Simultaneous Analysis of 2D Echo Views for Left Atrial Segmentation and Disease Quantification

by

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Abstract

We propose a joint information framework for automatic analysis of 2D echocardiography (echo) data. The analysis combines \textit{a priori} images, their segmentations and patient diagnostic information within a unified framework to determine various clinical parameters, such as cardiac chamber volumes, and cardiac disease labels. The main idea behind the framework is to employ joint Independent Component Analysis of both echo image intensity information and corresponding segmentation labels to generate models that jointly describe the image and label space of echo patients on multiple apical views jointly, instead of independently. These models are then both used for segmentation and volume estimation of cardiac chambers such as the left atrium and for detecting pathological abnormalities such as mitral regurgitation. We validate the approach on a large cohort of echos obtained from 6,993 studies. We report performance of the proposed framework in estimation of the left-atrium volume and diagnosis of mitral-regurgitation severity. A correlation coefficient of 0.87 was achieved for volume estimation of the left atrium when compared to the clinical report. Moreover, we classified patients that suffer from moderate or severe mitral regurgitation diagnosis with an average accuracy of 82%. Using only B-Mode echo information to automatically derive these clinical parameters, there is potential for this approach to be used clinically.
Preface

This thesis resulted from the collaboration between multiple researchers and is primarily based on a pending journal submission. The contribution of the author was in developing, implementing, evaluating the presented framework and created a local database of relevant data. Ethical approval for conducting the project titled, "Information Intelligence for Precision Cardiac Ultrasound Imaging", has been provided by the Vancouver Coastal Health Research Ethics Board, certificate numbers: H13-02370.

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Glossary

2D  Two-Dimensional
2DE  Two-Dimensional Echocardiography
3D  Three-Dimensional
3DE  Three-Dimensional Echocardiography
AAM  Active Appearance Model
AAMM  Active Appearance Motion Model
AICD  Automatic Implantable Cardioverter Defibrillator
AP2  Apical 2 Chamber
AP4  Apical 4 Chamber
ASE  American Society of Echocardiography
ASM  Active Shape Model
BC  British Columbia
BSA  Body Surface Area
CMR  Cardiovascular Magnetic Resonance
CSV  Comma-Separated Values
CT   Computed Tomography
DD   Diastolic Dysfunction
DICE Quantitative Dice Index
DICOM Digital Imaging and Communications in Medicine
ECHO Echocardiography
EF   Ejection Fraction
EROA Effective Regurgitation Orifice Area
FN   False Negative
FP   False Positive
GUI  Graphical User Interface
ICA  Independent Component Analysis
IT   Information Technology
jICA Joint Independent Component Analysis
LA   Left Atrium
LV   Left Ventricle
MAD  Mean Absolute Distance
MDL  Minimum Descriptive Length
MR   Mitral Regurgitation
MRI  Magnetic Resonance Imaging
mRMR Minimum Redundancy Maximum Relevancy
MRN  Medical Record Number
PACS Picture Archiving and Communication System

x
PCA  Principle Component Analysis

PDM  Point Distribution Model

PIVA Proximal Isovelocity Surface Area

RBF  Radial Basis Function

RF   Radio Frequency

ROC  Receiver Operating Characteristics

ROI  Region of Interest

SAX  Parasternal long axis

SSE  Sum of Squared Errors

SVM  Support Vector Machine

TEE  Transesophageal Echocardiography

TN   True Negative

TP   True Positive

tSNE T-Distributed Stochastic Neighbor Embedding

TTE  Transthoracic Echocardiography

UBC  University of British Columbia

US   Ultrasound

VCH  Vancouver Coastal Health

VGH  Vancouver General Hospital
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Chapter 1

Introduction

Cardiovascular disease is the number one cause of death globally [97]. Early diagnosis of cardiovascular diseases is important for monitoring and treatment. A patient’s cardiovascular risk is assessed by analyzing numerous parameters determined from features in the imaging data such as endocardium boundaries, which aids in measuring the Left Atrium and Left Ventricle volume. These measurements have a direct impact on clinical management of patient outcomes.

Cardiovascular diagnosis is performed using Cardiovascular Magnetic Resonance (CMR), Computed Tomography (CT), Three-Dimensional Echocardiography (3DE) and Two-Dimensional Echocardiography (2DE) imaging. While CMR and CT provide high quality images of the heart, such methods are not routine: do not allow high-patient-throughput due to long acquisition times and limited availability; patients with metal implants cannot be imaged using CMR; and patients imaged using CT are exposed to ionizing radiation. Echocardiography (ECHO) is a non-invasive, low-cost, portable, and widely available imaging modality - making ECHO increasingly the standard for diagnosis of various cardiac conditions, risk stratification, and prognostication. While 3DE has several advantages over 2DE in terms of reduced operator variability and improve ECHO workflow in terms of efficiency and accuracy through automation, current 3DE technology has a lower spatial and temporal resolution vs. 2DE, 3DE images are difficult to interpret, and the majority of sonographers, including at Vancouver General Hospital (VGH), only use 2DE in routine clinical exams.
The most common 2DE interrogation is Transthoracic Echocardiography (TTE). TTE is used to assess the structure and functionality of the heart using both B-mode and colour Doppler flow imaging. In TTE the heart is imaged from at least six standard views: parasternal long and short axes, Apical 2 Chamber, Apical 4 Chamber, subcostal, and suprasternal views. Despite the valuable role of TTE, analysis is operator dependent, subjective when visually detecting disease, and considerably variable in the quality of the measurements [14]. This variability comes from multiple sources including sonographers’ experience, workload and time pressure. Reducing the variability of TTE analysis could lead to a more standardized measurement process of the patient to aid in preventing adverse cardiac events, including heart failure or stroke [1, 91].

