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SCHOOL OF SCIENCES AND ENGINEERING

A Computational Model for Dilated Cardiomyopathy:

Morphology and Electromechanics

BY

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

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December 2018
Abstract

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A Computational Model For Dilated Cardiomyopathy: Morphology and Electromechanics

The aim of this thesis was to develop a computational model that can simulate the key changes in morphology and electrophysiology that are observed in patients of dilated cardiomyopathy (DCM), and to predict the associated diastolic (mechanical) dysfunction. The computational model herein developed was then applied to an in-silico study of cardiac resynchronization therapy (CRT) to assess its potential utility as an investigative tool in clinical research. Specifically, the DCM model herein developed captures three beats of a human heart (male, in his mid-twenties). The case of DCM represented herein also possesses a left bundle branch block (LBBB). LBBB alters the sequence of electrical activation across the cardiac domain, leading to ventricular asynchrony and hampering cardiac systolic and diastolic functions, as is typical in DCM patients.

A methodology for the cardiac growth and remodeling (morphing) was thus developed to represent the dilation of ventricles of DCM patients, based on an application of thermal expansion techniques. Then, a hierarchically coupled electromechanical model was set up to simulate the effect of DCM and LBBB on cardiac function. Predictions from our model were then compared to the literature and to clinical data that was made available to us by the Aswan Heart Centre (AHC) as part of a collaborative research project between the Magdi Yacoub Foundation (MYF) and the American University in Cairo (AUC). The computational platform used in this work is the SIMULIA Living Heart Human Model (LHHM), which is associated with the finite element solver ABAQUS. The LHHM is presently only available to members of the Living Heart Project (LHP).

The proposed methodologies have fairly produced relevant models representing LBBB and DCM, which was successfully validated in comparison to the literature and to clinical data.
Acknowledgment

I would like to thank all who in one way or another contributed in the completion of this thesis. First, I give thanks to God for protection and ability to do work. I would like to express my deep gratitude to my advisors Dr. Khalil El Khodary and Dr. Mohamed Badran for their patient guidance, invaluable help, unwavering support and constant motivation throughout this research work. My sincere thanks also go to Dr. Heba Aguib and all the research team in Magdi Yacoub Foundation for their collaboration and support in this research work. Finally, I wish to thank my family and friends for their support and encouragement throughout the study.
## Nomenclature

### List of Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACA</td>
<td>Adaptive Cellular Automaton</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AHC</td>
<td>Aswan Heart Center in Egypt</td>
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<tr>
<td>AP</td>
<td>Action Potential</td>
</tr>
<tr>
<td>AV</td>
<td>Atrio-ventricular node</td>
</tr>
<tr>
<td>AVB</td>
<td>Atrioventricular Block</td>
</tr>
<tr>
<td>AVD</td>
<td>Atrioventricular Delay</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats Per Minute</td>
</tr>
<tr>
<td>BVP</td>
<td>Biventricular Pacing</td>
</tr>
<tr>
<td>CRT</td>
<td>Cardiac Resynchronization Therapy</td>
</tr>
<tr>
<td>DCM</td>
<td>Dilated Cardiomyopathy</td>
</tr>
<tr>
<td>E/A</td>
<td>Ratio of early to late ventricular filling</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDV</td>
<td>End diastolic Volume</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection Fraction</td>
</tr>
<tr>
<td>ESPVR</td>
<td>End Systolic Pressure Volume Relationship</td>
</tr>
<tr>
<td>ESV</td>
<td>End Systolic Volume</td>
</tr>
<tr>
<td>HF</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
</tr>
<tr>
<td>LBB</td>
<td>Left Bundle Branch</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left Bundle Branch Block</td>
</tr>
<tr>
<td>LHHM</td>
<td>Living Heart Human Model</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
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<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVEDD</td>
<td>Left Ventricular End Diastolic Diameter</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>RA</td>
<td>Right Atrium</td>
</tr>
<tr>
<td>RBB</td>
<td>Right Bundle Branch</td>
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<tr>
<td>RBBB</td>
<td>Right Bundle Branch Block</td>
</tr>
<tr>
<td>RV</td>
<td>Right Ventricle</td>
</tr>
<tr>
<td>RVEF</td>
<td>Right Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>SA</td>
<td>Sinus-atrial node</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke Volume</td>
</tr>
<tr>
<td>VVD</td>
<td>Interventricular Delay</td>
</tr>
</tbody>
</table>
Table of Contents

Abstract ................................................................................................................................ II
Acknowledgment ................................................................................................................ III
Nomenclature ...................................................................................................................... IV
List of Abbreviations ....................................................................................................... IV
List of Figures ...................................................................................................................... X
List of Tables ................................................................................................................... XIV
Chapter I: Motivation ............................................................................................................. 1
  1.1 Thesis Contribution ............................................................................................... 2
  1.2 Thesis Organization ............................................................................................... 2
Chapter II: Medical Background and Literature Review ......................................................... 4
  2.1 The Structure and Function of the cardiovascular system ....................................... 4
    2.1.1 Anatomical Detail of the Heart ......................................................................... 4
    2.1.2 The Circulatory System of the Heart .................................................................. 6
    2.1.3 Cardiac Electrophysiology ............................................................................... 7
    2.1.4 Cardiac Conduction System ............................................................................. 9
    2.1.5 Electrocardiographic Interpretation of Cardiac Muscle ................................... 10
    2.1.6 Criterion for Assessing Cardiac Function ....................................................... 13
  2.2 Cardiac Pathologies of Interest ............................................................................. 14
    2.2.1 Cardiac Arrhythmias due to Heart Blockage .................................................. 15
    2.2.2 Dilated Cardiomyopathy ................................................................................ 16
  2.3 Cardiac Resynchronization Therapy ..................................................................... 17
    2.3.1 CRT Biventricular Pacing Device .................................................................. 18
      2.3.1.1 Implantation Techniques ......................................................................... 18
      2.3.1.2 Functionality Parameters ........................................................................ 18
      2.3.1.2.1 Lead Positioning ................................................................................. 18
      2.3.1.2.2 Timing Delays .................................................................................... 19
3.2.1 Implementation of Left Bundle Branch Block ................................................ 44
3.2.2 Implementation of Morphological changes as a result of DCM ...................... 46
3.2.3 Generation of a New Purkinje Network for the Morphed geometry ................ 48
3.2.4 Implementation of a full simulation for a heart exhibiting DCM..................... 48

Chapter IV: Results and Discussion ............................................................................. 50

4.1 LHHM Benchmarking ......................................................................................... 50

4.1.1 The LHHM under normal conditions (Control) .............................................. 50
4.1.2 Re-running the LHHM with a Modified Purkinje Network ............................. 58
4.1.3 Vascular Pressure Variation ........................................................................... 63
  4.1.3.1 Arterial Pressure ..................................................................................... 63
  4.1.3.2 Pulmonary pressure................................................................................. 64
  4.1.3.3 Venous Pressure...................................................................................... 66
4.1.4 Varying Myocardial Material Properties ........................................................ 67
  4.1.4.1 LV (contractility).................................................................................... 67
  4.1.4.2 LV Passive Stiffness ............................................................................... 68
4.1.5 Conclusions on the Benchmarking Exercise ................................................... 69

4.2 Assessment of Morphological changes implementation ....................................... 70

4.3 Case Studies ........................................................................................................ 73

4.3.1 Case Study I: LBBB Only Conditions ............................................................ 73
  4.3.1.1 Problem Setup ...................................................................................... 74
  4.3.1.2 Electrical Analysis ................................................................................ 74
  4.3.1.3 Mechanical Analysis ............................................................................ 76
4.3.2 Case Study II: DCM + LBBB Conditions....................................................... 77
  4.3.2.1 Problem Setup ...................................................................................... 77
  4.3.2.2 Electrical Analysis ................................................................................ 78
  4.3.2.3 Mechanical Analysis ............................................................................ 81
4.3.3 Case Study III: Assessing CRT treatment on a heart exhibiting DCM and LBBB

4.3.3.1 Problem Setup ........................................................................................................ 84
4.3.3.2 Electrical Analysis .................................................................................................. 85
4.3.3.3 Mechanical Analysis ............................................................................................ 87

Chapter V: Conclusion and Future Work ........................................................................... 89

References .......................................................................................................................... 91

Appendix A: Abaqus/CAE Interface .................................................................................. 99

A.1 Creating and Generating a Job File .............................................................................. 99
A.2 Vascular Pressure Variation ....................................................................................... 99
A.3 Varying Myocardial Material Properties .................................................................. 100
A.4 LBBB Implementation ............................................................................................... 101
A.5 Implementation of Morphological Changes ............................................................... 102
A.6 Implementation of CRT ........................................................................................... 104
List of Figures

Figure 1: Schematic of the heart main chambers ................................................................. 5
Figure 2: Heart Muscle Wall ............................................................................................... 6
Figure 3: Schematic of the heart Circulatory System (blood flow). Red color indicates oxygenated blood and blue color indicates deoxygenated blood ........................................... 8
Figure 4: Action Potential Representation ....................................................................... 9
Figure 5: Cardiac Conduction System ............................................................................. 11
Figure 6: ECG Representation .......................................................................................... 12
Figure 7: Action potential corresponding to different types of heart cells ...................... 13
Figure 8: Schematic of Tranmitral Flow Velocity Curve .................................................. 14
Figure 9: Types of Heart Dyssynchrony ......................................................................... 16
Figure 10: Schematic Representation of Dilated Cardiomyopathy ................................. 17
Figure 11: Schematic representation of Cardiac Resynchronization Therapy ................. 20
Figure 12: Fiber Bundles and Purkinje Network in LHHM ............................................. 27
Figure 13: Atrium Fiber Orientation: Colors indicate different myocardial regions and white lines show the local muscle fiber orientation. [6] .................................................. 32
Figure 14: Fiber Orientation of the Heart Model [6] ....................................................... 32
Figure 15: Blood Flow Model representation with LHHM [6] .............................................. 36
Figure 16: Electrical Potential of the SA node set within LHHM [6] ................................. 37
Figure 17: 6 Lead ECG locations corresponding to the LHHM geometry ........................ 39
Figure 18: Sequence for the assessment of the LHHM default model .............................. 40
Figure 19: Assessment steps for changing arterial pressure within LHHM ....................... 41
Figure 20: Assessment steps for changing pulmonary pressure within LHHM ............... 41
Figure 21: Assessment steps for changing venous pressure within LHHM ....................... 42
Figure 22: Assessment steps for changing LV contractility within LHHM ....................... 43
Figure 23: Assessment steps for changing LV stiffness within LHHM ............................ 43
Figure 24: Schematic Representation of LBBB in LHHM ................................................ 45
Figure 25: Sequence for the modeling of LBBB within LHHM ....................................... 45
Figure 26: Chosen LV set of elements for expansion and the orientation defined .......... 47
Figure 27: Sequence for the modeling of LBBB Morphological changes within LHHM .... 47
Figure 28: Sequence of generating a new Purkinje network corresponding to a specific geometry ...................................................................................................................... 49
Figure 29: Sequence for the modeling of DCM within LHHM ........................................ 49
Figure 30: Electrical Potential in the heart at different timings (90ms, 180ms, 260ms) ........................................ 51
Figure 31: Psuedo ECG for LHHM in comparison with clinical ECG for Lead V1 .............................................. 52
Figure 32: Psuedo ECG for LHHM in comparison with clinical ECG for Lead V2 .............................................. 52
Figure 33: Psuedo ECG for LHHM in comparison with clinical ECG for Lead V3 .............................................. 53
Figure 34: Psuedo ECG for LHHM in comparison with clinical ECG for Lead V4 .............................................. 53
Figure 35: Psuedo ECG for LHHM in comparison with clinical ECG for Lead V5 .............................................. 54
Figure 36: Psuedo ECG for LHHM in comparison with clinical ECG for Lead V6 .............................................. 54
Figure 37: Mechanical deformation of the heart at different timings of the beat cycle (0, 0.2, 0.4, 0.5, 0.7) – right to left (Longitudinal view) ........................................................................................................ 55
Figure 38: LV Pressure Volume Loop generated from LHHM – default model - 3rd Beat ....................................... 57
Figure 39: Wiggers diagram for LHHM default Model along with the approximated E/A wave .......................................................... 57
Figure 40: Comparison between new and old Purkinje network for normal conditions ................................. 58
Figure 41: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V1 ......................................................................................................................................... 59
Figure 42: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V2 ......................................................................................................................................... 59
Figure 43: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V3 ......................................................................................................................................... 60
Figure 44: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V4 ......................................................................................................................................... 60
Figure 45: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V5 ......................................................................................................................................... 61
Figure 46: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V6 ......................................................................................................................................... 61
Figure 47: Comparison between electrical potential of different models at different timings (90ms, 180ms, 260ms, 275ms) left to right – Frontal view ................................................................. 62
Figure 48: Comparison between electrical potential of different models at different timings (90ms, 180ms, 260ms, 275ms) left to right – Longitudinal section .................................................. 62
Figure 49: LV - PV loop comparison with respect to different Purkinje networks - 3rd Beat .................................... 63
Figure 50: LV PV Loop Comparison after changing Arterial Pressure - 3rd Beat ............................................. 64
Figure 51: RV PV Loop Comparison after changing Pulmonary Pressure - 3rd Beat ...................................... 65
Figure 52: LV PV Loop Comparison after changing Pulmonary Pressure – 3rd Beat .................................. 66
Figure 53: RV PV Loop Comparison after changing Venous Pressure - 3rd Beat .......................... 67
Figure 54: LV PV Loop Comparison after changing Left Ventricle contractility – 3rd Beat. 68
Figure 55: LV PV Loop Comparison after changing Left Ventricle stiffness - 3rd Beat ........ 69
Figure 56: Comparison between different LHHM models at 70% diastole ............................ 70
Figure 57: Ventricular Volume Comparison between different models: grey normal model, blue DCM, 300ml model, red DCM, 350ml model – Basal section ................................. 71
Figure 58: Ventricular Volume Comparison between different models: grey normal model, blue DCM, 300ml model, red DCM, 350ml model – Longitudinal section .......................... 71
Figure 59: 2D four chamber view comparison between LHHM DCM, 300ml and clinical MRI ........................................................................................................................................ 72
Figure 60: 2D four chamber view comparison between LHHM DCM, 350ml and clinical MRI ........................................................................................................................................ 73
Figure 61: LBBB elements (Red) chosen within LHHM ....................................................... 74
Figure 62: Fiber bundle activation comparison between models at different timing (180 ms, 205 ms, 260 ms) left to right ................................................................................... 75
Figure 63: Comparison between electrical potential of different models at different timings (90ms, 180ms, 260ms, 280ms, 305ms) left to right – Frontal view ........................................... 76
Figure 64: Comparison between electrical potential of different models at different timings (90ms, 180ms, 260ms, 280ms, 305ms) left to right – Longitudinal section .......................... 76
Figure 65: Left ventricular pressure volume relationship comparison between default model and LBBB model .................................................................................................. 77
Figure 66: Comparison between Purkinje network for different models ............................ 78
Figure 67: Comparison between Electrical Simulation output between normal and DCM- LBBB model 1 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Frontal view ........................................................................................................ 79
Figure 68: Comparison between Electrical Simulation output between normal and DCM- LBBB model 1 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal section ............................................................................................................ 80
Figure 69: Comparison between Electrical Simulation output between normal and DCM- LBBB model 2 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal section ............................................................................................................ 80
Figure 70: Comparison between Electrical Simulation output between normal and DCM-LBBB model 2 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal section ............................................................................................................ 80
Figure 71: Pressure volume loop comparison between default model and DCM-LBBB model 1 .......................................................................................................................................... 82
Figure 72: Pressure volume loop comparison between default model and DCM – LBBB model 2 ............................................................................................................................... 82
Figure 73: Wiggers Diagram for DCM Model along with the approximation of the E/A wave ........................................................................................................................................... 83
Figure 74: Schematic Representation of CRT leads in LHHM ........................................................................................................................................... 84
Figure 75: Detailed sequence followed for the modeling of CRT within LHHM ........................................................................................................................................... 85
Figure 76: LV and RV activation sequence in the CRT model at different timings left to right (190ms, 220ms, 240ms, 260ms) – Longitudinal section ........................................................................................................................................... 86
Figure 77: Comparison between Electrical Simulation output DCM-LBBB model 2 and DCM-LBBB + CRT at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Frontal view ........................................................................................................................................... 87
Figure 78: Comparison between Electrical Simulation output DCM-LBBB model 2 and DCM-LBBB + CRT at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal Section ........................................................................................................................................... 87
Figure 79: Pressure volume loop comparison between default model, DCM – LBBB model 2, and CRT model ........................................................................................................................................... 88
Figure 80: Generating a Job File ........................................................................................................................................... 99
Figure 81: Changing arterial pressure within LHHM using Abaqus/CAE interface ........................................................................................................................................... 99
Figure 82: Changing pulmonary pressure within LHHM using Abaqus/CAE interface ........................................................................................................................................... 100
Figure 83: Changing venous pressure within LHHM using Abaqus/CAE interface ........................................................................................................................................... 100
Figure 84: Scaling heart’s contractility within LHHM using Abaqus/CAE interface ........................................................................................................................................... 101
Figure 85: Scaling heart’s stiffness within LHHM using Abaqus/CAE interface ........................................................................................................................................... 101
Figure 86: Creating LBBB section using Abaqus/CAE interface ........................................................................................................................................... 102
Figure 87: Creating a new set for the implementation of Morphological Changes ........................................................................................................................................... 103
Figure 88: Creating a new set for the implementation of CRT ........................................................................................................................................... 104
Figure 89: Creating amplitude and boundary condition corresponding to CRT leads ........................................................................................................................................... 105
List of Tables

