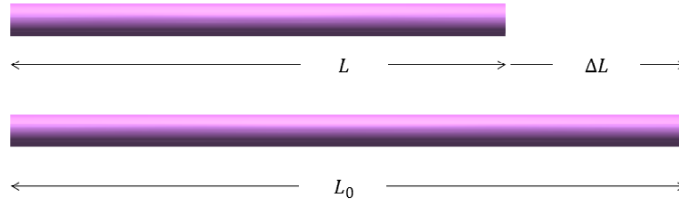


Figure 3.5.: Axial deformation ΔL of a rode of initial length L_0 and final length L .

The most commonly used axial strain measures are given for $\kappa = -2, -1, 0, 1, 2$ and are listed below.

Strain measure	Parameter k	Formula
Lagrange or Green	$\kappa = 2$	$\epsilon_{lag} = \frac{1}{2}(\lambda^2 - 1)$
Engineering or Biot	$\kappa = 1$	$\epsilon_{eng} = \lambda - 1$
Logarithmic or Henky	$\kappa = 0$	$\epsilon_{log} = \ln \lambda$
True or Swainger	$\kappa = -1$	$\epsilon_{true} = 1 - \frac{1}{\lambda}$
Almansi	$\kappa = -2$	$\epsilon_{alm} = \frac{1}{2}(1 - \frac{1}{\lambda^2})$

3.5.2. Discrepancy analysis

All Seth-Hill family strain measures are legitimate and equivalent; if stress can be written in terms of one strain measure, it can be written as a function of any other strain measure of Seth-Hill family. In the limit of infinitesimal deformation ($\Delta L \rightarrow 0 \Leftrightarrow \lambda \rightarrow 1$) all above measures are approximately equal to the Engineering strain $\epsilon_\kappa \approx \epsilon_{eng} = \lambda - 1$ as given by the two term Taylor series expansion of ϵ_κ around $\lambda = 1$. As deformation becomes larger,

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the discrepancy between Seth-Hill strain measures increases and it should be taken into consideration when comparing strain values of different or unknown strain measures. We define the relative discrepancy ξ between two strain measures of the Seth-Hill family as the ratio

$$\xi = \frac{\epsilon_\kappa - \epsilon_\mu}{\epsilon_\mu}, \quad \kappa \in \mathbb{Z} \quad \text{and} \quad \kappa > \mu$$

Below we prove that ξ is approximately equal to

$$|\xi| \approx \frac{|\lambda - 1||\kappa - \mu|}{2}, \quad \kappa, \mu \in \mathbb{Z} \quad \text{and} \quad \kappa > \mu$$

for small (not infinitesimal) deformations $|\frac{\Delta L}{L_0}| \ll 1 \Leftrightarrow |\lambda - 1| \ll 1$

• **Proof.**

The absolute value of relative discrepancy between 2 strain measures of Seth-Hill family of κ and μ order respectively is

$$|\xi_{\kappa\mu}| = \left| \frac{\epsilon_\kappa - \epsilon_\mu}{\epsilon_\mu} \right| = \left| \frac{\epsilon_\kappa}{\epsilon_\mu} - 1 \right|, \quad \kappa, \mu \in \mathbb{Z}$$

First we examine the case of non-logarithmic strain measures. For $\kappa, \mu \neq 0, \epsilon_k = \frac{\lambda^k - 1}{\kappa}$ and ξ becomes

$$\xi_{\kappa\mu} = \frac{\frac{\lambda^\kappa - 1}{\kappa} - \frac{\lambda^\mu - 1}{\mu}}{\frac{\lambda^\mu - 1}{\mu}}, \quad \kappa, \mu \in \mathbb{Z}^*$$

Suppose small deformation in the sense that change of length ΔL or displacement of points are assumed smaller than any relevant dimension $|\Delta L| \ll |L_0| \Leftrightarrow \left| \frac{\Delta L}{L_0} \right| \ll 1 \Leftrightarrow |\lambda - 1| \ll 1$. The three term Maclaurin series expansion of $f\left(\frac{\Delta L}{L_0}\right) = \left(1 + \frac{\Delta L}{L_0}\right)^\kappa = \lambda^\kappa$ is

$$\left(1 + \frac{\Delta L}{L_0}\right)^\kappa \approx 1 + \kappa \frac{\Delta L}{L_0} + \frac{\kappa(\kappa - 1)}{2} \left(\frac{\Delta L}{L_0}\right)^2$$

Hence the relative discrepancy $\xi_{\kappa\mu}(\Delta L)$ becomes approximately

$$\begin{aligned} \xi_{\kappa\mu} &= \xi_{\kappa\mu}(\Delta L) \approx \frac{\frac{1 + \kappa \frac{\Delta L}{L_0} + \frac{\kappa(\kappa-1)}{2} \left(\frac{\Delta L}{L_0}\right)^2 - 1}{\kappa} - \frac{1 + \mu \frac{\Delta L}{L_0} + \frac{\mu(\mu-1)}{2} \left(\frac{\Delta L}{L_0}\right)^2 - 1}{\mu}}{\frac{1 + \mu \frac{\Delta L}{L_0} + \frac{\mu(\mu-1)}{2} \left(\frac{\Delta L}{L_0}\right)^2 - 1}{\mu}} = \\ &= \frac{\left[\frac{\Delta L}{L_0} + \frac{\kappa-1}{2} \left(\frac{\Delta L}{L_0}\right)^2\right] - \left[\frac{\Delta L}{L_0} + \frac{\mu-1}{2} \left(\frac{\Delta L}{L_0}\right)^2\right]}{\frac{\Delta L}{L_0} + \frac{\mu-1}{2} \left(\frac{\Delta L}{L_0}\right)^2} = \frac{\frac{\kappa-\mu}{2} \frac{\Delta L}{L_0}}{1 + \frac{\mu-1}{2} \frac{\Delta L}{L_0}} \end{aligned}$$

Since $\left|\frac{\Delta L}{L_0}\right| \ll 1$, it can be assumed that $1 + \frac{\mu-1}{2} \frac{\Delta L}{L_0} \approx 1$ and the absolute value of relative discrepancy $|\xi_{\kappa\mu}(\Delta L)|$ is approximated to

$$|\xi_{\kappa\mu}(\Delta L)| \approx \frac{|\Delta L| |\kappa - \mu|}{2L_0} = \frac{|\lambda - 1| |\kappa - \mu|}{2}, \quad \kappa, \mu \in \mathbb{Z}^* \quad \text{and} \quad |\Delta L| \ll L_0$$

Similarly we will prove that the above approximation is also valid in case of Logarithmic strain. Suppose $\mu = 0$, the 0-th order Seth-Hill strain is $\epsilon_0 = \epsilon_{\log} = \ln \lambda$ and the relative discrepancy $\xi_{\kappa 0}$ becomes

$$\begin{aligned} \xi_{\kappa 0}(\Delta L) &= \frac{\epsilon_\kappa - \epsilon_0}{\epsilon_0} = \frac{\frac{\lambda^\kappa - 1}{\kappa} - \ln \lambda}{\ln \lambda} = \frac{\frac{(1 + \frac{\Delta L}{L_0})^\kappa - 1}{\kappa} - \ln \lambda (1 + \frac{\Delta L}{L_0})}{\ln \lambda (1 + \frac{\Delta L}{L_0})} = \\ &= \xi_{\kappa 0}(\Delta L), \quad \kappa \in \mathbb{Z}^* \end{aligned}$$

The three term Maclaurin series expansion of $f(\frac{\Delta L}{L_0}) = \ln \lambda(1 + \frac{\Delta L}{L_0})$ is

$$\ln \lambda(1 + \frac{\Delta L}{L_0}) \approx 0 + \frac{\Delta L}{L_0} - \frac{1}{2}(\frac{\Delta L}{L_0})^2$$

and, therefore, the relative discrepancy $\xi_{\kappa 0}(\Delta L)$ becomes approximately

$$\xi_{\kappa 0}(\Delta L) \approx \frac{[\frac{(1+\kappa\frac{\Delta L}{L_0} + \frac{\kappa(\kappa-1)}{2}(\frac{\Delta L}{L_0})^2 - 1)}{\kappa}] - [\frac{\Delta L}{L_0} - \frac{1}{2}(\frac{\Delta L}{L_0})^2]}{[\frac{\Delta L}{L_0} - \frac{1}{2}(\frac{\Delta L}{L_0})^2]} = \frac{\frac{\kappa}{2}\frac{\Delta L}{L_0}}{1 - \frac{\Delta L}{2L_0}}$$

Similar as above for $|\frac{\Delta L}{L_0}| \ll 1$ the denominator $1 - \frac{1}{2}\frac{\Delta L}{L_0} \approx 1$ and, therefore, the absolute value of relative discrepancy $|\xi_{\kappa 0}(\Delta L)|$ is approximated to

$$|\xi_{\kappa 0}(\Delta L)| \approx \frac{\kappa}{2}|\Delta L| = |\xi_{\kappa \mu}(\Delta L)|_{\mu=0}, \quad \kappa \in \mathbb{Z}^* \quad \text{and} \quad |\Delta L| \ll L_0$$

We have shown that for small deformation ΔL the absolute value of relative discrepancy between two strain measures of Seth-Hill family of κ and μ order respectively is given by

$$|\xi_{\kappa \mu}(\Delta L)| \approx \frac{|\Delta L|}{2} = \frac{|\lambda-1||\kappa-\mu|}{2} = |\hat{\xi}_{\kappa \mu}(\Delta L)|, \quad \kappa, \mu \in \mathbb{Z} \quad \text{and} \quad |\Delta L| \ll L_0$$

Hence, the absolute discrepancy is $|\epsilon_k - \epsilon_\mu| \approx \frac{|\kappa-\mu|}{2}\epsilon_\mu|\lambda-1| \geq \frac{1}{2}\epsilon_\mu|\lambda-1| = \frac{1}{2}\epsilon_\mu|g|$ for small deformation.

$$|\epsilon_k - \epsilon_\mu| \geq \frac{1}{2}\epsilon_\mu|g| \tag{3.24}$$

This means that if a strain measure ϵ_κ is assumed in place of ϵ_μ , the systematic error introduced is approximately $\frac{|\kappa-\mu|}{2}\epsilon_\mu|g|$ which means it is in the order of magnitude of $\epsilon_\mu|g|$. Consequently if a study reports strain values without specifying the strain measure ϵ_μ , the strain values can be trusted only up to their α^{th} decimal digit where $\alpha = |\text{order of magnitude of } \epsilon_\mu| + |\text{order of magnitude of } g| - 1$.⁸ Therefore, in order to compare strain values with the unknown values of ϵ_μ , all strain values should first be rounded

⁸Definition of the order of magnitude: If x can be written in the form $x = X * 10^n, 0 < X < 10$, the order of magnitude of x is n .

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around their α^{th} decimal digit.

As an example, let's assume stretch of $\lambda = 1.012345 = 1 + 0.012345$ which corresponds to displacement gradient $g = \lambda - 1 = 0.012345$ with measurement accuracy of 5 significant digits. The corresponding axial strain measures of 2, 1 and 0 order are $\epsilon_{lag} = 0.012421$, $\epsilon_{eng} = 0.012344$ and $\epsilon_{log} = 0.012269$ respectively. It can be observed that ϵ_{lag} , ϵ_{eng} and ϵ_{log} agree only up to the 3rd decimal digit ($\alpha = |-2| + |-2| - 1 = 3$) and we can securely say that $\epsilon \approx 0.012$ regardless the strain measure taken into consideration out of the above three. It can be noticed that although the accuracy of length measurements ($g = \frac{\Delta L}{L_0} = 0.012345$) is 5 significant digits, the accuracy of ϵ drops to 2 significant digits if the strain measure is not defined.

The following table gives the real discrepancy $\xi_{\kappa\mu}$ where $\kappa, \mu \in \mathbb{Z}^*$ and $\kappa > \mu$ between the most commonly used axial strain measures as a function of λ .

λ, κ	2	1	0	-1
1	$\xi_{21} = \frac{\lambda-1}{2}$			
0	$\xi_{20} = \frac{\lambda^2-1}{2\ln\lambda} - 1$		$\xi_{10} = \frac{\lambda-1}{\ln\lambda} - 1$	
-1	$\xi_{2-1} = \frac{1-\lambda}{2\lambda}$	$\xi_{1-1} = \lambda - 1$	$\xi_{0-1} = \frac{\lambda\ln\lambda}{\lambda-1} - 1$	
-2	$\xi_{2-2} = \lambda^2 - 1$	$\xi_{1-2} = \frac{2\lambda^2}{\lambda+1} - 1$	$\xi_{0-2} = \frac{2\lambda^2\ln\lambda}{\lambda^2-1} - 1$	$\xi_{-1-2} = \frac{\lambda-1}{\lambda+1}$

The plot in Figure 3.6 shows the real relative discrepancy ξ and the approximated relative discrepancy $\hat{\xi}$ between strain measures of various positive orders for four different deformations, $g = 0.1, -0.1, 0.01, -0.01$ respectively. It can be observed that the larger the deformation g or the order difference $|\kappa - \mu|$ of strain measures the larger the real and estimated discrepancies and the larger the distance between them. For tension ($\Delta L > 0 \Leftrightarrow g > 0 \Leftrightarrow \lambda > 1$) real discrepancy ξ is larger than estimated discrepancy $\hat{\xi}$ and the opposite applies for compression ($\Delta L < 0 \Leftrightarrow g < 0 \Leftrightarrow \lambda < 1$). For negative values of κ, μ the discrepancy $\xi_{\kappa\mu}(\lambda)$ can be calculated using the property $\xi_{-\kappa-\mu}(\lambda) = \xi_{\kappa\mu}(1/\lambda)$, which is proven as

$$\xi_{-\kappa-\mu}(\lambda) = \frac{\frac{\lambda^{-\kappa}-1}{-\kappa}}{\frac{\lambda^{-\mu}-1}{-\mu}} - 1 = \frac{\left(\frac{1}{\lambda}\right)^{\kappa}-1}{\frac{\left(\frac{1}{\lambda}\right)^{\mu}-1}{\mu}} - 1 = \xi_{\kappa\mu}(1/\lambda)$$

The plot in Figure 3.7 shows the relative discrepancy ξ over the stretch

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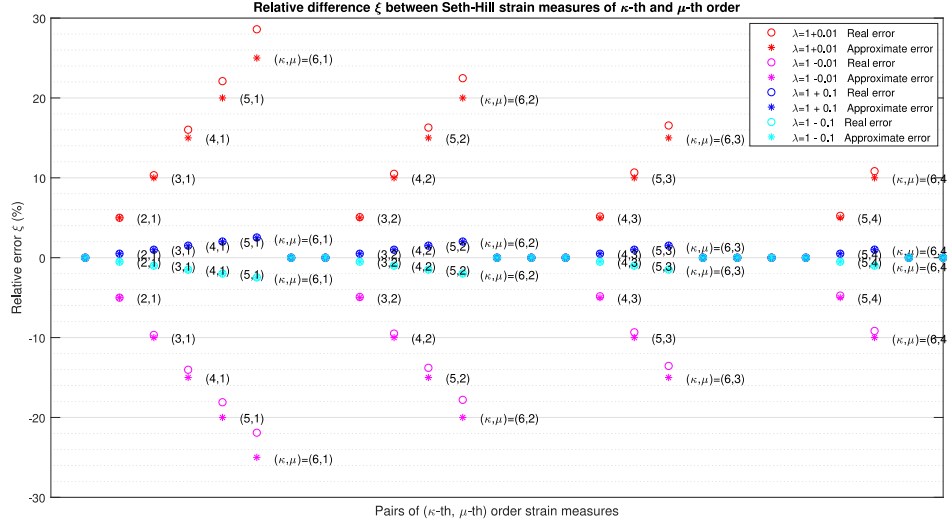


Figure 3.6.: Discrepancy between Seth-Hill strain measures.

λ . It can be observed that the larger the deformation (λ further from the value of 1) the larger the discrepancy. Also all curves of real discrepancy $\xi_{\kappa\mu}(\lambda)$ are tangent to the lines $\frac{|\lambda-1|}{2}$.

It can be seen and proved that

$$\xi_{\kappa\mu}(\lambda) \geq \hat{\xi}_{\kappa\mu}(\lambda) = \frac{(\lambda-1)(\kappa-\mu)}{2} \geq \frac{\lambda-1}{2},$$

where $2 > \lambda > 1 \Leftrightarrow \Delta L > 0$ and $\kappa, \mu \in \mathbb{Z}^*, \kappa > \mu > 0$

$$\frac{1-\lambda}{2} \leq |\xi_{\kappa\mu}(\lambda)| \leq |\hat{\xi}_{\kappa\mu}(\lambda)| = \frac{(1-\lambda)(\kappa-\mu)}{2},$$

where $\lambda < 1 \Leftrightarrow \Delta L < 0$ and $\kappa, \mu \in \mathbb{Z}^*, \kappa < \mu < 0$

Therefore, it can be concluded the relative discrepancy $\xi_{\kappa\mu}$ is larger than half the displacement gradient $|g|$ for $(\lambda-1)(\kappa-\mu) > 0$.

According to recent studies [145] the maximum normal myocardial deformation is estimated at about $g = 40\%$, which transcends the case of small deformation. Around those values the discrepancy between different strain measures is significant, for example the Lagrangian strain is 16% less than the Engineering strain and the Engineering strain is 60% less than the

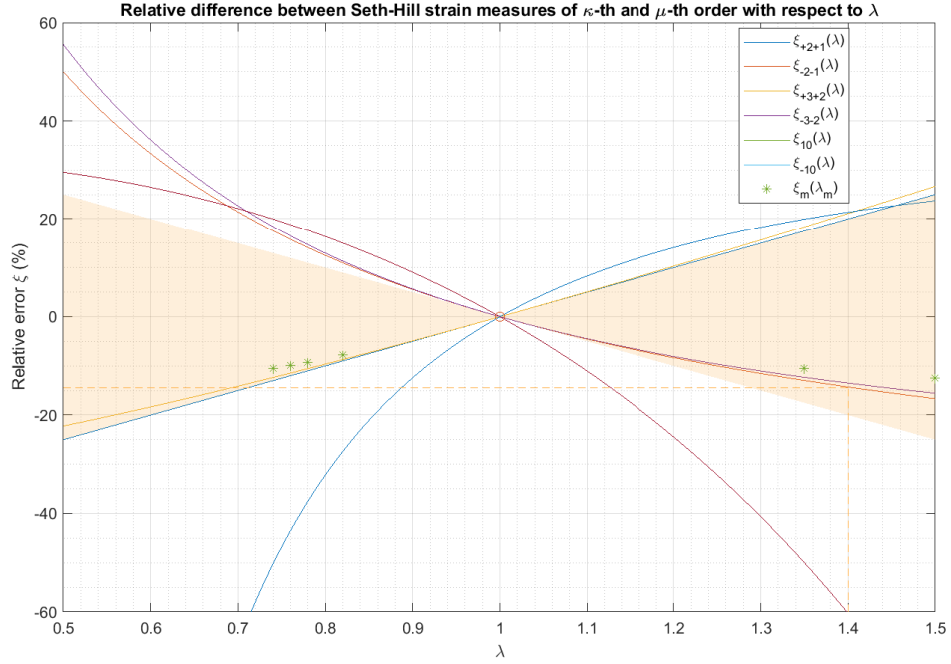


Figure 3.7.: Discrepancy between Seth-Hill strain measures for different values of axial stretch.

Logarithmic strain.

In this section we have presented the various definitions of axial strain and we have calculated the relative discrepancy between different strain measures of Seth-Hill family. Also we have provided a simpler estimate of the relative discrepancy for small deformation and we have given graphical and numerical examples. As a conclusion, when comparing strain measures from different studies, it is advised to take into consideration systematic errors caused by different definitions of strain. To avoid such errors researchers should be diligent about giving a clear definition of strain in their work.

3.5.3. Application to myocardial strain

According to the meta-analysis studies of Petitjean [99] and Yingchoncharoen [146], the maximal normal segmental myocardial strain has been reported to reach a value of 52 % in the radial direction, 26 % in the circum-

ferential direction and 22 % in the longitudinal direction with considerable variations across the participated studies. The largest segmental myocardial strain averaged over all studies has been calculated by Petitjean as 35 % for the radial direction 24 % for the circumferential direction and 18 % for the longitudinal direction.

On the grounds that the strain formulas ϵ_m are unknown, belong to the Seth Hill family and do not (all) coincide, the minimal expected discrepancy among them is given by the above inequality $\hat{\xi} \geq \frac{1}{2}\epsilon_m|g|$. The deformation measure $g = (k\epsilon_m + 1)^{1/m} - 1$ is also unknown in this case and thus we will apply the approximation $g \approx \epsilon_m$. Hence the above relation gives $|\hat{\xi}_{min}| \approx \frac{1}{2}\epsilon_m^2$ as the minimum estimated absolute discrepancy. For each aforementioned strain value, the minimum estimated discrepancy is given in the second column of the following table. The third column presents the corresponding discrepancy values $|\hat{\xi}_m|$ in absolute values, computed in the same way as the curves on Figure 3.7 and minimised across the examined (κ, μ) pairs; λ is here approximated with $1 + \epsilon_m$ in analogy to the above approximation. The difference between the two estimates of minimum absolute discrepancy $|\hat{\xi}_{min}|$ and $|\hat{\xi}_m|$ is attributed to, firstly, the looser low boundary that was set while simplifying the discrepancy inequality to the relation 3.24 and, secondly, to the approximation of g with ϵ_m . $|\hat{\xi}_m|$ is expected to provide a tighter low boundary to the real absolute discrepancy and, in fact, it is observed that $|\hat{\xi}_m|$ is considerably higher than $|\hat{\xi}_{min}|$ for most analysed strain values. For this reason, the minimum absolute discrepancy between strain measures is updated with the $|\hat{\xi}_m|$ values, while $|\hat{\xi}_{min}|$ is suitable to use for faster, despite less accurate, calculations.

Table 3.5.3 presents the largest and average peak normal myocardial strain for the radial, circumferential and longitudinal directions as reported in the literature [99] in the first column, the minimum estimated absolute strain discrepancy computed with the approximating formula in the second column and the minimum estimated absolute strain discrepancy given by the numerical study in the third columns. The results show that for a moderate peak normal radial strain of 35%, the minimum absolute discrepancy between the different Seth-Hill strain formulas is 10.5%. Similarly, for a moderate peak normal circumferential strain of 24%, the minimum absolute discrepancy is 9.9% and for a moderate peak normal longitudinal strain of 18%, the minimum absolute discrepancy is 7.8%. The strain discrepancy

Table 3.1.: Minimum estimated absolute discrepancy between strain values from different Seth Hill measures for the peak myocardial segmental strain reported in the literature.

	$\epsilon_m(\%)$	$ \hat{\xi}_{min} (\%)$	$ \hat{\xi}_m (\%)$
Max strain			
Radial	52	13.5	12.6
Circumferential	-26	3.4	10.5
Longitudinal	-22	2.4	9.2
Average of max strain			
Radial	35	6.1	10.5
Circumferential	-24	2.9	9.9
Longitudinal	-18	2.6	7.8

values are comparable to the measured strain values as their first significant digits lie at the same decimal ($35/10.5$) or close ($24/9.9$, $18/7.8$).

The above results show considerable estimated minimum discrepancy between different strain formulas for the levels of peak segmental myocardial strain reported in the literature. This means that unless the strain formula is known, the peak myocardial strain results cannot be trusted beyond their first significant digit and for large myocardial deformations uncertainty lies even in the first significant digit. This is an important finding, if we take into consideration that peak myocardial strain is a critical clinical indicator for myocardial disease. The above results confirm Yingchoncharoen's claim that a potential source of difference between myocardial strain analyses is the different approach to the calculation of strain. It also confirms our claim that the selection of strain formula needs to be clarified and taken into consideration when assessing and comparing strain analysis studies in order to avoid formula-related systematic errors.

3.6. Conclusions and Overview

This theoretical chapter has aimed at a more comprehensive and thorough description as well as quantification of myocardial contractility. A definition for myocardial contractility has been provided and the most common global and regional contractility measures encountered in myocardial studies have been reviewed. Contractility is a rather ambiguous term and its description has been endowed with concepts and quantities from the field of deformable

continuum mechanics. We have discussed the similarity of myocardial tissue to a continuum based on previous observations on myocardial anatomy and function and we have concluded that the myocardial tissue resembles a continuum that is potentially disrupted by sparse discontinuities; these discontinuities do not affect the applicability of the continuum mechanics principles at least across the continuous myocardial areas. Incompressibility is a much debatable property of the myocardium, which we have discussed in detail based on the available literature and we have concluded that although a degree of compressibility exists and should be taken into consideration, the incompressibility constraint has shown to improve myocardial deformation analysis in several studies because it compensates for measurement errors.

Myocardial contractility has been approached as three dimensional myocardial motion and deformation and quantities have been transferred from deformable continuum kinematics for its description. While the mapping function, displacement field and deformation tensor are well defined, the concepts of three dimensional strain and strain rate can be rather confusing. This is because the strain tensor has multiple different definitions, it is described in two specifications and spatial coordinate systems and, furthermore, it has been represented with a number of different derived scalars. Along these lines, strain has been defined inconsistently across studies and this impacts the deformation analysis assessment and comparison. We have attempted to clarify all the above concepts and provide an intuitive description for each involved quantity.

Moreover, we have performed a quantitative theoretical analysis of the discrepancy between different definitions of strain and we have shown that the strain error attributed to the selection of a different strain formula among the studied ones can reach the order of 10.5% in the radial direction, 9.9% in the circumferential direction and 7.8% in the longitudinal direction at maximum myocardial contraction, while the error may be negligible for small deformations. The establishment of a standardised definition for 3D myocardial strain is recommended for a more consistent inter-study myocardial deformation analysis.

4. Segmental analysis: improvement of consistency

4.1. Introduction

Segmental analysis has been popular in left ventricular myocardial contractility studies, as elaborated in Chapter 2 (section 2.2.4 and paragraph *Image analysis*). Segmental contractility analysis discards the excessive information and projects the contractility indices onto standardised maps of the LV, allowing for a fast intuitive assessment of contractility and inter-subject comparison. Furthermore, the averaging of pixel values to segmental values attenuates the effect of noise and other high frequency image artefacts on the contractility maps. The 17-segment AHA model has been established as a standardised model for the segmental contractility analysis of the LV and has been widely accepted in TVM analysis; published studies present velocity maps from clinical animals [24, 139], healthy human subjects [17, 22, 23, 142] and patients [73, 140, 143] of different sex [19] and age [19, 22, 140] groups. The basic guidelines of the AHA model [6] were clarified further by a supplementary report [15] that focuses on the division of myocardial segments with respect to the long axis and circumference of the LV. However, there still exist several obscure details with regard to the segmental division across the different frames and slices of a left ventricular stack, and these details determine the consistency of segmental analysis.

Segmental analysis requires myocardial segmentation and segmental division requires further the detection of the two IV as well as the central axis of the LV, which set the three reference points or *anatomical landmarks* on each short-axis image. Motion analysis is commonly performed in the heart's RCL coordinate system rather than the scanner's XYZ Cartesian coordinate system and conversion from XYZ to RCL coordinates is also affected by the position of the centre of the LV. Segmentation masks

and anatomical landmarks vary across the TVM images and anatomical landmarks in particular occupy different positions across different frames mainly because of the heart's (twisting) motion. Myocardial segmentation and landmark detection affect the segmental analysis and, besides, they are challenging tasks to perform especially on the big number of TVM images usually involved in myocardial studies. The aforementioned contractility studies do not explain how they perform these tasks and, therefore, it is likely that they straight project a steady segmental division onto multiple TVM images without taking into consideration the individual anatomical characteristics on each image. Moreover, although segmental analysis attenuates the effect of measurement errors in principle, it may be affected by extreme values like those that lie in myocardial segmentation residuals and like the phase wrapping artefacts; outlier alleviation is therefore another requirement in TVM segmental analysis.

The current chapter aims at the improvement in the consistency of segmental myocardial contractility analysis by presenting a complete and improved framework that addresses the challenges for accurate detection of the left ventricular anatomical landmarks, accurate myocardial segmentation and outlier measurement alleviation. Interactive tools for accelerated and accurate detection of anatomical landmarks and myocardial contours are presented, and a texture based method for the further correction of myocardial segmentation is proposed. Furthermore, the variation of anatomical landmarks across the TVM images is investigated in order to evaluate their role for an accurate segmental analysis. The XYZ and RCL AHA segmental maps are constructed with the proposed segmental analysis framework from 10 TVM datasets of the normal heart and the improvement of their consistency is assessed by means of agreement among the segmental velocity patterns over the 10 TVM datasets.

4.2. Framework and image pre-processing

4.2.1. Pipeline

The proposed framework for the segmental analysis of myocardial TVM velocities is described by the following pipeline (Figure 4.1), which also contains the TVM pre-processing steps.

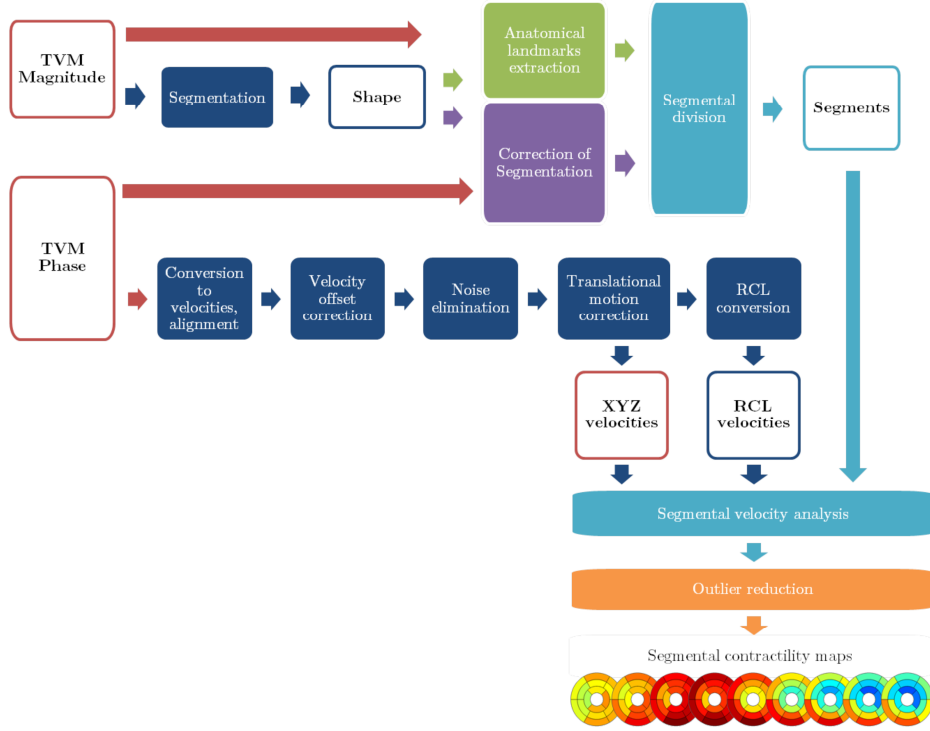


Figure 4.1.: Proposed framework for segmental myocardial velocity analysis.

4.2.2. TVM pre-processing

The TVM images are segmented to yield the left ventricular myocardial masks and volume. For this, the TVM magnitude images are selected because they contain clearer myocardial information than the corresponding TVM phase images and, besides, they are aligned to them; a cine SSFP dataset would provide images of better quality to segment but it would also require registration to the TVM dataset. For segmentation we have developed automatic methods based on graph-cuts and non-rigid registration, but for the following experiments we have preferred a semi-automatic segmentation in order to minimise the segmentation errors. Towards this, we have developed an interactive tool for semi-automatic segmentation that is presented below and use it to extract the myocardial masks.

The other pre-processing steps aim at the improvement of the myocardial velocity images that are used as input in the segmental analysis; these include phantom correction for background offset errors, image denoising with the TV restoration method developed and presented analytically in a

next chapter and velocity correction for translational motion with a novel method that is also presented in a following chapter.

4.2.3. Myocardial division

The division of the myocardium into segments is performed according to 17-segment AHA model, described in detail in Chapter 2 (section 2.1.2 *Left ventricular orientations and segments*) and visualised with the bull's eye plot shown in Figure 2.9 from the literature. The 17-segment model was introduced in 2002 by the American Heart Association [6] as a consensus for the division of the left ventricle into distinct segments, in order to enable the standardised quantification and visualisation of cardiac indices and, thus, facilitate intra-subject and cross-modality comparison. According to the AHA guidelines, the LV is portioned along its long axis into the *base*, the mid-cavity, the *apex* and the *apical cap*. The apical cap is extended from the tip of the epicardium to the start of the endocardium and it forms the 17th segment itself. The remainder of the LV up to the level of the mitral valve is divided into three levels with identical thickness along the long axis [15], which are adapted to the cardiac cycle meaning that slices can alternate levels along the cardiac cycle. Each one of these three portions is divided further into 16 pairwise equiangular circumferential *segments* or *wedges* using the RV-LV junctions, named also *IV*, as reference points [15]; the 16 segments are the *basal* and *mid anterior*, *anteroseptal*, *inferoseptal*, *inferior*, *inferolateral* and *anterolateral* segments and the *apical anterior*, *septal*, *inferior* and *lateral* segments. In Figure 4.2 we provide an intuitive illustration of the correspondence between the left ventricular 3D myocardial regions and the segments of the AHA plots.

4.2.4. TVM datasets

The segmental analysis framework proposed in the current chapter is evaluated on TVM datasets from 10 healthy volunteers. Each subject was scanned on a Siemens 3 Tesla scanner (MAGNETOM Skyra, Siemens AG Healthcare Sector, Germany) with the spiral PC-MRI sequence described in [23]. For each subject, 9 contiguous short-axis slices were acquired with 1.7×1.7 mm in-plane spatial resolution (reconstructed to 0.85×0.85 mm), 8 mm slice thickness, 20 cm/s and 30 cm/s in-plane and through-plane V_{enc}

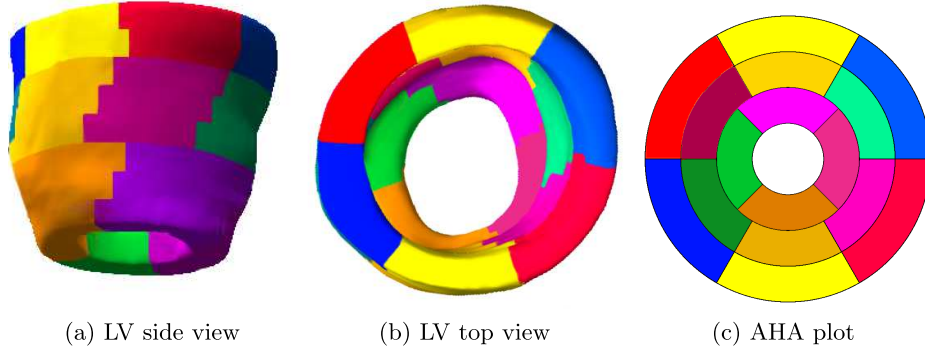


Figure 4.2.: Mapping between the left ventricular myocardial volume and the AHA plot. For the extraction of the left ventricular volume, a stack of cine SSFP was automatically segmented and visualised in MATLAB. The automatic segmentation was performed with a novel method based on graph-cuts that we have developed for CMR image segmentation (see *Appendix D*).

respectively. 50 frames per slice were reconstructed covering a full cardiac cycle and equally spaced through it. Blood flow and respiration artefact were suppressed with a black blood preparation pulse and breath-hold acquisitions. The datasets cover the base, mid-cavity and apex but not the apical cup of the LV allowing for 16-segment instead of 17-segment maps. The lack of the apical cap does not affect the proposed segmental framework and its evaluation, hence we will keep the term (17-segment) AHA model to ensure terminology consistency.

4.3. Anatomical landmarks

The division of the myocardium into segments is performed with reference to the positions of both IV. The centre of the LV as a third reference point contributes to the accuracy of the segmental division, despite not being necessary. It is necessary though in the conversion of velocities from the XYZ to the RCL coordinate system. Figure 4.4 presents the scheme of segmental division according to the AHA guidelines [6,15] for the basal and mid slices; pairs of equiangular circumferential segments or wedges rather than six fully equiangular wedges are generated.

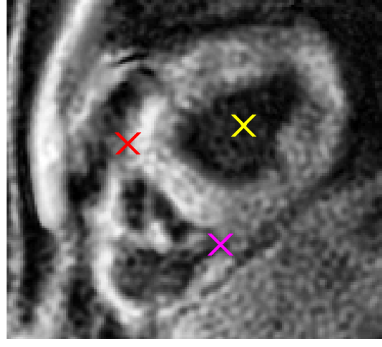


Figure 4.3.: Left ventricular anatomical landmarks.

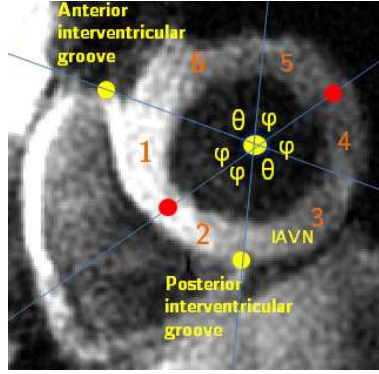


Figure 4.4.: The role of the left ventricular anatomical landmarks in the division of the short axis slices for formation of the AHA plots.

4.3.1. Centre of LV

Instead of manual marking, we propose to estimate the centre of the LV automatically as the centre of left ventricular myocardial mass by applying the relation $\vec{C} = \sum_i m_i \vec{r}_i$ onto each short axis slice, where $\vec{r}_i$ is the position of the i^{th} pixel weighted by the corresponding value m_i in the associated myocardial mask. The mean radius R of the LV is also computed as the mean Euclidean distance between the i^{th} pixel and the centre of the LV. Figure 4.5 shows the clusters of estimated LV centres per slice for all slices of a TVM stack. Examples of the estimated centre of the LV per TVM image are included in Figure 4.13.

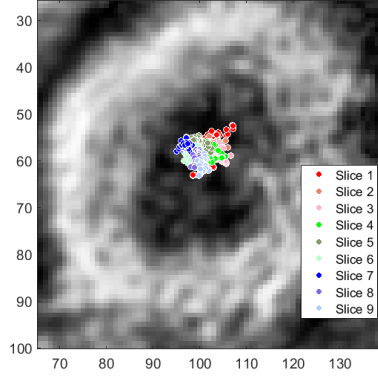


Figure 4.5.: Cluster of the estimated LV centre per slice and frame of a TVM dataset.

4.3.2. Interventricular grooves

The Interventricular grooves (IV) are the septal points of connection between the LV and the RV, they are distinguished into the PI and the Anterior Interventricular groove (AI) and they lie across the longitudinal dimension of the LV. In the short axis plane, they appear as small distinct regions or points and they constitute two of the few anatomical landmarks in the almost symmetric LV. The IV landmarks serve as reference points for the division of the myocardial wedges in short axis images, hence their role is important in the accuracy of segmental analysis and for this we investigate the need for their accurate detection with the following analysis.

- **Methods.**

Because of the low quality (poor contrast and high noise) of the TVM magnitude images, the automatic detection of the anatomical landmarks is quite challenging and, for this, we prefer the accuracy of semi-manual marking. To obtain the IV landmarks, we have developed an interactive tool in Matlab which facilitates and accelerates the manual marking of the IV points. For this part of segmental analysis, we have applied the IV tool to mark the IV positions in the TVM magnitude images for the 10 TVM datasets and we use this data to investigate the variability of the IV positions across the slices and frames of each dataset. We downsampled the number of frames for processing by a factor of 5 and we interpolated the

intermediate points with Catmull-Rom splines to yield smooth IV trajectory estimates. We also plotted the time courses of the IV coordinates for all slices. We use these trajectories and time courses to assess the mobility of the IV landmarks (variability across frames) and compare the IV mobility for the different slices of each stack. Besides the variability across frames, IV positions vary also across slices in the same stack.

- **Results.**

We first generated the clusters of IV points per slice for one TVM stack and for a few stacks and the corresponding centroids shown in Figure 4.6. The total variance of the AI position is 4.0px in the horizontal and 8.6px

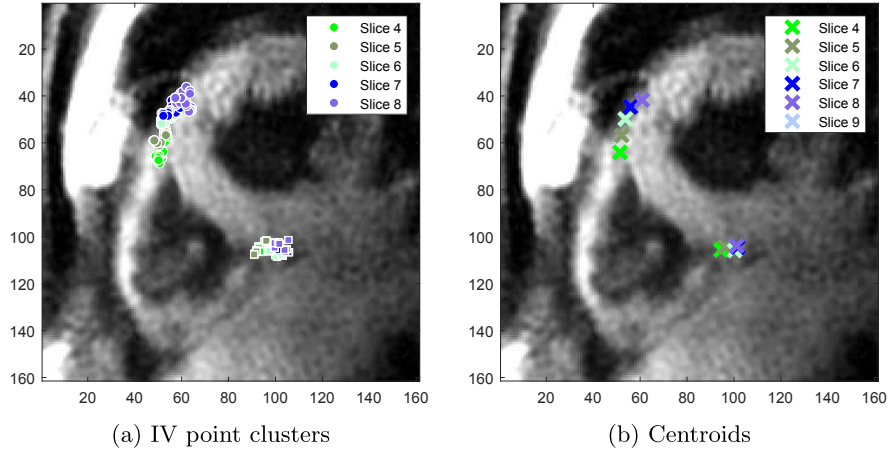


Figure 4.6.: Clusters and centroids of the IV points per slice for a normal TVM dataset.

in the vertical dimension and the corresponding values for the PI position are 5.0px and 3.4px. From the total variance and Figure 4.6 it can be observed that the PI position varies less than the AI position across the TVM dataset. This can be attributed to the higher mobility of the AI, the geometry of the LV or the poor image contrast around the AI area which increases the uncertainty in the detection of the AI point. Hence, if, for simplicity, one reference point is selected to be considered for the division of the myocardial wedges, we recommend this to be the PI point. The variance of the PI position across the slices of the stack are presented in Table 4.1. The apical slices (1-3) seem to show lower variance, which is expected as

Table 4.1.: Standard deviation (px) of the PI position coordinates along the horizontal and vertical image dimension.

Slice	1	2	3	4	5	6	7	8	Total
Horizontal dim	2.0	2.2	3.5	2.7	4.2	2.9	3.0	2.3	5.1
Vertical dim	1.7	1.4	0.6	1.7	2.0	1.5	1.2	1.07	3.4

the apex moved less than the base.

Figures 4.7 and 4.8 present the analysis of the PI positions and mobility for two TVM datasets, one with slice alignment and one with slice misalignment as revealed by their long axis views in Figures 4.9(b) and 4.10(b). Figures 4.7 and 4.8 show the clusters of PI points per slice, the corresponding centroids, the trajectories interpolated with Catmull-Rom Splines and the time courses of the in-planar PI position coordinates for all slices. The time courses of PI positions show higher fluctuation in the base as compared to the apex, attributed to the larger motion as well as the higher uncertainty in the localisation of the PI reference point in the apex compared to the base. The uncertainty in the detection of the PI points even in manual or semi-manual marking arises not only from poor image quality but also because the IV grooves are small regions rather than singles points and the selection of one point is sometimes equivocal. The cluster plots and time courses in Figures 4.7 and 4.8 indicate that although the PI displacements are small in principle, the distance between the furthest PI traces in time can be considerable i.e. between the max clockwise and anticlockwise rotation. The centroid plots show the variance of PI points across slices attributed to the geometry of the LV and occasional to patient's movement. When slices are aligned, the centroids lie also in a line or 2^{nd} degree curve following the natural geometry of the LV.

- **Conclusion.**

From the above analysis it is concluded that the IV positions vary across the images of a TVM stack and this needs to be taken into consideration for an accurate segmental analysis. We have developed and provide the tools for inspection and marking of the reference points across the TVM images. Several observed deviations in the following analysis are attributed to slice

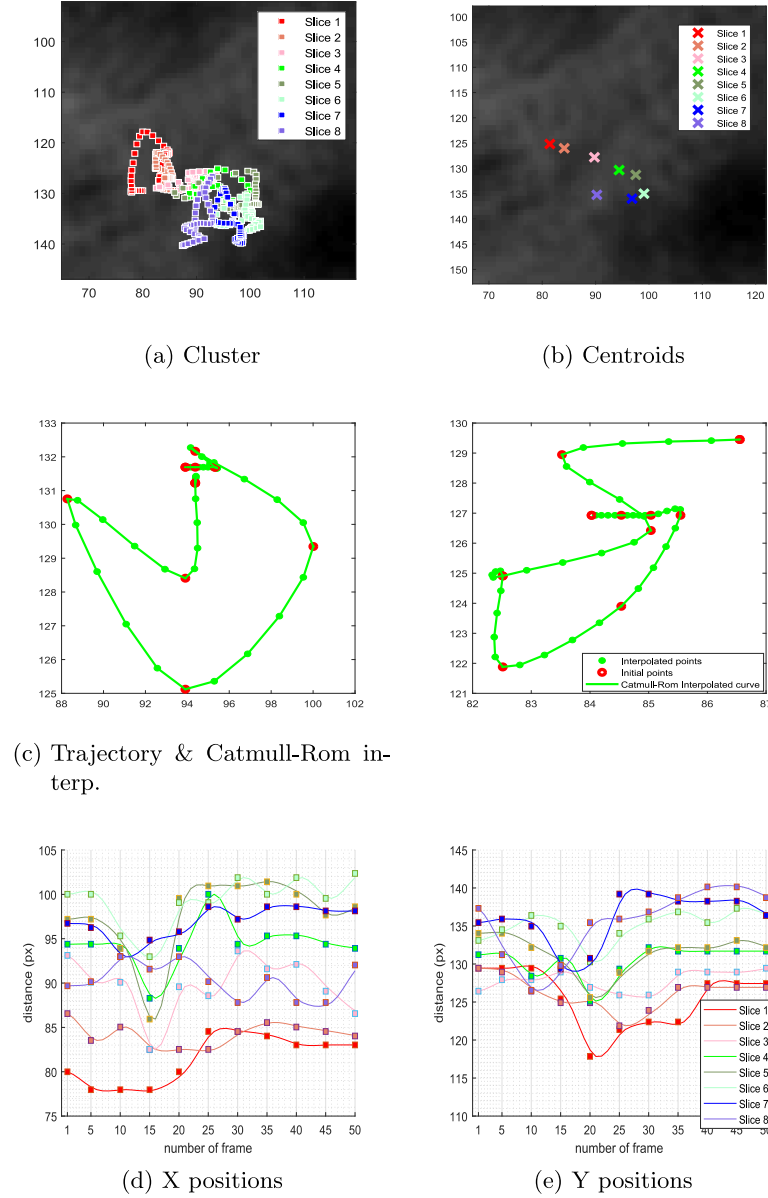


Figure 4.7.: Posterior interventricular groove (PI) positions and trajectories for the Subject 4 TVM dataset. The positions across the slices and frames are displayed as PI point clusters per slice (a) and the corresponding centroids per slice (b); each PI point colour encodes a slice and the colour changes gradually from red to green to indicate the slice location along the long axis. The PI trajectories (c) are inferred with Catmull-Rom interpolation on PI control points from a sample of the 50 frames per slice and the PI trajectories from two slices of the stack are presented as an example. The in-planar x and y PI coordinates are plotted per slice (d and e) following the same colour coding as above. These plots are used in the analysis of location and PI mobility.

