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**Identification of Mechanical Properties for Patient-Specific Left Ventricle
Models from CMR Using Virtual Fields Method**

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Thèse présentée en vue de l'obtention du diplôme de *Philosophiae Doctor*

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Cette thèse intitulée :

**Identification of Mechanical Properties for Patient-Specific Left Ventricle
Models from CMR Using Virtual Fields Method**

présentée par **Mehdi GHAFARINATANZI**

en vue de l'obtention du diplôme de *Philosophiae Doctor*

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DEDICATION

To my father,

His dream came true!

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First, I would like to declare my appreciation to my professor, Delphine Perie, for her continuous supports. She trusted and believed in me, and her wonderful attitude gave me the advantage I needed to finish my PhD as a Journey.

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RESUME

Le dysfonctionnement du ventricule gauche (VG) a récemment été investigué en utilisant l'estimation de la rigidité isotrope du myocarde à partir de l'imagerie par résonance magnétique (IRM) cardiaque. La combinaison de l'IRM et de la méthode des éléments finis (FEM) a été utilisée afin d'estimer la rigidité du myocarde de façon non invasive. Cependant, le myocarde est connu pour avoir une géométrie 3D complexe et irrégulière avec des propriétés anisotropiques, et un comportement hyper-élastique non-linéaire. Dans ce projet, nous avons développé et implémenté une approche inverse basée sur la méthode des champs virtuels (MCV) permettant d'identifier les propriétés mécaniques du cœur à partir des données IRM, en considérant des modèles matériels constitutifs linéaires et non linéaires du tissu cardiaque.

Notre projet incluait 9 survivants du cancer du projet PETALE qui cherche à étudier les effets à long terme de la cardiotoxicité chez des survivants de la leucémie lymphoblastique aiguë (LLA). L'objectif à long terme de notre projet est d'appliquer la technique inverse non invasive proposée pour prédire les changements fonctionnels à partir des paramètres mécaniques estimés chez les patients traités par chimiothérapie à base de doxorubicine. En particulier, le projet avait quelques objectifs spécifiques : (1) reconstruire les géométries VG spécifiques au patient afin d'appliquer la MCV, (2) créer une méthode combinant les champs virtuels et les éléments et valider cette méthode à l'aide de modèles éléments finis, (3) évaluer ensuite si les propriétés mécaniques estimées (indices cliniques) pouvaient détecter les changements fonctionnels chez des survivants de la leucémie lymphoblastique. En réalisant ces objectifs, le projet contribuera au développement de meilleures méthodes de diagnostic et de prédiction des maladies cardiaques.

Afin d'appliquer la méthode inverse au modèle VG d'un patient, deux types d'approches MCV sont présentés pour les modèles élastiques linéaires. En considérant le modèle constitutif isotrope, les champs virtuels définis par l'utilisateur et le champ complet de déformation du VG sont appliqués au principe du travail virtuel (PTV). Nous avons trouvé des paramètres indépendants (le module de Young et coefficient de Poisson). Par ailleurs, des champs virtuels par morceaux sont créés et appliqués sur le corps initial de la VG constitué de certains sous-domaines, qui fournissent une condition pour trouver certains paramètres anisotropes; module d'Young dans la direction des fibres et la direction transversale. L'évaluation du module de Young entre tous les sujets (SR, HR et HRdex) a été réalisée pour les phases systolique et diastolique. De plus, les

paramètres estimés du modèle isotrope et anisotrope entre E_1 et E_3 ont été comparés entre les sujets. Les résultats du modèle linéaire ont démontré que les valeurs du module d'élasticité chez les sujets HR sont plus élevées que celles des sujets SR et HRdex, en accord avec les travaux précédents. Cependant, l'estimation précise des paramètres dépend principalement du déplacement virtuel utilisé par deux MCV différents, du déplacement réel obtenu à partir des images ciné-IRM, de la direction des fibres assignée à l'axe et de la pression cardiaque en systole et en diastole.

En suivant les objectifs de la deuxième contribution, afin de créer un cadre de VFM basé sur les éléments finis, le modèle de maillage par éléments finis du ventricule gauche spécifique au patient est généré à partir des points de données CMR. Pour chaque élément, les champs de déformation réels sont reconstruits. Des champs virtuels non linéaires sont obtenus, puis les champs réels sont appliqués au principe du travail virtuel, ce qui génère une fonction de coût (CF) basée sur l'énergie. La fonction de coût est minimisée pour identifier de manière unique le cisaillement (μ) et le paramètre non linéaire (α) qui sont couplés dans la loi des matériaux hyperélastiques décrivant uniquement le comportement passif du myocarde. Afin de valider les résultats de la MCV en utilisant la FEM itérée (FEMU), les mêmes maillages de la LV sont importés et reconstruits sur le logiciel ABAQUS, et ensuite simulés pour la tâche d'optimisation. L'évaluation de la rigidité passive du VG (μ) entre tous les sujets (SR, HR et HRdex) a été réalisée en fin de diastole, où les valeurs HR (1,5 kPa) étaient plus élevées que SR (1,2 kPa) et HRdex (1,3 kPa). De plus, le cadre proposé permet d'étudier l'identifiable des paramètres dans la loi des matériaux et la relation non linéaire entre la contrainte de Cauchy et la déformation.

Enfin, nous avons utilisé notre modèle de ventricule gauche spécifique au patient pour évaluer les changements causés par la doxorubicine chez les survivants du cancer. En général, ce projet contribue de façon significative à la recherche sur le dysfonctionnement cardiaque. La MCV développée crée un outil efficace pour caractériser les dysfonctionnements cardiaques au début de la maladie. L'étude porte sur l'application de la MCV à la biomécanique du ventricule gauche, ce qui, à notre connaissance, est la première application de cette méthode à la géométrie du ventricule gauche reconstruite à partir d'images ciné-IRM. L'utilisation de cette technique d'identification dans la modélisation cardiaque présente des avantages, tels que l'efficacité de calcul, une solution rapide et directe, ainsi qu'une prédiction précise des propriétés mécaniques.

En plus, ce travail clarifie les avantages et les inconvénients de l'utilisation de la MCV et de la FEM pour générer des maillages à partir de ciné-IRM.

ABSTRACT

Left ventricle (LV) myocardial dysfunction has been recently investigated using the estimation of isotropic myocardial stiffness from Cardiac Magnetic Resonance (CMR) imaging. The combination of MRI and finite element method (FEM) has been used to non-invasively estimate myocardial stiffness. However, myocardium is known to have a 3D complex non-regular geometry with anisotropy properties, and non-linear hyperelastic behavior. In this research, we developed and implemented virtual fields method for identifying mechanical properties from the measured CMR data, given the linear and non-linear constitutive material models of myocardium tissue.

Our project included 9 cancer survivors from the PETALE project that aims to study long-term cardiotoxicity effects in acute lymphoblastic leukemia (ALL) survivors. The long-term objective of our project is to apply the proposed non-invasive inverse technique to predict functional changes from the estimated mechanical parameters in patients following doxorubicin-induced chemotherapy. In particular, the project had some specific objectives: (1) reconstruct patient-specific LV geometries in order to implement VFM, (2) create a framework combined of virtual fields with finite elements and validate with identification FE-based approach, (3) then evaluate if the estimated mechanical properties (clinical indices) could detect functional changes in patient subjects in the context of cancer survivor. By achieving these objectives, the project will contribute to the development of better methods for diagnosing and predicting heart disease.

In order to apply the inverse method to patient's LV model, two types of VFM approaches are presented for the linear elastic models. Considering the isotropic constitutive model, the user-defined virtual fields covering full-field LV measurements are implemented into the principal of virtual work. We found independent parameters (Young's modulus E , and Poisson's ratio ν). On the other hand, piecewise virtual fields are created and applied on initial LV body constructed of certain subdomains, which provide a condition to find some anisotropic parameters; Young's and shear modulus in fibre and transverse direction (E_3 , E_1 , G_{13}). The assessment of Young's modulus between ALL subjects (SR, HR and HRdex) performed for the systolic and diastolic phases. Moreover, the estimated parameters of isotropic and anisotropic model between E_1 and E_3 were compared within subjects. Results in linear model showed the elastic modulus values in HR are higher than SR and HRdex subjects in agreement with previous works. However, the accurate

estimation of parameters is mainly dependent on the virtual displacement employed by two different VFM, the actual displacement obtained from Cine-MR images, the fibre direction assigned to axis, and cardiac pressure in systole and diastole.

Following the objectives in the second contribution, in order to create FE-based VFM framework, the finite element mesh model of patient-specific left ventricle is generated from CMR data points. For each element, the actual strain fields are reconstructed into. Nonlinear virtual fields are obtained and then with actual fields implemented into the principal of virtual work, building up energy-based cost function (CF). Then cost function is minimized to identify uniquely the shear (μ) and nonlinear parameter (α) which are coupled in hyperelastic material law describing only passive myocardium behavior. To validate VFM results using FEM updating (FEMU), the same meshes of LV are imported and rebuilt into ABAQUS, then simulated for the optimization task. The assessment of LV passive stiffness (μ) between ALL subjects (SR, HR and HRdex) performed in late diastole, where HR values (1.5 kPa) were higher as compared to SR (1.2 kPa) and HRdex (1.3 kPa). In addition, from the proposed framework, the identifiability of nonlinear parameters in material law, and nonlinear stress-strain relation are investigated.

Then, we used our patient-specific LV model to assess particularly doxorubicin-induced changes in cancer survivors. In general, this project is a significant contribution in the research of cardiac dysfunction. The developed VFM creates efficient tool to characterize early cardiac dysfunction. The study investigates the application of VFM to the biomechanics of the left ventricle, which, to the best of our knowledge, is the first effort to implement this method into LV geometry reconstructed from Cine-MR images. Utilizing this identification technique in cardiac modelling provides benefits, such as computational efficiency, rapid and direct solution, and accurate prediction of mechanical properties. Moreover, this work clarifies the benefits and shortcomings of using VFM, and of using FEM to generate meshes from Cine-MRI.

TABLE OF CONTENTS

DEDICATION	III
ACKNOWLEDGMENT	IV
RESUME	V
ABSTRACT	VIII
TABLE OF CONTENTS	X
LIST OF TABLES	XV
LIST OF FIGURES.....	XVI
LIST OF SYMBOLS AND ABBREVIATIONS.....	XIX
LIST OF APPENDICES	XXI
CHAPTER 1 INTRODUCTION.....	1
1.1 Research Objectives	2
1.2 Outline of the thesis	2
CHAPTER 2 LITERATURE REVIEW	5
2.1 The Heart Function, Structure and Pathologies.....	5
2.1.1 Anatomy, Morphology, and microstructure of the heart	5
2.1.2 Physiology of the heart	6
2.1.3 Cardiac cycle	8
2.1.4 Movement of the heart.....	8
2.1.5 Cardiovascular pathologies.....	10
2.2 Cardiac Magnetic Resonance Imaging	13
2.2.1 MRI.....	13
2.2.2 Cine MRI	13
2.3 Modeling of Cardiac Movements	14
2.4 Cardiac Modeling	16

2.4.1	Passive and active mechanical properties.....	16
2.4.2	Material Models.....	17
2.4.3	Left Ventricular Models.	20
2.5	Non-Invasive Identification of Mechanical Properties.....	23
2.5.1	Soft tissue modeling	23
2.5.2	Inverse problem in biomechanics	23
2.6	Virtual Fields Method; Theory and Formulation	26
2.6.1	Estimation of mechanical properties by Imaging	26
2.6.2	Principle of virtual work.....	27
2.6.3	Constraints on virtual fields.....	27
2.6.4	Linear method.....	28
2.6.5	Special virtual fields	29
2.6.6	Non-linear method.....	31
2.6.7	Application in large deformations	31
2.7	Conclusion: Significant gaps in knowledge	32
CHAPTER 3 PRELIMINARY WORKS ON 2D FRAMEWORK: INVERSE IDENTIFICATION OF ELASTIC LINEAR PROPERTIES OF 2D MYOCARDIUM FROM CINEDENSE MRI AND FEM ANALYSIS		33
3.1	Introduction and objectives	33
3.2	Methodology.....	33
3.2.1	MRI acquisitions.....	33
3.2.2	DENSE Imaging.....	34
3.2.3	Finite element analysis	36
3.2.4	VFM Implementation	39
3.3	Results	41
3.3.1	Identification of elastic modulus by optimization	41
3.3.2	VFM Validation Results	43
3.4	Limitations of the proposed framework	44
3.5	Conclusion and suggestion	45

CHAPTER 4 ARTICLE 1: ESTIMATION OF ANISOTROPIC PROPERTIES OF CMR PATIENT-SPECIFIC LEFT VENTRICLE USING THE VIRTUAL FIELDS METHOD.....	46
4.1 Abstract.....	47
4.2 Introduction	49
4.3 Theories and Methods	52
4.3.1 Virtual fields method.....	52
4.3.2 Constitutive model and parameters	53
4.3.3 Special virtual fields	54
4.3.4 Constructing special virtual fields by subdomains	55
4.3.5 Data set and Materials	57
4.3.6 Inverse VFM in isotropic LV	59
4.3.7 Anisotropic VFM inversion approach	61
4.4 Results	65
4.4.1 Isotropic stiffness in LV subjects	65
4.4.2 Anisotropic stiffness in LV subjects.....	68
4.5 Discussion.....	72
4.5.1 Comparison of the estimated stiffness parameters	72
4.5.2 Isotropic VFM approach.....	73
4.5.3 Anisotropic VFM (FE-based VFM)	74
4.5.4 Limitations.....	75
4.6 Conclusion.....	76
CHAPTER 5 ARTICLE 2: IDENTIFICATION OF PATIENT-SPECIFIC LEFT VENTRICLE STIFFNESS USING INVERSE FRAMEWORK OF MRI-BASED FINITE ELEMENT MODELING AND VIRTUAL FIELDS METHOD.....	77
5.1 Abstract.....	78
5.2 Introduction	81
5.3 Theory.....	83
5.3.1 Hyperelastic Constitutive Law	83
5.3.2 Theory of Large deformation	84
5.3.3 Virtual Fields Method.....	85

5.3.4 Nonlinear VFM.....	86
5.3.5 Application of PVW into large deformations	86
5.4 Materials and Methods	87
5.4.1 Data set and Geometry Model	87
5.4.2 LV FE mesh generation.....	88
5.4.3 Virtual displacements field.....	93
5.4.4 Parameter estimation workflow.....	94
5.4.5 Comparison between subjects	96
5.4.6 Identifiability of Nonlinear behavior law	96
5.4.7 FEMU Hyperelastic Model Validation.....	96
5.5 Results	97
5.5.1 Stiffness comparison between subjects in Late-Diastole	97
5.5.2 Identifiability of the energy-based CF	98
5.5.3 FEMU Validation Results	100
5.6 Discussion.....	101
5.6.1 Comparison between subjects	101
5.6.2 Identifiability of energy law	101
5.6.3 FEMU Model.....	102
5.6.4 Limitations.....	103
5.7 Conclusion.....	104
CHAPTER 6 GENERAL DISCUSSION.....	105
6.1 Impact of the work.....	105
6.2 Discussion on Results.....	105
6.2.1 Isotropic VFM approach.....	105
6.2.2 Anisotropic VFM approach	106
6.2.3 Hyperelastic Nonlinear VFM approach.....	106
6.3 Limitations.....	107
CHAPTER 7 CONCLUSION AND RECOMMENDATIONS.....	108

BIBLIOGRAPHY	110
APPENDICES.....	118

LIST OF TABLES

Table 3.1 Results obtained from 20 frames are reported for 3 phases, in term of median value, presenting our objective quantities; Young's modulus, Iteration No, MS error.	42
Table 4.1 Resulting parameter estimated from the Isotropic and anisotropic formulation for Systole, Early Diastole, and Late Diastole in SR patients	72
Table 5.1 Comparison of FEMU solution with the VFM estimated parameters, one SR subject in late diastole.....	100
Table D. 1 The guide point format defined.....	137
Table D. 2 Output parameters of LV4x4SurfaceModel object	137

LIST OF FIGURES

Figure 2.1 Anatomy of Heart, Morphological view of Heart (https://training.seer.cancer.gov/anatomy/cardiovascular/heart/structure.html).....	6
Figure 2.2 Schematic representation of the left and right ventricles, with a commonly used (from the thesis of (Haddad, 2007)).....	7
Figure 2.3 AHA's proposed 17-segment division. The red part corresponds to the inferior interventricular artery, the blue part to the circumflex artery and the green part to the right coronary artery(Segmentation et al., 2002).....	8
Figure 2.4 Schematic representation of the three main movements of the heart during systole. CR: radial contraction, CL: longitudinal contraction, TL: longitudinal torsion.....	10
Figure 2.5 Chemical structure of doxorubicin (Lapointe, 2016).....	12
Figure 2.6 Images of the heart acquired in cine MRI, visualized in Micro-Dicom. Top, right short axis slices. Left, 2 chambers long axis slice. Bottom, Left 4 cavities long axis slice.	14
Figure 2.7 Stiffness modulus in tresnsevely isotropic material with fibers oriented in direction 3 (0 0 1).(Miller, 2018), showing Young modulus in a) fibre direction, (E_3), and b) transverse direction ($E_1=E_2$). The shear modulus c) ($G_{13} = G_{23}$) in plane parallel to fibre, and d) (G_{12}) perpendicular to the fibers.	19
Figure 2.7 Left: short-axis section of MR-TD volume 82-10 (Casta, 2012), showing the segmentation contour points (gold: endocardial contour, green: epicardial contour) and myocardial fiber vectors come from the diffusion tensor. The white areas around the core correspond to the hydrophilic gel. Right: the same enlarged RM-DT image, where we can better realize the orientation of the fibers in the myocardium.	19
Figure 2.8 Cardiac Coordinate System (SCC). (a) The three points red, yellow, and blue are set manually.	20
Figure 2.9 point-guided modelling technique (Gamba, 2019): long-axis (down) and Short-axis (top), epicardial (blue) and endocardial (green) surface contours, as well as associated guide points.	21
Figure 2.10 User-defined guide points (blue and green) and computer-generated image edge points are displayed in the short-axis slice (ranged from black to red color Based on relative edge sharpness) (Li et al., 2010)	21
Figure 2.11 FE Surface model (a) at the end-diastolic (b) the Hermit element.....	22

Figure 2.12 3D material points reconstructed from the marking lines at the (a) end-diastolic (b) end-systolic. Other phase of the cardiac cycle, superimposed on the endocardial surfaces of the LV (red).	23
Figure 2.13 Presentation of the inverse problem.....	25
Figure 2.14 Solid under uniaxial loading	28
Figure 3.1 Example of an MRI image used in the study.	34
Figure 3.2 Example of Delaunay triangulation and its automatic meshing generation (https://en.wikipedia.org/wiki/Delaunay_triangulation).....	35
Figure 3.3 Mesh of myocardium obtained from Delaunay triangulation at $t_0, t_2, t_5, t_8, t_{11}, t_{14}, t_{17}, t_{21}$. The end-diastolic phase is at the top left (only one phase out of three is represented).	36
Figure 3.4 Endocardium ventricular wall where radial forces simulate a pressure. Identifying nodes in the myocardium Lumen's nodes where the pressure needs to be applied.	37
Figure 3.5 Approximation of the left ventricular perimeter at the base	38
Figure 3.6 Pressure direction for a given segmentation. The pressure is applied perpendicular to the endocardium, at each point defining the segmentation. Showing constraints where two pink nodes had to be fixed like boundary condition.	39
Figure 3.9 Normal pressure direction and virtual displacement direction at endocardium points of basal.	41
Figure 3.7 Growth of quadratic error on the Young's modulus variations.	42
Figure 4.1 Biomechanical Framework from data measurements prepared to virtual field reconstruction into FE meshes.....	48
Figure 4.2 Flowchart of the present study structure for the two VFM approaches from implementation to identification.	49
Figure 4.3 Cubic Hermite subdomain (warped by cubic basis functions (Lamata, et al., 2011); (A) divided into 6 element mesh, by 4 new node coordinates: 2 red spheres (right), 2 sphere (left) located on endocardium and epicardium respectively (Lamata, et al., 2014)	56
Figure 4.4 Ventricular pressure simulated, at LV Ejection (Systole) and filling (Diastole); b) LV Deformation displayed in Systolic phases ($t=1$ to $t=11$, End-systole), Early diastole ($t=12-18$), Late-diastole started from $t=18$ to 25 (end-diastole).....	58
Figure 4.6 Boxplots of the estimated Young's modulus, using isotropic formulation, for the HR, SR, HRdex groups at systole. For each subject, the boxplots display standard deviation, median, mean, and outliers. ($P=0.0748$)	66

Figure 4.7 Results of the estimated Young's modulus, using isotropic formulation, for ALL subjects; (a) Early diastole ($P = 0.8844$) (Left) and (b) late diastole (Right) ($P = 0.5529$).....	67
Figure 4.8 Results from all sub-domains, using Anisotropic formulation, for subjects of SR HR and HRdex; (a) fiber Young's modulus (E_3) Systole (left, $P=0.97$), Diastole (right, $P=0.12$); (b) transverse Young's modulus (E_1) Systole (left, $P=0.27$), Diastole (right, $P=0.0021$); (c) fiber shear modulus (G_{13}) Systole, $P=0.17$), Diastole, $P=0.67$	72
Figure 5.1 Graphical abstract of inverse framework (FE mesh generation, VFM implementation and optimization).....	80
Figure 5.2. Mesh generation of Left Ventricle form MRI images	92
Figure 5.3. Intra-ventricular pressure simulated, at LV passive diastolic, and at RELAXATION (Isovolumetric). Analysis started (late-diastole) from frame 21 (minimum pressure) to frame 5 (21, 22, 23, 24, 25, 1, 2, 3, 4, 5). The 6 indicates the end-diastolic diastole frame.....	93
Figure 5.4. LV model imported into ABAQUS with 8-nodes cube elements.....	97
Figure 5.5 The estimated shear stiffness in late diastole for each HR SR and HRdex subject	98
Figure 5.6. The relationship between μ - α parameters from energy-based CF with using fitted curves, in late diastole for each of subject: (a) SR, (b) HR, (c) HRdex	99
Figure 5.7. Cauchy stress vs stretch. The simulation of the identified hyperelastic law behavior from stress-strain relationship.	100
Figure C. 1 Circular white planar fitted to Base plane points.	131
Figure C. 2 Markers points are used to define the coordinate system (a) in short axis model (b) long axis model. These points are LV centroid, RV points, basal centroid, and apex point.	132
Figure C. 3 prolate spherical coordinate as shown three parameters of λ , μ and θ , presenting the radial, azimuthal, and circumferential components respectively, (b) Initial ellipsoidal model of 16 regions from 34 points.	133
Figure C. 4 Segmentation processed in CIM, Short axis (left), long axis (right) view of MRI data through Guide-point modeling.....	134
Figure C. 5 Sampled surface points, Epi (black); Endocardium (red)	134

LIST OF SYMBOLS AND ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
CF	Cost Function
CIM	Cardiac Image Modeling
CMR	Cardiac Magnetic Resonance
DG	Gradient Deformation
E	Young's Modulus
ED	End-Diastole
ES	End-Systole
FEMU	Finite Element Method Updating
FE-VFM	Finite Element Based Virtual Fields Method
HR	High-Risk
HRdex	High-Risk Exposed to Dexrazoxane
KA	Kinematically Admissible
LV	Left Ventricle
MRI	Magnetic Resonance Imaging
p	Pressure
PC-VFs	Piece-Wise Virtual Fields
PVW	Principal of Virtual Work
Q	Unknown Constitutive Parameters
RV	Right Ventricle
S	Surface Area
T	Surface Traction Force
V	Volume
VFM	Virtual Fields Method
W_{ext}	External Virtual Work
W_{int}	Internal Virtual Work
μ	Shear Modulus
ν	Poisson Ratio
σ	Stress

u^*	Virtual Displacement
ϵ^*	Virtual Strain

LIST OF APPENDICES

APPENDIX A	MECHANICS OF SOLIDS	118
APPENDIX B	DEVELOPMENT OF VFM APPLICATION TO THE 3D LEFT	
VENTRICLE		121
APPENDIX C	CARDIAC IMAGE MODELING.....	130
APPENDIX D	MATLAB CODE IMPLEMENTATION	135

CHAPTER 1 INTRODUCTION

Heart failure is a common medical problem that occurs when the heart is damaged or weakened by diseases like cardiomyopathy (Singal & Iliskovic, 1998). Cancer survivors treated with anthracycline, or doxorubicin are particularly at risk of developing this condition. Much research has been performed to comprehend the mechanism of cardiomyopathy due to doxorubicin treatment. However, no effective tool was found in the diagnosis of this cardiotoxicity issue. Cardiac Magnetic Resonance (CMR) imaging is a non-invasive technic for the diagnosis, which allows the measurement of tissue deformation as well as the stiffness estimation. Regarding to the estimation of mechanical properties obtained by CMR, the assessment of cardiac strain function has been proposed as biomarkers to reveal late cardiotoxicity.

The mechanical parameter estimation based-on MRI is often obtained by finite element techniques. Finite element methods have the limitations that they need to interpolate displacements between nodes to obtain the desired parameters for a region of interest. They cannot provide an accurate estimation, which reduces the efficiency of material characterization methods. Additionally, for the inversion methods (reverse identification) without registration, which converts displacement data to stiffness information, the process might be iterative and the matrices to be inverted are sometimes irregular (Gao et al., 2015). Other inversion methods can be used (Miller, 2018), depending on the boundary conditions considered and the available imaging data. Besides, the mechanical properties obtained by these methods are isotropic stiffness, which assume that the myocardium has linear isotropic behaviours, which does not reflect the nature of the myocardial tissue. Therefore, in recent studies, the FEM inverse has been replaced by the virtual field's method (VFM), which directly employs full strain data to possibly estimate the transversely isotropic parameters. This approach avoids the ill-conditioning issue in algebraic matrix systems because it does not require the use of FE matrix calculations and iteration.

Having full-field deformation is the requirement of VFM application (Miller, 2018). However, CMR acquisition provides only a few slices each phase, which don't cover displacement fields over the full left ventricle volume of patients. Additionally, the conventional MRI segmentation

tools cannot track entire LV deformation from apex to base. Defining the constitutive equations of the parameters as well as using actual strain field directly constructed the available CMR data, which reports outputs in terms of elements and nodes, nodal virtual strain fields could be obtained.

More recently, the virtual fields are simulated by setting up a finite element model of the material, using FE simulation software such as ABAQUS (Kim et al., 2020). The model includes the geometry of the material, as well as the boundary and loading conditions. The predicted displacement fields from the FE model are used to construct virtual displacement fields in the VFM because the predicted fields represent the behavior of the material based on the known material properties. (Kim and Lee, 2021; Livens et al., 2021).

1.1 Research Objectives

The long-term objective of our research is to apply the non-invasive technique to predict functional changes from the estimated mechanical parameters in patients following doxorubicin-induced chemotherapy. The project develops and implements a VFM-based inverse method to identify mechanical properties for the left ventricle reconstructed from Cine-MR images.

The specific objectives were addressed:

To reconstruct patient-specific left ventricle and generate meshes from Cine-MIR images in order to implement VFM (in a fast, simple, and robust approach)

To propose inverse framework combined of FEM and VFM for the identification of mechanical properties for the linear and nonlinear constitutive material LV models and then validate with FEMU.

To compare the estimated mechanical properties between patients following doxorubicin-induced cardiotoxicity.

1.2 Outline of the thesis

Chapter 2 reviews the knowledge of heart microstructure and cardiac movement in global standard coordinate. In addition, it explains the physiology of systolic and diastolic function, how the myocardial dysfunction causes heart failure. Additionally, it introduces MRI, which acquires

short and long-axis slices of LV, allowing the measurement of myocardial strain with different techniques, and the observation of cardiac kinematics using Cine-MRI. This chapter also explains how to generally create a model in cardiac mechanics, consider constitutive material model and fibre direction, provide biomechanical framework using cardiac FEM, which uses displacement fields measured from MRI. The examples of image segmentation, mesh generation, surface reconstruction fitted to the endocardium and epicardium LV geometry, shape functions to satisfy boundary conditions, 3D LV movements are considered from literature. Additionally, this chapter reviewed studies that used the generic FE model of LV geometry, made up of 16 standards cubic-elements, myocardial fiber structure as well as the 3D visualization in software, where slices segmented, and fiber vectors extracted. The mathematical concept of inverse problem is presented, which is used in systems with unknown parameters, particularly for the identification of soft tissue properties. The application of VFM is then presented as a solution to this problem, with its benefits and limitations outlined. While the VFM approach offers a promising non-invasive and efficient method for estimating mechanical properties, further research is needed to address the identified gaps as well as the impact of material models on the estimation of mechanical parameters.

Chapter 3 presents my preliminary works. A conventional 2D framework of FEMU (finite element updating) was performed on basal myocardium, which minimize the difference between the FEM displacements and the measured displacements from Cine-Dense MRI technique. To validate the results, the VFM application to the identification of elastic modulus are investigated.

In chapter 4 (first paper), the finite element based VFM (piecewise) was applied to identify anisotropic material properties in the LV separated into a given number of large domains. Using VFM and MRI data, two identification methods, isotropic and anisotropic, were compared in the characterization of linear elastic properties of myocardium. In this chapter, according to the simple and complex LV geometry, two types of VFM approaches, both the analytic and piecewise VFMs, respectively, were tested with the same MRI data. Using the first, the virtual displacements allow whole-field simple LV to be implemented into PVW, which leads to directly estimate two independent parameters from isotropic constitutive relation. With the second, anisotropic parameters are estimated using finite element-based (piecewise) VFM. Some differences in estimated values were shown between the subjects of each ALL-survivor group.

Chapter 5 (second paper) outlines the application of nonlinear VFM to the hyperelastic myocardium identification. The inverse framework of FE-based VFM is provided to reconstruct a finite element model of the left ventricle using the CMR image data of each patient. The impact of cardiac pressure loading was discussed on the identified shear modulus for each patient group. The identifiability of the hyper-elastic parameters was tested with VFM-based optimization. Then, VFM results were compared to the FEMU results, validated by ABAQUS simulation.

Chapters 6 and 7 discuss and concludes respectively, the application of VFM throughout this research. It also contributes to the development of inverse method in identification of mechanical properties as well as advances in clinical diagnostics of heart failure.

CHAPTER 2 LITERATURE REVIEW

2.1 The Heart Function, Structure and Pathologies

2.1.1 Anatomy, Morphology, and microstructure of the heart

The heart is a hollow muscle located in the chest between the two lungs. Its function is to circulate blood through the circulatory system through periodic contractions.

From a morphological point of view, the heart is divided into a left part and a right part. Each part contains an (atrium) and a ventricle. Thus, the heart is composed of four cavities: the left ventricle (LV) and right (RV) and the atrium left (OG) and right (OD) (Figure 2.1).

The left and right ventricles are separated by the interventricular septum. The cavities are surrounded by a muscle, the myocardium, which itself surrounded by a membrane called the pericardium. The inner surface of the cavities is called the endocardium, and separates the blood from the heart muscle, while the outer surface is called the epicardium. The largest part of the heart wall constitutes the myocardium. The myocardium corresponds to the functional tissue of the wall, responsible for muscle contraction. It has a complex structure. For example, the left ventricular muscle is about 8 mm thick and is composed of fibres schematically organized in layers of different orientations. There are two approaches to describe myocardium. The first approach views heart muscle as a single muscle coiled in a helical pattern. The second approach considers the heart as a continuum made up of laminar sheets (Holzapfel et al., 2009).

In all cases, the myocardium is composed of myocytes forming muscle fibres as well as collagen and other interstitial components. The orientation of the fibres varies spatially. At the level of the papillary muscles, the predominant orientation performs a rotation through the thickness of the material. At the epicardium level, the direction is around 50° to 70° with respect to the circumferential direction of the LV. It is around 0° in the middle of the wall and ends around -50° to -70° in the sub-endocardial region (Holzapfel et al., 2009).

The thickness of this layer also varies spatial-temporally. It is larger at the base of the ventricle and narrower at the apex. During contraction, the muscle becomes thicker due to the contraction of muscle fibres.

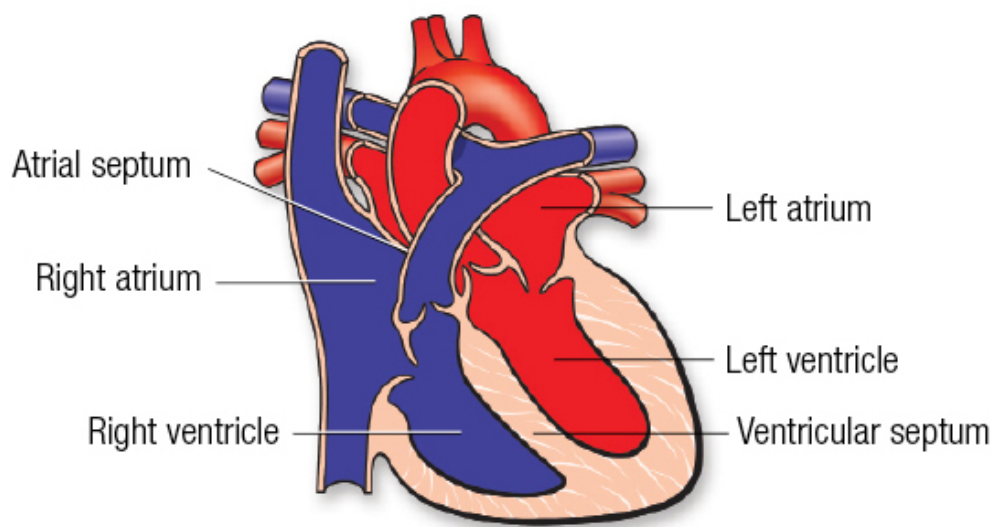


Figure 2.1 Anatomy of Heart, Morphological view of Heart
 (<https://training.seer.cancer.gov/anatomy/cardiovascular/heart/structure.html>).

2.1.2 Physiology of the heart

The tip of the heart is called the apex and the part located at the level of the valves is called the base. Assuming LV has an ellipse shape, the apex-base axis of LV is called the long axis, and the plane perpendicular to long axis, at the basal level of LV, called the short axis. The different areas of the left ventricle are often divided into segments, according to certain standards. A classic partition consists of cutting the left ventricle into four sectors: anterior wall, interventricular septum, lateral wall, inferior wall, as represented in Figure 2.2. (Fung, 2013; Houdas, 1990)

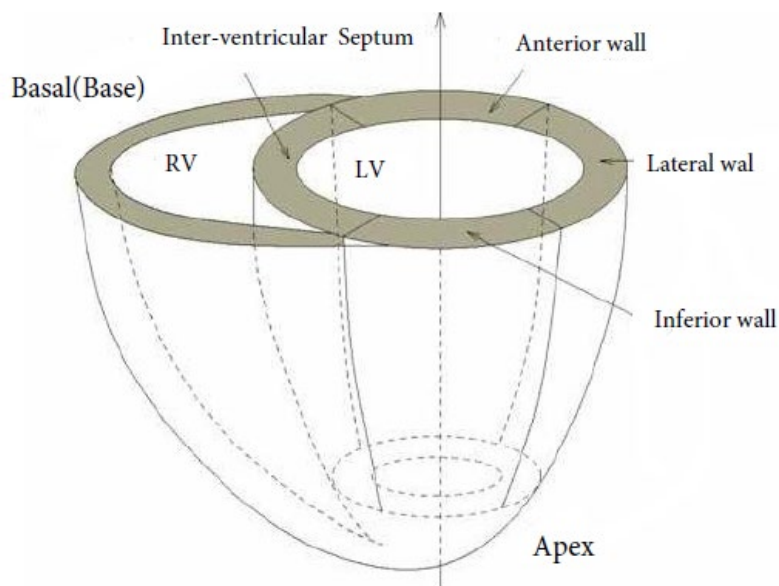
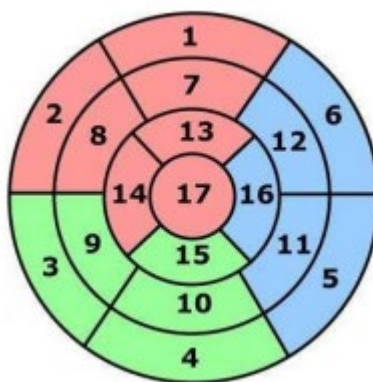


Figure 2.2 Schematic representation of the left and right ventricles, with a commonly used (from the thesis of (Haddad, 2007))

Another commonly used breakdown, which is a reference, is the 17-sector breakdown offered by the American Heart Association (AHA). These sectors correspond to the regions supplied by the coronary arteries (Segmentation et al., 2002) and are represented by the so-called bull's eye symbol in Figure 2.3.



- | | | |
|------------------------|-----------------------|---------------------|
| 1. Basal anterior | 8. Mid anteroseptal | 15. Apical inferior |
| 2. Basal anteroseptal | 9. Mid inferoseptal | 16. Apical lateral |
| 3. Basal inferoseptal | 10. Mid inferior | 17. Apex |
| 4. Basal inferior | 11. Mid inferolateral | |
| 5. Basal inferolateral | 12. Mid anterolateral | |
| 6. Basal anterolateral | 13. Apical anterior | |
| 7. Mid anterior | 14. Apical septal | |

Figure 2.3 AHA's proposed 17-segment division. The red part corresponds to the inferior interventricular artery, the blue part to the circumflex artery and the green part to the right coronary artery (Segmentation et al., 2002).

2.1.3 Cardiac cycle

Systole, which covers approximately 40% of the cardiac cycle, corresponds to the contraction of the ventricles during which the blood is ejected into the general and pulmonary circulations. In general, systole can be divided into two phases: the isovolumic contraction phase between the closing of the mitral valve and the opening of the aortic valve, and the ejection phase, in which the pressure in the pulmonary artery and aorta is lower than the pressure in the ventricles, and blood is ejected into the arterial trunks. (Figure 2.3)

Diastole, which covers approximately 60% of the cardiac cycle, corresponds to the filling of the ventricles during which the muscle relaxes. The atrioventricular valves (mitral and tricuspid) are open while the sigmoid valves (aortic and pulmonary) are closed. As intraventricular pressures become lower than those in the atria, the ventricles then fill with blood from the atria. At the end of diastole, the contraction of the atria (atrial systole) contributes to the end of the filling of the ventricles. At the end of the diastole, the LV is at the maximum state of relaxation, just before the start of the contraction of the ventricles.

2.1.4 Movement of the heart

Because of the heterogeneity of the medium, the movement of the heart is very complicated. However, the movement of the left ventricle of healthy heart during systole can be illustrated in a very schematic and simplified manner. It consists of three different main movements:

- Radial contraction (RC) of the endocardium, which is accompanied by a thickening of the LV wall.
- Longitudinal contraction (CL) along the major axis. Due to the lowering of the basal plane, this movement tends to decrease while the apex remains almost fixed.
- Torsion (TL) around the long axis of the LV.

These movements are represented schematically in Figure 2.4, to which a deformation of the long axis as well as rotation and a global translation must be added.

As seen in Figure 2.4, the movements are not uniform over the entire LV. If the rotation is in one direction in the basal plane, it will be in the opposite direction in the apical plane, thus resulting in a torsion of the heart around the long axis. Similarly, the radial contraction has different amplitudes in the wall. The endocardial zones have a larger amplitude movement than the epicardial zones.

Therefore, because of these complex and heterogeneous movements within the heart, it is very difficult to quantify the contractile function of the heart. The evaluation of the contractile function is very important because a defect in this function is directly linked to the functional state of the heart. A change in the contractile function is then characterized by a variation of different physiological parameters. Various global or semi-local parameters are commonly used to quantify myocardial contractile function. The global parameters include epicardial and endocardial volumes, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) defined as difference between EDV and ESV, and ejection fraction (EF). The ejection fraction (EF) is defined as the percentage of blood ejected by the left ventricle during its contraction, obtained from ratio between stroke and end-diastolic volume:

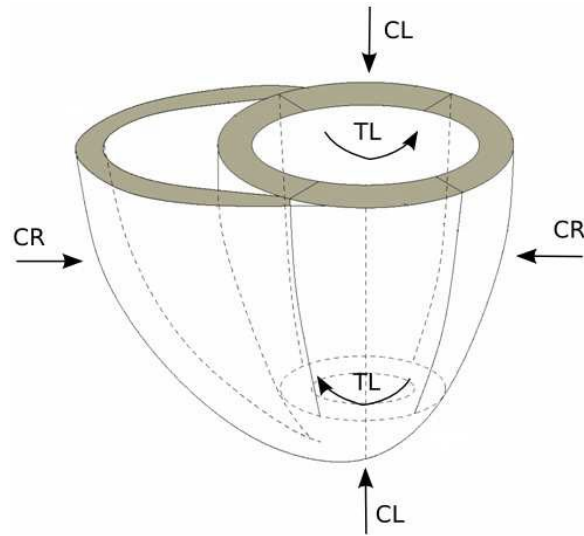


Figure 2.4 Schematic representation of the three main movements of the heart during systole. CR: radial contraction, CL: longitudinal contraction, TL: longitudinal torsion

Although the ejection fraction remains a physiological reference parameter, particularly in the clinic, a lot of research currently wants to determine the deformation of the myocardium during the cardiac cycle in a more precise and localized manner. Therefore, the myocardial deformation can be estimated using dynamic models calculating the 6-component strain tensor at any point of the myocardium.