Table 1: NYHA Heart Failure Classification ................................................................. 1
Table 2: LHHM output parameter comparison with normal published values .......... 56
Table 3: LHHM diastolic measurements comparison with normal published values .... 58
Table 4: Activation timing comparison between default model and LBBB model .......... 75
Table 5: Configurations of the proposed models ........................................................ 78
Table 6: Activation timing comparison between default model, DCM-LBBB model 1, DCM-LBBB model 2 ................................................................. 79
Table 7: Comparison of cardiac function parameters: 300 mL vs. clinical data from McCrohon et al.[75] study ........................................................................................................ 81
Table 8: Comparison of cardiac function parameters: 350 mL vs. clinical data from Akhmatov el al. study [76]. ................................................................................................. 81
Table 9: Comparison of transmitral flow velocity parameters between DCM-LBBB model 2 – clinical data [79] ............................................................................................. 83
Chapter I

Motivation

Heart Failure (HF) is a major cause of mortality worldwide, and is thus a health concern that is grabbing the world’s attention. Usually, HF is referred to as a progressive deterioration of the heart muscle’s ability to pump blood effectively. Based on the level of severity and the associated symptoms of HF, patients are classified according to the New York Heart Association (NYHA) into four classes [1], as per the quality of life, the limitation of physical activity, the level of fatigue during ordinary activity, the shortness of breath, and the presence of irregularity in heartbeats, see Table 1 [1].

Table 1: NYHA Heart Failure Classification

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Patient Symptoms</th>
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</table>
| I          | - No limitation in physical activity  
|            | - No excessive fatigue in ordinary physical activity  
|            | - No Shortness of breath nor irregularity in heart beat |
| II         | - Slight limitation in physical activity, comfortable at rest  
|            | - Ordinary physical activity results in fatigue,  
|            | - Shortness of breath and irregularity in heart beat |
| III        | - Obvious limitation in physical activity  
|            | - Less than ordinary physical activity causes fatigue,  
|            | - Shortness of and irregularity in heart beat |
| IV         | - Unable to perform any physical activity  
|            | - Symptoms of heart failure at rest |

In a great part of HF population classified by the NYHA as being of class III or IV, dilated cardiomyopathy (DCM) is at the cause. DCM is state in which the main pumping chamber of the heart namely the left ventricle (LV) becomes dilated, which leads to a decrease in systolic and diastolic functions. DCM is often associated with left bundle branch block (LBBB). LBBB is the state in which mechanical function of the LV deteriorated as a result of a loss in the normal electrical activation sequence that created an abnormal contraction pattern. Note that albeit, LBBB is considered to be a secondary cause of DCM in most patients, there is a high possibility that DCM be caused primarily LBBB-induced abnormal LV contraction patterns in some patients [2].
The first choice of therapy for patients with HF is medication. However, due to the severity of some HF cases, or a non-responsiveness of patients to drugs, alternative non-pharmacologic treatment options have evolved. Cardiac Resynchronization therapy (CRT) is one such emergent option. By biventricular pacing CRT treats patients with severe HF and abnormal ventricular activation sequencing and function [3]. CRT, however, only targets patients classified by NYHA as class III or IV, which account for 20% of the total HF population [3]. This group includes HF patients suffering from DCM and LBBB [3]. The success of CRT leads to an improvement in patient hemodynamics and cardiac function by coordinating biventricular activation and contraction. Ultimately, CRT reduces hospitalization rates [3]. Although CRT in general decreases hospitalization rate, there remains 20% to 30% of the selected patients who do not respond to its treatment. This may be due to several reasons, such as correct patient selection. For instance, the effectiveness of CRT can be negatively affected by other dysfunctions, e.g. apical LV dysfunction or posterolateral scar [4]. Other reasons of non-responsiveness to CRT may relate to biventricular pacing (BVP) device programming and/or lead positioning, since these should be optimized according to each patient [5]. It is thus important to identify responsive patients to CRT and to optimize CRT parameters to maximize its benefits. We therefore believe it is paramount to leverage modern computational techniques to accurately model LBBB and DCM in the first place, and ultimately to facilitate the classification of patients and their expected responsiveness to CRT.

1.1 Thesis Contribution

This thesis proposes a methodology that models morphological changes due to the cardiac growth associated with DCM, and models the electromechanics resulting from DCM and LBBB. The methodology is incorporated into the Living Heart Human Model (LHHM) produced by SIMULIA, a Multiphysics code that constitutes of sequentially coupled electromechanical solvers of a healthy male’s (in his mid-twenties) heart beat [6]. The methodology is then used to assess the role of CRT in treating DCM+LBBB patients.

1.2 Thesis Organization

The thesis is organized as follows. In chapter 2, a brief overview of the structure and function of the cardiovascular system is first introduced, in relation to cardiac electrophysiology, hemodynamics, and cardiac mechanics. Next, a current review of CRT and relevant electromechanical diseases is presented. Then, a review of the modeling methods that have been used to simulate the effects of relevant cardiac diseases and CRT is presented. Following the literature review, our proposed research methods are presented in chapter 3.
Finally, the results obtained are presented and discussed in chapter 4, followed by our conclusions and directions of future research in chapter 5.
Chapter II

Medical Background and Literature Review

This chapter will include a brief introduction about the cardiovascular system including heart’s anatomy and electrophysiology. Additionally, cardiac pathologies of interest within this study will be introduced, while identifying and illustrating one of the treatment options associated with them. The different modeling techniques in the literature will be presented with the identification of the drawbacks of each technique. Finally, the largest ongoing electromechanical modeling project namely the Living Heart Project on which the methodology of this study was based on will be presented and elaborated in details.

2.1 The Structure and Function of the cardiovascular system

The cardiovascular system is the system responsible for supplying oxygen and nutrients to the whole body. It consists of the heart, which can be categorized as a dual pump, and vessels, which can be classified as a blood carrying network forming the circulatory system [7]. The main function of the heart is to continuously pump oxygen and nutrients rich blood into the circulatory system, which in turn carries it via blood vessels to the whole body. The function of the cardiovascular system is achieved through periodic contraction and relaxation of the heart, controlling discharging and filling of blood within the heart muscle [8]. The periodic contraction and relaxation is controlled by the heart’s electrical conduction system, where the electrical signal initiation results in contraction of the heart walls, forcing blood to be pumped out of the heart [9].

2.1.1 Anatomical Detail of the Heart

The heart is a muscular pump, having a size that is equal to the human fist, located in the middle of the chest cavity between the lungs. The heart is composed of four main chambers namely the right and left atria, which comprises the upper chambers of the heart and the right and left ventricles which comprises the lower chambers of the heart. The heart can be considered as consisting of two halves that are separated by a wall, the septal wall, aiming to prevent any blood flow between opposing chambers as shown in Figure (1) [7], [9]–[11]. The two-upper chambers of the heart namely the right atrium (RA) and left atrium (LA), are considered to be a blood collector chambers aiming to collect blood from the body via the superior and inferior vena cava and from the lungs via the left and right pulmonary veins respectively. While the two lower chambers of the heart namely the right ventricle (RV) and
the left ventricle (LV), are considered to be pumping chambers, which aims of pumping blood to the lungs via the pulmonary artery and to the body via the aortic arch respectively [7], [9]–[11]. The blood flow between chambers and vessels is controlled by the use of valves to ensure unidirectional flow of blood through the heart. The valves separating heart chambers from each other are the tricuspid and mitral valve, which separates the RA from the RV and the LA from the LV respectively. Whereas the valves controlling the flow between chambers and blood vessels are the pulmonary and aortic valve controlling the blood flow from the RV to the pulmonary trunk and from the LV to the aorta respectively [7], [9]–[11].

![Figure 1: Schematic of the heart main chambers](chart.png)

The heart is being held and protected by the pericardium, which is a membranous structure. The pericardium provides enough space for the heart chambers to fill and empty. The outer
layer of the pericardium is attached to many parts of the body like the spinal column and diaphragm by ligaments and it surrounds the roots of the heart’s blood vessels [7], [9]–[11]. In the meantime, the inner layer of the pericardium is directly attached to the heart muscle. What lets the heart move as it beats is the coating fluid that separates the two membrane layers [7], [10], [11]. Three layers comprise the heart wall namely the endocardium, the myocardium and the epicardium as seen in Figure (2), which represents the inner, middle and outer wall respectively. The myocardium is defined as being the cardiac muscle cell. The thickness of the myocardium varies according to each of the heart’s chambers functionality, where the atria walls are thin since they are considered as only a pathway of blood to the ventricles [7], [9]–[11]. On the other hand, the ventricles myocardium walls are thicker as their function is to pump blood out of the heart. However, the LV myocardium wall is three times thicker than that of the RV. This is due to the fact that the RV pumps blood to the lungs, which have a little resistance to blood flow. Whereas, the LV pumps blood to the whole body, where resistance to blood flow is considered to be high [7], [9]–[11].

![Figure 2: Heart Muscle Wall](image)

2.1.2 The Circulatory System of the Heart

The main function of the heart is to collect deoxygenated blood from the body and pump oxygenated blood into the body. This is achieved through the circulatory system consisting of
a set of arteries and veins. The circulatory system is considered to be as closed loop system as seen in Figure (3). The deoxygenated blood from the body is fed to the right half of the heart via the superior and inferior vena cava, which are connected to the right atrium [8], [10], [11]. After the filling of the RA, the occurred pressure forces the tricuspid valve to open allowing the blood to flow to the RV, which is then pumped to the lungs via the pulmonary artery. Almost simultaneously, the oxygenated blood is fed to the left atrium though the pulmonary vein; then as soon as the mitral valves open it passes to the left ventricle. Once the LV is filled and the required high pressure is reached, the oxygenated blood is pumped to the whole body through the aorta [8], [10], [11]. The blood circulation between the heart and the lungs is known as the pulmonary circuit and is considered to be a short, low pressure circuit that functions strictly as a gas exchange. While the blood circulation between the heart and the whole body is known as the systemic circuit and is considered to be a long, high resistance pathway through the entire body that functions as gas and nutrient exchange. Since the heart is considered to be a dual pump, the right side of the heart is considered to be the pump of the pulmonary circuit while the left side of the heart is considered to be the pump of the systemic circuit. The pulmonary and systemic circuits can be divided in two halves as the heart, where the right and left sides circulate the deoxygenated and oxygenated blood respectively [7], [10]–[12].

2.1.3 Cardiac Electrophysiology

In order for the heart to be able to continuously and regularly pump blood, the heart goes through a periodic and continuous mechanical contraction. This contraction is a result of the interaction of many and different types of cardio-myocytes. The electrical excitation is initiated due to the different electrophysiological properties of the specialized myocytes; and after initiating the excitation, it conducts this excitation along defined paths in the heart and hence produces the mechanical tension of the heart [7], [11]. The cardiac-myocytes encloses ion channels, pumps, and exchangers. All of them enable the exchange of ions in the extra-cellular and intra-cellular spaces. The most relevant ions to the electro-physiological transport are the sodium ion $\text{Na}^+$, the potassium ion $\text{K}^+$, and the calcium ion $\text{Ca}^{2+}$ [13]. Their main driving forces are both the electrical and chemical concentration gradients across the membrane of the cells, that can be summed up to the so called the electrochemical gradient. The ion channels can be selective, meaning that only the ion matching the channel is dehydrated and allowed to pass through this channel [7], [11], [13]. Hence, the important ion channels are the same as the most relevant ions, which are: $\text{Na}^+$, $\text{K}^+$, and $\text{Ca}^{2+}$ channels [7], [11], [13]. The ion channels can be activated and deactivated; in other words, gated. The gating trigger can possibly be provided
through transmembrane voltage and other neuro-transmitter receptors. A gap junction connects the working myocardium of the myocytes, and it is responsible of conducting the excitation between the cells. The concentration of ions like the H$^+$, Na$^+$, Mg$^{2+}$, and Ca$^{2+}$ and the pH value of the extra-cellular medium control the resistivity of the gap junction [7], [11], [13].

![Figure 3: Schematic of the heart Circulatory System (blood flow). Red color indicates oxygenated blood and blue color indicates deoxygenated blood](image)

The concentration of ions in the extra-cellular space differs from their concentration in the intra-cellular space; and this is due to the activity of selective ion channels as well as the activity of ion pumps. The transmembrane voltage is the potential difference across the cell membrane and it is caused due to electrochemical gradient of ions [11]. The equilibrium voltage of an ion is when the electrical and chemical forces are in equilibrium. The resting voltage of the cardiac myocytes can range between -30mV and -100 mV, the exact value depends on the cell type [7], [11]. An external stimulus can depolarize the excitable cells in the body like the nervous and cardiac cells. The reaction of the cells to the external stimulus is known as the action potential. The action potential (AP) is mainly caused by the sequence of ion flux through the
membrane of the cells [14]. During AP the voltage of the transmembrane rises rapidly to a positive voltage value followed by a relatively slow return to the equilibrium state. The action potential is completed in 5 phases as shown in Figure (4), where

- **Phase 0**: quick repolarization, which is caused by the quick influx of Na\(^+\) into the cells
- **Phase 1**: quick partial repolarization
- **Phase 2**: the action potential flattens, which is caused by the inflow of Ca\(^{2+}\)
- **Phase 3**: stoppage of the Ca\(^{2+}\), and the outflow of K\(^+\) continues
- **Phase 4**: repolarization of the cell to its resting transmembrane potential [14]

![Figure 4: Action Potential Representation](image)

The action potential is only triggered by a stimulus that is greater than a certain level; this level is known as the threshold potential. In case of a stimulus less than the threshold value, only a passive response takes place, in order to try and reach the equilibrium voltage. Meanwhile, in case the stimulus is greater than the threshold value, the active response takes place and the action potential occurs [7], [11], [13], [14].