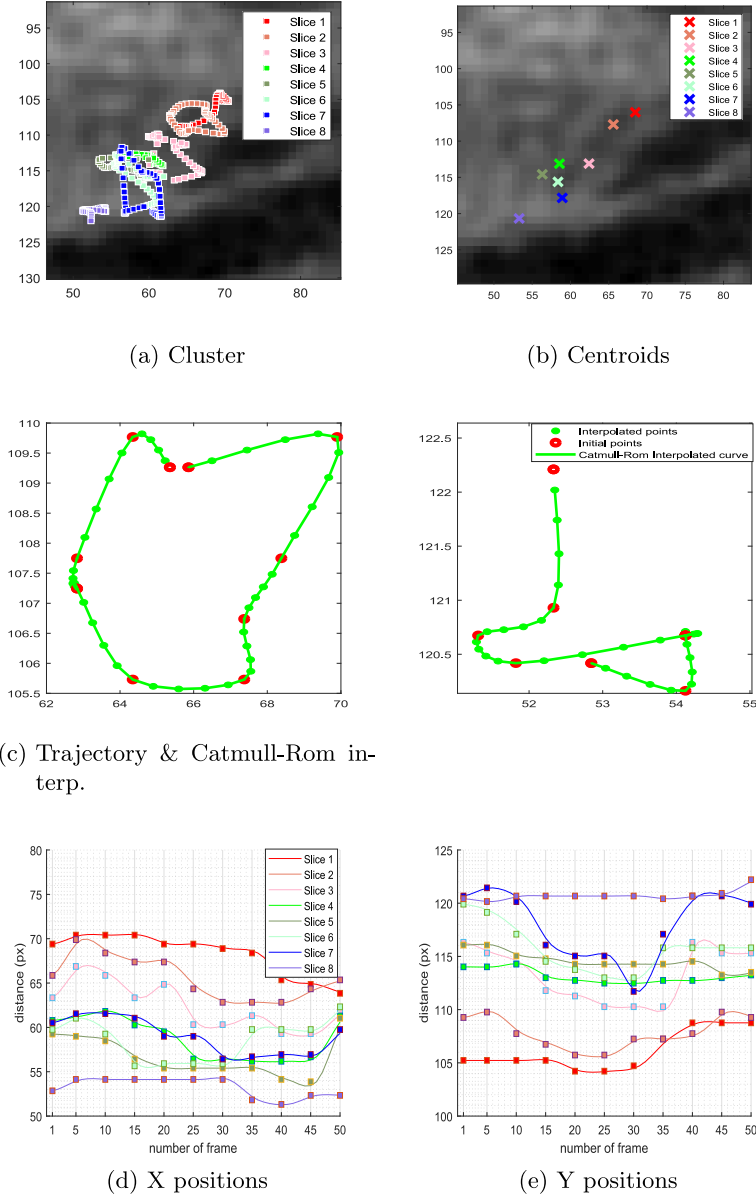


Figure 4.8.: Posterior interventricular groove (PI) positions and trajectories for the Subject 5 TVM dataset. The positions across the slices and frames are displayed as PI point clusters per slice (a) and the corresponding centroids per slice (b); each PI point colour encodes a slice and the colour changes gradually from red to green to indicate the slice location along the long axis. The PI trajectories (c) are inferred with Catmull-Rom interpolation on PI control points from a sample of the 50 frames per slice and the PI trajectories from two slices of the stack are presented as an example. The in-planar x and y PI coordinates are plotted per slice (d and e) following the same colour coding as above. These plots are used in the analysis of location and PI mobility.

misalignment elaborated below.¹

4.3.3. Slice alignment

IV variability across slices is partially attributed to the LV geometry and its orientation with respect to the acquisition plane, but it can also result from slice misalignment, i.e. due to the patient's movement during the acquisition. To further assess the source of IV slice variability in each case, we plotted the centroids of the centre of the LV in the longitudinal views, projected the epicardial contours on the short axis plane, and generated 3D visualisations for the stack of myocardial masks. We also composed the TVM images into a continuous stack incorporating a module for the interactive selection and visualisation of any three orthogonal slices; we used this tool primarily to reconstruct the long axis views of the LV from the short-axis images and study any slice misalignment.

Results from the aligned and a misaligned TVM stack analysed in the previous section are shown in Figures 4.9 and 4.10. Figure 4.11 shows the 3D visualisations of the myocardial masks for the fast qualitative assessment of misalignment in five TVM stacks including the above two stacks. While stacks 1 and 6 show good slice alignment, Subjects 3 and 5 seem to have moved considerably during the image acquisition; this impacts the location of the anatomical landmarks in the images as well as the 3D visualisation of the LV as shown in Figure 4.12.

The above results show that slice misalignment is likely to occur and affects the location of the anatomical landmarks within the TVM images. This observation enforces the statement that accurate detection of the anatomical landmarks is necessary for an accurate segmental analysis.

4.3.4. Myocardial wedges results

We performed segmental myocardial division on the 10 TVM image datasets using the anatomical landmarks tracked with the methodology suggested above. The results from a basal, mid and apical slice for one subject at key phases of the cardiac cycle are presented in Figure 4.13 along with the corresponding mean Magnitude of velocity AHA (M-AHA) maps. Figures

¹An interesting observation is that the PI trajectories do not necessarily resemble ellipses or closed curves, as expected and considered by other studies.

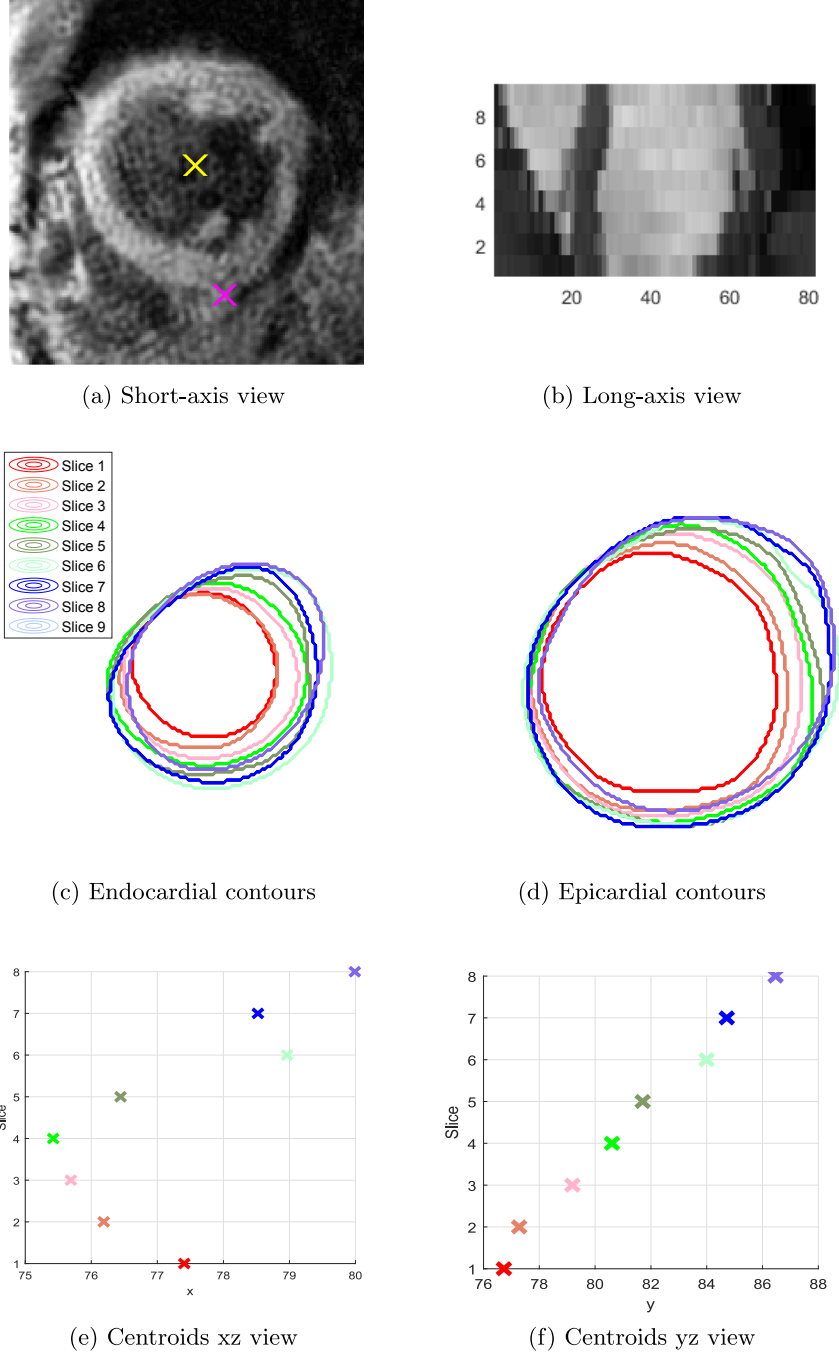
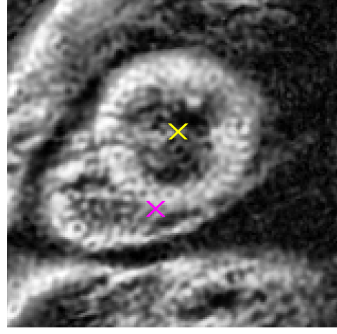
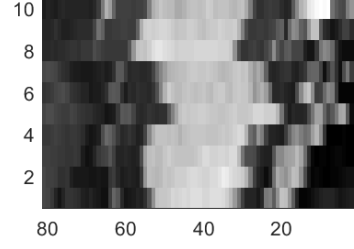


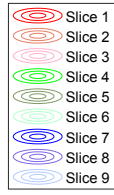
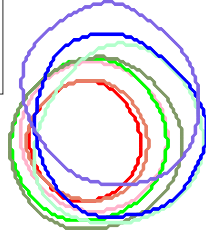
Figure 4.9.: Estimated positions of the LV centre in the Subject 4 TVM dataset for the assessment of slice alignment. This is an example of slice alignment as indicated by the long axis view (b). The slice alignment is confirmed and quantified by the endocardial (c) and epicardial (d) contour projections on the XY short-axis plane as well as the XZ and YZ long axis views (e and f) of the centroids. Subject 3 is the same subject analysed and presented in Figure 4.7.



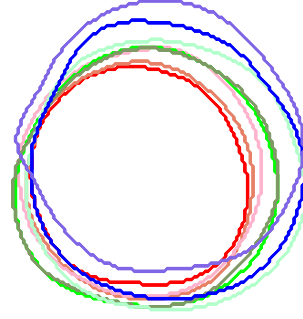
(a) Short-axis view



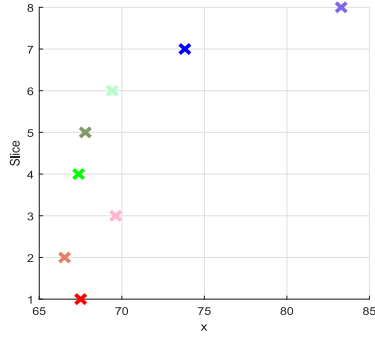
(b) Long-axis view



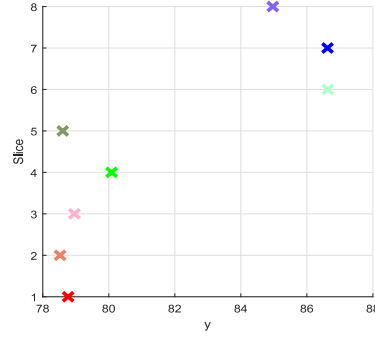
(c) Endocardial contours



(d) Epicardial contours



(e) Centroids xz view



(f) Centroids yz view

Figure 4.10.: Estimated positions of the LV centre in the Subject 5 TVM dataset for the assessment of slice alignment. This is an example of slice misalignment as indicated by the long axis view (b). The slice misalignment is confirmed and quantified by the endocardial (c) and epicardial (d) contour projections on the XY short-axis plane as well as the XZ and YZ long axis views (e and f) of the centroids. Subject 5 is the same subject analysed and presented in Figure 4.8.

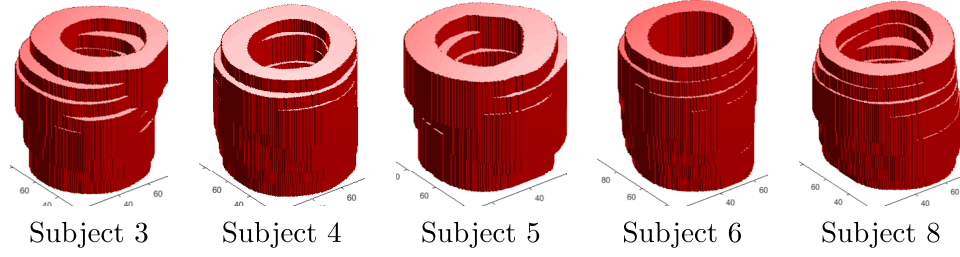


Figure 4.11.: Visualisation of the TVM stack for the assessment of slice alignment.

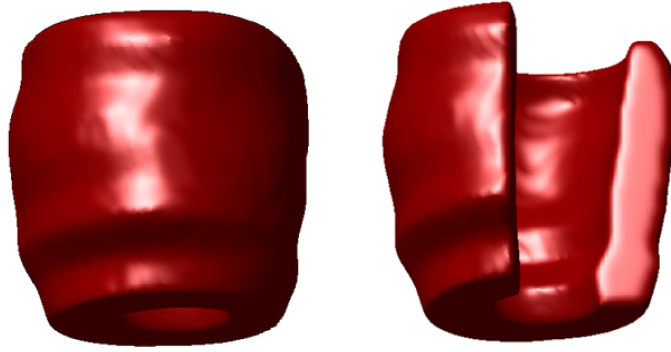


Figure 4.12.: 3D visualisation of the LV from a misaligned stack of slices.

4.14-4.19 show the divided wedges on a basal, mid and apical slice in mid systole and mid diastole for the 10 TVM datasets.

We observed the overall biggest difference in the myocardial wedges between the mid systole and mid diastole, where the LV performs the maximum rotations and this difference is more prominent in the apex than the base. This is also confirmed by the plot in Figure 2.10, Chapter 2 from the literature. The apex rotates anticlockwise during the entire systole with the biggest part of rotation occurring until the mid systole, and then anticlockwise until the mid diastole. The base rotates anticlockwise up to the mid systole, clockwise until the end of the systole and in diastole it performs the reverse motion.

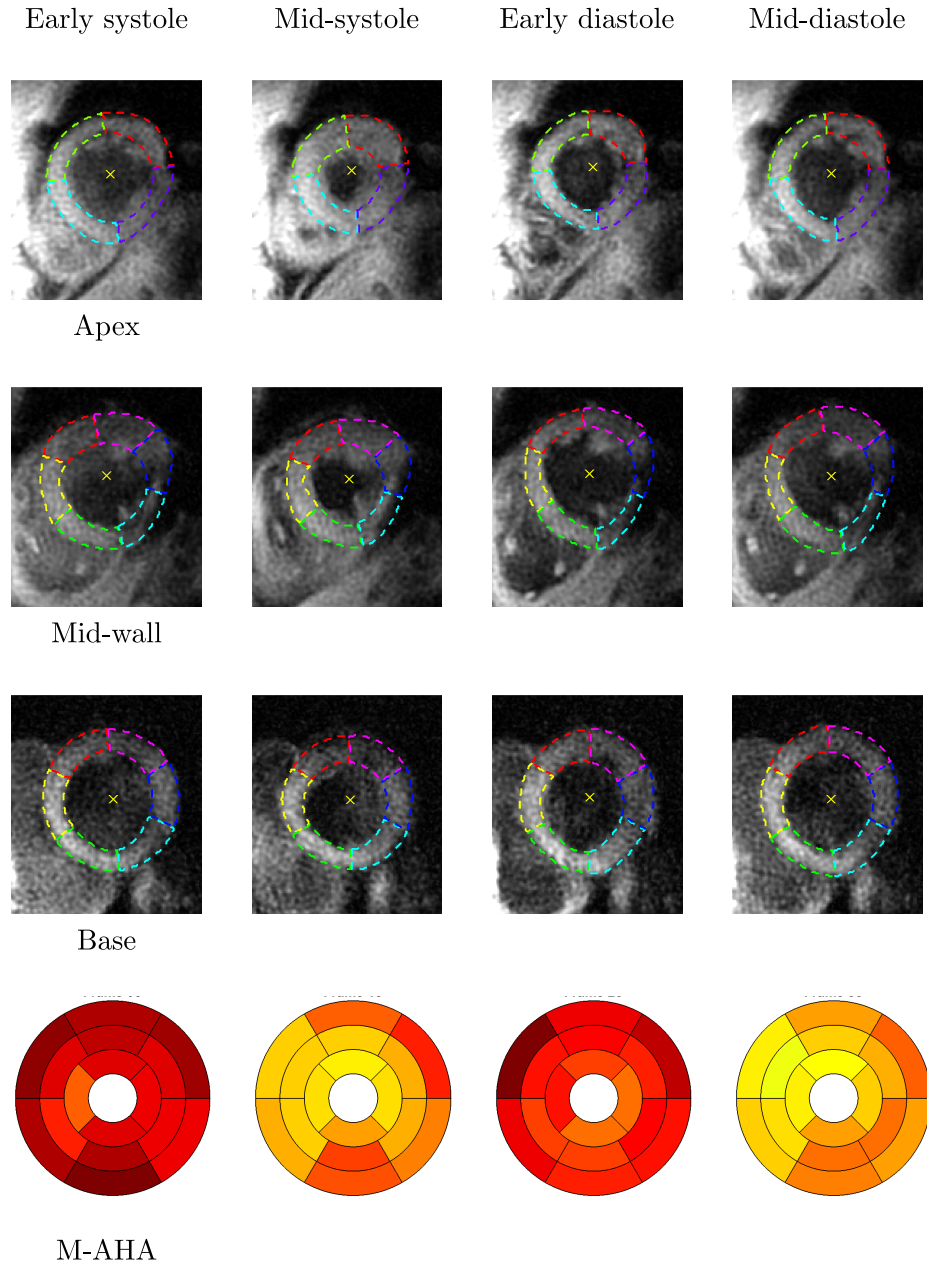


Figure 4.13.: Myocardial wedges on an apical, mid and basal left ventricular TVM slice from one subject in early systole, mid-systole, early diastole and mid-diastole and the corresponding AHA plots for the magnitude of velocity (M-AHA).

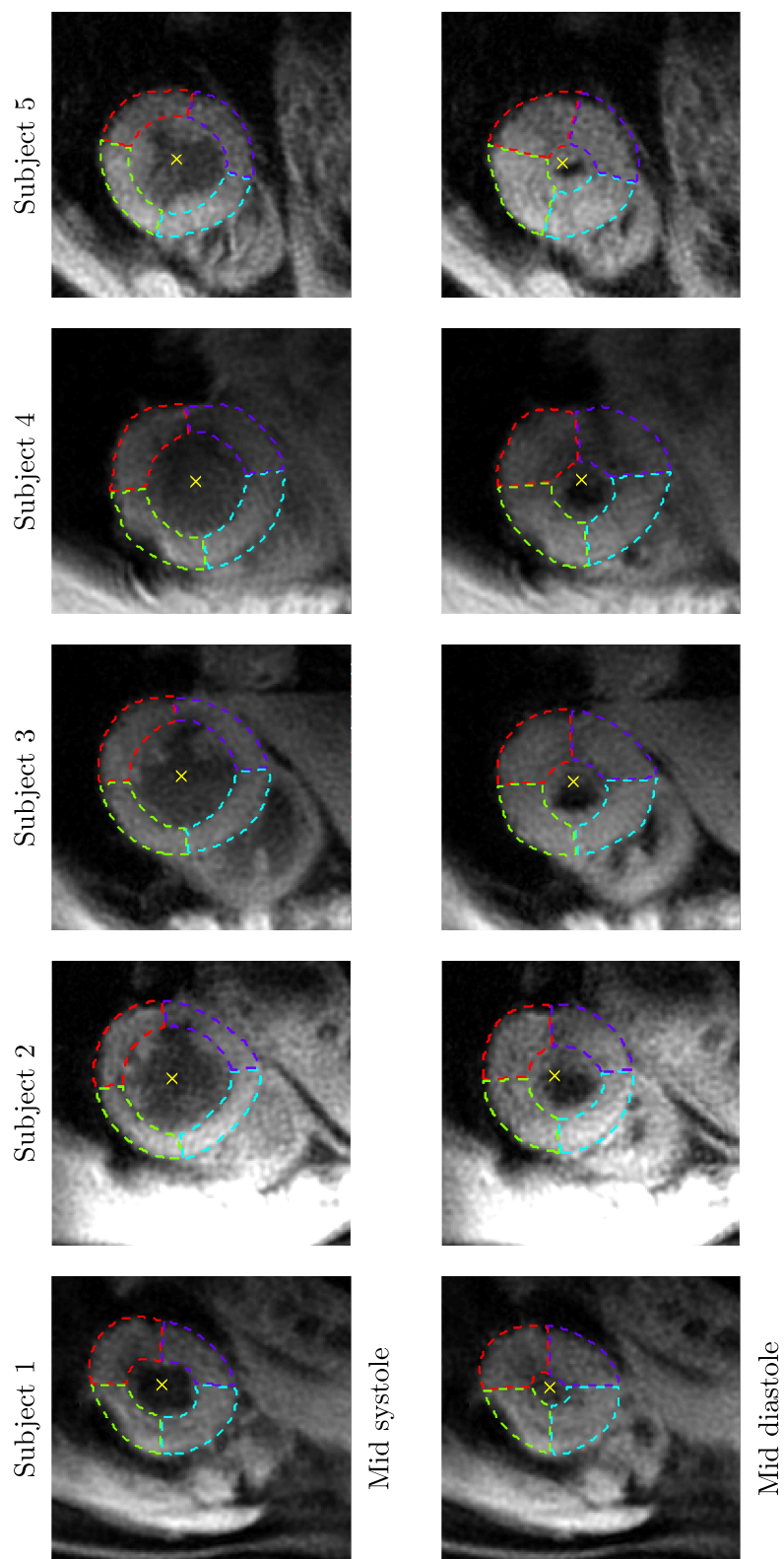


Figure 4.14.: Myocardial wedges on an apical left ventricular TVM slice in mid systole (top) and mid diastole (bottom) for the subjects 1-5.

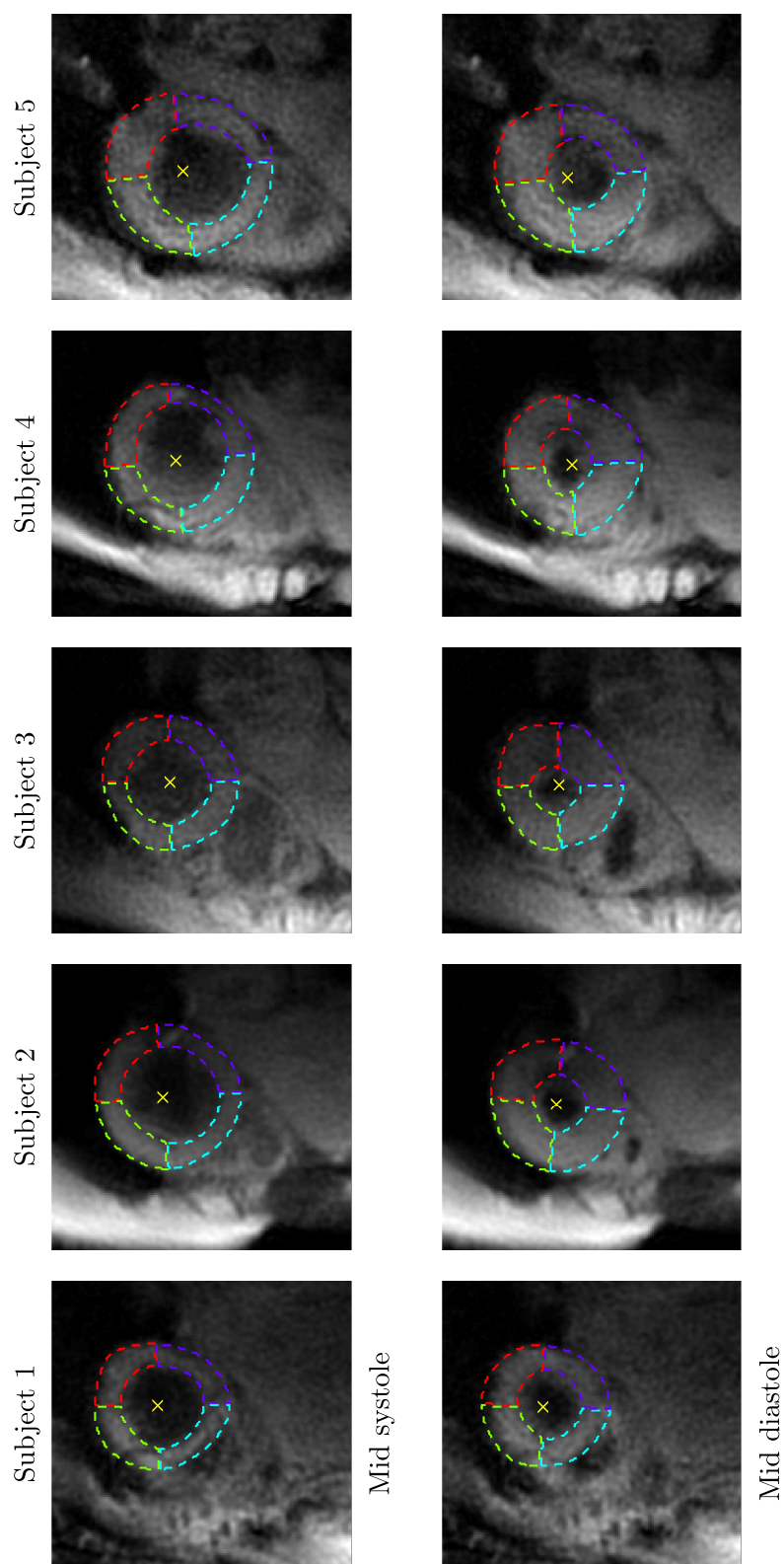


Figure 4.15.: Myocardial wedges on an apical left ventricular TVM slice in mid systole (top) and mid diastole (bottom) for the subjects 6-10.

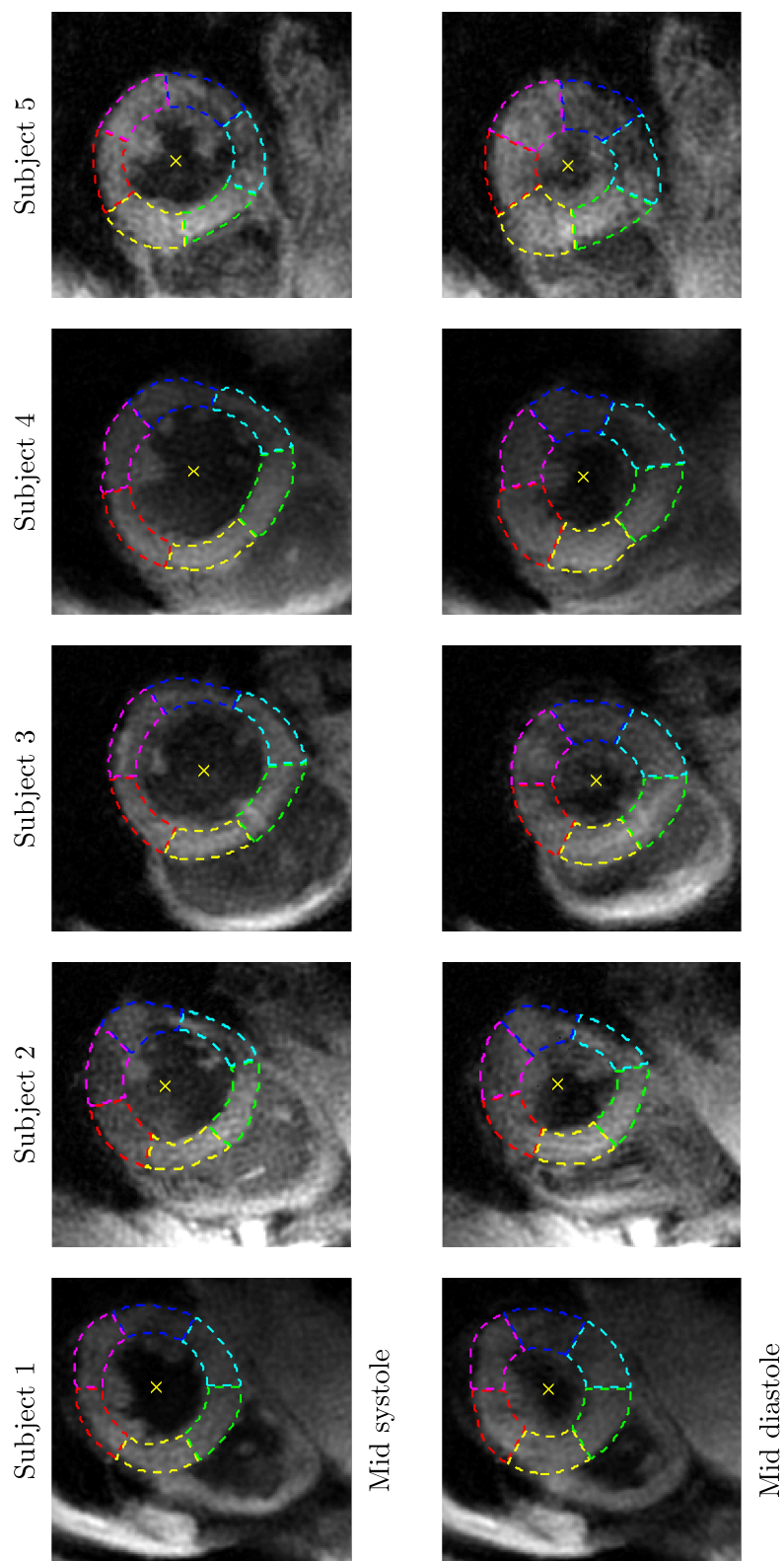


Figure 4.16.: Myocardial wedges on a mid left ventricular TVM slice in mid systole (top) and mid diastole (bottom) for the subjects 1-5.

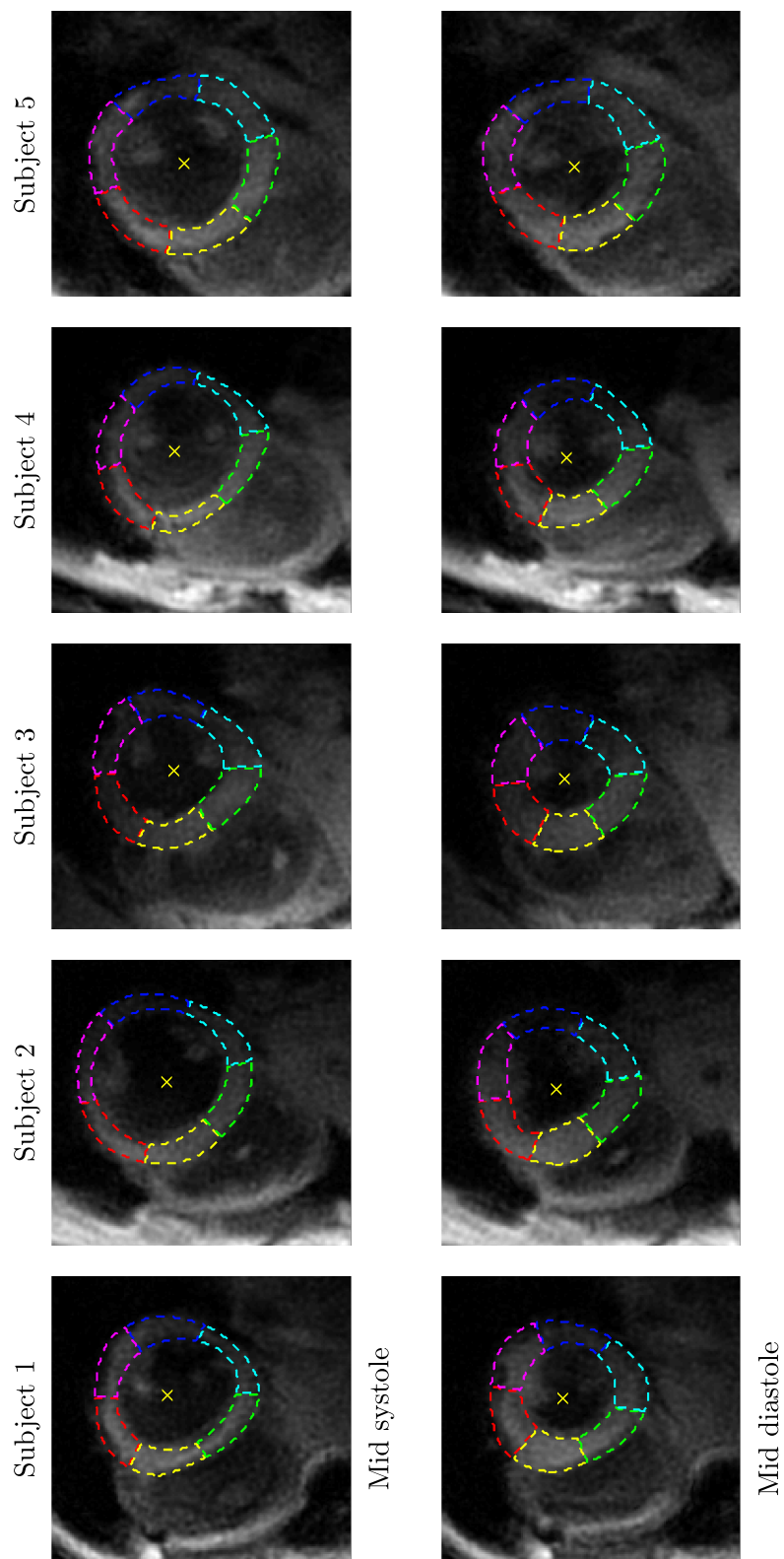


Figure 4.17.: Myocardial wedges on a mid left ventricular TVM slice in mid systole (top) and mid diastole (bottom) for the subjects 6-10.

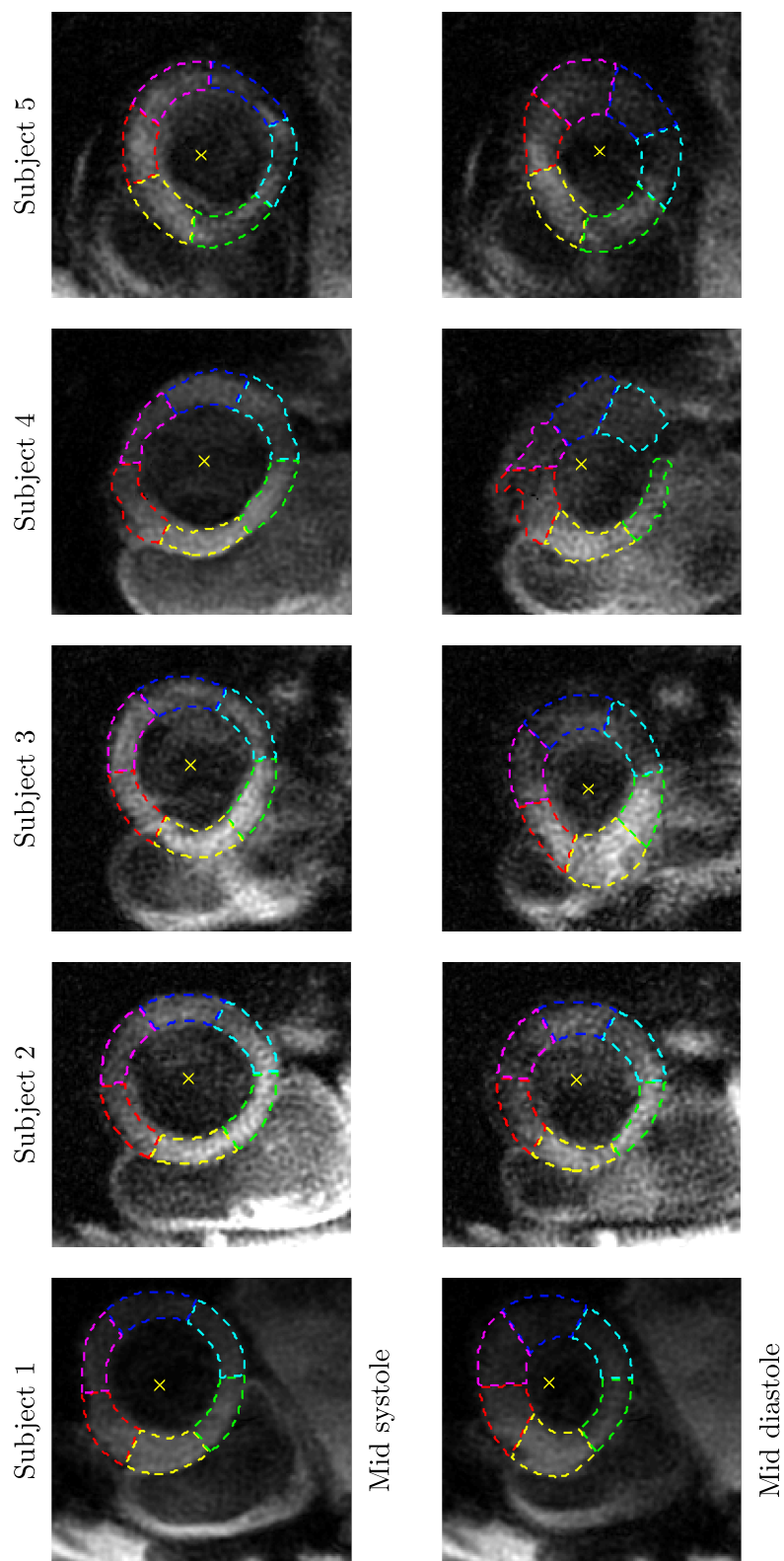


Figure 4.18.: Myocardial wedges on a basal left ventricular TVM slice in mid systole (top) and mid diastole (bottom) for the subjects 1-5.

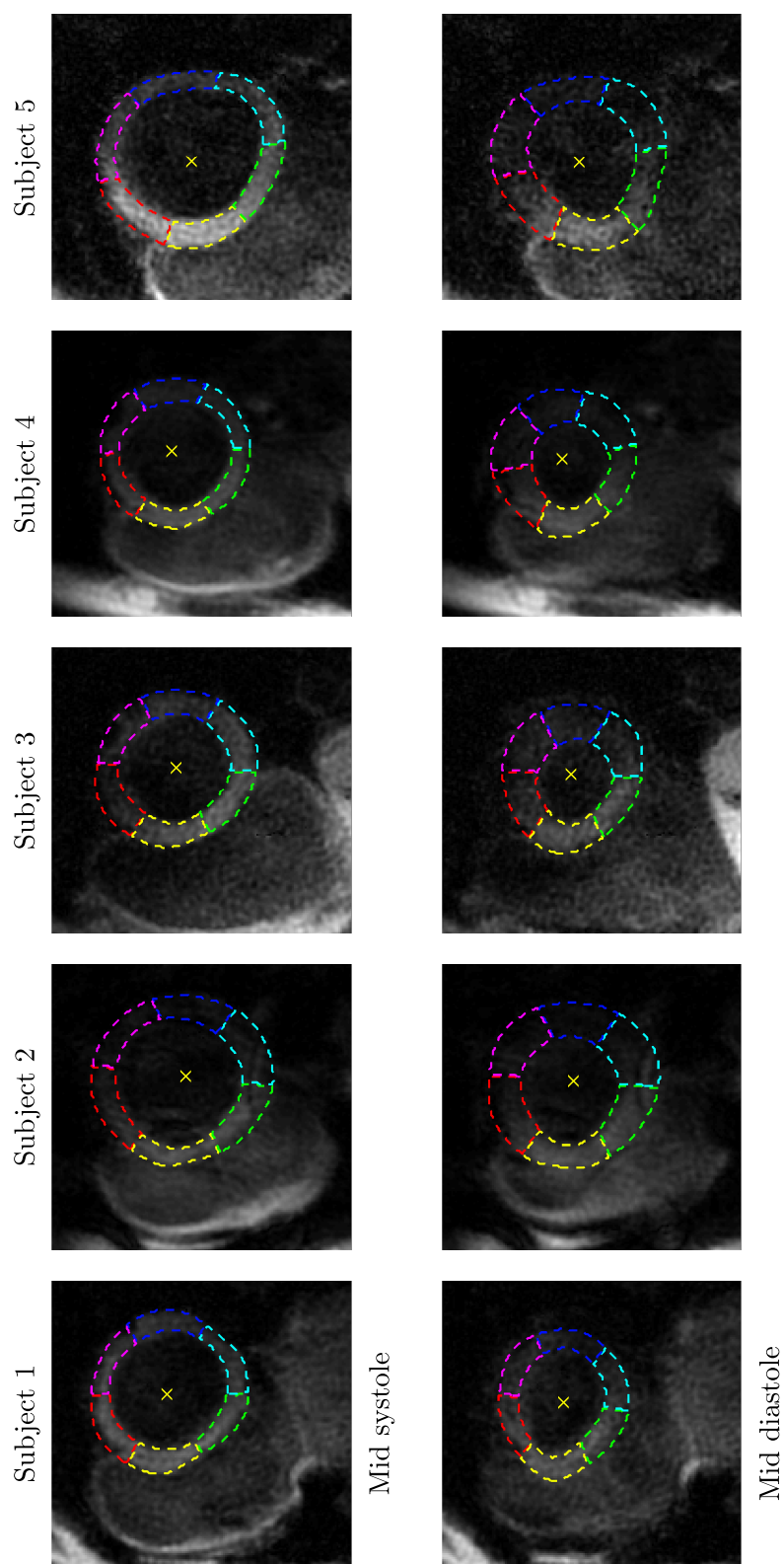


Figure 4.19.: Myocardial wedges on a basal left ventricular TVM slice in mid systole (top) and mid diastole (bottom) for Subjects 6–10.

4.4. Correction of myocardial segmentation

4.4.1. Myocardial segmentation

For the segmentation of the myocardium we developed a semi-manual interactive tool in Matlab that facilitates and accelerates the delineation of the epicardial and endocardial borders. The user draws selects a few points along the desired contour on the first frame (blue points), which are then interpolated by a B-spline (magenta line) to form a closed smooth curve that is the initial contour. Interactive control points are distributed evenly along the closed curve and the user can displace, delete or create them in order to adjust the initial contour to a corrected contour. The curve is propagated to the next frame where the user can adjust the new control points if needed and the same procedure repeats iteratively for all frames. Because the contours show small changes between successive frames, usually only a few control points need adjustment and this saves considerable time compared to a full automatic delineation. An option is to delineate only a sample of frames and interpolate the intermediate contours, but in the following experiments we performed the delineation frame by frame for higher accuracy. The same datasets can be used for evaluation of the automatic segmentation methods. The epicardial and endocardial contours are combined to yield the myocardial mask.

Figure 4.20 shows the myocardial segmentation performed on a TVM dataset using the developed semi-manual interactive tool. This tool can be used with any kind of images and it is particularly useful in TVM where the quality of images impacts the performance of the automatic methods. This tool accelerates segmentation while it offers control over the artefactual areas or the papillary muscles regions, where an automatic method would not perform adequately. Figure 4.20(b) shows an example of loss of signal near the epicardial boundary, an example of a LV image with papillary muscles and a blurred image with indiscernible contours.

4.4.2. Correction of segmentation method

Some of the initially constructed AHA maps (see Figure 4.22 and 4.23) have segments with extreme values at the level of V_{enc} , particularly on the inferior, anterior and lateral side of the maps. These errors are attributed to

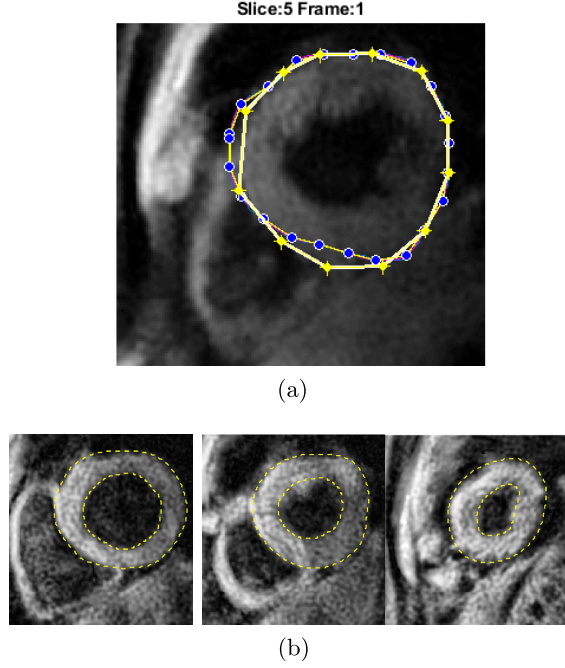


Figure 4.20.: Interactive tool for semi-manual segmentation (a) and examples of TVM segmentation .

segmentation residuals and show more clearly on Standard Deviation of the magnitude of velocity AHA (SD-AHA) plots. The extreme values in the segmentation residuals originate from the null signal of the vacant space; the null signal is assigned random phases that are shown on the TVM phase images and correspond to velocities in the $\pm V_{\text{enc}}$ range. Such segmentation residuals on the non septal-side of the LV can impact significantly the segmental analysis and it is therefore necessary to alleviate them. At the same time, it is also desirable to maintain a high number of myocardial pixels per segment in order to ensure fidelity in the segmental analysis. For the correction of myocardial masks, we propose a texture-based method that distinguishes the background areas from the myocardium on TVM phase images and corrects the myocardial masks accordingly.

- **Method.**

The 3 TVM phase images of each slice and frame are combined to a *norm* image analogous to the magnitude of velocities, which should not be confused with the TVM magnitude image. The norm image is filtered by a cluster

of Gabor filters (of minimum wavelength and equiangular directions) and the resulting images are combined to an overall texture image. The texture image is binarised to a mask and processed with morphological operators to unify the myocardial and background regions; the myocardial contours are further smoothed to a small degree.

- **Results.**

The correction of segmentation method was evaluated on TVM images that were masked with a "wrong" myocardial mask and an example is presented below (Figure 4.21)

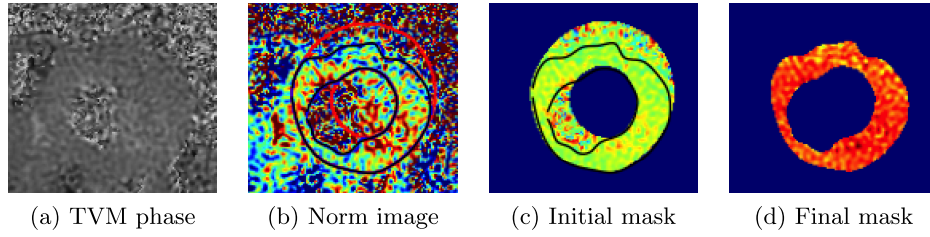


Figure 4.21.: Correction of segmentation method. The 3 TVM phase images (a) were combined to a norm image (b) initially masked with the wrong myocardial mask (red contour) (c), which was then corrected with the proposed method to the new mask (black contour). The masked velocities are shown before (c) and after the correction (d) and the colormaps are adjusted to the extreme values in each case.

It can be seen that the myocardial background residuals have been successfully removed while the myocardial regions near the corrected myocardial borders have been adequately preserved. The adjustment of the final masked velocity image to a lower colour level indicates that extreme values of velocity have been successfully removed.

- **Application to segmental analysis.**

The proposed correction of segmentation method was applied to the TVM datasets and the results from an apical, mid and basal slice and two frames from a TVM dataset are presented in Figure 4.22. The colour maps illustrate the raw TVM velocity measurements within the myocardial mask before and after the correction of the mask. The colormaps are adjusted to the range of raw velocities. The correction scheme removes small background areas from

the periphery of the myocardial mask which contain random phase and thus also extreme values that affect the segmental velocities. The removal of the background areas and their extreme values results in the readjustment of the range of the colourmap and the unveiling of the velocity patterns. This is a fast way to quantitatively assess the improvement. The corresponding SD-AHA maps show the improvement of segmental analysis in terms of reduction of the variance attributed to the segmental residuals. Figure 4.23 illustrates the corresponding M-AHA maps and their improvement for the same subject on several frames of the cardiac cycle including the frames shown in Figure 4.22.

With the proposed correction of segmentation method the segmental analysis has improved; extreme discontinuous values are significantly reduced in both M- and SD-AHA maps and standard deviation lies in overall lower values. It should be noted that the proposed method is developed for TVM images and it is tailored to the needs of segmental analysis rather than shape analysis as the shape information is discarded. For this reason the resulting myocardial contours are not necessarily smooth, as the method mostly favours the removal of extreme values.

4.4.3. Outlier reduction

To certify the alleviation of extreme values, we consider only the values that fall in the 90% Confidence Interval (CI). Results are presented in Figure 4.23 and show further improvement of the AHA maps in terms of variance reduction, increase in the SD uniformity and M smoothness.

4.5. Segmental analysis results and evaluation

The proposed segmental analysis framework was applied to the 10 TVM datasets and the generated AHA plots are presented below. The AHA plots were generated for the M-AHA and each XYZ and RCL mean velocity component. The AHA plots for the standard deviation of the SD-AHA are also presented; segmental velocity variance is another potential clinical index and an evaluation measure for segmental analysis improvement, as already implied.