2.1.5 Cardiovascular pathologies

Heart pathologies are part of a larger set of cardiovascular diseases, generally classified into four categories.

Heart failure

Heart failure (HF) corresponds to a condition where an abnormality in cardiac function makes the myocardium unable to provide sufficient cardiac output for the proper performance of the body. This failure can come from an abnormality in the contraction of the LV (systolic dysfunction) as well as in the filling (diastolic dysfunction). This disease has the potential to be serious, life-threatening, and mostly disabling.

The failure of systolic function may happen as well. Since the cardiac output depends on contractility, which is the heart's power to pump blood, afterload, which is the resistance to

ventricular ejection, and preload, which results in the blood filling the ventricles, heart failure can result from a change in just one of these factors.

Diastolic function can be reduced when there is an abnormality in relaxation. The LV relaxation after its contraction normally leads to a decrease in intraventricular pressure at the beginning of diastole. This pressure is lower than the pressure in left atrium, resulting in rapid ventricular filling due to ventricular aspiration. The change of relaxation will lead to a decrease in the filling of the left ventricle by loss of post-systolic aspiration. In addition, there is an increase in intraventricular pressure and blood conditions.

Myocardial ischemia

Several co-factors are essential for the heart to function properly in optimal conditions. As described previously, the contractile function of the heart represents the deformation capability of the myocardial fibers. Blood supply defines myocardial perfusion and myocardial metabolism is the process by which energy substances are consumed in the myocyte.

A balance between these three co-factors is permanently established for the normal myocardium. Myocardial ischemia refers to a defect in myocardial perfusion. It causes an imbalance between contractile function, perfusion, and metabolism, which results in a series of events known as the ischemic cascade (Kaandorp et al., 2005).

Cardiomyopathy

Cardiomyopathies (or myocardiodisorders) are a diverse group of diseases affecting the myocardium and cause its dysfunction. They can have both external origin (caused by a disorder outside the heart muscle) and inherent origin (primary loss to the heart muscle). People with cardiomyopathy are at risk of heart failure, arrhythmias, and even sudden death (Bigger Jr et al., 1977).

Cardiac diseases of external origin can be the cardiovascular origin, such as ischemic heart disease (infarction). They can be also the systemic origin, related to the system, result of the metabolic type (diabetes). Finally, they can result from taking toxins (alcohol, drugs) or occur in the context of malnutrition.

Therefore, there are many pathologies of the heart. We can therefore obviously see the connection that exists between all of these cardiovascular pathologies and the need to study and understand them in order to better treat them.

Cardiotoxicity related to anthracyclines.

This project focuses on cardiomyopathies induced by doxorubicin (see Figure 2.5). This molecule belongs to the anthracycline family. This drug is used in chemotherapy to treat various cancers such as acute lymphoblastic leukemia (ALL) in children. The proposed mechanisms for its therapeutic effect include DNA chemical interaction leading to inhibition of macromolecule synthesis, generation of reactive oxygen species and DNA bonding.

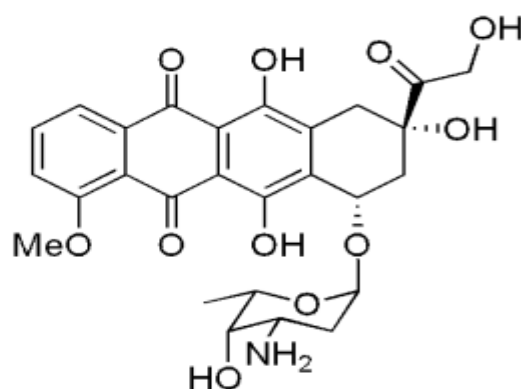


Figure 2.5 Chemical structure of doxorubicin (Lapointe, 2016)

The cardiotoxic effects of doxorubicin chemotherapy for acute leukemia mainly depends on the cumulative dose (Singal & Iliskovic, 1998) (Lefrak et al., 1973) (Koiwa et al., 2002) (Hequet et al., 2004) (Tallaj et al., 2005). The cardiotoxicity not only affects the molecular mechanism but also influences the global and regional function of the heart.

Most patients who develop doxorubicin-induced cardiomyopathy show cardiac dysfunction within 6 months after therapy (Ali et al., 1994). However, it has been shown that these patients can show late cardio toxic effects, even for low cumulative doses (Lipshultz et al., 2005). Early functional changes include the increased blood pressure, heart rate, heart weight, abnormalities in systolic interval times, and ventricular dilatation (Chatterjee et al., 2010).

2.2 Cardiac Magnetic Resonance Imaging

Various medical imaging techniques make it possible to visualize anatomical structures and morphological abnormalities in the heart. Dynamic imaging techniques (Clarysse, 2011) allow to access a visualization of the cardiac movement or even to consider its quantification, thus better understanding of its mechanical function.

2.2.1 MRI

Although echocardiography is low-cost and simply available in clinical application, MRI currently remains an alternative method mostly used for the assessment of myocardial function and perfusion as well as for the tissue characterization. Conventional cardiovascular MRI measures the fundamental parameters of cardiac function. Using the basic indices of cardiac function and morphological characteristics, such as left ventricular ejection fraction, ventricular volumes, and mass, can be used to improve predictions. Cardiovascular imaging with high quality from MRI can provide the cardiomyopathy diagnosis.

However, MRI may not allow measurement of 3D intra-myocardial strain unlike MRI tagging (Hermand et al., 2002), or Cine DENSE imaging (Garot, 2005), (Spottiswoode et al., 2006) and (Germain et al., 2010). By measuring the deformation of the pattern that has been marked to encode movement, MRI-tagging enables the calculation of the deformations. In this thesis, we briefly introduce a type of MRI commonly used to observe the deformation inside cardiac organs.

2.2.2 Cine MRI

Cine MRI is a variation of the gradient echo acquisition technique and refers to sequences allowing observation of cardiac kinematics. Therefore, we can see and analyse the movement and deformation of the heart during the cardiac cycle in sequences of 15 to 40 of 2D images. The temporal resolution of this type of acquisition is usually 30 to 40 ms with a spatial resolution of 2 x 2 mm, and a slice thickness ranging from 2 to 10 mm. Therefore, it is possible to cover all of the ventricle's body by acquiring between 10 and 15 adjacent slices. In clinical application, we generally acquire 3-4 short axis slices and 2-3 long axis slices to limit the acquisition time. Cine-MRI enables the assessment of cardiac function both globally (the estimation of the ejection fraction) and locally, by visualizing the displacement and thickening of the various sectors of the

myocardium and its deviations. In addition, it allows visualizing the volume, the mass and the morphology of the heart.

Figure 2.6 presents the different types of slices usually acquired in Cine-MRI.

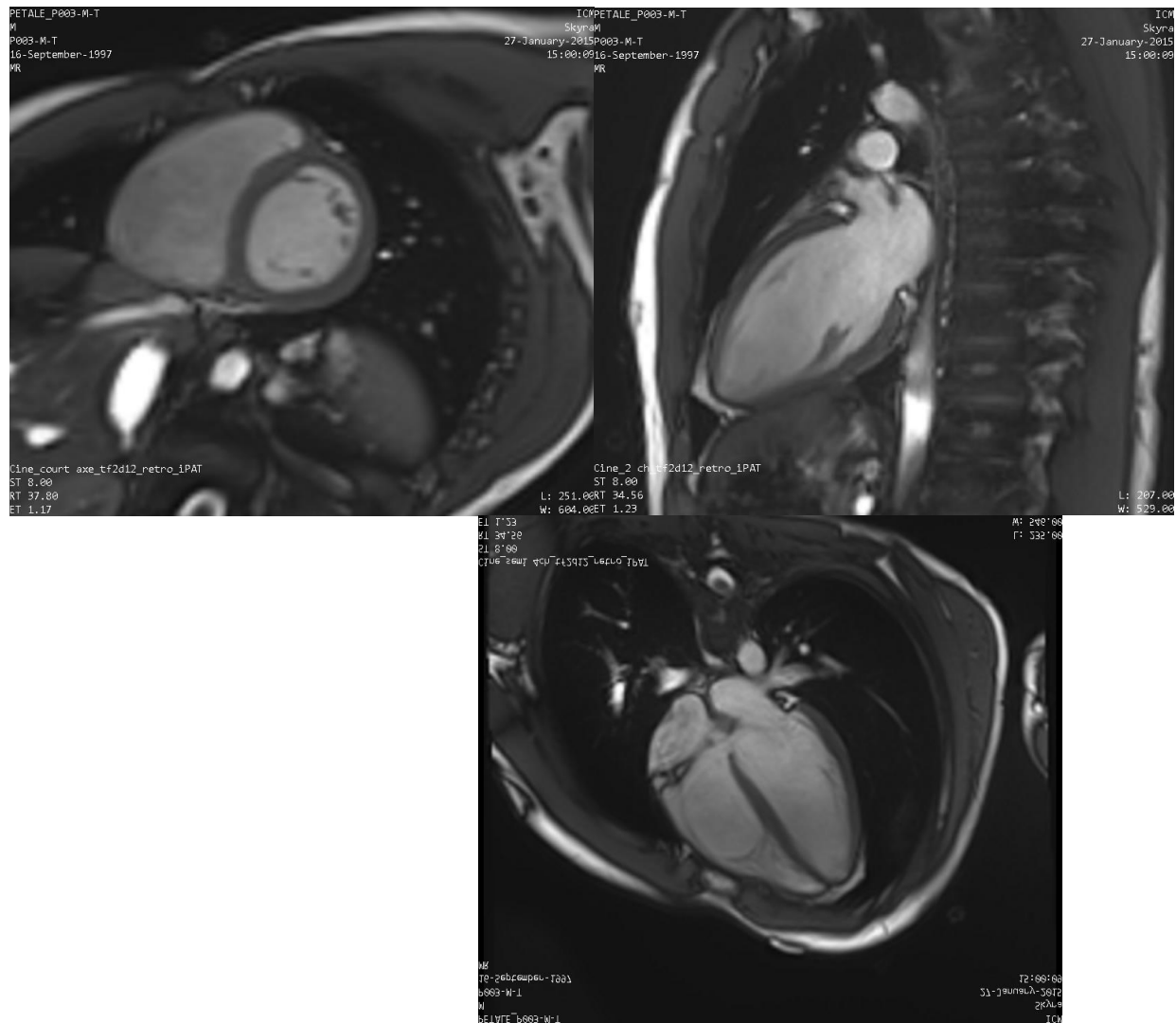


Figure 2.6 Images of the heart acquired in cine MRI, visualized in Micro-Dicom. Top, right short axis slices. Left, 2 chambers long axis slice. Bottom, Left 4 cavities long axis slice.

2.3 Modeling of Cardiac Movements

The main objective of CMR image segmentation and motion estimation is the ability to track the movement of the myocardium during the cardiac cycle. It is important to accurately identify the cardiac structures from the images and closely track their deformations.

The problem is the large variability in cardiac structures, with differences in the size, shape, and movements of the heart. Cardiac pathologies change cardiac function, causing the heart to become much thinner and move abnormally. In addition, MRI sequences from different devices show different image qualities. The acquisition parameters (orientation, number of slices, spatial and temporal resolution, and contrast) also change according to the radiologist and the acquisition constraints. As a result, the image characteristics of the cardiac structures can considerably vary from one sequence to another. Therefore, it's required to use a cardiac model sufficiently flexible to be able to take into account all the variations in the shape of the heart through the sequences, while efficiently being constrained to recognize the cardiac structures from the other structures presented in the images.

Mechanic deformable solids

This section provides a notions of deformation mechanics, which is essential for comprehending the project. Appendix A includes a concise summary of fundamental concepts.

Every problem related to the mechanics of deformable solids involves three types of quantities that vary from point to point in the body: displacement ($\mathbf{u}$), strain (ϵ), and stress (σ). Displacement is showed with a vector, while strain and stress are modeled with second-rank tensors (A.1). These three quantities are connected through three main types of equations, which are equilibrium (A.2), kinematic relations (A.3) and constitutive law.

Constitutive law

A constitutive law is a mathematical expression that describes the mechanical behavior of a material by linking the tensor of constraints to the tensor of deformations. A linear law depends linearly on its mechanical parameters, whereas a non-linear law does not. By considering small deformations, Robert Hooke introduced an isotropic linear elastic law that allows to link the stress tensor to the deformation tensor, thanks to an elasticity tensor. In linear elasticity, if the material is isotropic, the stress tensor is related to the strain tensor by the stiffness matrix $\mathbf{C}$:

$$\sigma_{ij} = C_{ijkl} \epsilon_{kl} \quad 2.1$$

Elasticity tensor is a function of only two mechanical parameters: the Young's modulus E , and the Poisson's ratio ν . In modified Voigt notation, the stiffness matrix has the following form:

$$\mathbf{C} = \frac{E}{(1+\nu)(1-2\nu)} \begin{bmatrix} 1-\nu & \nu & \nu & 0 & 0 & 0 \\ \nu & 1-\nu & \nu & 0 & 0 & 0 \\ \nu & \nu & 1-\nu & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} \end{bmatrix} \quad 2.2$$

In hyperelasticity, the constitutive laws are formulated based on the strain energy density W , which represents the amount of energy that remains in a solid material once a load has been applied to. This energy density is defined as:

$$W = \int_0^{\varepsilon_{ij}} \sigma_{ij} d\varepsilon_{ij} \quad 2.3$$

2.4 Cardiac Modeling

The heart is a highly complex biological pump in terms of mechanics. Mathematical modeling of the heart allows for a better understanding of its behavior and the potential to predict functional changes associated with cardiac dysfunction. To achieve this goal, a cardiac model must take into account the specific geometry, microstructure, mechanical properties as well as boundary conditions. These boundary conditions are difficult to model because they are externally affected by the traction of the organs and internally affected by the pressure of the blood, an incompressible fluid (Ambrosi & Pezzuto, 2012). In addition, to accurately represent the different phases of the cardiac cycle, the model must incorporate both the active (contraction) and passive (relaxation) properties of the heart.

2.4.1 Passive and active mechanical properties

Most studies are used to model myocardium with strain energy function (W) so that it is anisotropic with respect to the local fiber direction, exponential fiber b_f , and transverse b_t (equation 2.5). Those all are included in energy law, consequently, get involved into optimization process to minimize energy-based function, and finally will be identified (Zhang et al., 2021).

$$W_{str} = \frac{1}{2} C_1 (\exp(Q) - I) \quad 2.4$$

$$Q(\bar{E}) = [b_f \bar{E}_{11}^2 + b_t (\bar{E}_{22}^2 + \bar{E}_{33}^2 + \bar{E}_{23}^2 + \bar{E}_{32}^2) + b_{fs} (\bar{E}_{12}^2 + \bar{E}_{21}^2 + \bar{E}_{13}^2 + \bar{E}_{31}^2)] \quad 2.5$$

Where the parameter, C_1 , scaling factor of stiffness, and $\bar{E}_{11}$, $\bar{E}_{22}$, $\bar{E}_{33}$ shows normal strain (Green-Lagrange strain) in fibre, cross-fibre, and radial direction, respectively. Also $\bar{E}_{23}$, $\bar{E}_{12}$, $\bar{E}_{13}$ are shear strain in transvers plane, fiber-cross fiber plane and fiber-radial plane, respectively. The **stress-strain relationship** can be calculated for each of fibre b_f , cross-fibre b_{fs} and transverse b_t parameters (anisotropy ratio).

Cardiac contraction (systolic function) is caused by the action of myocytes that use energy on a microscopic scale to produce a macroscopic deformation. This contraction is produced by the exciting of cells by an electrical potential.

In terms of physiology, active stress is influenced by the stretching of muscle fibers and has a **non-linear relationship** with it, acting in the same direction as the fibers. **Hunter et al.** proposed a steady-state model that considers the activation of muscle cells by calcium flow to represent this active stress (Wang et al., 2013). According to this model, the active stress is defined as:

$$T_a = T_{Ca}(1 + \beta(\gamma - 1)) \quad 2.6$$

Where γ the fiber stretch ratio, β is a parameter that describes the level of activation of cells as a function of muscle fiber length, and T_{Ca} is the fiber tension at cell activation (Hunter et al., 1998; Wang et al., 2013). **Linear elasticity** that used **Hook's law** to find anisotropic parameters should take a linear solution technique (Avril, Bonnet, et al., 2008; Grédiac et al., 2002). Then, it's hard that model follows direction planes based-on fibre orientation previously extracted from experiments. It's important to explain about obtaining fiber orientation in modelling LV geometry structure (Wang, 2012).

2.4.2 Material Models

Studies such as the one by Holzapfel and Ogden (2009) have shown that anisotropic models can better represent the mechanical behavior of the myocardium, particularly in cases of transversely isotropy, Figure 2.7 (Miller, 2018). The challenge, however, is that extracting myocardial fiber orientation and deformation from MRI data is time-consuming and technically difficult due to the large number of slices and density of segmentation points involved.

Myocardial fiber deformation and orientation

Several studies present the methodology which all are required to the extraction and statistical analysis of myocardial fiber deformation. The biomechanical finite element models integrate the main direction of the fibers at any point of the LV, from the acquisitions MRI of diffusion tensor (DT-MRI) as well as motion estimation from tagged MRI sequences. This combination of the two methods allows to estimate the deformation of the fibers during the cardiac cycle. The main difficulty is the formation of a geometric registration between the ex vivo DT-MRI data and in vivo tagged MRI for LV.

In many studies, it has been shown that the orientation of the fibers is correlated with the direction of the maximum diffusion of water molecules (Hsu et al., 1998). Principal components (PCA) has been implemented in order to calculate the first eigenvector of the diffusion tensor in each element. The main eigenvector varies from about -60° in the epicardium to about 70° in the endocardium.

Problem, contribution and significance

The researchers developed a method to incorporate the fiber structure in the finite element model of the left ventricle. This method involved manual segmentation of the DT-MRI volume, construction of an FE model representing the geometry of the left ventricle, in the DT-MRI geometry, and analysis of fiber vectors and conversion to a cardiac coordinate system (Wang, 2012). Then studies compared the results of simulations using an isotropic model and a transversely isotropic model (Miller, 2018), in terms of their ability to accurately estimate the mechanical properties of the left ventricle.

This is important, as it allows for a more accurate representation of the myocardial fiber structure and the deformation of the left ventricle, allowing for improved predictions of the effects of cardiac pathologies on the structure of the ventricle. Additionally, this could provide insight into the development of novel treatments for cardiac pathologies.

In order to determine whether an anisotropic model is necessary to provide better results than an isotropic model in linear elasticity, further research is needed. This would help to better understand the differences in terms of accuracy and precision of the two models.

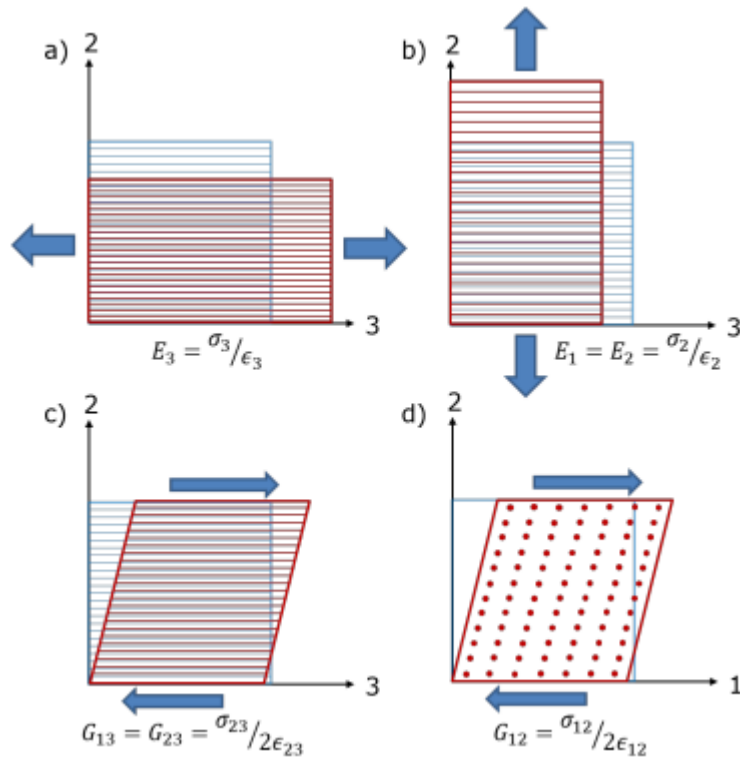


Figure 2.7 Stiffness modulus in transversely isotropic material with fibers oriented in direction 3 (0 0 1). (Miller, 2018), showing Young modulus in a) fibre direction, (E_3), and b) transverse direction ($E_1=E_2$). The shear modulus c) ($G_{13} = G_{23}$) in plane parallel to fibre, and d) (G_{12}) perpendicular to the fibers.

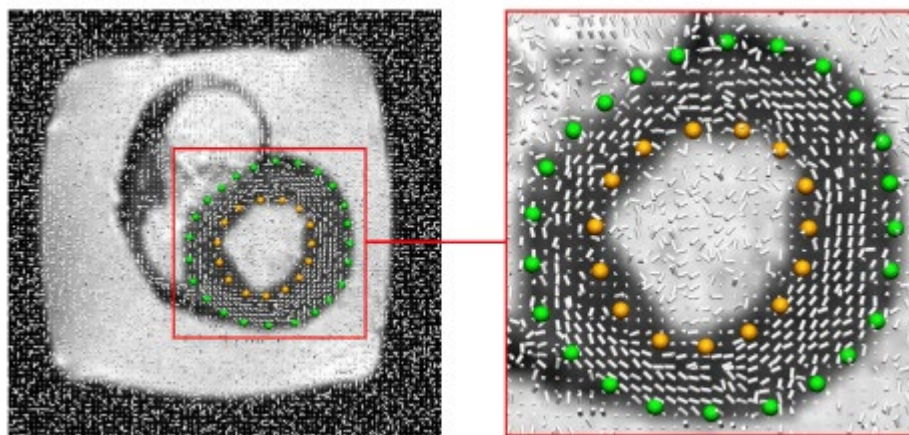


Figure 2.8 Left: short-axis section of MR-TD volume 82-10 (Casta, 2012), showing the segmentation contour points (gold: endocardial contour, green: epicardial contour) and

myocardial fiber vectors come from the diffusion tensor. The white areas around the core correspond to the hydrophilic gel. Right: the same enlarged RM-DT image, where we can better realize the orientation of the fibers in the myocardium.

2.4.3 Left Ventricular Models.

The process of geometric modeling of left ventricle begins with the definition of three reference points in order to construct a cardiac coordinate system, which allows the matching of different geometry acquired under different conditions (Figure 2.9).

The cardiac coordinate system (SCC) is constructed by manually selecting three reference points in the given dataset: a point at the center of the LV on the top basal slice, where the two ventricles are visible (Figure 2.9, red point), a point at the center of the RV on the same slice (Figure 2.9, yellow), and finally a point at the center of the LV in the apical slice (blue). These three points define the axis of the coordinate system, with the direction of X going from the base of the LV to the apex of the LV, Y going from the center of the LV to the center of the RV, and Z is orthogonal to these two vectors. From this SCC, a transformation matrix can be constructed to convert the coordinates of the useful data from the image coordinate system to the heart coordinate system.

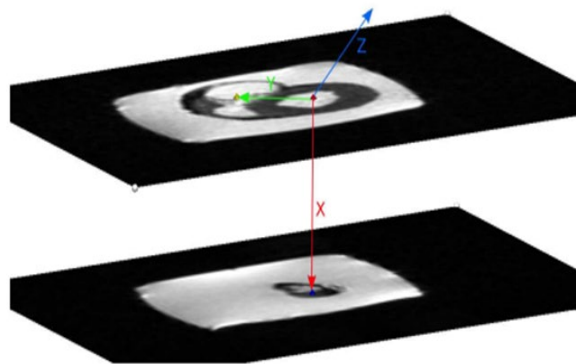


Figure 2.9 Cardiac Coordinate System (SCC). (a) The three points red, yellow, and blue are set manually.

Later, the endocardial and epicardial surfaces of the LV are segmented using a point-guided modelling technique. The objective is to make a generic EF model of the LV that is deformed in order to follow the geometry of the heart during the cardiac cycle. This deformation is carried out using guide points defined by a specialized analyst, Figure 2.10 (Gamba, 2019). Then, Least-

squares optimization is applied to interactively fit the model using guide points provided by the operator and computer-generated data points derived from the image which used an edge detection algorithm (Figure 2.11).

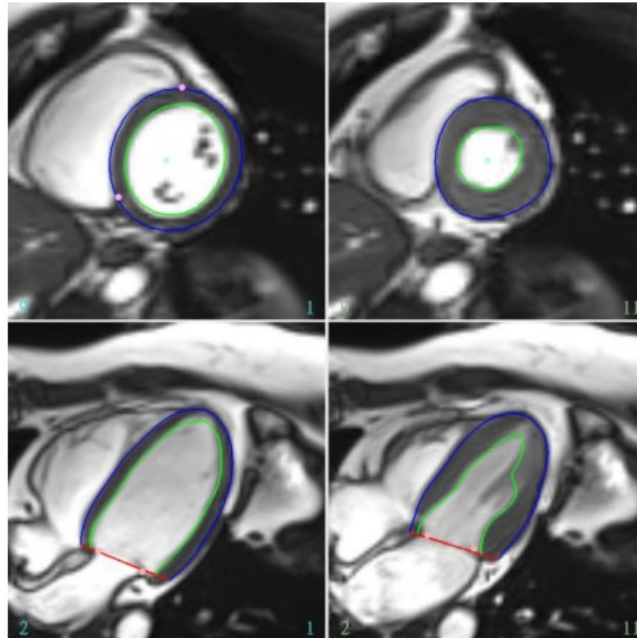


Figure 2.10 point-guided modelling technique (Gamba, 2019): long-axis (down) and Short-axis (top), epicardial (blue) and endocardial (green) surface contours, as well as associated guide points.

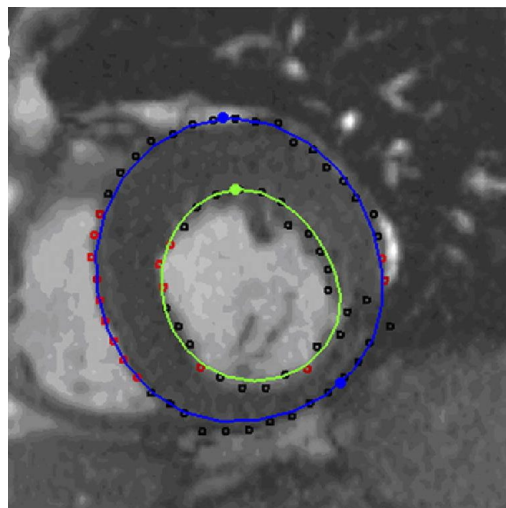


Figure 2.11 User-defined guide points (blue and green) and computer-generated image edge points are displayed in the short-axis slice (ranged from black to red color Based on relative edge sharpness) (Li et al., 2010)

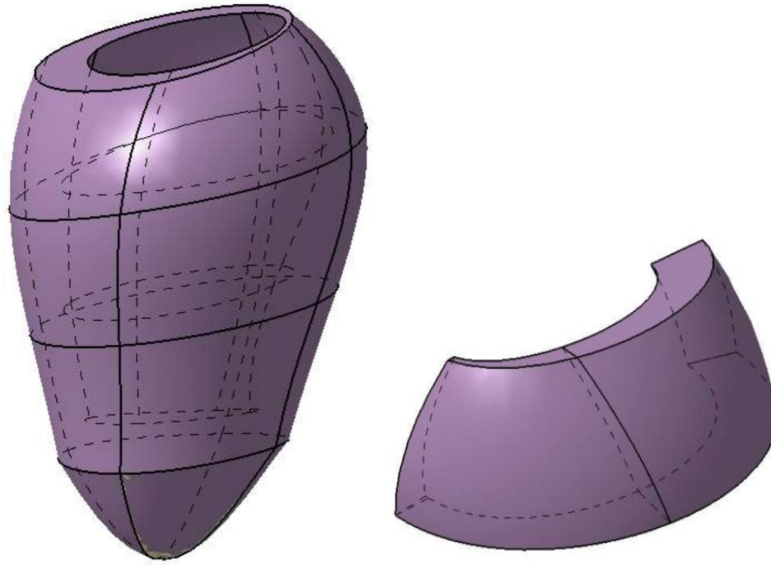


Figure 2.12 FE Surface model (a) at the end-diastolic (b) the Hermit element.

After segmenting the LV surfaces, the tissue marking lines on the minor and major axis sections were tracked separately using a non-rigid matching method (Li et al., 2010). All the lines (all the phases) readjusted are employed in order to reconstruct a 3D deformation field of the LV. This 3D displacement data are defined by a group of material points, which was merged into the model at one phase (where the marking lines are not deformed, reference phase). Then, the deformation of the model for the other phases of the model was calculated by using the 3D movement reconstructed from the material points (Figure 2.13).

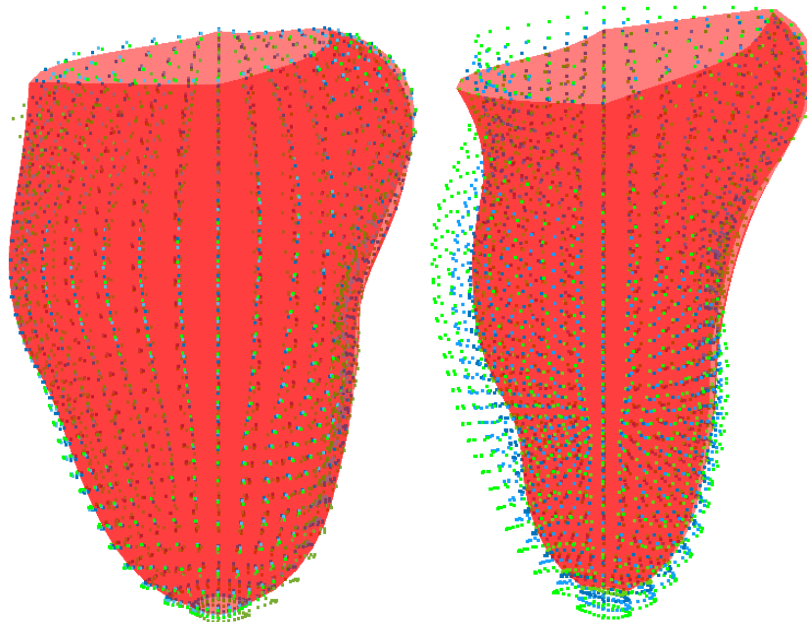


Figure 2.13 3D material points reconstructed from the marking lines at the (a) end-diastolic (b) end-systolic. Other phase of the cardiac cycle, superimposed on the endocardial surfaces of the LV (red).

The root means square error measures the difference between the material points after reconstruction of the movement at a certain phase and those originally measured by the analyst at the same phase. Finally, from the models built previously, we can extract global parameters relating to the patients, such as the left ventricular mass, the volume at the end of 3D material points (green and blue colour) reconstructed from the tagged lines at the end diastolic phase (a) and end-systolic (b) of the cardiac cycle, superimposed on the endocardial surfaces of the LV (red).

2.5 Non-Invasive Identification of Mechanical Properties

The identification of mechanical properties has been used in clinical diagnostics (Avril, Bonnet, et al., 2008) to diagnose diseases such as aneurism. Various models have been established to characterize the elasticity of the vascular wall (Vassal et al., 2009)

2.5.1 Soft tissue modeling

Cardiac tissue exhibits nonlinear behavior. Therefore, the modeling of the tissue often passes through a hyper-elastic model (Blatz & Ko, 1962), (Chuong & Fung, 1983), (Fung, 1967). Myocardium modeling of heart requires to assess the mechanic of continuums in large and small deformations. Knowing the movement of a continuous medium is the movement of each of the particles that represent it, this medium being structured as a set of material particles.

This assumes that each of these particles can be recognized at any time. Therefore, in order to describe the movement of a particle, we must be able to recognize its position at the reference time, then to locate its positions at other times.

2.5.2 Inverse problem in biomechanics

Before going into the details of inverse analysis, we define mathematically what a direct problem and an inverse problem are.

Direct problem: a mechanical system (S) is characterized by its inherent parameters (p). We can mention parameters as the Young's modulus, the Poisson's ratio, the compressibility modulus, etc.

The direct problem is to know what the response (d) of the system is when it's subjected to a request (X). Mathematically, this problem is solved by:

$$F(X, d; p) = 0 \quad 2.7$$

Where F function is derived from the mechanical equilibrium equations.

The direct problem is often well posed. This means that the problem has the solution, that it's unique and stable with respect to the small perturbations.

If the problem can be written in the form $d = F(X, p)$, then it's called explicit form.

Inverse problem: We are in the presence of an inverse problem when we do not know certain information of the system, such as the inherent parameters of the system. To fill this information gap, it's necessary to have information on requests (input) and also on the response (output).

Consider a system S with p parameters, requested by X, and where d represents the result of this requests (the response).

$$d = f(X, p) \text{ or } f(X, d, p) = 0 \quad 2.8$$

By considering the known terms, measurement d and the stress X, we go back to (p) using an algorithm allowing the successive choice of optimal candidates for the realization of a numerical measurement (dis_{num}) as close as possible to the experimental measurement (dis_{exp}) (Figure 2.14).

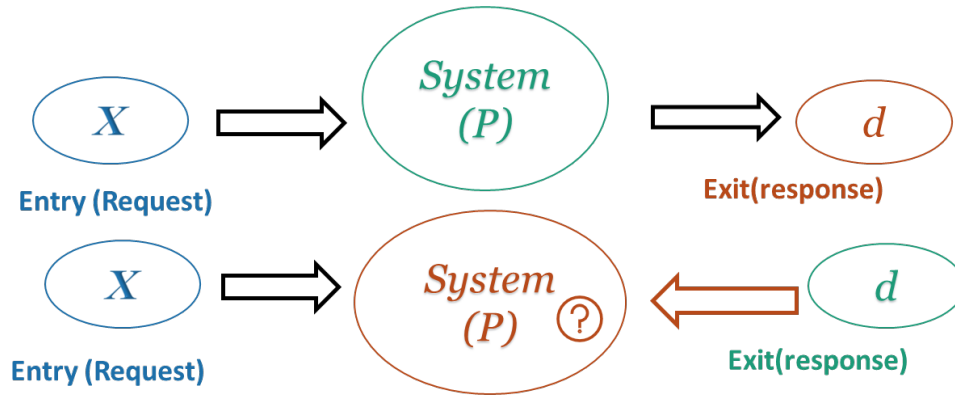


Figure 2.14 Presentation of the inverse problem

The solution of such problems can be analytical in some very simple cases or go through a numerical process of minimizing a cost function.

$$H(p) = \|d - d(p)\|^2 \quad 2.9$$

Where cost function $H(p)$ represents the norm of difference between the numerical model (d) and the experimental data $d(p)$. These methods are based on two steps: first, measurement steps by MRI, second, an optimization step using a finite element calculation code.

Therefore, the inverse problem for a given direct problem requires to determine certain characteristics from data associated with the direct problem solution. However, the inverse analysis is not considered in such a trivial way. In fact, there are two different categories of inverse problems. Those problems that have unique solution and certain initial boundary conditions are stated to be well-posed. But many of the problems we meet in many cases are ill-posed. The latter represent some cases where the uniqueness, or continuity of the solution with respect to the measurements are not all verified.

It also requires evaluating the noise to allow for good convergence. This noise may be related to: uncertainties related to experimental data, the lack of collected data and the existing model. It represents a source of uncertainty because the real problem is idealized using the simplified assumptions. Depending on the problem statement, mathematical methods and strategies are considered to reduce sensitivity to uncertainties.

Contribution to non-invasive methods

The non-invasive mechanical study of the myocardium is a hot topic. However, before carrying out patient-specific studies, various material laws have been developed and validated on in-vivo measurements. These laws are mostly time exponential and try to simulate the behaviour of the different biological fibres, which undergo the blood circulation or ventricular pressure. As a conclusion, non-invasive patient-specific inverse problems attempts to find the parameters linked to these mechanical laws using MRI or ultrasound data. Once these parameters are known, a diagnosis can be established on the patient-specific condition.

2.6 Virtual Fields Method; Theory and Formulation

2.6.1 Estimation of mechanical properties by Imaging

Field measurements: Imaging allow to measure heterogeneous displacement fields and to precisely measure the state of a material subjected to a non-standard test. Consequently, using an inversion technique, it's possible to determine the mechanical properties and the stress field associated with the tested material. In cardiac modelling, the field of displacements and deformations are measured from medical images and the mechanical properties are then estimated. To apply these techniques in a clinical setting, one of the main challenges in this field is to reduce the time and the work needed to optimize each personalized model. This might be one of the reasons why the evaluation of the mechanical properties of cardiac tissue is not yet part of the clinical diagnostic resource.

The virtual fields method (VFM) might provide a solution to this challenge. It is an inversion method designed to solve the problem of identification of mechanical properties from measurements of kinematic fields. This approach proved to be robust (Avril et al., 2004), insensitive to uncertainties on the boundary conditions (Bonnet et al., 2005), and to have a rapid convergence (Avril et al., 2007). Additionally, it's independent of the geometry of the tested specimen. VFM has been effectively used to different materials with nonlinear behavior such as elastomers (Promma et al., 2009) (Palmieri et al., 2011), and in a biological setting, to a phantom (gel) (Pierron et al., 2013), isotropic (Miller, 2018) and anisotropic phantom (Qin et al., 2013) by magnetic resonance elastography (MRE). Avril et. al applied this technique to an experimental setup to study human arteries ex-vivo considering the nonlinear anisotropic properties (Avril,

Huntley, et al., 2008). VFM can also be used to find the local mechanical parameters of tissues by separating the geometry into regions (Avril, 2015).

2.6.2 Principle of virtual work

VFM is based on the principle of virtual work (PVW). This principle is equivalent to the formulation weak of the local equilibrium equation:

$$-\int_V \boldsymbol{\sigma} : \boldsymbol{\epsilon}^* dV + \int_S \mathbf{T} \cdot \mathbf{u}^* dS + \int_V \mathbf{b} \cdot \mathbf{u}^* dV = 0 \quad 2.10$$

The detail of each energy term is described in section 4.3.1.

If we consider a body at rest, neglect the volume forces $\mathbf{b}$ and consider a plane stress state (Fig 3.1), we can write equation 2.10 in the following form:

$$\int (\sigma_{11}\epsilon_{11}^* + \sigma_{22}\epsilon_{22}^* + \sigma_{12}\epsilon_{12}^*) ds = \int_S \mathbf{T} \cdot \mathbf{u}^* dS \quad 2.11$$

This equation is valid for any kinematic admissible virtual displacement field, which is zero where the LV body is supported.

2.6.3 Constraints on virtual fields

The virtual fields $\mathbf{u}^*$ are mathematical functions which represent a virtual displacement field. These can be considered as a kinematically admissible variation of the displacements caused by the loading within the material (actual displacements). The only constraint on virtual fields is that they must be kinematically admissible. This implies that the field must be zero where the solid is supported. In addition, the field must be continuous throughout the material. The required order of continuity is only C^0 because the principle of virtual works is based on the weak form of the local equilibrium equation.