### 2.1.4 Cardiac Conduction System

The cardiac conduction system is composed of a group of specialized cells; the main function of them is to ensure rapid conduction. The conduction system can be divided into two main components: the pacemakers and the conducting tissues. The main pacemaker of the heart is located in the right atrium and is known as the sinus-atrial (SA) node. SA node and other pacemakers in the heart are responsible for the heart’s periodic spontaneous depolarization.
Their rate can be altered through the nervous signals in order to maintain the required heart rate (Beats/Minute) for the body to function properly according to the load subjected to the body [7], [11]. When the pacemaker cells in the SA node is depolarized, the excitation propagates to the whole heart passing through both atria till it reaches the atrio-ventricular (AV) node, which is the only conducting node between both atria and both ventricles of the heart. The main function the AV node is to delay the propagation of the excitation between the atria and ventricles. In addition, it functions as a frequency limiter; meaning that it limits the excitation frequency of the ventricles in case the SA node gets higher than normal; and this is done in order to ensure the stability of heart’s function of pumping blood. The ventricular conduction system is composed of the bundle of His and The Purkinje fibers, which guide the transmission of the excitation from the AV node down to the septum, and to both ventricle [7], [11]. Figure (5) shows a representation of the cardiac conduction system.

2.1.5 Electrocardiographic Interpretation of Cardiac Muscle

The electrocardiogram (ECG) reflects the depolarization and repolarization phases of the heart, and it can be obtained through a non-invasive method of measuring since it is recorded from the surface of the body [11], [15].

The representation of ECG of a normal healthy heart is shown in Figure (6) consisting of:

1. P wave: represents the contraction of the atria; in other words, atria’s depolarization starting from the SA node to the AV node
2. QRS complex: represents the contraction of the ventricles; in other words, the ventricles’ depolarization
3. T wave: represents the ventricles’ repolarization [15]
The action potential is generated with every new spontaneous depolarization of the heart and it represents one complete electrical cycle of depolarization and repolarization of one cell [7], [11], [15]. There are three main types of cells that form the heart: the pacemaker cells, the electrical conduction cells, and the myocardial cells. The pacemaker cells are small in size, and in normal and healthy hearts they are responsible for initiation the depolarization. One complete cycle of contraction and relaxation of the heart is initiated by one spontaneous depolarization of the pacemaker cells. The AP of the pacemaker cells differs from the AP of other cells due to the fact that there no resting potential for these types of cells. The electrical charge of the pacemaker cells drops to a minimum negative potential which is held for a small period of time, then it rises again gradually till it reaches its threshold value [15]. All the heart’s cell can behave like the pacemaker cells, but they never do except when the SA node fails or they are subjected to external stimuli. Electrical Conduction cells are longer and thinner than the pacemaker cells, and they are responsible for conducting the current quickly to the different and distant parts of the heart [7], [11], [15]. Myocardial cells form the tissue that forms the major part of the heart. Their main function is to contract and relax the heart, and they are able
to do so because they are rich in contractile proteins: myosin and actin. When depolarization takes place, it reaches the myocardial cells, and then the calcium is released in the cells, which causes them to contract. Since the myocardial cells have the same ability as the electrical conduction cells in transmitting the current, but less effective, the depolarization wave spreads relatively slow across the myocardium [11]. Figure (7) shows a representation of AP for different cells.

Figure 6: ECG Representation
2.1.6 Criterion for Assessing Cardiac Function

Although ECG can be used to recognize and assess electromechanical disorder, other parameters are needed to assess the function of the heart [16]. This includes the end diastolic volume (EDV), which represents the ventricular blood volume at the end of the diastolic phase, end systolic volume (ESV) representing the blood volume left in the ventricles at the end of systole after ejection is complete and the ejection fraction (EF) which represents the percentage blood ejected by the ventricle during the contraction phase of the cardiac cycle. The difference between ventricular blood volume before and after contraction is presented by the stroke volume (SV), where small SV will lead to heart failure. The SV is calculated as follows

$$SV = EDV - ESV$$

The SV is then used to calculate the EF where,

$$EF = \frac{SV}{EDV} \times 100\%$$

Another functionality parameter is the ratio of early to late ventricular filling (E/A), which is a representative measure of the left ventricle function. This ratio is calculated by the use of echocardiography, where the E-wave and the A-wave are displayed representing the peak velocity flow in early and late diastole respectively [16]. The rapid filling phase of the left ventricular diastolic filling phase and the contribution of the atrial contraction to it are
Abnormalities in the E/A ratio are a good representation of diastolic dysfunction, where the left ventricle is not properly filled with blood in order to pump it to the systemic circulation.

Figure 8: Schematic of Transmitral Flow Velocity Curve

2.2 Cardiac Pathologies of Interest

Heart’s mechanical activity and functionality is associated with the heart’s electrical activity pattern. Thus, any abnormalities in the sequence of electrical activation may lead to a deviation in the mechanical contractile activity of the heart leading to a severe heart failure. Abnormalities in the rhythm may occur due to several reasons including atrial flutter, atrial or ventricular fibrillation and heart blockage. The main pathologies of interest within the framework of this work are abnormalities in the rhythm as a result of heart block including left or right bundle branch block and heart failure due to cardiomyopathy specifically dilated cardiomyopathy.
2.2.1 Cardiac Arrhythmias due to Heart Blockage

Heart blockage is an expression referring to a defect in the cardiac conduction system causing an irregular sequence of activation between atria and ventricles. Heart block results in a deviation in heart’s electrical activation, leading to a delay between atrial and ventricular contraction [17]. The delay of activation resulted from heart block arise as the electrical impulses cannot be conducted from the atria to the ventricles through the preferred pathway across the bundle of his and the bundle branches. Consequently, impulses follow alternative pathways, where they are conducted through muscle fibers allowing for ventricular depolarization. However, these alternative pathways result in a slow electrical movement leading to a prolonged ventricular depolarization and a change in the impulses direction causing a loss of ventricular synchrony [17]. There are three main types of heart blockage including Atrio-ventricular Block (AVB), Left Bundle Branch Block (LBBB), and Right Bundle Branch Block (RBBB). AVB is the type of block occurred after AV node disconnecting it from the bundle of His preventing the electrical impulses from reaching the ventricles and thus causing a dyssynchrony between atria and ventricle contraction. On the other hand, LBBB and RBBB are types of blocks occurred in the left and right sides of the bundle branches disconnecting the bundle of His and the left or right bundle branches respectively [17]–[19]. This disconnection prevents the excitation to propagate to the left or right ventricle leading to a delayed excitation of the left or right ventricle. This delay of excitation between ventricles resulted from LBBB or RBBB will lead to asynchronous ventricular contraction causing over time a severe heart failure.

Mechanical dyssynchrony can be divided based on the disruption in physiological relationship between heart chambers as shown in Figure (9). Atrioventricular (AV) dyssynchrony is caused as a result of AVB where the ventricular contraction is delayed with respect to the atrial contraction producing a shortened ventricular filling time along with the superimposition of atrial contraction on early passive filling leading also to the reduction of left ventricular filling and hence affecting cardiac output [17]–[20]. Interventricular dyssynchrony is most likely initiated as a result of LBBB leading to a delay between ventricle activation with respect to each other where the RV contraction precedes the LV contraction. This delay between RV and LV activation leads to a decreased LV ejection fraction as a result of abnormal septal motion and uncoordinated LV contraction. Intraventricular dyssynchrony refers to the irregular sequence of activation of the LV wall resulting in uncoordinated contraction of the LV segments. The earlier segments to contract do not contribute to the left
ventricular blood ejection, while the other segments contract late at a higher wall stress leading to the stretching of the early contracted segments. Accordingly, the heart’s mechanical efficiency is decreased along with a decline in systolic performance [17]–[20].

![Types of Heart Dyssynchrony](image)

**Figure 9: Types of Heart Dyssynchrony**

### 2.2.2 Dilated Cardiomyopathy

The inadequate performance of the heart’s electrical and mechanical systems leads to heart failure. *Dilated Cardiomyopathy* (DCM) is one of the main causes of the deterioration of the heart cardiac output and hence leading to heart failure. According to the *American Heart Association* (AHA), DCM can classified as being primary disease affecting the heart or as secondary resulted from other systemic diseases [21]. DCM is a condition in which a portion of heart muscle gets dilated leading to an enlarged and weakened left ventricles as seen in Figure (10), affecting the efficiency of pumping blood throughout the body [22], [23]. Having a dilated cardiomyopathy affects and reduces the cardiac output by decreasing the stroke volume leading to systolic dysfunction. This happens when the left ventricle dilates while thinning the walls causing an inefficiency in contraction and ejection fraction.
2.3 Cardiac Resynchronization Therapy

Based on several research studies, CRT responders and non-responders have been identified based on several heart functionality parameters including LVEF and QRS complex [24]–[26]. Accordingly, eligible patients for CRT treatment are those having a wide QRS complex with a duration greater than 120ms, a LVEF less than 35%, and a left ventricular end diastolic diameter (LVEDD) greater than 55mm [24]–[26]. Additionally, patients diagnosed as having interventricular dyssynchrony due to bundle branch block or any intraventricular delay are also eligible for CRT treatment. Although, the targeted candidates for CRT are defined based on clinical indications, still 20% to 30% of the targeted patients do not respond to CRT treatment [24]–[26]. For instance, the effectiveness of the CRT treatment can be negatively altered by the presence of apical left ventricular dysfunction, or posterolateral scar [26]. Thus, responsivity for CRT treatment can be classified as being patient specific. The success of CRT treatment leads to the improvement of patients’ hemodynamics and cardiac function resulted from the coordination of the ventricular activation and contraction and
therefore, reducing of hospitalization rate. Accordingly, it is important to exactly identify responders’ patients for CRT treatment and optimizing the CRT functionality parameters in order to maximize its benefits.

2.3.1 CRT Biventricular Pacing Device

CRT treatment aims to improve ventricular synchronization and left ventricular systolic performance for patients with heart failure especially those having a left bundle branch block. This achieved through the implementation of a biventricular pacing device, which consists of a pacemaker and three electrodes leads to be positioned in the heart as seen in Figure (11) [26]. The pacemaker is externally programmed, achieving the finest pacing mode through electrical potential impulses carried by the leads to the heart. Accordingly, in order to achieve a synchronous and balanced ventricular contraction, two of the leads are located in the RV and LV, where the pacing can either be done simultaneously or sequentially [26]. While, the third lead is a sensing electrode located in the RA carrying information signal of the normal excitation of the heart to the pacemaker.

2.3.1.1 Implantation Techniques

Implementation of CRT is based on two main criteria endocardial and epicardial approaches. The BVP device is implanted from the chest through a small incision where the pacemaker device and the electrode leads are inserted [27]. The BVP is positioned beneath the collarbone and its leads are guided to the heart via the subclavian vein to the RA, RV and LV respectively. With the aid of fluoroscopy machine, the three leads are positioned in the heart achieving the required electrode conduction to the heart. The lead tips are attached to the heart muscle where the RA and RV leads are positioned inside the heart and the LV lead is positioned on the left ventricular wall [26], [27]. The RA lead is positioned near the SA node specifically in the right atrium appendage, while the RV lead is positioned near the right ventricle septum. On the other hand, the LV lead is positioned transvenously using a coronary sinus branch on the LV wall usually the lateral, anterolateral and posterolateral sections.

2.3.1.2 Functionality Parameters

The success of CRT is dependent on several parameters including lead positioning and the BVP device configuration in terms of timing delays. This section will briefly introduce the CRT functionality parameters, and how they contribute in the efficiency of CRT.

2.3.1.2.1 Lead Positioning

The effectiveness of the CRT treatment can be altered based on the ventricular leads positioning specifically the one located in the LV. Most studies suggest that the LV pacing
sites producing better hemodynamic response are those classified as being the latest to be activated during contraction [25], [28]–[30]. Based on several studies, the sites of latest activation are most likely to be on the lateral wall having with a 35% probability, while the anterior and posterior region have a lower probability of 26% and 23% respectively [25], [28]–[30]. For this reason, most likely the LV lead is implanted either in the lateral, anterolateral or posterolateral sites.

2.3.1.2.2 Timing Delays

The BVP device comprise three leads where two of them are pacing electrode located in the RV and LV and the third is a sensing electrode located in the RA near the SA node. The main aim of the RA sensing electrode is to carry information of the normal excitation of the heart to the BVP device after which the stimulation of both ventricles is carried out using the other two pacing leads with a pre-programmed timing including the Atrioventricular delay (AVD) and the interventricular delay (VVD) delay [26]. The AVD is defined as being the time between the normal excitation of the heart, which is the information signal carried out from the RA sensing lead and the LV lead pacing. While the VVD is defined as being the time between the LV and RV pacing. Several studies suggest that proper time programming of the BVP would result in the improvement of the cardiac output [26].
2.4 Modeling Techniques Described in Literature

The aim of this section is to review the heart modeling techniques specifically models that aim to contribute in the understanding, diagnosis and treatment of cardiac diseases including cardiac growth and cardiac arrhythmias. First, we will focus on models that aim to model cardiac growth due to several cardiac diseases including dilated cardiomyopathy and hypertrophy. Second, we will focus on models that aim to model electrical deviation due to left bundle branch block.

2.4.1 Modeling of Cardiac Growth

The existing models that will be discussed later in this section are constructed based on the principle of continuum mechanics at the tissue - organ level being able to account for any change that occur in the geometry, structure and material properties of the heart. The broad classification of cardiac growth and remodeling models can be classified based on their origins as follows: (1) structural adaption theory, (2) volumetric growth theory and (3) constrained mixture theory.
2.4.1.1 Structural Adaption Theory

Arts et al. [31] proposed one of the first cardiac growth and remodeling (G&R) models where cylindrical shells were used to model the heart. A myofiber orientation was applied to each shell, aiming to optimize the local deviation of the shortening the fiber at systole, and the sarcomere length at the start of the blood ejection from the heart. This G&R model results were in line and consistent with the ones found from experiments in terms of transmural variation of myofiber orientation. The same results were reached through finite element analysis model that was developed in a subsequent study by Kroon et al. [32], where truncated ellipsoids were used instead of cylindrical shells, while applying different remodeling law in which the adaption of the myofibers is based on minimizing the shear strain between fibers.

2.4.1.2 Constrained Mixture Theory

Another theory of modeling cardiac growth and remodeling was proposed by Humphrey and Rajagopal [33], which was referred as constrained mixture theory. The hypothesis on which this theory was built on is that each tissue constituent has the capability of turning over at different rates, while possessing different stress-free configurations that change throughout the growth and remodeling phase. This theory is also supported by the fact that the deformation of each tissue is constrained as a continuum within the mixture. The theory suggests that the decomposition of new constituents occurs at the current step configuration, where the deformation of a constituent of type \( k \) deposited at time \( \tau \) is described at a later time \( t \) as follows

\[
F_{n(\tau)}(t) = F(t)F^{-1}(\tau)G^k(\tau)
\]  

(1)

Where,

\( G^k(\tau) \) is predefined a homeostatic stretch.