ECHOs are obtained by the imaging technician, or sonographer, who is a medical professional accredited by the Canadian Medical Association to operate the Ultrasound (US) machine. An example of a common challenge faced by sonographers during 2DE acquisition is the foreshortening of the LV, which can cause inaccurate measurements by a cardiologist, who relies on optimal acquisition. Another source of error stems from the ultrasound image formation, where variability of the probe’s angle not only makes measurement discrepancies, but also increases the difficulty of ECHO image segmentation too. The segmentation difficulty increases as the boundary between the chamber tissue and blood pool becomes less defined, which is related to:

- Noise in inhomogeneous regions
- Orientation of the view
- Limited field of view through the patient’s rib cage
- Irregular geometry of the LA
- Maintaining orthogonal views between the AP4 and AP2.

During a standard study, there are numerous parameters determined from ECHO data, including endocardium boundaries, LA volume, Mitral Regurgitation (MR) severity and diastolic dysfunction. Several essential clinical measurements for diagnosis are derived by delineating the LA’s boundary accurately in multiple TTE
views. Undefined boundaries, related to the points mentioned above, increase the variability in measurements performed by 2DE and may have a direct impact on patient care and the clinical management of heart conditions. Performing reliable measurements, despite the inherent variability of 2DE, could lead to a more standardized examination of the patient to aid in preventing irreversible cardiac dysfunction.

One such essential clinical measurement is derived by delineating the LA’s boundary accurately in multiple ECHO views to correctly determine a patient’s maximal LA volume. This volume is useful in assessment of risk for first ischemic stroke. Stroke is the third most common cause of death worldwide [60]. Clinical trials have suggested that assessment of LA volume provides a quantitative assessment of risk for first ischemic and an independent predictor of death [6]. Overestimation of LA volume may lead to device implantation of an Automatic Implantable Cardioverter Defibrillator (AICD) in patients who may not benefit from this expensive therapy. Underestimation may deprive some deserving patients of the survival benefit afforded by AICD. Furthermore, LA volume has also been used for investigational procedures to determine LA enlargement, since it has been discovered to be a reliable marker for predicting stroke and mortality [35, 68, 80, 82, 107]. An enlarged LA is also associated with severe MR, a condition that must be closely monitored should it become symptomatic. Detecting MR before it becomes unmanageable allows physicians to alleviate diastolic dysfunction and safely manage heart failure [89], since without proper treatment, symptomatic patients have an annual death rate of over 5% a year [20].

Determining LA enlargement can be performed using traditional 2DE or newer 3DE methods. LA volumes determined from 3DE have been compared to CMR imaging and have demonstrated an improved accuracy over 2DE imaging with high correlation to CMR (r = 0.93) [69]. However, as of 2015, the American Association of Echocardiography does not recommend the use of 3DE for assessing LA volume, as there is limited data [5] and lack of standardized methodology to determine normal LA values [53].

Currently, to determine LA enlargement health care professionals must segment the end-systole frame of LA in both apical views separately, which is a highly repetitive process. Significant effort has been invested in standardizing LV ECHO cham-
ber segmentation through both semi-automatic and automatic analysis of cardiac data over the last few decades, but it still remains an open problem due to these mentioned issues [72]. Many variations on segmenting the blood-tissue boundary have been proposed in the literature such as: morphological image processing methods [50], neural networks [13, 21], active appearance model [15], active shape models [29], convexity pursuit algorithms [19], shape regression machines [40, 102] and active contour variants [10, 11, 39, 58, 64, 66, 83, 86]. The segmentation of the LA blood-tissue barrier has not been looked at extensively within the literature when compared to the LV. Segmentation of the LA is considered more difficult due to a) its more complex shape, b) there being less contrast between the endocardium and blood volume, c) the segmentation must cut through the LA appendage and through the mitral annulus, and d) the LA chamber is the furthest away from the transducer; resulting in ECHO images missing important anatomical features, such as the LA edges. However, the aforementioned LV segmentation methods do not deal with these obstacles, and do not incorporate the information from additional apical ECHO views.

Additionally, other parameters could be improved by having an algorithm that aids cardiologists in edge cases where they are unable to classify patients based on strict ECHO guidelines. During a standard study, cardiologists must mark a patient as indeterminate for the diastolic function or filling pressure, should their patient not meet the required parameters. As a result, the frequency of a patient’s recurring visits could be altered. Further incorporation of clinical ECHO parameters could potentially be used to further define these indeterminate groups.