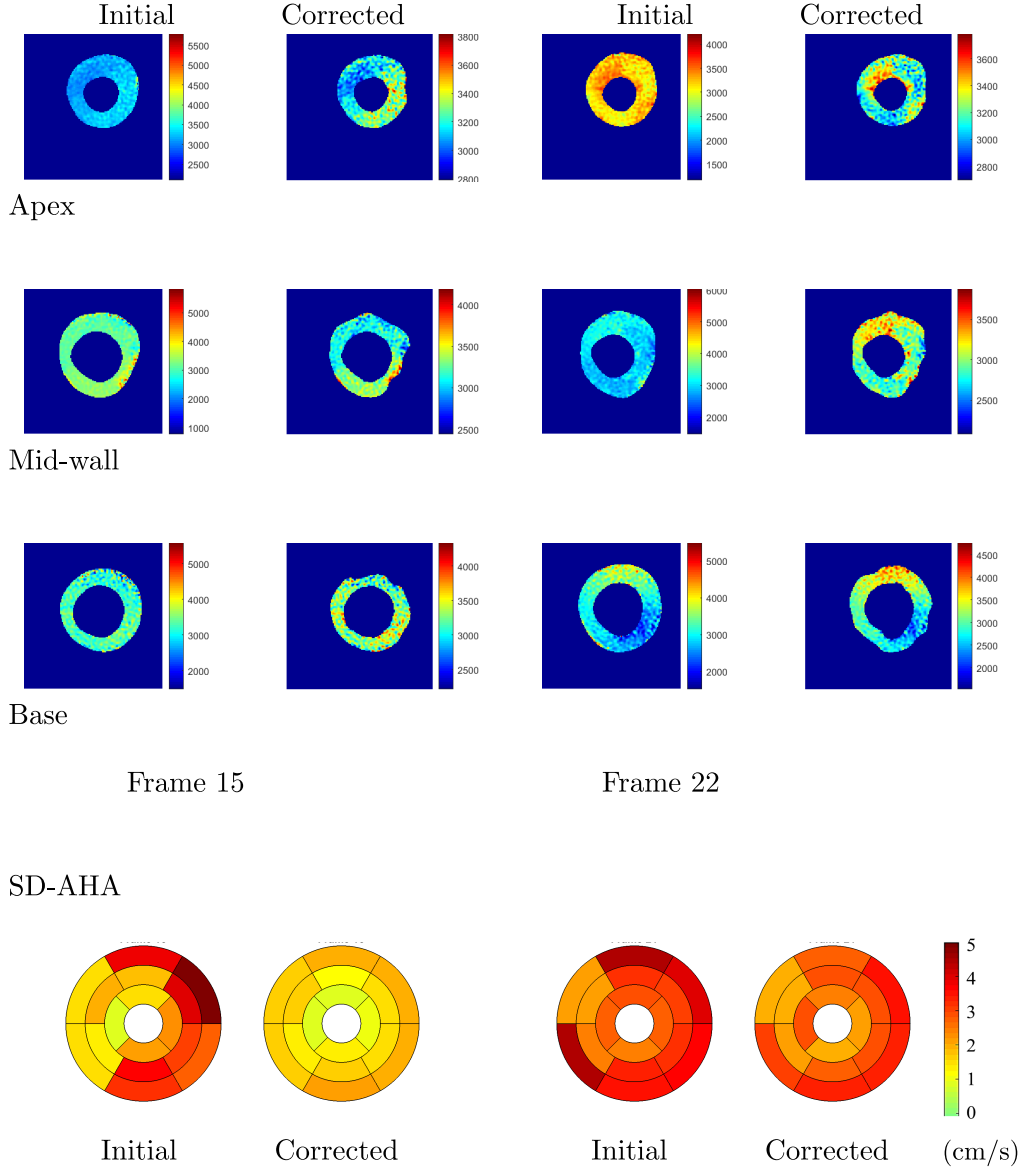


Figure 4.22.: Correction of myocardial segmentation for segmental analysis presented on a basal, mid and apical slice and two instances of the cardiac cycle. The velocity maps (top) show the raw velocities within the myocardial mask before (initial) and after the correction (corrected) of segmentation. The velocity colormap is adjusted to show the exclusion of the extreme values of the background. The corresponding SD-AHA maps show the improvement in terms of variance.

4.5.1. AHA maps for evaluation of improvement

Figure 4.23 shows SD-AHA and M-AHA maps generated before and after the correction of segmentation and outlier reduction. The SD-AHA maps show the improvement of the segmental analysis after the correction for segmentation residuals and outliers having a reduction of variance and increase of the map uniformity. The M-AHA maps show the reduction of extreme values and increase of the map smoothness.

4.5.2. AHA maps for intra-subject assessment

Figure 4.24 presents the segmental velocity maps generated with the proposed framework for one TVM mapping dataset. Each 26-frame plot of segmental maps shows the evolution of velocities during the cardiac cycle². The 26-frame RCL-AHA plot is suitable for the clinical assessment of the myocardial motion, as it allows the easy identification of predominant motion directions and the phases of the cardiac cycle. The TI-AHA plot provides similar and more abstract information. The XYZ-AHA map plot is suggested for the analysis of TVM images rather than a clinical assessment; it offers an overview of the TVM datasets and allows, for instance, the fast evaluation of velocity directions and artefact impact on the velocity images. The M-AHA plot is a compact representation of the evolution of segmental velocity during the cardiac cycle, which accommodates the inter-subject comparison and a preliminary identification of abnormal myocardial segments.

4.5.3. AHA maps for inter-subject comparison

Figure 4.25 presents the 26-frame M-AHA map plots for the 10 subjects for inter-subject comparison and Figure 4.26 shows the corresponding standard deviation values.

4.5.4. AHA maps for evaluation of consistency

Figure 4.27 illustrates the time courses of the magnitude velocity per segment averaged over the 10 TVM datasets before and after the correction of segmental mask and alleviation of outliers. The revealed segmental velocity

²The 50 frames of the cardiac cycle were downsampled to 25 for illustration purposes.

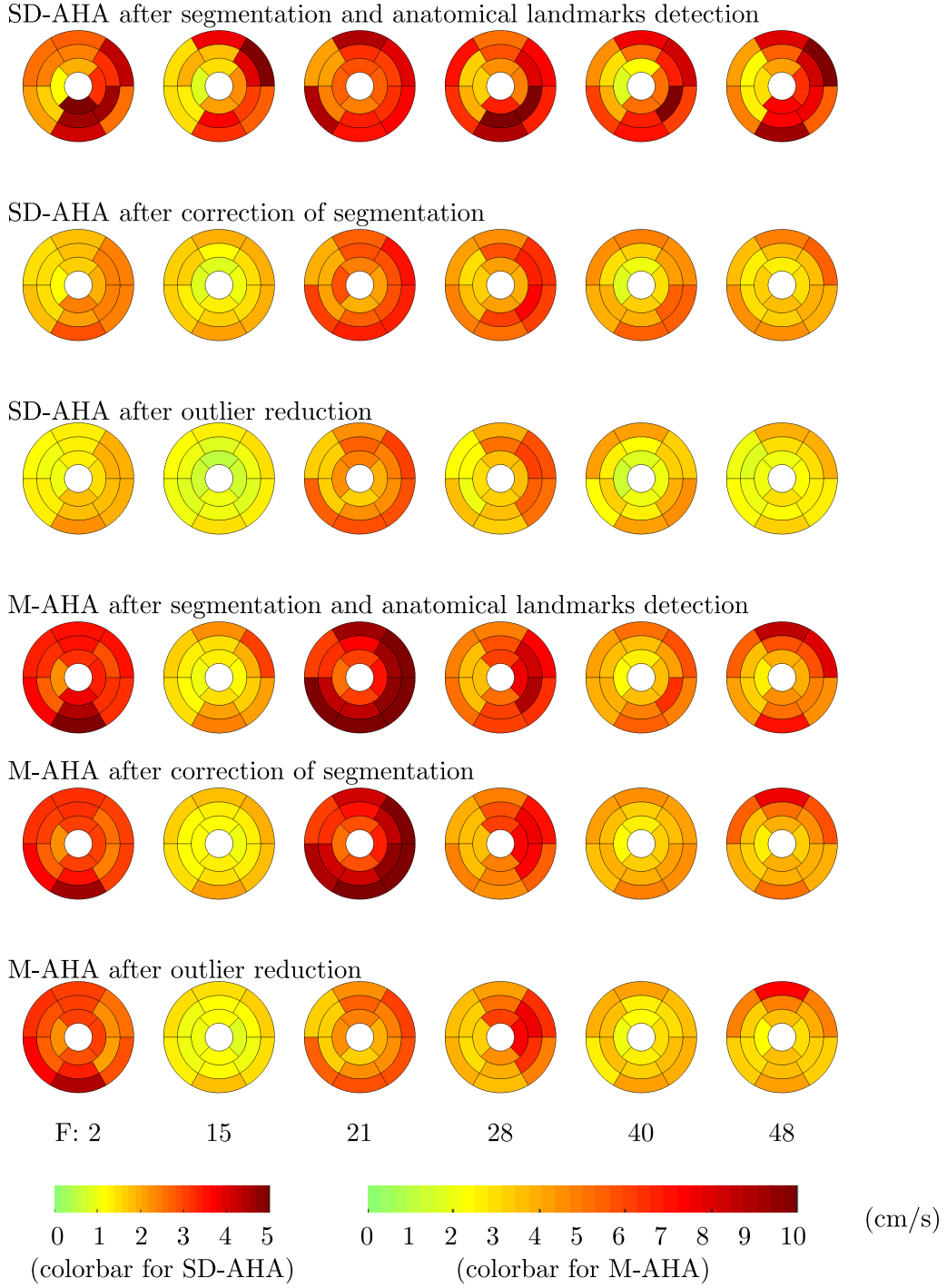


Figure 4.23.: SD-AHA maps (top) from a normal TVM dataset at several instances (F) of the cardiac cycle show the reduction in velocity variance after the correction of segmentation. M-AHA maps (bottom) reflect the improvement in the magnitude of segmental velocities.

AHA plots for intra-subject assessment

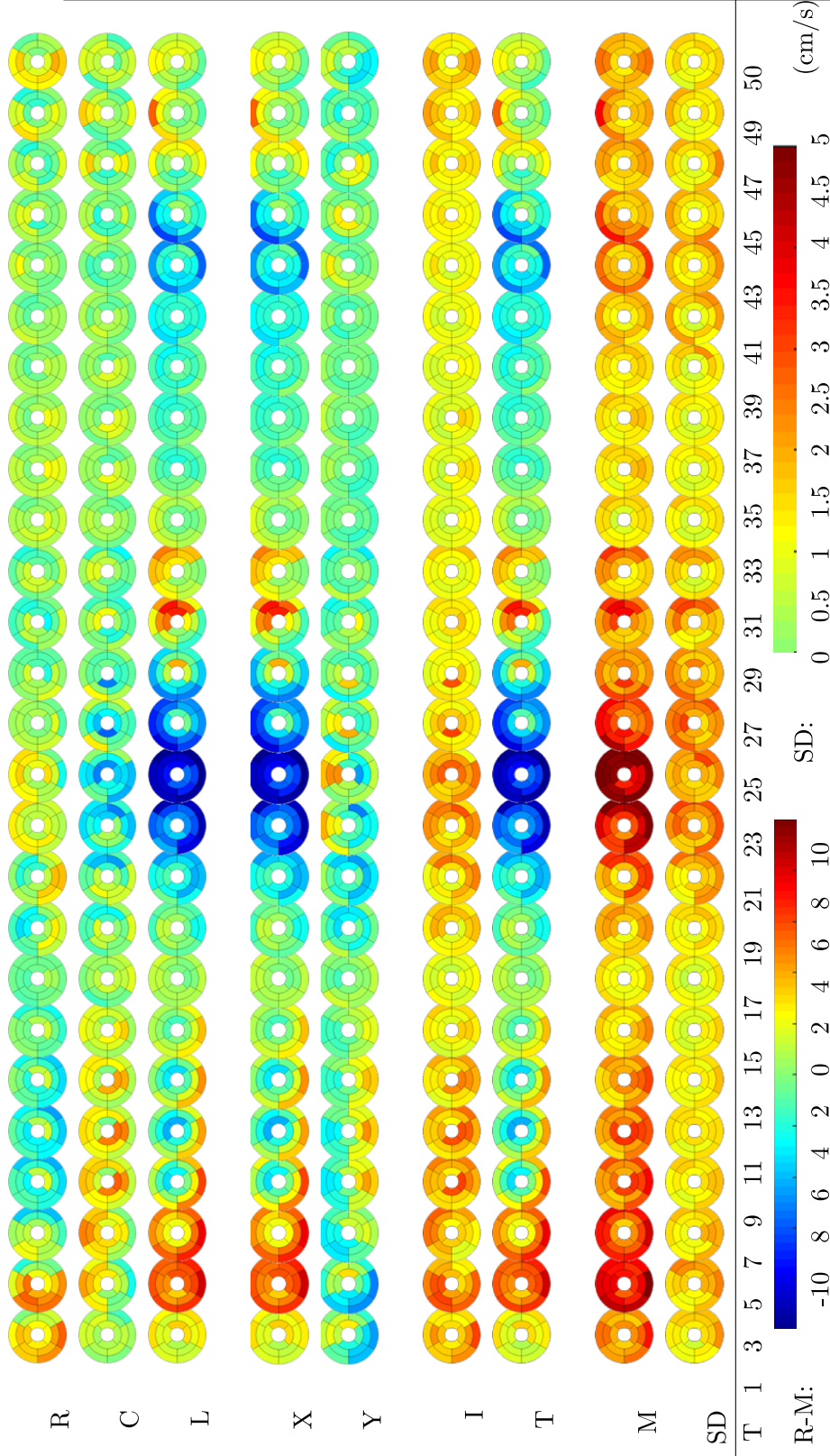


Figure 4.24.: AHA maps from a normal TVM dataset at 26 instances of a full cardiac cycle according to the proposed framework. The plots show the mean RCL, XY, IT velocities and the standard deviation of the magnitude of velocity (SD) in each segment. The right colorbar (SD) refers to the base to the apex (L), anti-clockwise as seen from the apex (C), inward direction (R), from left to right (X), from top to bottom (Y).

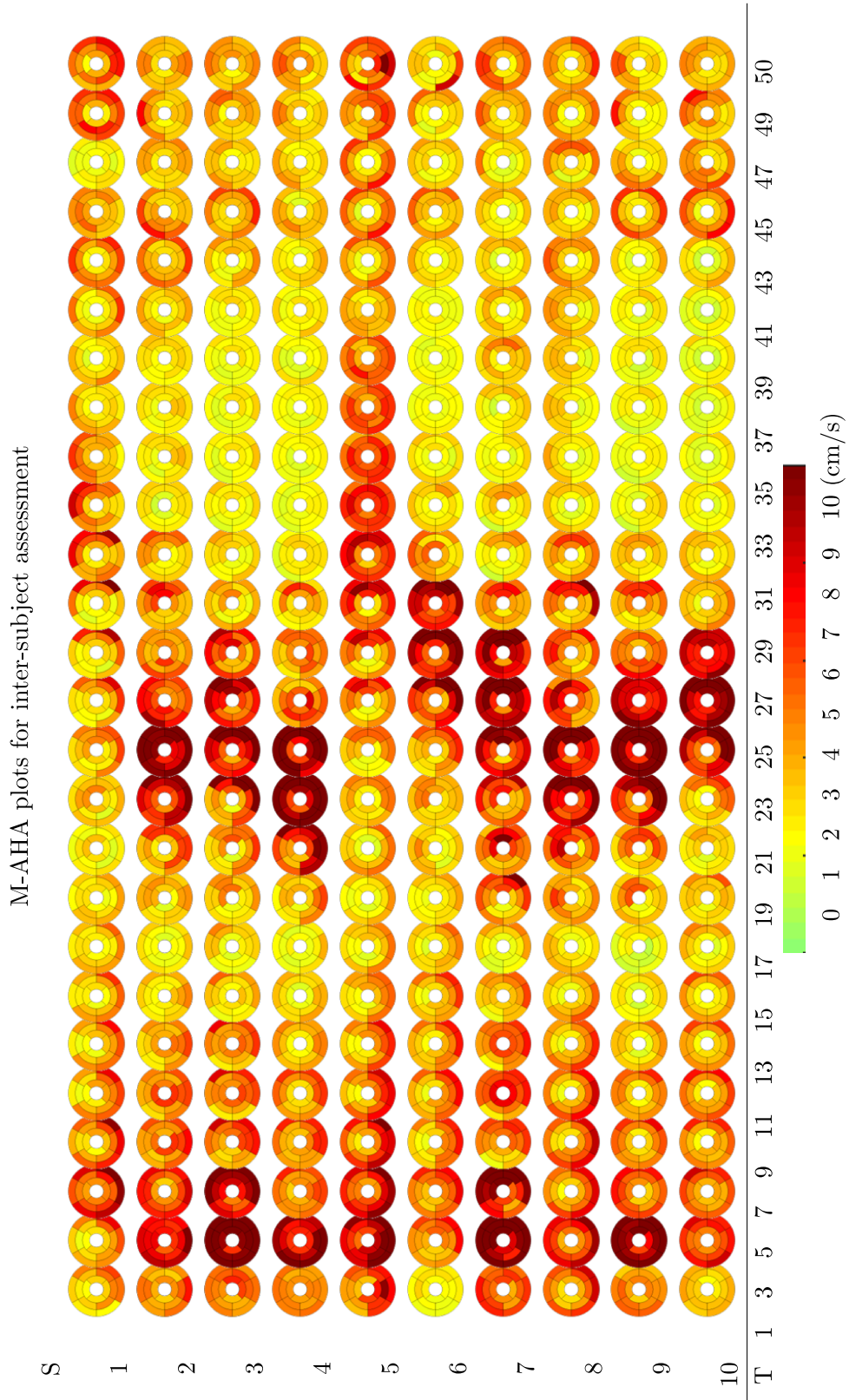


Figure 4.25.: M-AHA plots from 10 normal TVM datasets at 26 instances of a full cardiac cycle.

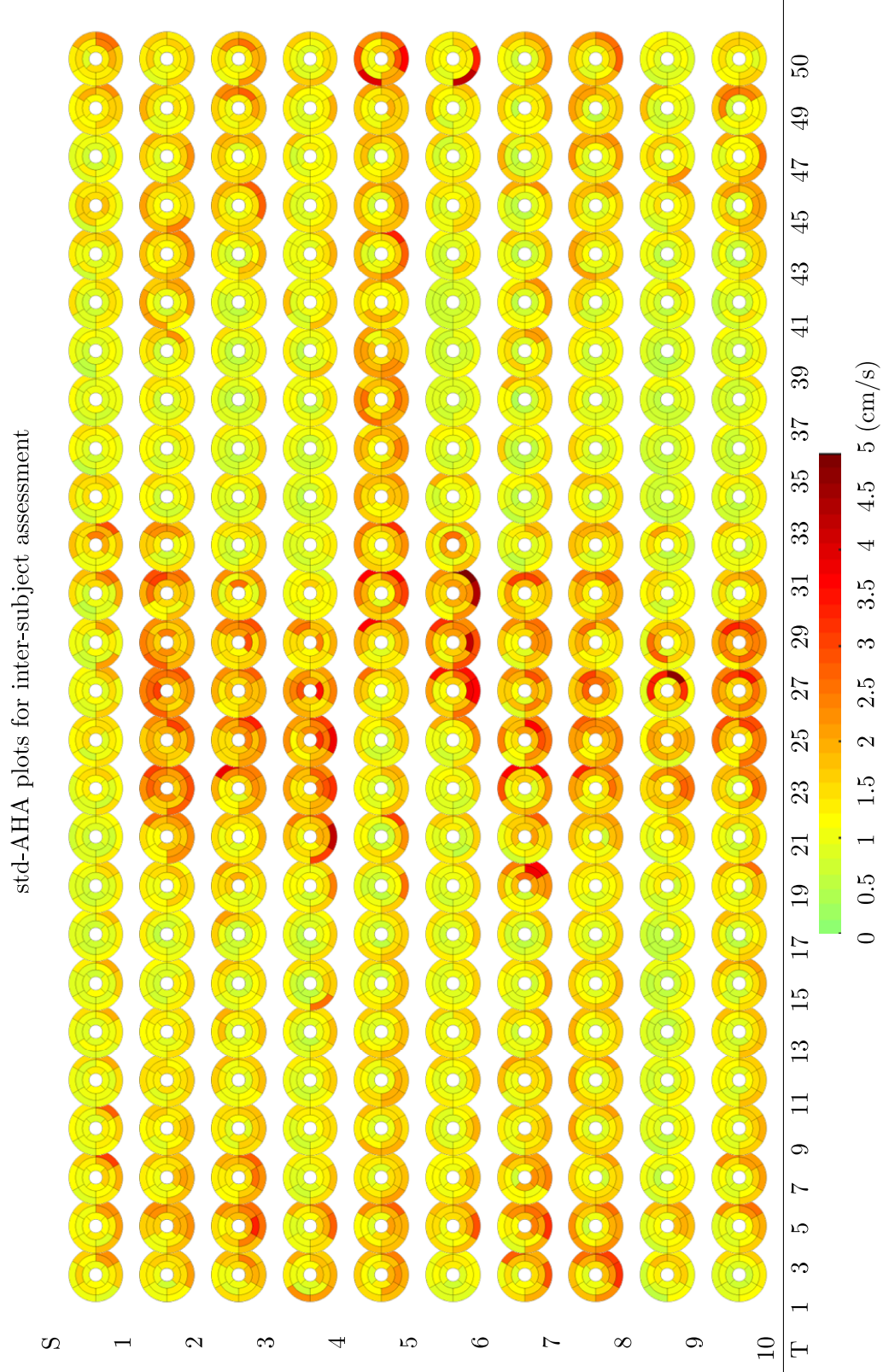


Figure 4.26.: SD-AHA plots from 10 normal TVM datasets at 26 instances of a full cardiac cycle.

patterns are in accordance with the literature. As explained earlier, the improvement of the maps results in the reduction of the velocity variance that comes from artefacts and misplacement of the reference points for myocardial division. This also results in the increase of inter-subject segmental velocity agreement, which is shown as narrowing of the CI in the estimation of segmental velocity patterns. The narrower the CI, the higher the segmental analysis consistency. These results evaluate the consistency before and after the correction of segmentation and outlier exclusion and after the accurate detection of anatomical landmarks. Results without an accurate detection of anatomical landmarks, like in a steady segmental division, are expected to show lower consistency.

4.6. Discussion and conclusion

In the current chapter we have proposed a framework for the improvement of consistency of the segmental analysis along with the required image processing tools.

In order to investigate the role of the anatomical landmarks in the accurate division of myocardial segments, we have examined the variability of the LV centre and IV positions across the TVM stack of images. The results have shown that the IV points, in particular, vary across the frames as well as the slices of a stack probably because of the normal myocardial motion, geometry and slice misalignment by the potential patient's movement in the scanner. We have concluded that the IV positions vary enough across the TVM images and we suggest that their accurate tracking will improve the accuracy of segmental analysis. Towards this, we have developed tools for the accelerated accurate marking of the IV points as well as the myocardial segmentation.

We have observed that the segmentation residuals have high impact on the segmental velocity values; we have proposed a novel texture-based method for the correction of the myocardial mask in order to alleviate the segmentation residuals automatically while preserving the unaffected myocardial regions. The proposed method, which is tailored to the characteristics of the TVM images and needs of segmental analysis, show to improve the AHA segmental maps considerably.

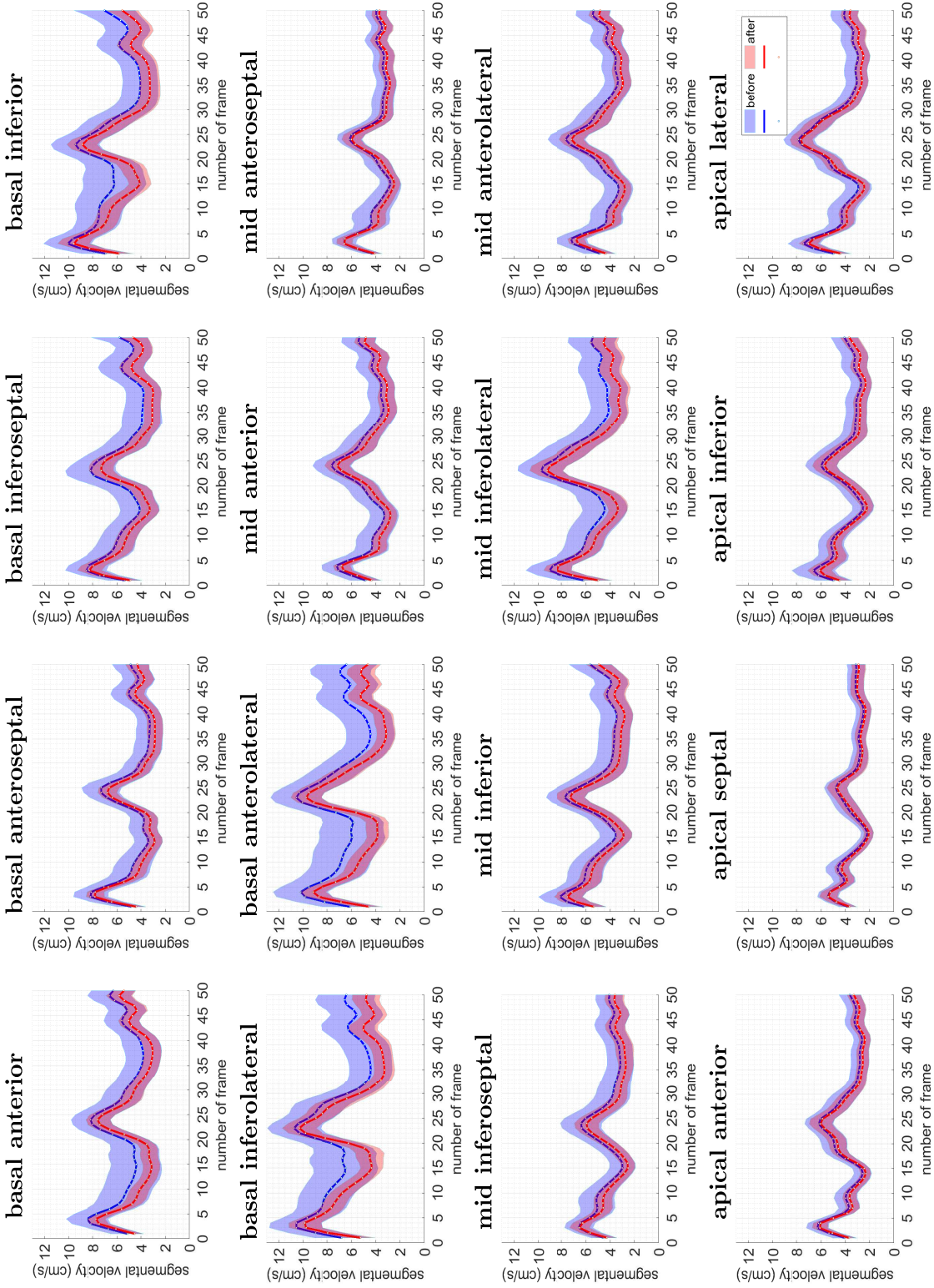


Figure 4.27.: Segmental velocity time courses for the evaluation of the consistency of the proposed segmental analysis framework. Each plot illustrates the mean segmental velocity (curves) and 90% confidence interval (shaded areas) for each segment averaged over the 10 TVM datasets and estimated before (blue) and after (red) the correction of segmentation and alleviation of outliers. (Red shaded area appears magenta where it overlaps with the blue shaded area.)

We have analysed 10 TVM datasets³ from healthy volunteers following the proposed method and presented the AHA maps. The SD-AHA maps illustrate the improvement of segmental analysis by means of variance uniformity and overall variance reduction. For intra-subject assessment we have suggested a series of AHA maps plots that show the evolution of the various types of AHA maps during the cardiac cycle. The same series of plots can be used for the observation and processing assessment of the TVM datasets. Plots of M-AHA maps have been suggested for inter-subject comparison. Lastly, we have evaluated the improvement of segmental analysis consistency by means of increase of agreement between the time courses of segmental values across the TVM datasets. Interesting findings have occurred from these results.

- **Left ventricular motion assessment.**

The velocity patterns presented in Figure 4.27 show that the basal segments develop higher velocities than the corresponding mid wall segments and the same applies for the mid wall segments and the apical segments. This finding is in accordance to the literature. Furthermore, the lateral segments in all partitions of the LV show higher velocities than the septal segments.

- **Left ventricular symmetry.**

The velocity plots indicate also motion symmetry about the bisector line of the angle formed by the AI, LV centre and PI; specifically the pairs anterior-inferior, inferolateral-anterolateral and inferoseptal-anteroseptal segments show similar segmental velocity patterns. The left ventricular motion symmetry is an interesting and novel finding, which we use in the following chapter of motion correction. Earlier examination of the literature [98, 141, 147] gave us an indication of the left ventricular motion symmetry but this was not clear until now because not all plots agreed to this. We assumed that either the motion symmetry did not apply in principle or several segmental velocity measurements and plots were disturbed by inaccuracies in the division of the myocardial segments. The results of the current study en-

³It should be noted that for the presented experiments, the TVM datasets were not pre-processed for bulk motion and offset correction; application of the pre-processing steps is estimated to yield further consistent segmental maps. Moreover, the AHA maps can be used, in reverse, for the evaluation of each pre-processing step. The above tools were developed from scratch.

force the second case of assumption, thus, support the claim of LV motion symmetry and prove further the value of the presented framework in the improvement of segmental analysis accuracy and consistency.

- **Assessment of consistency.**

The velocity plots in Figure 4.27 show significant increase in the confidence of segmental velocity estimation after the application of the correction of segmentation method and outlier alleviation, as the CI bands are almost half width after the corrections. Smaller CI bands indicate the reduction of this part of variance that is attributed to image analysis errors and therefore the increase in the consistency of the segmental analysis with the proposed framework. In all plots the mean magnitude of segmental velocity lowers after the corrections, which indicates that a systematic error resides in the uncorrected segmental analysis and is corrected by our proposed framework.

The above findings support the claim that the proposed framework along with the developed tools improve significantly the consistency and accuracy of segmental analysis and it is therefore suggested in future studies.

5. TV Restoration

5.1. Introduction and previous work

A successful quantification analysis and visualisation of myocardial contractility depends significantly on the quality of MRI data. PC-MR images are particularly prone to noise and other artefacts¹ [221–224] associated with hardware set up, acquisition sequence and subject’s motion, as elaborated in Chapter 2. Furthermore, a compromise between acceptable SNR and short acquisition time, which is occasionally made, contributes to the manifestation of noise in PC-MR images. Although an advanced acquisition sequence [225] improves the quality of data, a considerable amount of noise is still present. Effective restoration of PC-MRI data prior to their analysis is, therefore, necessary.

The key requirement for PC-MRI restoration is preservation of detailed contractile patterns of myocardial motion [17], which are formed by the complex structure of the myocardium and the mechanism of cardiac conduction. The anisotropic discontinuities of myocardial contraction can be interpreted by the *myocardial band model* [226] and the organization of cardiac muscle fibers [223, 227], as well as the discontinuous propagation of action potentials across the cardiac muscle [228]. Due to the structure and electric conduction properties of the heart, neighbouring myocardial regions which belong to different fibre bundles are likely to contract in different directions and time phases, forming velocity field boundaries in between them. Unlike linear filtering, which blurs edges [229], non-linear filtering methods and particularly Total Variation (TV) restoration seem promising for the maintenance of fidelity of this complex underlying myocardial motion.

The basis for TV restoration is Laplace’s L1 estimation algorithms. The TV restoration algorithm for scalar images was first introduced by Rudin

¹Motion artefacts, blood flow artefacts, phase wrapping, ECG variability, chemical shifts, truncation, background offset errors, misalignment of encoded and non-encoded PC images, eddy-currents.

et al. [7] and was extended for vector-valued images by Blomgren and Chan [230] who then developed a version of this multidimensional restoration algorithm for non-flat images [231], as well as CB and HSV images [230], and proposed a digital TV filter [232]. Tadmor applied successive TV restoration to decompose a noisy image into its original and noisy part [233]. Osher extended this approach with a correction step which reinvolves the removed noise into the restoration process [234]. The directional version of TV restoration was developed and first applied to CMR data by Ng and Yang for the restoration of blood flow [235]. In [175] Huntbach presents a maximum a posteriori restoration technique that relies on Bayes theory. This chapter presents a new robust restoration method for PC-MR velocity images based on the Digital TV filter with reduced complexities. The method is evaluated on both simulated and in vivo data with detailed analysis of its robustness and fidelity.

5.2. Method

5.2.1. Minimisation of total variation

The objective of a TV restoration algorithm is to minimize the total variation of velocity fields based on prior information on the noise level, which is expressed by its variance.

$$u_o(\mathbf{a}) = u(\mathbf{a}) + n(\mathbf{a}) \quad (5.1)$$

where $\mathbf{a} = (x, y) \in \Omega$ is the set of pixels. The TV Restoration approach indicates the minimization of the $L1$ norm of the total variation

$$TV(u(\mathbf{a})) = \iint_{\Omega} |\nabla u(\mathbf{a})| dx dy \quad (5.2)$$

over the image, under the constraints

$$\sigma^2 = \frac{1}{|\Omega|} \iint_{\Omega} (u(\mathbf{a}) - u_o(\mathbf{a}))^2 dx dy, \quad \iint_{\Omega} u(\mathbf{a}) dx dy = \iint_{\Omega} u_o(\mathbf{a}) dx dy \quad (5.3)$$

where σ^2 is the variance of noise n and $|\Omega|$ the number of pixels on the image.

According to the first order Lagrangian method the above constrained problem is equivalent to the minimisation of

$$L(x, y, \lambda) = \iint_{\Omega} |\nabla u(\mathbf{a})| dx dy + \frac{\lambda}{2} \iint_{\Omega} (u(\mathbf{a}) - u_o(\mathbf{a}))^2 dx dy \quad (5.4)$$

where $\frac{\lambda}{2}$ is the Lagrange multiplier and λ is named also regularization parameter [232]. The Lagrange multiplier is selected as $\frac{\lambda}{2}$ for computational convenience.

The steepest descent method, solves the above problem with the following formula.

$$\frac{\partial u}{\partial t} = \frac{\nabla u}{|\nabla u|} + \lambda * (u - u_o) \quad (5.5)$$

The aforementioned TV restoration studies [7, 230, 232] drop the second constraint and Rudin [7] explains that this is enforced by the evolution of the steepest descent procedure if u is initialised as u_o .

The discrete solution to the above minimization problem given in [230] is

$$\hat{u}_t(\mathbf{a}) = \sum_{b\alpha} h_{ab}(\mathbf{a}; \mathbf{b}) u(\mathbf{b}) + h_{aa}(\mathbf{a}; \mathbf{a}) u_o(\mathbf{a}) \quad (5.6)$$

where $\hat{u}_t(\mathbf{a})$ denotes the calculated value of the restored image on the i^{th} iteration on pixel α . In the above equation, $\mathbf{b}$ denotes the neighbouring pixels of pixel α , excluding the pixel α . The coefficients h_{ab} and h_{aa} are calculated by the formulae:

$$h_{ab}(\mathbf{a}; \mathbf{b}) = \frac{w_{ab}(\mathbf{a})}{\lambda + \sum_{\gamma \alpha} w_{\alpha\gamma}(\alpha; \gamma)}, h_{aa}(\mathbf{a}; \mathbf{a}) = \frac{\lambda}{\lambda + \sum_{\gamma \alpha} w_{\alpha\gamma}(\alpha; \gamma)}, \quad (5.7)$$

where $w_{\alpha\gamma}$ is the weight indicating the level of likeness of the pixels α and γ compared to their neighbours [232].

5.2.2. Regularization parameter

For consistent results, the choice of regularization parameter is critical. The amount of smoothing and preservation of the initial value of a pixel are controlled by the coefficients h_{ab} and h_{aa} respectively and, hence, by the fitting parameter λ . This parameter incorporates the prior noise information

into the restoration algorithm, and therefore its value is essential for the convergence to the real underlying image. In this study, a constant value of $1/\sqrt{(\sigma^2)}$, the optimum value of λ , is used. The noise variance σ^2 is estimated from a uniform small area whose velocity is regarded constant. In this study a 25 x 25 pixel region located on the chest wall was chosen for this purpose.

5.2.3. Evaluation criteria

For the assessment of the suggested restoration algorithm, the following estimation criteria are introduced: Mode of Removed Noise (MRN), Modified MRN (MMRN) and Percentage Variance Reduction (PVR).

The MRN criterion is denoted as the mode of the distribution of the PRN measure, which expresses the Percentage Removed Noise on each pixel $\mathbf{a}$.

$$PRN(x, y) = 100 * \frac{u_o(\mathbf{a}) - \hat{u}_t(\mathbf{a})}{u_o(\mathbf{a}) - u(\mathbf{a})} \% \quad (5.8)$$

The PRN criterion requires knowledge of the underlying image and, therefore, it can be applied only on synthetic images of known noise. For the evaluation of the algorithm on real data, MRN is replaced by its estimation, the MMRN criterion, which is denoted as the mode of the distribution of the Modified PRN (MPRN) measure.

$$MPRN(x, y) = 100 * \frac{u_o(\mathbf{a}) - \hat{u}_t(\mathbf{a})}{u_o(\mathbf{a}) - \tilde{u}_t(\mathbf{a})} \% \quad (5.9)$$

The MMRN criterion is applied to a uniform area of an image, where it can be assumed that $\bar{u}_o(x, y) = u(x, y) = \tilde{u}_o(x, y)$, and therefore, the values of the underlying area can be replaced by the mean value of the restored area without significant loss of accuracy. The PVR criterion expresses the percentage reduction of variance and it is defined as

$$PVR(x, y) = 100 * \frac{\sigma^2 - \hat{\sigma}^2}{\sigma^2} \% \quad (5.10)$$

where σ^2 and $\hat{\sigma}^2$ denote the noise variances of the noisy and restored images respectively, as they are estimated from the selected uniform area. PVR applies both to trial and real images.

For MRN and MMRN the optimum value is 100. A value over 100 indicates under-denoising whereas a value under 100 over-denoising. PVR values range from 0 to 100. The above criteria reflect primarily the performance of restoration on underlying smooth areas rather than areas adjacent to edges. The restoration of the latest can be evaluated qualitatively by visual observation of the restored image and the noise method.

With the *noise method* [224], visual evaluation of the restoration process in addition to the above numerical criteria is performed. According to this method the removed noise rather than the restored image is examined. The requirement for effective restoration is the removed noise defined as $u_o - \hat{u}_t = n_t$ to approximate the real white noise n . As elaborated in *Appendix section C.4.4*, the TVM phase noise follows a rather complicated distribution which can be approximated, though, by a Gaussian distribution with zero mean (white noise) in image areas of high SNR. The assumption of high SNR is fulfilled for the flowing blood in flow velocity mapping and we hold the same assumption for the myocardial tissue in TVM, although tissue velocities are relatively low. We apply the TV Restoration method on each velocity component image accordingly.

5.2.4. In vivo data

To evaluate the proposed restoration algorithm, the method was first applied to synthetic images corrupted with white Gaussian noise of known variance. For in vivo validation, images from 10 healthy volunteers were analysed. Each subject was scanned with the spiral PC-MRI sequence described in [236]. For each subject, 11 short axis slices were acquired with 1.7 x 1.7mm spatial resolution (reconstructed to 0.85 x 0.85 mm) on a Siemens 3 Tesla scanner (MAGNETOM Skyra, Siemens AG Healthcare Sector, Germany). A slice thickness of 8mm and a slice separation of 8mm was adopted. Each imaging slice was acquired in a 13 cardiac cycle breathhold with a temporal resolution of 24 ms. The velocity sensitivity was 20 cm/s in-plane and 30 cm/s through-plane. The acquisitions were retrospectively cardiac gated which allowed full coverage of the cardiac cycle, including atrial systole which is not acquired when using conventional prospective cardiac gating approaches. Each acquisition was accelerated by a factor of 3 with non-Cartesian SENSE implemented on the Gadgetron GPU system [79]. For

one subject, the proposed restoration approach was applied to an entire ventricular stack. For each of the 10 subjects, a single mid-ventricular slice consisting 50 image frames over the full cardiac cycle was restored.

5.3. Results and Discussion

5.3.1. Synthetic data

The restoration algorithm was first tested on trial images. For this purpose, a grey and an RGB image were chosen. Figure 5 shows the proposed restoration technique applied to a synthetic grey image with 2 values of intensities, 0.3 and 0.7. The original image (a) was augmented with Gaussian white noise (d) with a variance of 0.01. The suggested TV restoration technique was then used to restore the original image (c). Image (d) shows the Gaussian white noise added to the original image, image (e) the removed noise with the proposed restoration method and image (f) the remaining noise on the image after the restoration.

The λ parameter was calculated based on the variance of the marked uniform area. The values of variance σ^2 , parameter λ as well as the MRN and MMRN and PVR criteria are presented in Table E.2. The corresponding PRN and MPRN distributions are shown in Figure 5.2.

It can be seen that the grey image was successfully restored. The noise was removed, the edges were maintained, and the smooth areas were revealed whilst keeping their initial intensity. The removed noise is very similar to the initial white noise. The efficacy of the algorithm was quantified by the MRN and MMRN criteria, whose values 101% and 99% respectively lie very close to the desired value of 100%. The estimated variance of noise having a value of 0.0091 is quite close to its real value of 0.01 leading to the calculation of an appropriate value for the regularisation parameter.

Table 5.1.: Restoration of a trial grey image: Parameters and Criteria

Estimated variance	0.0091
λ Parameter	10.47
MRN(%)	101.25
MMRN(%)	99.12
PVR(%)	99.61

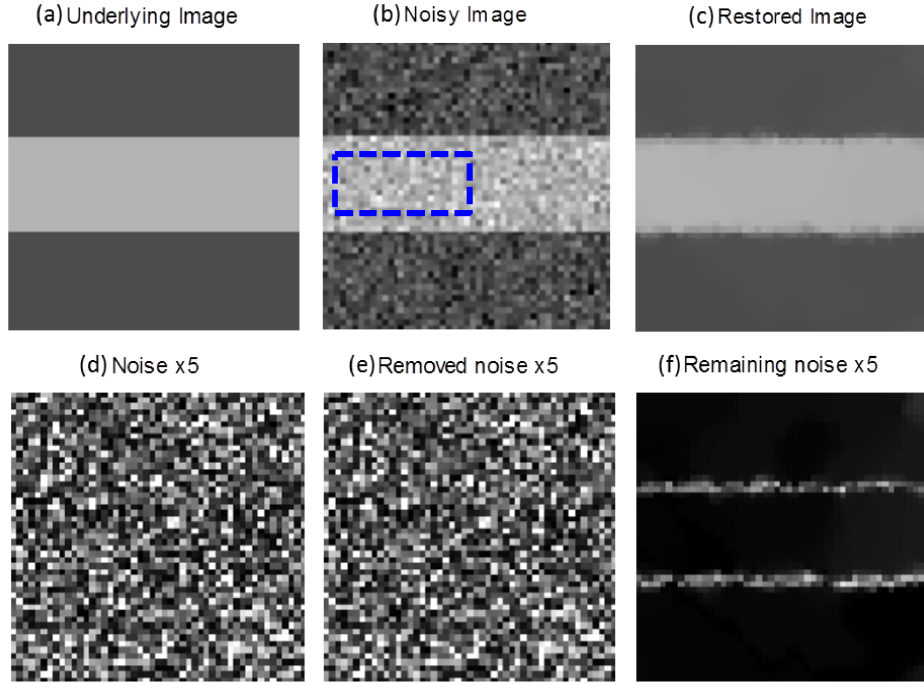


Figure 5.1.: (a) Original grey image, (b) its noisy version, (c) restored image and (b) uniform area for the calculation of λ marked in blue. (d) Initial noise amplified by 5, (e) removed noise amplified by 5 and (f) remaining noise after restoration amplified by 5.

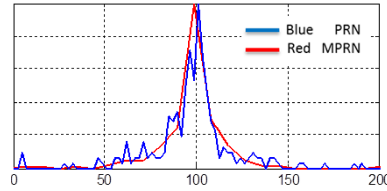


Figure 5.2.: Distributions of PRN and MPRN.

The advantage of the proposed TV Restoration algorithm methods becomes clearer when it is compared to a denoising method, like linear filtering. Figure 5.3 presents the results of filtering with a Gaussian kernel applied on the same trial image. Looking at image (c) it is obvious that actual smooth areas were not properly denoised and, besides, the edges were blurred. From images (e) and (f) it can be assumed that the removed noise is dissimilar to white Gaussian.

In the trials presented above a variance of 0.01 which approaches the noise

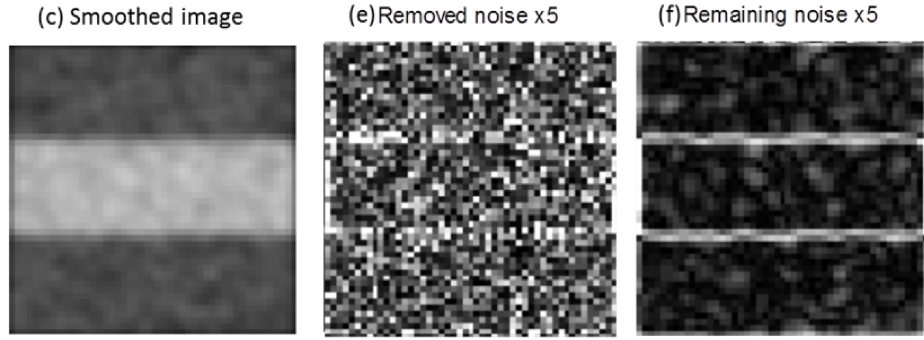


Figure 5.3.: Denoising of the trial grey image presented above with linear filtering. (c) Smoothed image with a Gaussian filter (standard deviation 1), (e) removed noise amplified by 5 and (f) remaining noise after smoothing amplified by 5.

level of PC-MRI data was used. The effect of the proposed TV Restoration method as well as linear filtering on images with various levels of noise is presented in Figure 5.4. It can be seen that TV Restoration removes successfully noise with variances up to the size of 0.1 and performs better than linear filtering in all cases. Quantitative assessment of the effectiveness of TV Restoration and comparison to linear filtering was performed with the aforementioned criteria as demonstrated in Table 5.2. Quantitative and qualitative assessments are in agreement. It can be noted that noise with a variance of 1 is an extreme case where most of added noise is comparable to the intensity values of the image and, for this reason, the underlying image in (a) is not discernible anymore. Although TV restoration is not that accurate in this case, it succeeds in revealing roughly the underlying features unlike linear filtering.

Table 5.2.: Restoration and Linear Filtering of a trial grey image for various levels of noise: Parameters, Criteria and Comparison.

Real Noise variance	TV Restoration					Linear Filtering			Improvement		
	Estimated Variance	λ parameter	MRN	MMRN	PVR	MRN	MMRN	PVR	(Rest-Filt)/Filt		
0.001	0.0010	30.92	100.22	94.05	99.54	77.54	77.98	92.05	29 %	21 %	8 %
0.01	0.0099	10.07	101.89	95.22	99.70	84.17	83.56	92.48	21 %	14 %	8 %
0.1	0.1023	3.13	105.82	101.14	99.97	76.41	78.75	90.57	38 %	28 %	10 %
1	0.9336	1.03	107.58	100.34	100.00	88.18	85.87	94.86	22 %	17 %	5 %

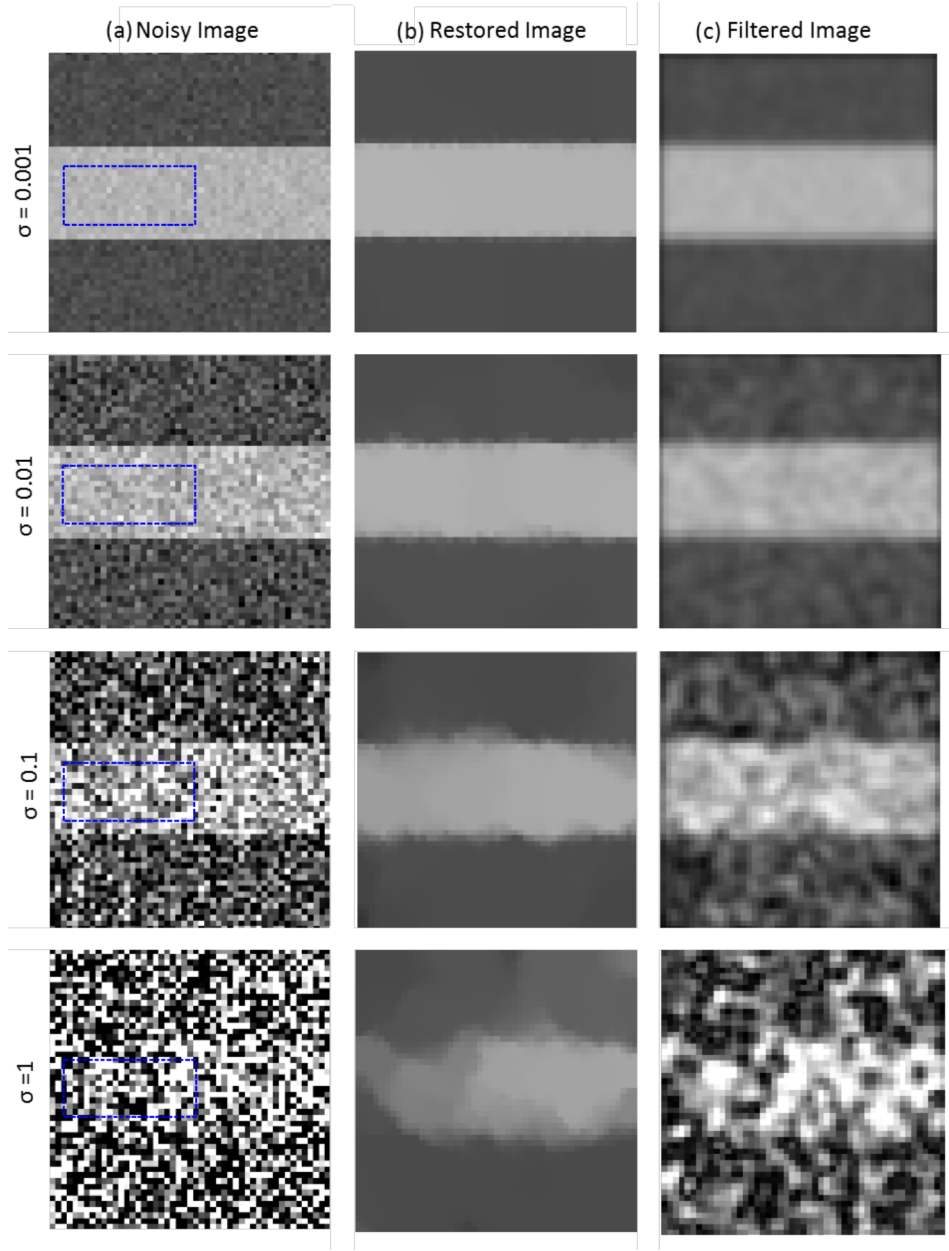


Figure 5.4.: (a) Initial image exposed to various levels of noise, (b) restored image with the TV method and (c) filtered image with a Gaussian kernel.