And thus, the stress/strain state that deposited constituents of different time step will experience will be different even if they are of the same type. One of the main features of this model is the alteration of tissue mechanical properties throughout the growth and remodeling process without the necessity to redevelop the existing material constitutive stress/strain relationship of the constituents. Although, this model has only been implemented on the growth and remodeling of arterial using simplified geometry, it can be used to model myocardial growth and remodeling based on its features. Despite all the features of this model, it is relatively complex to work with because of its inability to track the natural evolution configuration of the constituents during growth and remodeling [33].
2.4.1.3 Volumetric Growth Theory

The volumetric growth theory is one of the prevalent frameworks for modeling cardiac growth and remodeling in myocardial tissue within the framework of continuum mechanics that was firstly proposed by Rodriguez et al. [34]. The theory is based on the decomposition of the spatial gradient deformation tensor $F$ into an elastic component $F^e$ and a plastic component representing the growth deformation gradient $F^g$ where

$$ F = F^e \cdot F^g $$

(2)

In the context of finite growth, the growth deformation gradient tensor is generally associated with an incompatible configuration degrading the capability of deriving from it a unique displacement field, while the continuous mapping required by the gradient tensor $F$ is restored by the use of the elastic component gradient tensor $F^e$. Due to the incompatibility of the growth tensor, residual stresses and strains may possibly exist in a body subjected to growth, which seems to be relevant in modeling of ventricular growth because usually residual stresses and strains are present in ventricular walls. Nevertheless, the presence of these residual stresses and strains may not be only due to growth and remodeling, but may only be as a result of other mechanisms such as tissue swellings [35]. The modeling of growth deformation gradient can be classified based on the axis on which the expansion will occur while capturing the change in the tissue stress-free configuration. The constitutive relationship of the growth tensor in the long axis is described as [35],

$$ F^g = I + (\theta - 1)f_0 \otimes f_0 $$

(3)

while in the transverse axis is described as [35],

$$ F^g = I + (\theta - 1)s_0 \otimes s_0 $$

[35] (4)

Volumetric growth theory has shown good potential in the modeling of cardiac growth and remodeling, and thus over the years several constitutive models have been developed based on the framework of this theory representing various physiological and pathological conditions of the heart. One of the first constitutive models developed on the basis of volumetric growth theory was developed by Taber and his team within the framework of several studies [36]–[38], where cardiac growth was defined using ordinary differential equation while assuming that the growth rate is a linear function of the stimulus. The growth stimulus $S$ was prescribed in this model as a stress tensor, where its deviation from the targeted value $S_0$ is the basic on
which the rate of change of $\dot{F}^a$ is determined [36]-[38]. By this means and without the presence of any physiological bound that limits the amount of growth, it is considered that growth will always continue as long as $S \neq S_0$. This representation of cardiac growth was used in several studies to stimulate growth in the LV [39], [40]. The myofiber and cross-myofibers strains was used as the growth stimuli, which should not be the case because this means that a reference state is needed for the calculation of strains, which may change during growth and remodeling. However, the proposed growth stimulus was to use Cauchy stress instead because its calculation does not depend on a reference configuration state [34].

Goketepe et al. [41] developed alternative growth constitutive models to stimulate different cardiac hypertrophy during pressure and volume overload. The hypothesis, on which these models, is built on is that the myocardial wall stress and strain can respectively be used as the stimulus for concentric and eccentric cardiac hypertrophy. Alternatively, from other presented model, the deviation of the myofiber stretch and the Mandel stress relative to their corresponding set point is the driving force of the cardiac growth regardless the direction either myofiber or cross-fiber directions. Additionally, this model differs from the previous models is that growth is restricted by the use of a rate-limiting function that is set within physiological limits. Also, one of the key features of this model is that it can predict pressure overload which results in wall thickening and volume overload which results in heart dilation [41].

Another constitutive growth model was developed by Kerckhoff's et al. [42] where the growth rates were described by nonlinear sigmoidal functions of growth stimuli regardless its fiber direction, capturing the features associated with both concentric and eccentric hypertrophy. The growth stimuli in this model are represented by different components of myocardial strain and are driven by any deviation of myofiber and cross myofiber strains from their corresponding set points while being restricted to lie within a prescribed physiological limit [42].

Another strain-driven growth model to stimulate a reversal of cardiac growth and remodeling was further developed by Lee et al. [43] where an independently elevated myocardial stress and strain can be used to model concentric and eccentric hypertrophy respectively. This model is used to model the cardiac muscle growth and remodeling as a result of a reduction in the hemodynamics parameters and is also one of the first models that have integrated cardiac electromechanics [43].
Lastly Genet et al. [44] proposed that the spatial gradient $F$ is decomposed into $F^e$ and $F^g$ where both tensors are considered to be associated with incompatible configuration and do not derive as gradients from a vector field. This model has been used to model both transverse and longitudinal growth. The modeling of transverse cardiac growth is achieved through cardiomyocyte thickening by implementing a cardiac growth multiplier $\theta^\perp$ representing the parallel deposition of sarcomeres on the molecular level. Transverse growth occurs in the plane perpendicular to the fiber direction $f_0$, and thus the growth tensor is considered the rank-one update for the growth weighted second order unity tensor in this direction. The representation of the transverse growth tensor can further by used to derive an explicit representation of the elastic tensor by inverting it using the Sherman–Morrison formula [44]. And therefore, this model differs from the previously stated models due to the fact that the growth is associated with a cross sectional area growth perpendicular to the muscle fiber direction axis $f_0$ in contrast with previous models which performs cardiac transverse growth in the sheet direction $s_0$. On the other hand, longitudinal fiber growth is achieved through cardiomyocyte lengthening by implementing a scalar valued cardiac growth multiplier $\theta^\parallel$ representing the serial deposition of sarcomeres on the molecular level. Longitudinal growth occurs along the fiber direction $f_0$, and thus the growth tensor is considered the rank-one update for the growth weighted second order unity tensor $I$ in this direction [44].

One of the main drawbacks of all the constitutive models based on the volumetric growth theory is that they do not account for any change in the tissue mechanical properties during growth and remodeling; however, they only predict any occurred geometrical changes. And thus existing constitutive models needs to be modified with an additional input in the growth tensor that accounts for any change in the tissue mechanical properties [38].

### 2.4.2 Modeling of Left Bundle Branch Block

Towards achieving a computational representation of cardiac arrhythmias, specifically LBBB, several human action potential models describing the depolarization and repolarization phases of the cardiac muscle, have been described in the literature, while illustrating the proposed changes to the model achieving cardiac arrhythmias.

Vigmond et al. [45] proposed that the heart’s electrical activity can be modeled by initiating a 1 ms transmembrane stimulation pulse at a region corresponding to the SA node, which in turn activates the RA. Since both atria are disconnected, the activation of the LA is set to be initiated after 15 ms of the initiation of the SA node potential pulse at a predefined region
representing the attachment point of Bachmann’s bundle. Following the activation of both atria, the activation of the Purkinje network and hence the ventricle is initiated after a delay of 100ms representing the AV node delay. The activation of the ventricles was modeled by the use of Purkinje-myocyte junctions (PMJs) as current injection points. For each ventricle 100 PMJs were defined, where the LV points confined the entire circumference, which was not the case in the RV. The current was injected into each PMJ with a time delay relative to the distance between PMJ and the apex since Purkinje activation was set to be a linear function of the distance from the apex. And thus, it was proposed that modeling of bundle branch block can be achieved by eliminating Purkinje-myocyte junctions (PMJs) to the desired ventricle producing the required bundle branch block which is either RBBB or LBBB [45].

Additionally, Miri [26] proposed that the simulation of electrical excitation initiation and propagation can be achieved by the implementation of a pacemaker model and an excitation conduction system into a cardiac model, where the excitation propagation is based on an adaptive cellular automaton (ACA) model. The Purkinje network is manually generated based on an anatomical atlas, where the right bundle branch (RBB) originates as a single slender bundle that reaches the right ventricle endocardial septal wall, the anterior papillary muscle, and the other to the RV free wall, while passing through the interventricular septum. On the other hand, the left bundle branch (LBB) originates into three main branches that cover the whole LV starting from the left ventricular septal wall extending to the anterior and posterior papillary muscle, reaching the septum and the inferior and superior free wall. Thus, the generated Purkinje network covers the whole ventricles, by generating its end points on the endocardium based on a density parameter set. The ACA model on which the excitation propagation in this proposed model is based on, is governed by a pre-calculated action potential derived from ionic current equations. The ACA model is composed of a finite number of nodes corresponding to a set of cardio myocytes having same properties, where at a given time instant their state (transmembrane voltage) changes according to the state of a neighboring nodes and the node’s own state in the previous time steps. The transition between node is based on different parameters including electrophysiological parameter, conduction velocity and fiber orientation of the myocardium, type of cardiac tissue and finally the transmembrane voltage during current and previous excitation. Getting to the modeling of LBBB pathology, it was achieved by creating a disconnection in the Purkinje network created just after the bundle of His, in addition to some modification in the excitation propagation including the adjustment of the cellular automaton parameters in a way preventing the excitation to go through the LBB.
Another alternative for the modeling of the LBBB is to set a zero velocity for the excitation conduction along the LBB [26].

2.5 The living Heart Project

The living heart project is the largest ongoing project that is based on a group of researchers, clinicians and international industries aiming to produce a unified foundation for the modeling of a coupled electrical-mechanical analysis of a full beat cycle. Based on their successful combination of accurate heart geometry and material properties, a Multiphysics based model representing a sequentially coupled electrical-mechanical analysis of a healthy male heart beat cycle corresponding to a heart rate of 60 beats per minute (BPM) have been produced named as the Living Heart Human Model (LHHM) [6]. It is a dynamic high-fidelity model representing the four main chambers of the heart as well as all its anatomic details and proximal vasculature. The model also includes a realistic representation of the cardiac conduction system and blood flow physics that are used to assess the mechanical response of the heart. Although the LHHM offers a realistic representation of a healthy heart, it can be used to model abnormalities including cardiac arrhythmias and heart failure. Besides modeling abnormalities, LHHM also can be used to model treatment options including medical devices implementation and their effect on cardiac function. In the next few sections all the three-dimensional designs along with all the computational methods used with the LHHM will be described in details [6].

2.5.1 3D Heart Model Representation

The heart geometry presented in the LHHM was adopted by the use of the three-dimensional computer aided design model presented by Zygote Media Group, Inc., with minimal changes to enhance mesh discretization [6]. This three-dimensional representation includes the heart’s four main chambers along with the heart’s main arteries and veins including aortic arch, pulmonary artery and superior vena cava. The final generated discretized finite element heart model consists of 266,381 linear tetrahedral elements and 71,389 nodes having 220,707 degrees of freedom where 67,299 are associated with the scalar electrical potential $\phi$ degrees of freedom, while the remaining 153,408 degrees of freedom are associated with the deformation vector $\varphi$ [46]. The model also includes a representation of the muscle fiber orientation, consisting of 266,381 discrete fiber $f_0$ and sheet direction $S_0$. A representation of the bundle of His and Purkinje network Figure (12), was created based on the excitation of the cardiac tissue methods described in Kotikanyadanam et al. [47], where the fiber elements are considered to be a 1D electrical conduction element.
2.5.2 Continuum Model of Electro-Mechanical Coupling

The sequentially coupled electrical-mechanical analysis produced using LHHM is based on a continuum model consisting of a set of kinematics equations representing finite deformation, balance equations and a set of constitutive equations representing the excitation contraction coupling. The kinematics equations introduce the deformation vector $\varphi$, which maps a particle from its undeformed configuration to the deformed configuration. The deformation gradient $F$ is set to be the derivative of the deformation vector $\varphi$ with respect to the un-deformed configuration of the particle. The representation of the deformation gradient $F$ is as follows [46]

$$ F = \bar{F}. F^{vol} = \nabla \varphi \quad (5) $$

Where, $F$ is decomposed into a volumetric part $F^{vol}$ and an isochoric part $\bar{F}$ expressed in terms of Jacobian of the deformation gradient $J$ and the unit tensor $I$. 

*Figure 12: Fiber Bundles and Purkinje Network in LHHM*
$F^{vol} = J^{1/3} I$ \hspace{1cm} (6)

$\bar{F} = J^{-1/3} F$ \hspace{1cm} (7)

$J = \det F$ \hspace{1cm} (8)

Associated with the deformation gradient $F$ is the right Cauchy-Green tensor $C$ defined as $C = F^t \cdot F$, from which the isochoric right Cauchy-Green deformation tensor is identified as follows [46],

$\bar{C} = \bar{F}^t \cdot F = J^{-2/3} C$ \hspace{1cm} (9)

The right Cauchy-Green deformation tensor is associated with four principal invariants resulted from the projection of $C$ onto the unit tensor $I$ and from the preferred direction in the reference configuration of the myocardium namely the fiber direction $f_0$ and sheet direction $s_0$. The four invariants can be expressed as follows [46],

$I_i = \bar{C} : I$ \hspace{1cm} (10)

$I_{ff} = \bar{C} : [f_0 \otimes f_0]$ \hspace{1cm} (11)

$I_{ss} = \bar{C} : [s_0 \otimes s_0]$ \hspace{1cm} (12)

$I_{fs} = \bar{C} : [f_0 \otimes s_0]$ \hspace{1cm} (13)

The isochoric stretch of the myocardium in the fiber and sheet are expressed using the squared lengths of the fiber and sheet vectors, which is taken into consideration in the invariant $I_{ff}$ and $I_{ss}$. The squared lengths of the sheet and fiber vectors are expressed as follows [46],

$f = \bar{F} \cdot f_0$ \hspace{1cm} (14)

$s = \bar{F} \cdot s_0$ \hspace{1cm} (15)
On the other hand, the fiber-sheet shear is expressed using the invariant $I_{fs}$. Electromechanical coupling is based on balance equations representing both the electrical problem and the mechanical problem of the heart simulation. The electrical model is based on a monodomain model where the action potential, $\emptyset$, is expressed using the electrical flux $q$ and the source term $f^\emptyset$ as follows [46],

$$\dot{\emptyset} = \text{Div}(q) + f^\emptyset$$

(16)

The electrical flux $q$ and the source term $f^\emptyset$ are expressed using sets of constitutive equations classified as being the material property of the excitation of the cardiac tissue. While the mechanical problem is expressed in the form of balanced linear momentum equation of the deformation vector $\varphi$, expressed by constitutive equation of the tissue stresses and strain while having an active and passive responses [46]. These sets of constitutive equation will be introduced in the next sections.