Having a framework that would provide fast, consistent and accurate analysis of LA’s anatomy, volume, diastolic function and filling pressure would aid in diagnosing cardiovascular diseases, which would translate into direct benefits in patient care. The demand for ECHO assessment is escalating given the aging population and the rapid increase in the numbers of patients with cardiovascular disease. Publicly funded resources are limited. Currently, at VGH and University of British Columbia (UBC) Hospital, the wait time for a non-urgent ECHO is \( \geq 3 \) months. The ECHO laboratories across this province are facing the same crisis. There is a pressing need for more efficient application of the automatic image analysis techniques to meet this growing demand.
1.1 Proposed Framework

We propose a joint information framework for fusion of ECHO image intensity information and their segmentations from multiple 2D views of the heart to automatically estimate clinical parameters and diagnostic labels. Our proposed framework, using standard ECHO paired with clinical measurements, aims to reduce the number of manual measurements performed during a standard ECHO study and to ease the clinical workflow and reduce measurement variability. Here, we introduce the Joint Independent Component Analysis model [18] for this framework to learn patterns from the observable correlation between each ultrasound intensity voxel and the corresponding segmentation label. We use these patterns for LA volume estimation and classification of individuals with MR. The framework consists of four components, as seen in Figure 1.1: 1) model generation and alignment; 2) localization; 3) joint source reconstruction; and 4) classification and estimation of patient labels. We use the jICA framework to reduce our large database into compact, maximally independent basis functions, which combine intensity and shape information into a unified space to reveal diagnosis labels. As a corollary objective, we analyze final common measurements performed during routine studies to predict diastolic dysfunction and filling pressure for patients.

1.1.1 Contributions

Our research goal has been to develop a framework for LA volume estimation and disease label analysis on ECHO imaging information. In the course of this project, the following contributions were made:

- Obtaining a largest of its kind dataset of medical information by interfacing with VGH’s medical ECHO storage system (Philip’s Xcelera™) and clinical database (Filemaker™).
- Proposing a LA segmentation technique that uses the joint information from different apical views.
- Investigating a new technique for classifying normal and moderate or more severe mitral regurgitation based on jICA reconstruction coefficients.
Alignment and Model Generation
- Apical view selection
- Register database of image
- Stratify patients based on their anatomy

Left Atrium Localization
- Query database for most similar image
- Initialize template matching algorithm
- Define left atrium region

Joint Source Reconstruction
- Generate multiple joint ICA models
- Calculate segmentation probability maps
- Perform optimal segmentation selection

Classification and Estimation
- Calculate left atrium volume
- Categorize by mitral regurgitation severity

**Figure 1.1:** Overview of the proposed joint fusion information framework. The main processes of the four steps are unpacked above.
• Investigating the use of combining clinical features for analysis diastolic dysfunction and filling pressure to prevent indeterminate classification.

1.2 Structure of Thesis

This thesis consists of seven chapters. We provide an overview of each chapter and the associated contributions below:

Chapter 2: Background and Related Works

In this chapter, we review the basic anatomy of the heart to gain an understanding of its global function and the importance of the LA within the pulmonary circuit. We also provide a detailed walk-through of a typical sonographer routine study, specifically discussing patient positions, image acquisition protocol, and various measurements for the cardiologist’s report. The work flow of the attending cardiologist and their responsibilities are also revealed. Furthermore, we demonstrate the importance of the LA by discussing LA dynamics, measurement protocols, clinical importance for symptom management and disease related to LA dynamics, such as MR.

Chapter 3: Materials

In this chapter we describe the datasets obtained from the Philip’s Xcelera™ and Filemaker™ systems, which were used to train the multiple models employed by the joint framework. The ECHO data materials were obtained from Xcelera™, which were extracted from routine studies since as early as 2005 from multiple sonographers and ultrasound machines. We will use this ECHO data in future chapters. Patients’ clinical measurements were acquired from the Filemaker™ database; this data contains over 200,000 records and were used to label patient ECHOs with their correct disease labels and volume information.
Chapter 4: Methods
We explore:

1. **Localization:** Automatic localization of the LA Region of Interest (ROI) from AP4 and AP2 ECHO views. We use this localization step to create a bounding box around the anatomy, such that only the local variations of the LA are learned through jICA. To determine the bounding box that encompasses the entire LA region we use a centroid estimation matching technique paired with an intensity-based registration.

2. **Fusion Analysis for Volume Estimation:** We propose to classify individuals based on the anatomical shape of their LA chamber to create a set of structure-specific models. We aim to create a comprehensive set of models by leveraging our diverse database to stratify patients into cohorts. Patients are grouped based on their coefficients from Principle Component Analysis (PCA) decomposition of their AP4 and AP2 segmentations. Here, we use the set of models to generate spatially independent joint sources using jICA within a Support Vector Machine classification method [32]. Each model’s joint sources are used to produce a segmentation probability map through linear recombination with a patient’s ECHO image. The reconstruction profiles from each model were used within an SVM component to select the model most capable of representing the anatomy’s structural variations with the most representative reconstruction coefficients. Post-processing of the AP4 and AP2 segmentation labels are performed to calculate LA surface area and perform volume estimation.