The restoration algorithm was also evaluated with a synthetic RGB image as demonstrated in Figure 5.5. As above, each colour component of the original image (a) was augmented with white Gaussian noise with a variance

of 0.01 resembling the noise corrupting each component of PC-MRI data. The TV restoration algorithm was applied to the noisy image (b) to generate the restored image (c). As in the previous application, (d) shows the initial noise, (e) the removed noise and (f) the remaining noise after the restoration. Figure 5.6 presents analytically the restoration results per colour channel.

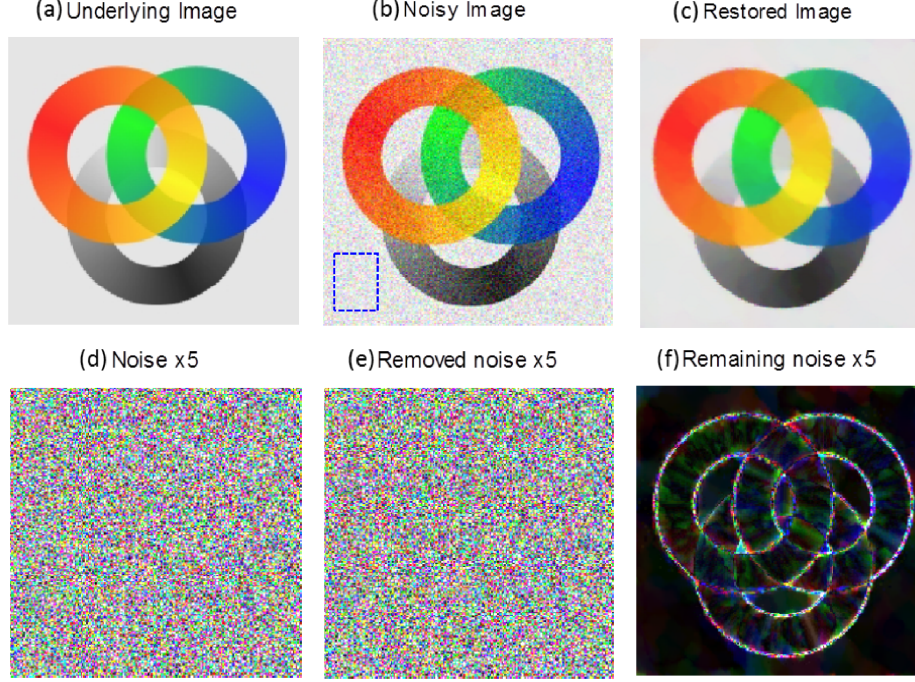


Figure 5.5.: (a) Original RGB image, (b) its noisy version, (c) restored image and (b) uniform area for the calculation of marked in blue. (d) Initial noise amplified by 5, (e) removed noise amplified by 5 and (f) remaining noise after restoration amplified by 5.

The λ parameters were calculated based on the variance of the marked uniform area (b). The PVR, MRN, MMRN criteria and the corresponding PRN and MPRN distributions per colour component are shown in Figure 5.7. The values of the criteria, variance σ^2 and parameter λ for each of the R,G,B channels are presented in Table E.2. The algorithm performed 850 iterations per channel in 28mins in total.

This second application of TV restoration on trial images confirms also the efficacy of the suggested TV restoration algorithm. The RGB image was also successfully restored, the noise was removed while the visual image features and intensity of the colours were maintained. The MRN, MMRN

and PVR criteria with total values of $(95.78 \pm 0.83)\%$, $(99.11 \pm 0.91)\%$ and $(99.92 \pm 0.07)\%$ respectively approach the desired value of 100%. The error in the estimation of noise variance is no more than 1% for all colour components, indicating a good approximation of the real noise variance and, consequently, a good estimation of the optimum λ parameter.

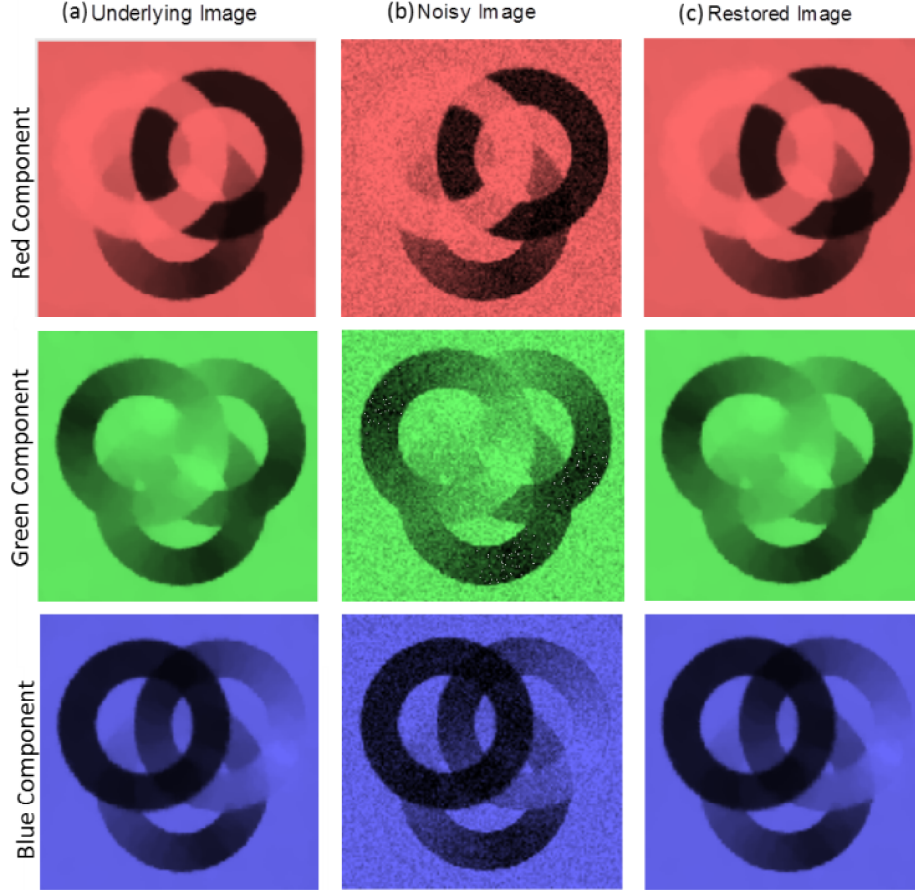


Figure 5.6.: Horizontally: (a) Clean colour component, (b) its noisy version and (c) the restored colour component. Vertically: red, green, blue colour channels distributions of PRN and MPRN per colour channel.

5.3.2. In vivo data

After the evaluation of the algorithm on trial images, the restoration method was applied to 2 sets of in-vivo PC-MRI data; a short axis full stack of 11

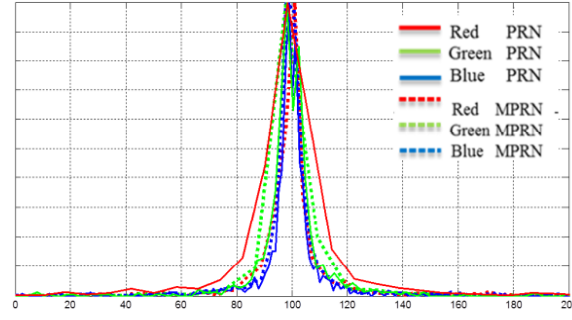


Figure 5.7.: Distributions of PRN and MPRN per colour channel.

Table 5.3.: Restoration of trial RGB image: Parameters and Criteria

Estimated variance	0.0099	0.0105	0.0099
λ Parameter	10.05	9.76	10.06
MRN(%)	96.69	95.55	95.09
MMRN(%)	98.44	98.75	100.14
PVR(%)	99.93	98.85	99.98

slices from an asymptomatic subject and a set of short axis mid-ventricular slices from 10 asymptomatic subjects. All slices consist of 50 time frames over 1 entire cardiac cycle Figure 5.8 (a) presents the restored slices of the stack at peak expansion and table (b) the MMRN and PVR criteria at peak expansion. The MMRN and PVR criteria have a total value of $(97.66 \pm 28.8)\%$ and $(83.8 \pm 11.9)\%$, respectively, approaching the optimum value of 100%. The MMRN and PVR criteria were calculated also for the rest of time frames and for each slice. Their distributions, drawn in (c), are sufficiently narrow and their peaks are near 100%. From the above numerical data, graph and images it can be claimed that the in-vivo myocardial velocities were successfully restored.

The proposed TV Restoration technique was applied to the second data set also on each velocity component and for all time frames. A sample of this second group of results is presented in Figure 5.9 . The figure illustrates the unrestored (b) and restored (c) velocity fields in yellow and removed noise (c) in red at peak anticlockwise rotation, peak contraction, peak clockwise rotation and peak expansion respectively. The yellow frame in (a) encloses the corresponding illustrated region of the myocardium.

Significant improvement in the myocardial velocity field is visually ob-

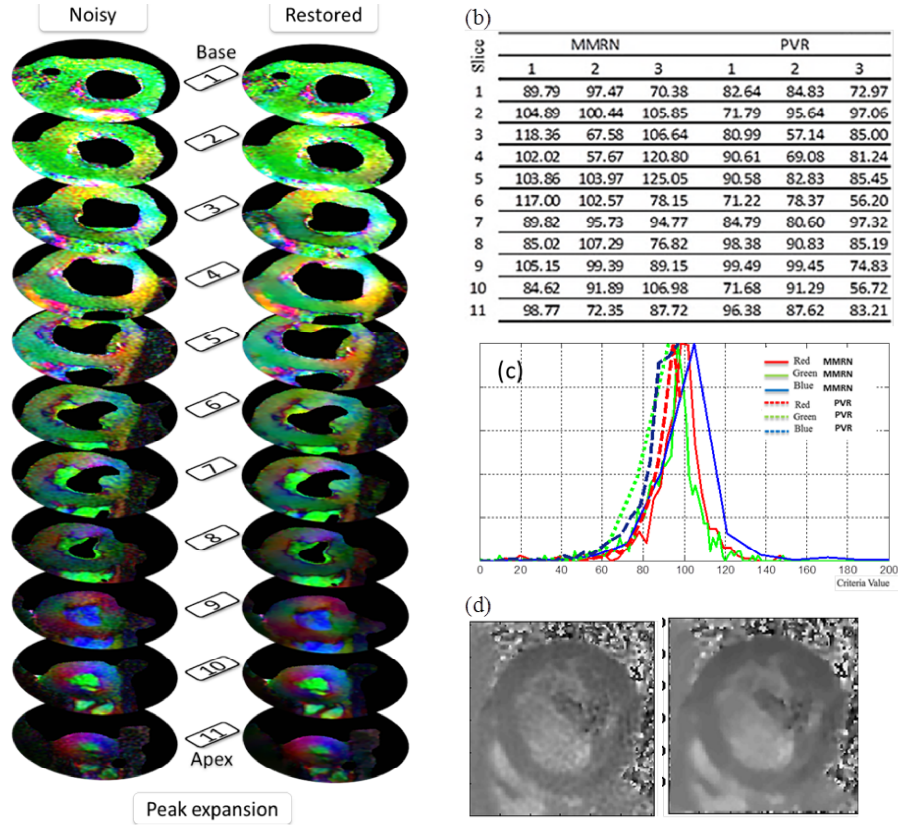


Figure 5.8.: (a) Noisy and restored velocity fields of a full stack from an asymptomatic subject at peak expansion. RGB colours represent 3D velocity components. Red: vertical, Green: horizontal and Blue: transplanar velocities. (b) MMRN and PVR criteria for each colour component on 11 slices. (c) Distributions of MMRN and PVR criteria for each channel over 11 slices x 50 time frames. (d) Example of noisy (left) and restored (right) velocity images.

served. Discrete myocardial regions made up of smooth velocities are revealed by the proposed restoration process. This myocardial velocity pattern is in accordance with the studies in the myocardium structure and function described in the literature.

Figure 5.10 presents the MMRN and PVR criteria calculated for the above application for the 3 velocity components at peak contraction. Their values, which lie in $(84.1 \pm 12.2)\%$ and $(88.3 \pm 8.5)\%$ respectively, confirm the

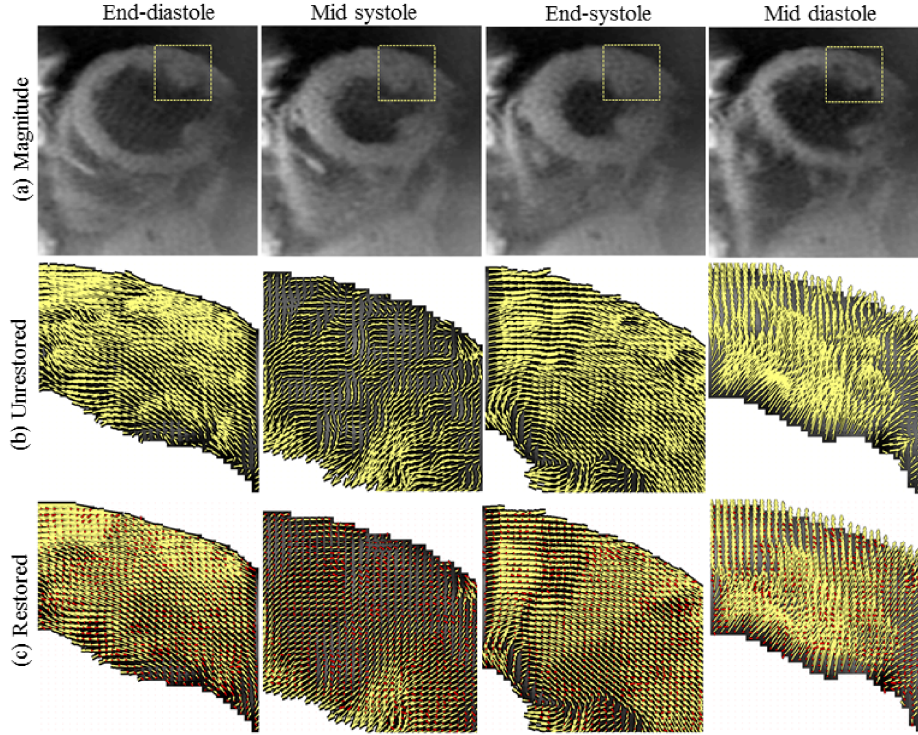


Figure 5.9.: (a) Mid-ventricular slice at peak anticlockwise rotation, peak contraction, peak clockwise rotation and peak expansion respectively and selected region for illustration in (b) and (c), (b) Unrestored velocity field, (c) Restored velocity field in yellow and removed noise vectors in red.

successful restoration observed in the visual representation of myocardial velocities above.

5.4. Discussion and Conclusion

5.4.1. Comparison with previous TV methods

- **Comparison with Chan and Shen's TV Restoration**

The proposed restoration method assumes a constant value of the regularization parameter λ rather than its iterative estimation, as seen in Chan and Shen's studies. In this way, the computation complexity of the restoration process is reduced while the efficacy of the method remains high. Cautious

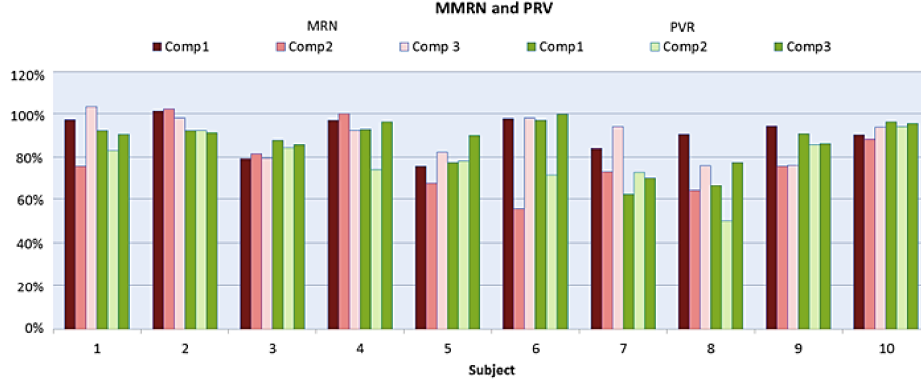


Figure 5.10.: MMRN and PRN criteria for the proposed restoration technique applied to a left ventricular short axis mid-slice stack for 10 asymptomatic subjects at peak contraction.

selection of a uniform area, as performed in this study, allows a good estimation of noise variance and, therefore, the calculation of an appropriate value for λ .

- **Comparison with other denoising methods**

Numerous other methods have been developed for image denoising and each one of them presents different advantages, weaknesses and level of suitability for the denoising of CMR and TVM data. Mohan [237] reviews and classifies the MR image denoising algorithms presented in the literature based on image filtering, domain transformation and statistical approaches. Filtering approaches employ convolution of the image with a filter either in the spatial or frequency domain and their main weaknesses are blurring and possible aliasing artefacts. We selectively mention existing image denoising methods below.

Anisotropic diffusion filtering is a multiscale filtering that enforces convolution of the image in the direction of minimum intensity gradient; this means that blurring or diffusion occurs along the boundaries of the image but not across them. This way the underlying smooth regions are smoothed and the boundaries are preserved simultaneously. Like TV restoration, conventional anisotropic diffusion filtering assumes white Gaussian noise and underlying piecewise constant or slowly variant small regions in the image. It preserves the boundaries well but it performs poorly in removing the noise from the flat regions, unlike TV restoration. On the other hand, TV

restoration may oversmooth texture when a small λ parameter is selected. A variation of the anisotropic diffusion filtering uses the information of curvature instead of the intensity gradient to direct the filtering and another variation [238] incorporates the information of Rician distribution and the local characteristics of noise in the filter in order to improve its performance on MR magnitude images; the main limitation of this variation comes from the fact that it requires a good estimation of the noise characteristics and distribution.

The Non-Local means (NL) [224] method makes use of the self similarity, that is to say redundancy, of an image. It estimates the value at each pixel as an average of the values of all pixels which have a similar neighbourhood to its neighbourhood. This method seems to perform quite well both on the smooth and discontinuous regions of an image. Its main disadvantage is its computational complexity and several variations have been proposed to tackle this. Since the NL method is based on the self-similarity of an image, it may be suitable for natural images where different objects are likely to be distinguished by their texture, but it might not perform well on MRI images where different features in two distant areas of the image might have similar texture.

The group of wavelet-based denoising methods describes the locally features either in the spatial or frequency domain and facilitates denoising by enabling separation of the noise in the frequency domain. However, wavelet-based denoising methods are not suitable for image features that contain high frequencies like the anatomical structure boundaries and velocity field discontinuities in CMR and TVM.

The bilateral filter is another smoothing filter that preserves discontinuities by making use of the geometric and photometric similarities around the neighbourhood of a pixel. The curvelet and contourlet transforms offer improved preservation of curves and contours but they do not behave well on smooth areas and smooth contours respectively.

The statistical approaches usually require the estimation of the noise variance of the image. The maximum likelihood approach achieves denoising by reconstructing the image using the maximum likelihood estimator on the nonlocal neighborhood at each pixel in order to predict the underlying noise. Other statistical approaches described in Mohan's review [237] are the linear minimum mean square error estimation, the phase error estima-

tion, the non-parametric estimation method and the Singularity function analysis.

Machine Learning (ML) and Deep Learning (DL) are increasingly used in image processing and seem promising in MR image denoising [239, 240]. Although an ML TVM image denoising method would eliminate the requirement for prior knowledge of the noise for an accurate restoration, it would introduce other challenges like the requirement for large TVM datasets and TVM ground truth datasets, which are not available, as well as questions about the interpretability of the results especially in case of extreme or rare pathologies which may lie outside the space of the training dataset.

5.4.2. Conclusion

In this chapter, we have demonstrated a robust restoration method for PC-MR velocity images from the left ventricle based on the Digital TV Filter. The restoration technique was first evaluated on a grey and an RGB artificial image and, subsequently, was applied on two sets of PC-MRI data mid-ventricular slices from ten healthy volunteers and one full stack from one healthy volunteer over a cardiac cycle. The MRN, MMRN and PVR criteria are introduced to evaluate the effectiveness of the method. The main advantage of the proposed method is its efficacy on PC-MR data, while being simple and computationally inexpensive. The restoration of myocardial velocity images will contribute to the fidelity of a future cardiac contractility atlas from PC-MRI data.

6. Translational velocity compensation

6.1. Introduction

Estimation of tissue motion, deformation and position often plays an important role not only in the diagnosis of a tissue condition but also in the effectiveness of a Computer Assisted Intervention (CAI) system. Medical imaging provides the necessary visual feedback for spatial navigation and guidance in CAI. Medical images can be acquired pre-operatively with CT or MRI to obtain a detailed visualisation of a pathology, which is then registered on the corresponding intra-operative data to transfer the detailed visual information to clinicians during the intervention. In this process, organ shift and soft tissue deformation that may occur before, at the start or during interventions need to be taken into consideration to ensure accuracy in the navigation and guidance [241]. This consideration is particularly important in abdominal and cardiothoracic surgery, where respiration and heart beating involve significant tissue motion that affects not only the participating organs but also the surrounding tissues. Previously presented strategies for the compensation of soft tissue motion in CAI include marker tracking, gating and real-time image registration [242, 243] techniques, which are either invasive, complex or of limited accuracy. The accurate non-invasive soft tissue motion estimation and compensation in an acceptably short time for real-time applications still remains a challenge.

Among the established medical imaging techniques for measuring tissue motion and deformation, Tissue Velocity Mapping (TVM) presents significant advantages as it provides direct measurements of tissue velocities in three orthogonal directions with high spatial and temporal resolution [128]. TVM yields velocities in reference to the scanner's coordinate system and, therefore, it captures motion that is attributed not only to tissue deforma-

tion but also to other sources of motion such as bulk movement of the heart due to beating, respiration and patient movement in the scanner. Moreover TVM data is affected by phase errors attributed to gradient eddy current residuals, concomitant field terms and gradient field distortions that appear as velocity offsets [128,170]. Velocity offsets vary smoothly across the image introducing an apparent translational velocity component to the measured TVM velocities.

For accurate assessment of myocardial deformation, correction of TVM for actual and apparent translational velocity is necessary. To this end, we propose a novel image processing translational motion compensation method, in two versions depending on the clinical study. The method is evaluated for effectiveness and robustness on synthetic and semi-synthetic velocity datasets and in vivo TVM datasets from 10 healthy volunteers. Results indicate excellent performance and robustness of the proposed method. Its applicability can be extended to any annular structure of soft tissue.

6.2. Methods

6.2.1. Theoretical analysis of velocities

Let $\vec{U} = \vec{U}(X, Y, Z)$ be the velocity of a tissue voxel measured with TVM at a position (X, Y) , in the Z^{th} slice and T^{th} frame of the cardiac cycle. $\vec{U}$ can be analysed into the following components

$$\vec{U} = \vec{U}_{motion} + \vec{U}_{offset} + \vec{U}_{noise} \quad (6.1)$$

where $\vec{U}_{motion}$ is the voxel's actual velocity expressed in the scanner's reference system, $\vec{U}_{offset}$ is the apparent velocity due to phase offset errors and $\vec{U}_{noise}$ is the noise in velocity measurements. $\vec{U}_{noise}$ can be compensated using the TV Restoration method presented in [244] and it is not considered further in the study. Since offset errors vary slowly across the image, they account for an apparent translational velocity in the tissue velocity measurements which is also compensated by our method. For the moment, it is assumed that $\vec{U}_{offset}$ term is incorporated into the translational motion or alternatively dismissed, thus

$$\vec{U} \approx \vec{U}_{motion} + \vec{U}_{offset} \approx \vec{U}_{motion} \quad (6.2)$$

Tissue velocity expressed in a local coordinate system (rather than the scanner's reference system) is a more intuitive representation of the regional tissue deformation and this is what is defined as *velocity from deformation* in the present study. The current motion compensation method relies on the conversion of velocities from the scanner's reference coordinate system to a local coordinate system adjacent to the heart according to the equation

$$\vec{U}_{motion} = \vec{U}_{transl} + \vec{u} \quad (6.3)$$

where $\vec{U}_{motion} = \vec{U}_{motion}(X, Y, Z)$ is the voxel's velocity expressed in the scanner's reference system, $\vec{u}$ is the voxel's velocity expressed in the local LV system and $\vec{U}_{transl}$ is the relative velocity of the local system (LV) with respect to the reference system (scanner). In other words, the goal of the motion compensation method is to estimate the translational velocity component $\vec{U}_{transl}$ and subtract it from the initial velocity measurements $\vec{U}_{motion}$.

The definition of $\vec{u}$ is not unequivocal as it depends on the definition of the local LV coordinate system. The local LV system, in turn, is defined based on what the clinician is trying to observe. In general the local LV system is an orthogonal coordinate system aligned with the short axis of the LV following the LV bulk motion. For clinical studies where deformation is examined across the entire volume simultaneously, a local LV system centered around the centre of mass $\vec{M}$ of the LV (V-local system) is more convenient. On the other hand, in clinical studies where deformation is examined slice by slice a local LV system centered around the centre of mass $\vec{m}(Z)$ of that specific slice Z (S-local system) is recommended.

In the V-local system $\vec{U}_{transl} = \vec{U}_{transl}^{(V)}$ expresses the bulk translational motion of the LV as seen from the scanner and it coincides with the velocity of $\vec{M}$ in the scanner's reference system. Likewise, in the S-local system $\vec{U}_{transl} = \vec{U}_{transl}^{(Sz)}$ expresses the bulk translational motion of the Z^{th} slice as seen from the scanner and it coincides with the velocity of $\vec{m}(Z)$ in the scanner's reference system. The difference between $\vec{U}_{transl}^{(V)}$ and $\vec{U}_{transl}^{(Sz)}$ is the relative velocity of $\vec{m}(z)$ with respect to $\vec{M}$. Due to the assumption made with equation Equation 6.2, the difference $\vec{U}_{transl}^{(V)} - \vec{U}_{transl}^{(Sz)}$ may incorporate differences in the offset errors across different slices as offset errors may vary across the longitudinal LV axis.

6.2.2. Velocity symmetry

The deformation of the normal LV is governed by a certain degree of symmetry, as it can be observed from previous studies on left ventricular shape and function. Short axis LV segments (according to the American Heart Association - AHA model) show pairwise similarity in velocity time courses [22] and systolic deformation parameters (strain, strain rate, velocity, displacement) [147]. Likewise AHA velocity plots [24] manifest pairwise segmental similarity indicating planar or cylindrical symmetry of myocardial deformation, a hypothesis that is adequately supported by finer segmental velocity plots [26] and pixel-wise velocity maps [28]. Velocities in the LV base and mid-wall match sufficiently the assumption of planar symmetry while apical velocities indicate either cylindrical or planar symmetry, (with poor agreement between the anterior and inferior segments.)

For this study the assumption of myocardial velocity field symmetry is held and for this, two models are defined: **Model A** is a model of cylindrical velocity vector symmetry around the LV short axis (lines interpolating the centres of mass $\vec{m}(Z)$). **Model B** is a combined model of i) planar velocity magnitude symmetry with respect to the bisectal plane of the 3D angle formed between the atrioventricular grooves and short axis of the LV and ii) cylindrical velocity directions symmetry similar to model A.

6.2.3. Motion correction method

Assuming either of the two types of velocity symmetry, $\vec{U}_{transl}$ is estimated by integration of $\vec{U}_{motion}$ in an appropriate region V contained in the LV and Equation 6.3 becomes

$$\int_V \vec{U}_{motion} dV = \int_V \vec{U}_{transl} dV + \int_V \vec{u} dV \quad (6.4)$$

With appropriate selection of the Region Of Integration (ROI) the $\int_V \vec{u} dV$ term is nulled (see proof below) and since $\vec{U}_{transl}$ is assumed constant across the entire region V , $\vec{U}_{transl}$ is estimated as

$$\vec{U}_{transl} = \frac{1}{V} \int_V \vec{U}_{motion} dV = \text{mean}_{\{V\}}(\vec{U}) \quad (6.5)$$

and the velocity from deformation is

$$\vec{u} = \vec{U}_{motion} - \vec{U}_{transl} \quad (6.6)$$

- **Region of integration.**

In a LV model of the shape of a perfect hollow truncated ellipsoid, the ROI is defined as a subregion of the LV of similar shape and smaller width aligned with the LV short axis. The cross sections of this region with the slice planes are rings of various radii and constant width. It is important that the ROI is equi-width and equidistant from the LV endocardial and epicardial surfaces in order that the error in integration is minimum. To take into consideration variations of the real LV shape from this LV shape model, the ROI is adjusted to another equiwidth and equidistant region sitting in the LV wall. This region is formed by closed straps around the medial axis of the LV cross sections on each slice, which are extended along the longitudinal direction. The closed straps (also called *rings* in this work), are computed as the dilated skeleton of the myocardial mask on each slice.

- **Proof.**

Assume a ring (ROI) from the Z^{th} slice of a real dataset has area S , as shown in Figure 6.1. Let dS_1 (in blue, Fig. 6.1a) and dS_2 (in red, Figure 6.1a) be two infinitesimal segments of S that are symmetric about the centre. Then $dS_1 = w d\theta_1$ and $dS_2 = w d\theta_2$, where w is the constant width of the ring by definition and $d\theta_1$, $d\theta_2$ are the circumferential infinitesimal lengths of dS_1 and dS_2 respectively. Because there is negligible variation of the mask along the circumference of the ring, it can be considered that $w d\theta_1 \approx w d\theta_2$, hence $dS_1 \approx dS_2$. If $\vec{u}_1$ and $\vec{u}_2$ are the velocities at dS_1 and dS_2 respectively and model A symmetry applies, $\vec{u}_1 = -\vec{u}_2$ and thus $\vec{u}_1 dS_1 \approx -\vec{u}_2 dS_2$ or $\vec{u}_1 dS_1 + \vec{u}_2 dS_2 \approx 0$. Integrating the latest relationship, it is proved that $\int_S \vec{u} dS \approx 0$, for each slice. If ROI is defined in the 3D space $\int_S \vec{u} dS = \sum_z (\int_{S_z} \vec{u} dS_z) \approx 0$.

In case of model B symmetry, it is also proved that $\int_S \vec{u} dS \approx 0$. Let dS_1 (in blue, Figure 6.1c), dS_2 (in green, Figure 6.1c), dS_3 (in red, Figure 6.1c) and dS_4 (in orange, Figure 6.1c) be four infinitesimal segments of S with $\{dS_1, dS_2\}$ and $\{dS_3, dS_4\}$ located symmetrically in pairs about the bisector line as defined in model B, $\{dS_1, dS_3\}$ and $\{dS_2, dS_4\}$ located symmetrically

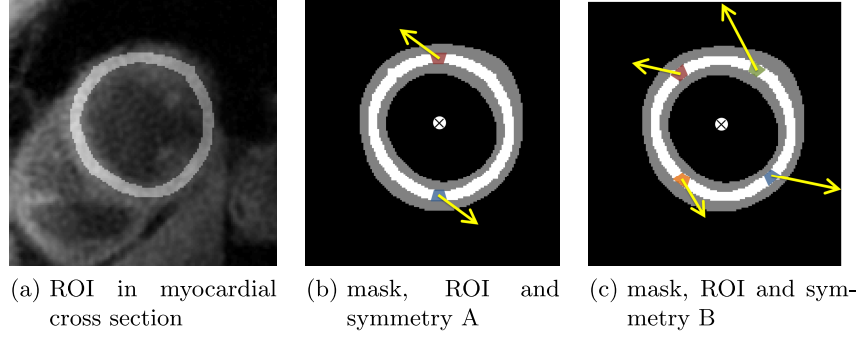


Figure 6.1.: Region of integration (ROI) on a short axis slice (a) superimposed on the corresponding TVM image and (b-c) superimposed on the corresponding mask, showing pairs of symmetric infinitesimal myocardial segments in case of (a) cylindrical and (b) planar symmetry.

in pairs about the centre. As above $dS_1 \approx dS_2 \approx dS_3 \approx dS_4$. If $\vec{u}_1, \vec{u}_2, \vec{u}_3, \vec{u}_4$ are the corresponding velocities at dS_1, dS_2, dS_3, dS_4 and since model B symmetry applies, the following relationships for the velocity magnitudes $u_1 = u_2, u_3 = u_4$ and velocity directions $\hat{u}_1 = -\hat{u}_3, \hat{u}_2 = -\hat{u}_4$ occur. For this, the sum $\vec{u}_1 + \vec{u}_2 + \vec{u}_3 + \vec{u}_4 = 0$, hence as above $\vec{u}_1 dS_1 + \vec{u}_2 dS_2 + \vec{u}_3 dS_3 + \vec{u}_4 dS_4 \approx 0$. By integration over the entire S it is proved that $\int_S \vec{u} dS \approx 0$ and thus $\int_S \vec{u} dS = \sum_z (\int_{S_z} \vec{u} dS_z) \approx 0$.

- **Motion correction.**

For this study, two versions of the motion correction method were implemented and evaluated. For the first variation **method 1**, the velocity from deformation $\vec{u}$ is expressed in the S-local coordinate system on each slice. The ROI is a 2D region within the myocardial mask on each slice, from which the mean velocity is calculated per frame and slice and then subtracted from the initial velocity image. For the second variation **method 2**, the velocity from deformation $\vec{u}$ is expressed in the V-local coordinate system, the ROI is a 3D region within the myocardium, from which the mean velocity is calculated per frame across all slices and then subtracted from the initial velocity images.

6.3. Experiments

6.3.1. Numerical validation

To evaluate the effectiveness and robustness of the proposed motion correction algorithms, synthetic and semi-synthetic velocity datasets were constructed and corrupted with a large known translational velocity.

- **Simulated synthetic data.**

The simulated synthetic velocity datasets were generated with the following specifications: i) the myocardial mask is a hollow disk centred at C_m , ii) the 2D velocity field has the symmetry of model A or model B and is centered at C_v , iii) C_m and C_v coincide, iv) the velocity vectors increase progressively from the outer boundary (epicardium) to the inner boundary (endocardium) to model the higher deformation of the endocardium as compared to the epicardium and v) the velocity directions evolve periodically over time passing through the phases of anti-clockwise rotations, rotation, clock-wise rotation and expansion.

Let:

$$\vec{u} = u\hat{u}T \quad (6.7)$$

be the velocity of a pixel in the simulated dataset at time t , u the magnitude of velocity at each pixel, $\hat{u}$ the unit vector in the direction of velocity at each pixel and $T(t)$ be a sinusoidal term attributing periodicity over time t . For **model A** the terms in Equation 6.7 become $u = u_r(r)$ and $\hat{u} = \hat{u}(\theta)$, where $u_r(r)$ is reversely proportional to the distance r of each pixel from C_v and $\hat{u}(\theta)$ is a function of the angle θ formed between the line connecting C_v with each pixel and the horizontal axis. In other words the vectors $\vec{u}$ are symmetric about the centre of the vector field C_v . For **model B** the terms in Equation 6.7 become $u = u_r(r)u_\theta(\theta)$ and $\hat{u} = \hat{u}(\theta)$, where $u_\theta(\theta)$ is a magnitude term that varies smoothly along the circumferential direction of the dataset nulling at the positions of the suppositional atrioventricular grooves and $u_r(r)$ and $\hat{u}(\theta)$ are defined as above. In this case the velocity magnitude u is symmetric about the bisector of the angle formed between the centre and the suppositional atrioventricular grooves whereas vector directions $\hat{u}$ maintain the symmetry about the centre C_v .

Translational velocity of large magnitude (200% of maximum u) was

added to the synthetic velocity field to form the *uncorrected* dataset. To examine robustness, *distorted* synthetic datasets were generated from the above synthetic datasets with distortion of the mask symmetry and misalignment between the mask and the velocity field. The motion correction method 1 was then applied.

- **Realistic semi-synthetic data.**

To take into consideration other deviations from symmetry and unmodelled characteristics of realistic data, the motion correction method was evaluated on a realistic semi-synthetic dataset. The semi-synthetic dataset was created from an in vivo 3D-t TVM velocity dataset that was used as a template on which a known translational velocity was added. Motion correction methods 1 & 2 were then applied and the corrected velocity fields were compared to the template.

6.3.2. In vivo study

For in vivo validation, TVM velocity data from 10 healthy volunteers were analysed. Each subject was scanned with the breath-hold spiral PC-MRI sequence described in [134] on a Siemens 3 Tesla scanner (MAGNETOM Skyra, Siemens AG Healthcare Sector, Germany). Nine contiguous short-axis slices were acquired with an in-plane spatial resolution of 1.7 x 1.7mm (reconstructed to 0.85 x 0.85 mm), slice thickness of 8mm, three-directional velocity encoding with in-plane and through-plane velocity sensitivity (V_{enc}) of 20 cm/sec and 30cm/sec respectively. Fifty frames per slice were reconstructed covering a full cardiac cycle and equally spaced through it. Blood flow and respiration artefacts were suppressed with a black blood preparation pulse and breath-hold acquisitions correspondingly.

TVM data were processed prior to motion correction. Pre-processing includes alignment of images to a common Cartesian coordinate system, conversion of phase measurements to velocities according to the V_{enc} parameters and restoration of velocities for noise with the TV Restoration-based method described in [244]. For visualization purposes the myocardial region on each image was semi-automatically delineated. The proposed translational motion correction method was then applied. Analysis and visualization of all images were performed with in-house software built in MATLAB (The Mathworks Inc, Natick, MA) for this study.

Table 6.1.: Percentage error in the estimation of the ground truth translational velocity of the synthetic velocity field with method 1.

	Model A	Model B	Model A/distorted	Model B/distorted
x axis	+0.26 %	+0.14 %	- 0.17 %	- 0.02 %
y axis	- 0.06 %	- 0.05 %	+0.23 %	+0.10 %

6.4. Results

6.4.1. Synthetic dataset

Motion correction method 1 was first applied on the *uncorrected* simulated synthetic datasets of model symmetry A & B and their distorted versions, as defined above. Results of motion correction from an intermediate frame of combined contraction and anti-clockwise rotation for the four types of simulated datasets are presented in Figure 6.2. The corrected images look identical to the ground truth images. As shown in Table 6.1, in all cases the percentage error in estimating the translational velocity does not exceed 0.3% of the ground truth translational velocity, despite its large value (200% of the maximum underlying velocity) and despite the imposed velocity field distortions, indicating excellent effectiveness and robustness of motion correction method 1.

6.4.2. Semi-synthetic dataset

Motion correction methods 1 & 2 were then applied on the realistic semi-synthetic dataset corrupted, as described above. Results of motion correction method 1 from an apical, mid-wall and basal slice of the LV at peak anti-clockwise rotation are presented in Figure 6.3. The translational component is successfully removed and no remaining errors are observed. The corrected images look identical to the ground truth images confirming the effectiveness of the method.

6.4.3. In vivo dataset

The proposed motion correction was subsequently applied to 8 slices and 50 frames of each of the 10 in vivo TVM datasets and a sample of this group of results is illustrated in Figure 6.4. The figure shows the in-planar myocardial

velocity field from an apical, mid-wall and basal slice of the LV at peak anti-clockwise rotation and peak contraction, before and after motion correction with method 1. Regions of enhanced velocities lying opposite to regions of suppressed velocities appear in the uncorrected velocity fields and, thus, indicate the presence of translational velocity on top of the velocity from deformation. Such distortions of velocity are not visible in the corrected images, indicating the effectiveness of the method.

Figure 6.5 demonstrates a 3D visualisation of the 3D velocity field from a full stack of TVM at peak expansion (a) before translational motion compensation, (c) after before translational motion compensation with method 1 and (b) method 2. The 3D visualisation of the uncorrected stack shows a bias in the velocity field caused by translational velocity, whereas the corrected stacks look more balanced. This visualisation of results pictures the difference in the two methods: Method 1 yields a stack which looks overall more symmetric as correction has been applied slice by slice taking into account the centre of mass per slice. On the other hand method 2 yields a stack where the base seems to move in the opposite direction to the mid-wall and apex, revealing a relative motion between the lower and upper part of the LV. Visualisation of the second stack is looks more realistic and method 2 is recommended when examining deformation from the entire volume. When looking at the deformation slice by slice method 1 yields more intuitive results and it is recommended in that case.

6.4.4. Time courses

Time courses of the estimated translational component per subject, frame, slice and volume along the 3 velocity directions x , y and z are presented in Figure 6.6 - Figure 6.8.

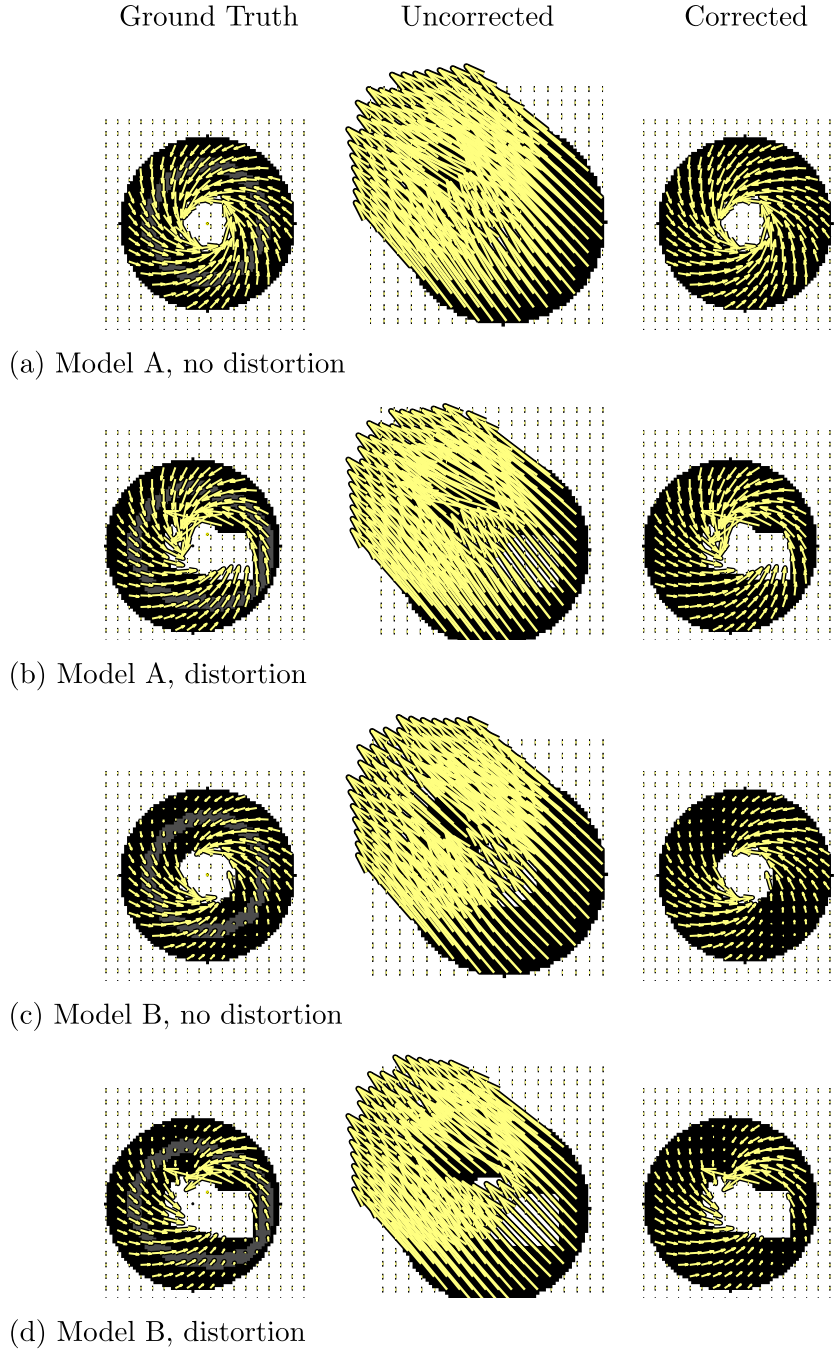


Figure 6.2.: Evaluation of motion correction method 1 on a 2D synthetic velocity field of (a) model A symmetry (b)model A symmetry with mask distortion, velocity field and mask misalignment, (c)model B symmetry, (d)model B symmetry with mask distortion, velocity field and mask misalignment. Estimation error of the translational velocity in x and y directions is no more than 0.3 % of actual added translational velocity in all cases.

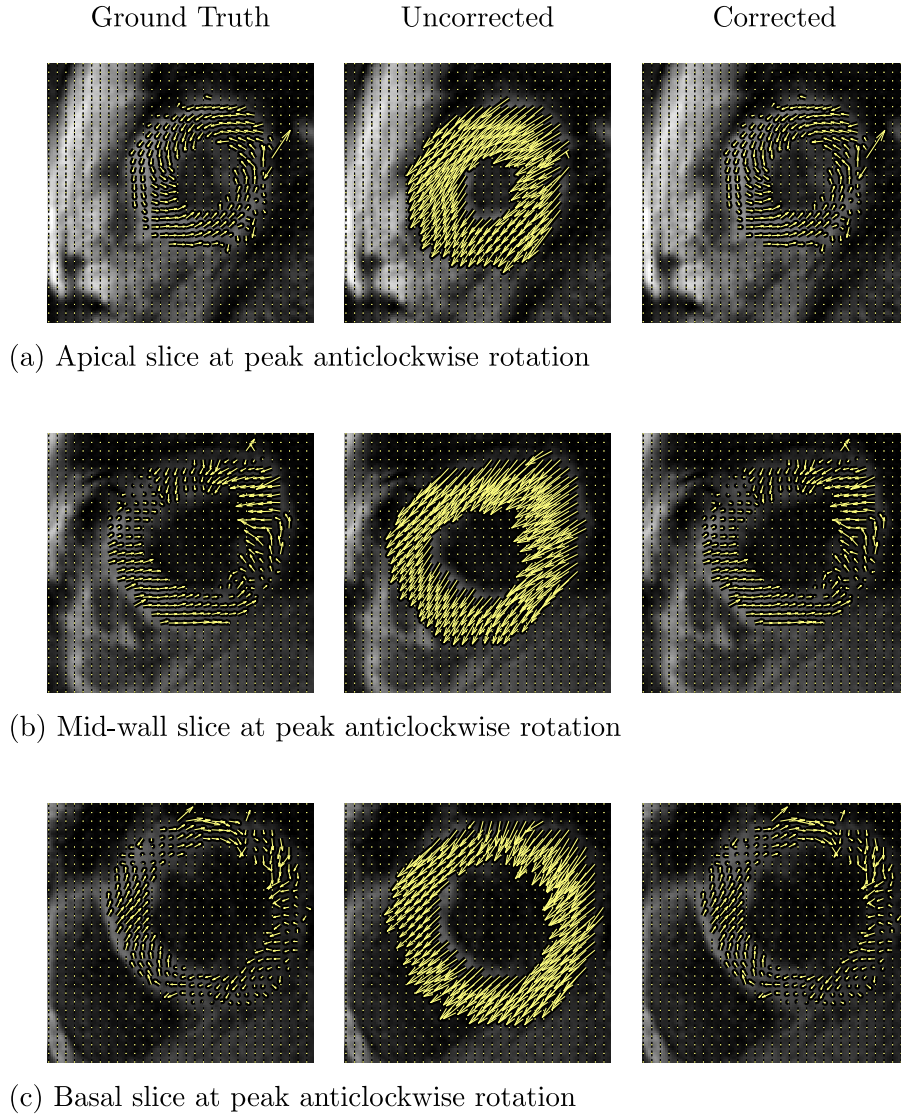
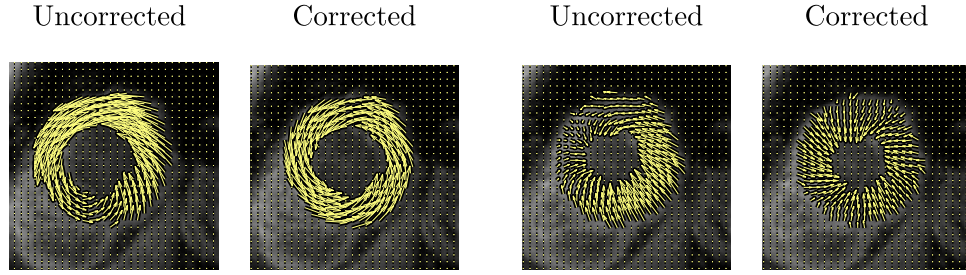
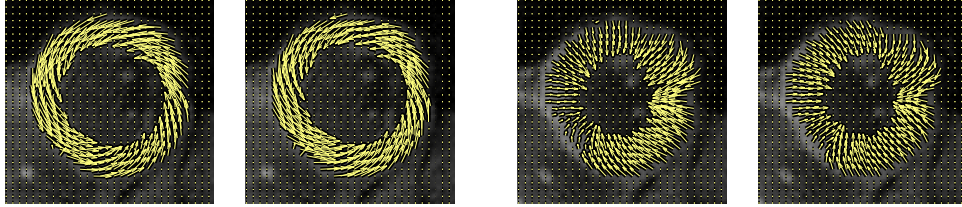


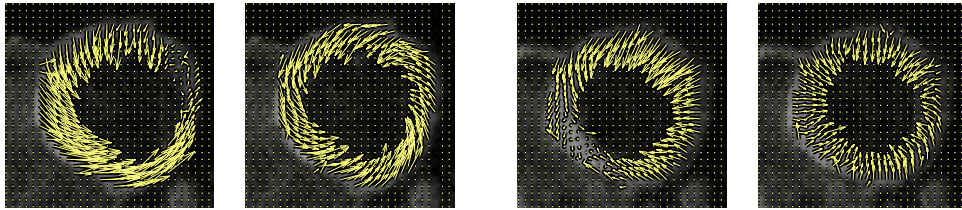
Figure 6.3.: In-planar velocity field from an (a) apical (b) mid-ventricular and (c) basal short axis slice of a semi-synthetic TVM velocity stack at peak anti-clockwise rotation without translational motion, with translational motion and corrected for translational motion with method 1.