### 2.5.3 Electrical Activity of Cardiac Tissue

Modeling of cardiac tissue excitation can be achieved by the use of set of equations representing the cardiac action potential along with a set of variables representing the effects of charged calcium, sodium and potassium currents. The electrical tissue response predefined in LHH model assumes a monodomain response where the electrical activation is characterized by an action potential, $\emptyset$, along with a recovery variable, $r$ [48]. The global equation also includes the flux term, $q$, which corresponds to the nature of propagation of electricity signals. The global equation can be presented through the spatial propagation of the action potential $\emptyset$ in terms of the flux $q$, and the transmembrane current $f^\emptyset$ [48],

$$\dot{\emptyset} + \text{div}(q(\emptyset)) = f^\emptyset(\emptyset, r)$$

(17)

The flux term $\text{div}(q)$ representing the nature of electrical waves propagation can be presented as follows,

$$q = -D \nabla \emptyset$$

(18)

Where, $D$ is a second-order diffusion tensor used to characterize the behavior of the action potential, while accounting for the isotropic and anisotropic propagation along a chosen path.
The source term $f^\emptyset$ comprises a cubic polynomial representing the oscillation threshold $\alpha$ characterizing pacemakers (-ve $\alpha$) and non-pacemaker (cardiac) cells (+ve $\alpha$) with regards to the action potential $\emptyset$, alongside with a coupling term representing the cardiac muscle cell recovery period through the recovery variable, $r$.

$$f^\emptyset(\emptyset, r) = c\emptyset[\emptyset - \alpha][1 - \emptyset] - r\emptyset$$

The temporal evolution of the recovery variable, $r$ can be assumed to be strictly local and can be presented as follows,

$$\dot{r} = f^r(\emptyset, r)$$

Where the source term $f^r$ represents the relaxing properties of the action potential through a set of constitutive parameters for the electrical response. $f^r$ is presented as follows,

$$f^r(\emptyset, r) = [\gamma + r\bar{\gamma}(\emptyset)][-r - c\emptyset[\emptyset - b - 1]]$$

Where $\gamma$ is the refractoriness period;

$c$ represents the scaling of the source term, $f^\emptyset$;

$b$ a phenomenological scaling parameter;

$\bar{\gamma}(\emptyset)$ is a scaling parameter used to tune the restitution curve as follows;

$$\bar{\gamma}(\emptyset) = \frac{\mu_1}{\mu_2 + \emptyset}$$

2.5.4 Tissue Mechanics

2.5.4.1 Cardiac Tissue Fiber Orientation

The complexity of the fiber orientations is considered to be as a result of the complex geometry of the heart, and the change occurring in the fiber orientations across the surface of the heart and the thickness of the heart wall [6]. Local material orientation is defined for each part, namely atria and ventricles, defined at its respective centroid. The left ventricle is considered to have the thickest wall compared to other chambers, varying along the surface of the heart where the thickest wall is found at the base and the equator, while the thinnest wall is found at the apex. Thus, the left ventricular wall can be considered as a continuum of myocardial fibers, having a smooth change in the fiber orientation along its thickness and
across the surface. The left ventricular wall can be assumed as being composed of parallel sheets of myocytes accounting for 70% of the wall volume [49]. Whereas, the remaining 30% are considered to be consisting of various interstitial components, where 2-5% of it is occupied by collagen arranged with respect to the circumferential direction of the LV as a network forming the lateral connection of the muscle fiber direction. This network is considered to rotate from +50 to +70 near the sub epicardial region to 0 in the mid wall region to -50 to -70 in the sub endocardial region [50], [51]. Thus, the fiber angle of the ventricles is considered within the LHHM to be ranging from -60 on the epicardium to +60 on the endocardium [50], [51]. The fiber orientation of the atria arch was approximated based on the orientation presented in euHeart Final Project Report [52], which were derived using electrophysiological simulations on models created from real life images of the inner surface of the atria as shown in Figure (13). The fiber orientation for the superior vena cava, pulmonary trunk and aortic arch were approximated to be having the normal direction matching to the normal of the surface geometry, and the sheet or fiber direction to be identified using a geometric edge [52]. Figure (14) shows a visualization of the whole heart fiber orientation where the red, blue and green identifies epicardial, endocardial and average fiber orientations respectively.
Figure 13: Atrium Fiber Orientation: Colors indicate different myocardial regions and white lines show the local muscle fiber orientation. [6]

Figure 14: Fiber Orientation of the Heart Model [6]
2.5.4.2 Active Stress Model

Stress components in the fiber and sheet directions are affected as a result of the active tissue response such that [53],

\[
\sigma_f = \sigma_{pf} + \sigma_{af} \tag{31}
\]

\[
\sigma_s = \sigma_{ps} + n \cdot \sigma_{af} \tag{32}
\]

\(\sigma_{af}\) is the active stress in the tissue’s fiber direction defined by a time varying elastance model as follows,

\[
\sigma_{af}(t, E_{ff}) = \frac{T_{max}}{2} \frac{C a_0^2}{C a_0^2 + E C a_{50}^2 E_{ff}} \left(1 - \cos \left(\omega(t, E_{ff})\right)\right) \tag{33}
\]

Where,

- \(E_{ff}\) is the strain in the fiber direction;
- \(C a_0\) is the peak intercellular calcium concentration;
- \(T_{max}\) is constitutive law contractility factor;
- \(\omega(t, E_{ff}) = \pi \frac{t}{t_0}\) for \(0 \leq t \leq t_0\)
- \(= \pi \frac{t - t_0 + t_r(l(E_{ff}))}{t_r}\) for \(t_0 \leq t \leq t_0 + t_r(l(E_{ff}))\)
- \(= 0\) for \(t \geq t_0 + t_r(l(E_{ff}))\)

Where \(t_r(l) = ml + b\), (\(m\ & b\) are constants representing the shape of the linear relaxation duration and sarcomere length relaxation)

\(E C a_{50}(E_{ff})\) is the length dependent calcium sensitivity defined as,

\[
E C a_{50}(E_{ff}) = \frac{C a_{0 \ max}}{\sqrt{e^{B(l(E_{ff})-l_0)} - 1}} \tag{34}
\]

Where,

- \(C a_{0 \ max}\) is the maximum intercellular calcium concentration
- \(B\) is a constant responsible for the shape of the peak isometric length relation between tension and sarcomere
- \(l_0\) is the sarcomere length below which no active tension progresses
\( l \) is the sarcomere length defined as \( l = l_R \sqrt{2 E_{ff}} + 1 \); \( l_R \) is the initial sarcomere length.

### 2.5.4.3 Passive Stress Model

The passive tissue response used in LHHM is based on the proposed anisotropic hyperplastic formulation model in Holzapfel and Ogden [49]. This model is characterized by its ability to differentiate tissue responses in different directions including fiber \( f \), sheet \( s \), and normal \( n \) directing and by having orthogonal components of energy. The deviatoric response of passive tissue is governed by the below strain energy density equation as follows

\[
\psi_{dev} = \frac{a}{2b} e^{b(l_1-3)} + \sum_{i=f,s} \frac{a_i}{2b_i} \left[ e^{b_i(l_1(l_{4i}^{-1})^2)} - 1 \right] + \frac{a_{fs}}{2b_{fs}} \left[ e^{b_{fs}(l_{fs}^2)} - 1 \right] \tag{35}
\]

Where \( a, b \) are material parameters governing the isotropic response of the tissue.

\( a_f, b_f \) are material parameters governing the additional stiffness in the fiber direction.

\( a_s, b_s \) are material parameters governing the additional stiffness in the sheet direction.

\( a_{fs}, b_{fs} \) are material parameters governing the additional stiffness in the fiber and sheet direction.

\( I_1 \) is a Cauchy-Green strain \( C \) invariant characterizing the behavior of the non-muscular and non-collagenous parts of the tissue.

\( I_{4i} \) is an invariant of Cauchy-Green strain \( C \) defined as \( A_i.C. A_i \) where is \( A_i \) is a position vector in a reference direction in the tissue, which account for anisotropy.

\( I_{Bfs} \) is a coupling invariant of Cauchy-Green strain \( C \) defined as \( A_f.C. A_s \) which accounts for the shear inside the cardiac tissue.

On the other hand, the volumetric part the third deformation invariant \( J \) scaled by multiple of bulk modulus \( D \) as follows,

\[
\psi_{vol} = \frac{1}{D} \left[ \frac{J^2 - 1}{2} - \ln(J) \right] \tag{36}
\]

### 2.5.5 Blood Flow Model

The blood flow model predefined in LHHM is based on a hybrid closed-loop model representing the cardiovascular system as lumped parameters and 3D elements. It consists of a set of capacitors and resistors representing structural compliances and flow resistances respectively [54]. While, the heart four main chambers are presented as 3D finite elements as
shown in Figure (15). The compliances of the venous, pulmonary and arterials systems are presented as cubic volumes with initial dimensions set to allow a blood flow circulation of 5L within the LHHM analysis [6]. The closed loop model representing the blood flow includes a preload section representing the venous and pulmonary systems, and an afterload section representing the total arterial compliance and total peripheral resistance $R_{system}$ which operates as a blood flow connector from the arterial to the venous systems, resulting in a closed loop system with a constant blood flow volume [54]. Heart valves are modeled as lumped resistors allowing for blood flow and resistance as per the direction of the positive pressure gradient. This includes $R_{tricuspid}$, $R_{pulmonary}$, $R_{mitral}$, and $R_{aorta}$ representing the tricuspid, pulmonary, mitral and aortic valves respectively. Lumped capacitive elements $C_{venous}$, $C_{pulmonary}$ and $C_{arterial}$ are used to model the effect of the total compliances of the systemic veins, lungs and arteries respectively [6]. While lumped resistive elements $R_{venous}$, $R_{pulmonary-system}$ and $R_{system}$ are used to model the venous flow resistance, pulmonary flow resistance and total peripheral resistance respectively. The flow rate between two adjacent chambers is assumed to be proportional to the pressure difference scaled by the intermediate valve resistance as follows [46],

$$Q_{c \rightarrow c+1} = \frac{P_c - P_{c \rightarrow c+1}}{R_{c \rightarrow c+1}}$$

(37)

The representation of the four main chambers is based on surface-based fluid cavity representation where the change in a chamber volume flow rate is calculated as follows [46],

$$V_c = Q_{c-1 \rightarrow c} - Q_{c \rightarrow c+1}$$

(38)
2.5.6 Electrical and Mechanical Analysis in LHHM

The sequentially couples electrical-mechanical analysis in LHHM is based on two independent analyses where the electrical analysis is conducted first generating the electrical potentials which are then used as the excitation source in the mechanical analysis. The electrical analysis begins at 70% diastole of the cardiac cycle as the electrical potential pulses from the SA node are initiated varying from -80 mv to 20 mv over 200 ms [6]. Figure (16) illustrates the electrical potential of the SA node.
Figure 16: Electrical Potential of the SA node set within LHHM [6]

The mechanical analysis is performed using the action potential from the electrical analysis while accounting for all chambers pressure that presents the normal hemodynamics parameters of a normal heart at 70% diastole. The mechanical beat cycle is performed in 1s where 0.5s represents the atrial and ventricular contraction phase of the cardiac cycle while the other 0.5s accounts for cardiac relaxation and ventricular filling phase.
Chapter III

Proposed Methodology and Benchmarking

In this chapter, the proposed methodology of assessing and benchmarking the proposed living heart human model presented within the framework of the living heart project will be presented. Moreover, the proposed methodology of modelling the cardiovascular diseases of interest will be presented, along with the modeling of the associated treatment.

3.1 Understanding LHHM and Benchmarking

In this section, the methods followed to assess and benchmark the LHHM will be introduced. This includes identifying the model ability to model a full electro-mechanical beat cycle, while representing the basic features and outputs of a cardiac excitation contraction cycle, and its capability to model abnormalities in terms of varying preload, afterload, and myocardium material properties.

3.1.1 Assessing the LHHM default model

To assess LHHM basic features and outputs of a cardiac excitation contraction cycle, a full electro-mechanical beat cycle is simulated under normal condition set within the model. Usually, the electrical simulation is performed preceding the mechanical simulation, since mechanical response is driven by the generated electrical excitation output. The LHHM electrical behavior is assessed by analyzing the excitation propagation sequence and timing within the atria, Purkinje network and ventricles respectively. Also, the electrophysiological behavior of the LHHM electrical excitation output is evaluated by generating and analyzing the Pseudo-ECG in comparison with clinical ECGs courtesy collected from AHC in Egypt for a patient within normal heart conditions. The Pseudo ECG is extracted from the electrical excitation output using different toolboxes including Matlab, Paraview, Python and chaste C++ library, which were programmed by fellow colleagues in the research team. The extracted ECG were based on 6 lead ECG position as per the locations shown in Figure (17).

On the other hand, LHHM mechanical response is evaluated by analyzing the mechanical deformation sequence with respect to the electrophysiological behavior. Additionally, from the mechanical simulation output, cardiac function parameters are extracted, which are then compared to normal published ranges. Also, evaluation of the output of the mechanical response can also be validated by generating the correspondent left ventricular pressure volume loop and the correspondent transmitral flow velocity curve, and comparing them with clinical
data collected from AHC for a patient within normal heart conditions. The pressure-volume loops are generated internally within the LHHM by plotting the chamber volume versus chamber pressure for a full beat cycle. While the transmitral flow velocity curve are proposed to be generated externally by applying Bernoulli’s equation assuming that the E/A wave profiles are triangular. This is achieved by extracting pressures from the mechanical response output across the mitral valve. The general form of Bernoulli’s equation is as follows

\[
\left(\frac{P_1}{y_1} + \frac{v_1^2}{2g}\right) = \left(\frac{P_2}{y_2} + \frac{v_2^2}{2g}\right)
\]  

(39)

Assuming that the initial velocity of the flow just as the mitral valve opens is zero, thus the above equation can be simplified as follows,

\[
\Delta P = 4V^2
\]  

(40)

Where,

- \(P\) is pressure in mmHg
- \(v\) is velocity in m/s

![Figure 17: 6 Lead ECG locations corresponding to the LHHM geometry](image)

Figure (18) show the detailed sequence of assessing the LHHM under normal condition.
3.1.2 Assessing the LHHM capabilities of varying vascular pressure

In order to better assess the LHHM capabilities in modeling abnormalities. The effect of varying several vascular pressures will be studied. Variation of vascular pressure may be resulted from several disease state and have direct effect on the heart’s pumping chambers. Vascular pressure my have effect on chambers preload and afterload. A chamber preload is defined as the initial stretch of cardiomyocytes prior to contraction. Preload is affected by several parameters including cardiac compliance and filling pressures [55]. Compliance can be defined as a chamber ability to expand and increase in volume as a result of increase in pressure [56]. Thus, any deviation in the chamber’s compliance and/or filling pressure affects the correspondent chamber preload. On the other hand, Afterload can be defined simply as the load that heart must need to overcome to eject blood, which may also be affected by vascular pressure.

3.1.2.1 Varying in Arterial Pressure

The arterial compliance cubic volume existing within the LHHM represents the arterial system, which is a part of the systemic circulation system responsible for carrying oxygenated blood from the heart to the body through arteries. Changes in the arterial pressure usually affects the afterload (resistance) that the LV needs to overcome in order to be able to eject
blood out of it [57]. Initially, the arterial pressure is set to be at 80mmHg at 70% diastole, and thus any change in the arterial pressure would correspond to a change of cardiac output. Varying in arterial pressure is achieved by changing the initial pressure defined within the model from the boundary condition manager within Abaqus/CAE. Figure (19) shows the steps followed to change the arterial pressure and run the mechanical simulation.

![Figure 19: Assessment steps for changing arterial pressure within LHHM](image)

### 3.1.2.2 Varying in Pulmonary Pressure

The pulmonary compliance cubic volume existing within the LHHM represents the pulmonary circulation system responsible for carrying the blood from the heart to the lungs and back to the heart. Blood flows from the RV to the lungs via the pulmonary arteries. Thus, changes in the pulmonary pressure usually affects the afterload (resistance) that the RV needs to overcome in order to be able to eject blood out of it [57]. Initially, the pulmonary pressure is set to be at 8mmHg at 70% diastole, and thus any change in the pulmonary veins pressure would correspond to a change of cardiac output. Varying in pulmonary compliance is achieved by changing the initial pulmonary compliance pressure defined within the model from the boundary condition manager within Abaqus/CAE. Figure (20) shows the steps followed to change the pulmonary compliance and run the mechanical simulation.