For example, considering the 2D solid basal myocardium problem, which is subjected to in-plane mechanical loading in Figure 2.15. This is supported around epicardium in $y = 0$ and enforced to a uniform pressure linear force in $y = L$. it's a very simple virtual field could be chosen for the study in the state plane of strain or stress as follow:

$$\begin{cases} u_x^* = 0 \\ u_y^* = y \end{cases} \begin{cases} \varepsilon_x^* = 0 \\ \varepsilon_y^* = 1 \\ \varepsilon_{xy}^* = 0 \end{cases} \quad 2.12$$

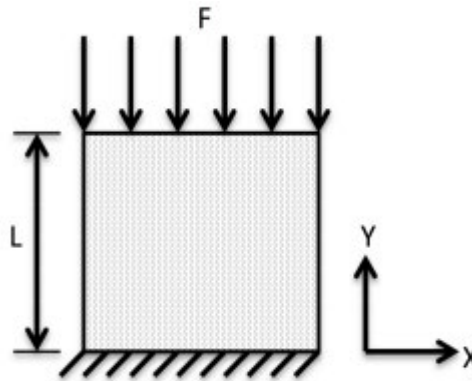


Figure 2.15 Solid under uniaxial loading

The definition of virtual fields is specific to each test configuration. Some of VFs may be more sensitive to certain loading condition. Others can be very sensitive to noise in the data. Field measurement techniques invariably introduce noise into the measured fields. There is a method that allows Figure 3.1 myocardium solid under uniaxial loading to be optimized virtual fields to make them less sensitive to noise by using special virtual fields. This technique is described in (Pierron & Grédiac, 2012).

2.6.4 Linear method

When the constitutive equations depend linearly on the mechanical parameters, the VFM consists of inserting the constitutive law into equation 2.10 and defining as many virtual fields as there are mechanical parameters. This condition allows to create a system of equations that can easily be reversed. For example, in the case of a homogeneous, isotropic, and linear elastic material, two constants define the behavior of the material. If the specimen is flat and is subjected to a loading in the plan of the material, we can rewrite the equation 2.10 with two independent virtual fields. After some mathematical calculation, we obtain the following system of equations:

$$\mathbf{A} \mathbf{Q} = \mathbf{B} \quad 2.13$$

And where $\mathbf{Q}$ are the mechanical parameters defining the stiffness tensor. The details of the mathematical manipulations are described in Matrix A, Q, B derived from 2.11 and written as:

$$\mathbf{A} = \begin{bmatrix} \int \left(\varepsilon_{11}\epsilon_{11}^{*(1)} + \varepsilon_{22}\epsilon_{22}^{*(1)} + \frac{1}{2}\varepsilon_{12}\epsilon_{12}^{*(1)} \right) ds & \int \left(\varepsilon_{11}\epsilon_{22}^{*(1)} + \varepsilon_{22}\epsilon_{11}^{*(1)} - \frac{1}{2}\varepsilon_{12}\epsilon_{12}^{*(1)} \right) ds \\ \int \left(\varepsilon_{11}\epsilon_{11}^{*(2)} + \varepsilon_{22}\epsilon_{22}^{*(2)} + \frac{1}{2}\varepsilon_{12}\epsilon_{12}^{*(2)} \right) ds & \int \left(\varepsilon_{11}\epsilon_{22}^{*(2)} + \varepsilon_{22}\epsilon_{11}^{*(2)} - \frac{1}{2}\varepsilon_{12}\epsilon_{12}^{*(2)} \right) ds \end{bmatrix} \quad 2.14$$

$$\mathbf{Q} = \begin{Bmatrix} Q_{11} \\ Q_{12} \end{Bmatrix} \text{ and } \mathbf{B} = \begin{Bmatrix} \int \bar{T}_i u_i^{*(1)} dl \\ \int \bar{T}_i u_i^{*(2)} dl \end{Bmatrix} \quad 2.15$$

In this case, VFM becomes a very effective inversion method, as it offers an analytical solution to the identification problem. The difficulty of the VFM then is to choose a good virtual field's u^* . This option is intuitive. The virtual field must satisfy the boundary conditions for the displacements. As there are an infinity of virtual fields, the idea here is to introduce constraints to identify the appropriate fields called the Special Virtual Fields.

2.6.5 Special virtual fields

Virtual fields can be obtained using a particular property, if $(\mathbf{A})$ in equation 2.16 is equal to the identity matrix $\mathbf{I}$.

$$\begin{aligned} \mathbf{Q} &= \mathbf{A}^{-1}\mathbf{B} \\ \mathbf{Q} &= \mathbf{I}^{-1}\mathbf{B} \\ \mathbf{Q} &= \mathbf{B} \end{aligned} \quad 2.16$$

The physical terms on the main diagonal of the matrix $(\mathbf{A})$ in equation 2.14 are assumed to return Identity matrix (with ones). Special virtual fields obtained by adding constraints to 2.16, for each unknown parameter, resulting in two equations if the material is isotropic, five or six equations if the material is transversely or fully anisotropic, respectively. In orthotropic material results in four equations in plane.

To construct these special virtual fields, polynomial, sinusoidal or other types of functions can be used. To illustrate the method, we will consider polynomial functions to determine these special virtual fields. Consider a body, subjected to a force $\mathbf{F}$, and supported by supports at N different points.

This example is considered to explain the method of virtual fields, with boundary conditions, the choice of polynomial functions is just symbolic, other functions can be considered. The desired virtual fields are expanded with polynomial functions which are the following:

$$\begin{cases} u_1^* = \sum_{i=0}^m \sum_{j=0}^n A_{ij} \left(\frac{x_1}{l}\right)^i \left(\frac{x_2}{w}\right)^j \\ u_2^* = \sum_{i=0}^p \sum_{j=0}^q B_{ij} \left(\frac{x_1}{l}\right)^i \left(\frac{x_2}{w}\right)^j \end{cases} \quad 2.17$$

With (A_{ij}) and (B_{ij}) , are the coefficients of the polynomial functions to be determined, m , n , p , and q are natural numbers, which define the maximum number of coefficients used for the expansions of the polynomial functions. (L) and (w) are the dimensions of the body considered, in the two directions, respectively.

The components of the virtual displacement fields are assumed using the expression $\epsilon_{ij} = \frac{1}{2}(u_{ij} + u_{ji})$, which gives us the following expressions:

$$\begin{cases} \epsilon_1^* = \sum_{i=0}^m \sum_{j=0}^n \frac{i}{l} A_{ij} \left(\frac{x_1}{l}\right)^{i-1} \left(\frac{x_2}{w}\right)^{j-1} \\ \epsilon_2^* = \sum_{i=0}^p \sum_{j=0}^q \frac{j}{w} B_{ij} \left(\frac{x_1}{l}\right)^i \left(\frac{x_2}{w}\right)^{j-1} \\ \epsilon_{12}^* = \sum_{i=0}^m \sum_{j=0}^n \frac{j}{w} A_{ij} \left(\frac{x_1}{l}\right)^i \left(\frac{x_2}{w}\right)^{j-1} + \sum_{i=0}^p \sum_{j=0}^q \frac{i}{l} B_{ij} \left(\frac{x_1}{l}\right)^{i-1} \left(\frac{x_2}{w}\right)^j \end{cases} \quad 2.18$$

The virtual fields must be cinematically admissible, which comes to satisfy the 2N boundary equations at support points:

$$\left\{ \begin{array}{l} u_1^*(x_1^{(1)}, x_2^{(1)}) = \sum_{i=0}^m \sum_{j=0}^n A_{ij} \left(\frac{x_1^{(1)}}{l} \right)^i \left(\frac{x_2^{(1)}}{w} \right)^j \\ u_1^*(x_1^{(N)}, x_2^{(N)}) = \sum_{i=0}^m \sum_{j=0}^n A_{ij} \left(\frac{x_1^{(N)}}{l} \right)^i \left(\frac{x_2^{(N)}}{w} \right)^j \\ u_2^*(x_1^{(1)}, x_2^{(1)}) = \sum_{i=0}^p \sum_{j=0}^q B_{ij} \left(\frac{x_1^{(1)}}{l} \right)^i \left(\frac{x_2^{(1)}}{w} \right)^j \\ u_2^*(x_1^{(N)}, x_2^{(N)}) = \sum_{i=0}^p \sum_{j=0}^q B_{ij} \left(\frac{x_1^{(N)}}{l} \right)^i \left(\frac{x_2^{(N)}}{w} \right)^j \end{array} \right. \quad 2.19$$

Using (2.17) and (2.18), to identify the A_{ij} and B_{ij} , the number of virtual fields is equal to those of the unknown constitutive parameters, which come back to solve the following system:

$$\mathbf{MC} = \mathbf{D} \quad 2.20$$

2.6.6 Non-linear method

The VFM can also be used in the case where the constitutive law of the material does not depend linearly on the mechanical parameters. In this case, we obtain a non-linear system of equations. This system of equations can be solved by minimizing a cost function. This function can be, for example, the squared residuals between the internal and external virtual work.

$$f = (W_{int} - W_{ext})^2 \quad 2.21$$

The optimization scheme can be organized that offers a framework for the identification of mechanical properties, which guides the optimization process towards the desired solution.

2.6.7 Application in large deformations

Since the heart is considered hyperelastic, the theory of large deformations must be used. There are three formulations of the principle of virtual work in large deformation mechanics. We will use the formulation in the current frame of configuration, thus involving the Cauchy stress tensor, since the deformations are calculated in the deformed frame of reference.

$$\int_V \left(\sigma_{ij} \frac{\partial u_i^*}{\partial x_j^*} \right) dV + \int_S \sigma_{ij} n_j n_i^* dS \quad 2.22$$

Where V is the volume and S is the area of the solid in the current configuration. Virtual fields are expressed in the current configuration.

If the sample is considered flat, the stress distribution is uniform through the thickness of the sample and the loading is in the plane defined by the solid (plane state of stress), we can restate the equation 2.22:

$$-\int_s \left[\sigma_{11} \frac{\partial u_1^*}{\partial x_1^*} + \sigma_{22} \frac{\partial u_2^*}{\partial x_1^*} + \sigma_{12} \left(\frac{\partial u_1^*}{\partial x_2^*} + \frac{\partial u_2^*}{\partial x_1^*} \right) \right] ds + \int_l \sigma_{ij} n_j n_i^* dl = 0 \quad 2.23$$

In conclusion, myocardial stiffness can be estimated to determine cardiac function from CMR measurements using the modelling of cardiac movement's inverse methods and may be served as a diagnostic biomarker for cardiac failure like cardiotoxicity.

2.7 Conclusion: Significant gaps in knowledge

After evaluating the existing literature, It's worth noting that noninvasive identification methods have limitations and drawbacks, which do not fully consider the real 3d geometry of left ventricle as well as different material models and behavior of myocardium. VFM has the potential to identify the mechanical parameters quickly and accurately. In cancer survivors, these parameters could be used as personalized biomarkers in each patient to detect subtle changes for myocardial dysfunction. Therefore, the methodology developed in this thesis will make it possible to use cardiac magnetic resonance imaging (CMR) to clinically assess myocardial mechanical properties in patient-specific models. In Chapter 4 and 5, the VFM-based approaches are investigated, which take into account the patient-specific geometry of left ventricle, include material models with respect to the cardiac material modeling (sec 2.4.1).

However, before going into the thesis methodology, chapter 3 tests a 2d geometry with a linear isotropic model by the verified reference algorithm. Also, 2D VFM is applied to the model to validate and compare the results obtained. If the results obtained from the VFM in 2D are comparable to the reference method, it can be expected that 3D VFM-based methodology developed in this thesis will be feasible for assessing the mechanical properties of the left ventricle from Cine-MRI.

CHAPTER 3 PRELIMINARY WORKS ON 2D FRAMEWORK: INVERSE IDENTIFICATION OF ELASTIC LINEAR PROPERTIES OF 2D MYOCARDIUM FROM CINEDENSE MRI AND FEM ANALYSIS

3.1 Introduction and objectives

In this chapter, we applied an inverse identification framework to estimate the elastic linear mechanical properties of 2D myocardium using finite element analysis (FEA) optimization. We used an algorithm developed by (Spottiswoode, Zhong et al. 2006), which allows for the reconstruction of the displacement of each voxel within myocardium in both the spatial and temporal domains. This algorithm also includes a semi-automatic segmentation (Spottiswoode et al., 2009), which enable the user to easily segment and analyse MRI images obtained through the Cine-Dense technique. Thereafter, we used the obtained MRI displacements to start finite element analysis (FEA) updating, which find the optimal Young's modulus.

To validate the results, the virtual fields method (VFM) was implemented, which already has been applied successfully to echocardiographic images in short axis view (2D) (Lapointe, 2016). As the inversion method can be presented by either finite element updating (iteration method) or virtual fields technique (direct method), the future goal of this project is to extend the framework to 3D geometries and investigate the potential of virtual fields in identifying mechanical properties of the myocardium in 3D space as well as the early detection of cardiac abnormalities. However, the focus of the proposed FEM-based framework is on finding the elastic linear mechanical properties of basal myocardium by optimization from previously prepared Cine-MR images.

3.2 Methodology

3.2.1 MRI acquisitions

The imaging technique used for this study was MRI, and it was obtained from the image bank of the research program entitled (PETALE) which translates to: Preventing late effects of treatments for acute lymphoblastic leukemia (ALL) in children.

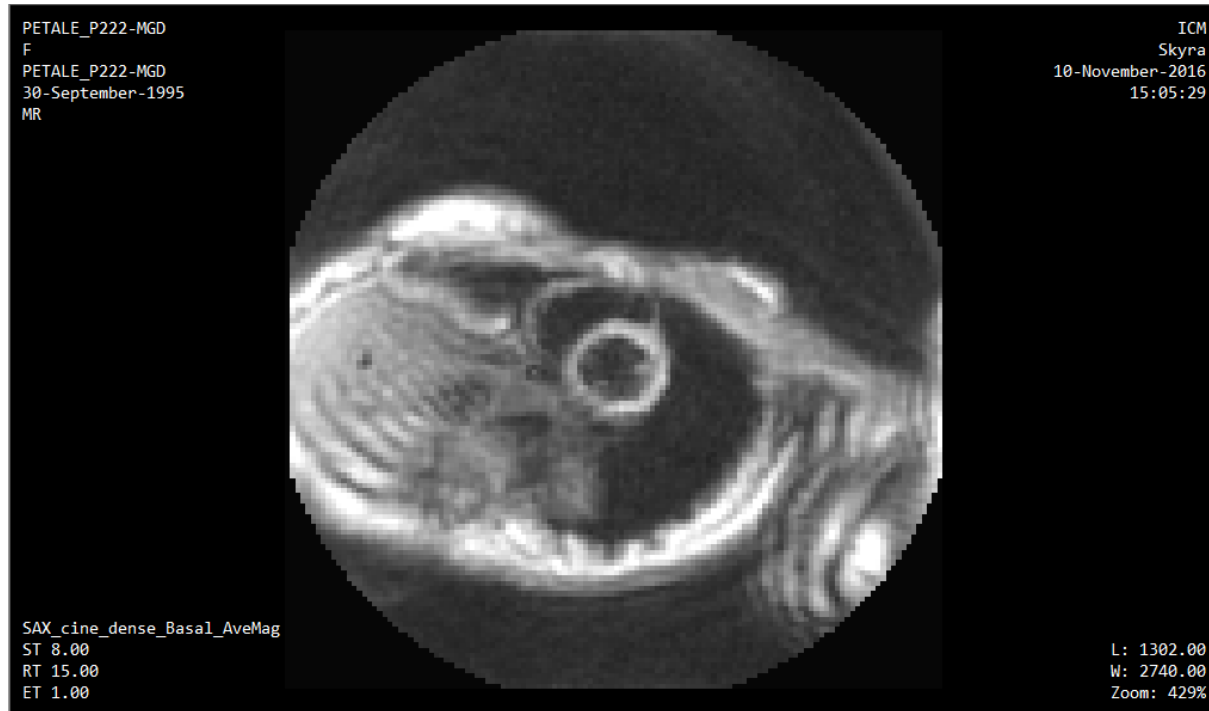


Figure 3.1 Example of an MRI image used in the study.

The data acquisition was done with the Magnetom Skyra, a three Tesla MRI machine produced by Siemens Healthcare from Erlangen, Germany and it was realized at the Montreal Heart Institute which is affiliated with Université de Montréal. The following parameters were included with the sequence of images: each pixel represents a square area of $7,4768 \text{ mm}^2$ (each side measuring $2,734375 \text{ mm}$), each slice has a thickness of 8 mm , the repetition timing was 15 ms and the echo timing was 1 ms . These parameters were able to capture a complete cardiac cycle within 26 frames.

3.2.2 DENSE Imaging

The DENSE (Displacement Encoding with Stimulated Echoes) technique was utilized in the study to obtain magnetic resonance images that encoded deformations in each phase.

The MRI sequence used in the DENSE imaging technique encodes the deformations that occur between the application of the first and second coding gradients during the sequence. This encoding allows the acquisition of images that show the displacement of the myocardium tissue during the cardiac cycle. The displacement or deformation of the myocardium tissue is expected to repeat in a cyclic pattern to enable complete acquisition of the image space using the DENSE

technique. However, this technique requires high frequencies, which often lead to distortion in phase, causing the phase to overlap and making it challenging to extract the accurate deformations. However, an algorithm presented by (Spottiswoode, Zhong et al. 2006) allows the user to unfold the phase both in the spatial and temporal domain which then allows the reconstruction of every absolute displacement of every voxel of the myocardium. This algorithm was then coupled with a semi-automatic segmentation method which was again presented by (Spottiswoode et al., 2009) in a subsequent publication. Based on the second research, Spottiswoode and his team were able to develop a MATLAB script which integrated algorithm presented in their research papers. This program called DENSE Analysis allows the user to easily segment and analyze MRI images obtained via the Cine Dense method.

Mesh Generation

With the DENSE imaging technique and the developed MATLAB script, the obtained MRI images for the short axis were analysed. This analysis made it possible to determine the position and displacement of each voxel in the myocardium tissue. Using the voxel positions, a mesh was constructed in MATLAB and each node was marked with the corresponding position. The positioning of each element within the mesh was then finalized using the controlled Delaunay triangulation method.

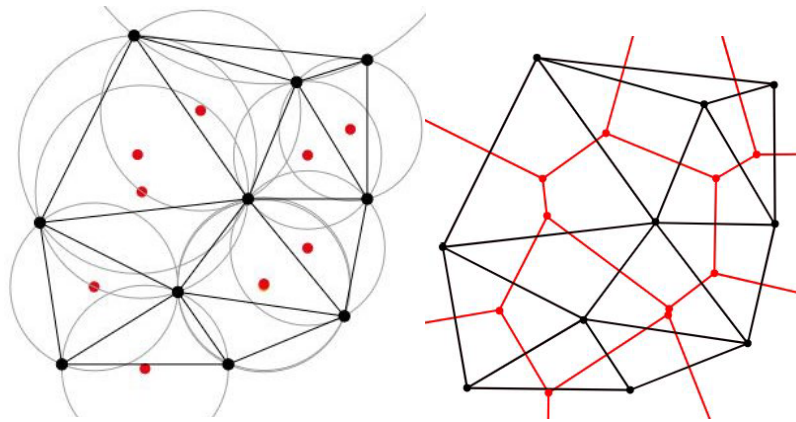


Figure 3.2 Example of Delaunay triangulation and its automatic meshing generation
(https://en.wikipedia.org/wiki/Delaunay_triangulation)

After the construction of the mesh, a cleaning process is carried out to remove any elements generated within the interior of the left ventricle. The resulting mesh for some slices of the cardiac cycle is shown below.

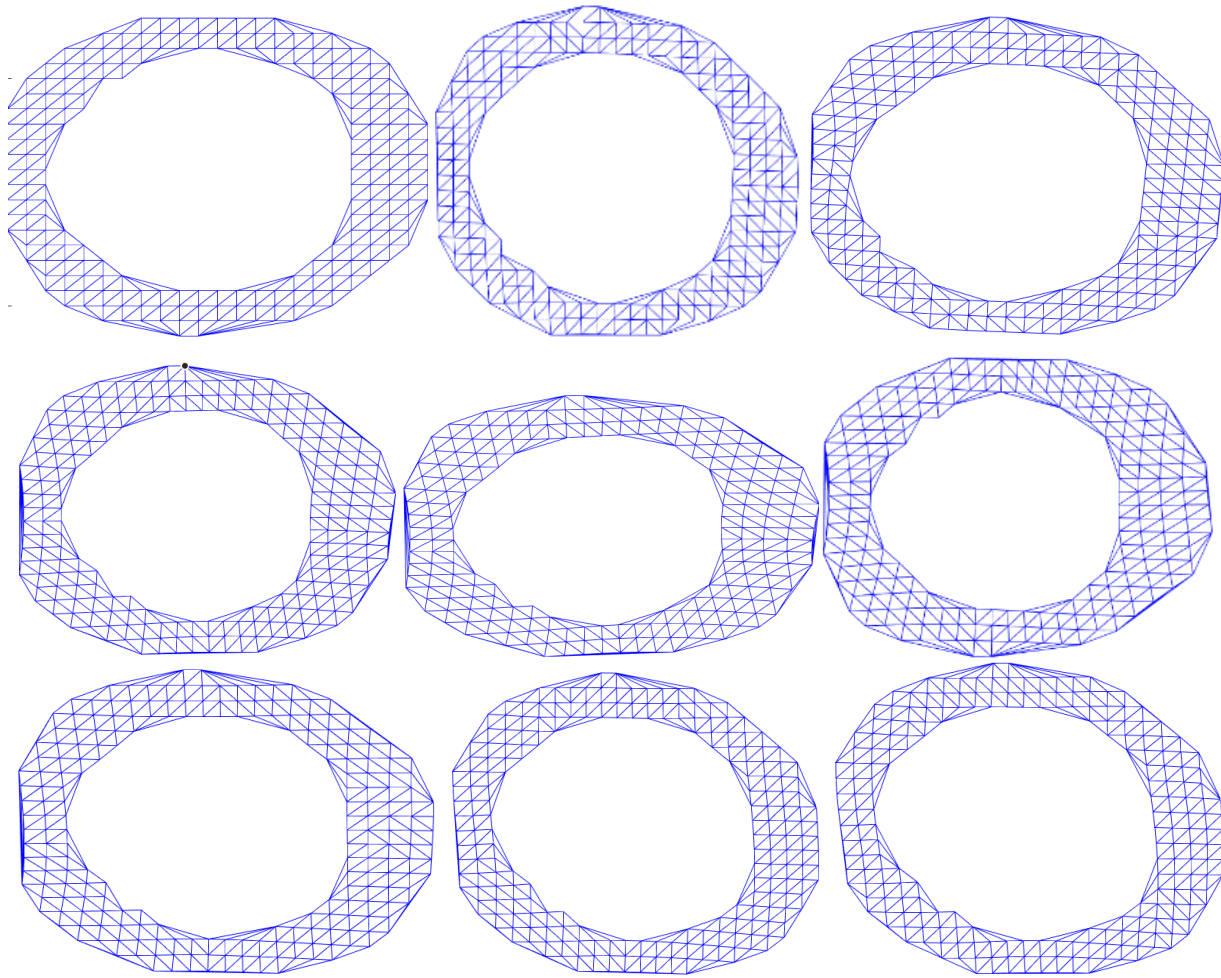


Figure 3.3 Mesh of myocardium obtained from Delaunay triangulation at $t_0, t_2, t_5, t_8, t_{11}, t_{14}, t_{17}, t_{21}$. The end-diastolic phase is at the top left (only one phase out of three is represented).

3.2.3 Finite element analysis

Once the reconstruction of the geometry model is completed, a 2D conforming mesh model was generated, based on (Ding et al., 2001) and (Montgomery et al., 2007). The input data for this study comprised a 2D mesh composed of in-plane triangles, with each triangle consisting of 3 nodes. To apply boundary constraints on the nodes, the first step in the finite element analysis was to determine which nodes to select. This process is done by comparing the mean average of displacement of each node in the mesh. We then recognize the two points which moved the minimum distance between t_0 and t_1 , and then fix these nodes. Even though we know that in real time none of the parts of the myocardium are fixed, choosing those two points near the septum offer the most realistic simulation.

Following the completion of the geometric model reconstruction, the nodes corresponding to the inner portion of the ventricular wall (endocardium) were manually selected. This selection procedure enabled the identification of the specific nodes in myocardium's Lumen where the pressure is required to be applied (Lumen's nodes). Subsequently, the code was developed to compute the centroid of the mesh and subsequently, the direction of the force to be applied. To simulate pressure on the inner ventricular wall, the force direction was obtained by computing the angle between the centroid and each node situated on the inner wall. The resulting model is presented below.

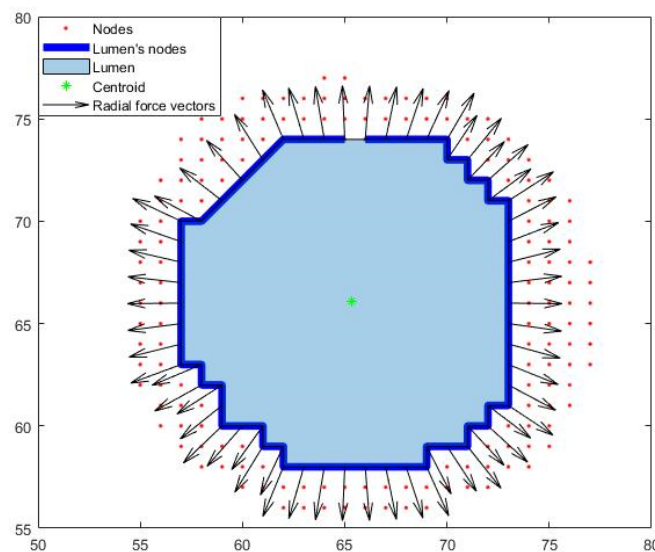


Figure 3.4 Endocardium ventricular wall where radial forces simulate a pressure. Identifying nodes in the myocardium Lumen's nodes where the pressure needs to be applied.

In order to determine the appropriate magnitude of force to be applied to each node, various parameters from existing literature are utilized. The method used to derive the passive elastic properties of the myocardium involves applying a cardiac pressure to a mesh based on images taken between the diastolic and systolic phase of the cardiac cycle. Since pressure must be converted into a force vector with two component values, we should find the area parameters (length, width) from measurement:

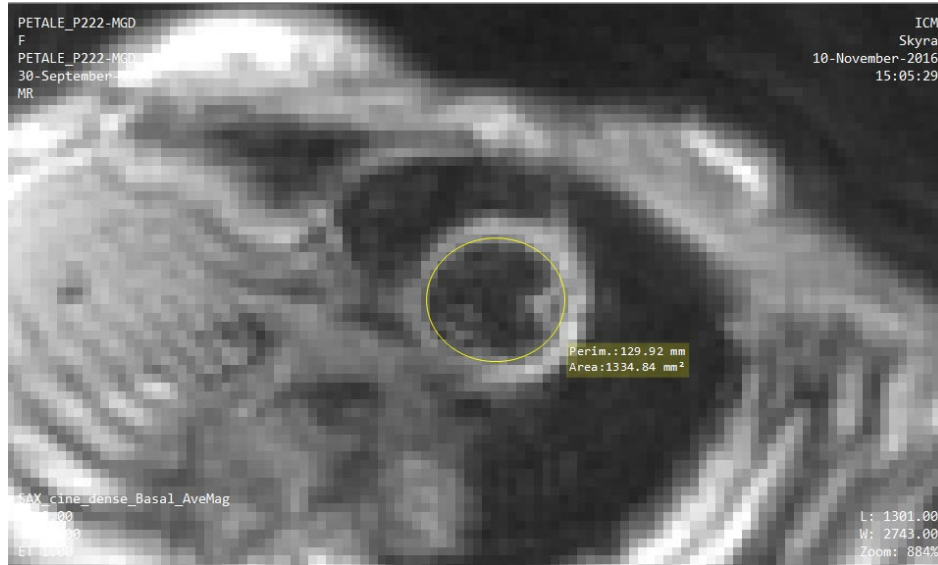


Figure 3.5 Approximation of the left ventricular perimeter at the base

The software MicroDicom was used to open and view the original MRI images. This software provided tools for measuring based on the pixels and associated real time interval. The boundary of the left ventricle was approximated 3 mm at the basal slice. Moreover, we knew that each slice of the MRI scan has certain 8 mm thickness. These two parameters were used to approximate the total force to be applied to the inner wall. This force was then equally redistributed to each of the 60 nodes composing the inner wall of the ventricle.

In the two-dimensional study, the pressure was assumed to be applied perpendicular to the endocardium wall. The pressure vector was then calculated at each point where the endocardium surface was defined. This vector is calculated by considering the resulting direction of the vectors defined by the segments forming the point of interest (Figure 3.6). To impose boundary conditions on the myocardium in finite element solution, we determined the two nodes with the minimum normal displacement and constrained their displacements to zero (Figure 3.6).

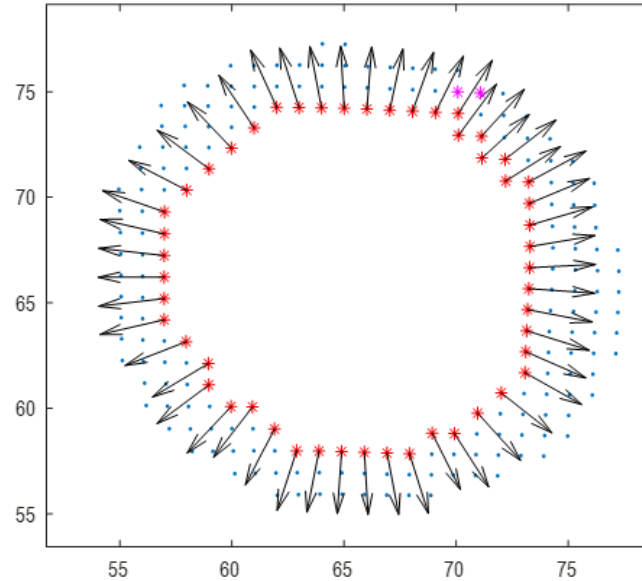


Figure 3.6 Pressure direction for a given segmentation. The pressure is applied perpendicular to the endocardium, at each point defining the segmentation. Showing constraints where two pink nodes had to be fixed like boundary condition.

Once all the parameters were set, we adapted an existing MATLAB code, which had been written in the context of the MECH4326 course from the University of Texas in El Paso. This MATLAB function originally coded by (Wang et al., 2008) is able to calculate the displacement of each node in a 2D plane

3.2.4 VFM Implementation

According to section 2.6.4, assuming the **constitutive law** is isotropic consisting of two constants mechanical parameters, the VFM equation 2.10 needs two virtual displacement fields which should be implemented independently. Therefore, we can rewrite the equation 2.10 with two chosen independent virtual fields.

Virtual displacement fields

Because of the quasi-cylindrical geometry of the myocardium in the short-axis view, the virtual fields are defined in cylindrical coordinates. They are then transformed into Cartesian coordinates for the purpose of calculations.

The virtual field must satisfy the boundary conditions for the displacements. As there are an infinity of virtual fields, the idea here is to introduce constraints to identify the appropriate fields.

The first virtual field is a displacement field which decreases as a function of the radius. **Virtual hydrostatic extension** expressed as:

$$\begin{cases} u_1^{*(1)} = \frac{R_0}{r} \cos \theta \\ u_2^{*(1)} = \frac{R_0}{r} \sin \theta \end{cases} \quad 3.1$$

Where R_0 is a mean radius located between the epicardium and the endocardium.

The second virtual field expressed as virtual radial extension:

$$\begin{cases} u_1^{*(2)} = R_0 \cos \theta \\ u_2^{*(2)} = R_0 \sin \theta \end{cases} \quad 3.2$$

According to two chosen virtual displacements, the right-hand side of equation 2.10 is equal to:

$$\begin{aligned} W^{*(1)} &= \int_S \mathbf{T} \cdot \mathbf{u}^{*(1)} dS = \sum \sum \left(\mathbf{P} \cos \theta \cos \theta \frac{R_0}{r} + \mathbf{P} \sin \theta \sin \theta \frac{R_0}{r} \right) \Delta S \\ W^{*(2)} &= \int_S \mathbf{T} \cdot \mathbf{u}^{*(2)} dS = \sum \sum (\mathbf{P} \cos \theta R_0 \cos \theta + \mathbf{P} \sin \theta R_0 \sin \theta) \Delta S \end{aligned} \quad 3.3$$

In equation 3.3, a scalar product is carried out between the vector of pressure and each virtual field defined in the Cartesian coordinate system (Figure 3.7). Thereafter, we approximate the integrals by discrete sums over the available data points. The input data previously obtained and saved in **MATLAB** file, which includes all displacements, strains in myocardial plane for all cardiac frames, and also image features like pixel dimension and pixel area.

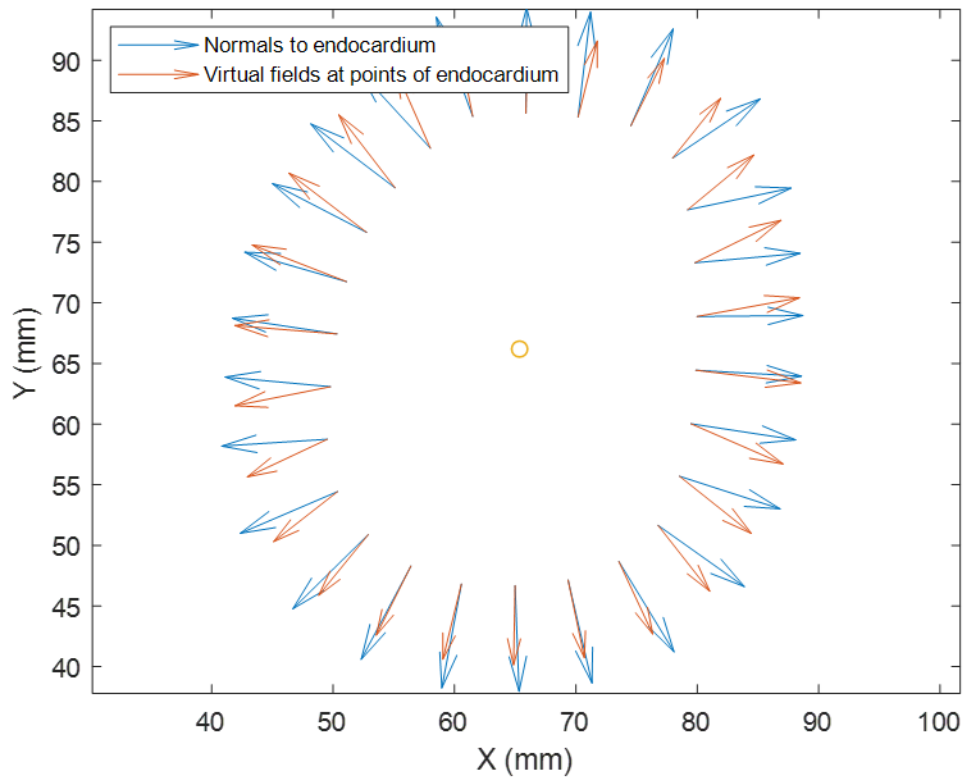


Figure 3.7 Normal pressure direction and virtual displacement direction at endocardium points of basal

3.3 Results

3.3.1 Identification of elastic modulus by optimization

The optimization process was executed using a for-loop that iteratively evaluated the function over a range of values for Young's modulus. Each iteration runs the FEM simulation for the value of Young ranged between 1 kPa and 500 kPa. For each iteration, the force on each node is the same and the Poisson's ratio set to 0.49. The output of this function is a matrix in which the new position of each node is recorded. The criteria used for optimization is the mean quadratic error between the displacement calculated by finite element analysis and the displacement measured from Cine-Dense MR images. The resulting optimization outcome can be expressed as follows:

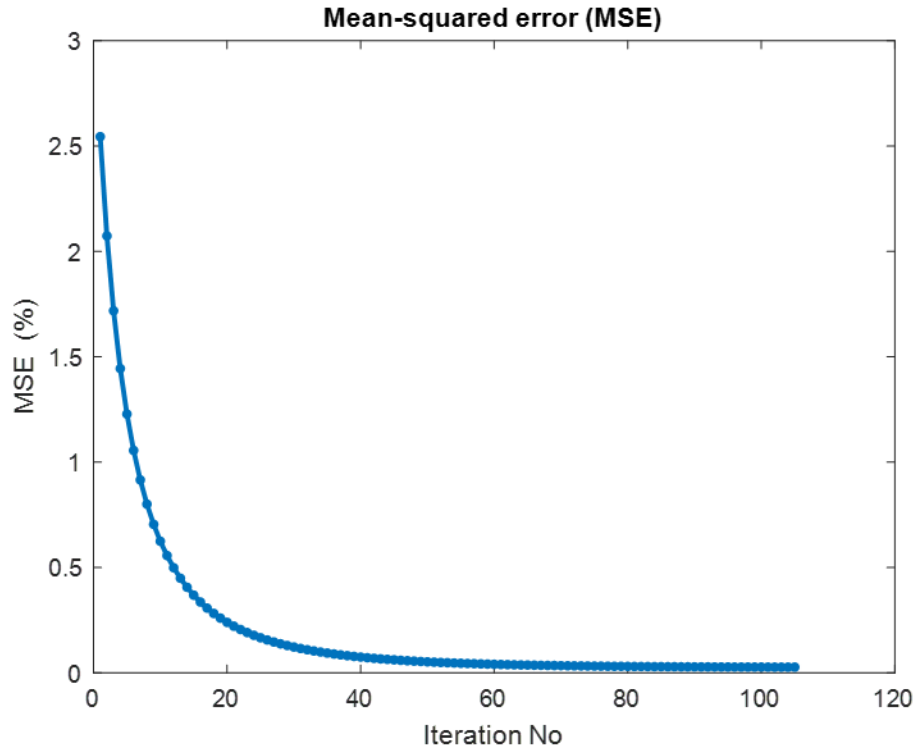


Figure 3.8 Growth of quadratic error on the Young's modulus variations.

As can be seen from the above figure, the optimal parameter is determined after a large number of iterations controlled to accurate condition for the right convergency, with increasing Young's modulus corresponding to a value of 15.97 kPa at the end-diastolic frame. This value corresponds with the estimated Young's value found within the research paper of (Hu et al., 2003), which relates to normal direction to the fibre at the end-diastolic phase.

Table 3.1 Results obtained from 20 frames are reported for 3 phases, in term of median value, presenting our objective quantities; Young's modulus, Iteration No, MS error.

Phase	Frame. No	Young Modulus (kPa)	Iteration No	MSE (%)
Systole	10	325.03	4388	0.0983
Early Diastole	7	140.46	1225	0.0447
Late Diastole	3	15.97	300	0.0376

As presented in the table above, the array of Young's modulus values were iterated until the mean errors value reached a certain threshold, with the number of iterations recorded for each

frame. The Optimal Young's value was achieved, while considering the criteria for the Mean Squared Errors within the loop of the array from 1 to 500 kPa. The optimal values of Young's modulus were determined for each of the 20 frames, corresponding to the systole, early diastole, and late diastole phases. By considering these three phases, the median value of Young's modulus could be reported in the table for the comparison.

Discussion on FEM framework

Regarding the criteria for the Mean Squared Errors (MSE) within the loop of the array from 1 to 500 kPa, the maximum iteration numbers as well as the convergency of Young's values varied in each phase. Therefore, some modification of the stopping criteria, which required to breaks the iteration process are recommended, which resulted in different numbers of iterations for each phase.

The FEM results obtained here may not be entirely representative since two nodes in the spatial domain had to be fixed to solve a linear system with the constraint that displacement is equal to zero. Then, using FEM to enforce boundary conditions may limit the accuracy of the results. However, we were able to perform a multi-step iterative simulation that accounts for the significant deformation experienced by the basal myocardium during a cardiac cycle, which comes close to the reality. In fact, the calculated error of 0.032 was negligible given the large number of nodes that were compared.

3.3.2 VFM Validation Results

The linear virtual fields were applied to the 2D model with linear elastic and isotropic behaviour, and the results of the validation are compared to FEM results achieved by optimization.

The Young's modulus and Poisson ratio was identified for each of the 20 frames, corresponding to the systole, early diastole, and late diastole phases. By considering these three phases, the median value of Young's modulus (16.34, 86.69 and 6.92 kPa) respectively and Poisson ratio (0.51) totally could be reported.