(a) Apical slice at peak anticlockwise rotation (left) and peak contraction (right)



(b) Mid-wall slice at peak anticlockwise rotation (left) and peak contraction (right)



(c) Basal slice at peak anticlockwise rotation (left) and peak contraction (right)

Figure 6.4.: In-planar velocity field from an (a) apical (b) mid-ventricular and (c) basal short axis slice of a TVM velocity stack from a healthy volunteer at peak anti-clockwise rotation and peak contraction before and after translational motion compensation with method 1.

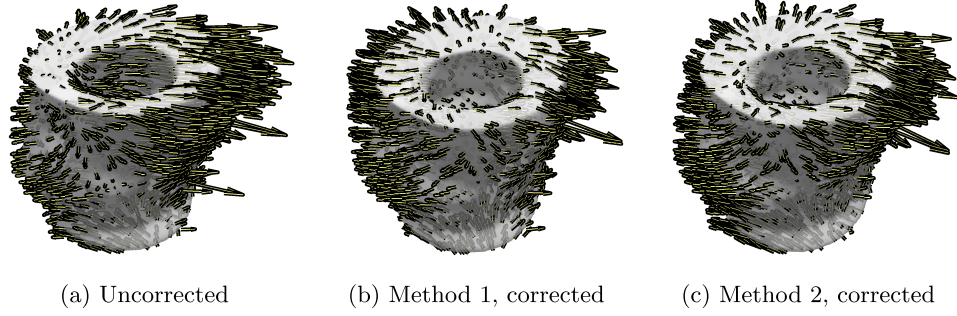


Figure 6.5.: 3D velocity field from a full stack of TVM data from a healthy subject at peak expansion (a) before motion correction, (b) after motion correction with method 1 and (c) method 2.

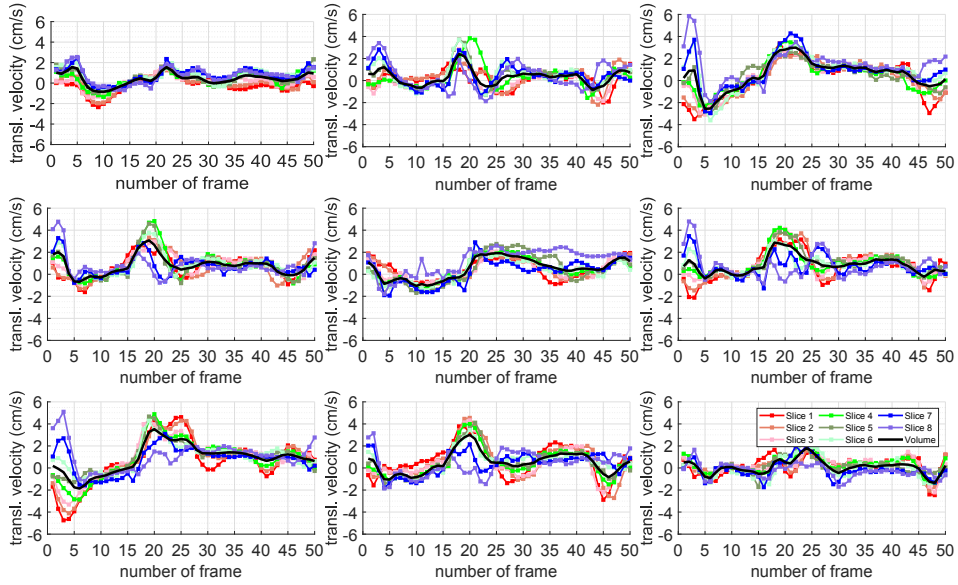


Figure 6.6.: Time courses of removed translational velocity component per slice with method 1 (coloured lines) and per volume with method 2 (black line) in x direction for 9 TVM datasets.

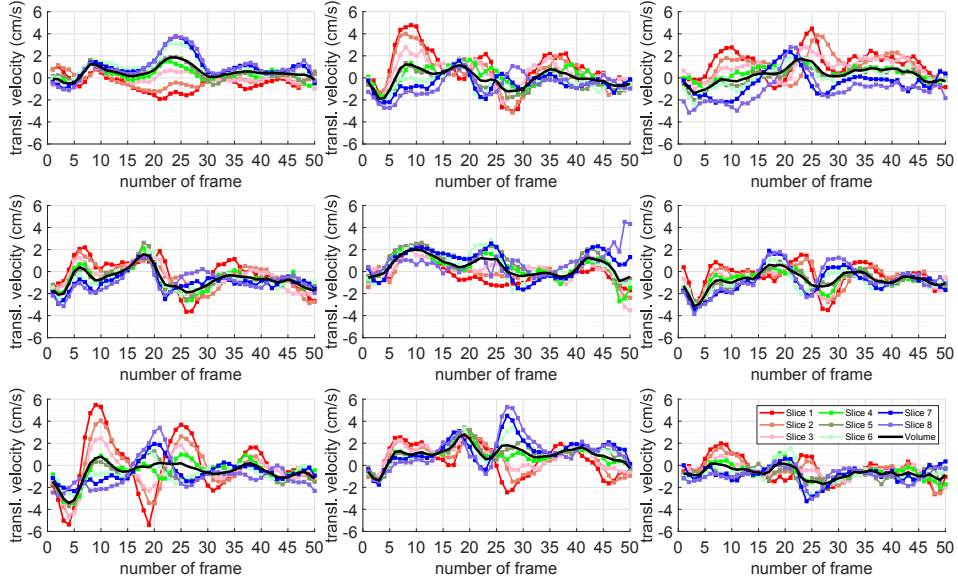


Figure 6.7.: Time courses of removed translational velocity component per slice with method 1 (coloured lines) and per volume with method 2 (black line) in y direction for 9 TVM datasets.

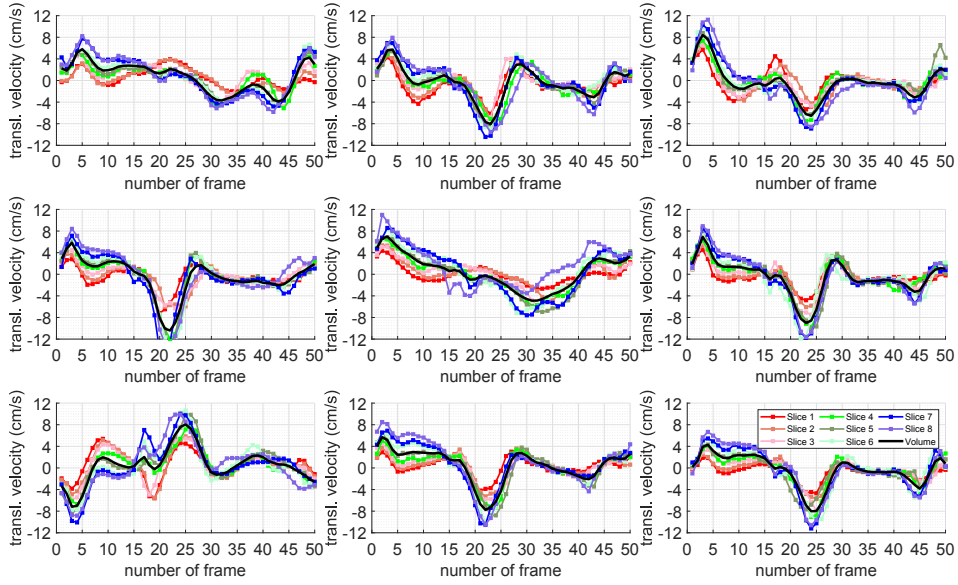


Figure 6.8.: Time courses of removed translational velocity component per slice with method 1 (coloured lines) and per volume with method 2 (black line) in z direction for 9 TVM datasets.

6.5. Discussion and conclusions

In this study we have proposed a novel, effective and robust method for motion correction of myocardial tissue velocities. Translational velocity of the left ventricle is estimated from a 2D or 3D region in the left ventricular myocardial wall and deducted from the total measured myocardial velocities. The selection of the region is critical in the efficiency of the method and it is important that it follows the deformation of the LV during the cardiac cycle. Furthermore, the selected region is independent from circumferential variations in the wall thickness that might occur in several myocardial conditions such as myocardial infarction or hibernation. The fundamental assumption in the proposed method states that the left ventricular deformation is governed by a degree of symmetry, which we have based on the observation of results from previously published studies on myocardial deformation. Accordingly, we have suggested two models for the distribution of the in-planar left ventricular myocardial velocities assuming planar symmetry for the one model and cylindrical symmetry for the other model. We used these models to generate synthetic velocity datasets and in-vivo TVM images to generate semi-synthetic datasets for the evaluation of the proposed motion correction method. The method showed excellent performance both on the synthetic and semi-synthetic datasets. The method was, subsequently, applied on TVM images from 10 healthy subjects and visual observation of the corrected velocity field 2D and 3D visualisations indicated similarly remarkable performance.

Motion correction was applied on a per slice and a per volume basis, which is equivalent to velocity transformation from the scanner's reference coordinate system to a local coordinate system that follows the slice in the first case, and the volume of the LV in the second case. The per slice and per volume estimated translational velocities can combine for the estimation of further motion parameters, for instance the rotation of the LV; rotation and per volume translation together describe the rigid body motion of the LV, if image artefacts are dismissed. After rigid body motion compensation, the residual velocities are attributed to myocardial tissue deformation. Although strain and strain rate are most established measures for the description of regional myocardial deformation, their derivation from the commonly used imaging modalities is followed by notable enhancement

of the image noise and artefacts, which severely interferes with the generated strain and strain rate maps. For meaningful deformation maps, the strain and strain rate values are usually averaged over larger groups of pixels or segments and this has the consequence to overlie finer details of myocardial deformation and potential abnormalities. We propose the corrected velocity maps as an alternative intuitive representation of regional deformation at a per pixel level, which is significantly less affected by image noise and artefacts. Along with the translational motion, the proposed method corrects also for spatially slowly varying TVM image artefacts like the velocity offset errors and respiratory motion artefacts that affect primarily the free-breathing acquisitions.

The proposed translational motion compensation method is non-invasive, computationally inexpensive and without prior information requirements. For this study, the method has been evaluated on cardiac MRI from the LV primarily developed for cardiac disease diagnosis. The applicability of the method is appraised quite broadly though, as it solves the generic engineering problem of motion correction. It is suited to any deforming soft tissue that has annular cross sections and fulfils the symmetry requirements. It also applies to velocity fields captured by any imaging modality or other technique beyond the bounds of TVM. The method can potentially benefit intraoperative image guidance and tracking, for instance in cardiac interventions, as it permits real-time processing. However, there is a certain amount of research to be done towards this end, in order to allow for real-time acquisitions of high quality tissue velocity images.

7. Discussion and conclusions

7.1. Overview and contributions of this thesis

Cardiac disease is a leading cause of mortality and morbidity worldwide urging the need for accurate and early cardiac disease diagnosis, as confirmed by the latest statistics. Since cardiac disease and conditions affect primarily the LV and are associated with alterations in myocardial contractility, we have adopted the claim that the myocardial contractility can serve as a diagnostic means for cardiac disease. As global indices of cardiac function are commonly not affected at the early stages of a disease because of the preeminent compensatory mechanisms of the heart, we focus on the study of the local cardiac indices in the LV. This thesis has made several contributions towards the construction of consistent and detailed myocardial contractility maps from the LV, with the ultimate goal to incorporate these maps into the study of the underlying mechanism of cardiac conduction and, most importantly, translate them into the clinical setting for an early and accurate cardiac disease diagnosis and prognosis.

We have performed a thorough review of the literature covering cardiac studies and the available imaging modalities for the detailed depiction of cardiac anatomy and function; specifically we have discussed the principles of each technique, their image types, advantages and limitations and we have drawn the conclusion that CMR imaging offers a number of significant advantages including safety, sufficient spatiotemporal resolution, tomographic plane flexibility and particularly versatility. The four advanced CMR techniques dedicated to the measurement of myocardial tissue motion and deformation have also been discussed in terms of advantages, challenges, applications and, in particular, the analysis methods for the extraction of meaningful contractility indices from their images. The reasons that have led to the selection of PC-MRI and TVM for the current work have been discussed in detail in *Chapter 2*.

Prior to the extraction of contractility information from the TVM images, we investigated the available measures for the quantification of myocardial contractility in *Chapter 3*. The chapter has provided a thorough review of the contractility measures across the cardiac studies as well as a description of the 3D deformation measures that can be translated from the field of continuum kinematics to myocardial deformation studies. A critical approach to the literature has led to the conclusion that the myocardial tissue behaves as a continuum that is potentially disrupted by discontinuities, to which the principles of continuum kinematics can be applied. Along these lines the incompressibility constraint has been investigated and the drawn conclusion is that although the myocardium is compressible in principle, the incompressibility constraint still improves the performance of several analysis methods. The main contribution of this chapter is the claim that a degree of inconsistency resides among the strain analysis myocardial studies, which is attributed to the wide variety of strain formulas that are employed. We have provided a theoretical analysis of the discrepancy between different strain formulas, numerical studies for the accurate computation of the discrepancy and a formula for its analytical approximation along with its proof. By applying the discrepancy analysis on myocardial strain values reported in the literature, we have shown that the discrepancy between the different strain formulas can have a considerable impact on the significance of strain results, if the strain formula is unclarified. We have, therefore, introduced the statement that it is necessary to clarify the strain formula in each study, consider it in the assessment of strain results and ensure compatibility of myocardial strain studies prior to their comparison.

In *Chapter 4* we have proposed a novel framework for the improvement of segmental myocardial analysis and have provided the associated newly developed tools. We have claimed that myocardial division plays an important role in the accuracy of the segmental analysis and we have made the remark that the existing studies do not clarify the details of myocardial division, which implies that a simplified and most likely inaccurate schemes have been followed. We have stated that myocardial division needs to be tailored to each TVM image by performing an original analysis of the IV positions across the TVM stack images, which has shown that the two most important reference points for the segmental division vary considerably across the TVM images. The IV positions, in particular, show considerable displace-

ment between the maximum clockwise and anticlockwise rotations. The inter-slice variation is concluded to be attributed to the geometry of the LV only partially. 50% roughly of the datasets have shown a degree of slice misalignment despite the instruction before and during the acquisition. We have also developed the tools for the quantitative and qualitative examination of slice alignment and this is another original contribution of this chapter. To improve the segmental consistency via the accurate adjustment of the myocardial division, we have developed and proposed interactive tools for accelerated semi-manual marking of the IV points and the delineation of myocardial contours. We have suggested a method for automatic estimation of the third reference point, that is the LV centre to be the centre of mass of the segmental mask and we have shown that the LV centre position does not vary considerably. We have explained why small segmental residuals from TVM images can have a tremendous effect on the segmental maps and we have developed a novel, automatic and effective texture-based method for the correction of the myocardial masks tailored to the needs of segmental analysis. We have also proposed new plots of AHA maps that provide a clinically meaningful spatiotemporal overview of the left ventricular contractility and are suitable for inter- and intra-subject assessment. We have presented the time courses of segmental velocities over 10 TVM datasets and have assessed the improvement of segmental velocity consistency by means of CI width reduction. All time courses have confirmed that the proposed framework succeeds in the improvement of segmental analysis consistency. Moreover, we have introduced the concept of LV motion symmetry based on the observation of our results of segmental velocity time courses.

Chapter 5 has presented a new TV restoration method for the denoising of TVM images and the improvement of regional myocardial velocity consistency. The main advantage of the proposed method over its similar methods is the reduction in computational complexity which is achieved with the experimental estimation of the λ parameter from a selected region in the TVM images, instead of its iterative computational estimation. The proposed TV restoration method has shown to restore successfully synthetic and in vivo datasets while preserving underlying discontinuities. The proposed method has also shown increased robustness at the execution of the experiments and it is suggested for a sufficiently accurate restoration of TVM images.

Another original contribution of the current thesis is the translational ve-

locity compensation method described in *Chapter 6*. The proposed method has been based on the assumption of LV motion symmetry and its efficacy has been first proved analytically. Again, the new concept of LV motion symmetry is introduced and two models of LV symmetry have been considered and investigated based on observation of cardiac motion results from the literature. The method has been evaluated for its effectiveness and robustness on synthetic, semi-synthetic and in vivo datasets and has shown excellent performance. The velocities that remain after the deduction of the translational motion reflect the deformational motion of the myocardial tissue and have shown to provide an intuition into the myocardial contractility. An original idea is to employ the deformational velocity field as an alternative contractility map, which is perhaps less meaningful than the strain maps but easier to compute.

7.2. Future work

The work presented in the main body of this thesis has excluded a considerable amount of related research work, which has been either incomplete or unreported due to data limitations, but it opens new interesting research topics for future investigation. We describe these topics below along with new ideas and research challenges that have been initiated from the presented analysis.

- **TVM analysis framework.**

Image analysis methods have been presented to address individual TVM image processing challenges i.e. noise alleviation, translational motion compensation, contractility quantification, contractility analysis evaluation etc., which were meant to compose a generic standardised TVM analysis framework, which has already been mentioned in the presented work but not described yet. We have designed and proposed such a generic framework outlined by the pipeline in Figure 7.1. The pipeline is comprised of a main branch for velocity analysis and improvement of its consistency and a secondary branch for the segmentation and division of the LV. It also includes a visualisation step for the intuitive representation of contractility indices and a statistical analysis step for more accurate inter- and intra-subject contractility assessment. For each of the outlined processing steps, preliminary work has been done and we are planning its future completion, evaluation or extension.

- **TVM artefact reduction.**

The reduction of background phase offsets has been attempted with the subtraction of homologous steady phantom datasets from the in-vivo datasets and the corrected datasets have been used for the evaluation of the TV restoration method in *Chapter 5*. As explained in *Chapter 2*, phantom correction reduces background offsets only to a certain degree and we believe that if phantom correction is combined with surface fitting, which is another approach of background offset correction, the background offsets can reduce further. Furthermore, the phantom TVM datasets acquired with the latest version of Simpson’s TVM sequence [23] presented an unexpected drift over time and a circular artefact pattern, which is presumably associated with the spiral sampling of the k-space. We have initiated the study of this TVM

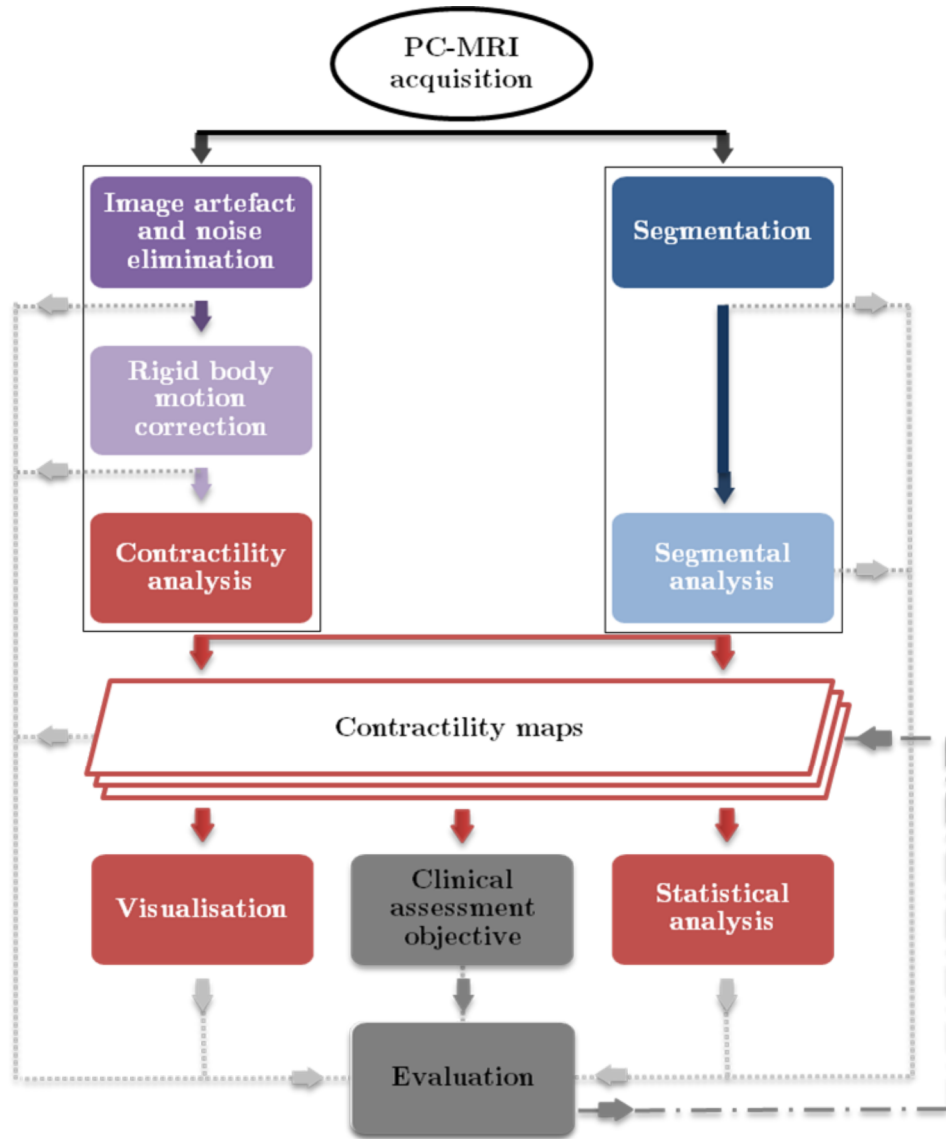


Figure 7.1.: Pipeline for the generic framework of myocardial contractility analysis from TVM. The left branch outlines the velocity analysis and the right branch outlines the anatomical analysis from TVM.

artefact and we believe that it opens a potential interesting topic for further investigation.

- **TVM image denoising.**

For the alleviation of TVM noise, we have proposed the TV restoration method which makes the simplified assumption of independent Gaussian noise. However, we have elucidated that TVM phase noise follows a rather complicated distribution, described by Equation C.4 for a single coil acquisition and expected to be even more complicated under the conditions of spiral k-space sampling, parallel imaging and SENSE reconstruction, as in the case of the Simpson’s technique [23]. The investigation of TVM noise distribution in such a case is a challenging and interesting topic and we suggest it for future research. In addition, we suggest the investigation of a TVM image denoising method that either takes this complicated noise distribution into consideration or is unaffected by the noise distribution; this is an interesting and rather challenging image processing topic partially approached but still not solved. We attempted to suggest such a restoration method, based on the sequential Monte Carlo filtering, as presented in *Appendix E*. The results and theoretical analysis showed that the proposed scheme was not effective due to pixel size limitations that amplify through the image processing to impose unsatisfying levels of accuracy to the velocity estimates. We suggest either modification of the Monte Carlo restoration scheme or its application to the strain/strain rate maps rather than the velocity field; we expect that the pixel size limitations in this case will have a smaller effect on the estimated velocity accuracy but the analysis of strain maps will likely give rise to a number of other challenges and this is again an interesting research topic for further investigation.

- **Myocardial segmentation.**

Although myocardial segmentation has been extensively investigated, it remains a challenging research topic particularly when it comes to the automatic segmentation of a non clinically available CMR image type like TVM, which automatically excludes all the powerful machine learning techniques through the lack of data. For the automatic segmentation of CMR we have developed and presented in the *Appendix* an automatic segmentation method based on graph-cuts that performs well on the delineation of the

endocardium and has been successfully evaluated on cine SSFP datasets. We have also presented an automatic segmentation method based on non-rigid registration which outperforms the graph-cuts based method on the delineation of the epicardium and has been evaluated again on cine SSFP images. However, neither of these methods performs well on TVM images as they have lower and different contrast levels, higher noise and more artefacts compared to the cine SSFP images. Myocardial segmentation specifically for TVM images is a particularly challenging task, there is little related work and we believe that it is an open interesting and useful area of research, enabling TVM to move towards clinical applicability.

- **Contractility analysis.**

The proposed TVM image analysis methods of the current thesis were ultimately aiming at the generation of LV strain and strain rate maps from the transformation of the resulting consistent velocity field. According to the theoretical strain analysis in *Chapter 3*, this transformation turns out equivocal and, for this reason and time limitations, we constructed only preliminary strain and strain rate maps. We are planning to extend the current work to the next step of strain and strain rate analysis and assess the maps before and after each proposed TVM analysis method as follows. The improved segmental analysis framework of *Chapter 4* can be easily extended to the generation of the analogous consistent strain and strain rate LV maps. It will be interesting to examine the effect of the *Chapter 5* velocity field restoration method on the myocardial strain rate maps and extend this to comparing the effect from different velocity field restoration algorithms. Although translational motion does not affect the strain measures in theory, we observed a deviation of strain rate maps in the presence of rigid body motion and this can be possibly attributed to image digitising errors in combination with the selected strain rate formula. It would be interesting to investigate experimentally the effect of the rigid motion compensation method presented in *Chapter 6* on a larger number of myocardial strain rate maps. Another interesting future research task can be the experimental evaluation of the theoretical strain discrepancy analysis presented in *Chapter 3* by comparing strain maps from different formulas.

Chapters 4 and *6* have introduced the new concept of left ventricular

motion symmetry in the normal heart, which we believe has a revolutionary potential in LV image analysis and we suggest the investigation of this claim in a larger scale study. We recently discovered that the translational motion estimation method presented in *Chapter 6* can be readily extended to the estimation of rotational motion and, thus, estimate the total rigid body motion, which is another listed future research task. Due to the phantom uninterpreted artefacts mentioned above, the TVM image analysis experiments in *Chapter 4* did not include correction of the background offsets and we would like to regenerate the AHA maps after this correction and confirm our expectation for the noticeable further improvement of the maps. The AHA maps can be used in turn for the evaluation of each image analysis step.

We suggest summarising and incorporating the methods for all the above image processing challenges into the proposed generic TVM image analysis framework and examine the consistency of the final contractility maps. We suggest further validation of the results on a deformable phantom, as reviewed in *Chapter 2*, and evaluation of the maps by clinical experts. We then suggest application of the framework to a larger cohort of TVM datasets from the normal and diseased hearts and statistical analysis of the results for the construction of global contractility atlases for the normal and each diseased heart.

Side work has been done on the myocardial tissue characterisation with T1-mapping for the differential diagnosis of the infiltrative disease Amyloidosis. Further to the texture analysis maps presented in a short paper and *Appendix F*, we have extracted a large number of texture features and comparison of results from subjects with Amyloidosis, HCM and a normal subject have indicated a potential diagnostic value of several features. However the size of the analysed cohort is too small to make a significant claim for this, and thus, we suggest the analysis of a larger cohort of the normal and diseased hearts as well as further extension of this work. Lastly we suggest that motion analysis, shape analysis and T1-mapping can potentially compose a broader framework for accurate cardiac disease diagnosis and differentiation among a wide range of myocardial conditions including the rarest ones.

The role of machine learning and deep learning in current and

future TVM image analysis research.

Machine Learning (ML) has drawn a tremendous amount of attention over the last few years with deep neural networks being currently the state of the art in many computer vision applications. Deep Learning (DL) has entered the field of medical image analysis and has shown a great potential in disease diagnosis [240]. Existing applications of DL address MR image processing challenges like image restoration, segmentation, synthesis and super-resolution and could potentially be extended to the analysis of TVM. For example, an autoencoder with skip interconnections was introduced for the restoration of T1 weighted images and ensembles of deep neural networks have been introduced for the denoising of contrast-enhanced MRI. A DL method for the denoising of TVM images could potentially overcome the challenge of modeling the complex phase noise distribution and its spatial dependency across the image. DL methods have been introduced also for the detection and removal of the ghosting artefact in spectroscopy and the patient motion in MRI. Likewise, a DL approach could probably serve as an alternative for the estimation of translational motion in TVM, further improvement of the TVM quality and restoration.

Deformable registration and segmentation [245] are two other MR image processing tasks that DL methods have addressed. DL has shown great potential in cardiac segmentation as it performs better in regions of low contrast where automatic non-ML methods tend to underperform [245]. Another image processing task which DL seems to revolutionise is the synthesis of realistic MRI datasets with specific tissue contrast without requiring detailed knowledge of the datasets' characteristics. This opens new doors to MR image processing validation as well as to data augmentation which will in turn facilitate the application of ML.

Currently, the biggest limitation in the application of ML and DL in TVM is the limited size of the available datasets. This happens because TVM is not a part of clinical practice yet and hospital databases are not part of the list of potential sources of big TVM datasets. Datasets come, therefore, from acquisitions performed on volunteers for the needs of each research study. Sharing TVM datasets across research groups is also challenging as this would require use of the same sequence, type of MR scanner and acquisition parameters which is not commonly the case. Another challenge in the applicability of DL image processing methods is the fact that DL

can model only cases that fall in the space covered by the training dataset, which means that the ML/DL method will likely underperform on patients' data with extreme or rare pathologies for which the network has not been trained.

8. References

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Appendices

A. Mathematical Proofs

A.1. RF excitation pulse at Larmor frequency

During one precession, the variant magnetic field $\vec{B}_1 = B_1 \cos \omega t \hat{x}$ transfers energy $\Re(\Delta U)$ to the precessing dipole, where $\Delta U = \int_0^{\frac{1}{f_0}} \mu e^{j\omega_0 t} B_1 e^{j\omega_1 t} dt = \mu B_1 \int_0^{\frac{1}{f_0}} e^{j(\omega_0 - \omega_1)t} dt$. Correspondingly the transferred energy over n precessions is the real part of the phasor integral $\Delta U_n = \mu B_1 \int_0^{\frac{n}{f_0}} e^{j(\omega_0 - \omega_1)t} dt$, $\Re(\Delta U_n)$.

In case $\omega_0 \neq \omega_1$, then the integral becomes $\Delta U_n = \frac{\mu B_1}{j2\pi(f_1 - f_0)} e^{j2\pi n \frac{f_1}{f_0}}$ and $\Re(\Delta U_n) = -\frac{\mu B_1}{2\pi(f_1 - f_0)} \sin(2\pi n \frac{f_1}{f_0})$, which means that over precessions energy will be periodically exchanged between the precessing dipole and $\vec{B}_1$ without net energy transfer towards the dipole.

In case $\omega_0 = \omega_1$, the integral becomes $\Delta U_n = \mu B_1 \frac{n}{f_0} = \Re(\Delta U_n)$ which means that energy is transferred from $\vec{B}_1$ to the dipole in a constant rate (until it reaches a maximum). In this case the variant magnetic field $\vec{B}_1$ oscillates with the Larmor frequency transferring net energy to the dipole that excites the net magnetisation $\vec{M}$; For this $\vec{B}_1$ is called *RF excitation pulse* and the magnetic moments $\vec{\mu}$ and variant magnetic field $\vec{B}_1$ are said to be *on resonance*.

A.2. Blood volume fluctuations

Assume that the regional displacement of the tissue due to blood fluctuations is a periodic function of n frames approximated with a sinusoidal signal $l_{blood} = 0.28 \sin(\frac{2\pi}{N_f} n + \phi)$, where N_f is the number of frames covering one full cycle. A point with zero displacement reaches maximum displacement in an interval of $N_f/4$ frames. The mean l_{blood} displacement between successive frames is $\frac{4}{N_f} \int_0^{\frac{N_f}{4}} 0.28 \sin(\frac{2\pi}{N_f} n') dn' = 0.28 \times \frac{2}{\pi} = 0.1783 \text{ mm}$.

A.3. Deformation tensor and material line elements

Mathematical proof. By applying the chain rule to the expression of $\vec{x}$ in the Lagrangian specification $\vec{x} = \vec{x}(\vec{X}, t)$, it emerges that

$$d\vec{x} = \frac{\partial \vec{x}}{\partial \vec{X}} d\vec{X} = \mathbf{F} d\vec{X}. \quad (\text{A.1})$$

Graphical proof. Let $\vec{U}(\vec{X}, t)$ be the displacement vector of the first material point and $\vec{U}(\vec{X} + d\vec{X}, t)$ the displacement vector of the second material point expressed in the Lagrangian specification. As seen in Figure 3.3,

$$d\vec{x} = \vec{U}(\vec{X} + d\vec{X}, t) - \vec{U}(\vec{X}, t) + d\vec{X} \quad (\text{A.2})$$

From Taylor approximation around $\vec{X}$ and relation 3.11,

$$\vec{U}(\vec{X} + d\vec{X}, t) \approx \vec{U}(\vec{X}, t) + \nabla_{\vec{X}} \vec{U}(\vec{X}, t) d\vec{X} = \vec{U}(\vec{X}, t) + (\mathbf{F} - \mathbf{I}) d\vec{X} \quad (\text{A.3})$$

and, therefore,

$$d\vec{x} = (\mathbf{F} - \mathbf{I}) d\vec{X} + d\vec{X} = \mathbf{F} d\vec{X} \quad (\text{A.4})$$

(For relation 3.17)

A.4. Change of basis and vector mapping

Change of basis Assume an orthonormal basis $\{\hat{G}_j\}_{j=\{1,2,3\}}$ and another basis $\{\vec{g}_j\}_{j=\{1,2,3\}}$. If $\vec{g}_j^{(i)}, i = \{1, 2, 3\}$ are the coordinates of the $\vec{g}_j, j = \{1, 2, 3\}$ vector in the orthonormal basis such that

$$\begin{aligned} \vec{g}_1 &= g_1^{(1)} \hat{G}_1 + g_1^{(2)} \hat{G}_2 + g_1^{(3)} \hat{G}_3 \\ \vec{g}_2 &= g_2^{(1)} \hat{G}_1 + g_2^{(2)} \hat{G}_2 + g_2^{(3)} \hat{G}_3 \\ \vec{g}_3 &= g_3^{(1)} \hat{G}_1 + g_3^{(2)} \hat{G}_2 + g_3^{(3)} \hat{G}_3 \end{aligned}$$

the transformation matrix is

$$\mathbf{T} = \begin{bmatrix} g_1^{(1)} & g_2^{(1)} & g_3^{(1)} \\ g_1^{(2)} & g_2^{(2)} & g_3^{(2)} \\ g_1^{(3)} & g_2^{(2)} & g_3^{(3)} \end{bmatrix} \quad (\text{A.5})$$

Because $\hat{G}_1 = [1, 0, 0]^T$, $\hat{G}_2 = [0, 1, 0]^T$ and $\hat{G}_3 = [0, 0, 1]^T$, the vectors $\vec{g}_1, \vec{g}_2, \vec{g}_3$ can be written as

$$\vec{g}_j = \mathbf{T}\hat{G}_j, j = \{1, 2, 3\}. \quad (\text{A.6})$$

Let $\vec{A} = A_1\hat{G}_1 + A_2\hat{G}_2 + A_3\hat{G}_3 = [A_1, A_2, A_3]^T = [\vec{A}]_{\{\hat{G}_j\}}$ be a vector expressed in the $\{\hat{G}_j\}_{j=\{1,2,3\}}$ basis. The same vector expressed in the $\{\vec{g}_j\}_{j=\{1,2,3\}}$ basis is given by $\vec{A} = a_1\vec{g}_1 + a_2\vec{g}_2 + a_3\vec{g}_3 = a_1T\hat{G}_1 + a_2T\hat{G}_2 + a_3T\hat{G}_3 = T(a_1\hat{G}_1 + a_2\hat{G}_2 + a_3\hat{G}_3) = T[a_1, a_2, a_3]^T$. The above two expressions of $\vec{A}$ are equivalent, therefore $[A_1, A_2, A_3]^T = T[a_1, a_2, a_3]^T$, or $[\vec{A}]_{\{\vec{g}_j\}} = [a_1, a_2, a_3] = T^{-1}[A_1, A_2, A_3]^T = T^{-1}[\vec{A}]_{\{\hat{G}_j\}}$, where $j = \{1, 2, 3\}$. Hence, the change of basis occurs according to the relation

$$[\vec{A}]_{\{\hat{G}_j\}} = \mathbf{T}[\vec{A}]_{\{\vec{g}_j\}}, j = \{1, 2, 3\} \quad (\text{A.7})$$

Vector mapping. The linear mapping of a material vector from the initial to the deformed configuration is equivalent to the change of coordinate system from $\{o, \vec{g}_j\}$ to $\{O, \hat{G}_j\}$, where $j = \{1, 2, 3\}$. Assume a material vector $\vec{M} = M_1\hat{G}_1 + M_2\hat{G}_2 + M_3\hat{G}_3 = [M_1, M_2, M_3] = [\vec{M}]_{\{\hat{G}_j\}}$ in the initial configuration which is mapped to $\vec{m}$ in the deformed configuration. As the material vector follows the tissue, it maintains its coordinates with respect to the axes such that $\vec{m} = M_1\vec{g}_1 + M_2\vec{g}_2 + M_3\vec{g}_3$ or $[\vec{m}]_{\{\vec{g}_j\}} = [M_1, M_2, M_3]^T$. According to relation A.7, vector $\vec{m}$ expressed in the basis $\{\hat{G}_j\}$ is given by

$$[\vec{m}]_{\{\hat{G}_j\}} = \mathbf{T}[\vec{m}]_{\{\vec{g}_j\}} = T[M_1, M_2, M_3] = T[\vec{M}]_{\{\hat{G}_j\}}$$

where $j = \{1, 2, 3\}$, or

$$\vec{m} = \mathbf{T}\vec{M} \quad (\text{A.8})$$

Let the material vector $\vec{M}$ be the difference of two material position vectors such that $\vec{M} = \vec{X}_2 - \vec{X}_1$ and accordingly $\vec{m} = \vec{x}_2 - \vec{x}_1$. Let also integration

of relation 3.17 with respect to $\vec{X}$, recalling that $\mathbf{F}$ is invariant from position in linear mapping, such that $\vec{x}_i = \mathbf{F}\vec{X}_i + \vec{c}$, where $i = \{1, 2\}$. Then

$$\vec{m} = \vec{x}_2 - \vec{x}_1 = \mathbf{F}(\vec{X}_2 - \vec{X}_1) = \mathbf{F}\vec{M}$$

and recalling relation A.8, it is proven that $\mathbf{F} \equiv \mathbf{T}$ meaning that the transformation matrix $\mathbf{T}$ coincides with $\mathbf{F}$. Hence, relations A.9 and A.7 become

$$\vec{g}_j = \mathbf{F}\hat{G}_j, j = \{1, 2, 3\} \quad (\text{A.9})$$

and

$$[\vec{A}]_{\{\hat{G}_j\}} = \mathbf{F}[\vec{A}]_{\{\vec{g}_j\}}, j = \{1, 2, 3\} \quad (\text{A.10})$$

respectively.

B. Cardiac Imaging Modalities

Medical imaging plays an important role in disease diagnosis and prevention, as well as the planning and guidance of a treatment. Medical imaging started with *X-ray* in 1896, expanded with the introduction of ultrasound in the 1970's and *Computed Tomography (CT)*, *Radioactive Cardiology* and *Magnetic Resonance Imaging (MRI)* in the 20th century [246]. Nowadays medical imaging is evolving rapidly with new acquisition and processing techniques that aim at increasing the quality of images, introducing new types of images, improving the accuracy of diagnosis and expanding its applicability across the medical field.

Medical imaging has an important role in the area of cardiac medicine as it offers non-invasive and comprehensive tools for the assessment of the heart's anatomy and function [247,248]. Recent advances in cardiac imaging allow more precise estimation of the global as well as regional myocardial mechanics [202,249]. Imaging for the assessment of myocardial mechanics in the left ventricle, in particular, has attracted a lot of attention [250,251]. Each medical imaging modality relies on a different technique, depicts a different range of features in the heart, has possibly different clinical applicability, and varies in terms of strengths and limitations as elaborated below.

B.1. Cardiac X-ray

B.1.1. Technique

X-ray imaging is based on the attenuation of X-rays as they traverse different tissues in the body. Traversing X-ray photons are absorbed or scattered by the encountered tissues resulting in attenuation of the X-ray beam. The attenuation of X-ray depends on the attenuating properties and thickness of the traversed tissues and it is measured with a photon detector (flat screen or film photon) placed below the patient. The detected photons are

converted into an image according to their distribution on the detector. The X-ray image is, therefore, a 2 dimensional (2D) projection of the attenuating properties of the tissues located in the 3 dimensional (3D) space that is traversed by the X-rays. In X-ray imaging, contrast and signal-to-noise ratio increase when the applied radiation increases; the dose of radiation is subject to limitations for the patient's safety. Another way to enhance the contrast between particular tissues is with the administration of a contrast agent that alters the attenuating properties of the tissues; this technique known as contrast-enhanced X-Ray is particularly useful for intravascular and intracavitary imaging [252].

B.1.2. Types and applications

While conventional X-ray imaging or *radiography* is widely used in dentistry, orthopaedics and mammography, its applicability in cardiology is limited. The main reason is the similar attenuating properties of the heart's building parts i.e. the myocardium, epicardium, endocardium, fat, blood, vasculature and valves, which results in a poor contrast among these cardiac structures in the radiographic image. However, X-ray imaging shows good contrast between the heart and the lungs, because the lungs absorb radiation in a significantly lower degree than the heart, which means that cardiac borders are discernible in X-ray imaging. Cardiac X-ray imaging is, thus, applied for the initial assessment of the heart's condition, for example in dilated cardiomyopathy, via the estimation of the size of the heart's chambers, the pulmonary artery and the aorta [55].

Unlike radiography which produces static images, fluoroscopy is another type of X-ray imaging that produces dynamic and real time images. Real timing makes fluoroscopy suitable for the guidance of examinations and interventions as well as the monitoring of the contrast agent movements within the body. A particular type of fluoroscopy is the *X-ray angiography*, which is performed to image blood vessels, usually in the heart or the brain, in order to identify pathologies like stenosis, occlusion or aneurysms. Cardiac X-ray angiography is commonly performed in conjunction with cardiac catheterisation, during which a catheter is steered towards an artery or a chamber. Cardiac X-ray angiography involves also the administration of a radiopaque contrast agent to increase the visibility of the blood vessels.

X-ray angiography of the coronary arteries or *X-ray coronary angiography* is considered the gold standard in the assessment of coronary artery disease; it is performed for the detection of coronary artery occlusion, thrombosis and the measurement of coronary arterial pressure [253]. X-ray angiography is also applied for the assessment of ventricular anatomy and function for the diagnosis of ischaemia, cardiomyopathies and valvular disorders [55].

B.1.3. Advantages and limitations

The main advantages of X-ray imaging are the high resolution, fast and real time acquisitions. The main disadvantages of X-ray imaging is the loss of depth information over the 2D projection operation, the poor contrast among the imaged cardiac structures with the exception of blood vessels and, furthermore, the emission of ionising radiation that can cause serious health implications to the persons involved. For safety reasons, the repeatability of X-ray imaging is restricted and, besides, X-ray for cardiology is being gradually replaced by safer imaging modalities that involve less or no ionizing radiation like cardiac MRI and echocardiography.

B.2. Cardiac Computed Tomography

B.2.1. Technique

Computed Tomography (CT) is a computerised imaging modality that combines multiple X-ray acquisitions to generate cross sectional images from the body. It can be considered as the evolution of X-ray imaging in the 3 dimensions and its physics is also based on the attenuation of X-rays as they traverse different tissues in the body. Conventional CT is performed with the gantry, which is a circular rotating frame with an X-ray tube mounted on one side and a detector placed diametrically opposite on the other side. As the gantry rotates around the body, focused X-ray beams are emitted in a large number of angles and, accordingly, X-ray projections of the imaged area are generated from a large number of angles. By combining the projections from different angles, the attenuation of each point is computed and a cross sectional CT image is reconstructed. In other words, the depth information that is lost in X-ray imaging is deduced computationally from the multiple projections in CT [252].

B.2.2. Types and applications

There are four main types of CT systems; these are the conventional CT, the spiral CT and the electron beam CT and the multidetector spiral row CT. In *conventional CT*, a stack of cross sections is acquired sequentially by moving the patient along the horizontal direction and repeating the CT acquisition. Conventional CT has a relatively long acquisition time and for this its practicality in cardiology has been limited. In *spiral CT*, on the other hand, acquisition and translation of the patient are performed simultaneously. Compared to conventional CT, spiral CT has shorter acquisition time and so it can produce images from the heart in a single breath-hold. Another important advantage of spiral CT compared to conventional CT is the shorter exposure time to radiation.

Electron beam CT (EBCT) has a significantly higher temporal resolution compared to conventional and spiral CT and this is achieved by replacing the mechanically rotating gantry with a fixed gantry that incorporates a system of electronic sweeping of the electron beam across fixed tungsten targets arranged along the frame. EBCT systems achieve a temporal resolution of 30-50 msec [202,254], slice thickness of 1.5-3.0mm and a spatial resolution of about 0.5mm. The high temporal resolution allows the acquisition of multiple frames from the heart, for example from the end-diastole and end-systole phases, within a single heartbeat and in real time, and this is useful for the assessment of cardiac anatomy and global function. EBCT has been widely used for non invasive identification of the calcium deposition in the coronary arteries that is related to coronary atherosclerosis.

Multidetector spiral row CT (MDCT) was introduced in 2005 and it represents the latest technology of CT systems. As implied by the name, MDCT is a type of spiral CT for accelerated acquisitions with the aid of multiple detectors. MDCT technology reintroduces the use of the mechanical gantry and, as a result, it provides lower temporal resolution than EBCT. On the other hand, it provides significantly higher spatial resolution of about $500\mu\text{m}$ and for this it has been preferred in coronary artery imaging. Along these lines, MDCT has been introduced primarily for the diagnosis of coronary artery disease while the assessment of cardiac function and anatomy is arising as a biproduct of that. Min [255] states that the accuracy of MDCT for structural and anatomical cardiac assessment and tissue characterisation

needs further investigation. Kinno [250] states that MDCT shows good correlation with CMR for the assessment of the left ventricular volumes and EF but its applicability for regional functional analysis has been limited.

Overall, cardiac CT is an established modality for the diagnosis of coronary artery disease and in this case it is also known as CT coronary angiography. Thanks to its high spatial resolution, cardiac CT is also suitable for the study of cardiac anatomy and global function [202, 251]. In this case, the administration of a contrast agent is necessary to enhance the contrast between the myocardium and the blood pools. As for the study of regional function, the utility of cardiac CT has not been shown yet. The main limiting factors to this are the low temporal resolution and lack of image markers, for example myocardial texture, that are necessary for the estimation of myocardial deformation. Another limiting factor against the functional analysis with cardiac CT is the high exposure to radiation when the full cardiac cycle is imaged. In CT coronary angiography, the exposure to radiation is not as high because CT coronary angiography constitutes of only one snap-shot of the cardiac cycle and imaging requires a shorter time.

B.2.3. Advantages and limitations

The main advantages of cardiac CT are the high spatial resolution, small slice thickness and fast acquisition. Furthermore, cardiac CT is not restricted by the presence of metallic objects implanted or attached to the body like pacemakers, defibrillators or tattoos, as it is restricted in the case of cardiac MRI. The main disadvantages of cardiac CT are the moderate to low temporal resolution, the involvement of ionizing radiation and the use of contrast agents that can be nephrotoxic. Like X-ray imaging, the repeatability of CT is also restricted for safety reasons.

CT angiography, particularly by MDCT, provides more detailed images of the blood vessels than X-ray angiography. The high spatial resolution of cardiac CT makes it suitable for the assessment of cardiac anatomy and global function. On the other hand, cardiac CT has not been evaluated for the analysis of regional cardiac function yet and the main reasons are the low temporal resolution, high radiation dose for the coverage of the entire cardiac cycle, lack of technique for the estimation of deformation and, lastly, the availability of alternative non ionizing modalities i.e. ultrasound and

cardiac MRI [202, 251].

B.3. Radionuclide imaging

Radionuclide imaging belongs to *molecular imaging* that is a broad category of imaging modalities based on the interaction of an imaging probe with a molecular target. Unlike other diagnostic imaging modalities that depict the anatomy and macroscopic function of the heart, cardiac molecular imaging has been designed for the study of smaller scale (molecular or cellular) phenomena, like perfusion, that may underlie a cardiac disease process. According to the nature of the imaging probe and technique, molecular imaging is distinguished into (or overlaps with) fluorescence, bioluminescence, molecular ultrasound, contrast-enhanced magnetic resonance, contrast-enhanced computed tomography and radionuclide imaging [256].