![Figure 20: Assessment steps for changing pulmonary pressure within LHHM](image)

### 3.1.2.3 Varying in Venous Pressure

The venous compliance cubic volume existing within the LHHM represents the venous system, which is the part of the systemic circulation system responsible of carrying
deoxygenated blood to the heart via the right atrium through veins. Changes in the venous pressure usually affects the preload of RV, with no effect on the LV [57]. Initially, the venous compliance pressure is set to be at 2mmHg at 70% diastole, and thus any change in the venous veins pressure would correspond to a change of cardiac output of the RV. Varying in venous compliance is achieved by changing the initial venous compliance pressure defined within the model from the boundary condition manager within Abaqus/CAE. Figure (21) shows the steps followed to change the venous compliance and run the mechanical simulation.

3.1.3 Assessing the LHHM capabilities of varying myocardium properties

Cardiac pathologies are always associated with changes in cardiac tissue properties. Thus, assessing the effect of changing material properties in LHHM model is important in order to be able to model cardiovascular diseases. Since, the aim of this study is to model dilated cardiomyopathy; the effect of varying left ventricular material properties will be evaluated.

3.1.3.1 Variation of Left Ventricle Active Material Property

Changes in myocardial contractile state are often associated with changes in the left ventricle pressure volume relation relationship and the slope and position of the end systolic pressure volume relation (ESPVR). Contractility is proportional to the slope of the ESPVR, where the ESPVR flattens and shifts to the right along with a decreased myocardial contractile function, while the ESPVR slope increases when there is an increase in contractility [58], [59]. Accordingly, it is essential to assess the LHHM capability in expressing changes of the left ventricular pressure volume loop with respect to changes in contractility. Varying in contractility is achieved by scaling the contractility scaling parameter $T_{\text{max}}$ with respect to the predefined value within the LHHM. This is achieved by using the LHHM built in plugins through the Abaqus CAE, which in turn generates a new material input file for the LV. The generated material input file will then be used within the simulation of the mechanical analysis. Figure (22) shows the steps followed to scale the contractility and to run the mechanical simulation.
3.1.3.2 Variation of Left Ventricle Passive Material Property

Changes in myocardial stiffness state are often associated with changes in the left ventricle pressure volume relation relationship. An increase in the left ventricle passive stiffness leads to a stiffer ESPVR, which is associated with a reduction in preload, peak systolic pressure and left ventricle ejection fraction [59]. Thus, the relationship between stiffness and left ventricle ejection fraction is inversely proportional, where a decrease in stiffness would increase the LV ejection fraction. Accordingly, it is essential to assess the LHHM capability in expressing changes of the left ventricular pressure volume loop with respect to changes in left ventricular stiffness. Varying in stiffness is achieved by scaling the Holzapfel and Ogden [49] passive material property with respect to the predefined value within the LHHM. This is achieved by using the LHHM built in plugins through the Abaqus CAE, which in turn generate a new material input file for the LV. The generated material input file will then be used within the simulation of the mechanical analysis. Figure (23) shows the steps followed to scale the stiffness and to run the mechanical simulation.

3.2 Specification of the needed amendment to the LHHM

Since the aim of this study is to model electromechanical deviations as a result of LBBB and morphological variations, thus it is essential to modify the LHHM healthy heart model in
order to represent the required cardiac pathology. This includes modeling of LBBB, DCM and CRT.

3.2.1 Implementation of Left Bundle Branch Block

The flow of electrical stimulus through the ventricles is controlled by a network of Purkinje fibers. Thus, any deviation in the normal ventricles’ sequence of activation result from a defect in the Purkinje network. LBBB results in ventricular dyssynchrony, where the LV activation is delayed causing the RV contraction to precede the LV contraction. Therefore, it is required to produce using LHHM a delay between the left and right ventricular activation by modeling the effect of LBBB achieving the required delay between ventricular activation. The electrical analysis simulation in LHHM representing the heart’s electrical conduction is performed using the diffusion heat transfer procedure in Abaqus/CAE as both governing equations are similar. Therefore, LBBB is modeled in LHHM by choosing a set of Purkinje elements to represent the bundle block, while changing in the material properties corresponding to these elements in order to account for the change in electrical propagation within the left fibers. This includes changing the fiber conductivity, length and cross-sectional area. Figure (24) shows a schematic representation of the LBBB elements chosen set within the Abaqus/CAE. While Figure (25) shows the steps followed to scale the model LBBB and to run the electrical simulation, which are detailed in Appendix A.4.
Figure 24: Schematic Representation of LBBB in LHHM

1. Create a new set within the fiber bundles part module

2. Assign to the new created set some elements of the left bundle branch that represent the length of the block

3. Deselect the chosen LBBB elements from the Left fibers set

4. Create a new material that corresponds to the features of a block where the conductivity is minimized

5. Create a new section in which the new material is assigned too and the cross-sectional area is defined

6. Assign the created section to the created elements set within the fiber bundle part module

7. Generate the job file for the electrical simulation after amending the required changes

8. Run the electrical simulation job file in order to generate the electrical activation output

9. Analysing the output in terms of excitation propagation sequence and timing across the while heart

Figure 25: Sequence for the modeling of LBBB within LHHM
3.2.2 Implementation of Morphological changes as a result of DCM

DCM can be caused as a result of LBBB, affecting the heart’s main pumping chamber the LV, which becomes enlarged and weakened. The heart morphological changes as a result of DCM are modeled in LHHM using the Abaqus/CAE thermal expansion feature. Thermal expansion is defined within a material property by specifying specific expansion coefficient that it is used to compute thermal strains as follows:

\[
e^{th} = \alpha(\theta, f_\beta)(\theta - \theta^0) - \alpha(\theta^I, f_\beta^I)(\theta^I - \theta^0)
\]  

(41)

Where

- \(\alpha(\theta, f_\beta)\) is the thermal expansion coefficient;
- \(\theta\) is the current temperature;
- \(\theta^I\) is the initial temperature;
- \(f_\beta\) are the current values of the predefined field variables;
- \(f_\beta^I\) are the initial values of the field variables; and
- \(\theta^0\) is the reference temperature for the thermal expansion coefficient.

Therefore, DCM morphological changes is achieved by applying thermal expansion to the left ventricle with a defined thermal expansion coefficient corresponding to the level of the disease. Thermal expansion is defined as a material property of orthotropic nature for a set of elements representing the left ventricle while excluding the septum to avoid thickening of the septum. The orthotropic nature allows the assignment of different thermal expansions coefficients for each material direction. The expansion simulation run is then performed after amending the required changes to generate the new morphed heart geometry. Using in house Python code programmed by fellow colleagues, the nodes and elements of the new morphed geometry is extracted from the expansion simulation output in order to be used to run the electromechanical simulation of a dilated heart. Figure (26) illustrates the selected set of left ventricular elements while excluding the septum and the material orientation defined for the new left ventricular material in which the thermal expansion is defined respectively. While Figure (27) shows the detailed steps followed to achieve a morphed geometry corresponding to a dilated heart, which are detailed in Appendix A.5.
1. Create a new set of elements within the ventricles part module

2. Assign to the new created set all of the left ventricle elements while excluding the septum elements

3. Create a new material left ventricle material in which the thermal expansion is defined

4. The thermal expansion is defined as being of orthotropic nature allowing different thermal expansion coefficients to be assigned for each material direction

5. Assigning a material orientation for the new created left ventricle material

6. Create a new step after the preload in which thermal expansion will take place

7. Suppress the beat and recovery steps

8. Generate the job file for the expansion simulation after amending the required changes

9. Run the expansion simulation job file in order to generate the new heart morphed geometry

Figure 26: Chosen LV set of elements for expansion and the orientation defined

Figure 27: Sequence for the modeling of LBBB Morphological changes within LHHM
3.2.3 Generation of a New Purkinje Network for the Morphed geometry

Additionally, the mechanical analysis in LHHM model is dependent on a pre-simulation with the heart’s electrical activation, thus it is required to use the electrical analysis output that corresponds to the diseased model. Therefore, it is required first to model the change in the Purkinje network as a result of the heart dilation in order to be able to perform the mechanical full beat cycle analysis. The algorithm followed for Purkinje regeneration is developed by Costabal, Hurtado and Kuhl [60], where network are grown on the non-smooth endocardium surface. The three parameters that controls the Fractal tree algorithms and hence the shape of the generated network are the branch angle, the branch length and the repulsion parameter which accounts for the branch curvature [60]. Therefore, the first step for Purkinje generation is to extract from the generated dilated heart geometry, the endocardium nodes for both ventricles, which is achieved using MATLAB codes developed in house by fellow colleagues and other toolboxes including Paraview. The outputs are then used as input for the fractal tree python code, while changing the parameters as required. Using additional MATLAB code developed in house, a new Purkinje part file is generated that is compatible with Abaqus/CAE. Figure (28) shows the detailed steps followed to generate a new Purkinje part, replacing the old Purkinje network and performing the electrical simulation with the new Purkinje network and morphed geometry.

3.2.4 Implementation of a full simulation for a heart exhibiting DCM

Finally, modeling of a full electromechanical beat cycle for a heart exhibiting DCM is performed by changing the nodes input files used within the simulation for the whole heart parts with the now morphed nodes, use the electrical activation output for the new deformed Purkinje network generated, and generate a new left ventricular material property as previously described that account for the change in contractility and stiffness as result of DCM. Figure (29) shows the detailed steps followed to generate and analyze a DCM based model.
Figure 28: Sequence of generating a new Purkinje network corresponding to a specific geometry

1. Using different toolboxes, the ventricles endocardium are extracted

2. Run Fractal Tree algorithm python code

3. Use the output of fractal, run a matlab code to generate the new Purkinje part

4. Change within the generated job file, all the heart geometry nodes with the dilated nodes including Atria and ventricles

5. Generate the job file for the electrical simulation after amending the required changes

6. Replace the old Purkinje network with the new one within Abaqus/CAE

7. Run the electrical simulation job file in order to generate the electrical activation output with the new Purkinje network and morphed geometry

Figure 29: Sequence for the modeling of DCM within LHHM

1. Scale the left ventricular material using LHHM plugins within Abaqus/CAE to account for the change resulted from DCM

2. Generate the a new LV material file to be used in the mechanical simulation

3. Generate the job file for the mechanical simulation

4. Analyse the mechanical simulation output by comparing cardiac function parameter with clinical data

5. Run the mechanical simulation job file using the electrical simulation output of the new morphed geometry and Purkinje network

6. Change in the simulation directory the whole heart nodes input files

7. Analyse the mechanical simulation output by comparing cardiac function parameter with clinical data

8. Generate the ventricular pressure volume loop and transmitral flow velocity curve in order to compare it with clinical outputs
Chapter IV

Results and Discussion

4.1 LHHM Benchmarking

4.1.1 The LHHM under normal conditions (Control)

Running the LHHM under normal conditions produces clinically consistent output in general, when comparing to published data. In particular, the electrical excitation pattern obtained from the LHHM exhibits a flow of electricity that is roughly consistent with clinical expectation. Initially the model begins the cardiac cycle at rest with a potential of -80mV across all its cells (in the middle of the p-wave of the ECG). Electrical excitation propagates from the SA node with a potential of 20mV, and spreads rapidly across the atria to reach the AV node. The excitation wave then stalls at the AV node for 90ms, before resuming its flow through the bundle of His to reach the left and right ventricles to complete cardiac depolarization (ending the QRS complex on the ECG). Following depolarization, the heart is then returned to its original state as the ventricles (following the atria) are gradually repolarized (completing the T-wave on the ECG). However, the LV and RV activation sequences predicted on the LHHM is incorrect. It assumes electrical flow from apex to base. Whereas, normally the LV activation usually begins on the basal anterior para-septal, the mid-septum and the posterior apex, which are referred as early activation sites [61]. The activation then propagates transmurally to the other regions of the LV [61]. Whereas, the RV early activation site is found to be on the free wall near the insertion of the anterior papillary muscle [61]. The incorrect LV and RV activation sequence suggests the default electrical model is in need of significant modification, as will be addressed in the coming section.

The total time of the LHHM electrical cycle from the beginning of heart depolarization to the end of the repolarization phase is set to be 500ms corresponding to a heart rate of 60 BPM. Cardiac activation times obtained from the LHHM is roughly consistent with clinical expectation except for minor deviations. Atrial depolarization is complete within about 100ms from the initiation of the SA node signal, whereas, normally the duration ranges from 80 – 90ms [61]. Following atrial depolarization and after a delay at the AV node, the signal begins to travel through the fiber bundles activating the septum at 160ms after SA node signal firing, which complies with clinical data [61]. The septum becomes totally activated 20 ms later, and the signal reaches the ventricle at 180ms. Accordingly, the period from beginning of atrial
depolarization to the beginning of ventricular depolarization (PR interval) is 180ms, falling within the expected clinical range, where normally the duration ranges from 180 – 220 ms [61]. Finally, all the ventricular mass is totally activated at about 260ms deviating 10 – 30 ms from clinical expectation [61]. However, the period from the beginning of ventricular depolarization to the end of repolarization (ST interval) is 320 ms falling within the expected clinical range, which is normally 260 – 490 ms [61]. Figure (30) shows the spatiotemporal evolution of the electrical potential across the LHHM. The LHHM is further analyzed by generating a pseudo-ECG. In particular, Figure (31) to Figure (36) show a comparison between the pseudo-ECG generated from the LHHM under normal conditions when compared with clinical ECGs (v1-v6 leads) obtained from Aswan Heart Center (AHC) for a patient with normal heart conditions. As can be seen, there is a significant deviation between the pseudo-ECGs and the clinical ones, e.g. the reflected T-waves and misshapen QRS complexes.

Figure 30: Electrical Potential in the heart at different timings (90ms, 180ms, 260ms)
Figure 31: Pseudo ECG for LHHM in comparison with clinical ECG for Lead V1

Figure 32: Pseudo ECG for LHHM in comparison with clinical ECG for Lead V2
Figure 33: Pseudo ECG for LHHM in comparison with clinical ECG for Lead V3

Figure 34: Pseudo ECG for LHHM in comparison with clinical ECG for Lead V4
Figure 35: Pseudo ECG for LHHM in comparison with clinical ECG for Lead V5

Figure 36: Pseudo ECG for LHHM in comparison with clinical ECG for Lead V6
These predicted ECGs indicate that the default electrical model on the LHHM is in significant need of adjustment; another finding of our benchmarking exercise that will be addressed in the coming section.

Furthermore, modeling of cardiac mechanical deformation on the LHHM is governed by the electrical solution outlined above. Deformation is divided into two steps, namely, systole and diastole, where muscle fibers contract and relax respectively. During contraction, muscle fibers shorten to lift the apex upwards and to induce apical twist, which drive ventricular blood ejection. During relaxation, muscle fibers gradually relax to allow for ventricular filling and the gradual returns of the apex to its position, cf. [62]. Figure (37) shows the corresponding states of mechanical deformation across the heart over the cardiac cycle.

![Figure 37: Mechanical deformation of the heart at different timings of the beat cycle (0, 0.2, 0.4, 0.5, 0.7) – right to left (Longitudinal view)](image)

Hence, the LHHM follows normal deformation patterns of the heart. Moreover, predicted cardiac output parameters fall within normal published ranges [63]–[65] as shown in Table (2). Furthermore, the LV pressure-volume (PV) loop Figure (38) and the transmitral flow velocity (TFV, Figure (39)) can be extracted from the LHHM to help assess systolic and diastolic functions.