Assuming Poisson's ratio set to 0.49, the values obtained from the VFM identification process ($Y_{\text{VFM}} = 3.25$ kPa) were compared with the values of Young's modulus obtained from finite element analysis ($Y_{\text{FEM}} = 13.95$ kPa) particularly at the end-diastolic phases.

Discussion on VFM results

The results obtained from the Virtual Fields Method (VFM) for Young's modulus were found to be lower compared to those obtained from the Finite Element Analysis (FEA). This difference can be attributed to various factors. For example, the external work pressure was affected directly by virtual fields vector in VFM identification. On the other hand, the FEM optimization involves an iterative process to estimate Young's modulus, which can also contribute to the observed differences. However, VFM is a direct method and does not require iteration, unlike FEA.

3.4 Limitations of the proposed framework

Finite element analysis (FEA) is a popular approach to simulate myocardial behaviour in MATLAB or finite element software. Thus, we proposed an improved approach using the inversion algorithm based on FEM optimization to find mechanical properties as well as VFM validation. The virtual fields method (VFM) is alternative of inverse method that does not require iteration, unlike the FEMU. However, the challenge is to choose the appropriate virtual fields and kinematic condition based on the given data.

During preliminary finite element analysis, we discovered two main limitations. Firstly, contour extraction caused errors due to segmentation from one phase to another. We can reduce this limitation by adding more anatomical points to the curve between phases. Secondly, the choice of constitutive law was limited by the **isotropic model** of myocardial behaviour. A more accurate model would consider the anisotropic myocardium behaviour, which can be achieved by simulating fibre orientation.

Finally, loading, and kinematic constraints play an important role in determining myocardial mechanical behaviour. In this study, we applied the observed pressure uniformly over the surface. However, this may not be appropriate, as it neglects the blood's inertia when it enters the LV. Therefore, incorporating this effect in future studies can enhance our understanding of myocardial behaviours.

3.5 Conclusion and suggestion

By using a comprehensive approach that combines Cine-MRI sequences, myocardial contour segmentation, displacement and deformation patterns, inversion algorithms to derive constitutive parameters, and biomechanical metrics (including von Mises, principal stresses, principal or total strain components), our chances would increase to the early detection of cardiac abnormalities. Particularly, as this study was performed on the given patient's data from PETAL project, the future developed framework is expected to determine parameters efficiently for the 3D image data in the future studies. Therefore, the future of VFM and FEM provides detailed insights into the inversion algorithm and facilitates coding in MATLAB, applying the innovative strategy to the even more 3D complex left ventricle models.

CHAPTER 4 ARTICLE 1: ESTIMATION OF ANISOTROPIC PROPERTIES OF CMR PATIENT-SPECIFIC LEFT VENTRICLE USING THE VIRTUAL FIELDS METHOD

This manuscript presents the comparison of isotropic and anisotropic LV models based on VFM approaches. The development of Piecewise (FE-based) VFM framework for LV models consisting of FE meshes is described. The developed model has been contributed to resolve the principal of virtual work (PVW). Especially, this development consists of generating patient-specific (personalized) meshes of LV geometry from Cine-MIR images to identify anisotropic stiffness. Besides, this study contributes to previous research to characterize early cardiac dysfunction caused by doxorubicin therapy.

My contribution to this study includes the development of the inverse VFM-based identification constructing virtual fields by subdomains and 3D reconstruction of patient-specific LV models (80%), collecting the input data from the segmented images (90%), and quantitative analysis (descriptive statistics) of the estimated myocardial stiffness (90%). My contribution to the article includes design and writing of the paper as well.

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4.1 Abstract

Left ventricle (LV) myocardial dysfunction has been recently investigated using the estimation of isotropic myocardial stiffness from Magnetic resonance imaging (MRI). However, Myocardium is known to have a 3D complex geometry with anisotropic stiffness. The assessment of the anisotropy properties characterizes structural changes in myocardium as a consequence of heart failure (HF). From image data, the virtual fields method (VFM) can determine material stiffness in a non-invasive manner. In the present work, the objective is to compare two inverse identification methods, given the isotropic and anisotropic models in the characterization of properties of myocardium in acute lymphoblastic leukemia (ALL) survivors using VFM and MRI.

Two types of VFM approach are presented. Using the first, the virtual displacements) allow whole-field LV to be imposed into VFM formulation and caused to directly estimate two independent parameters from isotropic constitutive relation. With the second, anisotropic parameters are estimated using piecewise (Finite element-based) VFM.

The resulting values showed significant differences between the subjects in comparative study of leukemia survivors, and variance in estimated parameters by two different VFM approach. This approach would be an efficient tool to characterize early cardiac dysfunction. This work elucidates the benefits and shortcomings of using VFM to determine anisotropic parameters of LV myocardium in linear elastic and of using the FEM application to generate meshes of patient-specific LVs from MRI images.

Keywords: Myocardial stiffness; CMR; Anisotropy; virtual field's method; acute lymphoblastic leukemia (ALL); Finite element method.

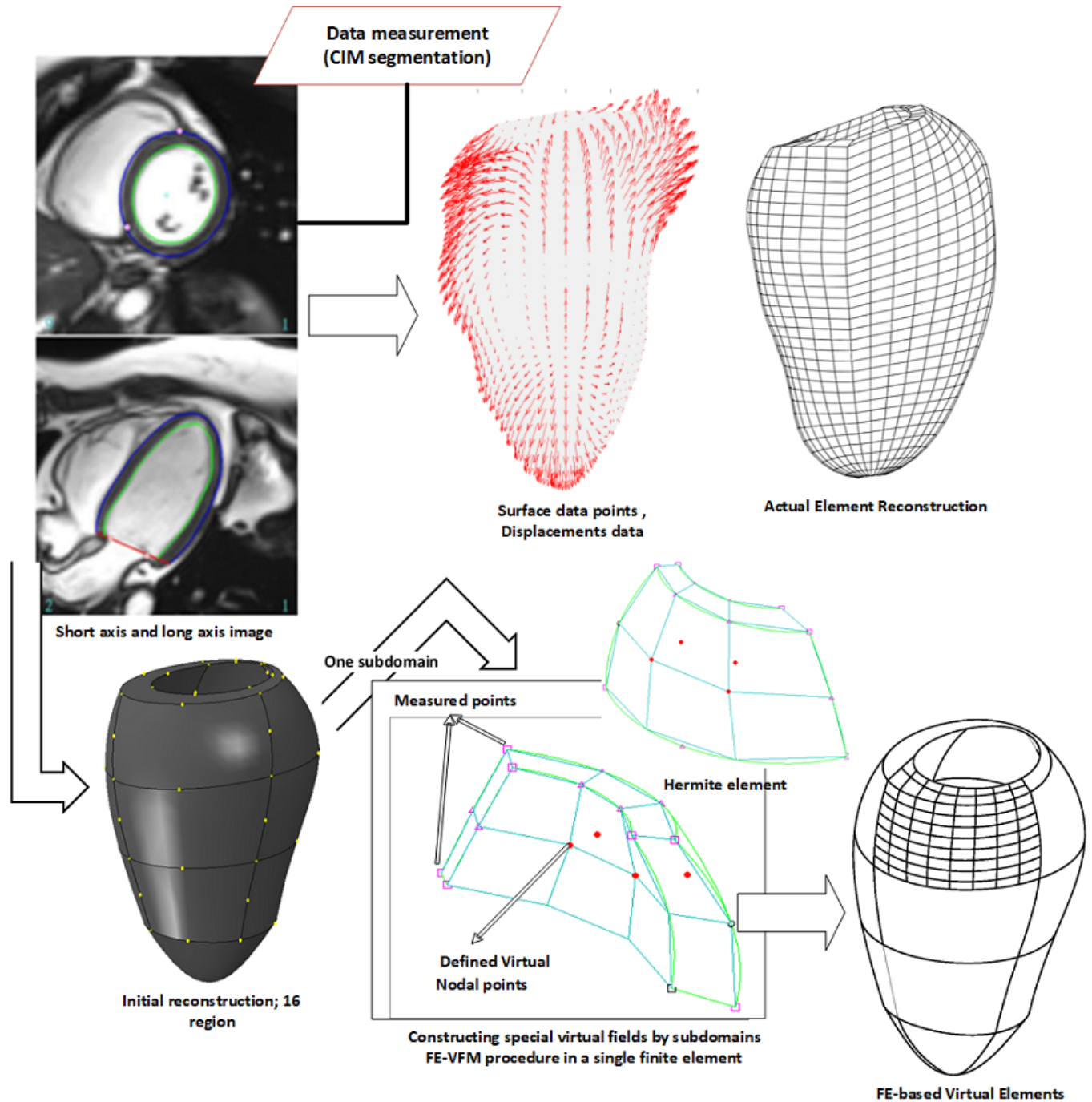


Figure 4.1 Biomechanical Framework from data measurements prepared to virtual field reconstruction into FE meshes.

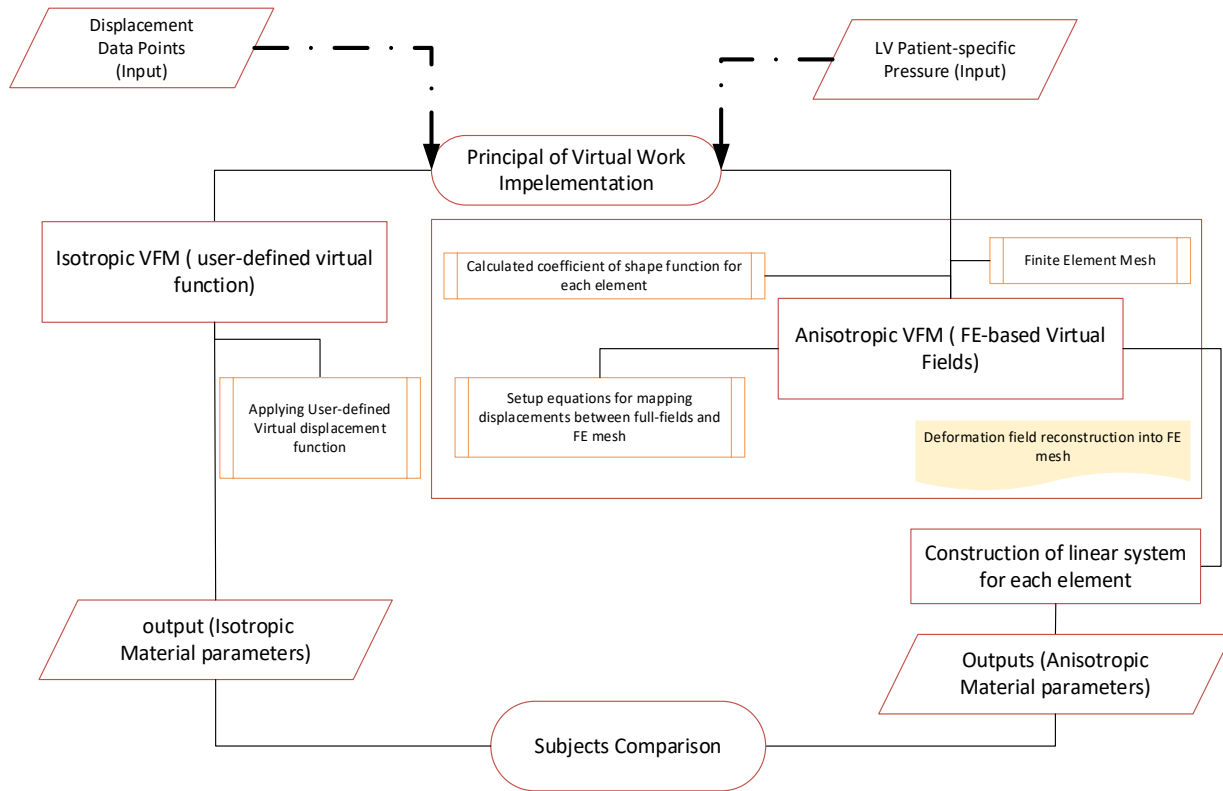


Figure 4.2 Flowchart of the present study structure for the two VFM approaches from implementation to identification.

4.2 Introduction

Cardiac function depends significantly on the myocardium material properties. Heart failure is a general cause of cardiovascular disease that may occur in the presence of changes of these myocardial properties, leading to the systolic and diastolic LV dysfunction (Ennis, et al., 2003) (Zile, et al., 2004). Because of the heart's complex geometry, the characterization of the material properties of the myocardium remains challenging. Knowing the mechanical properties and LV's structure is required for modelling the mechanical behavior of the myocardium (Holzapfel & Ogden, 2009).

Cardiac magnetic resonance (CMR) is considered as the gold standard for the assessment of myocardial function (Ohyama, et al., 2016). CMR tissue tracking methods are non-invasive imaging technic that allows the measurement and analyse of soft-tissue deformation, and, along with modelling methods, the quantification of tissue stiffness (Young, et al., 1995; Glaser, et al., 2012; da Silveira, et al., 2016). Some previous studies assumed that myocardium is an isotropic

hyperelastic material exhibiting non-linear elasticity (Guccione, et al., 1991; Avril, et al., 2010). However, the myocardium can possess either anisotropic or orthotropic properties. For instance, the transversely isotropic Guccione law has been widely used for cardiac modelling (Xi, et al., 2011; Nasopoulou, et al., 2017; Asner, et al., 2016). Despite isotropic material assumption, an anisotropic material model of soft tissue can describe shear anisotropy of fibers in certain directions measured from histology (LeGrice, et al., 1995). This model can determine anisotropic stiffness parameters from magnetic resonance elastography (MRE) data using finite element analysis (Miller, et al., 2015). In these studies, however, constitutive relations which describe the anisotropy behavior are limited to a simplified model and reduced unknown parameters. The elastic parameters in the case of anisotropy have been identified from MRE displacements through iterative inversion methods.

The inversion algorithm converts displacement data into stiffness data. The most popular inverse method for estimating material parameters is finite element model updating (FEMU) (Doyley, et al., 2000). This method allows the material properties to be iteratively updated, thereby minimizing the differences between the displacements predicted by the model and those measured experimentally. In one study, the energy functions were minimized to determine shear modulus distribution from inverse problems, derived from quantitative elasticity imaging, using gradient-based algorithm (Oberai, et al., 2003).

Recently, to assess the spatial stiffness distribution in soft materials, a comparison of two constitutive models using an inverse approach has been performed (Mei, et al., 2018). This study found that the contrast within the mapped shear modulus for the linear elastic model was higher than the hyperelastic model (neo-Hookean model). While the FEMU has been developed and implemented in LV models, FE models of the LV, along with reverse identification methods, are computationally expensive (memory and time consuming) (Avril & Pierron, 2007). A well-recognized alternative to FEMU is the virtual fields method (VFM) which requires full-field data to accurately identify parameters (Grédiac & Pierron, 2006; Nguyen, et al., 2014). This approach is well posed to FE implementation in nonlinear elasticity (Mei, et al., 2021), and directly applied to coherence tomography (CT) imaging data throughout a volume of interest. By introducing the regularized VFM, the small-scale optimization problem is proposed to reconstruct the distribution of the local variation of Young's modulus (Mei, et al., 2021).

Previously, VFM approach has been applied to MRE images of LV geometry. This application showed the advantages of using VFM in the identification of the transversely isotropic models (Miller, et al., 2015). Additionally, the piece-wise virtual fields strategy is more flexible than the general VFM. The VFM based-on the finite element (FE-VFM) was applied to smooth full-field measurements (Kim & Lee, 2021). In this approach, displacement fields were reconstructed into FE meshes using local shape function, as defined locally over the subdomain of the specimen. Then, new virtual fields can be interpolated with nodal actual displacements and internal virtual work integrated for each element. Moreover, generating the FE meshes obtained from real deformation fields as well as choosing the quad element for heterogeneous materials improved the FE-VFM accuracy (Toussaint, et al., 2006; Kaufmann, et al., 2019). Comparing the results of FE-based VFM to the conventional virtual fields that revealed the increased polynomial degrees causes numerical instabilities (Kim, et al., 2020), whereas FE meshes takes the advantage of lower degree of elements functions (Pierron, et al., 2007). Then, piece-wise VFM function does not require the calculation of high-order derivatives of the measured displacement field in one element, comparing to FEMU which calculates iteratively the simulated strain fields from the partial derivatives of shape functions in that element. Furthermore, using the special virtual fields improved VFM results compared to the manually selected virtual fields (Kim, et al., 2020), which should be carefully chosen and respective to the boundary and loading conditions.

The novelty of this paper lies in its application of VFM to patient-specific geometries for LV and its full-field measured displacements. The FE-based VFM approach is implemented to estimate material properties using the collected CMR data in the LV structure of subjects. Two cases of isotropic and anisotropic elasticity are tested with the virtual fields constructed on element meshes. Then, stiffness average values were obtained respect to the LV volume and compared for each LV subject. In particular, in a case study, the results contributes to previous research assessing subtle changes in LV structure and function in a group of long-term childhood survivors, receiving low to moderate dose of doxorubicin therapy, to detect the cardiotoxicity (Aissioui, et al., 2016; Aissioui, 2016; Lapointe, 2016; Begdouri, 2019).

4.3 Theories and Methods

4.3.1 Virtual fields method

The VFM finds material properties from a set of full-field displacements (also known as strains) by applying the principle of virtual work.

$$-\int_V \boldsymbol{\sigma} : \boldsymbol{\epsilon}^* dV + \int_S (\mathbf{T} + \mathbf{P}) \cdot \mathbf{u}^* dS + \int_V \mathbf{b} \cdot \boldsymbol{\epsilon}^* dV = 0 \quad 4.1$$

Where σ is internal stress, ϵ^* represents the virtual strain field, $\mathbf{T}$ stands for the boundary traction forces, $\mathbf{b}$ denotes volume forces, S is the surface, $\mathbf{P}$ denotes the pressure force traction (in this problem), and $\mathbf{u}^*$ represents the virtual displacement field. There is no limit to how many virtual displacement fields might be found that satisfy the principle of virtual work, as described in equation (4.1). equation (4.1) can be simplified by changing the virtual displacement field at the boundaries to zero and removing surface traction acting on only boundaries ($\int \mathbf{T} \cdot \mathbf{u}^* dS$) (Miller, et al., 2018), while pressure force acting on endocardium surfaces was remained. Furthermore, it should be assumed that in absences of volume forces ($\mathbf{b}$) (Kim, et al., 2012), based on those assumptions, equation (4.1) was simplified into equation (4.2):

$$\int_V \boldsymbol{\sigma} : \boldsymbol{\epsilon}^* dV + \int_S \mathbf{P} \cdot \mathbf{u}^* dS = 0 \quad 4.2$$

Where $\mathbf{P}$ is the load or unit pressure per area in the present problem. As a result, equation 4.2 is dependent on a few variables: the internal stress field (which depends on the unknown material parameters and the actual displacement field as discussed below), volume, surface, and internal pressure of Left ventricle.

Equation (4.2) is valid regardless of the kinematically admissible (KA) virtual field ($\mathbf{u}^*$; $\boldsymbol{\epsilon}^*$) applied (i.e., $\mathbf{u}^*=0$) for any boundaries that encompass the entire LV body and $\mathbf{u}^*$ continuous over it. From the constitutive law stating that stress σ is related to strain ϵ , it follows that equation (4.2) directly involves the actual strain field. Therefore, since equation (4.2) includes unknown constitutive parameters of the body, choosing the appropriate virtual field ($\mathbf{u}^*$; $\boldsymbol{\epsilon}^*$) allows them to be determined directly by solving the identification problem.

4.3.2 Constitutive model and parameters

In our study, the soft tissue is clearly assumed linear elastic material while soft tissues usually obey nonlinear elastic behaviours. An anisotropic linear elastic stiffness matrix has 21 independent parameters in the elasticity matrix. By assigning specific directions within the local reference frame of the fibres, it allows for solving independently elastic coefficients (Q_{11} , Q_{33} , Q_{12} , Q_{13} , Q_{44} , Q_{66}) (Mazumder, 2016; Guo, et al., 2016) represented by the engineering constants (E_1 , E_3 , G_{13} , G_{12} , ν_{13} , ν_{23}) (Romano, et al., 2008; Romano, et al., 2014).

The term internal stress has been expanded to include present in detail the stress-strain relationship (Pierron & Grédiac, 2012):

$$\begin{Bmatrix} \sigma_{11} \\ \sigma_{22} \\ \sigma_{33} \\ \sigma_{23} \\ \sigma_{13} \\ \sigma_{12} \end{Bmatrix} = \begin{bmatrix} Q_{11} & Q_{12} & Q_{13} & 0 & 0 & 0 \\ & Q_{22} & Q_{13} & 0 & 0 & 0 \\ & & Q_{33} & 0 & 0 & 0 \\ & & & Q_{44} & 0 & 0 \\ & & & & Q_{66} & 0 \\ & & & & & Q_{66} \end{bmatrix} \begin{Bmatrix} \epsilon_{11} \\ \epsilon_{22} \\ \epsilon_{33} \\ \epsilon_{23} \\ \epsilon_{13} \\ \epsilon_{12} \end{Bmatrix} \quad 4.3$$

Equation (4.3) was substituted into equation (4.2) after terms that have similar material constants were grouped together. The resulting equation is as follows:

$$I_{11}Q_{11} + I_{33}Q_{33} + I_{12}Q_{12} + I_{13}Q_{13} + I_{44}Q_{44} + I_{66}Q_{66} = \int_S P \cdot u^* dS \quad 4.4$$

In the above equation, I_{11} , I_{33} , I_{12} , I_{13} , I_{44} and I_{66} are written to show the linear function of measured strains. It is possible to present the virtual strain fields as below:

$$I_{11} = \int (\epsilon_{11}\epsilon_{11}^* + \epsilon_{22}\epsilon_{22}^*)dV; \quad 4.5$$

$$I_{33} = \int \epsilon_{33}\epsilon_{33}^* dV;$$

$$I_{12} = \int (\epsilon_{22}\epsilon_{11}^* + \epsilon_{11}\epsilon_{22}^*)dV;$$

$$I_{13} = \int (\epsilon_{33}\epsilon_{11}^* + \epsilon_{11}\epsilon_{33}^*) dV;$$

$$I_{44} = 2 \int \epsilon_{12}\epsilon_{12}^* dV;$$

$$I_{66} = 2 \int \epsilon_{13}\epsilon_{13}^* + \epsilon_{23}\epsilon_{23}^*dV;$$

4.3.3 Special virtual fields

The VFM consists of rewriting equation (4.1) so that it includes different virtual fields ($\mathbf{u}^*$, ϵ^*).

A unique virtual field is needed to solve each unknown material parameter when applying the VFM. Therefore, considering equation (4.1), six different virtual fields (labelled I_{11} to I_{66} ; e.g., $\mathbf{u}^{*1}$) have been implemented because there are six unknown material parameters that need to be solved (i.e., Q_{11} , Q_{33} , Q_{12} , Q_{13} , Q_{44} , and Q_{66} .)

Moreover, the special virtual fields are applied in VFM by assuming that 5 of the 6 parameters I_{ij} are zero, whilst the sixth one is equal to 1 m³ (Grédiac, et al., 2002).

with $\mathbf{u}^{*1}$; $I_{11} = 1$, $I_{22} = 0$, $I_{33} = 0$, $I_{44} = 0$, $I_{55} = 0$, $I_{66} = 0$ and

$$Q_{11} = \int_S \mathbf{P} \cdot \mathbf{u}^{*1} dS \quad 4.6$$

The specialization constraints related to each constitutive virtual displacement field ($\mathbf{u}^{*1}, \mathbf{u}^{*2}, \mathbf{u}^{*3}, \mathbf{u}^{*4}, \mathbf{u}^{*5}$, and $\mathbf{u}^{*6}$) are applied by replacing the one in equation (4.6) That is, when one constraint is assumed to be equal to 1, all other restraints equal 0. With these constraints, equation (4.4) is as follows:

$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ & 1 & 0 & 0 & 0 & 0 \\ & & 1 & 0 & 0 & 0 \\ & & & 1 & 0 & 0 \\ & & & & 1 & 0 \\ & & & & & 1 \end{bmatrix} \begin{Bmatrix} Q_{11} \\ Q_{33} \\ Q_{12} \\ Q_{13} \\ Q_{44} \\ Q_{66} \end{Bmatrix} = \begin{Bmatrix} \int_V \mathbf{P} \cdot \mathbf{u}^{*1} dS \\ \int_V \mathbf{P} \cdot \mathbf{u}^{*2} dS \\ \int_V \mathbf{P} \cdot \mathbf{u}^{*3} dS \\ \int_V \mathbf{P} \cdot \mathbf{u}^{*4} dS \\ \int_V \mathbf{P} \cdot \mathbf{u}^{*5} dS \\ \int_V \mathbf{P} \cdot \mathbf{u}^{*6} dS \end{Bmatrix} \quad 4.7$$

The parameters that resulted from this process were then calculated by considering the terms on the right side of equation (4.7). The details explaining how the specialization and other constraints were implemented are available in (Pierron & Grédiac, 2012).

The virtual displacement field was calculated numerically by expanding the VFM formulation by breaking the entire field up into sub-fields. This process allows the parameters to be estimated with greater accuracy. Hence, the $\mathbf{u}^*$ can be expressed with piece-wise functions serving as the basis of the independent functions expanded over each sub-field. For instance, the piece-wise

functions can be expanded as the basis of polynomials. Similarly, the actual displacements are presented piece-wisely by approximating polynomial shape functions defined for each sub-field (element).

4.3.4 Constructing special virtual fields by subdomains

4.3.4.1 FE-VFM procedure in single subdomain

A general approach has previously been proposed in (Avril, et al., 2008) to create special virtual fields expanded by polynomials. The present work defines the virtual fields by subdomains where model geometry consists of N certain domains (16). Each domain is divided into q sub-domain Figure 4.3. Consequently, The virtual displacements $\mathbf{u}^*$ defined in piece-wise manner (finite elements) over each subdomain. The integrals in equation (4.5) write in this case:

$$\begin{aligned}
 I_{11} &= \sum_{i=1}^q \int_{V_i} \epsilon_{11} \epsilon_{11}^* + \epsilon_{22} \epsilon_{22}^* dV \\
 &\vdots \\
 I_{66} &= \sum_{i=1}^q \int_{V_i} \epsilon_{13} \epsilon_{13}^* + \epsilon_{23} \epsilon_{23}^* dV
 \end{aligned} \tag{4.8}$$

The full description of equation (4.8) is shown in (Toussaint, et al., 2006).

Where V_i and S_i are the volume and surface of each subdomain, respectively.

The selection of the shape of the subdomains (element) means that $\mathbf{u}^*$ could be written as the product of the shape functions N_i and nodal virtual displacements $\mathbf{u}_i^*$. This expression is also relevant to the finite element method, as described in (Li, 2008) .

$$\mathbf{u}^* = \sum_{i=1}^{n_{nodes}} N_i \mathbf{u}_i^* = \mathbf{N} \mathbf{u}^* \tag{4.9}$$

Where n_{nodes} expresses how many nodes are in each subdomain.

And $\mathbf{u}^*$ writes in Cartesian coordinate as:

$$u^* = \begin{bmatrix} u_{x1}^* \\ u_{y1}^* \\ u_{z1}^* \\ \vdots \\ u_{xn_{node}}^* \\ u_{yn_{node}}^* \\ u_{zn_{node}}^* \end{bmatrix} \quad 4.10$$

And (N_i) terms are the shape functions (Lamata, et al., 2011).

The virtual strain components in the subdomains are obtained by differentiation of the equation (4.9), that is:

$$\boldsymbol{\varepsilon}^* = \mathbf{B} \mathbf{u}^* \quad 4.11$$

Where $\mathbf{B}$ is a 6×24 linear differential operator:

Where $\mathbf{B}$ is the strain matrix which relates virtual nodal displacements to each element of virtual strain. The matrix is composed of the partial derivatives of the shape functions with respect to the global Cartesian directions.

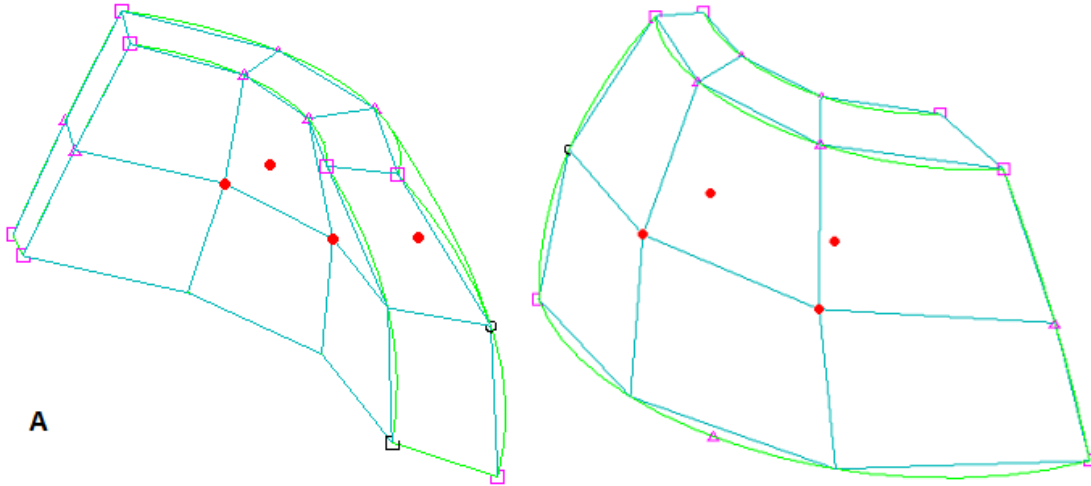


Figure 4.3 Cubic Hermite subdomain (warped by cubic basis functions (Lamata, et al., 2011); (A) divided into 6 element mesh, by 4 new node coordinates: 2 red spheres (right), 2 sphere (left) located on endocardium and epicardium respectively (Lamata, et al., 2014)

4.3.5 Data set and Materials

4.3.5.1 Patients

In the present study, the case study concept is to understand if cardiotoxicity may trigger remodelling of LV geometry after doxorubicin therapy (Lipshultz, et al., 2005; Adams & Lipshultz, 2005). It is associated with changes in myocardial stiffness in systolic contraction and diastolic filling. In systolic dysfunction, the LV volume expands, and LV thickness become thinner and could not contract properly (Di Somma, et al., 2000). Similarly, in diastolic dysfunction, LV relaxes abnormally, and filling of the LV is incomplete.

To realize the remodelling issue caused by the cardiotoxicity, a subset of acute lymphoblastic leukemia (ALL) survivors was retrospectively included and separated into 3 groups according to their prognostic risk: standard risk (SR, n=3), High risk (HR, n=3) and High-risk group (HRdex, n=3) who received dexrazoxane with a cardio protective medication (Marcoux, et al., 2017). One-way analysis of variance (ANOVA) on the ranks (also called Kruskal-Wallis test) was performed on the estimated parameters (stiffness) to investigate significant differences between groups. .

4.3.5.2 CMR acquisition and analysis

The CMR acquisitions were performed on a Siemens Skyra 3T MR system using an 18-channel phased-array body matrix coil and included an ECG-gated cine TruFISP sequence (14 slices in short axis and 5 slices in long axis, slice thickness 8mm, repetition time 34.6ms, effective echo time 1.2ms, flip angle 38°, IPAT factor 3, matrix 208x210 and in-plane pixel size 1.25x1.25 mm).

Using Cardiac Image Modeler (CIM v8.1.5, University of Auckland), the initial LV model was created by fitting 16 cubic Hermite elements, to connect 34 nodes (Hasaballa, et al., 2019). Corresponding to the endocardial and epicardial surface points of the LV at each cardiac frame; our model was built up in cardiac coordinate (prolate-spheroidal).

4.3.5.3 LV pressure measurements

As indicated in Figure 4.4, the simulated Patient-specific LV pressures (both in systole and diastole), were derived from Physio Flow measurements at rest (Manatec Biomedical, Macheren, France) and CircAdapt simulations (Gamba, 2019). There are 25 cardiac time points, starting

from systole at ($t=0$) to the end of diastole at ($t=25$). According to the known pressure-volume loop, early diastole was assumed to start around (at $t=11-12$) and continue until ($t=19-20$), where the late diastole was supposed to begin and end up at 25th frame.

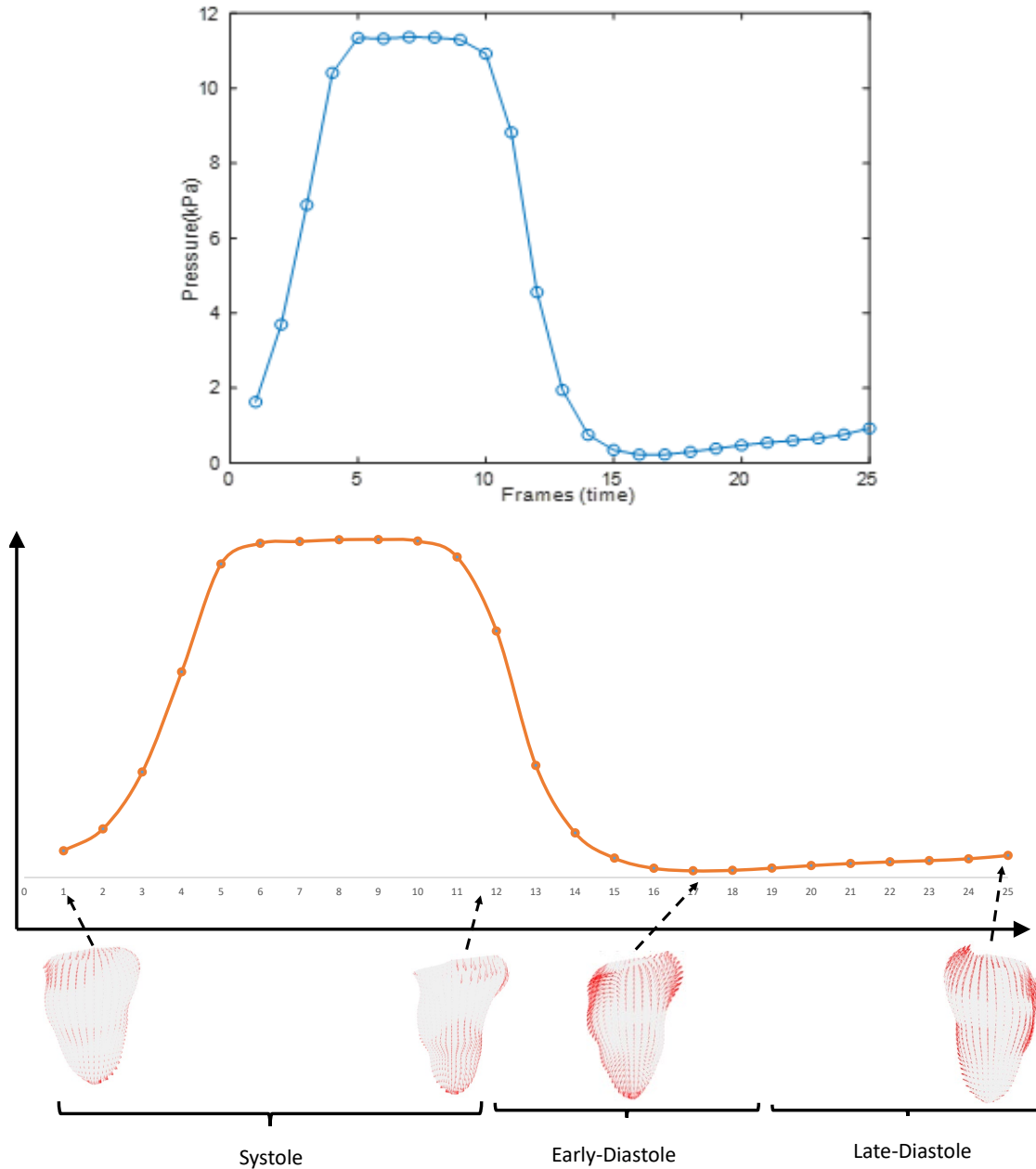


Figure 4.4 Ventricular pressure simulated, at LV Ejection (Systole) and filling (Diastole); b) LV Deformation displayed in Systolic phases ($t=1$ to $t=11$, End-systole), Early diastole ($t=12-18$), Late-diastole started from $t=18$ to 25 (end-diastole)

4.3.6 Inverse VFM in isotropic LV

The common strategy is to apply user-defined virtual fields (UDVFs), using expansion bases like polynomials or harmonic functions. The user must thoroughly comprehend the approach in order to be able to choose these fields in a way that can provide the efficiency of these user-defined virtual fields. The user of VFM can choose mathematical functions as virtual fields, which can be called as user defined (or manually selected) virtual fields.

The Isotropic model of LV was tested using the user defined VFM, leading to so-called analytical virtual fields, to estimate two independent parameters Q_{11} , Q_{13} , represented as more commonly used constants: Young's modulus, and Poisson's ratio in the elasticity matrix. The isotropic VFM was tested with harmonic displacement fields on the LV geometry model, assuming two hyperboloid functions, which are kinematically admissible to the LV displacement field. The geometry model was collected from the CMR data.

Considering the nature of the cardiac pressure, its response, and its value at each cardiac time point, the right-hand side equation (4.1) can be written in terms of solely the virtual displacements on the endocardium surface over the cardiac cycle. Using the transformation from prolate-spherical coordinate $(\lambda, \varnothing, \theta)$ to Cartesian coordinate (x, y, z) , manually defined virtual fields were applied to show a displacement function of undeformed coordinates $(x, y, \text{ and } z)$. The following displacement functions can be expressed in LV space model (F. B. Pierron).

The resulting virtual displacement field applied was:

$$\begin{cases} u_{\lambda}^* = -2 \sin(\varnothing) \\ u_{\varnothing}^* = 0 \\ u_{\theta}^* = -\lambda \sin(2\varnothing) \end{cases} \quad 4.12$$

Where λ is the parameter of the elliptic, $\varnothing$ is the parameter of hyperboloid, and θ is the azimuthal angle which all controlled the LV shape in apex, basal and walls. They are all normalized by the density of the left ventricle $(\lambda / \rho, \varnothing / \rho, \theta / \rho)$.

The Sinus function, polarized in the $\varnothing$ direction, was used since it closely matched the harmonic displacement field measured experimentally, in which λ & θ displacement was applied on both walls of LV.