B.3.1. Technique

Radionuclide imaging also known as *nuclear medicine imaging* is based on the detection of γ -rays emitted by radioactive markers that are injected previously into the body; it should not be confused with *nuclear magnetic resonance* that is the primary name for *magnetic resonance imaging*, which involves no ionizing radiation. The imaging probes in radionuclide imaging are *radioactive markers* also named *radiotracers*, *radionuclides* and *radio-pharmaceuticals*. The radioactive markers follow the metabolic processes in the body while emitting γ -rays and, for this, radionuclide imaging is suitable for imaging the myocardial perfusion and blood circulation. Moreover, the radioactive markers concentrate differently in the diseased and healthy tissue and, thus, radionuclide imaging is applied for the detection of scars or tumours in the heart. The γ -rays are detected with a γ -camera and the generated image shows the distribution of the tracer in the body.

B.3.2. Types

Three main types of radionuclide imaging are distinguished; these are planar scintigraphy, single photon emission computed tomography and positron emission tomography. *Planar scintigraphy* is the preliminary type of radionuclide imaging and provides 2D projections of the distribution of the

tracer in the body with the use of a γ -emitting radionuclide. Scintigraphy scans are analogous to X-ray scans and they are usually performed for whole body screening for the detection of tumors. A heart-specific scintigraphy is the *thallium stress test*, which is performed for the assessment of myocardial perfusion and viability; thallium stress test employs thallium-201 which correlates with tissue blood supply and it is performed before and after physical exercise.

Single Photon Emission CT (SPECT) and *Positron Emission Tomography (PET)* are the evolution of scintigraphy in the 3 dimensions, analogous to X-ray CT. They both generate a series of contiguous 2D images illustrating the distribution of a radioactive tracer in the body. They mainly differ in the type of radioactive tracer they involve and the mechanism they employ for the generation and detection of γ -rays. SPECT involves a γ -emitting radionuclide like technetium-99, indium-111, iodine-123 and iodine-131, similarly to scintigraphy; the radionuclide emits γ -rays directly, which are then detected by γ -cameras. PET, on the other hand, involves a positron-emitting radionuclide like oxygen-15, nitrogen-13, carbon-11 and fluorine-18; in this case γ -rays are generated after the collision and annihilation of an emitted positron with a nearby electron.

PET imaging has significantly higher sensitivity, SNR and better resolution compared to SPECT, in other words PET images are of significantly higher quality than SPECT images allowing the detailed examination of myocardial perfusion. The main advantage of cardiac SPECT imaging over PET is the possibility to combine the former with exercise stress testing; the reason for that is because radionuclides for SPECT have a half-life in the order of hours, whereas radionuclides for PET have a half-life of only several seconds that is too short for stress testing. As a result, among the two technologies SPECT is suitable for the examination and comparison of myocardial perfusion between resting and stress testing conditions [257].

B.3.3. Applications

Radionuclide imaging, particularly PET, is commonly employed in oncological diagnosis. Other applications of radionuclide imaging are infection, thyroid, lung and functional brain imaging as well as bone scintigraphy.

In cardiology, the main application of radionuclide imaging is myocardial

perfusion imaging. Myocardial perfusion imaging delineates the passage of blood across the myocardium that is the perfusion and it is employed for the assessment of myocardial viability and ischaemia. Myocardial perfusion imaging, in particular, allows differentiation among normal, infarcted and hibernating myocardium. A myocardial perfusion test is cardiac SPECT imaging combined with pharmacological or exercise stress testing, known as *nuclear cardiac stress test*. Nuclear cardiac stress is usually performed when there is suspicion of coronary artery disease and ischaemia. Radionuclide imaging is a non invasive alternative for the diagnosis of coronary artery disease.

Apart from myocardial perfusion, radionuclide imaging is performed to image the blood circulation through the cardiac chambers with an examination known as *nuclear ventriculography*, which is SPECT imaging of the ventricles. Nuclear ventriculography is performed to measure resting and exercise EF when there is suspicion of coronary artery disease, valvular heart disease, and congenital heart disease. Left ventriculography is also performed for the detection of left ventricular aneurysms.

The role of radionuclide imaging in the assessment of regional myocardial function is indirect, through the identification of infarcted or hibernating myocardial regions that are also non-contractile. Coregistration of SPECT/PET with CT or MRI allows the anatomical localisation of these areas [256].

B.3.4. Advantages and limitations

The main advantage of radionuclide imaging compared to other imaging modalities is the high specificity and sensitivity in the detection of the target molecules. Nonetheless, recent studies have shown that the diagnostic accuracy of stress SPECT is similar to stress MRI for the diagnosis of coronary artery disease [258] and lower than stress SPECT for the detection of myocardial ischemia [259]. The main disadvantages of radionuclide imaging compared to other imaging modalities are the low spatial resolution, which ranges between 5-10mm for PET and 12- 15mm for SPECT, the poor SNR and low acquisition. Furthermore, it involves ionizing radiation and administration of a radioactive marker, which questions its safety and possibility of repetition. Lastly, SPECT and PET have been established for myocar-

dial perfusion imaging but their role in the assessment of regional cardiac function is only assistive in conjunction with other imaging modalities like CT, MRI and ultrasound.

B.4. Echocardiography

B.4.1. Technique

Echocardiography is based on the phenomenon that ultrasonic waves are partially reflected when they transverse materials with different acoustic impedance. Acoustic impedance depends on the density of the matter and, therefore, it changes at the interfaces between different adjacent tissues, like the interface between blood and the endocardium. In an homogenous medium ultrasonic waves travel in straight line, but when they encounter such an interface they partially reflect and refract. The ratio of reflection and refraction depends on the difference in the acoustic impedance at the tissue interface. In echocardiographic acquisition, a transducer emits ultrasonic waves towards the heart and measures their returning reflections or *echoes* generated at the tissues interfaces. Based on the amplitude of echoes and time interval between their transmission and reception, the intensity and depth of tissue boundaries are estimated and an echocardiogram is reconstructed [252, 260]

B.4.2. Types

We distinguish three types of conventional echocardiography; these are the M-mode, two-dimensional and Doppler echocardiography [261]. The *M-mode echocardiography* or motion echocardiography is the initial form of cardiac ultrasound, in which a single ultrasonic beam is directed towards the heart and the reflected signals are displayed on an oscillograph. The M-mode echocardiography provides information about only one spatial dimension that is the depth of the encountered cardiac structures, with respect to time. Motion is detected on a M-mode echocardiogram via the change of depth and this permits the precise measurement of cardiac time intervals, for instance the time between systole and diastole; further anatomical or function information is limited with this type of echocardiography. *B-mode echocardiography* or brightness echocardiography is the evolution of M-mode

echocardiography in the second spatial dimension; it is acquired by sweeping the ultrasonic beam back and forth through an arc to generate a cross sectional image. Cross sectional images from B-mode echocardiography reveal the anatomy of several cardiac structures.

Doppler echocardiography is based on the Doppler effect that is the shift in frequency when sound waves are reflected by moving structures. Conventional Doppler echocardiography generates cross sectional images that carry the information of motion in one direction that is the direction of the ultrasonic beam; Doppler echocardiography was initially introduced for the assessment of valvular regurgitation and since then it has been popular for the non invasive measurement of blood flow. B-mode and Doppler echocardiography were combined to generate colour-coded flow images that synthesize anatomical and flow information; this technique is known as *Colour Doppler flow imaging* and enables the examination of blood flow patterns in the cardiac chambers and major arteries.

With newer technological advancements, more types of echocardiography have been developed [261]. 2D echocardiography has been extended to 3D by combining multiple ECG-gated 2D echocardiographic images that are acquired from varying known positions (angles) of the transducer. Various types of real-time 3D echocardiography are currently available, for example the extension of the B-mode to *3D echocardiography* that allows imaging of the 3D anatomy of the cardiac structures and the extension of Doppler to *3D Doppler echocardiography* that shows one directional motion in the 3 dimensional cardiac space. *Contrast echocardiography* involves the injection of a contrast agent and it is commonly performed for the visualisation of intracardiac shunts; in this case a contrast agent that opacifies only the right-sided cardiac chambers is selected. Contrast echocardiography is also used for myocardial perfusion imaging and contractility analysis, for which a fluorocarbon-based contrast agent is selected. *Transesophageal echocardiography* is an alternative to transthoracic echocardiography, which is the conventional and most frequent way to obtain an echocardiogram, and it is acquired when detailed cardiac images are requested. Transesophageal echocardiography is performed through the oesophagus, while transthoracic echocardiography is acquired with the transducer placed on the chest of the patient. Other types of echocardiography like stress and intraoperative echocardiography can be found in the reference number [261].

Two types of echocardiography have been introduced for the evaluation of cardiac function [247] and have been established in myocardial deformation imaging [249]; these are tissue Doppler imaging and Speckle Tracking Echocardiography (STE). *Tissue Doppler Imaging (TDI)* is an extension of Doppler echocardiography from measuring blood flow velocity to measuring myocardial tissue velocity. Myocardial tissue velocity lies considerably lower than blood flow velocity and its separation is achieved with the application of low pass filters on the echo signal that reject the part of the signal originating from the blood flow. The measured myocardial velocities are shown with real-time Colour Doppler imaging. Myocardial velocities are spatially derived to yield regional strain rate and temporal integration of strain rate over time yields regional myocardial strain; strain and strain rate are measures of regional myocardial deformation. TDI can assist the diagnosis of myocardial ischemia, evaluation of diastolic dysfunction and assessment of ventricular dyssynchrony in cardiac resynchronization therapy. A main limitation of TDI is the measurement of myocardial velocity only in the direction of the ultrasound beam, therefore, measurements depend on the angle of the ultrasound probe with respect to the heart. As an alternative and angle-independent method, STE has been introduced.

STE analyses motion by tracking natural acoustic markers called *speckles* across frames of 2D echocardiography [262]. Speckles result from the interaction of the ultrasound beam with acoustic interfaces i.e. myocardial fibres that are smaller than the ultrasound wavelength. In such case, the reflection of the ultrasound beam generates scatter echoes instead of specular echoes that lie parallel to the ultrasound beam instead of perpendicularly; scatter echoes appear like dark artefacts attributing a grainy texture to the myocardium in contrast to the specular echoes which constitute the main echocardiographic signal. STE echocardiography exploits the information carried by these scatter echoes or speckles; it filters out noise, keeps the temporally stable speckles and tracks them from frame to frame commonly using block matching algorithms. Block matching algorithms compare and match blocks around homologous speckles in successive images using intensity based similarity measures such as mutual information or cross correlation. From the relative change in distance of the speckles in time, regional strain is computed and, thus, regional myocardial deformation is estimated

in all three circumferential, radial and longitudinal directions. The main advantages of STE over TDI are the independence of STE from the acquisition angle which makes it more robust, the direct measurement of strain rather than strain rate, motion estimation in all three orthogonal directions rather than a single direction that of the ultrasound beam and the measurements independent from the reference system. STE has also shown good correlation with CMR tagging in the estimation of regional myocardial deformation. The main clinical applications of STE are the evaluation of regional ventricular and atrial myocardial function and the assessment of atrial and ventricular dyssynchrony.

B.4.3. Applications

Echocardiography provides information on cardiac morphology, function, and hemodynamics and its applications are numerous and different for each type of echocardiography [55, 247, 249, 263]. Applications of each type of echocardiography are already mentioned and reviewed briefly here.

M-mode echocardiography is the oldest type and nowadays its role is mainly assistive to other modalities. B-mode echocardiography depicts the anatomy and global movement of the cardiac structures; it is suitable for the estimation of global cardiac parameters like wall thickness, cavity size, mass index and the detection of wall and valve abnormalities. Doppler imaging is employed mainly for imaging the blood flow and evaluation of flow abnormalities. Contrast echocardiography is performed for the detection of intercardial shunts, assessment of myocardial perfusion and viability. Transesophageal acquisition is useful for detailed imaging of the mitral valve, aortic valve, left- and right-ventricular anatomy and deformation as well as for monitoring artificial heart valves. Echocardiography is also applied for the detection of valvular lesions, septal defects, diagnosis of coronary artery disease, cardiomyopathies, ventricular hypertrophy, as well as pericardial, aortic and congenital heart disease.

For the assessment of regional myocardial function, echocardiography is currently the most available modality. It has been widely used in studies for the assessment of left ventricular anatomy, motion and deformation. It facilitates measurement of global parameters like left ventricular mass, volume, wall thickness, and EF. TDI and STE enable the estimation of

regional parameters like myocardial velocities, strain and strain rate that are employed in the assessment of left ventricular function for the diagnosis of cardiomyopathies, ischaemia and other myocardial diseases.

B.4.4. Advantages and limitations

Echocardiography the most frequent cardiovascular diagnostic test after electrocardiography and the most common cardiac imaging modality. This is attributed to the relative affordability, portability and safety of the modality. Thanks to the absence of ionizing radiation echocardiography is safe for pregnancy and there is no restriction in the repeatability of echocardiographic scans, unlike X-ray and CT imaging. In contrast to MRI, the application of echocardiography is not prohibited to patients with metallic implants, metallic object or dyes attached to their bodies or patients with claustrophobia. Another important advantage of echocardiography is the high temporal resolution and short image reconstruction time that enables fast acquisitions and real time imaging. An additional advantage is multimodality, which makes echocardiography suitable for plenty of clinical applications.

The main disadvantages of echocardiography are low spatial resolution, significant noise, restrictions in the acquisition field and orientation of cross sectional planes. Restriction in the orientation of acquisition planes relies on the fact that only structures that are encountered perpendicularly by the ultrasound beam can be imaged and echocardiography cannot be performed in any angle. Also the acoustic window to the heart is restricted because ultrasound is almost entirely reflected by bones and lungs. With regard to velocity, Doppler echocardiography provides measurements only in the direction of the ultrasonic beam.

C. Cardiac Magnetic Resonance (CMR) imaging

Cardiovascular Magnetic Resonance (CMR) imaging relies on the interaction of MR active atomic nuclei with static magnetic fields and radio waves in order to generate anatomical or functional images from the heart [236]. The physical principles of nuclear magnetic resonance, several types of CMR imaging, their characteristics, advantages and clinical applications are presented below.

C.1. Physics of nuclear Magnetic Resonance (MR)

Nuclei of atoms consist of protons and neutrons with protons being positively charged and neutrons electrically neutral. Protons and neutrons spin around their axes with a spin of $\frac{1}{2}$ or $-\frac{1}{2}$ denoting the clockwise or anti-clockwise direction. By virtue of their spin and positive charge, protons behave like minuscule magnetic dipoles with magnetic moment¹ $\vec{\mu}$ as represented in Figure C.1. Protons with opposite spins possess opposite magnetic moments $\vec{\mu}$. Despite their zero electric charge, neutrons possess also a non-zero but different magnetic moment that is attributed to the non-uniform distribution of electric charge across their internal structure. The numbers and magnetic moments of protons and neutrons in a nucleus determine its nuclear magnetic moment. In the ground state of a nucleus, protons and neutrons tend to pair up with parallel and antiparallel spins and if both are in even numbers, the net nuclear spin and nuclear magnetic moment are zero. In any other case, the nuclear magnetic moment is a non-zero vector able to interact with external magnetic fields and the nucleus is characterised as *MR active*. Several MR active nuclei have been proposed for MRI

¹Magnetic moment $\vec{\mu}$ is a vector that describes the torque acting on the dipole from an external magnetic field; it is a measure of strength of the magnetic dipole and it is aligned from its south pole to its north pole

such as ^{13}P , ^{23}Na , ^{19}F , ^{13}C and ^1H ; each type of nuclei is MR selectable by its resonance frequency, which is explicated hereinafter. Amongst them, the nucleus of the ^1H or *hydrogen proton* has been preferred by reason of its abundance in the body and high sensitivity to magnetic fields.

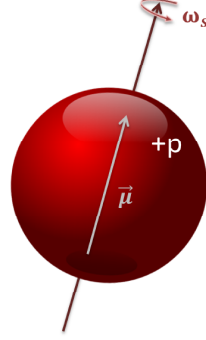


Figure C.1.: A proton by virtue of its spin and positive charge possesses magnetic moment $\vec{\mu}$ and thus it can interact with magnetic fields.

As the magnetic dipoles are distributed across the heart, they attribute magnetisation $\vec{M}$ to the tissue and blood that is defined as the distribution of magnetic moments $\frac{d\vec{m}}{dV}$. In the absence of any external magnetic field, the magnetic dipoles orient randomly in any small volume dV of the matter resulting in a null net magnetisation $\vec{M}$. In the presence of an external magnetic field, each magnetic dipole experiences a torque $\vec{\tau} = \vec{\mu} \times \vec{B}$ which tends to align the magnetic dipole to the external magnetic field² of *magnetic flux density* $\vec{B}$. According to their positive or negative spins, magnetic dipoles align parallel and antiparallel to the magnetic field cancelling out the great majority of nuclear magnetic moments. A small but essential excess of parallel spins is maintained under the impact of the external magnetic field and accounts for a non-zero net magnetisation $\vec{M}$ in the direction of $\vec{B}$, as shown in Figure C.3.

²This is shown by the formula for the equivalent force $\vec{F} = \nabla(\vec{\mu}\vec{B}) = \nabla(\mu B \cos\phi)$ [264], which implies that $\vec{F}$ acts towards the direction of minimisation of the angle ϕ between $\vec{\mu}$ and $\vec{B}$.

C.1.1. Nuclear Precession

Alignment of magnetic dipoles to the magnetic field does not mean that the axes of the hydrogen proton $^1H^+$ spins align to the magnetic field; the precession axes of $^1H^+$ follow the alignment instead. When a magnetic field is applied rather than spinning about a steady axis, each hydrogen proton performs a complex motion known as *nuclear precession* and this is the spinning about an axis that rotates about a second axis called the *precession axis*. A mechanical equivalent of nuclear precession is the motion of a gyroscope as shown in Figure C.2. The angular frequency of precession ω_0 is known as the *Larmor frequency* and is given by

$$\omega_0 = \gamma B \quad (C.1)$$

The Larmor frequency depends on the strength of the magnetic field acting on the nucleus and its gyromagnetic ratio γ , which is characteristic to the MR active nucleus. For the hydrogen proton ^1H , the gyromagnetic ratio is $\gamma = 267.513 \times 10^6 \text{ rad s}^{-1} \text{ T}^{-1}$. The majority of MRI scanners operate at 1.5, 3 or 7 T setting the Larmor frequency $f_0 = \omega_0/2\pi$ of the hydrogen proton at 63.86, 127.76 and 298.03 MHz respectively. Upon the exertion of a

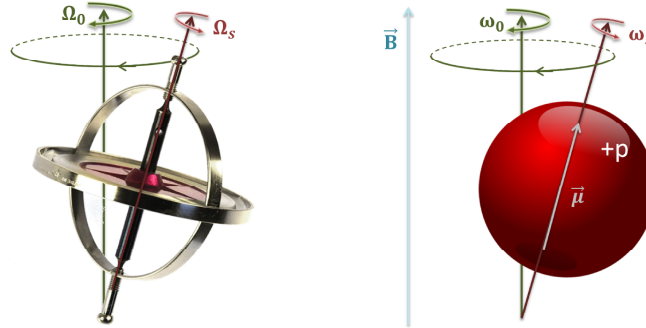


Figure C.2.: The gyroscopic precession (left) is a mechanical equivalent to the nuclear precession (right). The gyroscope spins about its spinning axis showing in red with angular frequency Ω_s while the spinning axis rotates around the precession axis showing in green with angular frequency Ω_0 . Similarly the hydrogen proton spins about its spinning axis while this rotates around the precession axis with the Larmor angular frequency ω_0 .

high external magnetic field, all hydrogen protons align their precession axes to the magnetic field and they perform the precession in random phases, as represented in Figure C.3, such that the projections of their magnetic moments transversely to $\vec{B}$ are cancelled out, whereas the projections of their magnetic moments along the $\vec{B}$ axis are summed up; this is how the net magnetisation $\vec{M}$ occurs in the direction of $\vec{B}$.

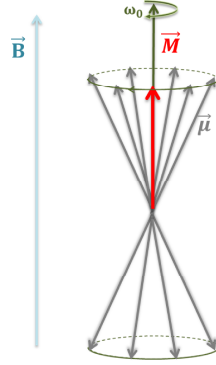


Figure C.3.: Left: Magnetisation $\vec{M}$ is the distribution of net magnetic moment in the matter. The net magnetic moment is the vectorial sum of the magnetic moments $\vec{\mu}$ of the nuclei that precess parallel and antiparallel to the applied magnetic field $\vec{B}$ in random phases. The net magnetic moment is attributed to the small excess of parallel spins under the effect of $\vec{B}$. Right: Nuclear resonance.

C.1.2. Excitation

As seen above, a powerful constant magnetic field $\vec{B}$ causes the magnetisation $\vec{M}$ of the tissue that contains MR active nuclei and sets $\vec{M}$ parallel to $\vec{B}$. It is possible to cause *excitation* that is to divert $\vec{M}$ from its initial alignment to $\vec{B}$ and set it on precession about $\vec{B}$ with the application of a much weaker variant magnetic field $\vec{B}_1$ taking advantage of the *resonance* phenomenon. We will try to explain this from the aspect of magnetic dipole energy.

Assume a magnetic dipole precessing in a constant magnetic field $\vec{B}$ and a, approximately ten times weaker, variant magnetic field $\vec{B}_1 = B_1 \cos \omega t \hat{x}$ applied in a direction perpendicular to $\vec{B}$ and $\vec{M}$ as represented in Figure C.4.

$\vec{B}_1$ transfers energy $\Delta U = \int_0^{\Delta t} \vec{\mu} \vec{B}_1 dt$ [265] to the magnetic dipole in time Δt . Let the projection of $\vec{\mu}$ on the transverse plane represented by the phasor $\mu e^{j\omega_0 t}$ and $\vec{B}_1$ represented by the phasor $B_1 e^{j\omega_1 t}$. During one precession, $\vec{B}_1$ transfers energy $\Delta U = \Re(\int_0^{\frac{1}{f_0}} \mu e^{j\omega_0 t} B_1 e^{j\omega_1 t} dt) = \mu B_1 \Re(\int_0^{\frac{1}{f_0}} e^{j(\omega_0 - \omega_1)t} dt)$ to the dipole. Over several precessions ΔU will not oscillate between positive and negative values (periodic exchange of energy between the dipole and $\vec{B}_1$) and will rather increase with time if and only if $\omega_0 = \omega_1$, that is if and only if $\vec{B}_1$ oscillates with the Larmor frequency or in other words if the magnetic moments $\vec{\mu}$ and variant magnetic field $\vec{B}_1$ are *on resonance* (See proof A.1 in Appendix). If $\vec{B}_1$ and thus resonance lasts for several precessions, a considerable amount of energy is transferred to the magnetic dipoles.

Then resonance causes a dual effect on $\vec{M}$. The first effect is the *spin-flip transition* of precessing protons. Spin-flip transition happens when low energy hydrogen nuclei of spin $+1/2$ absorb the exact energy to transit to the higher energy state that is to become high energy (excited) hydrogen nuclei of spin $-1/2$ [266]. It is proved that the energy absorbed by the excited nuclei is the ΔU energy mentioned above [265] (and see proof A.1 in Appendix). Dixon [266] shows the equality $\Delta U = \frac{h\omega_0}{2\pi}$, which gives a quantum mechanical explanation on why energy absorption occurs at the Larmor frequency. The spin-flip transition proceeds as long as $\vec{B}_1$ is applied or until all spins end up antiparallel. The second phenomenon is the *synchronisation of precessions* meaning that the hydrogen protons precess *in-phase*. In-phase precession results in the appearance of the transverse component of magnetisation $\vec{M}_{xy}$.

The overall result of resonance is the magnetisation $\vec{M}$ to flip, increase magnitude and precess about $\vec{B}$ with the Larmor frequency. Flipping occurs with $\vec{M}$ nutating clockwise from the z axis over several precessions to reach the flip excitation angle as shown in Figure C.4; this nutation entails from the classical equation of motion $\frac{d\vec{M}}{dt} = \vec{M} \times \gamma \vec{B}_{total}$ as explained in [266]. The flip angle of $\vec{M}$ depends on the duration of $\vec{B}_1$ and ranges between 0° and 180° . At 90° flip angle, $\vec{M}$ has the maximum amplitude, maximum transverse component M_{xy} and zero longitudinal component M_z (see Figure C.4).

This perturbation of $\vec{M}$ from its initial orientation is the *excitation* phenomenon. The variant magnetic field $\vec{B}_1$ that causes excitation is commonly named *RF (radiofrequency) excitation pulse* by reason of its fre-

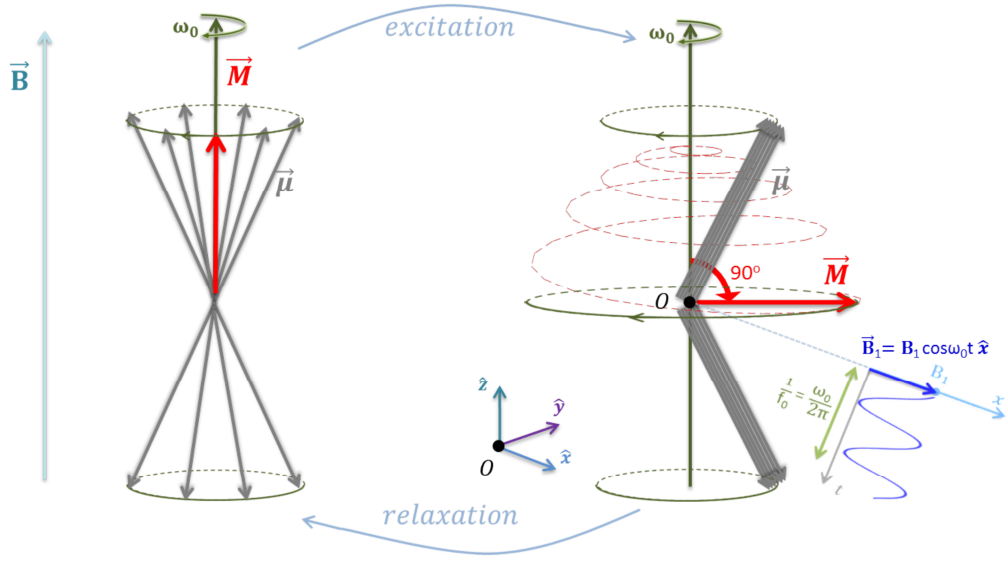


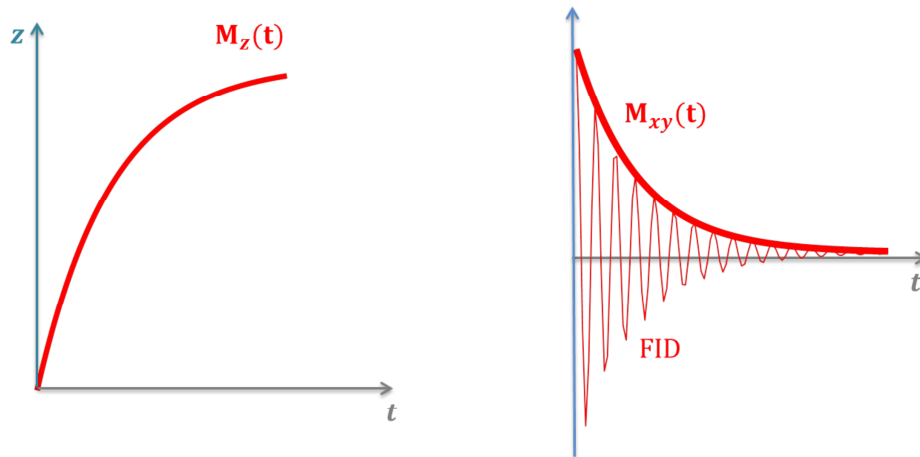
Figure C.4.: Excitation and relaxation.

quency bandwidth and finite duration. The RF pulse that causes $\vec{M}$ to flip 90° or 180° is called 90° or 180° RF excitation pulse respectively. If there were no energy losses, after the RF pulse termination the magnetisation $\vec{M}$ would continue precession about $\vec{B}$ with the Larmor frequency preserving the flip excitation angle. Experiments showed that the magnetisation $\vec{M}$ performs *relaxation* instead, which is followed by the emission of electromagnetic signals and on these signals the design of MRI is based.

C.1.3. Relaxation

After the RF pulse termination, $\vec{M}$ gradually recovers its initial orientation and magnitude performing the *relaxation* phenomenon (it is the reverse of excitation). The cause of relaxation is the energy loss from the system of precessing hydrogen protons (spins) resulting from interactions with their neighbouring atoms (lattice) as well as the energy exchange among the spins themselves. Reversely to excitation, relaxation causes a dual effect on $\vec{M}$ that is the *reverse spin-flip* from antiparallel to parallel spins and the *dephasing* of the spinning hydrogen proton precessions. This effect on $\vec{M}$ shows as the T_1 relaxation and T_2 relaxation as explained subsequently.

T_1 relaxation. The reverse spin-flip from antiparallel to parallel spins is a

Figure C.5.: T_1 relaxation (left) and T_2 relaxation (right).

results of *spin-lattice* interactions. The reverse spin-flip transitions release energy that is transferred to the lattice as thermal kinetic energy. This phenomenon is stimulated by the fluctuating magnetic fields from molecular motions in the lattice and specifically those fluctuations that occur in the Larmor frequency. The reverse spin-flip increases the ratio of antiparallel to parallel spins and as a result the magnetisation $\vec{M}$ flips back to its initial alignment and, thus, the longitudinal magnetisation M_z recovers. This phenomenon is called T_1 relaxation and it is described by the exponential equation

$$M_z(t) = M(1 - e^{-\frac{t}{T_1}}) \quad (\text{C.2})$$

where T_1 is the T_1 relaxation time (see Figure C.5).

T_2 relaxation. While spin-lattice interactions result in T_1 relaxation, *spin-spin* interactions cause the T_2 relaxation via the dephasing of the hydrogen proton precessions. The mechanism of dephasing is based on the slightly different constant magnetic field that is experienced by different hydrogen protons in a neighbourhood. Providing the external magnetic field is free of inhomogeneities, these local inhomogeneities are attributed to internal magnetic fields exerted by neighbouring spins due to their magnetic moments. This interaction of internal magnetic fields is the so called *spin – spin* interaction and is accompanied by energy exchange between the neighbouring

spins. The experience of a slightly different constant magnetic field causes neighbouring spins to precess in slightly different Larmor frequencies leading to a progressive spreading of the corresponding magnetic moments that is the *dephasing* of the precessions. Dephasing causes the decay of the transverse magnetisation M_{xy} and this phenomenon is called T_2 relaxation. The decay of M_{xy} occurs exponentially with time obeying the equation

$$M_{xy}(t) = M e^{-\frac{t}{T_2}} \quad (\text{C.3})$$

where T_2 is the T_2 relaxation time (see Figure C.5).

C.1.4. Magnetic parameters, proton density and MRI types

T_1 relaxation time (Equation C.2) is characteristic to the consistency of the magnetised tissue and it reflects the easiness in energy exchange between the hydrogen protons and the macromolecules of the lattice; T_1 relaxation time is shorter for the fat than the water and, thus, fat recovers faster than water. The maximum distance between their T_1 relaxation curves occurs when longitudinal magnetisation M_z is at 63% recovery as derived from Equation C.2. If MRI acquisition occurs about this time, the generated MR images show maximum contrast between fat and water and respectively between myocardial tissue and blood with the fat and myocardium appearing brighter than the water and blood. This type of MR imaging is the T_1 -weighted imaging.

T_1 relaxation time can noticeably shorten with the injection of a paramagnetic contrast agent that works as an energy sponge absorbing the energy from the reverse spin-flip transitions. Along these lines gadolinium-based paramagnetic contrast agents are commonly used in cardiovascular magnetic resonance imaging for the assessment of blood flow, myocardial perfusion, infarction and viability [267]; Late-gadolinium enhancement techniques are based on the localisation of the gadolinium-based agent in the diseased myocardium where it appears in higher concentration and these techniques have been popular in myocardial disease diagnosis including acute and chronic myocardial infarction, hypertrophic and dilate cardiomyopathy, malignant arrhythmias and inflammatory heart disease [57, 72]. In the presence of a myocardial disease, the constitution of the tissue alters and the T_1 relaxation time of the diseased tissue deviates from the normal

values accordingly. This deviation can serve as diagnostic or prognostic indicator for myocardial disease, and for this, T_1 mapping was developed. T_1 mapping [268] includes advanced CMR acquisition and postprocessing techniques for the estimation of T_1 relaxation times per myocardial tissue region with the purpose of diagnosis in the suspicion of a difficult or rare disease [269] such as the myocardial amyloidosis [270].

T_2 relaxation time (Equation C.3) is characteristic to the state of the magnetised matter; the more fixed the positions between the neighbouring atoms are, the more persistent the spin-spin interactions are and the shorter the T_2 relaxation time is. Unlike solids, molecular motion in liquids is rapid and random preventing from the creation of local internal inhomogeneities and, according to this, solids have shorter T_2 relaxation times than liquids; bone and soft tissue decay faster than water. For the same reason it also applies that $T_2 \approx T_1$ in liquids whereas $T_2 \ll T_1$ in solids. The maximum distance between T_2 relaxation curves from different tissues occurs when transverse magnetisation M_{xy} decays at about 37% of its initial value. If MRI acquisition is tuned at this time, the generated MR images show maximum contrast between myocardial tissue and fat versus water and blood, with water and blood appearing brighter. This type of MR imaging is the *T_2 -weighted imaging*. Above, we mentioned the assumption that local inhomogeneities are attributed to internal magnetic fields from neighbouring spins. In fact more sources than the neighbouring spins contribute to the local magnetic inhomogeneities that cause decay of the transverse magnetisation M_{xy} and if they are not compensated, the type of MR imaging we get is the T_2^* -weighted imaging. To distinguish the shorter relaxation time of this case, we use the annotation T_2^* ; it always applies that $T_2^* < T_2$.

T_2 relaxation time is also affected by the uniformity of the matter i.e. concentration in macromolecules and, therefore, diseased tissue being usually more oedematous than healthy tissue has longer T_2 relaxation time. Like the T_1 relaxation time, gadolinium-based paramagnetic contrast agents shorten the T_2 relaxation time via the addition of macromolecules to the tissue. T_1 -weighted imaging is generally preferred to T_2 -weighted imaging due to the fact that T_2 relaxation time is generally shorter to T_1 relaxation time and in several cases like in gadolinium enhanced imaging better contrast can be achieved with T_1 -weighted imaging.

As seen taking advantage of the different magnetic constants of tissues

and blood, by tuning the excitation and acquisition times it is possible to highlight tissue with more fat or more water. Because T_2 is generally shorter than T_1 , the times can be tuned such that the effects of T_1 relaxation and T_2 relaxation are almost decoupled. In T_1 -weighted imaging, T_2 relaxation precedes the acquisition whereas in T_2 -weighted imaging, acquisition occurs early enough such that the effect of T_1 relaxation is still not significant. If the excitation and acquisition times are tuned such that T_2 relaxation has preceded and T_1 relaxation is at its beginning, the acquired images do not display the magnetic characteristics of the hydrogen protons but rather reflect the number of hydrogen protons in the imaged area. This type of MR imaging is the *proton density* imaging. Proton density imaging highlights areas with high proton density and, therefore, distinguishes between fat and soft tissue versus bone and water. Proton density imaging along with T_1 -weighted and T_2 -weighted imaging constitute the conventional types of MRI.

C.2. Principles of CMR Imaging.

CMR imaging, like MRI in general, includes techniques for observing the resonance phenomenon via the measurement of the MR signals, the decoupling as well as localisation of MR signals in space and eventually their reconstruction into MR images. Additionally to MRI, CMR incorporates techniques for the compensation of cardiac and respiratory motion during the image acquisition; to this, acceleration methods are included that not only reduce the scanning time but also prevent motion artefacts further. CMR employs also techniques for encoding or suppressing specific properties of the cardiac tissues³ into the resonance phenomenon allowing for the acquisition of a wide variety of CMR image types that enable the detection of anatomical or functional abnormalities in the heart.

C.2.1. MR signal measurement

The relaxing magnetisation $\vec{M}$ behaves like a rotating magnet and, according to Faraday's law, it can induce electromotive force (emf) at the terminals of a receiver coil that is the measured MR signal. If the receiver

³Blood included

coil orients its axis in the transverse plane, for example along the x axis, and connects to a transducer, the recorded emf gives the MR signal known as Free Induction Decay (FID) signal. Because $\vec{M}$ rotates at the Larmor frequency, FID is a sinusoidal signal also at the Larmor frequency. Since the receiver coil lies in the transverse plane, the amplitude of FID follows the transverse magnetisation M_{xy} and reflects the T_2^* decay. FID therefore carries the information about the Larmor frequency of spins in the area where it is emitted from and the initial amplitude of the transverse magnetisation M_{xy} in this area.

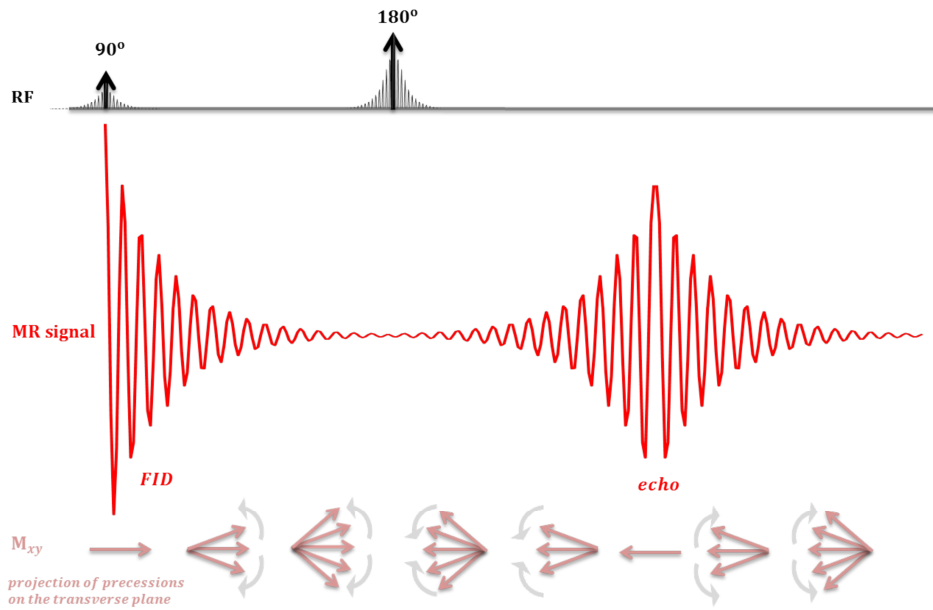


Figure C.6.: Free induction decay (FID) signal and its echo. Here spin echo.

As seen earlier, FID signal is a sinusoidal signal with decaying magnitude, partially attributed to T_2 relaxation that is the dephasing of proton precessions. In order to facilitate the MR measurements, echoes of the FID signals rather than the initial signals are induced and measured [271, 272] at the time of the T_2/T_2^* relaxation compensation. Echoes are induced with two main techniques, the spine echo and the gradient echo technique. A *spin echo* is generated when a 90° excitation pulse and the corresponding FID are followed by a 180° inversion pulse (see Figures C.7 and C.8), which inverses the magnetisation and leads protons to precess in the opposite di-

recession resulting in the rephasing of the precessions that is the reverse of their dephasing. This process generates a mirror FID collated with a second FID that is the *echo* as represented in Figure C.6; a degree of signal attenuation residues in the echo due to the T_1 -relaxation effect. The peak of the echo is at its centre and corresponds to the time when proton precessions rephase, or in other words, when T_2 relaxation is compensated with the T_2^* effects (off-resonance effects) removed. A *gradient echo* is generated with the application of a dedicated bipolar gradient that, first, causes accelerated dephasing of proton precessions and, subsequently, forces their rephrasing. (The rephrasing gradient is combined with the frequency encoding gradient in the example of Figure C.8). Gradient echo has a similar profile to the spin echo with a lower peak, though, because the gradient echo technique compensates only for the T_2 relaxation but not for the off-resonance effects. Thanks to the enforced early dephasing and rephasing of proton precessions, gradient echoes can be generated faster than spin echoes and, thus, gradient echo imaging allows for rapid image acquisition.

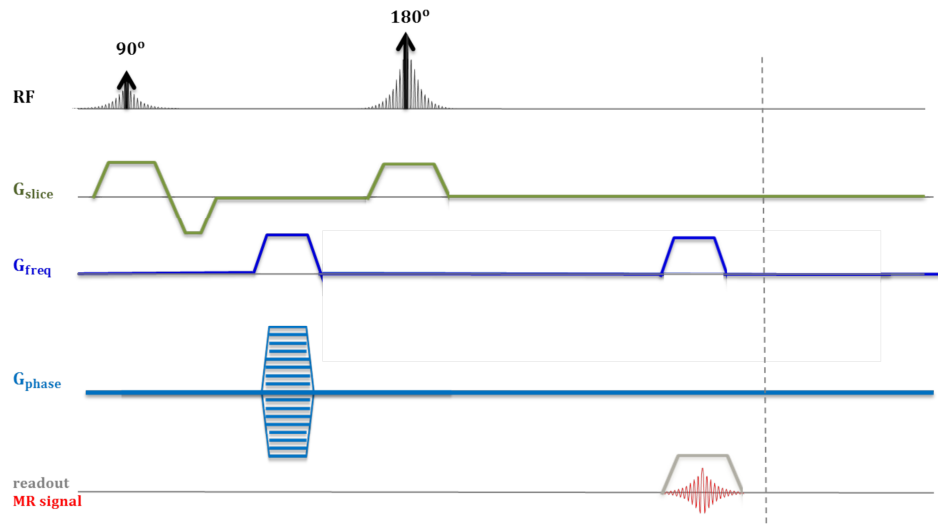


Figure C.7.: Conventional spin echo sequence. A 90° degree excitation pulse is followed by a 180° inversion pulse to induce the generation of a spin echo MR signal at the readout.

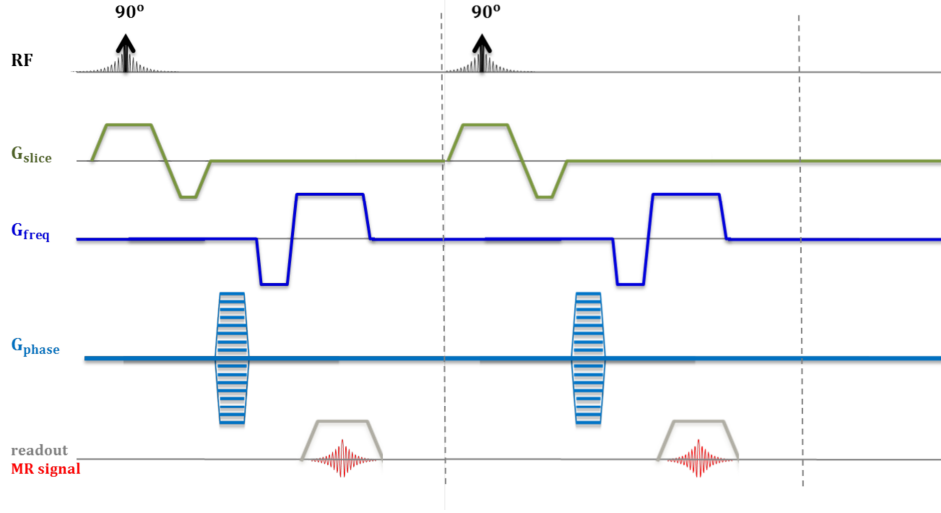


Figure C.8.: Conventional gradient echo sequence. A bipolar gradient defocuses and refocuses rapidly the proton precessions inducing a gradient echo MR signal at the readout.

C.2.2. MR signal localisation

The MR signal induced at the receiver coil is one-dimensional and a combination of FID signals from many different locations in the imaged body area. To reconstruct the MR images, it is required to decouple the signals from voxels in different locations; this is achieved with the application of finite-time additional constant gradient magnetic fields in the three orthogonal directions. The first gradient achieves slice separation and the other two gradients in-slice localisation by encoding the information of the in-slice coordinates in the phase and frequency of the FID signals.

Slice separation, phase and frequency encoding take advantage of the linear dependency of the Larmor frequency on the applied magnetic field $\vec{B}$ (Equation C.1). This means that by applying a gradient of additional constant magnetic field (parallel to $\vec{B}$) along one direction $\vec{\lambda}$, it is possible to spread the Larmor frequencies of spins along that direction because each spin will experience slightly different magnetic field $\omega_0(\lambda) = \gamma(B + G_{\vec{\lambda}}\lambda)$. In three dimensions this is translated into spreading the Larmor frequencies across parallel planes. Slice separation is achieved with the application of the first gradient (G_{slice}) during the RF pulse emission (see Figure C.7);

the RF pulse will cause spin excitation only in the slice that is on-resonance with the RF pulse, setting the first coordinate of each voxel.

Frequency encoding is achieved with the application of the third (in terms of time) gradient (G_{phase}) during the readout of the receiver coil(s) along a direction perpendicular to the first gradient (see Figure C.7); the frequency-encoding gradient causes spreading of the Larmor frequency along this direction during the readout and the recorded MR signal is a combination of FID signals with different frequencies corresponding to different lines across the direction of the gradient.

Phase encoding is achieved with the application of the second gradient (G_{freq}) after the termination of the RF pulse and slice separation and before the readout and frequency encoding along the remaining orthogonal direction (see Figure C.7). The phase encoding gradient causes spreading of the Larmor frequencies along this direction, which results in dephasing of spins at the end of the gradient pulse in a way that the phases of the spins are proportional to their location along the direction of the phase encoding gradient. This means that the second coordinate of each voxel is encoded in the phase of each FID signal but not in its frequency, which encodes the third coordinate, since the effect of the phase encoding gradient on the Larmor frequencies ends before the readout and frequency encoding. Like phase-encoding is used for the encoding of the second spatial coordinate of spins, phase-encoding is also used for the encoding of the velocity of spins in the Phase-Contrast MRI technique, as explained later.

Repetition of the MR sequence with phase encoding gradients of different strengths and recording of the corresponding MR signals results in a collection of MR signals which altogether carry sufficient information for the in-slice localisation of the component FID signals. The orientation of the magnetic gradients can be tuned in the scanner and this a major advantage of MRI.

C.2.3. MR image reconstruction

The MR signals are collected in a 2D matrix that is the row data domain known as *k-space*. Each line in the k-space is a digitised sequence of the values of an MR signal corresponding to one echo. The k-space domain is mathematically related to the image domain via the inverse Fourier trans-

form [273] such that transformation of a k-space matrix results in the reconstruction of an MR image or slice. Sampling of the k-space, i.e. the filling of k-space matrix, determines the image quality both in terms of resolution and artefacts and, moreover it affects the duration of the MR acquisition.

Conventional k-sampling is performed row-by-row with each row containing information from a (symmetric) spectrum of frequencies defined by the frequency encoding gradient at a specific strength of the phase encoding gradient. The horizontal and vertical dimensions of the k-space matrix save information about the frequency and phase of the MR signals respectively and, besides, the k-space matrix is conjugate symmetric about its centre. The central region of the k-space contains information about low spatial frequencies and determines the brightness of the related image, whereas the periphery contains information about high spatial variations like edges or rough textured regions. Based on this knowledge, manipulation of the k-space matrix permits the modification of the image contrast and artefact correction.

k-sampling is performed in combinations of cartesian trajectories but also radial or spiral trajectories; the selection of a non cartesian k-space sampling trajectory may accelerate the acquisition remarkably [133, 134] but also affect the acquisition robustness and sensitivity to artefacts as well as complicate the expression of artefacts in the image domain [170]. More information about the MR image reconstruction techniques can be found in [272].

C.2.4. Cardiac motion (compensation)

The imaged region is preferred to remain still during the MRI acquisition, in order to avoid motion artefacts from the fault correspondence between spin excitation and localisation in the three dimensional space. The heart is a deformable organ, though, which performs a complex intrinsic deformational motion and at the same time follows the chest motion from respiration. Several images are, therefore, required to visualise the heart at several phases of the cardiac cycle, and over the acquisition of each phase the heart is requested to appear motionless. The impact of respiratory motion is eliminated with techniques such as respiratory gating with navigator echoes [25, 274], for example, which restricts the data acquisition to the ex-

piratory pause or breath holding [134] providing that the acquisition time is sufficiently short to complete in a breathhold. Shorter acquisition time is achieved with acceleration techniques [133,187,275] such as parallel imaging and shorter k-space sampling trajectories [134].

- **Segmented k-space imaging.**

Despite the elimination of respiratory motion, the intrinsic motion of the heart remains a challenge during the in vivo CMR acquisition process. One approach to meet this challenge could be to acquire consecutive images with short repetition times corresponding to the phases of the cardiac cycle, but this would result in images with poor spatiotemporal resolution and significant motion artefacts. The approach that has been established, to date, is the segmented *k-space imaging* combined with *cardiac gating*. The segmented k-space imaging relies on the partitioning of the k-space matrix of each phase of the cardiac cycle into segments and the partial filling of the same segment for all phases during a cardiac cycle. The k-space segments are completed with repetition of the aforementioned process over a number of cardiac cycles. For each phase, all k-space segments are assembled and reconstructed to an image and collecting all phases results in a sequence of cardiac images or so called a cardiac cine MRI dataset. The number of k-space segments and sampling trajectories sets the trade-off between spatial resolution on one side and temporal resolution, artefacts and acquisition time on the other side.