3. **Disease Label Estimation:** We use both the feature information from the joint sources outputted from the jICA framework and common clinical measurements to create a disease prediction component. We first look to separate healthy patients and those with moderate MR solely based on the information gathered from 2D M-mode. Furthermore,
we seek to improve the current standard-of-care diastolic dysfunction classification and filling pressure to prevent indeterminate patient identification. This goal is accomplished by using a continuous spectrum of features for classification, instead of current discrete clinical guidelines, using a multi-stage SVM component and feature reduction method, Minimum Redundancy Maximum Relevancy (mRMR) [76].

Chapter 5: Experiments
To evaluate the presented joint segmentation and labeling framework, we perform a validation on 6,993 studies that were acquired from the routine cardiology care. We use the end-systolic frame of each acquired ECHO cine, to classify the the current apical view, clinical LA segmentation contour for AP4 and AP2 views, and MR disease labels. Additionally, using solely only clinical measurements, we assess diastolic dysfunction and filling pressure from the archival data.

Chapter 6: Results & Discussion
We present the results of the proposed segmentation method and the classification of mitral regurgitation. Using the segmentation method, we investigate and quantify the added advantage of the joint information model for segmentation and MR classification over the single view information model. Next, we analyze the major modulation of these sources created by jICA for the single and combined models and discuss their clinical interpretation. As an example, we perform MR identification using the jICA sources to achieve 82% identification accuracy between healthy patients and those with moderate and severe mitral regurgitation. We also perform diastolic dysfunction and filling pressure classification of varying severity levels. Finally, we visualize the ECHO ROI data by using T-Distributed Stochastic Neighbor Embedding (tSNE) [34] to learn how the reconstruction coefficients outputted from the framework represent the variability in LA anatomy.
Chapter 7: Conclusion and Future Work
We conclude the thesis with a short summary followed by the major contributions along with the suggestions of future work in this area. We also review potential improvements, like enhanced model selection for the framework, to increase segmentation and classification accuracy.
Chapter 2

Background

2.1 Anatomy of the Heart

The heart is a muscular organ that supplies blood through the circulatory system. It is located in the middle of the mediastinum, behind the breastbone. As seen in Figure 2.1, the supplied de-oxygenated blood from the superior and inferior vena cavae enters the right atrium, which is then pumped to the right ventricle. The right ventricle passes the blood to the pulmonary circuit, where the blood becomes oxygenated and feeds into the LA. Inside the LA, the blood is further pumped into the left ventricle, through the mitral valve, and out through the aorta.

The pumping of blood through the four chambers follows a cardiac rhythm. The rhythm of a heartbeat can be broken up into two components: systole and diastole. In systole, the ventricles in the heart contract and then are followed by a relaxation, which occurs in diastole. Conversely, the atria perform the opposite action to the ventricle within each phase. For example, when the LV begins to relax in diastole, the LA begins to contract. The LA is at its maximal volume during end-systolic, which is before the opening of the mitral valve. Blood is pumped most efficiently when the ventricles and atria work in concert.

The heart’s wall is made up of three layers, the endocardium, the my-
occardium and the epicardium. The innermost boundary that interfaces with the blood is the endocardium. The endocardium is joined with the myocardium, the middle layer, which is the connective muscle within the heart. Finally, the outer layer of the heart is the epicardium that supplies blood vessels and nerves.

2.2 Ultrasound Images

The basic ultrasound image is formulated by first using an ultrasound transducer to first transmit and then receive Radio Frequency (RF) signals. These signals are converted to digital RF signal, which is then filtered to produce an envelope-detected signal. The envelope-detected signal then undergoes post-processing to produce the final B-mode image. Additionally, ECHO clinics also interpret colour flow Doppler for measurements.
2.2.1 B-Mode

The B-mode ECHO is the most common method of imaging for both 2DE and 3DE, which produces a visual interface for the interrogated anatomy. The position of the ECHO is determined from the transducer’s angle and the transmit time of the ultrasound signal. This image acquisition method is real time, allowing up to 50-70 images per second in 2DE.

2.2.2 Colour Doppler

Colour Doppler allows medical specialists observe the blood flow between chambers of the heart. This is done by colour-encoding Doppler information and overlaying the colours of the 2D ECHO image. Each colour represents the speed of the blood flow within the ROI. Blood flow towards the transducer is red and flow away from the transducer is blue. These colours also vary with shades of red and blue depending on the velocity and direction. Colour Doppler can be used to view blood flow in many areas of the heart simultaneously; however, colour Doppler only allows semi-quantitative assessment of regurgitant blood velocity. The severity of the regurgitant jet is limited by technical and physiological variables that affect the appearance of the jet. Eccentric jets will travel along the wall of the atrium and will provide erroneous flow measurements, leading to misclassified regurgitant severity.