The resulting virtual normal strain fields converted into Cartesian coordinate were:

$$\begin{aligned}
 u_x^* &= \frac{\cosh(\lambda) \sin(\emptyset) \cos(\theta)}{\sqrt{\sinh^2(\lambda) + \sin^2(\emptyset)}} u_\lambda^* + \frac{\sinh(\lambda) \cos(\emptyset) \cos(\theta)}{\sqrt{\sinh^2(\lambda) + \sin^2(\emptyset)}} u_\emptyset^* - \sin(\theta) u_\theta^* \\
 u_z^* &= \frac{\sinh(\lambda) \cos(\emptyset)}{\sqrt{\sinh^2(\lambda) + \sin^2(\emptyset)}} u_\lambda^* + \frac{\cosh(\lambda) \sin(\emptyset)}{\sqrt{\sinh^2(\lambda) + \sin^2(\emptyset)}} u_\emptyset^* \\
 u_y^* &= \frac{\cosh(\lambda) \sin(\emptyset) \sin(\theta)}{\sqrt{\sinh^2(\lambda) + \sin^2(\emptyset)}} u_\lambda^* + \frac{\sinh(\lambda) \cos(\emptyset) \sin(\theta)}{\sqrt{\sinh^2(\lambda) + \sin^2(\emptyset)}} u_\emptyset^* + \cos(\theta) u_\theta^*
 \end{aligned} \tag{4.13}$$

And the resulting in shear strains: ϵ_{12} , ϵ_{13} and ϵ_{23} as well ($\epsilon_6 = \epsilon_{12} = \epsilon_{13} = \epsilon_{23}$) and

$$\epsilon_{11} = \epsilon_{22} = \epsilon_{33}.$$

With the chosen virtual displacement field, equation (4.2) is then simplified to:

$$\begin{aligned}
 & Q_{11} \left(\int_V (\epsilon_{11} \epsilon_{11}^* + \epsilon_{22} \epsilon_{22}^* + \epsilon_{33} \epsilon_{33}^*) dV \right) + \\
 & Q_{22} \left(\int_V (\epsilon_{11} \epsilon_{22}^* + \epsilon_{22} \epsilon_{11}^*) + (\epsilon_{11} \epsilon_{33}^* + \epsilon_{33} \epsilon_{11}^*) + (\epsilon_{22} \epsilon_{33}^* + \epsilon_{33} \epsilon_{22}^*) dV \right) + \\
 & \left(\frac{Q_{11} + Q_{22}}{2} \right) \left(\int_V (\epsilon_{12} \epsilon_{12}^* + \epsilon_{13} \epsilon_{13}^* + \epsilon_{23} \epsilon_{23}^*) dV \right) \\
 & = \int_S P u_1 \cdot u_1^* dS
 \end{aligned} \tag{4.14}$$

A sum was used to approximate the integrals in the equation (4.14) of virtual work. Equation (4.12) and (4.13) were substituted into equation (4.14) written in terms of the Young's modulus, E and Poisson's ratio, ν .

$$\begin{aligned}
 E &= \frac{W_{ext}^{(1)} (1 + \nu) (1 - 2\nu)}{(1 - \nu)a^{(1)} + \nu b^{(1)} + \frac{(1 - 2\nu)}{2} c^{(1)}} \\
 \nu &= \frac{W_{ext}^{(2)} \left(a^{(1)} + \frac{c^{(1)}}{2} \right) - W_{ext}^{(1)} \left(a^{(2)} + \frac{c^{(2)}}{2} \right)}{W_{ext}^{(2)} (a^{(1)} - b^{(1)} + c^{(1)}) - W_{ext}^{(1)} (a^{(2)} - b^{(2)} + c^{(2)})}
 \end{aligned} \tag{4.15}$$

Where the coefficients of a, b, c and W_{ext} were found:

$$\begin{aligned}
a &= \int_V \left(\epsilon_{11} \frac{\partial u^*}{\partial x_{11}} + \epsilon_{22} \frac{\partial u^*}{\partial x_{22}} + \epsilon_{33} \frac{\partial u^*}{\partial x_{33}} \right) dV \\
b &= \int_V \left((\epsilon_{22} + \epsilon_{33}) \frac{\partial u^*}{\partial x_{11}} + (\epsilon_{11} + \epsilon_{33}) \frac{\partial u^*}{\partial x_{22}} + (\epsilon_{11} + \epsilon_{22}) \frac{\partial u^*}{\partial x_{33}} \right) dV \\
c &= \int_V \left(\left(\frac{\partial u^*}{\partial x_{21}} + \frac{\partial u^*}{\partial x_{12}} \right) \epsilon_{12} + \left(\frac{\partial u^*}{\partial x_{31}} + \frac{\partial u^*}{\partial x_{13}} \right) \epsilon_{31} + \left(\frac{\partial u^*}{\partial x_{32}} + \frac{\partial u^*}{\partial x_{23}} \right) \epsilon_{23} \right) dV \\
W_{ext} &= \int_S P u_1 \cdot u_1^* dS
\end{aligned} \tag{4.16}$$

As a result, user-defined virtual fields that enforce zero virtual displacements on the boundaries as well as separate Young's modulus from other shear parameters can easily be developed in regular geometries.

Then, for one subject of each group (HR, HRdex, SR), systolic and diastolic frames (see 4.3) were examined to assess the impact on the estimated parameter.

4.3.7 Anisotropic VFM inversion approach

With the user defined VFM, the accurate estimates of the modulus are obtained when the chosen virtual displacement field pattern closely matched the measured displacement field (Miller, et al., 2018). When dealing with the heart and other such complex geometries, it is very challenging to apply user-defined virtual fields. For this reason, the previous study investigated the advantages of the optimized FE-based VFM (Miller, et al., 2018) when used to solve for a virtual displacement field so that the estimated parameters would contain as little variance as possible.

The isotropic stiffness is not directly comparable to any of the anisotropic properties (Babaei, et al., 2021). Then, in order to provide clear explanation leading to the comparison study, we introduced two VFM approach for the isotropic and anisotropic LV case. The identified parameters from both approaches are supposed to compare patient subjects in the result section 4.4.

4.3.7.1 Cubic Hermite sub-domains

The first step was to represent the LV body into a specific number of sub-domains. It initially consisted of regular cubic hexahedral elements. In geometry, a volume Cubic Hermite shape represented with Hermite interpolation of basic functions has 6 faces, 12 edges, and 8 vertex

corners (Wang, 2012) . The steps for creating 16 cubic Hermite mesh of a left ventricle (LV) were performed in CIM. Then data were prepared, collected (Lamata, et al., 2014) and stored in nodal and element format for import in MATLAB (nodal values and derivatives with respect to the local coordinate). Figure 4.5 shows how to subsequently convert the Hermite subdomain into two set of points of the endocardium and epicardium and build up the different individual meshes for the finite element formulation. Therefore, the model was recreated by building up hexahedral elements from discretization of initial cubic Hermite meshes having solely their own spatial parameters.

4.3.7.2 Construction of the linear system

The second step was to discretize each Hermite element into the smaller elements (sub-domains) and generate 4 sub-Hermite meshes (Figure 4.3), which have 2 nodes on endocardium and epicardium surfaces with unknown local coordinates that could be prepared to place in piecewise-defined polynomials. Therefore, in equation (4.5), it is considered:

Each sub-Hermite has 8 nodes and is implemented into integrals as:

$$I_{ij} = \sum_{q=1}^4 \int_{V^{(q)}} \epsilon_{ij}^{(q)} (\epsilon_{ij,q}^*) dx dy dz \quad 4.17$$

Where $i = 1,2,3$

$$j = 1,2,3 \quad q = 1,2,3,4$$

The virtual displacements, in each subdomain, can be written as follows:

$$u^{*(q)} = \sum_{i=1}^n N_i^{(q)} u_i^{*(q)} = \mathbf{N} \mathbf{u}^* \quad n = 8 \quad 4.18$$

$$\epsilon_{ij,q}^* = \mathbf{B} \mathbf{u}^{*(q)}$$

Where the matrix of shape functions is written:

$$N = \begin{bmatrix} \overbrace{N_1} & \overbrace{N_2} & \overbrace{N_3} & \overbrace{N_4} \\ N_1 & N_2 & N_3 & N_4 \\ \overbrace{N_5} & \overbrace{N_6} & \overbrace{N_7} & \overbrace{N_8} \\ N_5 & N_6 & N_7 & N_8 \end{bmatrix}$$

And the components of matrix B are only determined by space-derivation of the shape functions of each hermit element:

$$B = \begin{bmatrix} \frac{\partial N_i}{\partial x} & 0 & 0 \\ 0 & \frac{\partial N_i}{\partial y} & 0 \\ 0 & 0 & \frac{\partial N_i}{\partial z} \\ \frac{\partial N_i}{\partial y} & \frac{\partial N_i}{\partial x} & 0 \\ \frac{\partial N_i}{\partial z} & 0 & \frac{\partial N_i}{\partial x} \\ 0 & \frac{\partial N_i}{\partial z} & \frac{\partial N_i}{\partial y} \end{bmatrix} = \begin{bmatrix} \frac{\partial N_1}{\partial x} & 0 & 0 & \frac{\partial N_4}{\partial x} & 0 & 0 \\ 0 & \frac{\partial N_1}{\partial y} & 0 & 0 & \frac{\partial N_4}{\partial y} & 0 \\ 0 & 0 & \frac{\partial N_1}{\partial z} & 0 & 0 & \frac{\partial N_4}{\partial z} \\ \frac{\partial N_1}{\partial y} & \frac{\partial N_1}{\partial x} & 0 & \frac{\partial N_4}{\partial y} & \frac{\partial N_4}{\partial x} & 0 \\ \frac{\partial N_1}{\partial z} & 0 & \frac{\partial N_1}{\partial x} & \frac{\partial N_4}{\partial z} & 0 & \frac{\partial N_4}{\partial x} \\ 0 & \frac{\partial N_1}{\partial z} & \frac{\partial N_1}{\partial y} & 0 & \frac{\partial N_4}{\partial z} & \frac{\partial N_4}{\partial y} \\ \hline \frac{\partial N_5}{\partial x} & 0 & 0 & \frac{\partial N_8}{\partial x} & 0 & 0 \\ 0 & \frac{\partial N_5}{\partial y} & 0 & 0 & \frac{\partial N_8}{\partial y} & 0 \\ 0 & 0 & \frac{\partial N_5}{\partial z} & 0 & 0 & \frac{\partial N_8}{\partial z} \\ \frac{\partial N_5}{\partial y} & \frac{\partial N_5}{\partial x} & 0 & \frac{\partial N_8}{\partial y} & \frac{\partial N_8}{\partial x} & 0 \\ \frac{\partial N_5}{\partial z} & 0 & \frac{\partial N_5}{\partial x} & \frac{\partial N_8}{\partial z} & 0 & \frac{\partial N_8}{\partial x} \\ 0 & \frac{\partial N_5}{\partial z} & \frac{\partial N_5}{\partial y} & 0 & \frac{\partial N_8}{\partial z} & \frac{\partial N_8}{\partial y} \end{bmatrix}$$

Hence, the volume was broken up into the smaller size elements, and formulations of piece-wise VFs were implemented to each of them. Consequently, this way of mesh discretization was developed to generate the finer elements at where last step reached to totally 1024 elements.

4.3.7.3 Final system

Finally, equation (4.1) was eventually resulted in a linear system of equations with unknown displacements: $\{u_{x12}^*, u_{y12}^*, u_{z12}^*, u_{x11}^*, u_{y11}^*, u_{z11}^*\}$.

Each of these equations was used to find a virtual displacement. Furthermore, the vector of unknown virtual displacements is presented as follows:

$$[P]\{u^{*(q)}\} = \{Q\} \quad 4.19$$

Consequently, unknown parameters in constitutive relation could be determined from equation 4.7.

Note: The equations of liner system 4.19 are conditions which are required to obtain special virtual fields between virtual nodal displacements (Toussaint, et al., 2006). The matrices **P** and **Q**

are created by assembling the subdomains that make up Hermit shape. The number of conditions needed to obtain special virtual fields is equivalent to the number of constitutive parameters that need to be determined. In the case of transversely anisotropic material, this number is five, whereas it is six in full anisotropic.

Constitutive parameters

For the elastic material, Q_{11} , Q_{33} are the tension-compression parameters Q_{44} , Q_{66} are the shear parameters, and Q_{12} , Q_{13} describes the compressibility of the material:

$$Q_{11} = \frac{E_1 (E_3 - \nu_{31}^2 E_1)}{(1 + \nu_{12})D}$$

$$Q_{12} = \frac{E_1 (\nu_{12} E_3 + \nu_{31}^2 E_1)}{(1 + \nu_{12})D}$$

$$Q_{13} = \frac{E_1 (\nu_{31} E_3 E_1)}{D}$$

$$Q_{33} = \frac{(1 - \nu_{12}) E_3^2}{D}$$

$$Q_{44} = \mu_{13}$$

$$Q_{66} = \mu_{12}$$

$$D = (1 - \nu_{12})E_3 - 2\nu_{31}^2 E_1$$

4.3.7.4 Selection of constitutive parameters for identification

Results from the isotropic formulation were reported in terms of (E , ν) Young's modulus and Poisson Ratio for all direction. Using the rule-based method and assuming that the direction of the fiber matches $[0 \ 0 \ 1]$ z-axis, results from the anisotropic formulation were reported in terms of fiber Young's modulus (E_3), transverse Young's modulus (E_1), transverse shear modulus (G_{13}) and Poisson's ratio (ν_{31}). We should fix a value of Poisson's ratio in a plane where we can show fibre direction (plane 1-3). Assuming plane 1-3 is orthotropic (fibre direction in Z axis), then in-plane parameters (E_1 , E_3 , G_{13} , ν_{13}) presenting anisotropic properties would have obtained from elasticity matrix.

4.4 Results

4.4.1 Isotropic stiffness in LV subjects

Following the method, which was presented in section 4.3.5, all the phases were processed one by one. The proposed parameters were identified in each phase. Differences were found in the estimated active stiffness of left ventricle during systole between groups for Young's modulus (). The median value for the estimated Young's modulus was (9.5 kPa) in SR and increased in HR (13.9 kPa) as compared to HRdex (8.5 kPa). The Poisson's Ratio was set to 0.49 for all subjects. Moreover, differences were displayed in early diastole and late diastole between groups for the passive estimated parameters (Young's modulus); Regardless of early-diastole phases, HR results were the largest (42.1 kPa) as compared to SR (39.1 kPa) and HRdex (34.2 kPa) in late diastole (Figure 4.7). However, the reported p-value indicates the difference was not statistically significant at the 5% level ($P\text{-value} > 0.05$) between SR, HR, and HRdex (Gamba, 2019).

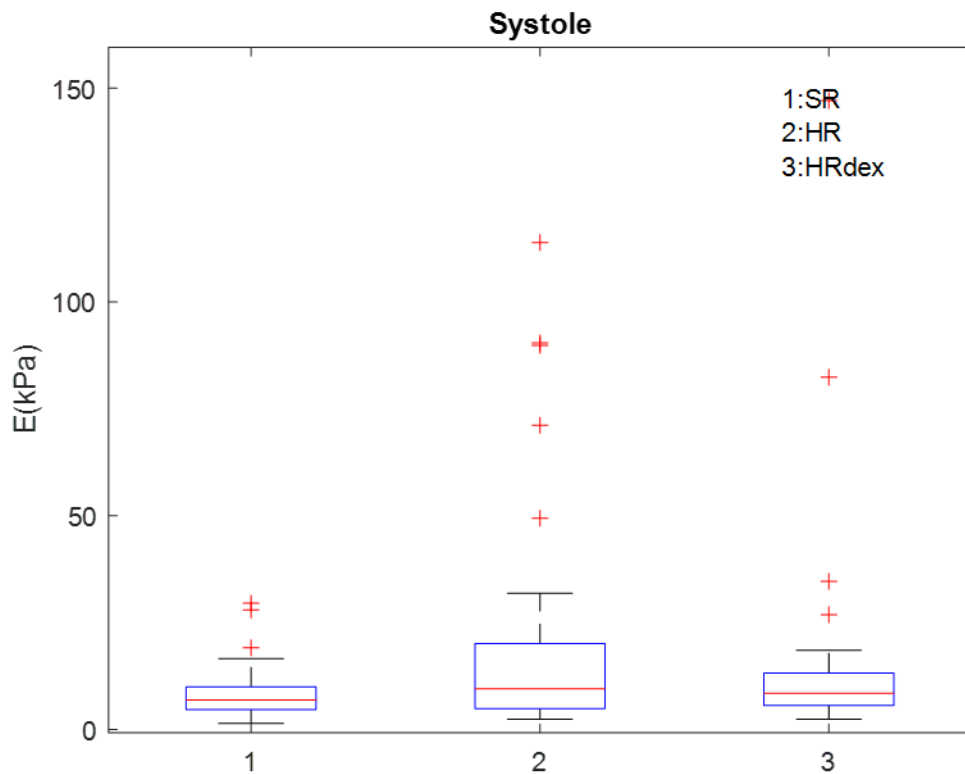


Figure 4.5 Boxplots of the estimated Young's modulus, using isotropic formulation, for the HR, SR, HRdex groups at systole. For each subject, the boxplots display standard deviation, median, mean, and outliers. (P=0.0748)

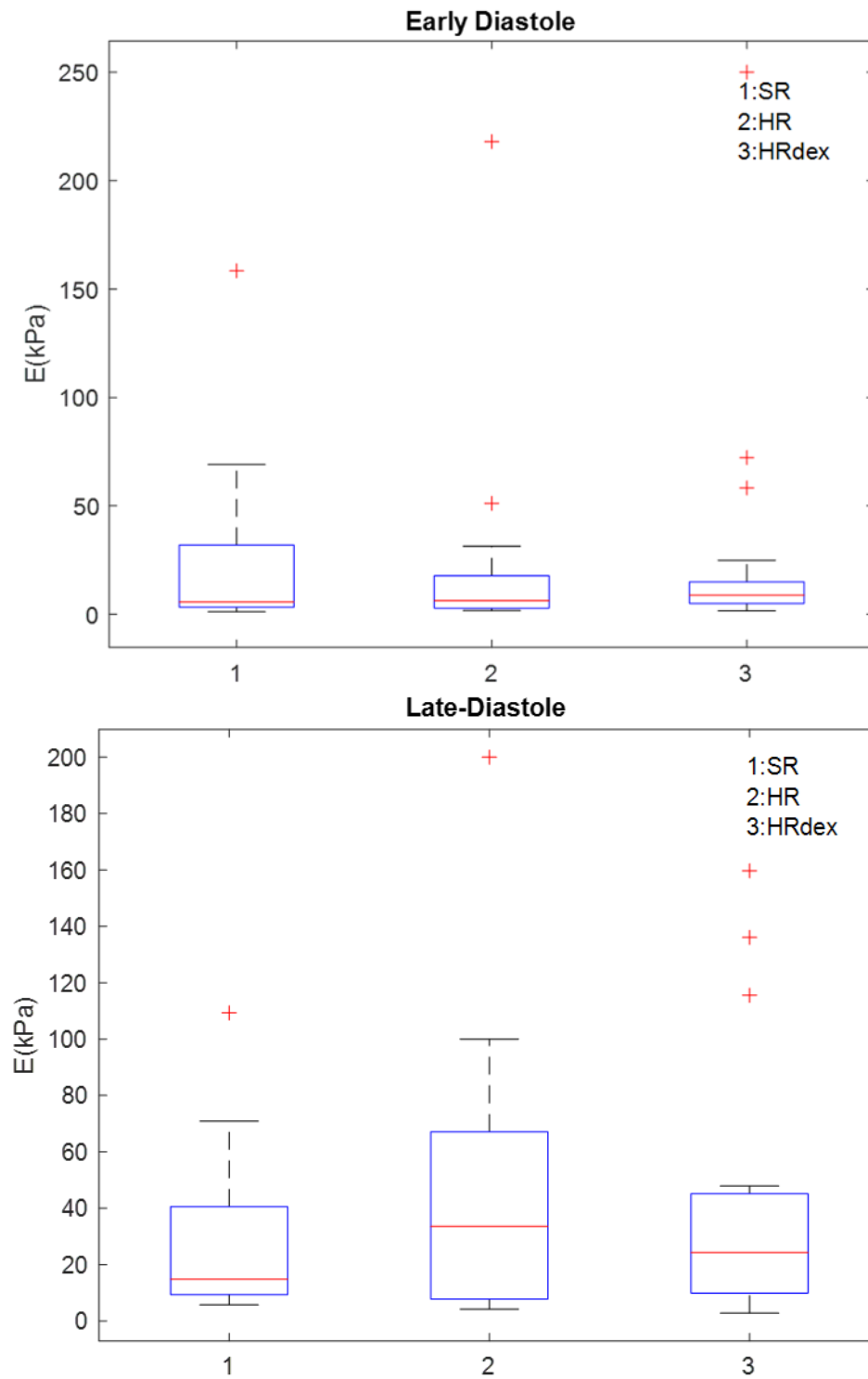
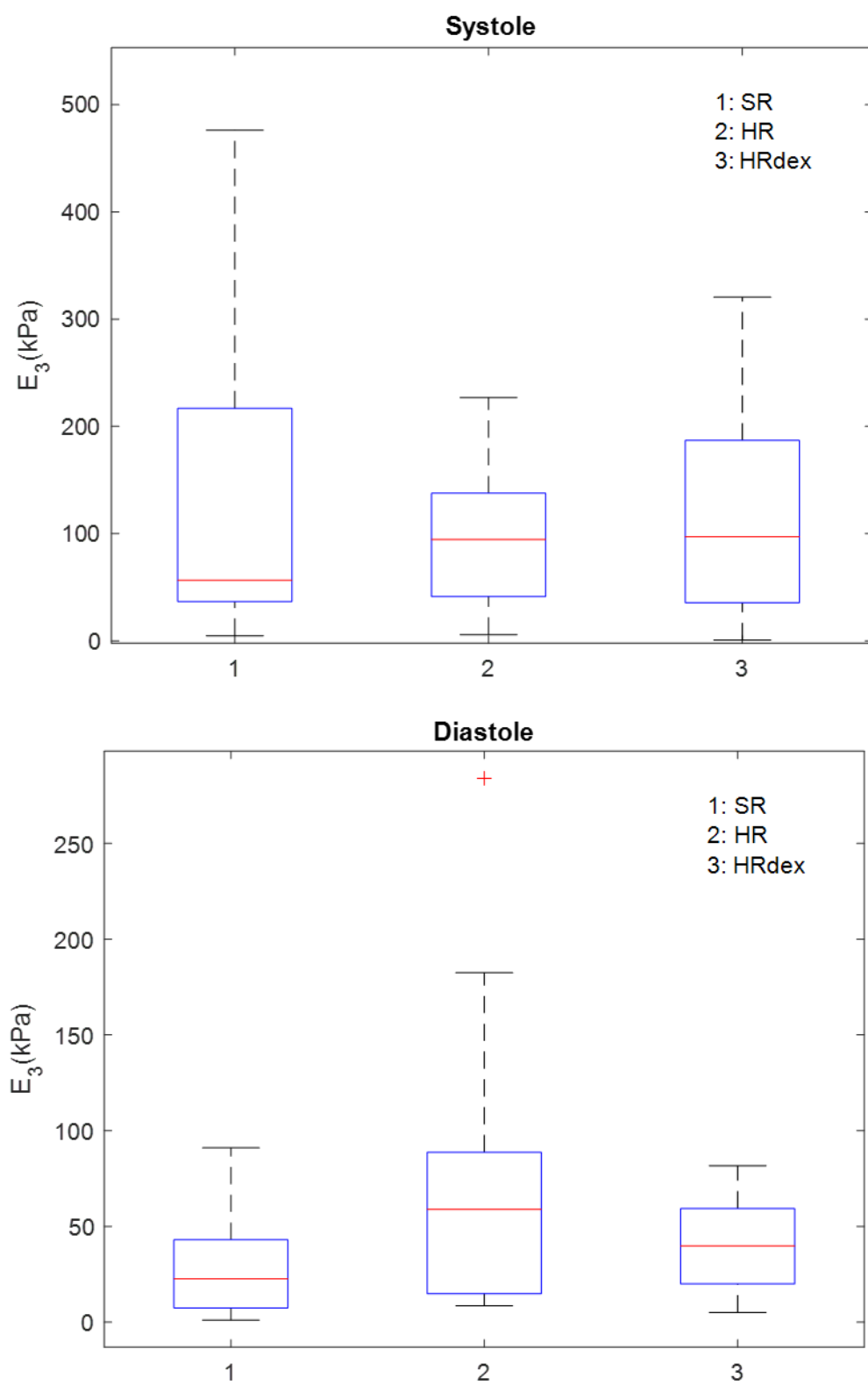


Figure 4.6 Results of the estimated Young's modulus, using isotropic formulation, for ALL subjects; Early diastole ($P = 0.8844$), and late diastole (Right) ($P = 0.5529$)

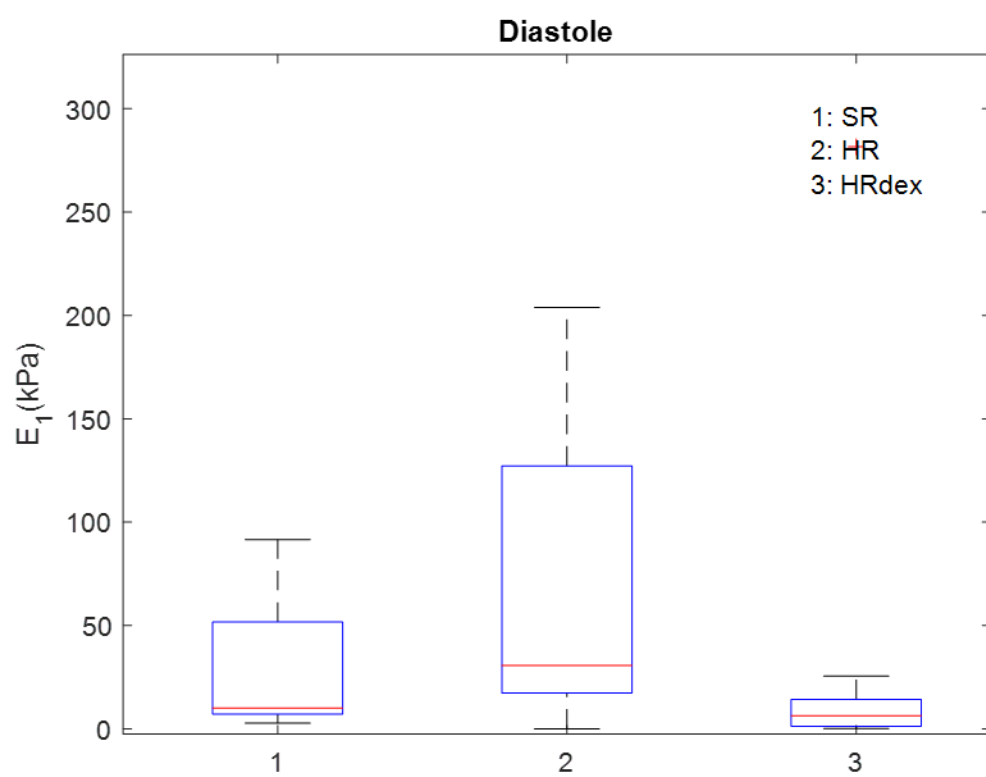
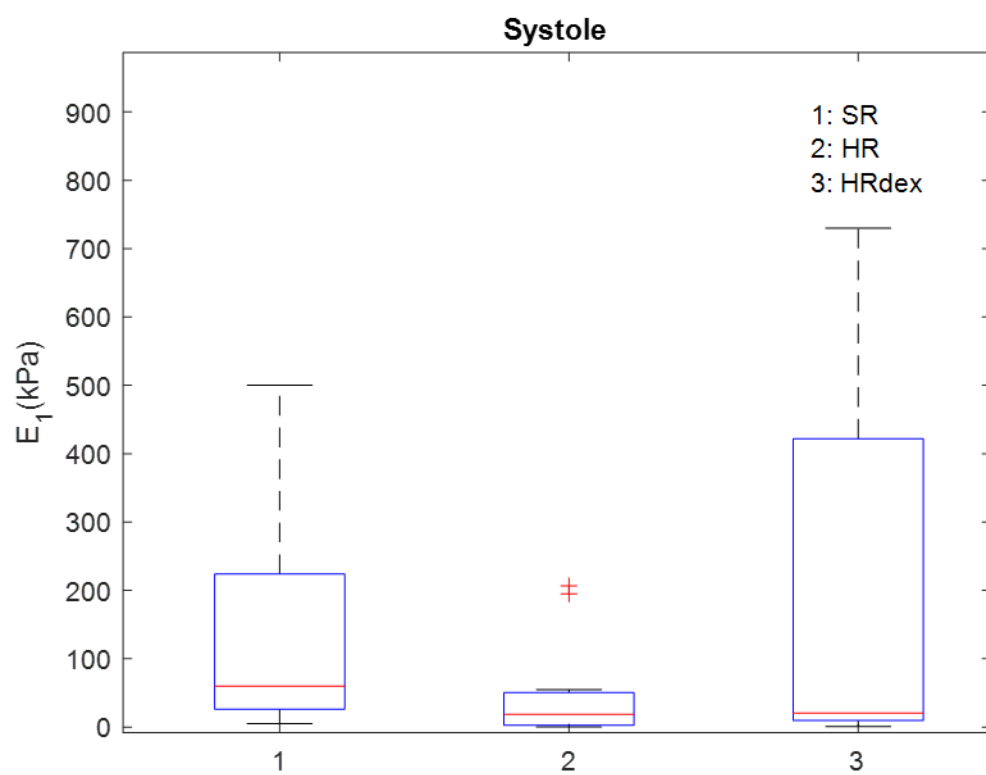
4.4.2 Anisotropic stiffness in LV subjects

The results showed a clear dependence of estimation of shear and Young's modulus on the cardiac pressure (during active systole and passive diastole) when VFM was applied. Also, modulus values were relative to the fibre direction, assuming a fibre direction assigned a Young's modulus (E_3) with the Z axis. The results were obtained using the piece-wise VFM formulation. Because the LV was anisotropic, the pairs of Young's modulus (E_1 and E_3), were not equal (Figure 4.7.a, Figure 4.7.b).

Fibre Young's modulus (E_3) are higher in HR (94.5 kPa) as compared to SR (56 kPa) and HRdex during systole and diastole (SR: 22.7 kPa, HR: 58.9 kPa, HRdex: 39.7 kPa) (Figure 4.7.b). But the transverse Young's modulus (E_1) resulted in HR values (18 kPa) are lower as compared to (SR: 59 kPa, HRdex: 20kPa) in systole. However, (E_1) HR values (41.4 kPa) are higher than SR (12.5 kPa) and HRdex (4.6 kPa) in diastole. The shear modulus G_{13} are reported in diastole for SR, HR and HRdex (33.1 kPa, 32.8 kPa, 28.7 kPa respectively). Results showed the fibre shear modulus G_{13} in SR group was statistically significant than the HR groups. Moreover, anisotropic VFM is validated by optimized approach of (Miller, et al., 2018) , resulting in the estimated parameters E_1 (61.5 kPa), E_3 (67.1 kPa), G_{13} (34.9 kPa) and G_{12} (33.5 kPa) respectively.



a



b

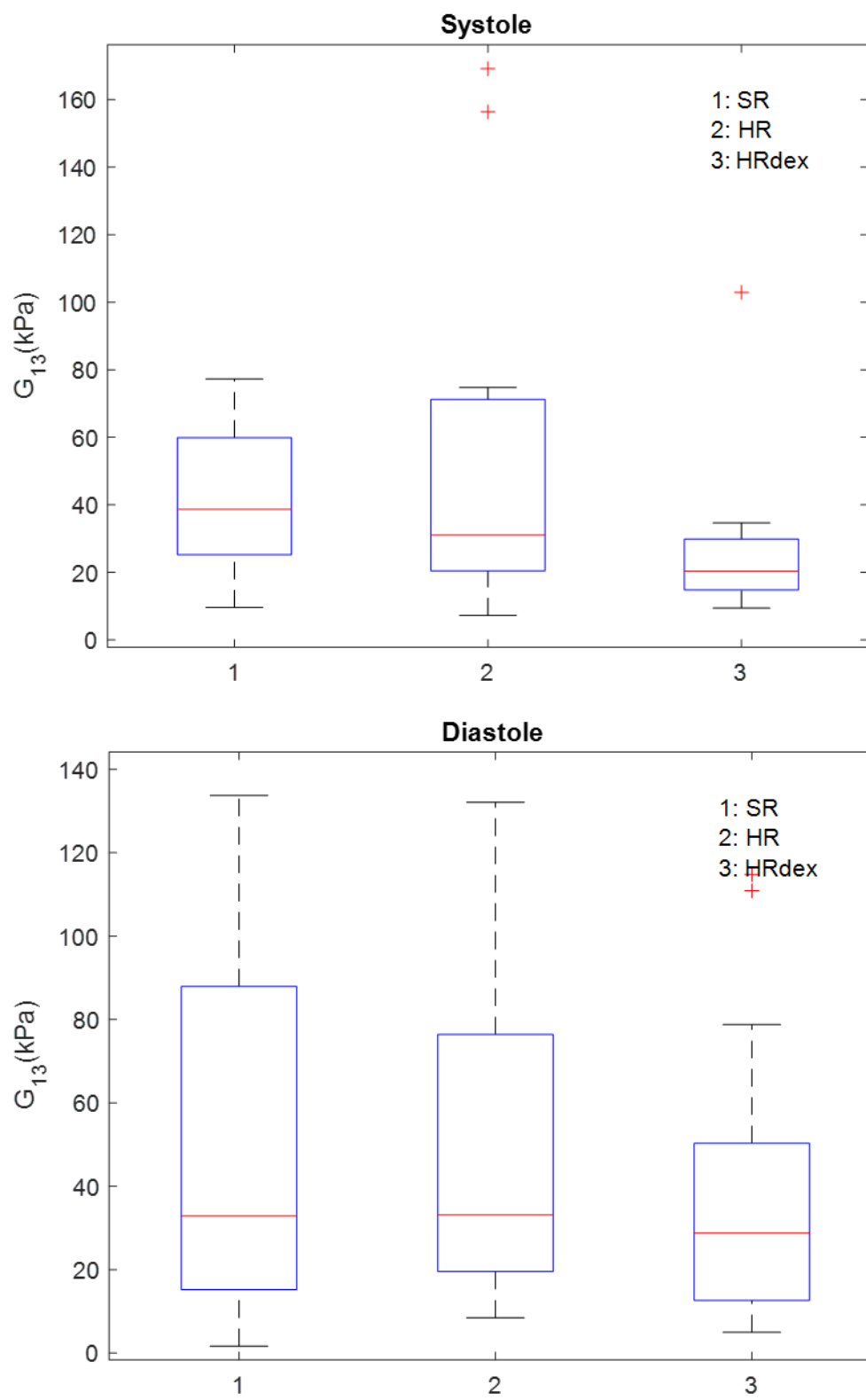


Figure 4.7 Results from all sub-domains, using Anisotropic formulation, for subjects of SR, HR and HRdex; (a) fiber Young's modulus (E_3) Systole ($P=0.97$), Diastole ($P=0.12$); (b) transverse Young's modulus (E_1) Systole ($P=0.27$), Diastole ($P=0.0021$); (c) fiber shear modulus (G_{13}) Systole, $P=0.17$), Diastole, $P=0.67$.

4.5 Discussion

4.5.1 Comparison of the estimated stiffness parameters

The estimated fiber Young's modulus (E_3), from the FE-based VFM formulation increased significantly as compared to the Young's values estimated by isotropic formulation for ALL subjects. Table 4.1 shows that the mean shear modulus G_{13} was 3 times greater than isotropic shear modulus (G) in Diastole, whereas no material direction was defined in isotropic case. The corresponding reference shear modulus obtained by FEMU is 23.82 kPa. In order to validate the virtual fields method, the reconstructed finite element meshes was built in ABAQUS commercial FEM software. The resulting Young's modulus optimized in the frame interest (time point) was compared to the corresponding Young's value resulted by VFM (Miller, et al., 2018).

Table 4.1 Resulting parameter estimated from the Isotropic and anisotropic formulation for Systole, Early Diastole, and Late Diastole in SR patients

SR	Isotropic		Anisotropic				
	E kPa (ν fixed)	G kPa	Fibre Young's Modulus E_3	Transverse Young's Modulus E_1	Fibre Shear Modulus G_{13}	Poisson's Ratio ν_{13}	
Systole	9.5	8.15	49.43	48.7	39.5	0.49	
Early Diastole	13.5	9.74	21.7	7.3	31.8	0.49	
Late Diastole	39.1	17.06	40.25	20.42	79.8	0.49	
FEMU (ED phase);	23.82	27.75					0.49

4.5.2 Isotropic VFM approach

Since the LV is approximately incompressible, if the value of Poisson's ratio remained closer to 0.5 (Miller, et al., 2018) (0.495), the isotropic VFM would provide better results. It helps obtaining more reasonable values for Young's modulus, and the following stiffness parameters. The variation in the resulting estimated Young's modulus can be attributed to the large differences in nodal displacements measured from each two consecutive phase.

In VFM, the user-defined virtual field is chosen so that a) it enforces zero virtual displacement on the boundaries, and b) it separates out-plane shear modulus from Young's modulus. Moreover, the user-defined VFM is not very accurate because the virtual displacement field could not be matched with the behavior of the measured displacements. Thus, the resulting values of Poisson ratio estimated in each phase has noticeable variation and are not well-determined. Furthermore, according to (Holzapfel & Ogden, 2009), it is important to increase the number of node points. As the numbers of nodal displacements rise, the value of Poisson's ratio will be closer to the 0.5.

LV pressure loading during filling, relaxation, and ejection has a significant impact on the outputs. During systole, when the pressure raised, inconsistency in the increased stiffness values appeared. Our finding is not in agreement with what has been observed in long-term survivors of ALL (Gamba, 2019), who reported lower stiffness in HR subjects compared to other group suggesting a myocardium tissue more prone to dilatation. On the contrary, during diastole, as the pressure drops, a decrease in passive stiffness occurred. The differences between estimated Young's modulus at (t=22-23) has been reduced as compared to the estimated values at the beginning of diastole.

To reach the impact of doxorubicin therapy on cardiotoxicity, given in an earlier section 4.3.5.1 we would've expected significant differences in Young's modulus between patient-groups (Begdouri, 2019) as well as lower stiffness in HR group (Gamba, 2019). However, our results were not in agreement with previous studies (Wang, 2013; Wassenaar, et al., 2016) (Figure 4.6, Figure 4.7).

4.5.3 Anisotropic VFM (FE-based VFM)

For measuring the myocardial strain or stiffness, many studies have been performed on CMR images through imaging modalities, including echocardiography (Fallah-Rad, et al., 2011; Lapointe, 2016; Lipshultz, et al., 2012) and elastography (Kolipaka, et al., 2010; Miller, et al., 2018). Furthermore, these studies used different anisotropic inversion methods to solve energy equation (Pierron, et al., 2012). For example, one previous study (Urban, et al., 2012) reported shear values (G_{13}) are between 1 - 15 kPa over cardiac cycle using FEMU inversion method and MRE imaging. Conversely, from the echocardiography and VFM application, (Lapointe, 2016) estimated shear modulus ranged approximately between 0.5-2 kPa and Young's modulus between 10-600 kPa, respectively for the hyperelastic and isotropic elastic myocardium. The discrepancy observed between estimated stiffness values because of not only the different inversion algorithm used, but also due to the fact that these studies use different scale of displacements depending on imaging modalities from either elastography (harmonic small displacement) (Tweten, et al., 2017; Tweten, et al., 2015) or echocardiography. However, we used large deformations, which previously obtained by CIM software over the cardiac cycle from cine-CMR images. Then, our results could somewhat verify that high difference between the estimated stiffness is due to the anisotropic VFM method used.

Piece-wise (FE-based) VFM implementation with LV anisotropic model demonstrated the ability of its application directly to the fully measured displacements from CMR. The identification of LV myocardial stiffness has still problems because of its complex geometry, nonlinear deformations, and fibre structures. However, this study showed that FE-based VFM approach could allow characterizing mechanical properties for early cardiac dysfunction given 3D LV geometry from CMR images, piece-wise domain of Hermite elements shape, and knowledge of the anisotropic constitutive relation.

The differences between the estimated parameters over LV elements were dependent on material orientation, virtual strain field of elements and the measured displacements from experiment. Regarding to the transverse Young's modulus (E_1) in anisotropic VFM, the results vary between 50 and 150 kPa, with extreme and unexpected values of around 600 kPa (Figure 4.7.b, c). Since the assessment of Young's modulus is averaged (median value) over the entire diastole and

systole, then E_1 values, Figure 4.7.b) did not show the same difference in comparison between ALL subjects as fiber Young's modulus (E_3) revealed (Figure 4.7.a).

When material was oriented (the anisotropic model) along the fibre direction (0 0 1), it was interesting to compare the large values of E_3 with the results in isotropic model which is not being assigned with any directions. However, some studies showed because the LV tissue behaves hyperelastic with nonlinear deformation (Hassan, et al., 2012), the instantaneous stiffness of the LV increases when the pressure is applied. Therefore, the linear elastic model would not be appropriate to compare anisotropic and isotropic material formulation for LV tissue.

4.5.4 Limitations

The in vivo identification of mechanical properties is nonlinearly dependent on loading condition (ventricular pressure model (CircAdapt)). Loading pressure is complex (non-uniform) on endocardial surface, and a simple model of pressure distribution cannot account for all regional variations in x, y, z direction. Therefore, in linear elasticity assumption, mechanical properties could not be estimated accurately for the anisotropic or isotropic models.

In Isotropic VFM of LV, according to the position of cardiac image plane in space, analytic virtual displacement function in prolate-spherical coordinate is constrain to the position, while the spheroidal-shape geometry measured (reconstructed from material points) at time t_0 can move to time $t+1$. Then, the average shape could not always track the same material points in instantaneous configurations. In the case of a prolate geometry, the spheroidal structure means that the algorithm can underestimate or overestimate the stiffness due to movement through the space.