- **Cardiac gating.**

Although each image in cine MRI represents an instance in the cardiac cycle, it is, in fact, a combination of several homologous instances over several cardiac cycles at roughly the same phase. To minimize errors, it is necessary to align the homologous phases compensating for potential variations in the heart rate. Alignment and normalisation of the homologous phases is achieved with *cardiac gating techniques*. Cardiac gating is the regulation of cine MRI acquisition or reconstruction process with the simultaneous acquisition of an ECG in the MRI scanner [25]. The recorded R waves of the QRS complex from each heartbeat are employed to either trigger the readouts of the MR signals in *prospective cardiac gating* or serve as landmarks for the normalisation and alignment of the analogous phases at

the image reconstruction stage in *retrospective cardiac gating*. Prospective cardiac gating is intermittent and allows imaging of about 90% of the cardiac cycle, whereas retrospective cardiac gating is continuous and permits the reconstruction of full cardiac cycles.

C.3. CMR sequences, techniques and image types.

A sequential combination of RF pulses, magnetic gradient field pulses and data acquisition times defines an MR pulse sequence (see Figures C.7 and C.8). An MR sequence tunes the acquisition process such that the read MR signal carries specific information about the imaged body area that is mapped on the MR image. Conventional CMR and MR images illustrate the T_1 , T_2 or T_2^* relaxation times or proton density in each voxel. More advanced CMR techniques map the velocity, displacement, strain, perfusion, water diffusion or retention of a contrast agent in each voxel of the imaged area. This way, an unlimited number of MR and CMR sequences can be designed and a wide variety of MR and CMR image types that visualise particular properties of the imaged body area have been developed. Each CMR image type assists the diagnosis of particular types of cardiac disease [236]. More details about the available MR techniques and sequences can be found in [266, 271, 272, 276, 277]. *In the current thesis, conventional CMR image types that are (cine) T_1 -weighted, T_2 -weighted and proton density images from the heart have already been mentioned, along with the late-gadolinium enhancement and T_1 -mapping (acquisition and post-processing) techniques. Types of advanced CMR techniques for measuring myocardial motion such as MR-Tagging, DENSE, SENC and, in particular, PC-MRI that is the focus of the current work are described subsequently.*

As seen, a CMR pulse sequence is a combination of RF pulses, magnetic gradient field pulses and data acquisition times and generates an image of the cardiac tissues with specific biological properties suppressed or accentuated. Advanced CMR pulse sequences can be regarded as a combination of two components. The main and second in time order component is the *host-sequence* [170] or *imaging engine* [278], which provides information about the spatial relationship of structures in the imaging field. The combination of gradients in the host sequence defines the k-sampling trajectories and

thus can play a role in the acceleration of the acquisition. The assistive component and first in time order is the *preparation pulse* [170] or *modifier* [278] and this accentuates or suppresses specific cardiac tissues or the blood, modulates the contrast or weighting between specific tissues, superimposes magnetisation tags or encodes physical properties such as distance, velocity and strain to the MR signals.

C.3.1. Host-sequences

The *host-sequence* is normally either *spin echo* or *gradient echo* depending on the rephrasing technique that is employed in each case. *Spin echo* sequences offer flexibility in the acquisition of MR images with different contrast, like *T1-weighted*, *T2-weighted* and *proton density-weighted*, by tuning the pulse and readout times and have the advantage of compensating for T_2^* effects. On the other hand, a conventional spin echo sequence has a relatively long acquisition time and thus it is sensitive to motion and flow. Accelerated spin echo sequences have been developed with the application of a series of 180° inversion RF pulses after a single 90° excitation pulse and are known as *Turbo Spin Echo (TSE)*, *Fast Spin Echo (FSE)* or acquisition with relaxation enhancement (*RARE*), such that a slice can be acquired in one breath-hold. TSE has been accelerated further by combining with partial Fourier acquisition to complete a slice acquisition in one heart cycle known as *HASTE*. Accelerated spin echo sequences allow the increase of temporal resolution at the cost of image quality though.

Gradient echo sequences provide the possibility of fast acquisition compared to spin echo sequences allowing for successive RF pulses with short repetition time but, on the other hand, they do not compensate for T_2^* effects and thus are susceptible to off-resonance related artefacts. The short repetition time does not allow the longitudinal magnetisation to fully recover before successive RF pulses, but the magnetisation rather establishes an equilibrium dynamic steady state after several repetitions and this type of sequences is called *Steady-State Free Precession (SSFP)* [279]. The remaining transverse magnetisation is either spoiled by a gradient or it is refocused by a reverse gradient and reused. The first group of sequences is called *Gradient Recalled-Echo (GRE)* or non-balanced Steady-State Free Precession (nbSSFP) and the most popular sequences of this group are the Fast Low-

Angle SHot (FLASH) , the Gradient Recalled Acquisition in the Steady State (GRASS), the Spoiled Gradient Recalled (SPGR sequence) and the Fast Field Echo (FFE) sequence. The second group of sequences has several names given by different manufacturers like balanced Steady-State Free Precession (SSFP) (*bSSFP*), true Fast Imaging with Steady state Precession (*TrueFISP*), balanced Fast Field Echo (bFFE) and Fast Imaging Employing Steady-state Acquisition (FIESTA). Both GRE and bSSFP sequences can be repeated fast to yield a series of images with relatively high temporal as well spatial resolution and for this they are ideal for cine imaging. GRE sequences have small flip angles, low SNR and are less susceptible to off-resonance effects than bSSFP sequences.

GRE sequences have been modified to yield multiple echoes per excitation similarly to TSE and the analogous technique is called echo planar imaging (*EPI*). When a few echoes are acquired per excitation the host-sequence is called hybrid EPI (*h-EPI*) or segmented-EPI and when an entire slice is acquired in one excitation the host-sequence is called *single-shot EPI* and it is rarely used.

C.3.2. Acceleration techniques

- **k-space trajectories.**

The frequency and phase encoding gradients in the host-sequence define the trajectories of k-sampling and, as mentioned earlier, radial and spiral k-sampling allow for faster acquisition than Cartesian sampling because they manage to cover the k-space in fewer acquisitions acquiring samples in higher density from central k-space, where the great amount of image information is commonly contained rather than the periphery and corners, which contribute little or not at all to the MR image [170]. However, non-Cartesian k-sampling trajectories produce a complicated expression of artefacts in the image domain, where additional artefacts from even small synchronisation errors of gradients add on, and furthermore, they complicate unfolding in parallel imaging with SENSE [280].

Acceleration of image acquisition is often achieved with advanced image reconstruction techniques such as *partial Fourier* or *parallel imaging*.

- **Partial Fourier.**

In partial Fourier, the inverse Fourier transformation is applied on a half filled k-space matrix. The other half of the k-space is either completed with zeros or reconstructed to a full k-space making use of its conjugate symmetry and this is the homodyne reconstruction. Partial Fourier results in lower SNR and it is affected more by off-resonance artefacts compared to images from inverse Fourier transformation on a complete k-space matrix [281].

- **Parallel imaging.**

In parallel imaging several coils of different sensitivities are employed to record the MR signals and this multiple information allows the sparser sampling of k-space for the same spatial resolution [275]. The number of different coil sensitivities equals the factor by which the number of lines in the k-space are reduced also known as acceleration factor R. Sparser sampling of the k-space entails a smaller field of view and possibly image wrapping, if an area of the imaged object falls outside the field of view. This potential artefact is prevented by filling the missing lines of k-space using the multiple information from all coils in a technique known as *GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA)* [131,133]. An alternative technique addresses image wrapping after its transformation from the k-space and unwraps it computationally using coil sensitivities information; this technique is known as *SENSitivity Encoding (SENSE)* [130] and it is quite popular in parallel imaging. Parallel imaging results in reduced SNR due to the reduced number of acquired k-space lines where another SNR penalty from location and distribution of coils is added. SENSE and GRAPPA can also combine with a technique for temporal undersampling called UNFORD to yield TSENSE and TGRAPPA respectively.

Preparation pulses

The preparation pulses can be classified into *inversion*, *suppression*, *tagging* and physical property *encoding* pulses and play a key role in the function of the embracing sequence and the formation of the corresponding MR technique.

C.3.3. Inversion recovery

Inversion recovery is a technique that selectively nulls the signal from a particular tissue with the aim of enhancing the contrast between specific tissues. *Inversion pulses* start with a 180° inversion pulse which inverts the longitudinal magnetisation and the acquisition process is further tuned to coincide with the instance when the magnetisation of a particular tissue with specific T_1 aligns to the transverse plane as it recovers. In this way the signal from the particular tissue is nulled and image contrast is tuned. Inversion recovery can be designed to act selectively over a large region, spatially or spectrally selectively. A spatially selective inversion pulse to null the signal from fat combined with TSE yields the triple inversion recovery (STIR) sequence.

C.3.4. Saturation recovery

Saturation recovery is another technique to null or suppress magnetisation. *Saturation pulses* start with a 90° RF pulse, which flips the magnetisation to the transverse plane, where it is spoiled by a dedicated spoiler gradient; right after and before recovery, the excitation pulse of the host sequence or next modifier is applied. Saturation recovery has the advantages that the magnetisation recovers in half the time and, besides, it does not require full longitudinal recovery before the next saturation pulse is applied; thus it is faster compared to inversion recovery and it is suitable in the presence of arrhythmias. Saturation recovery is not selective to T_1 but allows spatial or spectral selective suppression.

An example of a spatial selective saturation recovery modifier is the *dark* or *black blood* preparation pulse, which nulls the signal from the inflowing blood with the aid of two saturation bands adjacent on either sides of the imaging slice; black blood preparation is employed to alleviate ghosting effects from the flowing blood and it is very popular in Phase Contrast MRI sequences to suppress velocity artefacts related to blood flow [68, 134, 282]. Another example of a spectral selective saturation recovery modifier is the *fat saturation* preparation pulse, which nulls the signal from the fat taking advantage of its chemical shift and thus alleviates the chemical shift artefacts; in this case a narrow bandwidth saturation pulse that is centred at the resonance frequency of the fat is applied to excite the fat and subse-

quently suppress its signal. Saturation recovery is also applied in first pass perfusion imaging to enhance the signal from the contrast agent.

C.3.5. Tagging and strain encoding

MR tagging is a technique that produces non selective spatial tagging planes of saturated magnetisation that are perpendicular to the image plane and fade slowly enough to follow the deformation of the tagged tissues over a number of acquisitions; MR tagging has been established as the gold standard in cardiac deformation analysis as discussed later [84]. The *tagging pulse* consists of two non selective RF pulses separated by a gradient magnetic field along the direction of the desired tags [88]. The first RF pulse, which is applied immediately after the R wave, flips the magnetisation to the transverse plane; magnetisations along the tagging direction are in phase. Subsequently the tagging gradient causes spreading of the phase of magnetisation along the tagging direction similarly to phase encoding, which results in the sinusoidal spatial modulation of the phase of the transverse magnetisation. The longitudinal magnetisation partially recovers until the second RF pulse mixes it with the transverse magnetisation with modulated phase; the result of the summation of the two magnetisation vectors is the periodic spatial modulated magnetisation, in terms of amplitude this time. The remaining transverse magnetisation is suppressed with a spoiler gradient. The areas of zero and nearly zero amplitude form the dark tags along the tagging direction. Repetition of the tagging preparation pulse along the other orthogonal direction produces a 2D grid of tags and a stack of 2D tags combines to a 3D grid, which lasts during the T1 recovery. The common tagging sequence is called SPAMM [88] and it also participates in a more advanced technique called CSPAMM which combines images from complementary SPAMM sequences to generate MR tagged images of improved contrast.

The tagging pulse has been modified and incorporated in a relatively new type of imaging technique called Strain-ENCoded MRI (SENC) MRI [283] to generate MR images that encode longitudinal strain. The preparation pulse of the SPAMM sequence for SENC imaging has the tagging gradient field aligned with the longitudinal or through plane direction such that, unlike MR Tagging, the tagging surfaces are parallel to the transverse or

imaging plane. For the SENC technique the sequence is applied twice at different phase encodings and the corresponding images are subtracted to yield an image of regional Eulerian longitudinal strain, that is the relative change in distance between neighbouring spins. The tagging pulse can therefore induce the generation of strain encoded MR images too.

C.3.6. Displacement encoding

Displacement ENcoding with Stimulated Echoes (DENSE) is a sequence and technique that encodes displacement into the phase of the MR signals, that is the displacement travelled by the corresponding spins [109]. The *displacement encoding* pulse consists of 1-1 SPAMM tagging pulse with an one lobe tagging gradient, which causes spatial modulation of magnetisation along the gradient direction. This is followed by a third RF pulse which flips the modulated magnetisation to the transverse plane where a second one lobe gradient that is opposite (of equal amplitude) to the first gradient is applied. The phase dispersion caused by the first gradient rewinds by the second gradient; Spins that remain stationary during the displacement encoding experience the same degree of phase dispersion and rewind, which results in a zero net phase. On the contrary, spins that travel experience a difference between phase dispersion and rewind, which results in a net phase that is proportional to the distance travelled by the spins. From the displacement encoded phases, displacement images are constructed (DENSE images) and have also been employed for the study of cardiac deformation, as discussed later [117]⁴.

C.3.7. Velocity encoding

Phase-Contrast MRI (PC-MRI) is a sequence and a technique that encodes velocity into the phase of the MR signals [122, 124]. The *velocity encoding* pulse consists of a 90° RF pulse followed by a bipolar gradient along the direction of the desired velocity to measure [284]. The RF pulse flips the magnetisation to the transverse plane such that initially magnetisations along the velocity encoding direction are in phase. Subsequently, the first lobe of the velocity gradient causes dispersion of the phase of magnetisation along the velocity encoding direction, similarly to phase encoding for

⁴large displacements can be measured.

localisation. The second lobe, which is opposite to the first lobe of magnetisation, forces dispersion of the phase of magnetisation in the opposite direction. Spins that remain stationary during the velocity encoding experience the same phase shift in both directions, which results in a zero net phase shift. On the contrary, spins that travel experience a different clockwise and anticlockwise phase shift, which results in a net phase shift that is proportional to the velocity travelled by the spins, as explained in detailed in a following section. From the velocity encoded phases and a reference image, a velocity image is constructed (PC-MRI image) and with repetition of the sequence with the velocity encoding gradient along the other two orthogonal directions, velocity images for all three velocity components can be generated.

C.3.8. Image types

Combination of the aforementioned modifiers with host-sequences incorporating acceleration techniques yields a vast variety of CMR images. For example, Simpson [134] has combined spiral trajectories and parallel imaging with SENSE to accelerate a PC-MRI sequence for TVM incorporating retrospective cardiac gating, black blood and fat suppression while ensuring a high temporal and spatial resolution. We have used Simpson's sequence [134] to acquire the TVM images in this work.

Cine GRE and bSSFP sequences generate high quality images from the heart with good contrast between cardiac tissues and, for this, they have been established in cardiac anatomical studies as well as in functional analysis of the heart such as the measurement of stroke volume, EF and wall thickness variation during the cardiac cycle [81, 285, 286]. Gadolinium contrast agent (Gd) combined with GRE, h-EPI or bSSFP and saturation recovery has been employed for first pass myocardial perfusion [267]. Gd combined with GRE and inversion recovery has been used in LGE technique for the assessment of myocardial viability, myocardial infarction, fibrosis and cardiomyopathies [57, 72, 267, 287–290].

For the investigation of myocardial conditions, such as diffuse myocardial fibrosis, edema, inflammation, infiltrative diseases like amyloidosis, Fabry disease and hemosiderosis, that may be rare or difficult to distinguish with standard cine MRI or LGE, the techniques T_1 -mapping, T_2 -mapping and Ex-

traCellular Volume (ECV)- mapping have been proposed [268, 269, 291–294]. These techniques combine acquisition with a dedicated sequence and post-processing to generate T_1, T_2, T_2^* and ECV maps from the heart. The common sequences designed for T1-mapping are the Look Locker (LL) Inversion recovery, Modified LL Inversion recovery (MOLLI) and shortened MOLLI (shMOLLI), and they rely on one or several inversion recoveries followed by a series of T1-weighted acquisitions at different levels of T1 weighting with or without prior administration of a contrast agent like Gd. SATuration recovery single SHot Acquisition (SASHA) sequence is an alternative sequence developed for T_1 -mapping, which comprises of ten single shot bSSFP over consecutive heart beats with saturation preparation pulses and different saturation delay time in each repetition. In T_2 -mapping two types of sequences are employed and these are the dark blood TSE and bright blood T_2 weighted sequences [292]. ECV maps are generated from the post-processing of the T_1 maps acquired both before and after the administration of a contrast agent [291].

Coronary angiography is performed with bSSFP and navigator echoes to synchronise acquisition at the mid diastole phase, GRE with contrast enhanced T1 weighting or TSE with dark blood preparation and fat suppression [170, 295]. For the study of the blood flow, as mentioned earlier, Phase-Contrast MRI has been employed [122, 125, 128] and MR Tagging, DENSE, SENC and TVM have been proposed for the analysis of myocardial deformation [75, 80, 81, 83, 285].

C.4. Artefacts in CMR imaging.

The complexity of CMR acquisition and cardiac motion entails a series of artefacts that potentially affect the quality of CMR images, diagnostic procedure and may even be confused with cardiac pathologies [170, 222, 296–299]. It is important to understand the source and expression or pattern of artefacts in each type of CMR image and take them into consideration in the development of CMR image processing algorithms as well as the diagnostic interpretation of the images. Artefacts are related to the *patient*, the *hardware* or the *processing* of MR signals for the CMR image reconstruction.

C.4.1. Patient related artefacts.

Patient related artefacts arise from *patient movement, respiration, cardiac motion, blood flow, large susceptibility difference* of adjacent regions and *ferromagnetic materials* implanted, worn, attached or permanently applied to the patient's body. *Motion artefacts*, including the artefacts of the first four causes, manifest as ghosting, diffuse blurring or spatial misregistration and affect primarily the phase encoding direction [25, 170, 222]. *Blood flow artefacts*, apart from ghosting, blurring and spatial misregistration, may also cause local intensity enhancement or suppression and can be reduced with the addition of a black blood pre-saturation pulse in the MR sequence [23, 68].

Ferromagnetic materials found in surgical clips, pacemakers, prosthetic valves, stents or other implants, orthopaedic devices, outfit, as well as cobalt and iron containing dyes of permanent cosmetics (i.e. tattoos) distort severely the external magnetic field resulting in spatial image distortion, peripheral signal loss or enhancement [222, 298]; The pigments of permanent cosmetics (i.e. tattoos, permanent eye, lip and cheek makeup) often contains iron oxide to render the dark shades, which is ferromagnetic, furthermore their electrical conductivity may lead to overheating due to eddy currents induced by the alternating magnetic fields especially in closed drawings [298, 300–302]. Similar but less intense spatial distortions are observed at the interface of materials with remarkable *difference in magnetic susceptibilities*⁵ such as the interface between soft tissue and bone or soft tissue and air; the result is misregistration of pixels around the tissues boundaries, which causes geometrical distortion accompanied by local intensity enhancement and suppression in the frequency encoding direction [303, 304]. The balanced steady-state free precession (bSSFP) sequence is prone to magnetic susceptibility artefacts.

C.4.2. Signal processing related artefacts.

Signal processing related artefacts list the *partial volume effect, chemical shift, aliasing and the Gibbs-ringing* artefact. The *partial volume effect* ensues from limitations in the voxel size and is the averaging of structures

⁵Susceptibility is measure of the extent a material becomes magnetized when placed in an external magnetic field $\vec{M} = \mu_v \vec{H}$

that are smaller than a voxel. *Chemical shift* occurs at the lipid-water interface and results from the slightly different resonance frequencies of water and fat caused by the different micromagnetic environments within each molecule; the chemical shift artefact either causes misregistration in the frequency encoding direction showing as a bright or dark band along the fat-water boundaries or intensity suppression from the dephasing of both fat and water protons. *Aliasing* or image *wrapping* is encountered along the phase and frequency encoding directions when the selected Field Of View (FOV) is smaller than the size of the imaged region. The *Gibbs-ringing phenomenon* manifests as intensity oscillation, that is alternating bright and dark bands fading slowly with distance, near sharp boundaries both in the frequency and phase directions; it results from the undersampling of the high spatial frequencies that form the sharp boundaries in an image.

C.4.3. Hardware related artefacts.

Hardware related artefacts involve distortions of the external, gradient and RF magnetic fields along with imperfections in the receiver coils, electronic noise and other RF interferences.

Inhomogeneities in the external magnetic field ($\vec{B}$) result in geometric distortions or local signal loss and are inevitably caused not only by system imperfections but also by magnetic susceptibility effects when the patient is placed in the MR scanner such that each patient creates a different pattern of $\vec{B}$ inhomogeneities. These inhomogeneities are attributed to magnetic susceptibility variations across the body and particularly at the tissue-air interface (for example heart-lungs) and, furthermore, the presence of ferromagnetic foreign objects on and in the body, if any. Local $\vec{B}$ inhomogeneities cause local resonance frequency offsets from the scanner's central frequency leading to the off-resonance precession of the local protons and, thus, signal loss. The bSSFP sequence commonly used in cardiac functional analysis is particularly prone to external magnetic field inhomogeneity artefacts which, in relatively high frequency offsets, form characteristic dark bands that are regularly spaced in the image across the frequency encoding direction. Artefacts can be prospectively reduced with localised central frequency adjustment and shimming of the magnetic field in and around the area of the heart. Passive (non-specific) shimming is performed at the in-

stallation of the scanner and active (patient-specific) shimming is performed with dedicated shim coils and controlled by the MR operator.

Deviation of gradient fields (G_{λ}) from spatial linearity causes additional image distortion. Spatial linearity degrades while moving towards the high positive and negative values of the gradient; for localisation gradients this affects the dimensions of the voxel area in the body resulting in compression of anatomical proportions towards the periphery of an image or stack. Phase encoding direction is more prone to this type of distortion, for this it is ideally assigned to the small dimension of the FOV of an image. Moreover, the effect of this type of artefact is easily avoided by aligning the region of interest i.e. the heart with the centre of FOV, where the strength of gradient fields and, thus, the related anatomical distortion is low.

The *zipper artefact* appears as a regular striped pattern of lines perpendicular to the frequency encoding direction across all images and is caused by the interference of external environmental RF signals (outside the Faraday cage), from light bulbs for example, that create narrow-band RF noise. The *annefact artefact* is a similar artefact, which is formed a dashed line in the centre of the frequency encoding and along the phase encoding direction and arises from stimulated echoes outside the FOV picked up by the receiver coils due to RF noise from hardware malfunctioning within the scanner room (inside the Faraday cage), such as bad electronics or bad connections to surface coils. If these artefacts are concentrated into one cluster near the middle of the image, they form a *star artifact*.

Surface coil flare is the increased brightness of an MR image near the positions of the receiver coils i.e. the chest, which rapidly decreases with distance creating the artefact of a shading gradient on the image. Surface coil flare is a type of (received) RF inhomogeneity and results from the non-uniform sensitivity of receiver coils to signals from different distances in combination with signal attenuation⁶, such that the strength of the read signal is inverse to the depth of its source. This artefact is more prominent when smaller receiver coils are selected, which on the other hand offer the advantage of low SNR compared to larger receiver coils. *Inhomogeneous MR image brightness* may have other causes too, such as *non-uniform* (applied) *RF magnetic field*, variation in the energy that is required to flip magnetisation to a specific flip angle (usually 90° or 180°) named as *RF tip*

⁶not sure

angle inhomogeneity or tight bandwidth of filters applied to the MR signal that results in a *decrease of signal intensity along the frequency encoding direction*.

The *cross excitation* artefact is the signal loss observed in an MR slice from a stack of consecutively acquired slices due to the partial pre-excitation of the slice from the previous RF pulse that was aiming at the excitation of the adjacent slice. Similar is the *slice overlap* artefact, when the slices are obtained at slightly different angles instead of parallel resulting in their partial overlap with pre-excitation of the overlapping area and, thus, loss of signal in the later slice.

Hardware and patient induced inhomogeneity in the external magnetic field, RF inhomogeneity, gradient fields distortion, eddy currents, and other sources of MRI artefacts often account for a smooth spatial intensity variation across the MR images called *image intensity inhomogeneity*. This type of artefact is modelled as an additive or multiplicative component to the MR image intensities and includes hardware or imaged object specific terms. For its reduction, prospective hardware and sequence related methods have been developed as well as the phantom based method, which can achieve up to 70% of this artefact mostly sourcing from the hardware terms. For the alleviation also of the patient specific terms, (retrospective) image analysis methods have also been suggested [305] and several more of them are reviewed in Vovk's study [306].

C.4.4. Noise

- **Introduction and propagation of noise.**

MR images are corrupted by noise that may have a significant impact on their further processing and clinical interpretation. Noise is introduced to the MR imaging system via the receiver coils. By noise we imply the thermal or Johnson-Nyquist noise, which is present in all electronic devices, and it is attributed to the thermal agitation of the electrons in the metal of the coil. The thermal noise is statistically modelled as additive white noise onto the measured MR signals. Phase shifts caused by inhomogeneities, susceptibility, eddy currents and other sources of artefacts appear and are sometimes treated [307,308] as part of the noise, but in the current section

noise will be considered purely thermal. Noise propagates through the various stages of MR image reconstruction and processing until it is expressed in the returned MR image. We attempt to reduce noise with processing of the MR image and, for this, it is legitimate to understand first the form of the noise and how this transforms through the various stages of imaging.

MR signal measurements are commonly acquired with a pair of receiver coils that measure two signals with 90° phase difference between them and for this they are called quadrature coils⁷. The two signals compose the real and imaginary parts of complex numbers that fill the k-space matrix, which then transforms into an image upon the application of the inverse Fourier transform [273]. The image produced by the inverse Fourier transform would be real-valued as imposed by the Hermitian property of the k-space, if noise was absent⁸. However the thermal noise that is introduced at each coil and, thus, in the real and the imaginary part of the complex numbers, disturbs the Hermitian property. Therefore, the product of the inverse Fourier transform is a complex image with non-zero imaginary part and phase [307].

The complex image is decomposed into a pair of real and imaginary images or a pair of magnitude and phase images. The noise in each of the real and imaginary images remains independent, additive and white [309], because Fourier transform imposes a linear relation of the real and imaginary parts between the k-space and image domain. On the other hand, the magnitude and phase images are reconstructed with non-linear mapping of the real and imaginary images and, for this, noise in the magnitude and phase images is no longer Gaussian; it rather follows complicated distributions with different statistical characteristics than their real and imaginary counterparts.

The MR image that is returned to clinicians is commonly the magnitude image, for example in the case of SSFP, because it combines clinical information with reduced artefacts and noise as compared to the real or phase images; For this noise in the magnitude MR image has extensively been studied. When the clinically useful information is encoded into the phase of the MR signal like in SENC, DENSE and PC-MRI techniques, the returned MR image is the phase image, which does not contain only noise in

⁷They measure the magnetic flux of the precessing magnetisation in two orthogonal directions

⁸and in the case of no physical property encoding.

this case. In inversion recovery imaging, the real image is occasionally more convenient because it preserves the negative signal intensities. Denoising of MR images often requires understanding of the noise distribution and characteristics in each MR image.

- **Single receiver coil unit.**

First, we describe noise in MRI acquired with a single receiver unit that is one pair of quadrature coils. In pixels with high SNR meaning more than 3, and when no physical property encoding is involved, the magnitude approximates the real part of the signal, thus noise in the imaginary part can be neglected and the overall noise is considered white. In pixels with moderate SNR, magnitude intensity obeys the Rician distribution and phase noise obeys another complicated distribution. In pixels of low or zero SNR, magnitude intensity follows the Rayleigh distribution [308] and phase noise is uniformly distributed.

The characteristics of noise in the magnitude MR image was initially studied by Edelstein [310], who showed the Rayleigh distribution in areas of zero or low signal with non-zero mean value and a standard deviation that is 34% lower than the standard deviation of the white noise. Henkelman in [309] computed the mean and standard deviation of the noise in the magnitude MR image in both extreme cases of zero and high SNR and showed that in both cases the mean signal measurement becomes biased leading to an overestimation of the signal strength. This bias means that denoising based on local averaging of intensities will have a systematic positive error. Bernstein [307] extended this analysis to introduce the Rician distribution as the probability density function of noise in the magnitude MR image and based on this they suggested a phase minimisation method for the correction of low SNR MR magnitude images. Gudbjartsson and Patz [218] reviewed the distributions of noise in the magnitude and phase images as well as their approximations in the two cases of extreme SNR.

Gudbjartsson and Patz [218] also proposed a simple correction scheme of the noise bias in the magnitude MR image based on the estimation of noise variance from homogenous areas of zero signal in the background of the MR magnitude image. Their statistical results showed that the Rayleigh model was not verified in those areas, which indicates a possible autocorrelation of noise besides the artefacts like ghosting. Sijbers [311] improved

the estimation of noise characteristics from the image background replacing local spatial averaging with a Maximum-likelihood estimator. To reduce the error in noise variance estimation from the background of the MR image, the combination of two images from double acquisition was employed [312]; this allowed better estimation of the variance, yet, at the risk of errors from image misalignment and, thus, single image processing regained attention. Following methods used local statistics of the image background and properties of the Rayleigh distribution [313,314] to estimate. They also proposed a simple correction scheme of the noise bias in the magnitude MR image based on the estimation of noise variance from homogenous areas of zero signal in the background of the MR magnitude image. Their statistical results showed that the Rayleigh model was not verified in those areas, which indicates a possible autocorrelation of noise besides the artefacts like ghosting. Sijbers improved the estimation of noise characteristics from the image background replacing local spatial averaging with a Maximum-likelihood estimator [311]. To reduce the error in noise variance estimation from the background of the MR image, the combination of two images from double acquisition was employed [312]; this allowed better estimation of the variance, yet, at the risk of errors from image misalignment and, thus, single image processing regained attention. Following methods used local statistics of the image background and properties of the Rayleigh distribution [313,314] to estimate the characteristics of noise. Adaptive filtering methods using local neighbourhoods have been largely studied. Wavelet based filtering methods attracted attention and among the studies Nowak's paper [315] has been popular. More recently Coupe [316], proposed a method for the estimation of Rician noise characteristics from the foreground of an MR magnitude image, which is based on the Median Absolute Deviation estimator in the wavelet domain. For the same problem, Rajan [317] suggested a method that uses restricted local neighbourhoods. A number of more methods on MR noise bias correction schemes been suggested and followed by more advanced denoising and restoration techniques.

The characteristics and probability density functions of noise in MRI with a single receiver unit are presented below according to the aforementioned studies. Assume N the noise corrupting each pixel of intensity S in the real or imaginary MR images. N is white noise with standard deviation σ and

its distribution has the probability density function

$$P_N(N) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{N^2}{2\sigma^2}}$$

The intensity of each pixel in the *magnitude image* is computed as the square root of the square sum of the real and imaginary values. Let A be the intensity of the pixel in the magnitude image in the absence of noise, and M the corresponding reconstructed intensity in the presence of noise. The intensity M in the magnitude image follows the Rician distribution with probability density function

$$P_M(M) = \frac{M}{\sigma^2} e^{-\frac{(M^2+A^2)}{2\sigma^2}} I_0\left(\frac{AM}{\sigma^2}\right)$$

where I_0 is the modified zero-th order Bessel function of the first kind, and it is illustrated in Figure C.9.

In areas of *high SNR* the Rician distribution approximates the Gaussian distribution with probability density function

$$P_M(M) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(M-\sqrt{A^2+\sigma^2})^2}{2\sigma^2}}$$

In this case, the mean or the bias in the magnitude becomes $\sqrt{A^2 + \sigma^2}$. In areas of *low SNR*, the Rician distribution reduces to the Rayleigh distribution with probability density function

$$P_M(M) = \frac{M}{\sigma^2} e^{-\frac{M^2}{2\sigma^2}}$$

In this case the mean of the Rayleigh distribution or equivalently the bias in the magnitude becomes $M_{mean} = \sigma\sqrt{\pi/2}$ and the variance is $\sigma_M = (2 - \pi)\sigma^2$.

The intensity of each pixel in the *phase image* is computed as the arctangent of the ratio imaginary to real values falling in the interval $(-\pi, \pi]$. The distribution of the propagated noise N_ϕ that is the difference between the real and measured phase follows a complicated distribution with probability

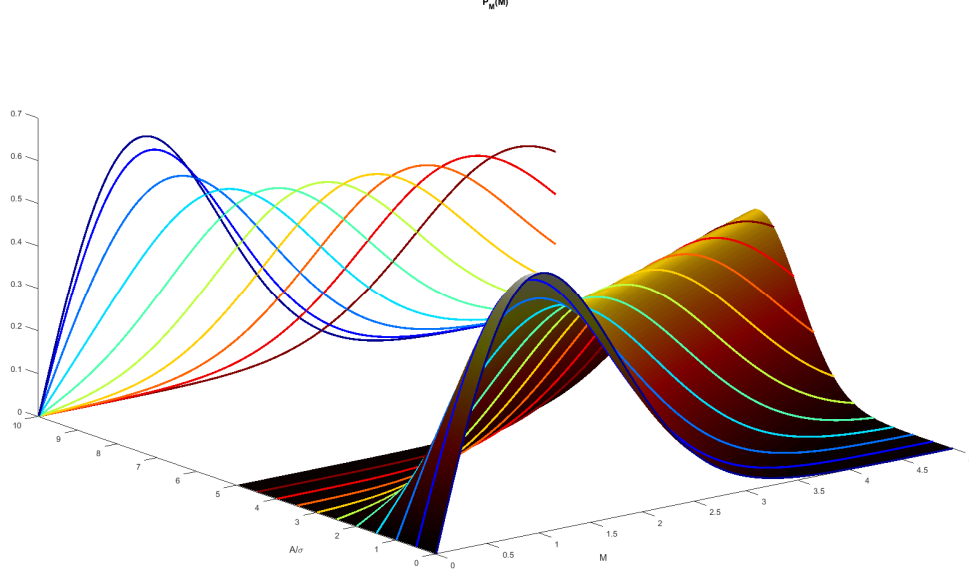


Figure C.9.: The surface illustrates the Rician distribution of the magnitude intensity M plotted against the corresponding intensity in the absence of noise A and the $SNR = A/\sigma$. The 2D curves illustrate the distribution of M for selected values of SNR. It can be seen that after $SNR=3$ the distribution is similar to the Gaussian but for lower SNR the distribution is quite asymmetric.

density function described as

$$P_\phi(N_\phi) = \frac{1}{2\pi} e^{-\frac{A^2}{2\sigma^2}} \left[1 + \frac{A}{\sigma} \sqrt{2\pi} \cos \Delta\phi \exp \frac{A^2 \cos^2 \Delta\phi}{2\sigma^2} \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{\frac{A \cos \Delta\phi}{\sigma}} e^{-\frac{t^2}{2}} dt \right] \quad (C.4)$$

and illustrated in Figure C.10. In areas of *high SNR*, the phase noise distribution is approximated by the Gaussian distribution with zero mean and variance that is inversely proportional to the signal strength $\sigma_\phi = \frac{\sigma}{A}$. Thus, the probability density function is given by

$$P_\phi(N_\phi) = \frac{1}{\frac{\sigma}{A} \sqrt{2\pi}} e^{-\frac{N_\phi^2}{2(\frac{\sigma}{A})^2}}$$

In areas of *low to zero SNR*, the phase noise is uniformly distributed in the interval $(-\pi, \pi]$ where the probability density function is given by

$$P_\phi(N_\phi) = \frac{1}{2\pi}$$

and it is zero outside this interval. The former approximation is physically interpreted by the fact that when the signal is high, the deviations along the direction of the complex measurements can be neglected and only the perpendicular Gaussian component of noise contributes to the total phase noise such that the higher the signal smaller the contribution. On the other hand, in the absence of signal, phase is randomly assigned without a

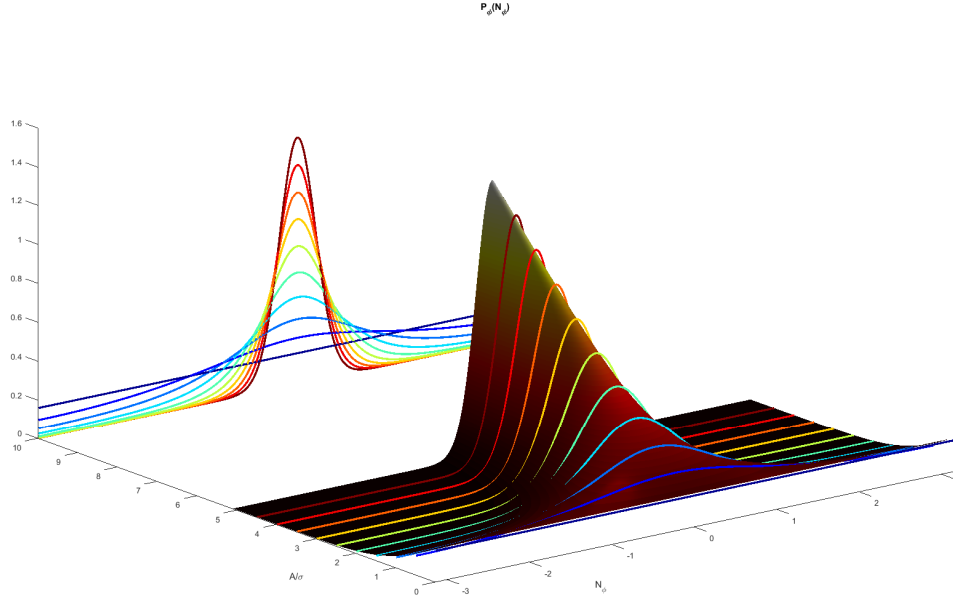


Figure C.10.: The figure illustrates the distribution of the noise in the phase image plotted against the SNR as above. It can be seen that after SNR=3 the distribution is similar to the Gaussian and for zero SNR the distribution is uniform.

- **Multiple receiver coil units.**

In the above description, noise has been assumed of zero mean (white) and uncorrelated with equal variance σ in both the real and imaginary parts. Variance σ has been also considered stationary, which means the same σ applied to the entire image. Based on these assumptions noise in single receiver coil unit acquisitions has shown to possess the aforementioned distributions. However in multiple receiver coil unit acquisitions the magnitude and phase noise distributions are different. Furthermore when acceleration techniques like parallel imaging and non-Cartesian k-space sampling as well as reconstruction filters [318] and other corrections such as shimming of the

magnetic field take place, the distributions and dependencies of the noise become more complicated.

In multiple receiver coil acquisitions, the magnitude noise can be modelled with the non-central χ -distribution as proposed by Constandinides [319]. In parallel imaging, reconstruction techniques like SENSE or GRAPPA affect the stationarity of noise variance σ^2 [314], which may vary even among the receiver coils. Under the assumption of nearly homogenous σ , Dietrich [320] showed that noisy magnitude intensities follow a general non central χ -distribution, which reduces to the Rician distribution in the case of SENSE reconstruction. If low spatial variability of σ is considered, noisy magnitude intensities in parallel imaging with GRAPPA reconstruction are assumed to follow a non-stationary χ -distribution, while in SENSE reconstruction noisy magnitude intensities may be considered Rician distributed with a spatially variant σ . Recently Aja-Fernandez [321] proposed a method for constructing the spatially variant component of the σ , which is considered to act multiplicatively on the noise, making the assumption that σ varies slower than the noise itself and they compared the method with previously proposed methods. Pieciak [322] proposed a method for the removal of the spatially variant component of noise for the case of non central χ -distribution like in GRAPPA reconstruction.

Lastly, although the aforementioned studies consider noise in each coil independent, there is evidence for noise correlations due to coupling of the coils and the eddy currents that also contribute to the spatial dependency of σ especially in areas of higher SNR [218, 319]. Also, it is worth mentioning that SNR is higher for higher voxel size and long acquisition time as stated by Macovski in [308] and, therefore, noise can be reduce to some extend by tuning the scanning parameters, which is not in the scope of the current work.

The majority of papers in MRI denoising have made use of the Gaussian approximations, which has been shown sufficient in situations of high to moderate SNR. However for images of low SNR like tissue phase mapping images, the consideration of biases or full distributions of noise would improve results. Furthermore, while noise in the magnitude MR images has been extensively studied, few are the studies on noise characteristics in the phase MR image, let alone in the field of CMR.

As pointed out, noise is an important artefact in the MR images and it is addressed in this work. Conventional MRI, which comprises of magnitude and real MR images, has moderate SNR and, therefore, noise can be considered Gaussian and removed with ordinary denoising methods. On the other hand, PC-MRI comprises mainly of phase images where noise is significantly more prominent, besides its complicated distribution. Unlike blood flow PC-MRI measurements, where SNR allows simplification of the phase noise distribution to the Gaussian distribution, denoising of TVM images is challenging. The main reason is because velocities in the myocardium are approximately 10 times lower than the blood and this low SNR not only urges the need for effective denoising before further processing of the myocardial velocities, but also requires a refined denoising procedure as ordinary denoising methods making use of the Gaussian approximation are less accurate in this case.

- **Notes.**

It would be interesting to see how the presented method of TV restoration is modified, if we take into consideration the complicated distribution of noise in my images and examine the improvement on the denoising result. A fast way to foresee the improvement is to generate images and corrupt them first with gaussian noise and then with the noise that follows the complicated distribution and apply the restoration method that is built around the gaussian distribution on both images and compare the results. Then try to built the restoration method around the new distribution and compare again. For modeling the noise I have to take into consideration the spiral k-trajectory along with the parallel imaging and SENSE reconstruction, the two different images background and phase encoded etc. I could dismiss the other corrections i.e. shimming that I am not sure how they work and impact noise and then see how the new distribution of noise comes out. Or alternatively use more universal denoising methods? Or apply a simple bias correction on my denoised results as implied by the complicated distribution and compare again my results.

C.5. Advantages and Clinical Applications.

A plethora of advantages has established CMR as the gold standard in medical imaging for the investigation of left ventricular anatomy and function in particular [81, 248]. On top of the non-invasive nature, CMR emits non ionizing radiation unlike Xray and CT, which allows its safe and repetitive application for monitoring and assessing the progression of cardiac disease even on vulnerable populations such as infants and fetuses. With CMR, acquisition of data is possible from any anatomical plane of the heart as compared to the 2D projections provided by Xray. The orientation of anatomical planes can be easily adjusted with tuning of the magnetic gradient parameters in the MR scanner, unlike with echocardiography. Programming the MRI scanner with a selection of MR sequences, a wide variety of CMR images types can be acquired on the same MRI scanner, with each image type visualising different anatomical and functional parameters in the heart. In terms of data quality, CMR achieves good contrast between soft tissues not easily visualised with the other imaging modalities, a sufficient spatial and temporal resolution that is higher than echocardiography and lower than CT trading off a SNR that is generally lower than echocardiography. In regional cardiac deformation studies in particular, CMR is providing the gold standard, by reason of its reliability and reproducibility and also because it offers techniques for direct measurement of myocardial motion and deformation measures.

Thanks to its great variety in techniques, high quality of images and the other aforementioned advantages, the current clinical applications of CMR are plentiful [236]. CMR is clinically used for measuring anatomical and functional features of the heart like blood pool volumes, myocardial mass and thickness, blood flow, vessel anatomy and perfusion setting up its clinical value.

CMR has been proven a valuable tool in the diagnosis of cardiomyopathies. Conventional CMR images allows more accurate measurements of the regional wall thickness and myocardial masses, which are markers of HCM, as compared to echocardiography. LGE and perfusion CMR show myocardial replacement fibrosis and microvascular dysfunction respectively, which are two more markers of HCM. Abnormal hypertrophy can be dif-

ferentiated from athletic hypertrophy based on the myocardial strain, shear and torsion computed with MR tagging. Other CMR techniques are employed assistively like CMR spectroscopy of ATP to show the bioenergetics defect in HCM and diffusion weighted tractography to reveal fibre disarray. LGE imaging contributes to the differentiation between HCM and rarer diseases of the myocardium with the same phenotype, like Fabry disease and cardiac amyloidosis, by revealing the different distributions of the gadolinium in each type of disease. Similarly, the study of LGE patterns enables the differentiation between DCM and the infarction following coronary disease. Siderotic cardiomyopathy, which is manifested in thalassemia and usually goes underdiagnosed due to lack of symptoms, is diagnosed with T2*-weighted imaging. CMR is also employed in the assessment of RV arrhythmogenic cardiomyopathy.

LGE is particularly useful in the differentiation between patients with HCM, DCM, ischaemic cardiomyopathy, viral myocarditis, sarcoidosis and cardiac amyloidosis [290]. However cardiac amyloidosis is not always diagnosed accurately with LGE or conventional CMR, especially at its early stages where functional and anatomical changes are similar to HCM and fibrosis is evenly distributed resulting in LGE images that may be misinterpreted as normal myocardium [290]. Differentiable [323] and more accurate diagnosis of diffusive disease and cardiac amyloidosis is achieved with T1 mapping and ECV mapping [268, 323], which are imaging and post-processing techniques making use of T1 weighted images from sequential inversion recoveries .

CMR is also accurate in the assessment of myocardial ischaemia with myocardial perfusion imaging and stress ventriculography serving as alternatives to myocardial perfusion single photon emission computed tomography (SPECT) or stress echocardiography⁹. Stress ventriculography is occasionally combined with MR tagging to quantify myocardial strain. T1-weighted T2-weighted and LGE are established as first line imaging techniques for the diagnosis of myocarditis and detection of transplant rejection and they are also used for the characterisation of masses towards the diagnosis of cardiac tumours. LGE and T2-weighted imaging are useful in the diagnosis of sarcoidosis and, furthermore, CMR can be used for the investigation of pericardial abnormalities like thickness, calcification, constriction with LGE

⁹ 2D echocardiography with dobutamine-induced (or other means) stress

specifically towards the diagnosis of pericarditis.

In the detection of acute and chronic infarction fibrosis and infiltration, LGE has high sensitivity and reproducibility and it is considerably more sensitive than perfusion SPECT. Differentiation between acute and chronic infarction is achieved with early gadolinium enhancement CMR, which reveals the microvascular obstruction in acute infarction and T2-weighted imaging, which shows the cellular oedema in acute infarction. Along these lines, T2-weighted imaging facilitates differentiation of reversible from irreversible ischemia. Early gadolinium enhancement is superior to echocardiography for the identification of ventricular thrombi and diffusion tensor tractography (DTT) is used for monitoring microstructure remodeling after infarction.

Moreover, CMR is employed in the imaging of vessels. SSFP depicts lesions, which appear clearer and in higher resolution with late gadolinium enhancement angiography; associated pathologies then, like collaterals¹⁰, can be detected. PC-MRI provides quantitative measurements of the jet flow and blood. CMR is ideal for imaging the aortic coarctation and other rarer abnormalities of the aorta; cine CMR is also used for monitoring the mitral and aortic valve stenosis and regurgitation as a second line technique whenever echocardiography with Doppler poses restrictions. Similarly CMR is used for the detection of abnormalities in the pulmonary circulation. Despite being inferior to invasive coronary angiography and CT angiography, contrast enhanced CMR angiography is a first line choice for the visualisation of coronary arteries in children, young adults and patients with Kawasaki disease where the use of radiation is precluded.

CMR shows promise in the assessment of further abnormalities in the heart and vessels setting the grounds for further future clinical applications. Some of them are the assessment of atherosclerosis mostly in the carotid artery via the measurement of the wall volume, and the assessment of the arterial function via the measurement of arterial diameter. CMR is potentially combined with electrophysiology for the assessment of arrhythmias via the detection of fibrotic tissue and monitoring of remodelling associated to beating abnormalities with LGE and DTI respectively, and subsequently the planning of ablation. CMR seems promising in the prediction and monitoring of cardiac resynchronisation therapy as well as the visualisation of

¹⁰Abnormal blood vessels that connect aorta with pulmonary arteries

soft tissue during interventions.

CMR and the four advanced imaging techniques MR-Tagging DENSE, PC-MRI and SENC are promising tools for the analysis of regional myocardial function, offering new insights into the prognosis, early diagnosis and differentiation of myocardial diseases that affect myocardial contractility [79, 81, 83, 324, 325]. Unlike echocardiography, regional deformation analysis with CMR has not been transferred to clinical practice yet, and the main hindrances are respiratory and cardiac gating issues, long acquisition times, complex scanning protocols, the challenging post-processing of MR tagging, for instance, or the complex noise and artefacts in the case of DENSE, PC-MRI and SENC [202]. MR-Tagging is considered as the gold standard for regional myocardial strain estimation in cardiac studies, but its current role in clinical practice is assistive rather than a first line diagnostic method. PC-MRI is employed clinically for imaging the blood flow but not for tissue motion analysis yet. However, it offers the potential for a detailed regional velocity and strain analysis in a per voxel level with less complex processing, providing prior alleviation of image artefacts and noise. The contribution of the current work is towards overcoming the hindrances of PC-MRI noise and post-processing reliability with the aim of extending its clinical application from blood flow analysis to regional myocardial contractility analysis.

Impediments against the wider use of CMR and MRI, in general, are the long acquisition time, usually non real-time image reconstruction, motion artefacts, heavy equipment and higher cost compared to echocardiography for instance. Contrast enhanced MRI [267] requires particular caution due to suspicions of toxicity and for this reason its repetition must be limited. Lastly, patients with metallic objects on or inside their body like defibrillators, pacemakers, prosthetic valves, stents, dental prosthetics, permanent body cosmetics and patients with severe arrhythmias or claustrophobia are likely precluded from MRI.