2.3 Echocardiography

In a modern ECHO laboratory, a study’s workflow is broken up into two stages: a) examination stage performed by the sonographer, and b) the reporting stage performed by the cardiologist (Figure 2.3). Diagnosis relies on accurate measurement of cardiac parameters from a sonographer’s interpretation of ECHO views. However, due to the low-resolution nature of ECHO and subjective judgment of sonographers, many of these segmentations lack in precision [12] and suffer from large observer variability [38]. The current unidirectional process (sonographer → cardiologist) makes it difficult
for improving accuracy of measurements in busy clinical laboratories. Below, we describe the workflow in the context of VGH ECHO Laboratory, as an example of a modern ECHO centre.

2.3.1 Sonographer Workflow

Acquisition

The sonographer’s workflow in a modern ECHO laboratory is time and labour intensive. Before the acquisition begins, a sonographer must spend time positioning a patient to obtain the best views, which can be a cumbersome process with the elderly. Patients are usually positioned lying perpendicular to the bed on their left side to allow for optimal imaging and ergonomics (Figure 2.2). Next, in the acquisition phase the sonographer
will follow a standard protocol to ensure consistent transducer orientations between imaging technicians. The views are obtained a sonographer placing a transducer on the patient’s chest wall (Figure 2.2). The AP4 view is achieved by placing the transducer at the apex (Figure 2.5), which allows simultaneous viewing of all four chambers. The AP2 (Figure 2.6) view is imaged counter-clockwise and perpendicularly to the AP4 imaging plane. Only the LV and LA can be witnessed in this plane. In the acquisition stage, the sonographer acquires electrocardiogram gated cine clips from a pre-defined list of views found in Table 2.1. For each view, the sonographer reviews each cine clip and chooses a section, containing single or multiple cardiac cycles, which best interrogates the desired anatomy. Additionally, if a sonographer identifies an emerging pathology during the acquisition, such as mitral regurgitation or a thrombus, the patient must be kept while a cardiologist is consulted. Sonographers are considered the first line of
Figure 2.4: Example LA segmentations of the AP4 (left) and AP2 (right). The area is estimated in each image using the method of disks, where each view’s area is the summation the many disks. This image is available under a Creative Commons Attribution Licence 2.0 at https://commons.wikimedia.org.

Table 2.1: Acquisition view protocol for sonographers to obtain cine.

<table>
<thead>
<tr>
<th>View</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasternal Long Axis</td>
<td>M-mode Sweep, 2D measurements, right ventricular inflow view</td>
</tr>
<tr>
<td>Parasternal Short Axis</td>
<td>2D images, 2D measurements</td>
</tr>
<tr>
<td>Apical 4 Chamber</td>
<td>2D images, tissue Doppler, 2D measurements</td>
</tr>
<tr>
<td>Apical 5 Chamber</td>
<td>2D images, tissue Doppler</td>
</tr>
<tr>
<td>Apical 2 Chamber</td>
<td>2D images, tissue Doppler</td>
</tr>
<tr>
<td>Apical 3 Chamber</td>
<td>2D images</td>
</tr>
<tr>
<td>Subcostal</td>
<td>2D images</td>
</tr>
<tr>
<td>Aortic Arch</td>
<td>2D images</td>
</tr>
<tr>
<td>Right Parasternal</td>
<td>2D images</td>
</tr>
</tbody>
</table>

diagnosis and cardiologists rely upon the sonographers skill to observe and diagnose any unforeseen pathology and avoid chamber-foreshortening. If sub-optimal images are selected, subsequent measurements and diagnoses may be affected.
2.3.2 Computer Workflow

Sonographers are responsible for making many of the measurements on the views obtained, seen in Table 2.2. Routinely, sonographers delineate the chambers in ECHO images, i.e. LV and LA (Figure 2.4) to measure cardiac parameters manually. Maximal LA volume is measured by tracing the blood-tissue boundary at end-ventricular systole. These measurements are performed on the ECHO images, which are uploaded automatically from US workstations to the ECHO storage system, Xcelera™ (Philips Healthcare, Netherlands). Once the sonographer finishes collecting measurements, they are entered into a preliminary report on VGH’s Filemaker™ database. Afterwards, a cardiologist enter the final report using into their custom records database, Filemaker™ (Subsidiary of Apple, California), after reviewing the measurements and cine clips from Xcelera™.
Figure 2.6: (Left) An Apical 2 Chamber transthoracic echocardiogram displaying the left ventricle (LV) and left atrium (LA). (Right) An anatomical diagram of the Apical 2 Chamber view. This image is available under a Creative Commons Attribution Licence 2.0 at https://commons.wikimedia.org.