The elements on the Hermite surfaces are assumed to have a uniform distribution. In most cases, such a distribution indicates inequality regarding how many virtual elements are present in the fiber and transverse directions and how many real data points there are. In some cases, it can cause an error at the beginning of the run that says, index exceeds the number of arrays in special matrix. This error originates from dimension of virtual plane where we create virtual smaller elements. It is important that working plane dimension cover all data point coordinate in all 25 frames where the deformed geometry data of left ventricle are collected, whereas the arrays value of assembly matrix might exceed the number of degrees of freedom at that element. In addition,

once the program reaches this error during the run, it does not go forward anymore. If the number of elements along fibre or transverse axis exceeds from the maximum number compared to 16 Hermite elements initially generated, the problem will not converge to accurate solution. This also confirms the fact the estimated values of Q_{12} and Q_{44} parameters decrease significantly when the number of nodal degrees of freedom is increased. These two quantities seem to be somewhat coupled in the identification.

4.6 Conclusion

The results of this study revealed that the material parameters identification using CMR data with the VFM is mainly dependent on the material formulation of the constitutive model and on the 3D reconstruction of the real LV geometry. The VFM approaches had different effects on both isotropic and anisotropic formulations.

The FE-based VFM application showed the estimation of anisotropic material properties from full-field measured displacements, so that piece-wise shape function is more applicable to the patient-specific LV models having non-regular geometry. In comparison to other inversion methods, for the patient-specific LV's, the piecewise VFM does not assume analytical function of coordinates in infinite medium, which has been employed to find a precise and explicit solution for the unknown stiffness parameters. In future studies, this method will be developed to be applied into non-linear material formulation and different types of higher-order elements.

Regardless of the LV pressure effects and global analysis of LV volume calculation (ED and ES volume) (Young, et al., 2000; Peng, et al., 2016), we can assume that the estimation of mechanical stiffness parameters can play an important role in the patient-specific LV function each of subject, so that LV shape's changed under loading pressure throughout the cardiac cycle and deformed with non-uniform displacement patterns.

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CHAPTER 5 ARTICLE 2: IDENTIFICATION OF PATIENT-SPECIFIC LEFT VENTRICLE STIFFNESS USING INVERSE FRAMEWORK OF MRI-BASED FINITE ELEMENT MODELING AND VIRTUAL FIELDS METHOD

This manuscript presents a nonlinear VFM-based framework, particularly for the hyperelastic myocardium identification due to respond to the general objective of this project. The generation of patient-specific (personalized) meshes for LV models from Cine-MIR images is described in a fast, simple and robust approach and answered to the first specific objective. The generated mesh has been provided to reconstruct patient's LV as well as validation using FEM updating. Therefore, this study contributes to create open-source inverse framework (MATLAB-based) for VFM, whereas much research has been employed commercial or home FE-based Software for Inverse estimation (FEMU).

My contribution to this study includes the 3D reconstruction of patient-specific LV models (80%), collecting the input data from the segmented images (90 %), FEMU validation (80%), optimization algorithm (90%), and the assessment of identifiability of hyperelastic parameters (90%) as well as comparative study of their values between subjects (SR, HR, and HRdex). Also, my contribution to the preparation and writing of the article is evaluated around (90%).

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5.1 Abstract

Detection of the left ventricle (LV) myocardial dysfunction after doxorubicin-based chemotherapy has been recently investigated through the determination of myocardial stiffness, which is a potential clinical biomarker for the monitoring of Heart failure. The combination of cardiac magnetic resonance (CMR) imaging and finite element method (FEM) has been used to non-invasively estimate myocardial anisotropic elastic stiffness in the LV. Myocardium also has a complex geometry with non-linearly hyper-elastic properties leading to large deformation. This study aims to generate the LV mesh model from CMR data, and then apply the virtual fields method (VFM) to determine the hyperelastic material parameters.

VFM-based identification technique, calculating the strain energy to build up a cost function using the squared residual between internal and external virtual works in the biomechanical LV model, is implemented. This cost function is nonlinear and then minimized to identify the hyperelastic parameters.

The finite element method is the primary part of this study that only justifies how to reconstruct the resulting strain field, given the displacement field of actual CMR data. Based on FEM, a non-regular geometry is subdivided into smaller, separated regions to build up elements. The solution is approximated by satisfying the strain-displacement relation for each element. The strain fields are approximated by using the first-order polynomial interpolation functions in 8-node cube (hexahedral). The initial LV model was created by using sixteen Cubic-Hermite elements in cardiac coordinate, fitting to the endocardial and epicardial surfaces of the LV at each cardiac phase. The principal of virtual work was required to build up energy-based cost function using the squared residual between strain energy and external work produced by cardiac pressure. Two

material parameters, which are coupled in nonlinear hyperelastic material law, were determined by minimizing the energy cost function. To validate VFM results using FEM updating (FEMU), the same meshes of LV model were imported and rebuilt into ABAQUS software, then simulated for the optimization task. In a case study of leukemia cancer survivors with doxorubicin treatment, who were separated into three risk groups: standard risk (SR), high risk (HR), and high risk with dexrazoxane (HRdex), the stiffness parameters were estimated to be compared quantitatively between groups. The differences were found in shear modulus values between these groups in late diastole (passive myocardial properties) while they were not statistically significant. Moreover, the relationship between stiffness parameters which exists in nonlinear hyperelastic law revealed changes in the identifiability of the energy law from energy-based CF between those study groups. In conclusion, given the proposed inverse framework, we successfully applied VFM for the reconstructed patient's LV and assessed the identifiability of hyperelastic material law from the measured CMR data.

Keywords: Myocardial stiffness; CMR; Hyperelastic model; Inverse identification; virtual fields' method; FEM

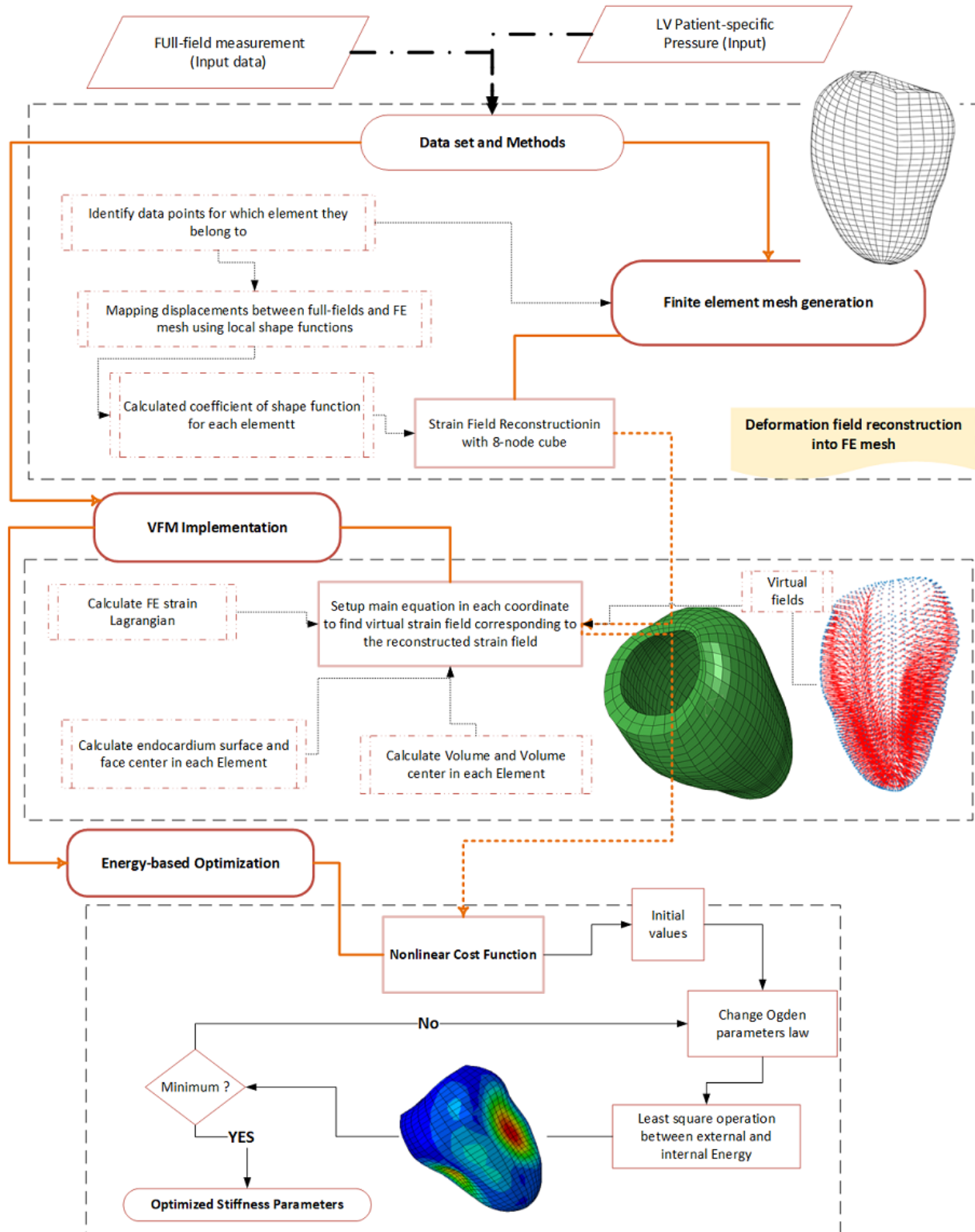


Figure 5.1 Graphical abstract of inverse framework (FE mesh generation, VFM implementation and optimization)

5.2 Introduction

Myocardial function depends significantly on its material properties. Changes in material properties are an important determinant of myocardial dysfunction and the main cause of heart failure.

Some previous methods used for the diagnosis of heart failure required invasive cardiac pressure measurements to estimate passive mechanical properties from clinical data (Hummel et al., 2017) (Mojsejenko et al., 2015). Advances in medical imaging and image processing were needed to provide non-invasive measures of diastolic function (da Silveira et al., 2016; Glaser et al., 2012; Young et al., 1995). Also, finite element (FE) approaches improved the identification of cardiac hyperelastic material properties (Augenstein et al., 2006) in patients with LV diastolic dysfunction (Xi et al., 2013). FE models associated with cardiac magnetic resonance (CMR) data allowed to determine the effects of myocardial ischemia (Zhang et al., 2020) and improved non-invasive measures of passive and active LV properties (Miller et al., 2015). Some CMR researches focused on improving inversion algorithms that reliably quantify stiffness using the measurement of diastolic strain from CMR tagging (Ryf et al., 2002; van Everdingen et al., 2018).

Inverse FE-based estimation of the myocardium material properties from Guccione and Holzapfel and Ogden laws (Gao et al., 2015; Guccione et al., 1991; Holzapfel et al., 2009) (Nikou et al., 2016) have been performed in large animals (Mojsejenko et al., 2015), normal human volunteers (Genet et al., 2014), and patients after myocardial infarction (MI) (Zhang et al., 2021). From our understanding, there are several forms of strain energy (Systèmes, 2007) (material law), which model hyperelastic parameters with different coefficients.

Inverse FE-based optimization provides the accurate parameter estimation for either LV systolic contractility or diastolic filling (from early diastolic to end-diastole) (Xi et al., 2014). However, a few investigations were performed to evaluate the performance of the objective function in parameter identifiability (Nasopoulou et al., 2017). These studies proposed novel geometry-based models of a cost function (Asner et al., 2016; Grédiac & Pierron, 2006; Xi et al., 2011) that allowed to take advantage of using the experimental strain fields extracted from CMR data. In addition, the application of energy-based CF models improved the identifiability of the Guccione law (Guccione et al., 1991).

The virtual field's method (VFM) is an alternative to FE-inverse that directly uses full image data throughout the domain and does not require the use of FE calculations and iterations (Avril et al., 2010; Grédiac & Pierron, 2006). Additionally, the nonlinear VFM based on the principle of virtual work (Rossi & Pierron, 2012) only requires equality between the external virtual work W_{ext} (the work produced by the external pressure acting on the tissue, regardless of gravity loads and surface traction effects) and the internal virtual strain energy W_{int} . For instance, Avril et al. applied VFM to the identification of the hyperelastic behavior of artery walls in vitro (Avril et al., 2010). Recently, the FE-based VFM approach reconstructed the measured displacement into FE meshes defined on the area of the sample (Kim and Lee, 2021; Livens et al., 2021). The VFM allowed to create a cost function using the sum of the squared residual between internal and external virtual works, and then minimizing this function with respect to constitutive objective parameters.

Most studies minimize the displacement objective functions (Miller et al., 2015) mostly posed in the FEM network (Inverse FE-based), where problem type 1 must be first solved iteratively to find the model-predicted strains and then solve problem type 2 to identify the mechanical properties. Recently, the FE-based VFM approach reconstructed the measured displacement into FE meshes defined on the area of the sample (Kim and Lee, 2021). More recently, this approach is implemented to open-source FE package FEniCSx (Deng et al., 2023) to identify nonlinear hyperelastic solids as well as a general FE-based framework in soft biological tissue (Mei et al., 2021). However, in this study, we proposed VFM-based inverse framework to identify the hyperelastic myocardium tissue, and particularly in patients LV affected by the doxorubicin-induced geometric remodeling (Aissiou et al., 2016; Aissiou et al., 2013; Gamba, 2019). We create a patient-specific FE model of LV, calculate LV diastolic strain in elements from the Cine MRI measurements, and then apply virtual strain fields into principal of virtual work (PVW) in order to estimate the passive mechanical properties. Then, we evaluate doxorubicin-induced changes in mechanical properties identified by VFM with regard to our previous study (Ghafarinatanzi and Perie, 2023).

5.3 Theory

Changes in myocardial stiffness accompany variations in LV function. In LV diastolic passive inflation, biomechanical models generally use large deformation mechanics. The LV model is assumed to deform in response to the existing LV pressure applied on the endocardium surface and myocardial tissue experienced the mechanical stretch (Genet, Lee et al. 2014; Zhang, Wang et al. 2021). We considered the myocardium to be incompressible, and its inertia and gravity impacts are negligible. .

5.3.1 Hyperelastic Constitutive Law

In hyper-elasticity, the constitutive laws are defined using the strain energy density W_{str} . This quantity corresponds to the energy stored in the solid after loading and is defined as:

$$W = \int_0^{\varepsilon_{ij}} \sigma_{ij} d\varepsilon_{ij} \quad 5.1$$

The mechanical passive properties are obtained by defining a strain energy density. Several strain energy density functions have been proposed to model passive behavior (Guccione et al., 1991; Holzapfel et al., 2009). Mainly, models are based on either exponential or polynomial functions of the strain invariants of deformation. The compressible formulation of Ogden's hyperelastic law (Hassan et al., 2012) is described by a strain energy density function expressed as a function of the principal stretches λ_j , $j = 1, 2, 3$ such that:

$$W_{str} = \sum_{n=1}^N \mu_n / \alpha_n (\lambda_1^{\alpha_n} + \lambda_2^{\alpha_n} + \lambda_3^{\alpha_n} - 3) \quad 5.2$$

Where n is the order of Ogden's law. The parameter μ_n called the shear modulus is constraint units (kPa) and the parameter α_n known as the nonlinearity ratio has no dimension.

In order to calculate stress tensor, the derivative of the strain energy with respect to the principal stretches is given by, in index notation:

$$\partial W_{str} / \partial \lambda_j = \sum_{n=1}^N \mu_n / \alpha_n (\alpha_n \lambda_j^{\alpha_n - 1}) = \sum_{n=1}^N \mu_n (\lambda_j^{\alpha_n - 1}) \quad 5.3$$

And the stress tensor of Cauchy is defined by:

$$\sigma_j = -p + \lambda_j \partial W / \partial \lambda_j \quad 5.4$$

Where p a Lagrange multiplier that satisfies the incompressibility constraint, and W is the strain energy density function. By taking $N=1$, there are only 2 parameters: μ and α .

5.3.2 Theory of Large deformation

Often, the deformations experienced by biological materials are too great to be considered infinitesimal. It is then required to recognize the reference configuration (non-deformed) and the current configuration (deformed). There are two ways of describing a vector according to the theory of large deformations: the Lagrange description (material coordinates) and the Eulerian description (spatial coordinates). These coordinate systems are denoted X_i , $i = 1, 2, 3$, and x_i , $i = 1, 2, 3$ respectively. The link between these two coordinate systems implies the displacement field U for each element.

$$\mathbf{x} = \mathbf{X} + \mathbf{U} \quad 5.5$$

The deformation gradient F involves both material and spatial coordinates.

$$F_{ij} = \partial x_i / \partial X_j \quad 5.6$$

Another description of the strain gradient goes through the displacement gradient ∇U defined according to the Lagrangian description:

$$\mathbf{F} = \mathbf{I} + \nabla \mathbf{U} \quad 5.7$$

Where $\mathbf{I}$ is the identity tensor of order three. Using this tensor, the principal stretch ratios of the material, λ_j , $J = 1, 2, 3$ can be determined. For any deformation, there are 3 orthogonal directions in which the material does not undergo any shearing. The value of stretches in these directions corresponds to the principal stresses. An analysis of the Eigen-space of the tensor $\mathbf{F}$ makes it possible to calculate the main stretches λ_j , which correspond to the eigenvalues, as well as the principal stretching directions which correspond to the eigenvectors. Thus, if the main directions of the material coincide with the principal stretching directions, the tensor $\mathbf{F}$ will be:

$$\mathbf{F} = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \quad 5.8$$

Moreover, if the material is incompressible, the determinant of $\mathbf{F}$, denoted by J , is unit.

$$J = \lambda_1 * \lambda_2 * \lambda_3 = 1 \quad 5.9$$

$$\lambda_3 = 1/(\lambda_1 * \lambda_2) \quad 5.10$$

In large deformation theory, tensor of Cauchy-Green left and right, $\mathbf{B}$ and $\mathbf{C}$ are defined.

$$\mathbf{B} = \mathbf{F} * \mathbf{F}_t \quad 5.11$$

$$\mathbf{C} = \mathbf{F}_t * \mathbf{F} \quad 5.12$$

Finally, the tensor of deformations Green-Lagrange can be defined:

$$\bar{E}_{GL} = 1/2 * (\mathbf{C} - \mathbf{I}) \quad 5.13$$

It is important to note that in the case where the strains are infinitesimal, this tensor is equivalent to ϵ .

5.3.3 Virtual Fields Method

The VFM is an inversion method used to identify mechanical properties by measurements of full-field displacements. VFM is based on the principle of virtual work. considering the previous assumptions in this study, this principle is simplified to:

$$-\int_V \boldsymbol{\sigma} : \boldsymbol{\epsilon}^* dV = \int_S \mathbf{P} \cdot \mathbf{u}^* dS \quad 5.14$$

When the first term for internal stress or work is expanded, given the strain-displacement relationship, we obtain:

$$\int_V (\sigma_{ij} \partial u_i^* / \partial x_j^*) dV = \int_S P_i \cdot u_i^* dS \quad 5.15$$

This equation is valid for any virtual displacement field that is kinematically admissible to the body displacement field.

5.3.4 Nonlinear VFM

Since the energy law of the hyperelastic material does not depend linearly on the mechanical parameters, the nonlinear VFM have to be used in this problem. The constitutive law, the strain Green tensor, the principal stresses, as well as the LV pressures are known terms described earlier. After entering these terms into principle of virtual work and choosing any kinematically admissible virtual fields, we obtain a nonlinear system of equations with respect to the nonlinear constitutive law. This system of equations can be solved by minimizing a cost function. For example, the squared residuals between internal and external virtual work:

$$f = (W_{int} - W_{ext})^2 \quad 5.16$$

Since the virtual fields method is not iterative, the resulting optimization problem would be solved more easily than minimizing the objective functions mostly posed in the FEM network (Inverse FE-based), where problem type 1 must be first solved iteratively to find the model-predicted strains and then solve problem type 2 in order to identify the mechanical properties.

5.3.5 Application of PVW into large deformations

We will use the principle of virtual work formulation in the current frame of reference, thus involving the Cauchy stress tensor since the strains are calculated in the deformed frame of reference. The virtual fields are expressed in the current configuration:

$$\begin{aligned} \int_V \left[\sigma_{11} \frac{\partial u_1^*}{\partial x_1^*} + \sigma_{22} \frac{\partial u_2^*}{\partial x_1^*} + \sigma_{33} \frac{\partial u_3^*}{\partial x_3^*} + \sigma_{12} \left(\frac{\partial u_1^*}{\partial x_2^*} + \frac{\partial u_2^*}{\partial x_1^*} \right) + \sigma_{13} \left(\frac{\partial u_1^*}{\partial x_3^*} + \frac{\partial u_3^*}{\partial x_1^*} \right) \right. \\ \left. + \sigma_{23} \left(\frac{\partial u_2^*}{\partial x_3^*} + \frac{\partial u_3^*}{\partial x_2^*} \right) \right] dV + \dots = \int_S P_i \cdot u_i^* dS \end{aligned} \quad 5.17$$

(All quantities are defined with respect to the current configuration)

5.4 Materials and Methods

5.4.1 Data set and Geometry Model

Patients

Our study included 9 cancer survivors from the PETALE project, approved by the institutional review board of the hospital (Marcoux et al., 2017). According to the doxorubicin dose received during the treatment, cancer survivors were divided into 3 risk groups. The standard risk (SR) group, the high-risk (HR) group, and the high risk with Dexrazoxane (HRdex) group, who received the same dose of Doxorubicin as the HR group combined with a dose of a cardio protective medication.

CMR acquisition

The CMR acquisitions were performed on a Siemens Skyra 3T MR system using an 18-channel phased-array body matrix coil and included an ECG-gated cine TruFISP sequence (14 slices in short axis and 5 slices in long axis, slice thickness 8mm, repetition time 34.6ms, effective echo time 1.2ms, flip angle 38°, IPAT factor 3, matrix 208x210 and in-plane pixel size 1.25x1.25 mm).

Image analysis

The data collection consisted of subject-specific LV image data covering diastole, systole and were collected previously from (CIM, v8.1, University of Auckland, New Zealand) to accurately characterized ventricular motion and shape. In CIM software, operator loaded the patients' image data, and created a configuration cardiac space by uploading the long-axis and short-axis MR slices. The output model was fitted to the endocardium and epicardium surfaces and presented LV deformation during cardiac cycle. In our CMR database, there were 25 segmented frames which track spatially the inner and outer LV walls from apex to base, as well as temporally continuous description of the cardiac LV motion from one image frame to the next one (Lam, 2012). The extracted data were used for the LV model described in the following sections.

5.4.2 LV FE mesh generation

To construct a desired LVFE model for the proceeding analysis, we created first-order trilinear mesh of hexahedral elements consistently from the epicardial and endocardial surface points of LV, which were derived in the guide point Modeling framework. These elements did not have

any overlap, twisting, or shape distortion (

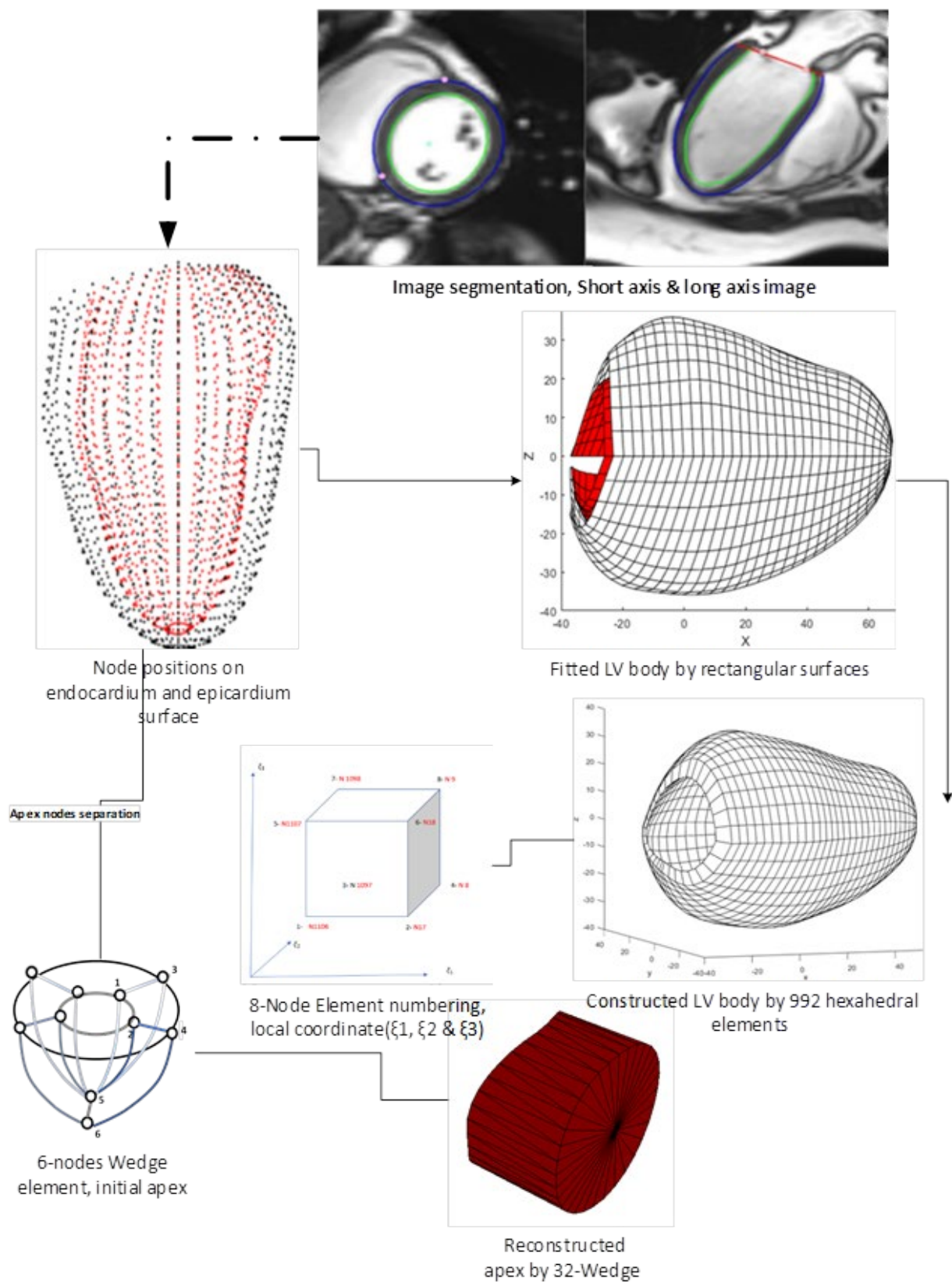


Figure 5.2). Also, the interpolation 1st (linear) or 2nd order can be applied to connect the endocardial and epicardial surfaces. During the element fitting, the endocardial points were smoothly connected to their respective epicardial points, while building up a FE geometry of 8-node hexahedral shapes. Also, to construct the FE apex, the last row of surface points was connected to the apical points in such a way to form a six-node wedge element.

Therefore, we generated LV finite element model from the meshes at each frame of the cardiac cycle. The resulting LV model contained 2048 nodes, 1024 uniform elements consisting of 992 first-order hexahedral elements (from apex to basal nodes), and 32 wedge elements while

building up meshes at the apex (between hexahedral meshes and apical node) (

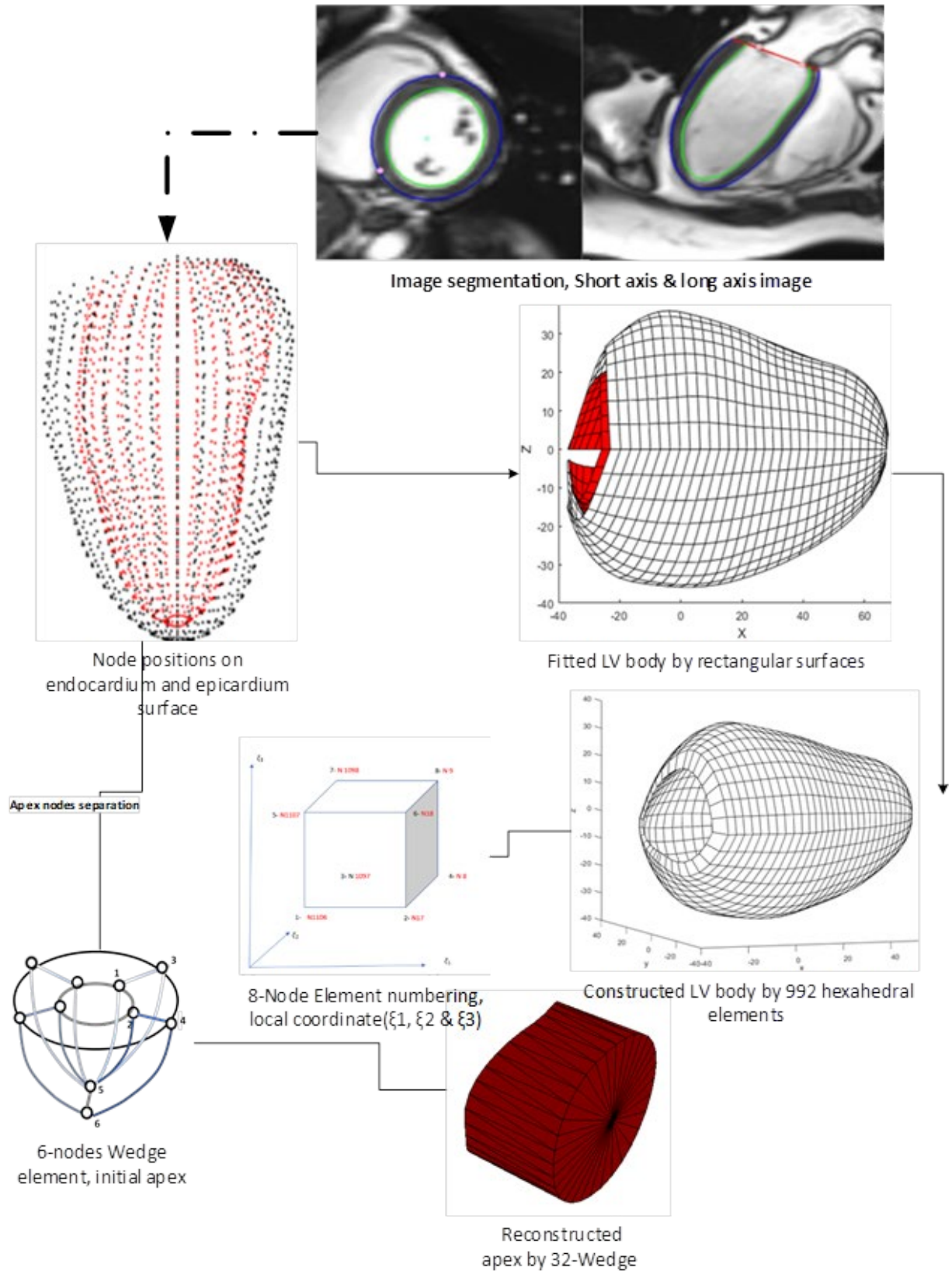


Figure 5.2).

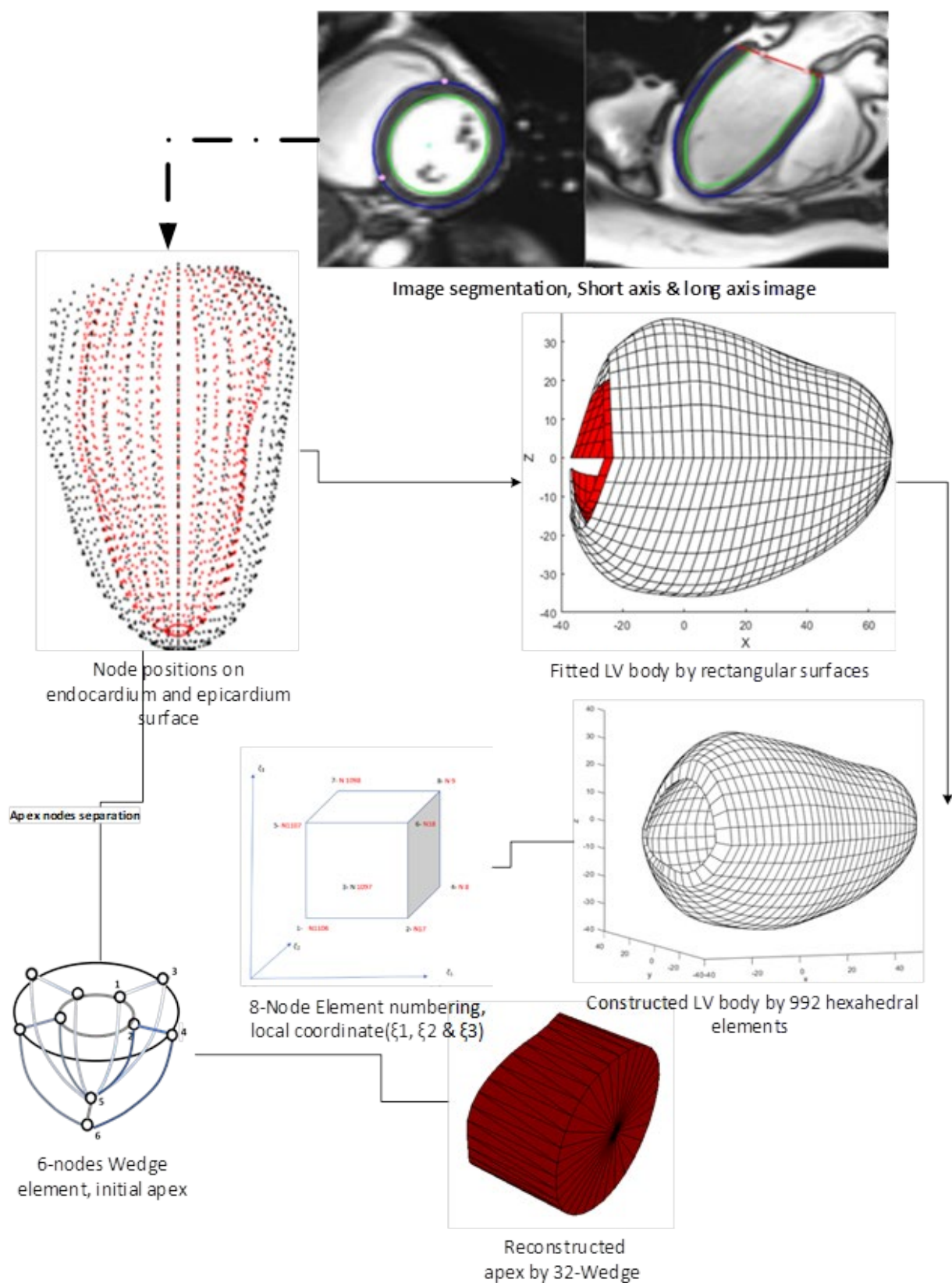


Figure 5.2. Mesh generation of Left Ventricle form MRI images

LV Pressure Estimation

The pressure-volume loop is a plot of the LV pressure versus LV volume. We can approximate the volume of the LV by the sum of the volumes of each hexahedral element.

As indicated in Figure 5.3, the simulated patient-specific LV pressures (both in systole and diastole) were derived from Physio Flow measurements at rest (Manatec Biomedical, Macheren, France) and CircAdapt simulations (Gamba, 2019).

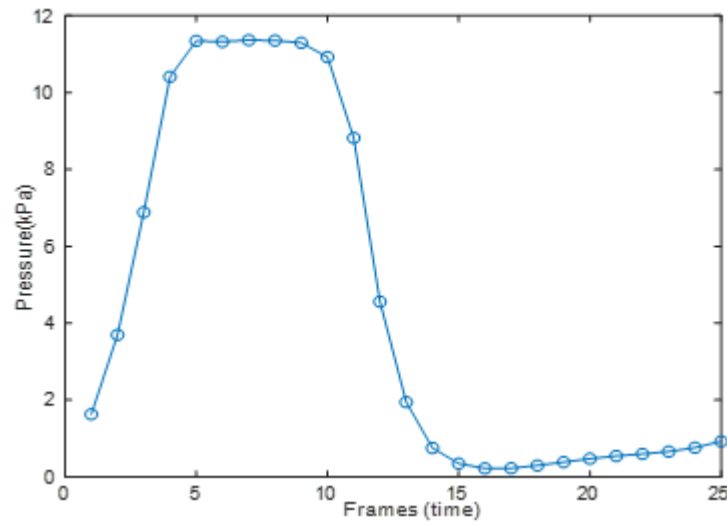


Figure 5.3. Intra-ventricular pressure simulated, at LV passive diastolic, and at RELAXATION (Isovolumetric). Analysis started (late-diastole) from frame 21 (minimum pressure) to frame 5 (21, 22, 23, 24, 25, 1, 2, 3, 4, 5). The 6 indicates the end-diastolic diastole frame.

5.4.3 Virtual displacements field

The choose of the virtual displacement field must be kinematically admissible for the deformation field of LV (Pierron and Grédiac, 2012). The main characteristic of this virtual field is to cancel the contribution of the hydrostatic pressure (A.4). The trace of the virtual strain tensor being zero, the hydrostatic part (related to the volume change) of the stress tensor is canceled in the calculation of the virtual work (Figure B. 1). The created model must respect LV's boundary conditions. Then, virtual fields must therefore be zero at the basal and apical level, and also be continuous over the rest of the geometry. Furthermore, it is important to indicate that the heart tissue fibers and their orientations were neglected in this model.

Due to the shape of the LV, the virtual fields were defined in spherical coordinates ($r, \varnothing, \theta$) (Ghafarinatanzi and Perie, 2023). They were then transformed into Cartesian coordinates for the purposes of the subsequent calculations. Hence, the following functions could be defined and selected. The resulting virtual displacement fields applied were:

$$\begin{aligned}
 & \begin{cases} u_r^* = -r * \sin(2\theta) * \cos(\varnothing)^2 \\ u_\theta^* = 0 \\ u_\varnothing^* = 0 \end{cases} \quad 5.18 \\
 & \begin{cases} u_r^* = -\sin(2\theta) * \sin(\varnothing)^2 \\ u_\theta^* = 0 \\ u_\varnothing^* = 0 \end{cases} \\
 & \begin{cases} u_r^* = \frac{A}{r^2} + \frac{Br}{3} \\ u_\theta^* = B * r * (\csc(\theta) - \cot(\theta)) \\ u_\varnothing^* = 0 \end{cases} \quad \begin{cases} A = \sin(2\theta) \\ B = \sin(2\theta) \end{cases}
 \end{aligned}$$

with $r \in [0, \infty]$, $\varnothing \in [0, \pi]$ and $\theta \in [0, 2\pi]$.

Where r is the radial distance, $\varnothing$ is the polar angle, and θ is the azimuthal angle which all controlled the LV shape in the apex, basal and wall. They are all normalized by the density of the left ventricle (r/ρ , $\varnothing/\rho$, θ/ρ).

5.4.4 Parameter estimation workflow

Principal stress and directions

The value of principal stress λ_j and the main direction P_j of the tensor B_{ij} must be found in Eq 5.4. The solution was proceeded using the Eigen function of MATLAB. The Cauchy stress tensor σ can be calculated using the principal stress value. Then, using the right and left Cauchy-Green deformation tensors in equation 5.10 and 5.11, the parameters B and C were defined and applied into Green-Lagrange strain in 5.12 for each hexahedral element. Moreover, the main directions of stress (eigenvectors) were found.

FE Strain Lagrangian

Note previously strain in all elements was calculated by FEM for the LV meshes assuming end-diastole (ED) frame is reference configuration. However, we needed Green strains (Payan & Ohayon, 2017) consisting of the small engineering strain, as the first part, and the nonlinear quadratic strain, as the unknown second part (Murea, 2017).

Stress tensor transformation

Since the strains are measured in the deformed state (eulerian space), the Cauchy stress tensor should be used. The stresses $\sigma_{\text{principal}}$ were calculated using the actual value of the parameters being optimized with the help of the principal stretches in each element as defined in Eq.5.4. Therefore, a change of basis is required, as the principal stretches are measured in the reference state of the associated eigenvectors. However, the deformation was measured in the image frame.

$$\sigma_{ij} = P_{ik} P_{jl} \sigma'_{kl} \quad 5.19$$

Where P contains the eigenvectors in each element.

Optimization of Ogden law's parameters

In MATLAB, the `lsqnonlin` function was used with the trust-region-reflective algorithm. The W_{int} and W_{ext} quantities can be placed in vector form.

$$f_{\text{cost}} = W_{\text{int}} - W_{\text{ext}} \quad 5.20$$

The algorithm then tried to find a set of the coupled μ and α parameters, that allowed equation 5.20 to be minimized over each phase of the cardiac sequence.