D. Myocardial segmentation and visualisation

Myocardial segmentation is required in shape analysis and often in motion and deformation analysis of the LV. Furthermore the combination of shape information and cardiac indices onto a 3D map can assist significantly the evaluation of the various image processing steps. For this, we have built segmentation and visualisation methods from scratch written in Matlab and some of the results are presented below.

For the automatic segmentation of the myocardium, we have developed a semi-automatic method based on graph-cuts [326,327]. The method requires only one pixel from the LV blood pool to segment one stack of CMR data. We have evaluated the method on cine SSFP datasets, late-gad datasets, TVM datasets and some of the results are presented in Figure D.1. The proposed method performed well in the segmentation of the endocardium in all datasets and well enough in the segmentation of the epicardium in the cine SSFP images. It was also applied successfully to the segmentation of the RV blood pool, as presented in Figure D.2.

The segmentation of the epicardium is a challenging task mainly because of the poor contrast between the posterior myocardial wall and its background. For this reason, a method based on local intensity does not perform adequately; instead we have used the overall information of the image. For the segmentation of the epicardium we have developed a method based on diffeomorphic registration [328] implemented with the demons algorithm [329]. The suggested method enables tracking of epicardial contours along the cardiac cycle by registering the masked background image of each frame to the corresponding masked background image of the first frame. The method was evaluated on cine SSFP data and results are presented in Figure D.3.

Myocardial segmentation is a quite challenging task and it often leaves

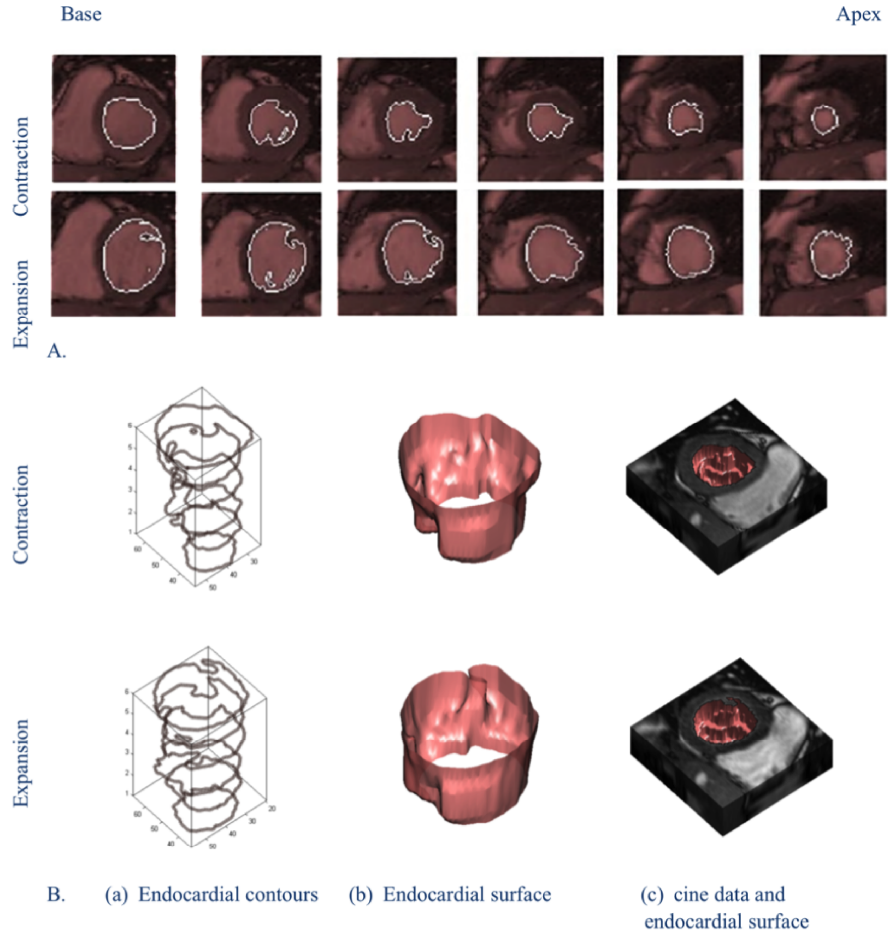


Figure D.1.: Proposed automatic segmentation method based on graph-cuts. (A) Segmentation and (B) visualisation of the endocardium from cine SSFP data.(a) Endocardial contours, (b) the corresponding endocardial surface (c) the corresponding endocardial surface and cine stack.

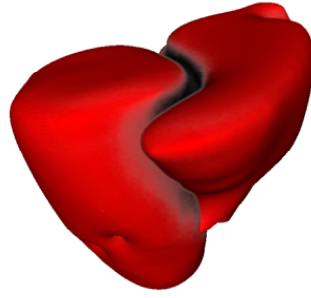


Figure D.2.: Segmentation and visualisation of the LV and RV blood pools. The segmentation was performed with the automatic graph-cut-based proposed method.

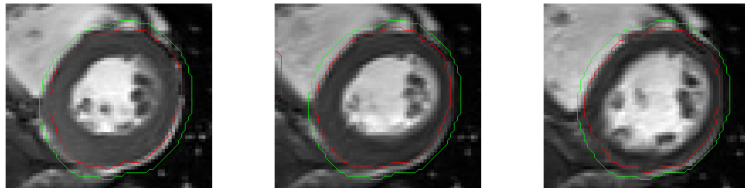


Figure D.3.: Epicardial segmentation with the proposed automatic registration-based method. The green contour of the first frame deforms to the red contour on the current frame to delineate the epicardium.

segmentation residuals. To correct the segmentation errors we have developed an interactive tool in Matlab, shown in Figure D.4, that imports the myocardial masks and allows the user to adjust the contours by dragging, creating and deleting control points.

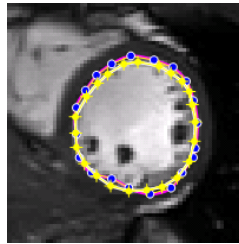


Figure D.4.: Interactive tool for contour correction

Figures D.5 shows 3D visualisations of the LV shape, developed in Matlab. The texture of the 3D objects encodes a cardiac index or other LV related information.

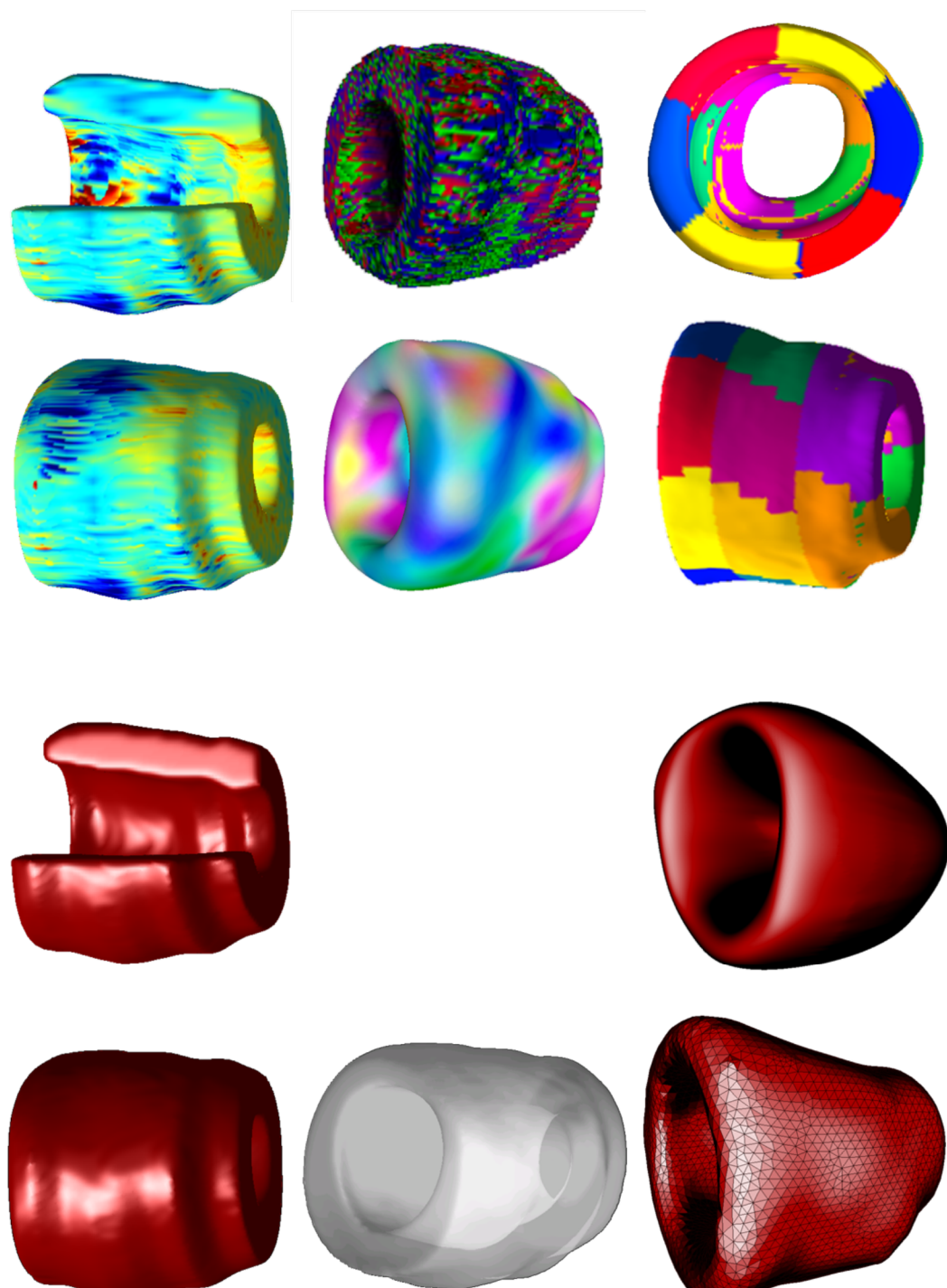


Figure D.5.: Developed visualisations of the LV

E. Sequential Monte Carlo Restoration

E.1. Introduction and Previous work

TV Restoration of PC-MRI yields tissue velocities with significantly less noise and well preserved edges. However the non-smooth strain rate maps generated from the restored velocities indicate the presence of residual noise. Residual noise can be attributed both to the noise model considered in TV Restoration and the morphology of the underlying data. As seen in Chapter 3, TV restoration prerequisites Gaussian noise with uniform pixel-independent standard deviation σ which is not the case in PC-MRI [218]. Gudbjartsson [218] states that the noise corrupting phase images follows Rician distribution which can be approximated by a Gaussian distribution only for pixels with significantly low magnitude to σ ratio. As per the data morphology, TV restoration trends towards piecewise-constant results and consequently in probable loss of significant curvature information.

To overcome the weaknesses of TV Restoration, we have been studying a novel restoration method based on Sequential Monte Carlo (SMC) algorithm. SMC does not require an accurate mathematical model of a system or the probability distribution of a stochastic variable; A random number of possible states is generated, instead, and the probability of each state is updated based on their match with the actual observations [330]. The term *Sequential* refers to the sequential capture of observations and the 1st order Markov property of states.

Although traditionally used for tracking, SMC has also been applied to several other medical imaging problems. Florin [331] presented a SMC method for the segmentation of the marginal artery on CT angiography which later on was extended by Cherry [332] and Wang [333]. The marginal artery was modelled as a sequence of successive segments and the particles

representing the alternative positions and orientations of the segments were weighted based on multiple visual cues. SMC has also been applied to visual tracking problems. For example, Hue [334] developed a SMC method for multitarget tracking and Brasnett [335] developed a SMC method for tracking in video sequences employing visual cues such as colour, texture and edge cues. SMC has also been used for the restoration of single images corrupted by non-Gaussian noise [336–338] represented by a casual half plane autoregressive image model.

In this Chapter we are presenting a SMC framework for the restoration of PC-MRI sequences. The method was expected to outperform TV Restoration because it is applicable to images with non-Gaussian type of noise as Rician is, it takes advantage of the sequential nature of PC-MRI along the cardiac cycle and it preserves adequately underlying curvature information of velocities.

E.2. Method

Let $\mathbf{x}_{t-1}$ be a variable vector that describes the hidden state $\mathbf{x} = (\mathbf{p}, \mathbf{v}, I)$, where $\mathbf{p}$ position, $\mathbf{v}$ velocity and I the intensity in a pixel-sized area of the myocardium as captured in frame t_{t-1} . We aim at estimating the hidden state $\mathbf{x}_t$ at time t_t . We assume that the sequence of states $\mathbf{x}_t$ has a 1st order Markov property $p(\mathbf{x}_t|\mathbf{x}_{1:t-1}) = p(\mathbf{x}_t|\mathbf{x}_{t-1})$. Our observations $\mathbf{y}_t = (\mathbf{v}, I)$, which represent the phase and magnitude values on each pixel, are only conditionally dependent on $\mathbf{x}_t$, which means $p(\mathbf{y}_t|\mathbf{y}_{1:t-1}, \mathbf{x}_{1:t}) = p(\mathbf{y}_t|\mathbf{x}_t)$. According to Markov chain dynamics, the transition from one state $\mathbf{x}_{t-1}$ to its subsequent $\mathbf{x}_t$ is described by a prediction step

$$p(\mathbf{x}_t|\mathbf{y}_{1:t-1}) = \int p(\mathbf{x}_t|\mathbf{x}_{t-1})p(\mathbf{x}_{t-1}|\mathbf{y}_{1:t-1}) \quad (\text{E.1})$$

and an update step

$$p(\mathbf{x}_t|\mathbf{y}_{1:t}) = \frac{p(\mathbf{y}_t|\mathbf{x}_t)p(\mathbf{x}_t|\mathbf{y}_{1:t-1})}{p(\mathbf{y}_{1:t})} \quad (\text{E.2})$$

For Bayesian problems where the analytic computation of probabilities is tedious or unfeasible, Metropolis [339] suggested a numerical solution that is generation of a large number of random states named particles and

subsequently their weighting according to a likelihood function which rates how close the observations $\hat{\mathbf{y}}_{t,i}$ that each particle i would yield are to the actual observations $\mathbf{y}_t$. Particles are filtered out at each step according to their weights and also they form the posterior probability $\mathbf{p}(\mathbf{x}_t|\mathbf{y}_{1:t})$ from which the state's estimate is calculated. The most predominant particles are propagated until the end of the chain and determine the hidden states $\hat{\mathbf{x}}_t$.

As a prediction model the following state space model is defined

$$\mathbf{x}_t = F * \mathbf{x}_{t-1} \quad (\text{E.3})$$

$$\mathbf{y}_t = G * \mathbf{x}_t \quad (\text{E.4})$$

For our application we assume that each myocardial point follows an ellipsoidal trajectory $\mathbf{x}(t) = \bar{\mathbf{x}} + A \sin(\omega t + \varphi)$ as represented in Figure E.1. Ellipsoidal trajectory model and, accordingly, ellipsoidal velocity model seems to approximate adequately myocardial regional motion as measured by Delfino [27]. The ellipsoidal model has also been used by Meyer in [157]. The transition function F from $\mathbf{x}_{t-1}$ to $\mathbf{x}_t$ in 2D takes, therefore, the following form

$$F = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ (1-c) & 0 & c & 0 & \frac{s}{r_v\omega} & 0 & 0 \\ 0 & (1-c) & 0 & c & 0 & \frac{s}{r_v\omega} & 0 \\ r_v\omega s & 0 & -r_v\omega s & 0 & c & 0 & 0 \\ 0 & r_v\omega s & 0 & -r_v\omega s & 0 & c & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \quad (\text{E.5})$$

where $\omega = 2\pi/T$, T the duration of cardiac cycle, $c = \cos(\varphi)$, $s = \sin(\varphi)$, $\varphi = 2\pi/n$, n the number of frames for an entire cardiac cycle, and r_v the in-plane pixel resolution.

The observation function G takes the form

$$G = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \quad (\text{E.6})$$

Our likelihood model $L(\mathbf{y}_t|\hat{\mathbf{x}}_t)$ is a fusion of multiple cues:

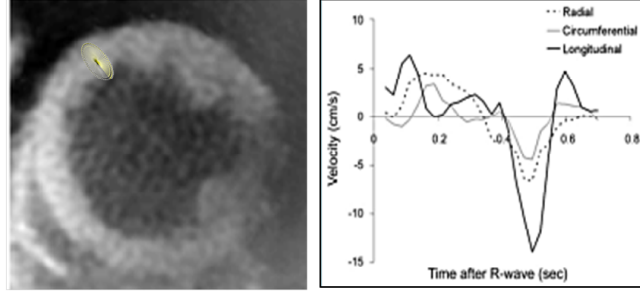


Figure E.1.: Ellipsoidal trajectory model and actual myocardial velocity curves [27]

- Magnitude similarity between the initial position $\hat{\mathbf{p}}_{t-1}$ and the current predicted position $\hat{\mathbf{p}}_{t,i}$
- Velocity similarity between the predicted velocity $\hat{\mathbf{v}}_{t,i}$ and the measured velocity $\mathbf{v}_t(\hat{\mathbf{p}}_t)$
- Angle consistency between successive position vectors $\hat{\mathbf{p}}_{t-1}$ and $\hat{\mathbf{p}}_{t,i}$. In our application the variable $X = \frac{\|cross(\hat{\mathbf{p}}_{t-1}, \hat{\mathbf{p}}_t)\|}{\|\hat{\mathbf{p}}_{t-1}\| \|\hat{\mathbf{p}}_t\|}$ follows a Gaussian distribution with mean 2.06.

A large number of random particles representing the first state are generated. At each step the following state for every particle is estimated with the prediction model. The particles in the new position are weighted according to the likelihood function and the posterior probability of the new state is estimated.

E.3. Results and Discussion

Trial data

The proposed SMC algorithm for image restoration was applied to a simple trial synthetic dataset as seen in Figure E.2. The features in magnitude image (a) at $t = 1$ are deformed under the effect of the horizontal constant velocity field (c) to yield a new magnitude image at $t = 2$. The magnitude and velocity images were corrupted with white Gaussian noise of $N(0, 0.001)$ and $N(0, 1)$ respectively yielding to the observed trial images (b) and (d).

The velocity field has been restored with the proposed Monte Carlo

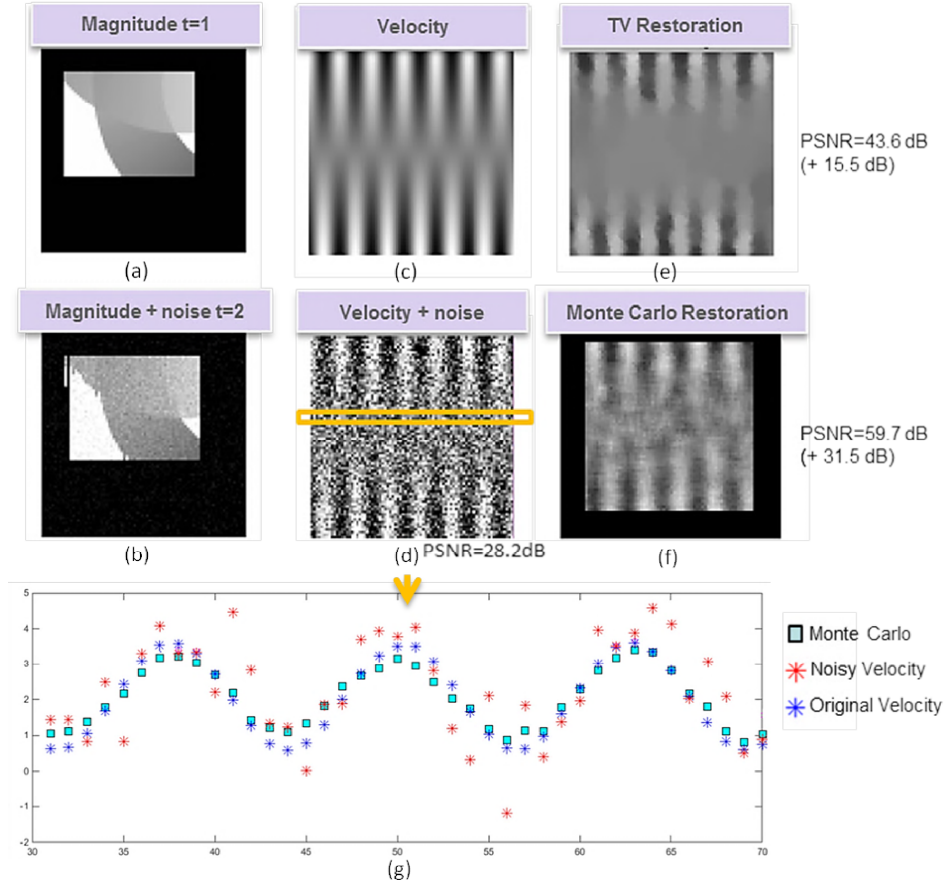


Figure E.2.: Monte Carlo Restoration. (a) Clean magnitude at $t=1$, (b) noisy magnitude at $t=2$, (c) clean constant velocity, (d) its noisy version with noise variance=1, (e) restored velocity field with TV Restoration algorithm, (f) restored velocity field with Monte Carlo Restoration algorithm, (g) values of clean, noisy, predicted and estimated after resampling velocities for the 70 pixels of the marked line in (d).

method (f) and the TV Restoration (e) presented in Chapter 3. It can be observed that Monte Carlo Restoration preserves better the pattern of velocity particularly in areas where signal values are comparable to noise. For quantified comparison the Peak SNR (PSNR) was calculated according to the following definition

$$PSNR = 10 * \log \frac{\max(V_{clean})^2}{\sum_m \sum_n (V_{noisy} - V_{clean})^2 / m * n} \quad (E.7)$$

where V_{clean} is the underlying real velocity field with dimensions $m * n$ and V_{noisy} is the noisy estimate of velocities. The PSNR=28.2dB of the initial noisy image was raised by 15.5dB with TV Restoration, whereas double was the corresponding increase with Monte Carlo in terms of dB; the restored image reaches a PSNR value of 59.7dB. The clean, noisy and restored velocities with Monte Carlo can be seen analytically for a selected row of pixels in diagram (g). The underlying sinusoidal velocity marked in blue is adequately approximated by its Monte Carlo estimates indicated with cyan squares, correcting the corresponding noisy values in red. The same processing was applied to a similar trial dataset with a lower level of white Gaussian noise of $N(0, 0.01)$ as seen below.

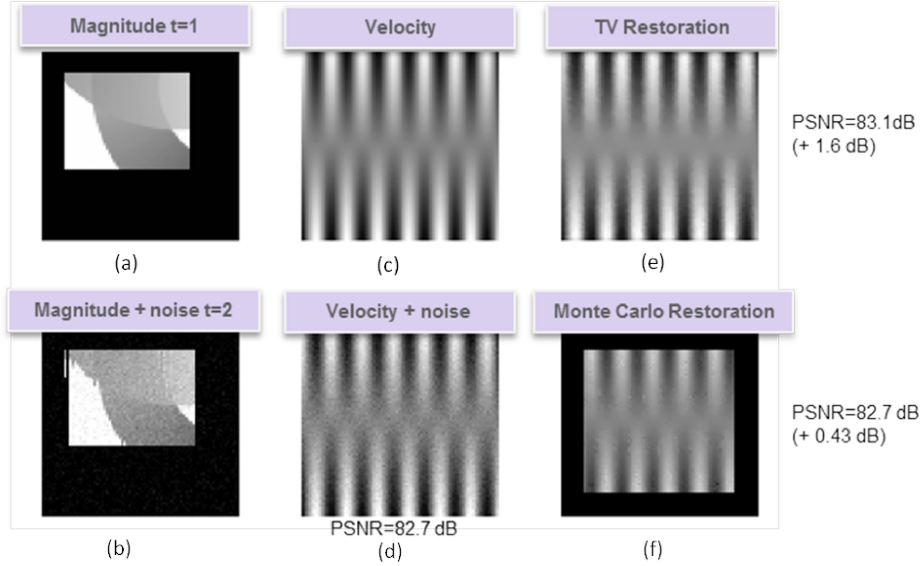


Figure E.3.: Monte Carlo Restoration. (a) Clean magnitude at $t=1$, (b) noisy magnitude at $t=2$, (c) clean constant velocity, (d) its noisy version with noise variance=0.01, (e) restored velocity field with TV Restoration algorithm, (f) restored velocity field with Monte Carlo Restoration algorithm.

In this case of lower noise, the TV Restoration performs slightly better than Monte Carlo method since the former achieves a 1.6dB increase of PSNR instead of 0.43dB that is achieved with Monte Carlo. Similar conclusions are drawn from the analysis of the removed noise, as shown in Figure E.4.

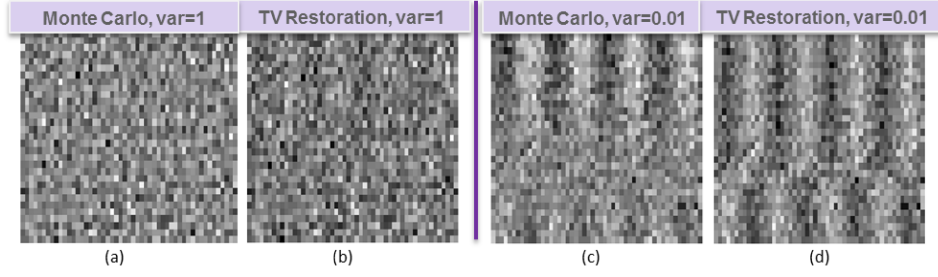


Figure E.4.: Removed noise. Noise of variance=1 was removed with (a) the proposed Monte Carlo Restoration and (b) TV Restoration method. Noise of variance=0.01 was removed with (c) the proposed Monte Carlo Restoration and (d) TV Restoration method respectively.

For all preceding images of removed noise, we performed a z-test to estimate the significance of the hypothesis that the removed noise follows a normal distribution with zero mean and a corresponding standard deviation, 1 or 0.1.

Table E.1.: Z-test for the hypothesis that the removed noise can be considered with a white Gaussian with a variance of 1 or 0.01

Restoration method	MC	MC	TV	TV
Variance of added noise	1	0.01	1	0.01
Null hypothesis	true	true	true	true
p-value	0.9941	0.9817	0.9611	0.9949

Considering the fact that all p-values are near 1, it can be stated that there is no presumption against the null hypothesis. In other words the removed noise follows the corresponding normal distributions $N(0,1)$ or $N(0,0.01)$, which indicates a successful removal of initial noise. For the high level of noise Monte Carlo restoration yields a higher p-value compared to TV Restoration, which implies the superiority of Monte Carlo to restore velocity fields of low PSNR. The opposite relation for low levels of noise reflects its vulnerability to restore velocities of high PSNR.s

On the grounds of PSNR improvement and the aforementioned p-value criterion, it can be claimed that the proposed Monte Carlo method performs clearly better on velocities of higher PSNR, whereas TV restoration is preferable in case of lower PSNR. A possible reason for that is the lim-

itation in velocity accuracy due to the quantized pixel size of magnitude image that is involved in the proposed Monte Carlo method. This particular weakness of the presented algorithm is better perceived when applied to a realistic simulated dataset, as follows.

Simulated and in vivo data

For the evaluation of the proposed Monte Carlo method, a trial data set was constructed as presented in Figure E.5. A magnitude image of actual PC-MRI data was smoothed and cropped in the shape of a ring (a) simulating the cross section of the left ventricle. For the same ring-shaped area, a 2D constant rotational velocity field (c) was created. The magnitude image was deformed according to the constructed velocity field (a). Subsequently white Gaussian noise was added both on the magnitude (b) and velocity images (d). Realistic values were selected for all parameters including noise level as summarized below.

Table E.2.: Parameters of simulated data

Magnitude of velocity	300
Maximum velocity measurement	2480
Maximum possible measured actual velocity	20 cm/s
Cardiac cycle length	120 ms
Frames per cardiac cycle (full coverage)	50
Spatial resolution	0.85 mm/pixel
Variance of noise in velocity images	1500
Variance of noise in magnitude images	1200

Although SMC restoration performs well on trial images, it does not restore successfully the simulated PC-MRI data. Similarly not adequately good are the results when SMC restoration is applied to in vivo PC-MRI as seen in Figure E.6. The main reason for this is the limited precision in the discrimination between particles when assigning weights. This limitation arises from the pixelisation of magnitude data and is propagated to our velocity estimates as described below.

Velocity of a particle is defined as

$$v = \frac{S}{T} \quad (\text{E.8})$$

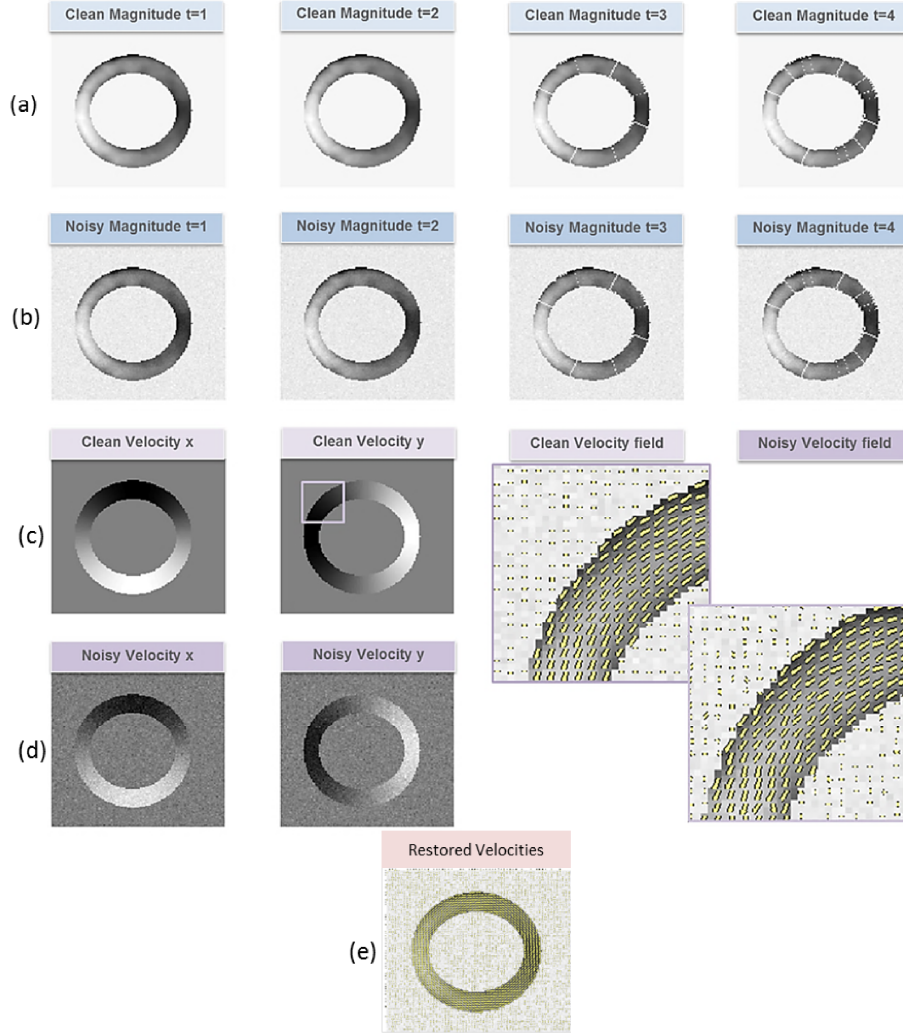


Figure E.5.: Simulated PC-MRI data. (a) A sequence of segmented magnitude images of the LV cross section, (b) the corresponding magnitude sequence augmented with white Gaussian noise, (c)-(d) components of in-planar velocities and their vector-field before and after adding noise, (e) restored velocity field.

where S is the distance covered by the particle and T is the time interval between successive frames. Discretisation of distance introduces an error ε so that

$$\hat{S} = S + \varepsilon \quad (\text{E.9})$$

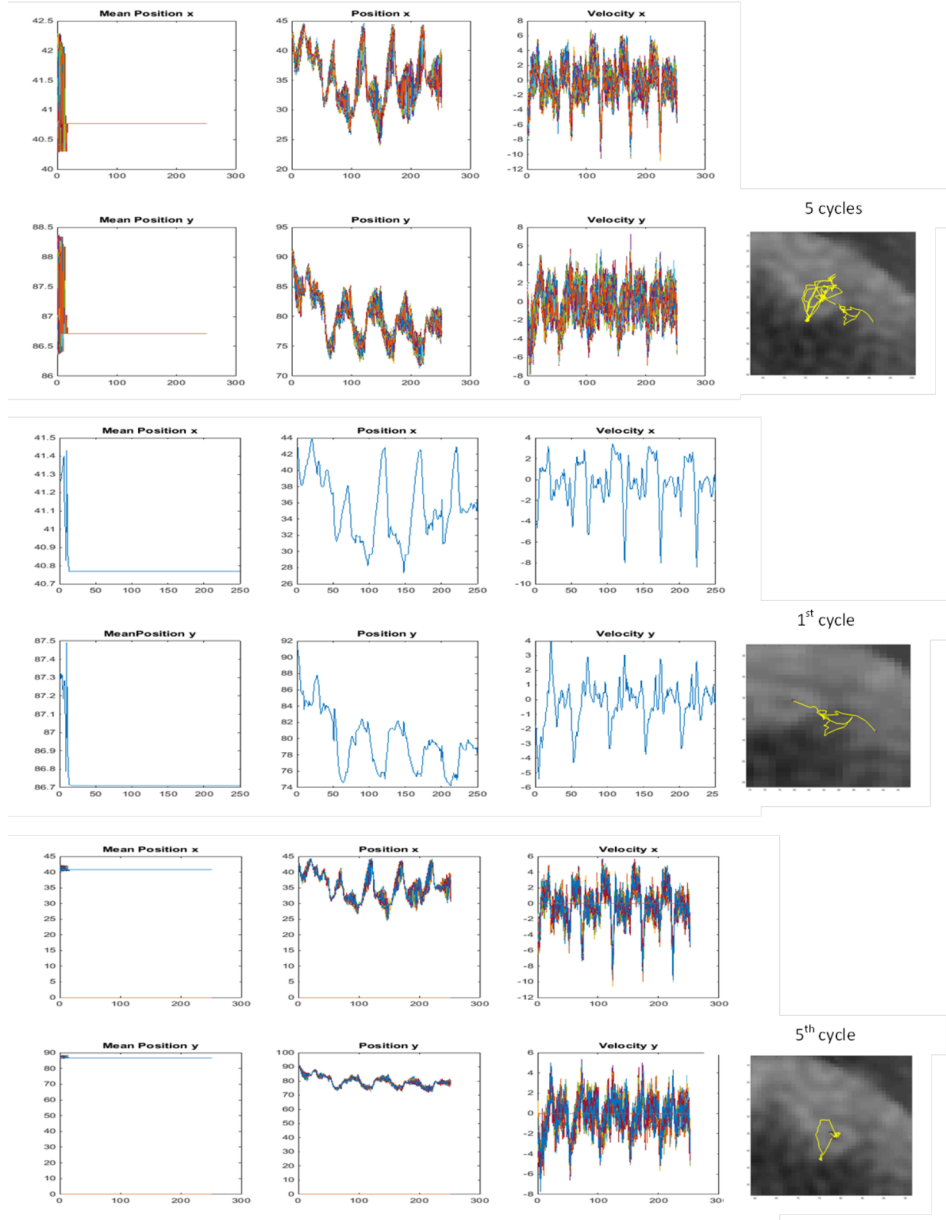


Figure E.6.: SMC Restoration of PC-MRI data.

Where $\hat{S}$ denotes the discretized distance and S the true distance. The error ε propagates to the velocity introducing the error ε_v so that

$$\hat{v} = v + \varepsilon_v = v + \frac{\varepsilon}{T} \quad (\text{E.10})$$

Assuming that all positions in an area of a pixel have the same probability and the maximum value of ϵ is $\Delta/2$, the error ϵ follows a uniform distribution with probability density function

$$f(\epsilon) = \begin{cases} \frac{2T}{\Delta}, & \text{if } 0 < \epsilon < \frac{\Delta}{2T} \\ 0, & \text{otherwise} \end{cases} \quad (\text{E.11})$$

where Δ is the side length of the pixel square equals the spatial resolution value.

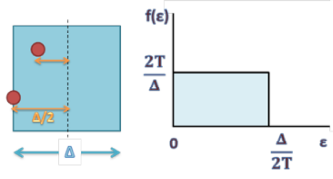


Figure E.7.: Pixel size and error probability density

The variance of the error ϵ is calculated as

$$\sigma^2 = \int_0^{\Delta/2T} \epsilon^2 f(\epsilon) d\epsilon = \frac{2T}{\Delta} \int_0^{\Delta/2T} \epsilon^2 d\epsilon = \frac{\Delta^2}{12T^2} \quad (\text{E.12})$$

The time interval T is

$$T = \frac{\text{Cardiac cycle length}}{\text{Number of frames per cardiac cycle}} = \frac{1200ms}{50} = 24ms \quad (\text{E.13})$$

and therefore the standard deviation of the velocity error is

$$s = \sqrt{\sigma^2} = \frac{\Delta}{\sqrt{12}T} = \frac{0.85mm}{\sqrt{12} * 24ms} = 1.02cm/s \quad (\text{E.14})$$

Considering that myocardial velocities in the apex do not exceed the value of 4cm/s [31] [17], velocity precision of 1.02 cm/s is accounted prohibitively high. It can therefore be concluded that the proposed method is not suitable for our restoration problem although it potentially restores successfully other similar datasets. Modification of the framework for Monte Carlo restoration is therefore required.

E.4. Conclusion

The presented SMC restoration method has not performed well on PC-MRI data due to pixelisation restrictions. However we believe that a modified version of this method which will base likelihood functions on smoothness of strain maps rather than intensity and velocity similarity can potentially yield significantly better results.

F. Tissue characterisation: T1-Mapping for the diagnosis of cardiac amyloidosis

F.1. Cardiac amyloidosis

Cardiac Amyloidosis (CAmyl) is a group of rare diseases that is manifested with a frequency of 6-10 per million population in the UK and the US [340] approximately. Severity of CAmyl varies with certain types of CAmyl being fairly aggressive as they progress fast and manifest high rates of morbidity. CAmyl usually goes underdiagnosed not only due to its rareness but also due to its wide spectrum and non-specificity of symptoms, which include dizziness, fainting, fatigue, fluid retention, low blood pressure, shortness of breath and arrhythmias. Novel methods for early diagnosis and surveillance of CAmyl are, therefore, a necessity and a rather challenging problem.

Amyloidosis is attributed to abnormal folding, aggregation and accumulation of proteins in the extracellular space of tissues and organs. Cardiac involvement is predominant with a percentage of 50% over all amyloidosis cases and its most common types of CAmyl are light-chain amyloidosis in 85% of the cases, senile systemic amyloidosis, and wild-type and hereditary transthyretin amyloidosis [340]. CAmyl may coexist with other disease or non-cardiac amyloidosis elsewhere in the body. Tissues and organs susceptible to amyloidosis are the kidneys, liver, lungs bones, skin, peripheral and autonomic nerves, tongue and abdominal fat [340].

The accumulated amyloid deposits disrupt the normal architecture of tissues and organs as shown in Figure F.1 with usual impacts on their anatomy and function. In CAmyl myocardial wall enlargement, progressively increased myocardial stiffness as well as electric conduction system disturbances often occur. Such anatomical and functional changes alter the

contractile profile of the heart and in late stages can potentially lead to congestive heart disease, heart failure or sudden cardiac death.

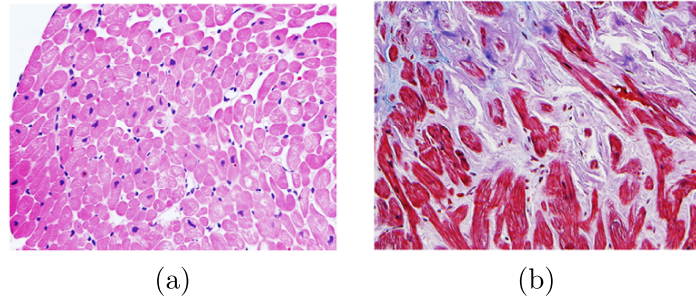


Figure F.1.: Cardiac biopsies in x400 magnification [58] showing (a) normal myocardial tissue (b) amyloid myocardial tissue. Normal tissue presents tight architecture of muscle fibres (stained pink) whereas amyloid tissue presents muscle fibres disrupted by amyloid deposits (stained pink-purple).

F.2. Morphological and functional myocardial alterations

Most common anatomical changes in CAmyl are concentric thickening of the left and right ventricular wall, dilation of atria, enlargement of valves and thickening of interatrial septum. Ventricular cavity size is preserved or reduced and the cardiac output usually maintained. In echocardiography the amyloid myocardium appears with speckled or granular texture [341, 342]. However wall thickness can be normal in CAmyl [343] particularly in early stages of the disease.

CAmyl can be classified as restricted cardiomyopathy due to increased stiffness and reduced contractile performance of the amyloid myocardium [54]. Diastolic dysfunction is likely even before morphological changes occur in CAmyl [54, 342]. Longitudinal early diastolic velocities, strain and strain rates are primarily affected, with basal motion being more restricted than apical motion [54]. Systolic strain, longitudinal in particular, decrease [54, 344] as the disease progresses, although studies show that this can occur also from an early stage [345] explained by the statement that systolic and diastolic motions are closely interweaved [345]. Longitudinal strain seems the most accurate diagnostic index [345], however circumferential and radial

strain are also affected along the progression of CAmyl. In early stage of CAmyl circumferential strain rate is enhanced working as a compensatory mechanism for the restricted blood filling, whereas in later stage it reduces due to the advanced impairment of the muscle [346]. Radial strain rate is usually maintained until late stages of CAmyl [54]. Different regions across the amyloid myocardium may present intra-subject heterogeneity in terms of alterations in myocardial stiffness and contractility [347] associated with the concentration of amyloid and, therefore, regional rather than global contractility investigation would be more meaningful.

Electric conduction system disturbances are also common in CAmyl. The electrocardiogram is usually affected so that QRS voltages appear low and R wave poor. Cardiac arrhythmias and pseudoinfarction patterns are likely while electromechanical dissociation can also occur and result in sudden death [341, 348].

From the above it seems there is an association between cardiac contractility performance and presence of amyloid. Regional strain could be investigated as a potential diagnostic index of CAmyl and possibly a discriminative criterion between patients with CAmyl from patients with other infiltrative disease, as it will be discussed later in this Chapter.

F.3. Diagnosis of cardiac amyloidosis

For the diagnosis of CAmyl biopsy has been the gold standard as histological tests are accurate and inexpensive. However the suitability of biopsy for the amyloidosis quantification and monitoring its progression is questionable as biopsy provides information only from a small sampled tissue area instead of the entire organ, it is prone to sampling errors and rather invasive [349].

To overcome the aforementioned impediments, novel methods in the areas of non-invasive imaging modalities for the detection and quantification of CAmyl are being developed. Echocardiography is a significant diagnostic modality for CAmyl but its efficacy in early diagnosis still remains a challenge. Sensitivity of echocardiography in the detection of CAmyl is achieved with a combination of features: anatomical features such as thickened myocardial wall and valves, functional features such as impaired diastolic function as well as tissue echogenicity such as granular or speckled appearance of scanned tissue [341, 348]. I-SAP (Serum amyloid P labelled with Iodine)

radionuclide imaging despite being the most accurate modality for screening of systemic amyloidosis of all types, it is unable to image the heart and, therefore, unsuitable for CAmyl diagnosis [349]. CT scans are not specific to amyloid concentration and the role of PET, which measures metabolic activity in amyloidosis, is still limited.

Cardiac Magnetic Resonance (CMR) has an increasingly important role in the diagnosis of CAmyl. Additional to morphological abnormalities that can be imaged with conventional CMR, intrinsic tissue characteristics can be measured with advanced CMR techniques before evident changes in morphology occur. Late gadolinium enhancement imaging (LGE) is sensitive to increased extracellular space and abnormal kinetics of gadolinium that amyloid deposition causes [350]. LGE information lies in the contrast between myocardial and blood pool signals rather than their absolute intensity level, which differs from one image to another [350]. Besides, the two types of signals can even null together or be reversed. This LGE characteristic hinders the quantification of fibrosis, the intra-subject comparison and monitoring of CAmyl progression.

Quantitative information for tissue fibrosis and induced by amyloidosis lies in the T1 and T2 relaxation times of the tissue as they alter in the presence of fibrosis. Along these lines T1 mapping [268,351–353] is emerging as a valuable clinical tool for the detection, quantification and monitoring of amyloidosis and it can also be used as discriminative criterion between CAmyl and other infiltrative diseases [59,323,354]

F.4. T1-mapping

T1 maps [268,351–353] are parametric reconstructed images, where each pixel value is an estimate of the T1 relaxation time of the analogous myocardial voxel. For each pixel, the T1 value is calculated from the inversion recovery curve, which in turn is estimated from fitting a 2 or 3-parameter exponential curve to the corresponding series of intensities acquired with LL or MOLLI MRI sequences [51] along with the appropriate corrections [268,355]. T1 mapping is performed with or without the administration of gadolinium contrast agent, (although contrast free T1 is claimed to have more diagnostic significance and reproducibility [351]).

Pre-contrast T1 and post-contrast T1 estimates depend on a variety of

confound factors such as field strength for the former and dose of gadolinium, time of measurement and haematocrit for the later [293] that should be taken into consideration in intra-subject and inter-subject assessment of T1. Alternatively extracellular volume fraction (ECV) mapping or equilibrium contrast CMR that is expected to eliminate the effect of the confound factors can be used [291]. The main weakness of ECV mapping is that it is prone to segmentation and registration of post-T1 maps to pre-T1 maps errors.

F.5. Differential diagnosis of HCM and CAMyl

T1-mapping has been proved to be a promising clinical tool for the detection and quantification of diffusive myocardial fibrosis [55]. Diffusive myocardial fibrosis though, can be attributed either to CAMyl or Hypertrophic Cardiomyopathy (HCM). The two types of myocardial disease may also manifest similar functional and anatomical changes such as myocardial thickening and stiffness [56] making their differentiation quite challenging. A potential differentiation feature between the two conditions, as indicated by echocardiography studies, is myocardial texture. In this work which was presented in EMBC 2016 we investigate the role of T1-mapping in the differential diagnosis of CAMyl from HCM based on intensity and texture features.

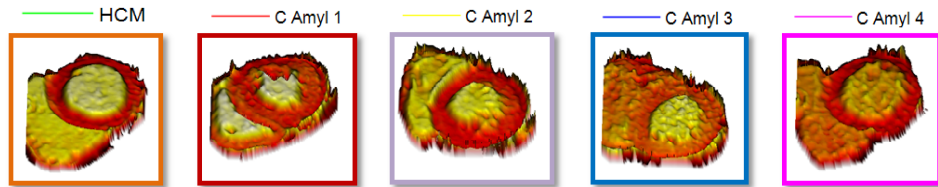


Figure F.2.: T1 maps. Both intensity and height correspond to T1 values.

Four patients with histologically confirmed CAMyl and one with HCM underwent CMR including non-contrast T1-mapping. One long axis and 3 or 4 short axis slices were acquired from each patient with MOLLI sequence [294] following the 5s(3s)3s protocol. T1-maps shown in Figure F.2 were generated by pixel-wise fitting of MOLLI intensities to the 3-parameter exponential inversion recovery signal model [268] using the Levenberg-Marquardt algorithm. Texture maps were generated by calculating the regional entropy in a 5x5 windows around each pixel of T1 maps. The histograms of

Table F.1.: Intensity and texture analysis

Subject	Mean T1	Mean Regional Entropy
HCM	1226 $\pm$ 42	1225 $\pm$ 66
C Amyl 1	1428 $\pm$ 74	1415 $\pm$ 83
C Amyl 2	1346 $\pm$ 46	1356 $\pm$ 59
C Amyl 3	1514 $\pm$ 61	1495 $\pm$ 66
C Amyl 4	1291 $\pm$ 41	1285 $\pm$ 50

myocardial T1 values and regional entropy are shown in Figure F.3. Table 3.1 summarizes the mean value and standard deviation of myocardial T1 and regional entropy per subject.

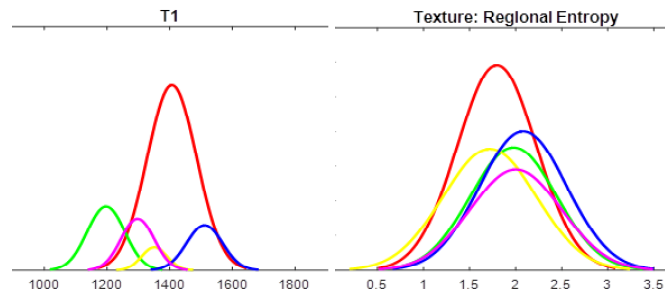


Figure F.3.: Distributions of myocardial T1 and the corresponding regional entropy for all subjects.

Results indicate that CAmyl may be related to lower myocardial T1 values and smoother texture than HCM. Extensive analysis on a bigger set of subjects will allow further investigation of the statistical significance of this difference and the potential construction of a classifier for HCM and CAmyl differential diagnosis.