The left ventricular pressure-volume relationship is known to be a useful tool of determining cardiac performance. Generally, the PV loop consists of 4 phases including diastolic filling, isovolumetric contraction, systolic ejection and isovolumetric relaxation [55], [66]. The LHHM left ventricular PV loop representation generally complies with representation described in literature, while capturing the major feature of the pre-described phases. However, there are minor deviations that need to be amended because they may affect the cardiac performance. This includes pressures at which the opening and closure of the aortic
valve occurs and pressure variation sequence during ejection phase. From Figure (38) and (39), the pressure at which the aortic valve opens and closes are predicted as follows: (1) Mitral valve closes, (2) Aortic valve opens, (3) aortic valve closes, and (4) Mitral valve opens. The aortic valve opens and closes at 60 mmHg and 125 mmHg respectively. Whereas, normally the aortic valve opens at a pressure ranging from 80 – 100 mmHg and closes at a pressure ranging from 110 – 130 mmHg [55], [66]. Furthermore, during ejection phase, an undesired drop and rise in pressure occurs, which alter the normal sequence of pressure variation. Generally, when the aortic valve opens, the LV pressure begins to increase reaching the peak systolic pressure and then decreases as the ventricle begins to relax reaching the pressure at which the aortic valve closes [55], [66]. Currently, TFV curve is used as a tool for the prediction of diastolic dysfunction. Diastolic measurements derived from TFV curve are E-wave, A-wave, E/A ratio, the E-wave deceleration time (DT), the mitral A wave duration and the isovolumic relaxation time (IVRT) [67]. From Figure (39), the measurements derived from the TFV were predicted. The calculated E/A ratio, A duration and the IVRT complies with normal published values for an age group from 21-40 years old [68] as seen in Table (3). However, the profile of the produced pseudo E/A wave corresponds to heart characterized by having delayed relaxation [69]. A delay relaxation time usually result in an increase in the E wave deceleration time, and a slower E-wave in comparison with the A-wave [69].

Table 2: LHHM output parameter comparison with normal published values

<table>
<thead>
<tr>
<th>Cardiac Output Parameter</th>
<th>LHHM Default Model</th>
<th>Published Normal Ranges [64] – [66]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Ventricle Ejection Fraction</td>
<td>56%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Max LV Pressure</td>
<td>136.3 mmHg</td>
<td>100 - 140 mmHg</td>
</tr>
<tr>
<td>Min LV Pressure</td>
<td>6.8 mmHg</td>
<td>3 - 12 mmHg</td>
</tr>
<tr>
<td>Right Ventricle Ejection Fraction</td>
<td>49%</td>
<td>40 – 60 %</td>
</tr>
<tr>
<td>Max RV Pressure</td>
<td>29.8 mmHg</td>
<td>15 - 30 mmHg</td>
</tr>
<tr>
<td>Min RV Pressure</td>
<td>0.2 mmHg</td>
<td>2 – 8 mmHg</td>
</tr>
<tr>
<td>Right Atrium Pressure Range</td>
<td>1.8-6.5 mmHg</td>
<td>2 – 6 mmHg</td>
</tr>
<tr>
<td>Left Atrium Pressure Range</td>
<td>8.7 – 24.5 mmHg</td>
<td>4 – 12 mmHg</td>
</tr>
</tbody>
</table>
Figure 38: LV Pressure Volume Loop generated from LHHM – default model -3rd Beat

Figure 39: Wiggers diagram for LHHM default Model along with the approximated E/A wave
Table 3: LHHM diastolic measurements comparison with normal published values

<table>
<thead>
<tr>
<th>Diastolic Measurements</th>
<th>LHHM Default Model</th>
<th>Published Normal Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVRT (ms)</td>
<td>80</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.88</td>
<td>1.53 ± 0.4</td>
</tr>
<tr>
<td>Deceleration time DT (ms)</td>
<td>225</td>
<td>166 ± 14</td>
</tr>
<tr>
<td>A Duration (ms)</td>
<td>120</td>
<td>127 ± 13</td>
</tr>
</tbody>
</table>

4.1.2 Re-running the LHHM with a Modified Purkinje Network

The benchmarking performed in section 4.1.1 indicated a need for a modified electrical model. Indeed, a Purkinje network model developed in-house (by other members of the research team) was incorporated into the LHHM, in lieu of its default network in order to overcome the improper activation sequence and to improve predicted ECGs. Figure (40) shows a representation of the new Purkinje network in comparison to the default LHHM.

Figure 40: Comparison between new and old Purkinje network for normal conditions

Figure (41) to Figure (46) show a comparison between the pseudo-ECGs for the LHHM using the in-house developed Purkinje network vs the default network and clinical ECGs obtained from AHC for a patient with normal heart conditions. As can be seen from the comparison, the in-house developed Purkinje network still needs improvements in order to better represent the electrical heart model. The ongoing modification is to take into account the early activation sites while generating the Purkinje network. Moreover, the electrical activation sequence did not tremendously change from the default model except for the PR interval and ST interval as can be seen from Figure (47) to Figure (48). The PR and ST intervals became 210 ms and 290 ms respectively, which are still complying with expected clinical range [61].
Figure 41: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V1

Figure 42: Psuedo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V2
Figure 43: Pseudo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V3

Figure 44: Pseudo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V4
Figure 45: Pseudo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V5

Figure 46: Pseudo ECG for LHHM old and new Purkinje network in comparison with clinical ECG for Lead V6
The change in the electrical activity after changing the Purkinje network also affected the LV PV-loop as shown in Figure (49). The undesired drop and rise in pressure during ejection phase was eliminated, approaching the normal sequence of pressure variation. However, still the pressure at which the aortic valve opens needs further modification.
Figure 49: LV - PV loop comparison with respect to different Purkinje networks - 3rd Beat

4.1.3 Vascular Pressure Variation

4.1.3.1 Arterial Pressure

Arterial pressure has a notable effect on multiple cardiac function parameters, including stroke volume (SV), and end-systolic volume (ESV). The relations between arterial pressure (afterload) and these parameters should be [57],

\[ Arterial\ pressure \propto \frac{1}{LVSV} \]  \hspace{1cm} (42)

\[ Arterial\ pressure \propto LVESV \]  \hspace{1cm} (43)

Figure (50), thus illustrates the predicted changes in SV and ESV on the LV’s PV-loop extracted from the LHHM. It is thus predicted that as arterial pressure rises, ESV increases, and corresponding SV decreases, consistent with the expectations of relations 42 and 43. The end systolic pressure volume relationship (ESPVR) remains unchanged, since it is only representing the inotropic state of the ventricle.
4.1.3.2 Pulmonary pressure

Since the heart is consisting of two pumps in series, thus there are two afterload pressure. As presented in the previous section, the arterial pressure represents the afterload of the LV. On the other hand, the afterload of the RV is represented by the pulmonary artery pressure [70]. Decreasing pulmonary pressure decreases RV afterload, and has effect on multiple parameters including RV SV and RVEDV. The relations between RV afterload and these parameters are [57],

\[ \text{Pulmonary pressure} \propto \frac{1}{RVSV} \quad (44) \]

\[ \text{Pulmonary pressure} \propto RVESV_{\text{ESPVR}} \quad (45) \]

Figure (51) illustrates changes in SV and RVEDV on the RV PV- loop, which are again consistent with the expectations of relations 44 and 45. As there is no change in the ventricle inotropic state due to changes in the pulmonary pressure, the ESPVR remains unchanged.
It is known that the left ventricular filling pressure is approximately equal to pulmonary venous pressure [57]. Thus, a decrease in the pulmonary pressure would result in a decrease in the LV filling pressure. Therefore, decreasing pulmonary pressure decreases LV preload, and has effect on multiple parameters including LVSV and LVEDV. The relations between pulmonary pressure and these parameters are [57],

\[ \text{Pulmonary Pressure} \propto \text{LVSV} \quad (46) \]

\[ \text{Pulmonary Pressure} \propto \text{LVEDV} \quad (47) \]

Figure (52) illustrates changes in SV and LVEDV on the LV PV-loop, which are again consistent with the expectations of relations 46 and 47. As there is no change in the ventricle inotropic state due to changes in the pulmonary pressure, the ESPVR remains unchanged.
4.1.3.3 Venous Pressure

Decreasing venous pressure decreases RV preload of the RV, and has effect on multiple parameters including RV SV and EDV. The relations between venous pressure and these parameters are [57],

\[ \text{Venous Pressure} \propto \text{RVSV} \] \hspace{1cm} (48)

\[ \text{Venous Pressure} \propto \text{RVEDV} \] \hspace{1cm} (49)

Figure (53) illustrates changes in SV and RVEDV on the RV PV-loop, which are again consistent with the expectations of relations 48 and 49. Again, as there is no change in the ventricle inotropic state due to changes in the pulmonary pressure, the ESPVR remains unchanged.
4.1.4 Varying Myocardial Material Properties

4.1.4.1 LV (contractility)

Changes in myocardial contractile state are often associated with changes in the LV pressure volume relations and the slope and position of the ESPVR. Contractility is proportional to the slope of the ESPVR. That is, ESPVR slants to the right with decreased myocardial contractility, while its slope steepens with an increase in contractility [58], [59]. This effect was reproduced on the LHHM by reducing myocardial contractility by modifying $T_{\text{max}}$ presented in equation 33 for the modeling of active myocardial properties. The change in contractility resulted in the LV pressure volume loops shown in Figure (54), consistent with clinical expectation [58], [59].
4.1.4.2 LV Passive Stiffness

Changes in myocardial stiffness are often associated with changes in the LV pressure volume loops. The relation between stiffness and LV ejection fraction is inversely proportional. Using the LHHM and changing LV passive stiffness by adjusting stiffness parameters in the sheet and fiber direction presented in equation 35 for the modeling of passive material properties. The resulting LV pressure volume loop is shown in Figure (55), which is consistent with clinical expectation [59].
4.1.5 Conclusions on the Benchmarking Exercise

To sum up, the LHHM has shown a great potential for the use of computational modeling in representing a human heart. The LHHM showed excellent mechanical predictive capabilities in term of capturing basic feature of systolic and diastolic phases i.e. apical twist. On the other hand, the LHHM showed good electrical predictive capabilities, however still in-house improvements need to be amended in terms of sequence activation to include early activation sites. Additionally, the LHHM showed excellent capabilities in terms of modeling abnormalities resulted from any disease state. This includes variation in preload, afterload, and cardiac inotropy.
4.2 Assessment of Morphological changes implementation

Varying the thermal expansion coefficient in a thermal step on ABAQUS, models cardiac growth and results in different degrees of LV dilation, which in turn enables a representation of varying degrees DCM. Figure (66) compares the frontal and cross-sectional views of the normal LHHM geometry (150mL LV) to two DCM geometries (300mL and 350mL, respectively), obtained with thermal expansion coefficients of 0.0125 and 0.025, respectively. Dilated of the LV volumes are here reported at 70% diastole. Figure (57) and Figure (58) further illustrate (respectively) a superposition of basal and longitudinal sections of the normal LV at 70% diastole and the corresponding dilated models. The general morphologies are seen to be consistent with the literature [71].

Figure 56: Comparison between different LHHM models at 70% diastole
These DCM geometries are also herein validated by comparing 2D four-chamber views of the models to clinical magnetic resonance imaging (MRI) obtained for patients from the Aswan Heart Center (AHC) with similar DCM LV volumes, as illustrated in Figure (59) and Figure (60). Again, it is seen that the predicted geometries compare very well to the clinical references.
Figure 59: 2D four chamber view comparison between LHHM DCM, 300ml and clinical MRI
Figure 60: 2D four chamber view comparison between LHHM DCM, 350ml and clinical MRI

4.3 Case Studies

4.3.1 Case Study I: LBBB Only Conditions
4.3.1.1 Problem Setup

LBBB is represented on our in-house developed Purkinje network by selecting a set of elements in the network to represent the block. Six elements in the left bundle branch were thus selected, as highlighted in Figure (61). Changing the electrical conductivity of the highlighted elements to 10% of its default value on the LHHM accounts for the delay in electrical propagation through the left branches. Furthermore, the numerical cross-section of the selected elements was set to be 0.1mm, in lieu of the default 1mm.

Figure 61: LBBB elements (Red) chosen within LHHM

4.3.1.2 Electrical Analysis

In our LBBB model we predict that RV endocardial activation begins 10ms sooner than the default model (at 175ms compared to 185ms). Furthermore, with LBBB the beginning of LV endocardial activation is delayed by 20ms in comparison to RV endocardial activation. Additionally, a delay between LV and RV endocardial activation completion times is predicted, where the RV endocardium becomes fully polarized at 205ms, while the LV endocardium at 225ms. This delay results from the delay arising in the blocked Purkinje network, see Figure (62). A delay in activation also extends through the ventricular walls, where the RV completes its polarization at 280ms, while the LV at 305ms (25ms delay), see Figure (63) and Figure (64). Table (4) summarize the activation timing for the default and LBBB model. That LBBB causes an abnormal electrical activation in not only the left but also the right ventricles is consistent with the literature, where it has been reported that RV endocardial activation is initiated at
times and even completed before LV endocardial activation [72]. Moreover, that LBBB results in an earlier activation of the RV with respect to the normal heart by 5ms to 26ms has also been reported (consistent with our model) [73].

*Table 4: Activation timing comparison between default model and LBBB model*

<table>
<thead>
<tr>
<th>Event</th>
<th>Default Model</th>
<th>LBBB Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning of RV endocardial activation (ms)</td>
<td>185</td>
<td>175</td>
</tr>
<tr>
<td>(RV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning of LV endocardial activation (ms)</td>
<td>185</td>
<td>195</td>
</tr>
<tr>
<td>(LV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion of RV endocardial activation (ms)</td>
<td>260</td>
<td>205</td>
</tr>
<tr>
<td>(RV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion of LV endocardial activation (ms)</td>
<td>260</td>
<td>230</td>
</tr>
<tr>
<td>(LV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Ventricle end of activation time (ms)</td>
<td>275</td>
<td>280</td>
</tr>
<tr>
<td>Left Ventricle end of activation time (ms)</td>
<td>275</td>
<td>305</td>
</tr>
</tbody>
</table>

*Figure 62: Fiber bundle activation comparison between models at different timing (180 ms, 205 ms, 260 ms) left to right*
4.3.1.3 Mechanical Analysis

LBBB is recognized as an electrophysiological abnormality characterized by producing asynchronous myocardial activation. The mechanical consequence of LBBB, however, is dependent on the level of change in myocardial contractility. Therefore, development of LBBB in the normal heart will only show minimal immediate effects on cardiac systolic and diastolic functions, which will become more substantial with time as ventricular remodeling evolves [72]. The LBBB model of this section thus reflects the onset of the block in absence of any change in the ventricular morphology, thus only minimal change to the LV PV-loops are expected, as predicted in Figure (65).
4.3.2 Case Study II: DCM + LBBB Conditions

4.3.2.1 Problem Setup

Three electromechanical cycles for the DCM + LBBB conditions are simulated to capture the electrophysiological and pathophysiological effects of DCM and LBBB. Morphological changes due to DCM were implemented via the thermal expansion technique described in section 4.2. The models investigated in this section correspond to the 300mL and 350mL cases (see Figure (56)). In each of these models, the Purkinje network has been generated using our in-house codes, using the parameters described in section 3.2.3, as summarized in Figure (55). Moreover, based on clinical data [74], a decrease in myocardial passive stiffness of 40% to 70% should ensue with DCM. Furthermore, a decrease in active contractility of 50% to 70% should also ensue [74]. Therefore, we scaled down ventricular stiffness and contractility with respect to the default values on the LHHM by 50% to better capture DCM.
For both the 300mL and 350mL conditions, an LBBB section was created consisting of six elements from the left bundle branch (same as in Figure (61)), where fiber conductivity was scaled to 10% of the default value of the LHHM, and their numerical cross-section was set to 0.1mm. Table (5) combines the parameters for each model.