To create the energy function CF (equation 5.20), two consecutive time point were selected. Its correspond to the diastolic frames (DF) in clinical study. For example, DF2 is the end-diastolic frame, and DF1 will be the frame prior to DF2. The external work was calculated for each time point by integrating the product of the pressure and volume change between successive frames. The energy-based cost function is only dependent on the parameters in Ogden's hyperelastic law in equation 5.2. Assuming the ratio α_n is constant; the modulus parameter μ_n has been uniquely identified using the cost function optimization.

5.4.5 Comparison between subjects

As mentioned in method section, each group includes three subjects for the comparison between the obtained values. Around six successive phases at the end of diastole were considered for each subject. Using the framework, which was presented in the parameter estimation workflow, those phases were processed one by one. The hyperelastic (Ogden's law of order 1) properties (μ and α) were identified in each phase. The estimated shear modulus was plotted using boxplots for the HR, SR, HRdex group, displaying standard deviation, median, mean, and outlier's values. Differences between groups were investigated visualization of summary statistics for the estimated data but not return numeric value.

5.4.6 Identifiability of Nonlinear behavior law

First, for all subjects, the subject-specific energy-based cost functions were minimized to identify uniquely α and μ parameters.

Second, when μ and α were set to the estimated reference value, the stress function (equation 5.4) used the Ogden energy law to calculate the principal stresses and compared them to the results of a prior study (Hassan et al., 2012), in which the parameters of the energy law have been optimized in the manner of least squares. The simulated curves of the identified law should predict the nature of nonlinear behavior in the original law, according to theory.

5.4.7 FEMU Hyperelastic Model Validation

To validate the virtual fields method, the finite element models previously created in MATLAB were built in ABAQUS commercial FEM software.

The optimization task was created to start an iterative process that updated the hyperelastic parameters as design variables. This process minimized the total strain energy on the model that configured the objective function of least squares on the strain energy data obtained from ABAQUS output. To keep running the design cycle, it was required to use Abaqus2Matlab tool that provided a connection between ABAQUS outputs and MATLAB codes. This tool linked two different jobs, simulation and programming. With considering a certain interval for the shear stiffness as design variable, we can execute the program. The resulting shear modulus optimized in each frame is corresponding to the given shear values, which was previously obtained with

VFM, approach in the same frame. In the validation study, we compared shear modulus only in one subject at late diastole between FEMU and VFM results.

However, using the two-variable optimization test, α range might be varied and probably affect the optimized shear responses μ due to iteration in two-dimension. As the optimized α remained in a certain range, one of the approaches was to hold this parameter on a fixed value in order to perform only single-task optimization. Therefore, this optimization process is including alpha versus the optimization with a fixed value of alpha.

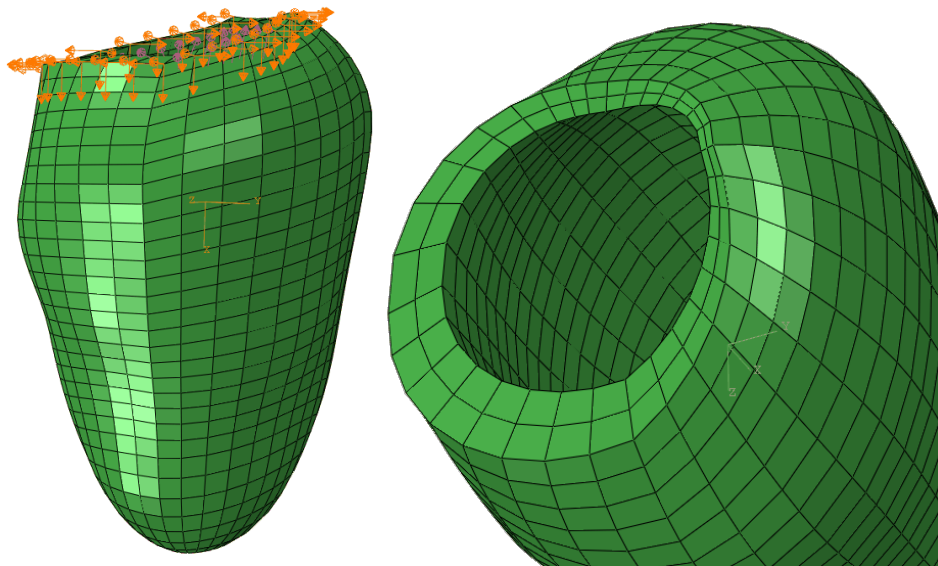


Figure 5.4. LV model imported into ABAQUS with 8-nodes cube elements.

5.5 Results

5.5.1 Stiffness comparison between subjects in Late-Diastole

Figure 5.5 showed some differences in the estimated shear modulus values during late diastole (passive behavior) between subjects. Shear values in HR subjects (1.5 kPa) were higher as compared to SR (1.2 kPa) and HRdex (1.3 kPa) ones. However, these differences were not significant (p -value: $0.45 > 0.05$).

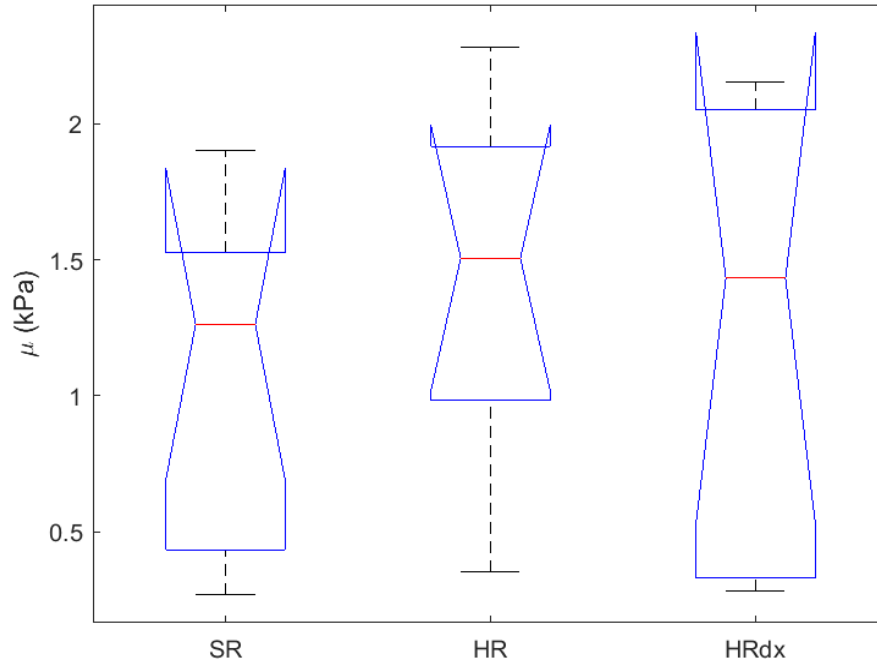


Figure 5.5 The estimated shear stiffness in late diastole for each HR SR and HRdex subject

5.5.2 Identifiability of the energy-based CF

Figure 5.6 confirmed that the μ - α parameter coupling exists for all subject-specific cost functions. Figure 5.6 also showed the exponential fitting in MATLAB to the relation between estimated parameters (parameter inter-correlations), where a curve was fitted to the μ - α data obtained from the cost function optimization process only in late-diastole frames. The discrepancy in the estimated curves between the three subjects has been revealed. The presence of larger deformations in one of the subjects can amplify the exponential term in the strain energy function.

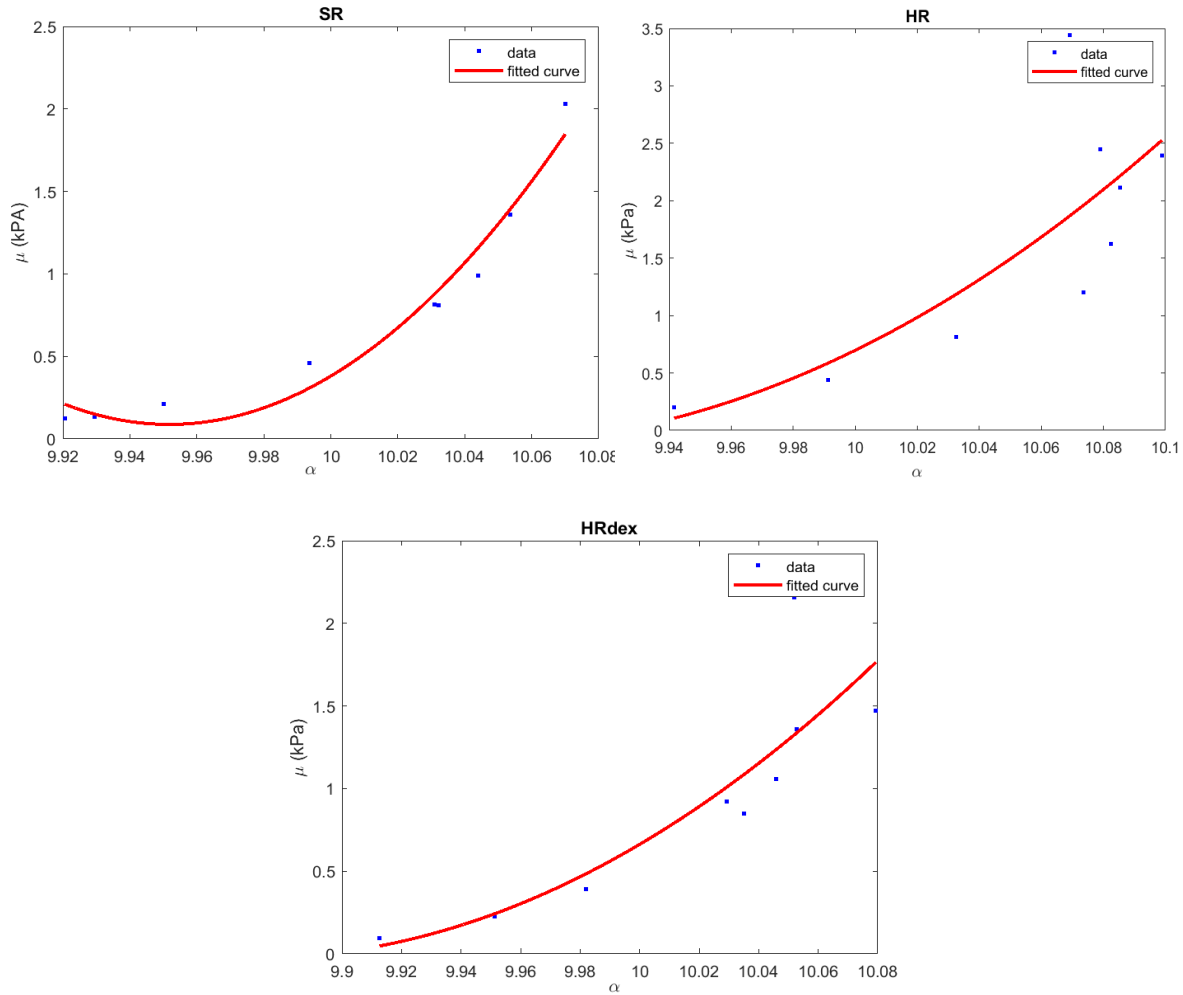


Figure 5.6. The relationship between μ - α parameters from energy-based CF with using fitted curves, in late diastole for each of subject: (a) SR, (b) HR, (c) HRdex

Figure 5.7 showed the result subjects of Ogden's law simulation using the estimated parameters from our cost function and a reference function (Hassan et al., 2012) which has been employed previously (Lapointe, 2016). In this case, the μ and α parameters were set to 0.6 kPa and 12, respectively. Cauchy stress versus stretch curve was achieved with respect to its principal direction (up to 125% stretch). The differences were found in stress-strain curves of the identified law compared to the reference law due to the existence of strain that varied exponentially in the energy function.

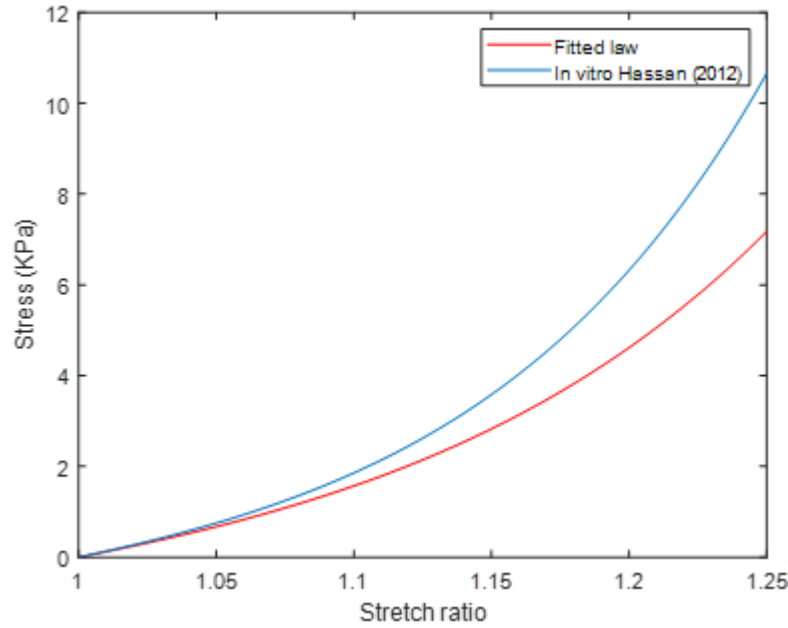


Figure 5.7. Cauchy stress vs stretch. The simulation of the identified hyperelastic law behavior from stress-strain relationship.

5.5.3 FEMU Validation Results

The shear modulus (μ_{sim}) estimated from FEMU was compared to the VFM shear (μ_{VFM}) in end of diastole (Table 5.1). The differences between their values were high. However, α parameter was tested in a specified interval and returned values around 30 in first step of optimization. According to the proposed single-task optimization in method section, if α was set to 30 in late diastole, the optimized shear modulus would be closed to the VFM outcome.

Table 5.1 Comparison of FEMU solution with the VFM estimated parameters, one SR subject in late diastole

	SR	HR	HRdex	Constraint
FEMU	$\mu = 2.2 \text{ kPa}$ $\alpha = 11$	$\mu = 0.037 \text{ kPa}$ $\alpha = 30$	$\mu = 0.045 \text{ kPa}$ $\alpha = 30$	Poisson = 0.495 $D_0(K_0/\mu_0) \gg 100$ $P = 0.75 \text{ kPa}$
	$\mu = 0.49 \text{ kPa}$ $\alpha = 30$			

VFM	$\mu = 0.65 \text{ kPa}$ $\alpha = 10.5$	$\mu = 0.44 \text{ kPa}$ $\alpha = 10.5$	$\mu = 0.39 \text{ kPa}$ $\alpha = 10.5$	
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5.6 Discussion

5.6.1 Comparison between subjects

Myocardium is approximately incompressible. The relative compressibility can be constrained to maximum one percent. In Ogden law, it is defined by the ratio of initial bulk modulus K_0 to initial shear modulus μ_0 , indicating the values of greater than 100 ($D=K_0/\mu_0$, or in Elastic law by Poisson's ratio greater than 0.49). If this constraint cannot be satisfied, the VFM optimization is not feasible. In fact, since this constraint is frequently changed in each iteration due to the iterated shear modulus, its impact on two optimized variables (α , μ) is high. Therefore, statistically significant differences between the subjects could not be found from hyperelastic model because of the irregular variation in the estimated stiffness results. However, if α parameter remained to a constant value, meaning it is removed from objective function, the VFM optimization would provide more reasonable values for μ .

5.6.2 Identifiability of energy law

The coupled parameters, which were identified from hyperelastic Ogden law, has been changed significantly between subjects. The parameter μ represents the stiffness of the material while the parameter α measures the non-linear part of the law. μ increases when α decreases and vice versa. Knowing that pressure has impact on parameter identification, we noticed those significant changes in Figure 5.6 because subject-specific LV pressure varies between subjects (Gamba, 2019).

When the estimated values, μ and α , were substituted into the energy function 5.20, the principal stress was calculated. As shown in Figure 5.7, they are exponentially increased in nonlinearity response to the input strain for the Ogden's law. This might illustrate that principal stretch (λ) is identified in presence of virtual strain, whereas the energy function was evaluated with the actual strain.

5.6.3 FEMU Model

We considered a constraint value during optimization for D_0 (Bulk ratio to shear modulus = 100, or Poisson's ratio of incompressible case = 0.49) in FEMU. Furthermore, the exponent value α obtained from VFM was fixed as the initial value to only preserve the single-variable objective function of (μ) on its interval (Table 5.1). To guarantee the convergence to a local minimum (μ_{VFM} modulus), these assumptions were taken into account. However, they may result in inaccurate estimation of material constants from the Ogden model for other subjects.

Additionally, the alpha (α) parameter is presented with different coefficients in material modeling in some research. For example, the Guccione hyperelastic model (Guccione et al., 1991) is an exponential function of α parameter and is referred to as anisotropy ratios ($\alpha = b_f + b_{ft} + b_t$). Although the strain energy function W is exponentially relative to anisotropic material constants (local fiber direction b_f , transverse b_t , and cross-fiber plane (b_{ft})). The Guccione model is similar to the formulation presented in Ogden model. This parameter contributes to different form of strain energy generalized Fung, Holzapfel-Ogden (Systèmes, 2007). Therefore, we set α to the fixed value to avoid its impact as design variable, due to iterative process.

Loading Pressure Constraint

As observed on VFM results, the pressure was applied for each frame corresponding to its cardiac pressure values ranged from 0.75 to 1.25 between subjects (Gamba, 2019). In the hyperelastic case, to ignore realistic pressure effects, if the pressure value is set to 0.75 kPa (close to 1 kPa) the estimated FEMU shear modulus showed the smallest variations as compared to the corresponding VFM ones.

Boundary condition effects

There were two options for boundary conditions modelling. The top of the LV should be constrained around the basal, and the bottom could be constrained around the apex. According to some sources, the outer boundary that includes epicardium nodes must be limited, while the inner boundary on the endocardium nodes remains free.

Besides, at the end of the phase, all nodes on the epicardium and endocardium surfaces are moved (from the initial step-to-step 1) to the final position, where the real displacement vector of x, y, z values happened.

Initial shear values

The quantity of material constants, which were previously estimated to compute the Ogden energy function, is taken as initial values to start the optimization task.

Then we assumed $\mu = 0.5$ and $\alpha=10$ from the VFM result. When α parameter changed to almost two times, the energy function has been drastically increased because the principal stretch takes the power of 2α . However, the estimated shear results were not sensitive to the increasing α (up to 30).

5.6.4 Limitations

Method limitation: Negative eigenvalues resulted from an excessively large deformation. It was assumed the strain matrix is positive definite. In term of mechanical behavior of materials, the element is under compression when the principal strain value is negative, and under tension when it is positive. Here, it was assumed to take into account the norm of eigenvalues in order to evaluate the principal strain.

Constitutive model: Due to constitutive law's behavior, during optimization task, the design parameter variable extremely increased when the input pressure was slightly increased, though the input pressure was not equivalent to its measured value in cardiac frame and was not changed spatially. However, constitutive models of tissue properties are a function of loading history, which varies spatiotemporally during the cardiac cycle, whereas its dependency was ignored during iteration process.

The impact of initial displacement in current FE LV model was discussed. The optimization algorithm appears to have difficulty identifying accurate nonlinear laws from the measured displacement data. Some of the estimated parameters were negative, which is not acceptable, and some were greatly overestimated. The failure of the algorithm for the FE LV model of the heart can be explained by the initial values as well as frame points that started from initial position. There are not tracked in instantaneous configurations to be updated in the iterations process. Since the LV shape is entirely deformed in each cardiac frame, the assumption of the initial value and initial displacement in all configurations might be completely irrelevant.

ABAQUS Optimization: Some constrain should be updated on Ogden material law in each iteration. The relative compressibility of the optimized model can be constrained to a maximum of 1 percent in Ogden Law by adjusting the ratio of its initial bulk modulus (K_0) to the initial shear modulus (μ_0), which must be mostly greater than 100 ($D=K_0/\mu_0$, or in Hook's Law by Poisson's ratio greater than 0.495). If this constraint cannot be satisfied in each step, the optimization will be stopped at that point.

5.7 Conclusion

In conclusion, we presented the simply open-source inversion routine to apply virtual displacements for the reconstructed patient's LV from the measured CMR data and revealed the identifiability of nonlinear hyperelastic parameters. The proposed characterization method is a significant step forward in the development of a biomarker, which utilize the estimated myocardial stiffness as clinical indices to detect subtle changes for myocardial dysfunction following doxorubicin chemotherapy. Moreover, this study verified the application of nonlinear VFM-based optimization which compared by FEMU results in a case study to prescribe its capability in the characterization of material parameter law.

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CHAPTER 6 GENERAL DISCUSSION

In this chapter, we first present the impact of this project. Then, we discuss significant reviews of the results obtained by different VFM approaches. At the end, the limitation merely related to the VFM application on heart motion will be reviewed.

6.1 Impact of the work

This research illustrated generally the implementation of linear and nonlinear VFM with LV models and its application to CMR, and particularly, FE mesh generation of patient-specific LV from the segmented images. The developed FE-based VFM that uses piece-wise virtual fields is more efficient than the conventional VFM that presents virtual fields as constant polynomial (Kim & Lee, 2021). In this approach, the reconstructed displacement fields into FE meshes using local shape function improved the accuracy of parameter identification in comparison with polynomial-based displacement fields that cannot cover full-field deformations.

6.2 Discussion on Results

In this project, in order to achieve the research objectives, the application of VFM to the stiffness estimation for isotropic, anisotropic and nonlinear hyperelastic models of LV myocardium has been achieved.

6.2.1 Isotropic VFM approach

The conventional VFM employed into isotropic case of LV that presents the user-defined (harmonic-based) virtual displacement fields (UDVFs), which could not be matched with the behaviour of the measured displacements. Thus, the resulting values of Poisson ratio estimated in each phase has noticeable variation and are not well determined. Assuming the LV is approximately incompressible, if the value of Poisson's ratio remained closer to 0.5 (0.4999), the isotropic VFM would provide better results. If the numbers of nodal displacements rise, the value of Poisson's ratio will be closer to the 0.5.

As LV filling during diastole experiences the minimum pressure and during systole pressure increases, differences in stiffness values has appeared. In isotropic case of LV myocardium, the estimated Young's modulus showed less variance than those estimated at higher LV pressures during systole.

6.2.2 Anisotropic VFM approach

For measuring the myocardial strain or stiffness in anisotropic case of myocardium, many studies has been performed through imaging modalities, including echocardiography (Fallah-Rad, et al., 2011; Lapointe, 2016; Lipshultz, et al., 2012) and elastography (Kolipaka, et al., 2010; Miller, et al., 2018). Furthermore, these studies used different anisotropic inversion methods to solve energy equation (Pierron, et al., 2012). For example, one previous study (Urban, et al., 2012) reported shear values (G_{13}) are between 1 - 15 kPa over cardiac cycle using FEMU inversion method and MRE imaging. Conversely, from the echocardiography and VFM application, (Lapointe, 2016) estimated shear modulus ranged approximately between 0.5-2 kPa and Young's modulus in fibre direction between 10-600 kPa, respectively for the hyperelastic and isotropic elastic myocardium. The discrepancy observed between estimated stiffness values because of not only the different inversion algorithm used, but also due to the fact that these studies use different scale of displacements depending on imaging modalities from either elastography (harmonic small displacement) (Tweten, et al., 2017; Tweten, et al., 2015) or echocardiography. However, we used large deformations, which previously obtained by CIM software over the cardiac cycle from cine-CMR images. Then, our results could somewhat verify that high difference between the estimated stiffness is due to the anisotropic VFM method used.

Piecewise VFM implementation with LV anisotropic case demonstrated the ability of its application to CMR. The identification of LV myocardial stiffness has even difficulties because of the mesh generation in complex geometry, nonlinear deformations, and fibre complex structures.

6.2.3 Hyperelastic Nonlinear VFM approach

In the proposed nonlinear VFM, on the top of everything, the primary results were obtained to find out whether it would be possible to separate the three groups of ALL-survivors based on hyperelastic parameters such as shear modulus. However, using FEMU simulation, it's been

proved that the estimated shear values for all of three subjects were affected significantly in presence of large displacements obtained from CMR acquisition. The effect of large displacements between time frames as well as boundary condition failed the identifiability of the material law within nonlinear cost function for the energy-based optimization.

6.3 Limitations

Since the heart is constantly beating, the dynamic study of its behaviour could provide a better understanding of the processes that cause dysfunction. In this study, a quasi-static hypothesis has been applied. This hypothesis greatly simplifies the complexity of VFM that was developed. However, incorporating the acceleration forces into the study of the heart would be interesting.

The assessment of LV stiffness (Young's and shear modulus) was performed within a small sample of patient subjects. Among the cancer survivors, we selected only nine of total subjects enrolled in PETALE study where SR, HR and HRdex group have three subjects respectively. To detect the probably subtle changes between groups, larger samples may be more appropriate. We consequently believe that the sizes of the three groups have affected our descriptive statistics to show high differences in myocardial stiffness.

In general, the measurements of the displacement field from CMR images can cause errors and discontinuities to obtain deformation field. Furthermore, the finite element approach approximates the strain fields for each element to apply into VFM. Therefore, this approximation essentially depends on the in-vivo measurements mostly affected by the resolution of the CMR images.

CHAPTER 7 CONCLUSION AND RECOMMENDATIONS

In this research project, the cardiac dysfunction caused by doxorubicin therapy was investigated by using the VFM identification of myocardial stiffness from CMR data. The results showed the capability of VFM method for the comparison of stiffness values between patients who were separated into three different group based on the cardiotoxicity level (dose). VFM has been estimated both anisotropic and hyperelastic properties for LV myocardium, respectively to the first and second article.

In parallel, this PhD research contributed to the development of (personalized) LV meshes model from Cine-MIR images which allowed to the application of FE-based (Piece-wise) virtual fields. In these approaches, the VFM application to the mechanical properties' estimation was mainly dependent on the constitutive model in which myocardium was assumed to be either isotropic or anisotropic. Likewise, optimizing a cost function based-on VFM allowed to investigate the identifiability of hyperelastic parameters in nonlinear material law. In addition, the latter was then validated on FEMU model.

Finally, this work clarified many unpredictable difficulties while applying VFM theory on full-field measurement data (experiment). These problems were to generate patient-specific mesh, to measure displacements from the segmented image data and to impose the cardiac pressure data, in term of external force that previously stored in our database. However, the advantages of using VFM in cardiac computational mechanics remains very applicable because of its performance in terms of computational efficiency (fast, robust, and simple approach) and the possibility that piece-wise virtual fields offer to locally characterize mechanical parameters.

In this project, we considered only one external force contribution, the cardiac pressure, which allows us to simplify our model with VFM implementation. However, it would be more accurate to study the heart motion by incorporating other loading impacts such as the volume forces and acceleration forces (inertial impact), which are not considered presently. In addition, in next studies, we aim to find the set of optimized virtual fields in presence of the noisy data that will be added to the measured displacements. Then, these virtual fields can be used to identify the constitutive parameter interest by minimizing the cost function.

The capability to reduce the impacts of uncertainty in the inverse problem results is demonstrated by (Deng et al., 2023; Mei et al., 2021) who visualized the regional changes of the identified stiffness parameters. Another perspective of this study is to implement different VFM approaches on the open-source finite element platforms. The proposed FE package can provide the distribution of the estimated local material properties over left ventricle volume without applying user-defined (manual) virtual fields. In addition, this perspective of FE-based VFM approach makes more convenient to present user-defined material constitutive models and find the stiffness parameter interest in ventricular soft tissues.

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APPENDICES

APPENDIX A MECHANICS OF SOLIDS

A.1 Definitions of the tensor

A tensor is a mathematical concept that allows multiple vectors to be grouped together. Tensors are commonly used in the field of solid mechanics to represent the state of a body under load.

In the Cartesian notation of tensors, the components of tensors are denoted by indices. In the stress tensor, for example, the component σ_{31} represents the shear vector in direction 3 acting on the face of the cube that is perpendicular to direction 1. It is worth noting that the stress tensor is always symmetric according to this definition.

The Einstein summation convention is based on the idea of summing over repeated indices within a term. Hence, we can express this concept in the following way:

$$\sum_i^3 u_i v_i = u_i v_i \quad \text{A 1}$$

The scalar product of two vectors therefore becomes:

$$\mathbf{u} \cdot \mathbf{v} = u_i v_i \quad \text{A 2}$$

In addition, the doubly contracted product between two second-order tensors is:

$$\mathbf{A} : \mathbf{B} = A_{ij} B_{ij} \quad \text{A 3}$$

In deformation mechanics, spatial derivations are often indicated by commas:

$$\sum_j^3 \frac{B_{ij}}{\partial x_j} = B_{ij,j} \quad \text{A 4}$$

A.2 Equilibrium

The equation of local equilibrium is applicable to any point within a body and can be expressed in the following:

$$\mathbf{div}\boldsymbol{\sigma} + \mathbf{b} = \rho\mathbf{a} \quad \text{A 5}$$

Where the variables of density (ρ), acceleration ($\mathbf{a}$), and volume force ($\mathbf{b}$) applied within the body. The traction vector $\mathbf{T}$ represents the force $\mathbf{f}$ that is applied to a surface dS . Also, it can be formulated as the scalar product of the Cauchy stress tensor $\boldsymbol{\sigma}$ and the normal vector $\mathbf{n}$:

$$\mathbf{T} = \frac{d\mathbf{f}}{dS} = \boldsymbol{\sigma} \cdot \mathbf{n} \quad \text{A 6}$$

A.3 Kinematics: Displacement–Strain Equation

According to the theory of infinitesimal deformations, the strain tensor is derived from displacement vector expressed by:

$$\varepsilon_{ij} = \frac{1}{2}(u_{i,j} + u_{j,i}) \quad \text{A 7}$$

A.4 Cancellation of the hydrostatic pressure by the virtual fields

The stress tensor can be divided into two parts: a hydrostatic part and a deviatoric part.

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^{hyd} + \boldsymbol{\sigma}^{dev} \quad \text{A 8}$$

The hydrostatic part corresponds to a fraction of the trace σ :

$$\sigma^{hyd} = \frac{1}{3}\sigma_{kk} = \frac{1}{3}tr(\boldsymbol{\sigma}) \quad \text{A 9}$$

We can represent the hydrostatic part in tensor form:

$$\boldsymbol{\sigma} = \begin{bmatrix} \sigma^{hyd} & 0 & 0 \\ 0 & \sigma^{hyd} & 0 \\ 0 & 0 & \sigma^{hyd} \end{bmatrix} \quad \text{A 10}$$

By integrating the two-part definition of the stress tensor, the internal energy of the material defined by:

$$W_{int} = \int_V (\sigma_{ij}\varepsilon_{ij}^*) dV \quad \text{A 11}$$

$$= \int_V \left(\left(\frac{1}{3} \sigma^{hyd} + \sigma_{11}^{dev} \right) \varepsilon_{11}^* + \left(\frac{1}{3} \sigma^{hyd} + \sigma_{22}^{dev} \right) \varepsilon_{22}^* + \left(\frac{1}{3} \sigma^{hyd} + \sigma_{33}^{dev} \right) \varepsilon_{33}^* + \sigma_{12}^{dev} \varepsilon_{21}^* + \dots \right) dV$$

$$\int_V \left(\frac{1}{3} \sigma^{hyd} (\varepsilon_{11}^* + \varepsilon_{22}^* + \varepsilon_{33}^*) \varepsilon_{11}^* + \sigma_{11}^{dev} \varepsilon_{11}^* + \sigma_{22}^{dev} \varepsilon_{22}^* + \sigma_{33}^{dev} \varepsilon_{33}^* + \sigma_{12}^{dev} \varepsilon_{21}^* + \dots \right) dV$$

A virtual field that cancels the contribution of the hydrostatic part of the tensor of stress tensor σ will therefore have the particularity of having a zero trace of strain tensor.

APPENDIX B DEVELOPMENT OF VFM APPLICATION TO THE 3D LEFT VENTRICLE

B.1 3D Methodology: Problem statement, Mathematical model, Hypothesis

In three dimensions, VFM can be applied to a volume of voxels rather than to an image formed by pixels. The main equations remain the same. The integrals of virtual work are calculated over the volume instead of the surface. Similarly, the integral of the external virtual work is calculated on the surface where the stress is applied instead of the line.

If we consider a constructed FE mesh, where the nodes are uniformly distributed in the geometry, we can then calculate the internal virtual work in the material by doing the sum over all the elements of the mesh. In the same way, we can calculate the external virtual work by making the sum on all the faces of the elements subjected to the external force.

First, it is necessary to calculate the location of the centroids of each element as well as the volume of these elements. Subsequently, the measured strain fields must be interpolated at the centroids. The virtual displacement and deformation fields are also calculated at the centroids of each element.

The calculation of the virtual external work requires a scalar product between the normal to the surfaces of the elements on the endocardium and the virtual field. Normal are obtained by taking the vector product of two edges that make up the endocardial surface of an element. Subsequently, the external work is calculated by summing over each element of the scalar product and multiplying by its element area.

The virtual internal work, meanwhile, is calculated by taking the tensor product of the stress tensor and the deformation field at the centroids of each element of the mesh multiplied by the volume of each element.

In order to simplify the calculations, the equations of the virtual fields are entered symbolically in MATLAB in order to automatically obtain the formulas of the derivatives of equations to the variable terms. This allows us to try several virtual fields quickly.

In order to apply the VFM to a case of 3D geometry, several assumptions will be considered:

- The myocardium can be characterized by linear elastic or incompressible hyperelastic behavior according to Ogden's law.
- The geometry mesh is used to discretize the energy equations in the principal of virtual work (PVW).
- Virtual fields (VFs) are described in prolate spheroidal or spherical coordinates.

In the initial FEM model, we need to use displacement boundary conditions to test the appropriate constraint being used for basal nodes. A fixed constraint is imposed at the basal level and a pressure is applied to the interior walls of the model (Wang, 2012).

B.2 Problem Formulation

The continuity of this research project aims to improve the solution of the 3D model by determining virtual fields kinematically admissible to the geometry and boundary conditions of the heart. These fields must be able to cancel the hydrostatic component of the stress tensor, (volumetric stress tensor) or mean normal stress tensor, is a component of stress which contains uniaxial stresses, and tends to change the volume of the LV under stress. In this manner, only the deviatoric part of stress tensor influences the results, which tends to distort LV.

The geometry being used is not subjected to any acceleration. Intraventricular pressure is applied to an endocardial surface generated from a network by finite element. Two coordinate systems are used in this study. First, the solution focuses on the non-uniform surface of cardiac geometries. The project is limited only to the left ventricle. This particular volume is defined according to a finite element network whose Cartesian data are used to represent the nodes.

To solve these equations, we will use the method of separation of variables. In addition, the Table B.1 shows the virtual fields solutions used to solve the geometry.

First, the method ensures to cancel the virtual fields applied to the end of model in boundaries by adding a component. This causes the phase of the final sinusoidal component to be equal to zero in those specific locations. In addition, this method effectively isolates all basal and apical nodes. These nodes are then used to particularly apply to the boundary condition.

B.2.1 Solution method

This innovative approach aims to use the ability of simple virtual fields to filter, naturally, the acquisition noise and to increase the solution speed when complex geometries are used. In other

words, VFM is a non-iterative method of solving problems that until now have only been solved by the finite element method (FE). According to this point of view, the use of the Virtual fields beyond FE is justified by its insensitivity to the geometry of solution and a better computing time.

The matrix equation 7.1 shows the link between the strain ϵ^* , and displacement u^* virtual in terms of spherical coordinates.

$$\begin{bmatrix} \epsilon_1^* \\ \epsilon_2^* \\ \epsilon_3^* \\ \epsilon_4^* \\ \epsilon_5^* \\ \epsilon_6^* \end{bmatrix} = \begin{bmatrix} \frac{\delta}{\delta r} & 0 & 0 \\ \frac{1}{r} & \frac{1}{r} \frac{\delta}{\delta \theta} & 0 \\ \frac{1}{r} & \frac{1}{r} \cot \theta & \frac{1}{r \sin \theta} \frac{\delta}{\delta \phi} \\ \frac{1}{r} \frac{\delta}{\delta \theta} & \left(\frac{-1}{r} + \frac{\delta}{\delta r} \right) & 0 \\ 0 & \frac{1}{r \sin \theta} \frac{\delta}{\delta \phi} & \frac{1}{r} \left(-\cot \theta + \frac{\delta}{\delta \theta} \right) \\ \frac{1}{r \sin \theta} \frac{\delta}{\delta \phi} & 0 & \left(\frac{-1}{r} + \frac{\delta}{\delta r} \right) \end{bmatrix} \begin{bmatrix} u_r^* \\ u_\theta^* \\ u_\phi^* \end{bmatrix} \quad 7.1$$

$$\begin{bmatrix} \epsilon_1^* \\ \epsilon_2^* \\ \epsilon_3^* \\ \epsilon_4^* \\ \epsilon_5^* \\ \epsilon_6^* \end{bmatrix} = \begin{bmatrix} \frac{\delta u_r^*}{\delta r} \\ \frac{u_r^*}{r} + \frac{1}{r} \frac{\delta u_\theta^*}{\delta \theta} \\ \frac{u_r^*}{r} + \frac{u_\theta^*}{r} \cot \theta + \frac{1}{r \sin \theta} \frac{\delta u_\phi^*}{\delta \phi} \\ \frac{1}{r} \frac{\delta u_r^*}{\delta \theta} + \left(\frac{-u_\theta^*}{r} + \frac{\delta u_\theta^*}{\delta r} \right) \\ \frac{1}{r \sin \theta} \frac{\delta u_\phi^*}{\delta \phi} + \frac{1}{r} \left(-\cot \theta \cdot u_\phi^* + \frac{\delta u_\phi^*}{\delta \theta} \right) \\ \frac{1}{r \sin \theta} \frac{\delta u_r^*}{\delta \phi} + \left(\frac{u_\phi^*}{r} + \frac{\delta u_\phi^*}{\delta r} \right) \end{bmatrix} \quad 7.2$$

The sum of the first three rows of the matrix (equation 7.2) in equation 7.3 is the general form showing the virtual field respects this condition. Knowing that the trace ($\epsilon_1^* + \epsilon_2^* + \epsilon_3^*$) must be zero, the VFs found are presented in Table B.1. The solutions result from the simplified system and the separation of variables.

$$\frac{\delta u_r^*}{\delta r} + \frac{2u_r^*}{r} + \frac{1}{r} \left(\frac{\delta u_\theta^*}{\delta \theta} + u_\theta^* \cot \theta \right) + \frac{1}{r \sin \theta} \frac{\delta u_\phi^*}{\delta \phi} \quad 7.3$$

The solution was made according to the following three possibilities:

$$\begin{aligned} u_r(r, \theta, \phi), \\ u_\theta(r, \theta, \phi) \text{ or} \\ u_\phi(r, \theta, \phi) \end{aligned} \quad 7.4$$

In this way the solution by separation of variables takes the form:

$$\begin{aligned} u^* &\equiv U_r(r)U_\theta(\theta), \\ u^* &\equiv U_r(r)U_\phi(\phi) \\ u^* &\equiv U_\theta(\theta)U_\phi(\phi) \end{aligned} \quad 7.5$$

	Virtual displacement fields	Associated constants	
VF1	$\begin{cases} u_r^* = -r * \sin(2\theta) * \cos(\phi)^2 \\ u_\theta^* = 0 \\ u_\phi^* = 0 \end{cases}$	No constant $\theta = \frac{\pi}{2} \cdot \frac{\alpha - \beta_{epi}}{\pi - \beta_{epi}} + \frac{\pi}{2}$	
VF2	$\begin{cases} u_r^* = -\sin(2\theta) * \sin(\phi)^2 \\ u_\theta^* = 0 \\ u_\phi^* = 0 \end{cases}$	No constant	
VF3	$\begin{cases} u_r^* = \frac{A}{r^2} + \frac{Br}{3} \\ u_\theta^* = B * r * (D * \csc(\theta) - \cot(\theta)) \\ u_\phi^* = 0 \end{cases}$	$\begin{cases} A = C_1 \sin(2\theta) \\ B = C_2 \sin(2\theta) \\ D = C_3 \end{cases}$	
VF4	$\begin{cases} u_r^* = 0 \\ u_\theta^* = \frac{-E+F\theta}{\sin(\theta)} \times r \\ u_\phi^* = (G - F\phi) \times r \end{cases}$	$\begin{cases} E = 0 \\ F = C_4 \frac{-F}{2\pi} \\ G = C_5 \sin(2\theta) \end{cases}$	

VF5	$\begin{cases} u_r^* = r^2 + \frac{lr}{3} \\ u_\theta^* = 0 \\ u_\phi^* = \frac{J}{\sin(\theta)} \end{cases}$	$\begin{cases} H = C_6 \sin(2\theta) \\ I = C_7 \sin(2\theta) \\ J = C_8 \end{cases}$	
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Table B. 1 Correspondence between virtual fields and notation used. To simplify the notation, assume $C_n \equiv 1$ ranging from $n=1$ to 8. However, each value of C_n is independent of the others.