Table 2.2: Common structures assessed during sonographer acquisition.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral Valve</td>
<td>Qualitative assessment of structure, function and regurgitation</td>
</tr>
<tr>
<td>Aortic Valve</td>
<td>Qualitative assessment of structure, function and leaflets</td>
</tr>
<tr>
<td>Tricuspid Valve</td>
<td>Qualitative assessment of structure, function and regurgitation</td>
</tr>
<tr>
<td>Pulmonary Valve</td>
<td>Qualitative assessment of structure and regurgitation</td>
</tr>
<tr>
<td>Aorta</td>
<td>Diameter and pericardial effusion</td>
</tr>
<tr>
<td>Left Atrium</td>
<td>Function, diameter, volume, area</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td>Function, filling pressure, wall movement and ejection fraction</td>
</tr>
<tr>
<td>Right Ventricle</td>
<td>Structure, function and width</td>
</tr>
</tbody>
</table>
2.3.3 Cardiologist Workflow

In the reporting stage (Figure 2.3), a cardiologist reviews the sonographer’s cine clips, comments, and confirms the correct landmarks were used for the measurements. These measurements, along with the final diagnosis, are used to create the final report. The quality of the subsequent report are directly based on the availability of appropriate images and the accuracy of measurements. If the physician is unsure that the ECHO views accurately reflect a patient’s pathology, a patient must be called back for a follow-up visit. Generally, cardiologists will not interact with the patient.

2.4 Echocardiography Diagnosis

2.4.1 Left Atrium Dynamics

The left atrium is located on the left posterior side of the heart, and it is one of four heart chambers. The LA is also the furthest chamber from the TTE probe, making it difficult to image. The LA acts as a reservoir for blood returning from the pulmonary circuit, which is then pumped to the left ventricle of the heart during ventricular systole (contraction). The LA can be visualized via transthoracic or, the more invasive, transesophageal echocardiography. Two-Dimensional (2D) imaging of the atria can provide important information that aids a clinician’s diagnosis or can be used for guidance during surgery. Imaging of the LA has traditionally been used to monitor for thromboembolic events, but has more recently been used more for investigational procedures to determine LA enlargement, since it has been discovered to be a reliable marker for predicting heart failure, stroke and mortality \[35, 68, 80, 82, 107\].

During routine patient visits, assessment of the LA is included in standard transthoracic 2DE imaging studies. From our findings, the LA is always segmented in a typical patient to assess atrial enlargement, whereas LV segmentation occurs only when requested by a clinician. A clinical study, aimed to determine how common LA enlargement was, found that in a ran-
A randomly sampled population of 2,000 patients, 16% of both sexes exhibited LA enlargement [77]. It is common knowledge that as patients age, their LA chamber naturally increases in volume. Regardless, special attention is paid to the LA anatomy as changes in its morphology can be associated with a number of disease states like diastolic dysfunction, mitral stenosis, MR, and atrial fibrillation.

Common measurements to discern the size on the LA chamber in 2DE are a) comparing the diameter of the LA to the diameter of the aorta, where LA enlargement is compared to aortic dilation; b) 2D single plane volume estimation; and c) 2D biplane volume estimation. The most performed method in clinical practice to determine left atrial size is 2D biplane volume estimation, as this method requires the least geometric assumptions and incorporates the irregular shape of the LA [54]. Calculating LA volume via 2DE imaging requires two orthogonal apical views, the AP4 and AP2 (Figure 2.4). Volume estimates can be calculated using the area-length algorithm as well as the method of disks; both methods have been validated using angiography and cardiac CT [49, 84]. The direct atrium volume estimation ($V_{LA}$) is calculated by analyzing the segmentation labels from each orthogonal view to determine the apical chamber areas ($A_{4C}, A_{2C}$) and the atrium’s length ($L_{4C}, L_{2C}$). The area can be calculated by summing the pixels within the segmented regions or by using planimetry. The planimetry technique first divides each apical area into at least 20 disks with a variable width ($a_i$) and fixed height ($b_i$), and then sums their individuals areas together (Figure 2.4). Once the area has been calculated, the volume can be estimated using the method of disks (Equation 2.1), single plane area-length (Equation 2.2) or the preferred area-length 2D method (Equation 2.3) [53]:

$$V_{LA} = \frac{\pi}{4} \sum_{i=1}^{20} a_i \times b_i \times \frac{\max(L_{4C}, L_{2C})}{20}$$  \hspace{1cm} (2.1)

$$V_{LA} = \frac{8}{3\pi} \times \frac{A^2}{L}$$  \hspace{1cm} (2.2)
Table 2.3: Recommended chamber quantification for LA volumes.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Male (mL)</th>
<th>Female (mL)</th>
<th>Indexed (mL/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18 - 58</td>
<td>22 - 52</td>
<td>22 ± 6</td>
</tr>
<tr>
<td>Mild</td>
<td>59 - 68</td>
<td>53 - 62</td>
<td>28 - 33</td>
</tr>
<tr>
<td>Moderate</td>
<td>69 - 78</td>
<td>63 - 72</td>
<td>34 - 40</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 79</td>
<td>≥ 73</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

Clinically, the LA long-axis dimension is defined as the distance perpendicular from the center of the mitral valve annulus to the apex of the atrium. However, in practice, the major axis is approximately perpendicular to account for unusual morphology, like LA enlargement. Additionally, determining the boundary of the LA to calculate the area for the above formulas can be increasingly difficult in sub-optimal images, as the boundaries of the endocardium’s soft tissue are not well defined.