Table 5: Configurations of the proposed models

<table>
<thead>
<tr>
<th>Model</th>
<th>Used Geometry</th>
<th>LBBB properties</th>
<th>Left Ventricle Material Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB–DCM Model 1 (300mL)</td>
<td>Morphed geometry achieved by applying a thermal expansion coefficient equal to 0.0125</td>
<td>6 elements</td>
<td>Stiffness reduced by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conductivity = 10%</td>
<td>Contractility reduced by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-section=0.1</td>
<td></td>
</tr>
<tr>
<td>LBBB–DCM Model 2 (350mL)</td>
<td>Morphed geometry achieved by applying a thermal expansion coefficient equal to 0.025</td>
<td>6 elements</td>
<td>Stiffness reduced by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conductivity = 10%</td>
<td>Contractility reduced by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-section=0.1</td>
<td></td>
</tr>
</tbody>
</table>

4.3.2.2 Electrical Analysis

Ventricular asynchrony is again predicted due to the LBBB, in both dilated models, where the LV polarization is delayed 15-20ms compared to RV polarization, consistent with the literature [73]. Table (6) summarizes all activation timings of interest for the 300mL and 350mL models in comparison to the normal model. Figure (67) to Figure (70) illustrate the corresponding electrical activation sequence from the frontal views and for the longitudinal sections. These results are akin to those predicted in section 4.1.2, where they have been described and shown to be consistent with the literature [73]. Hence, the dilation of the
ventricles to represent DCM and our Purkinje network regeneration have not negatively affected our models’ predictive capability of LBBB conditions.

Table 6: Activation timing comparison between default model, DCM-LBBB model 1, DCM-LBBB model 2

<table>
<thead>
<tr>
<th>Event</th>
<th>Default Model</th>
<th>DCM+LBBB Model 1</th>
<th>DCM+LBBB Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning of RV endocardial activation (ms)</td>
<td>185</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td>(RV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning of LV endocardial activation (ms)</td>
<td>185</td>
<td>205</td>
<td>215</td>
</tr>
<tr>
<td>(LV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion of RV endocardial activation (ms)</td>
<td>260</td>
<td>275</td>
<td>275</td>
</tr>
<tr>
<td>(RV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion of LV endocardial activation (ms)</td>
<td>260</td>
<td>290</td>
<td>290</td>
</tr>
<tr>
<td>(LV Purkinje Network beginning activation time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Ventricle end of activation time (ms)</td>
<td>275</td>
<td>285</td>
<td>285</td>
</tr>
<tr>
<td>Left Ventricle end of activation time (ms)</td>
<td>275</td>
<td>305</td>
<td>305</td>
</tr>
</tbody>
</table>

Figure 67: Comparison between Electrical Simulation output between normal and DCM-LBBB model 1 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Frontal view
Figure 68: Comparison between Electrical Simulation output between normal and DCM-LBBB model 1 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal section

Figure 69: Comparison between Electrical Simulation output between normal and DCM-LBBB model 2 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal section

Figure 70: Comparison between Electrical Simulation output between normal and DCM-LBBB model 2 at different timings left to right (90ms, 180ms, 260ms, 280ms, 310ms) – Longitudinal section
4.3.2.3 Mechanical Analysis

It is predicted that a reduction in ejection fraction will occur in both dilated models, due to the increase in ESV and EDV associated with LV dilation. Clinical data, based on [75] and [76], for a group of over 100 patients exhibiting DCM, is presented in Table (7) and Table (8), which indicates that our models are capable of accurately reproducing cardiac function under DCM conditions.

Table 7: Comparison of cardiac function parameters: 300 mL vs. clinical data from McCrohon et al. [75] study

<table>
<thead>
<tr>
<th>Cardiac Function Parameter</th>
<th>DCM [75]</th>
<th>DCM - LBBB Model 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDV [ml]</td>
<td>246 ± 79</td>
<td>299</td>
</tr>
<tr>
<td>LV ESV [ml]</td>
<td>155 ± 78</td>
<td>211</td>
</tr>
<tr>
<td>LV EF [%]</td>
<td>39 ± 13</td>
<td>29%</td>
</tr>
</tbody>
</table>

Table 8: Comparison of cardiac function parameters: 350 mL vs. clinical data from Akhmatov et al. study [76].

<table>
<thead>
<tr>
<th>Cardiac Function Parameter</th>
<th>DCM [76]</th>
<th>DCM - LBBB Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDV [ml]</td>
<td>296.29±68.61</td>
<td>349</td>
</tr>
<tr>
<td>LV ESV [ml]</td>
<td>200.88±70.65</td>
<td>260</td>
</tr>
<tr>
<td>LV EF [%]</td>
<td>30.59±7.13</td>
<td>25%</td>
</tr>
</tbody>
</table>

The PV-loops for the normal, 300mL, and 350mL models are compared in Figure (71) and Figure (72). Again, these predicted loops are consistent with the literature [77], which indicates the DCM need not be associated with an increase in pressures.
Figure 71: Pressure volume loop comparison between default model and DCM-LBBB model 1

Figure 72: Pressure volume loop comparison between default model and DCM – LBBB model 2
Next, the transmitral flow velocity is analyzed. The corresponding E/A waves are predicted for the 350mL model in Figure (73). DCM is usually associated with low E wave, a high A wave, a low E/A ratio, a prolonged E deceleration time, and a prolonged isovolumetric relaxation time, in the presence of normal or only slightly increased left ventricular filling pressure [78], [79], consistent with the Figure. Table (9) summarizes the E/A wave parameters in comparison with clinical data, again confirming consistency with the clinical.

Table 9: comparison of transmitral flow velocity parameters between DCM-LBBB model 2 – clinical data [79]

<table>
<thead>
<tr>
<th>Diastolic Measurements</th>
<th>Clinical DCM [79]</th>
<th>DCM-LBBB model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A Ratio</td>
<td>1.1± 0.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Deceleration time DT (ms)</td>
<td>171± 43</td>
<td>280 ms</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>121± 35</td>
<td>133 ms</td>
</tr>
</tbody>
</table>

Figure 73: Wiggers Diagram for DCM Model along with the approximation of the E/A wave
4.3.3 Case Study III: Assessing CRT treatment on a heart exhibiting DCM and LBBB

4.3.3.1 Problem Setup

As CRT is considered to be a promising treatment for cardiac asynchrony, thus for DCM, capturing in-silico its optimal effect would be of great value to the securing of its beneficial outcomes prior to its application to each patient. However, our modeling efforts in this thesis may only be regarded as a first attempt at a complete CRT model, with a primary focus on establishing model feasibility. As stated above, CRT comprises of a pulse generator and three leads with different purposes. The lead located near the SA node carries information of the rhythmic heart excitation timing to the pulse generator, and will not be included in our model since the SA signal is triggered at 0ms by definition. On the other hand, LV and RV leads are modeled by selecting a set of myocardial elements in each ventricle that coincide with the locations of lead pulsation, see Figure (74). The steps followed to model CRT on the LHHM are summarized in Figure (75), which are detailed in Appendix A.6.

![Figure 74: Schematic Representation of CRT leads in LHHM](image)
Based on several studies, the optimum location of the LV lead was identified at the most delayed site of LV activation, which usually falls along the lateral or post-lateral LV wall [80]–[83]. Conversely, the optimum location of the RV lead is at the RV septum [80]–[83]. Accordingly, we defined a pulse on the LV basal lateral wall (last LV activation site) to mimic the LV lead, and another on the RV septum to mimic the RV lead. The profile of the pulses defined was made to match the action potentials of the stimulated tissue, rather than the direct output obtained from the pulse generator, since resulting tissue activity is what is of interest. AV and VV delays were set based on the ranges defined in literature. AV delay ranges from 120ms to 200ms and the VV delays ranges from -30ms to 70ms [84]. These delays should in fact be based on optimization techniques tailored to each patient, which is out of scope of this present study [84]. Instead, we set the AV and VV delays to 180ms and 40ms, respectively.

4.3.3.2 Electrical Analysis

Ventricular asynchrony due to LBBB was overcame with our CRT model. RV activation sequence is, however, different from the LBBB model. In the default model and LBBB model, the RV myocardium, including almost 1/3 of the interventricular septum, was activated following almost the normal activation sequence pattern [85]. Additionally, in both models the RV epicardium preceded that of the LV epicardium, complying with literature [86].

---

**Figure 75: Detailed sequence followed for the modeling of CRT within LHHM**

1. Create a new sets within the ventricles parts for the LV and RV leads positions
2. Define the electrical potential stimulus for the RV and LV leads
3. Setting the delay between the onset of the electrical potential of the LV lead with respect to the onset of SA node electrical potential (AV-Delay)
4. Setting the delay between the onset of the electrical potential of the RV lead with respect to the preceding LV lead electrical potential (VV-Delay)
5. Generate the job file for the electrical simulation after amending the required changes
6. Run the electrical simulation job file in order to generate the electrical activation output
7. Analysing the output in terms of excitation propagation sequence and timing across the while heart
8. Run the mechanical simulation job file using the electrical simulation output of the new morphed geometry and Purkinje network
9. Analysing the effect of CRT on cardiac output by comparing left ventricular pressure volume loop for different models
the CRT model the RV activation proceeded from apex to base. Although, the sequence of RV activation is consistent with the literature, however, the base of the RV and of the interventricular septum were activated earlier than in LBBB simulation at 220 ms in comparison with in the LBBB+DCM 350mL model (260 ms), which should not be the case [85]. Figure (76) illustrates how the sequence of activation in the RV has proceeded, in comparison with default model. Figure (77) and Figure (78), compare activation outputs from our CRT simulation to the LBBB+DCM 350mL model. The activation in the CRT model was faster by 30ms than LBBB+DCM 350 mL model, where the ventricles were totally activated at 280 ms and 310 ms respectively. The delay between ventricle depolarization were diminished in the CRT model.

![Figure 76: LV and RV activation sequence in the CRT model at different timings left to right (190ms, 220ms, 240ms, 260ms) – Longitudinal section](image)
4.3.3.3 Mechanical Analysis

It is predicted that a significant improvement in LV ejection fraction and QRS duration will occur in the CRT model [87]. However, it is clinically known that the effect of CRT usually appears over a time period of 6 months to 1 year after CRT implementation [87]. The success of CRT leads to an improvement in the LV size, where the end systolic and end diastolic diameters decreases [87]. Therefore, our CRT model did not show any improvement in the LVEF because it did not account for the change in LV size resulted from the synchronizing the heart. Moreover, since still the LHHM electrical model is still in need of modification to better assess the Pseudo ECG, the change in ECG after CRT implementation is not captured. Consequently, implantation of CRT on LHHM is still in need of further modification. The PV-loops comparison for the normal, DCM-LBB 350mL, and CRT models are compared in Figure (79).
Figure 79: Pressure volume loop comparison between default model, DCM – LBBB model 2, and CRT model
Chapter V

Conclusion and Future Work

The objectives of this study were to develop a method for the morphing of the left ventricle and the modeling of changes in cardiac function due to LBBB and DCM, with a basic application of the resulting model to CRT. Necessary benchmarking of the computational platform used to develop our model was also conducted, which revealed both strengths to be leveraged and weaknesses that need to be addressed. Analyzing and Benchmarking the LHHM have revealed its capabilities in representing a sequentially coupled electrical-mechanical analysis of a heart beat cycle. Although, there are some needed amendments to the electrical model, the available flow electricity is roughly consistent with clinical expectation. Additionally, the LHHM showed excellent capabilities in terms of modeling abnormalities resulted from any disease state. This includes variation in preload, afterload and cardiac inotropy.

Our proposed methodology has shown good agreement with clinically measured ventricular asynchrony due to LBBB, and the corresponding deterioration of cardiac function associated with DCM. Our LBBB model produced an interventricular dyssynchrony of 25ms complying with literature which usually ranges from 15 -60 ms. On the other hand, our DCM model have captured the deterioration of the cardiac function where the ejection fraction reduced from 56% in the normal LHHM model to 25% in the DCM complying with literature where a DCM patient ejection fraction usually ranges from 20%-30%. Additionally, our first implementation of CRT modeling has also shown good agreement of the electrical response measured clinically, while its effect on cardiac function is still not properly captured. This may be due to the fact that the effect of CRT is not instantaneous; it stabilizes after a period of 6 months to 1 year after extensive ventricular remodeling [87]. Our CRT model have diminished the interventricular dyssynchrony due to LBBB, while capturing the improvement in cardiac function is still not yet achieved.

For the future work of this study, it is aimed to use the proposed methodology to produce disease specific models, by optimizing to a small population of DCM patients, based on CMRI heart geometries. Additionally, the modification of the electrical model and Purkinje network of the LHHM will be further studied to include heart’s early activation sites in order to better reproduce Pseudo ECG compared to clinical data. Finally, amending the CRT model to better
reproduce CRT effect will be considered, in addition to the optimization of CRT lead position and timing delays.
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Appendix A

Abaqus/CAE Interface

A.1 Creating and Generating a Job File
From the job module in Abaqus/CAE interface, you can generate the job input file required to run the job as shown in Figure (80).

A.2 Vascular Pressure Variation
Varying in arterial, pulmonary and venous pressure can be performed within abaqus/CAE interface as shown from Figure (81) to Figure (83).
Figure 82: Changing pulmonary pressure within LHHM using Abaqus/CAE interface

Figure 83: Changing venous pressure within LHHM using Abaqus/CAE interface

A.3 Varying Myocardial Material Properties

Adjusting myocardial properties of the LV can be done using LHHM plugins available in the Abaqus/CAE interface as shown from Figure (85) and Figure (86).
Figure 84: Scaling heart’s contractility within LHMM using Abaqus/CAE interface

Figure 85: Scaling heart’s stiffness within LHMM using Abaqus/CAE interface

A.4 LBBB Implementation
Creating an LBBB section within the fiber bundle part is done from the part module of the electrical model by creating a new set and adjusting to it the selected element, while identifying to them a new material property corresponding to the block as shown in Figure (86).

![Figure 86: creating LBBB section using Abaqus/CAE interface](image)

**A.5 Implementation of Morphological Changes**

Applying thermal expansion to change in the heart’s morphology is done from the part module of the mechanical model by creating a new set and assigning it with the chosen elements/ nodes, while identifying to them a new material property corresponding in which thermal expansion is defined as shown in Figure (87).
Figure 87: Creating a new set for the implementation of Morphological Changes
A.6 Implementation of CRT

Implementation of CRT is done within Abaqus interface by creating 2 new sets in the ventricle parts of the electrical model that corresponds to the position of the LV and RV leads. Followed by the creation of the amplitudes corresponding to each lead. The created set and amplitude will then be used to create the boundary condition. Figure and Figure illustrates the steps within Abaqus/CAE.

*Figure 88: Creating a new set for the implementation of CRT*
Figure 89: Creating amplitude and boundary condition corresponding to CRT leads