Obtaining the u^* virtual allows to find a general shape corresponding to the hydrostatic (trace equation 7.2) and deviatoric parts of the tensor. The solution of the matrix system provides displacement shape functions. The shape function creates the relation between virtual deformation and virtual displacements. Depending on the model description, the transformation matrices also can be written in prolate spherical or cylindrical coordinates.

Moreover, boundary conditions have been applied and used in order to simplify the equations later. The constants C_n , however, are preserved for this project and the further study to know whether it is possible to optimize the results with these constants.

B.2.2 Kinematic Conditions

The model must meet a few boundary conditions. We defined these conditions which affect the virtual fields earlier found (Table B.1). First, the geometry used within CIM network is assumed cut at the basal and apical levels of the left ventricle. The solution of this preliminary model is facilitated by considering the basal level to be fixed. The virtual fields must then be zero at the basal and apical level, in addition to be continuous over the rest of the geometry. Figure B.1 illustrates the areas for which the virtual field must be cancelled due to the shape of the network. The developed virtual fields will be tested to validate whether the hydrostatic component of the stress tensor is really cancelled.

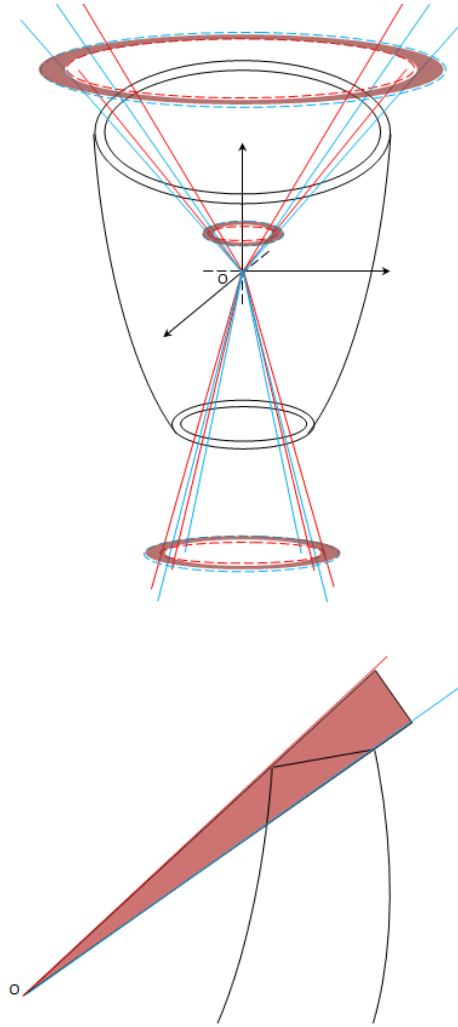


Figure B. 1 Definition of the boundary condition used to cancel the virtual fields according to the basal and apex levels of the traced network. (a) Red lines shown the paths crossing the endocardium, and blue lines are shown the paths crossing the epicardium. (b) The red portion represents the volume (conical areas) where the VFs must be zero.

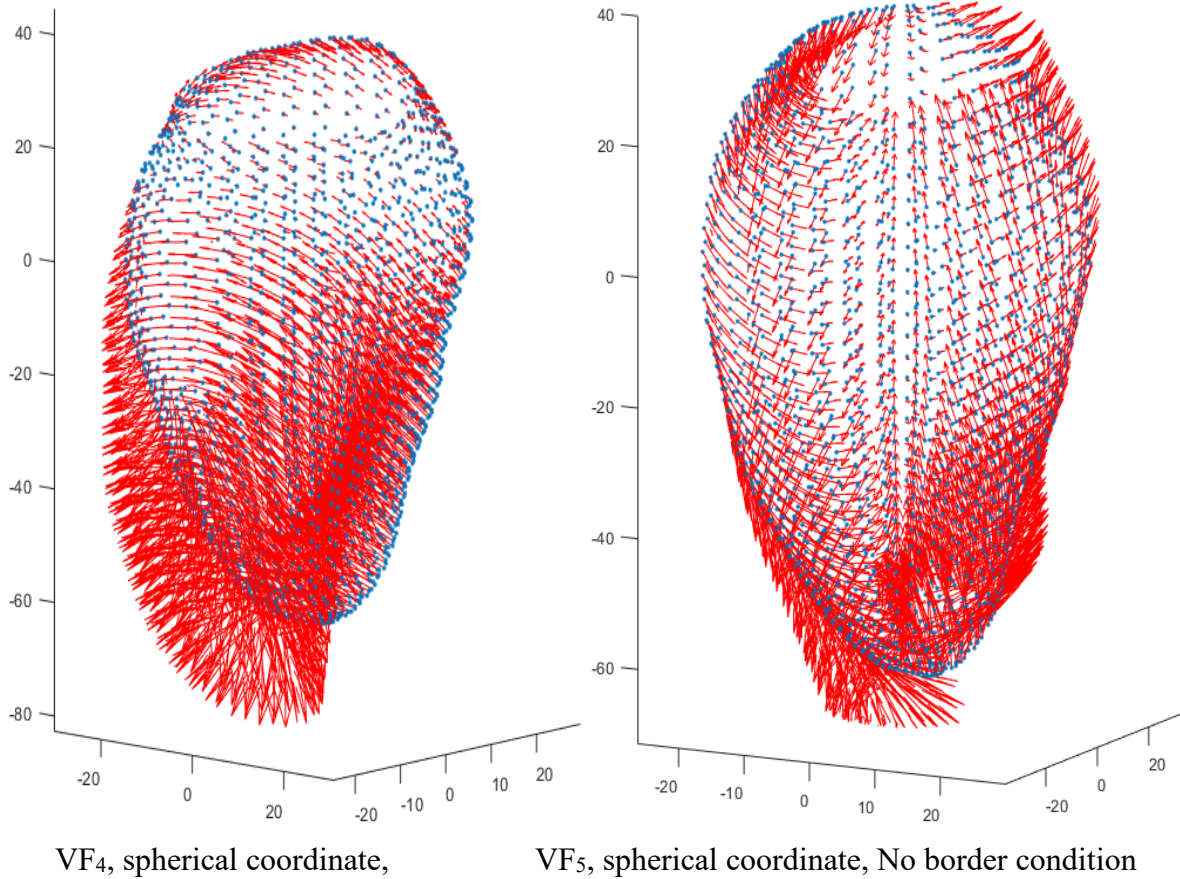
Basal Nodes Definition

For the accuracy of the results, in order to ensure that the boundary conditions are adequately implemented, it is necessary to validate the BC implementation. As the basal node's angle are no longer constant, it is important to determine the basal and apical epicardium nodes to apply zero virtual displacement $VF=0$ to them.

The initial model determines the set of endo and epicardial nodes of the basal plane and the apex. Since the format of the imported data is in Cartesian coordinates, the elevation angle θ is calculated earlier for these nodes to have sinusoidal components Table B.1.

Virtual fields Description

The virtual fields represented in MATLAB with the symbolic notation, so that they apply effectively to all the nodes Figure B.2 and speeds up the calculation process. Furthermore, it is important to mention that spherical coordinates are required for VF calculations, but the results are finally converted back to Cartesian coordinates.



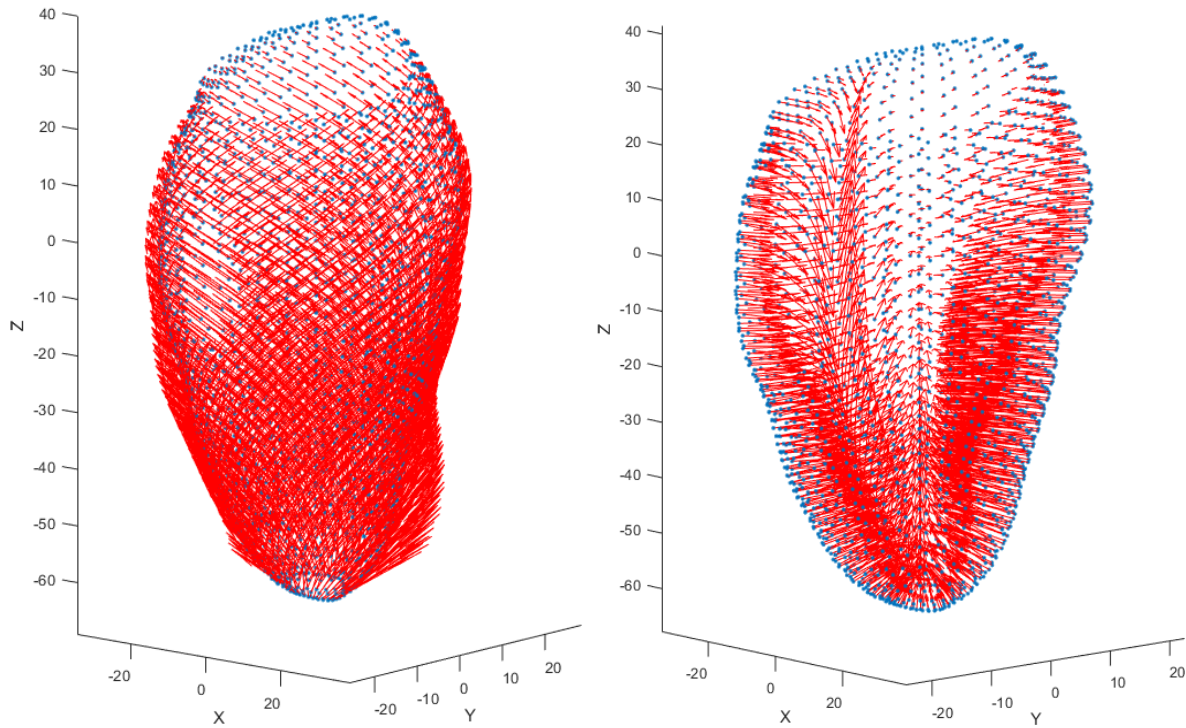


Figure B. 2 VF4, prolate-spherical coordinate, VF3, prolate-spherical coordinate,

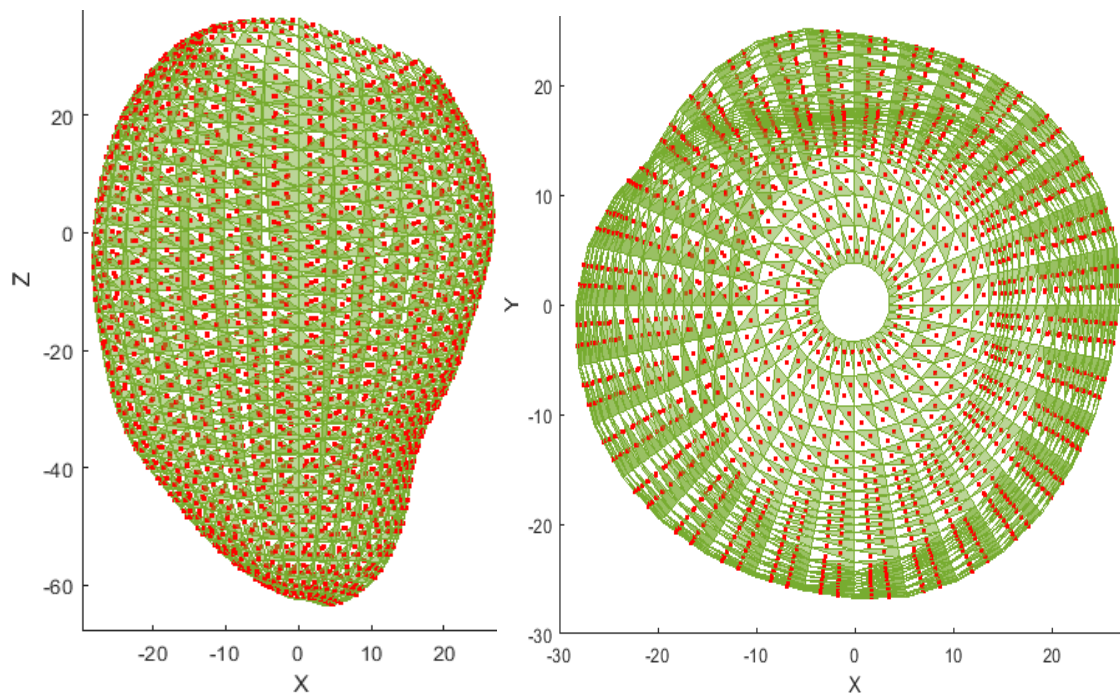


Figure B. 3 The centroids of each element surfaces (endocardium) for which each element belongs to, are well determined by points where the pressure is located.

B.3 Model Limitation

As the project is still in the preliminary phase, minimizing the potential uncertainties is very justifiable because the order of magnitude of the changes in the constitutive properties of the tissues is still unknown.

However, this model was created from the data exported by CIM program which was developed at the AUCKLAND University. In reality, working with raw data can be more complex in spite of the given space and the certain routine where the data is encoded in CIM. More ever, CIM is a three-dimensional visualization program where space is not defined by Cartesian coordinates. The first dimension of this environment is linear, the second is surface, and the third is volume. As CIM is based on a Gaussian point solution, it's difficult to determine precisely what is the displacement of each of the nodes of the finite element network. However, it is important to mention that the location of the 34 nodes required to generate the 16 subdomains in CIM is known.

APPENDIX C CARDIAC IMAGE MODELING

C.1 Details on the Measured Data

In this project, the initial problem was to realize numerical data and some parameters from the output CIM files exist. There were many kinds of quantitative data points saved for each cardiac frames (temporal tracking); spatial coordinates, first and higher order partial derivative values (displacement to the spatial components), Element numbers, Node numbers, nodal displacements, strain, and stress in elements which all were previously stored within Output CIM documents.

Moreover, there were a few slices (only 14 slices) obtained by CMR acquisition for each frame, which don't cover displacement fields over the full LV volume. Then, CIM couldn't track entire LV deformation from apex to base for the certain phase in Z direction, while semi-automatically doing segmentation in short axis view. Although we assumed the full field (actual or reconstructed strain) can be measured from the MR images exist, CIM output reported only a few elements number with specific node's index (connectivity node list) as well as their associated values in term of actual data. Given to this issue, in each element, we have to find unknown nodal virtual displacements, where the number of unknown material parameters are supposed to be equal to the number of those unknown virtual displacements.

Then, in this research, we should have explained how to derive finite element presentation from principal of virtual work, in other words, implementation of (Application) piece-wise function of virtual field displacements using FEM formulation. In particular, the technique made denotes a formulation of elastic matrix with some components, in terms of anisotropy. They are formulated by the standard shape function called cubic element with higher degrees of freedom, which probably ensure the continuity of virtual field displacements for the smooth representation of personalized LV shapes.

C.2 Cardiac Image Modeling (CIM)

Cardiac Image Modeling (CIM) represents a new approach to the analysis of cardiovascular MR images. The software (CIM) creates guide-point models to produce traces of LV cavity volume and wall mass as a function of time for the entire cycle. LV volumes and mass were calculated at

each frame throughout the cardiac cycle. In Cine-CMR, endocardial and epicardial surface data tracks LV deformation.

C.2.1 Geometry Display and Definition

Cardiac Axis. In the early stages of the Guide Point process, points are defined at the apex, base and at the insertion of the RV into the LV, Figure 2.9.

Base-Plane Points. CIM takes the Base-plane points and fits a circular plane through them for each phase of the cardiac cycle.

These points also create a plane in 3D which moves with the cardiac cycle to define a surface limit for the calculation of blood volume and mass.

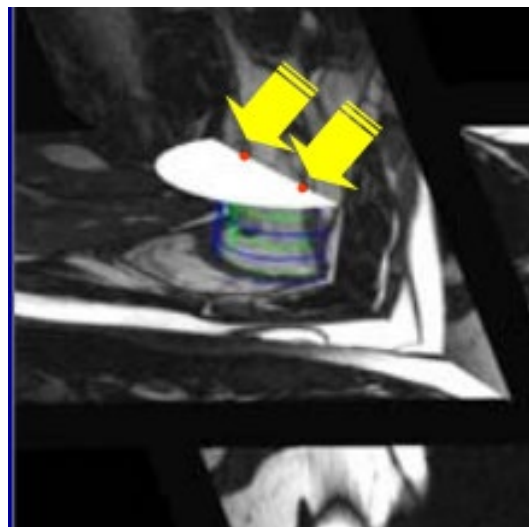


Figure C. 1 Circular white planar fitted to Base plane points.

RV Points. The RV insertion points are defined on the end-diastolic image only and therefore do not move with the cardiac cycle. This information is used to determine where the RV is for the purposes of defining regional wall motion.

Collectively, the apex, base and RV points are used to define a coordinate system, and then used to create 2D geometry contours by the guide point fitting. These points are also used to determine regions for the purposes of defining regional strain.

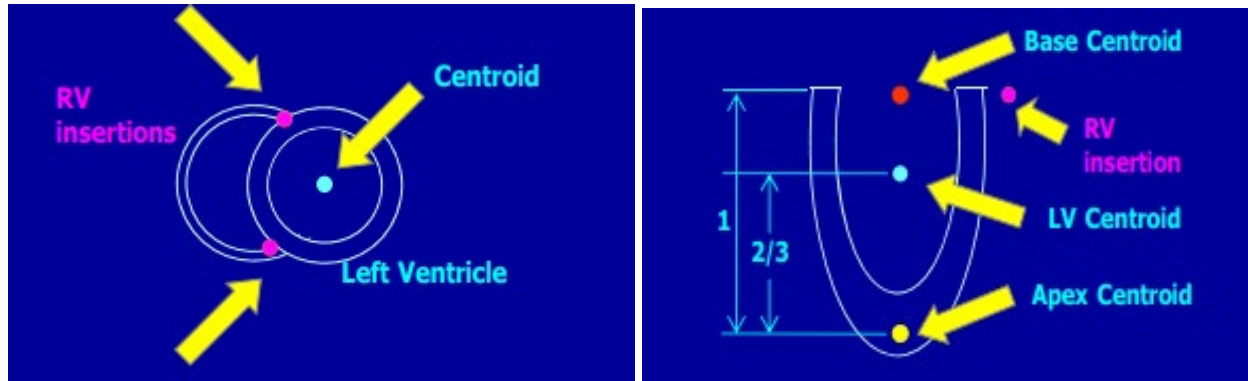


Figure C. 2 Markers points are used to define the coordinate system (a) in short axis model (b) long axis model. These points are LV centroid, RV points, basal centroid, and apex point.

C.2.2 Guide Point model

Six guide points were used to semi-automatically draw the inner and outer LV boundary walls:

- guide point of apex
- guide point of basal
- 2 insertion guide points of right ventricle
- 2 guide points of base plane

Placed at the end of systole by the operator, and any miss-registration errors manually corrected.

C.3 Image Segmentation

The data collection consists of subject-specific LV cavity pressure and LV image data covering diastole, systole and were collected previously from (CIM database Mariana) to characterize accurately the ventricular motion and shape. In CIM software, user/operator load the patients' image data, and create a configuration cardiac space by uploading the long-axis and short-axis MR slices. The images from the patient are registered and stored in the database model. The intersection of the model with each of the image planes is determined to represent the endocardial and epicardial contours. In second step, the beginning of segmentation/imaging process step, to accurately position and orientate the reference model from the database onto each patient's images, CIM needs to identify the location of apex, basal, LV centroid, base-plane points, and insertion of the right ventricle for each frame. Collectively, these points define a coordinate system to be used by guide-point fitting, separate endocardial and epicardial surfaces. In addition, the Base-plane which moves with the cardiac cycle to define the surface limits for volume

calculation. Guide points need to be placed on the endocardium and epicardium. CIM will then use these points to change the shape of the model. The model is designed to deform to match the patients' image data and move in response to two main types of Guide-Point input from the user. As a result, this information enables the adaptation of the original generic model to the subject's ventricle shape for a typical CMR dataset. Here, each CMR sequence has 25-segmented frames, which tracks the inner and outer LV wall boundaries spatially from apex to base, as well as temporally continuous description of the cardiac LV motion along the cycle from one image to the next one using a non-rigid registration (Lam, 2012). The geometric data extracted then will be used for the mechanical simulations described in the next sections.

C.4 3D initial generic model

MATLAB function creates struct array of CIM parameters are the following: 'Focal Length', which is scalar value representing average focal distance of points on truncated ellipsoid model of the Left Ventricle. ' λ Parameters', ' μ Parameters', ' θ Parameters' are vector respectively with 134, 40, 40 arrays in prolate spherical coordinate. They are called transmural (radial), azimuthal, and circumferential component of the LV model.

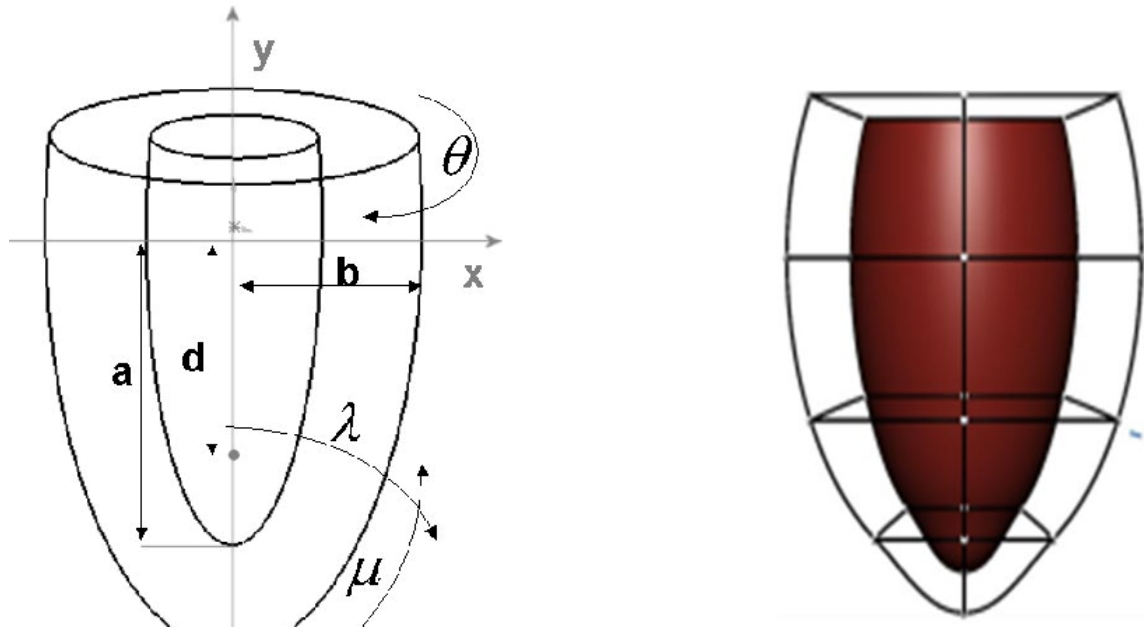


Figure C. 3 (a) prolate spherical coordinate as shown three parameters of λ , μ and θ , presenting the radial, azimuthal, and circumferential components respectively, (b) Initial ellipsoidal model of 16 regions from 34 points.

- θ and μ sample points.
- matrix sample elements E: sample values between element nodes, where N is the total number of samples.
- nodal elements: 4×16 , where each column is the 4 corners of the element.

To reconstruct and visualize CIM model in MATLAB, the LV4*4SurfaceModel object assumed consisted of 16 cubic Hermite elements, which consisted of 4 circumferential, 4 longitudinal, and 1 transmural element that connected 34 nodes. The Next step must create surface sampling Map ($\mu:33 \times \theta:33$), where the rows start from base (row=1) to apex (row=33), and columns start from 0 (first=1) to 2π (last=33).

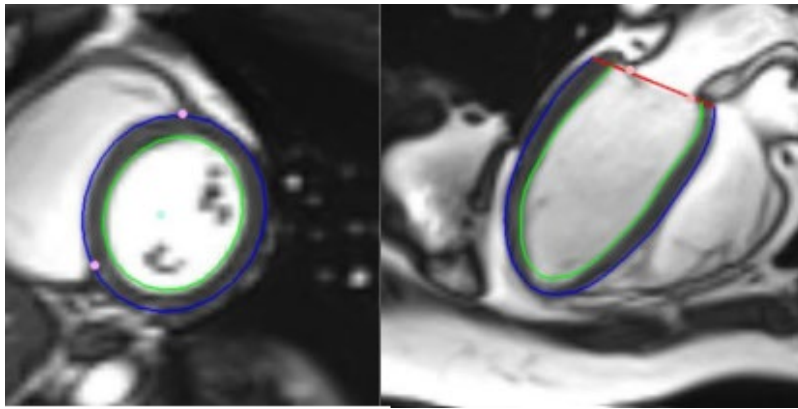


Figure C. 4 Segmentation processed in CIM, Short axis (left), long axis (right) view of MRI data through Guide-point modeling



Figure C. 5 Sampled surface points, Epi (black); Endocardium (red)

APPENDIX D MATLAB CODE IMPLEMENTATION

The implementations in terms of codes in MATLAB will let us load a CIM model (from output generated by guide point modelling technique) to perform various useful operations, from which we can then construct a FE model mesh:

Demo.m

We create a run file called Demo.m, and 2 model with different class are defined. To show LV motion model, the class defined as LVMM LV Motion Model with categorized properties. It has advantage to recall variable parameter once it requires to be updated.

LVMM properties are the following:

The name of patient model, frame number, ending diastolic frame ED, ending systolic frame ES, existing data of each file model, also 5 characteristic parameter of LV which refer to: end diastole volume EDV, end systole volume ESV, stroke volume SV and ejection fraction EF, and Mass.

The MATLAB codes that might be executed for the project are called:

ReadFromCIMfolder.m, ReadCIMdata.m, UdateGlobalLVfunction.m:

D.1 Function ReadFromCIMfolder.m

ReadFromCIMFolder is a static object factory function to create an LVMM **object** from a CIM (Cardiac Image Modeler) software package. It tries to read all CIM data files available in given folder of each patient model. They are planes, volume information and slices numbers, which all saved in model, format as outputs coming from CIM software.

This code allow user to just pass file path and remove searching difficulty for model files. Also, it precise model files in given folder and respectively sort/list all frame numbers.

To start reading this file, first check the existing current folder and the given direction. Then get model name. The models file contains a cell array of 25 model-file as given the cardiac frames.

The function ReadCIMModelFileRaw.m help to read raw data from CIM model filename. It creates struct array of CIM parameters are the following:

'Focal Length', which is scalar value representing average focal distance of points on truncated ellipsoid model of the Left Ventricle.

- 'LambdaParameters', a vector with 134 arrays in prolate spherical coordinate.
- 'MuParameters', a vector with 40 arrays.
- 'ThetaParameters', a vector with 40 arrays.
- 'BasePlanePoints', a vector with 3 elements or dimension.
- 'BasePlaneNormal' a vector with 3 elements or dimension.
- 'ModelToMagnetTransform', a 4-by-3 matrix of array dimension indicates transformation matrix indexed by i, j and k characters.

This code open CIM file, read line by line while skip empty line, count the number of elements, and find which type of parameter it is.

In continue, it estimates ES and ED frames by calculating frame index of the maximum and minimum EDV and add/put into LVMM object and will change the L.ed and L.es values.

Next, the function ReadCIMData.m help to update the LV Motion Model (LVMM) object. It Create structure array that groups related plane data using with 3 fields.

First, to get plane information, start reading plane files. This file contains the 3D-coordinates of the top left, top right, and bottom left corners of each of the planes (i.e., locations) for which data was recorded. It also stores slice and phase number listed in 2 more columns.

Second, then get slice number to specify Image Position offset of X, Y, Z, image orientation, and slice thickness.

Third, start reading guide points as given names for description of related data:

- GP_APEX_CENTRAL_AXIS: guide point of apex
- GP_BASE_CENTRAL_AXIS: guide point of basal or base
- GP_RV_INSERTION: guide points of right ventricle
- GP_BASE_PLANE: guide points of base plane
- GP_LV_ENDO: guide point of left ventricle endocardium surface
- GP_LV_EPI: guide point of left ventricle epicardium surface

D.2 Function L = ReadCIMGuidePoints (cim_folder, mfolder, varargin)

This function reads guide points from a CIM folder and update the LVMotionModel object L.

Table D. 1 The guide point format defined

1	2	3	4		5	6	7	8
X	Y	Z	TYPE		WEIGHT	SERIES(0,1)	SLICE(from_0)	PHASE(from_0)

D.3 Function UpdateGlobalLVFunctions(L)

Compute global LV functions: EDV, ESV, MASS, SV, and EF. End-diastolic volume EDV is estimated on the cardiac frame with the largest LV cavity volume, while End-systolic volume ESV is measured on the frame with the smallest cavity volume. Stroke volume is calculated as the difference between end-diastolic and end-systolic volumes. Estimates of ejection fraction are derived from the ratio between stroke volume and end-diastolic volume. LV mass is obtained by subtracting the endocardial from the epicardial volumes at each slice and by multiplying this difference by the density of myocardial tissue (1.05 g/mL). (Young et al., 2000).

When this function run, due to the parameters have changeable properties, which are defined in LVMM class, it allows user to access data LVMM structure. So, it gets frame number, then call main function model (L, Frame).m to create LV4*4SurfaceModel object. It's a class to generate sampling points for 4x4 LV surface FEM.

D.3.2 LV4x4SurfaceModel

It allows user to change some properties: theta and mu sample points, number of surfaces, RC transformation matrix and let user attach any data to model as a field of struct array.

It also contains read-only properties: and user can change these model parameters using SetParams function:

Table D. 2 Output parameters of LV4x4SurfaceModel object

lambdaParams	the transmural component of the LV model
---------------------	--

focal Length	Focal length of the LV model
muParams	the azimuthal component of the LV model
thetaParams	the circumferential component of the LV model
G2E	Global to element mapping for each prolate spherical components
surfacePoints	surface points in rectangular Cartesian columns are [X Y Z]
surfacePSPoints	surface points in prolate spherical coordinates columns are [theta mu
basis	basis functions
E	sample values between element nodes

E is N x 4 matrix, where N is the total number of samples, and each column is:

- col 1 = sample values for dimension 1 (theta)
- col 2 = sample values for dimension 2 (mu)
- col 3 = surface sample values
- col 4 = element numbers

Map anatomical mapping of the surface elements

Nodes nodal elements: 4x16, where each column is the 4 corners of the element in the following order: [bottom-right top-right bottom-left top-left]

It is a Class constructor and Calling `L = LV4x4SurfaceModel` will create an empty model with default properties: in default, it defines the number of samples between two element nodes on the LV surface and the number of surfaces (max 2).

D.3.3 Function `L = Create (focal Length, lambdaParams, muParams, thetaParams)`

Create an `LV4x4SurfaceModel` from with using 4 inputs: focal Length, lambdaParams, muParams, thetaParams, which all are previously presented.

Inputs: - focal Length = a scalar for the model's focal length,
lambdaParams = 134 elements of global lambda parameters,

muParams = 40 elements of global mu parameters,
 thetaParams = 40 elements of global theta parameters.

Optional arguments:

'Mapping', string or a struct.

Define GLM mapping to use. Default is 'CIM'.

Available mapping strings

If the struct is used, then it should have the following fields:

Lambda : [512x134] double

Mu : [128x40] double

Theta: [128x40] double

Empty model

L = LV4x4SurfaceModel.

D. 3.3.1 Function L = UpdateSampling (L)

This function is called usually because of changes in the number of samples / surfaces properties / (set parameters [Lambda Mu Theta]).

In order to create 4x4 finite element model of a 2D surface with each element contains 3x3 samples, it calls matrix sample elements E.

E = LV4x4SurfaceModel.RectangularSampling ([4 4], L.nSamples (9×9))

D. 3.3.1.1 Function E = RectangularSampling (nElements, nSamples)

It Generates samples between elements on a 2D surface without duplicate samples. The sample values are between 0 and 1 for each element.

Inputs: - elements is 2x1 vector to define the number of elements per dimension.

- nSamples is 2x1 vector of the number of sample values per dimension.

Columns of E = [e1, e2, e_{id}]

Output: - E (1089 x 3) will be a matrix of N x 3, where N is the total number of samples, and each column is:

- Col 1 = sample values for dimension 1,

- Col 2 = sample values for dimension 2,

- Col 3 = element numbers, 1089

Update basis functions

L.basis.Lambda = L.ComputeBasisFunctions (L.E, 32,'bicubic-linear'); % lambda

L.basis.Mu = L. ComputeBasisFunctions (L.E, 8,'trilinear'); % mu

L.basis.Theta = L. ComputeBasisFunctions (L.E, 8,'trilinear'); % theta

D. 3.3.1.2 Function **P = ComputeBasisFunctions (elmts, nBasis, basisType)**

It Calculate the basic functions from the LV model defined by 4x4 surface sampling (theta & mu) and the 2 surfaces: endo and epi.

Input: elmts is a Nx4 matrix of N sampling points, where columns are: $[2178 \times 4]$

- [dim1_samples, dim2_samples, dim3_samples, element number]
- nBasis is the number of basis:
- basisType value is the following:
- 'trilinear', B: $[2178 \times (3*2)]$
- 'bicubic-linear'

Output: P $[2178 \times (8*8*8)]$ is a sparse matrix that contains the basis functions for each element node.

D. 3.3.1.3 Function **[M, N] = CreateSamplingMap(L)**

Regarding to the given sampling elements (L.E), this function outputs the surface map M, where M is $n_{Mus} \times n_{Thetas}$ $[33 \times 33]$. The rows start from base (row=1) to apex (row= n_{Mus}). The columns start from 0 (first) to 2π (last).

The other output N is the nodal element indices: $[4 \times 16]$

Surface mapping M (33×33):
$$\begin{bmatrix} 9 \times 33 \\ 17 \times 33 \\ 25 \times 33 \\ ([Mus * Theta] || [0 - 2\pi]) \end{bmatrix}$$

First, start to get sample element value 9×9 to create the first element row (1, 2, 3, and 4)

Then, create the last three element rows (5-8) (9-12) (13-16)

And finally combine all created element row into M matrix

Nodal Element (4×16):
$$\begin{bmatrix} 1 - 4 \\ 5 - 8 \\ 9 - 12 \\ 13 - 16 \end{bmatrix}$$

D. 3.3.1.4 Function **L = AssingCIMMap(L)**

This function assign CIM's GLM mapping to an LV object

Read the global to element CIMM conversion (it's fixed).

And apply this mapping for 32 nodes:

Transform the local nodes to our numbering scheme using the map below:

Map (1×32) = [1, 2, 5, 6, 4, 3, 8, 7, 13, 14, 9, 10, 16, 15, 12, 11, 17, 18, 21, 22, 20, 19, 24, 23, 29, 30, 25, 26, 32, 31, 28, 27].

L.G2E.Lambda (512×134)

L.G2E.Mu (128×40)

L.G2E.Theta (128×40)

D. 3.3.1.5 **function L = UpdateModel(L)**

This function Update the LV model. Note this is a private method for LV4x4SurfaceModel class.

Calculate the element points (mind phase correction):

Lambdas = L. basis. Lambda (2178×512 sparse double) * L.G2E.Lambda (512×134) * L. lambdaParams (134×1);

mus = L. basis. Mu (2178×128 sparse double) * L.G2E.Mu (128×40) * L. muParams (40×1);

Thetas = L. basis. Theta (2178×128 sparse double) * PhaseCorrect (L.G2E.Theta * L. thetaParams (40×1));

Function out = PhaseCorrect(in)

That makes sure there are no large 'jumps' in the data from $3/2$ pi to 0 and converts 0 to pi.

Here, final surface points are updated:

L.surfacePSPoints = [thêtas mus lambda] ;

Now Prolate to Euclidean conversion

L.surfacePoints = LV4x4SurfaceModel.Prolate2Cart(L.focalLength,lambdas,mus,thetas);

When the function read completely, it returns to the function Updatesampling (L) D. 3.3.1, and then to the function Create (focalLength, lambdaParams, muParams, thetaParams) D.3.3 to finally set new parameters using function SetParams.

D. 3.3.2 **function SetParams (L, newFocalLength, newLambdas, newMus, newThetas)**

- L.focalLength = newFocalLength;
- L.lambdaParams = newLambdas.
- L.muParams = newMus.
- L.thetaParams = newThetas
- L.UpdateSampling.

End

Here, the last update of L = LV4x4SurfaceModel presented:

LV4x4SurfaceModel with properties:

- nSamples : [9 9]
- nSurfaces : 2
- T : [4×3 double]
- Data : [1×1 struct]
- lambdaParams: [134×1 double]
- focalLength: 38.0566
- muParams: [40×1 double]

- ThetaParams : [40×1 double]
- G2E : [1×1 struct]
- SurfacePoints : [2178×3 double]
- SurfacePSPoints : [2178×3 double]
- basis: [1×1 struct]
- E: [2178×4 double]
- map: [33×33 double]
- nodes: [4×16 double]
- nCirc: 33
- nAzimuth: 33

At the end it goes back to the Function UpdateGlobalLVFunctions(L) to update global LV functions: EDV, ESV, MASS, SV, and EF.

D. 3.3.2.1 function V = ComputeVolumes(L)

It computes endo and epicardial volumes for each frame. To find updates for next frames from 2end to nth frame, apply function SetParams (L, newFocalLength, newLambdas, newMus, newThetas) in a loop and then start to get volumes for all the frames.

For fi=2:L.nframes

Li.SetParams(L.focalLengths(fi),L.lambdas(:,fi),L.mus(:,fi),L.thetas(:,fi));

V.endo(fi) = Li.GetEndoVolume.

V.epi(fi) = Li.GetEpiVolume.

End

% volume & mass

V = CalculateVolume (L, si);

Function V = GetEndoVolume (L)

V = L. CalculateVolume (1);

End

D. 3.3.2.2 function V = CalculateVolume (L, Si)

It calculates volume defined by a surface index S_i

Input: S_i is a surface index from 1 (endo) to L.nSurfaces (epi).

Output: V is volume in ml.

- First get the enclosed surfaces represented by triangle, then make a structure with following fields: triangle faces that points indices, and list of vertices according to each face:
 - FV. Face: [2145 × 3]
 - FV. Vertices: [6337 × 3]

% get the enclosed volume

Function [FV] = GetClosedSurfaceTriangulation (L, si)

```

% Get the enclosed surface triangle representation.
%
% Output: - FV is a structure with the following fields:
%       FV. Faces: triangle faces those points' indices in FV. Vertices
%       FV. Vertices: list of vertices for each face
%       This representation is similar with patch
%       - To get face definition for a surface triangulation, create Matrix N×3 where N is the
%         number of faces defined by 3 points.
Function F = GetSurfaceFaces(L,si)
% Get the faces definition for a surface triangulation (see doc patch).
%
% Input: - Si is the surface index between 1 to L.nSurfaces,
%       or 'endo' or 'epi'
% Output: - F is Nx3 faces where N is the number of faces and each column points to a L. surface
%       Points row index that defines a vertex.
%       each row is one triangle face.

% if 2D mesh grid of the surface is defined by these indices:
%   1  2  3
%   4  5  6
%   7  8  9

% Then the faces are defined like this
% F1 = 1 4 2
% F2 = 2 5 3
% F3 = 4 7 5
% F4 = 5 8 6
% F5 = 2 4 5
% F6 = 3 5 6
% F7 = 5 7 8
% F8 = 6 8 9
Function V = VolumeByTriangulation (Faces, Vertices)
% Compute volume approximated by triangulation

```

```

%
% Volume of a patch is approximated by:
%  $V = | \det \begin{bmatrix} \text{FV1} & \text{FV2} & \text{FV3} \\ \text{C1} & \text{C2} & \text{C3} \end{bmatrix} |$ 
%      FV1 FV2 FV3
%      FV1 FV2 FV3
%      FV1 FV2 FV3
%      C1  C2  C3
%      ] |

```

Where [C1, C2, C3] is the mean point of the patch [FV1, FV2, FV3].

So, we can approximate the volume of the heart by sum of volumes of each Patch to the mean point. We assume that there is no hole in a heart.