These volumes are then indexed with the patient’s Body Surface Area (BSA) using the clinically standard Du Bois formula \( BSA = 0.007184 \times \text{Weight}^{0.425} \times \text{Height}^{0.725} \). This formula is used to normalize the LA size between men and women and removes the gender difference in LA size [51]. This allows the indexed LA volume to be compared against a normal population’s volume measurements (found in Table 2.3), which allows a patient’s atrial function and pathology to be stratified. These patients can then be placed into categories that are associated with their risk and treatment options [53]. There have been many indexing methods proposed; however, BSA indexing is the only method recommended by the American Society of Echocardiography [53]. Stratification guidelines have been recommended by the American Society of Echocardiography that outlines 28 mL/m² as the maximum normal LA indexed volume and severe dilation occurs at a volume of ≥ 40 mL/m² [52].
2.4.2 Mitral Regurgitation

The structural phenomenon, MR, is caused when the heart’s mitral valve does not close properly during a high-energy transfer of blood. The high-energy blood flow gradient is between the LA to the LV. Symptoms of the disease are caused by the incomplete seal of the mitral valve, a valve that is intended to prevent blood from flowing backward into the LA chamber, effectively decreasing the efficiency of the heart. Mitral regurgitation is recognized as one of the most common valvular heart diseases, which can require surgical intervention through surgical or percutaneous methods [96]. The early evaluation and detection of MR can be assessed semi-quantitatively by colour Doppler ECHO [71] and can be performed using either transthoracic or transosophogeal methods. Color flow imaging can reveal a jet of blood that enters the LA during ventricular systole. It is common practice to judge the regurgitant jet based on its size relative to the LA anatomy. A jet that occupies ≤ 20% is said to be mild and a jet that covers more than 40% is said to be severe MR. Visual diagnosis of MR, without colour flow Doppler, is more difficult because abnormalities associated with MR are not easily identifiable using ECHO (unless there is clear damage to the mitral valve). Instead, colour flow Doppler is more sensitive to detect MR severity, as opposed to focusing on the structure of the chamber and valves. Colour flow Doppler ECHO is used to examine the velocity of the regurgitant blood flow during the diastole phase. The measurements obtained from Doppler are used to calculate the transmitral waveform and the peak velocity across the mitral valve. Without these measurements, distinction between intermediate grades of MR severity is difficult, specifically between mild MR and moderate MR. Severe MR is most easily identified in patient’s due to severe LA enlargement. Additionally, CMR can be essential in evaluating eccentric MR, where the regurgitant jet’s measurements cannot be calculated from standard ECHO.

VGH sonographers stratify patients using the decision tree similar to Figure 2.7 based on the following visual estimates. Initially, patients are
screened based on the relative length, area and colour of the regurgitant jet from the colour flow Doppler ECHO. However, the size of the jet can be misleading to a sonographer, as it takes an experienced sonographer to properly calibrate the equipment to correctly show the size and color of a regurgitant jet [92]. If the jet is of moderate severity or more, further measurements, such as measuring the Proximal Isovelocity Surface Area (PISA) to calculate the Effective Regurgitation Orifice Area (EROA), are then performed and compared against the guidelines for severe MR. Essentially, the PISA signal creates a layered hemisphere that expands out of the mitral valve into the ventricle (Figure 2.8). Each layer is colour coded corresponding to the velocity of the jet, and as the hemispheric shells get smaller in area, the velocity within each shell increases. The PISA signal is used to measure the estimated radius of the ring closest to the mitral valve (r), the ring’s velocity (\(V_{PISA}\)) and the peak velocity of the jet (\(V_{Pk}\)) to calculate the EROA [92]:

\[
EROA = \frac{(2\pi r^2 \times V_{PISA})}{V_{Pk}}
\]  

(2.4)

The calculated EROA is the most predominate method used to quantify MR severity due to extensive testing [92], but it does have numerous limitations. These limitations are, PISA measurement makes geometrical assumptions, calculating the PISA measurement requires an experienced sonogra-
Figure 2.8: A visual representation of the PISA technique, where flow is a series of concentric hemispheres that decrease in size and increase in velocity.

...
able of modeling the shape and motion of the mitral annulus from Three-Dimensional (3D) Transesophageal Echocardiography (TEE) and CT images. Existing methods to analyze the mitral annulus’s shape and motion include semi-automated [85, 93] or fully automated [45, 62] valve modeling methods. However, these methods either employ 3D TEE or CT images that are of a higher quality when compared to 3D TTE. Two mitral annulus modeling methods for TTE have been proposed to provide quantitative measurements related to MR. Grady et al. presented the first system to measure PISA on a 3D TTE ultrasound by segmenting Color Doppler volumes to successfully classify patients into mild-moderate and moderate-severe regurgitation categories [41]. More recently, Wang et al. proposed a new framework to automatically quantify MR jet volume and EROA against expert measurements [96]. Using 3D features of both B-Mode and Colour Doppler, they created a classifier to detect MR jet position with good results. Recent advances in 3DE have made it possible to acquire volumetric and hemodynamical data simultaneously, which could aid in improving the accuracy of MR measurements.

2.4.3 Diastolic Function

Heart failure, a common and potentially fatal disease [63], can be caused by two major mechanisms: systolic dysfunction and diastolic dysfunction. Diastolic heart failure occurs when a patient experiences signs of heart failure, but exhibits normal Ejection Fraction (EF), normal maximal LA volumes and symptoms of diastolic dysfunction. Nearly one-half of congestive heart failures are categorized as diastolic heart failures [78], or associated with it [104]. The minimum diagnostic criteria for diastolic heart failure is outlined by the Heart Failure Society of America and it recommends that: a) there is clinical evidence of heart failure; b) by definition, normal EF levels; c) LA enlargement; and d) evidence of diastolic dysfunction [59]. Generally, Doppler ECHO is used to determine the severity of diastolic dysfunction and aids in the diagnosis of diastolic heart failure, but diastolic dysfunction does not indicate heart failure [106]. In particular, Doppler ECHO is used to
investigate the relaxation properties of the myocardium and stiffness of the LV since diastolic dysfunction is characterized by an abnormal relaxation, stiffness of the cardiac walls [105].

ECHO indicators sought for diagnosis of diastolic dysfunction include LA volume, transmitral Doppler inflow velocity patterns, pulmonary venous Doppler flow patterns, tissue Doppler velocities and M-mode flow propagation velocity. These measurements are then used in a decision tree to grade diastolic function from mild to severe [70]. There is also a trend that generally shows the severity of diastolic dysfunction also increases with a patient’s age, which can increase their risk for a heart failure event [46]. However, it has been indicated that these guidelines proposed are too strict to fully define certain patient groups with abnormal diastolic dysfunction, and according to the guidelines, be labelled as having indeterminate diastolic function [26]. This label presents a problem to clinicians who wish to reach a consensus on diagnosing diastolic heart failure.

**Filling Pressure**

In the ventricular diastole phase, the blood pressure in left and right ventricles will drop. As the pressure in the LV decreases, it will reach a trigger point where the LV pressure is less than the pressure in the LA. Consequently, the mitral valve will open, like a trap door, filing the LV with blood that was previously pumped into the LA. Likewise, the process also occurs in the right side of the heart, allowing blood to circulate in the heart. In both sides of the heart, the transfer of blood to the ventricles occurs in two steps. First, after the mitral valve opens, blood will rush in at a filling velocity, \(E\). Next, as some blood will remain in the atrium, the atrium will contract to push the remaining blood volume into the ventricle. This filling speed is labelled as the \(A\) filling velocity. Together, the \(E/A\) ratio is a metric to compare the rate of early to late ventricular filling velocity. In a healthy heart, the \(E\) filling velocity should be greater than the \(A\) velocity. With disease and aging, the \(E\) velocity will slow, lowering the \(E/A\) ratio. Additionally, the velocity of the blood through the mitral annulus is called
the annular velocity ($E'$). The ratio of $E/E'$ is also another metric used for diagnosis.

When grading a patient’s diastolic dysfunction severity, clinicians will use the LV filling pressure as an indicator. The patient’s LV filling pressure is determined using an algorithm, similar to Figure 2.9. Note, that there exists opportunities for LV filling pressure to be subjective when the filling velocities do not match the decision tree’s cutoff values.

![Figure 2.9: Algorithm for estimating LV filling pressure.](image)

### 2.5 Related Segmentation Works

Segmentation of ultrasound images is one of the most common image processing tasks in the biomedical field, but still remains an open problem due to the variability of ultrasound image quality. Traditionally, ultrasound images have been segmented using B-mode information and ultrasound RF signals, with the former method being more conventional. We focus our background search on the principle works of automatic segmentation of the endocardium for echocardiography. In the literature, US imaging includes 2D, 2D+t, 3D and 3D+t, although we focus on the 2DE and 2DE+t literature as it
is the most comprehensive and relevant to this work. In 2DE, great attention has been given to the implementation of automatic 2D LV endocardium segmentation, as it provides essential measurements for diagnosis. However, to the best of our knowledge, there is limited literature on LA endocardium segmentation since it has not been looked at extensively when compared with the LV chamber [19]. In consideration of the limited proposed semi- or completely automatic left atrial segmentation methods, we will provide an overview of closely related LV segmentation algorithms. Most LV segmentation methods have been performed using 2DE with various views, like the Parasternal long axis (SAX), AP4 and AP2. While each individual view has its own unique image acquisition challenges, segmentation still remains a challenging task due to the variability of anatomy positioning, abnormal and diseased pathology, and low signal-to-noise ratio [72]. However, there has been no proposed segmentation approaches to overcome these obstacles by simultaneously incorporating the intensity information from both the AP4 and AP2 ECHO to segment both LA views concurrently.

Below, we outline the related works for segmentation methods for the endocardium of the LV. We review several segmentation techniques, which can be divided into three main categories: (1) boundary-driven and region-based techniques, (2) model fitting techniques, and (3) RF techniques. In the case of multiple techniques being combined, they are grouped by their most related section.

2.5.1 Boundary-Driven & Region-Based Segmentation Techniques
Active contour models (snakes), first investigated by Kass et al., is one of the most common boundary-driven segmentation techniques used. The parametric active contour method evolves a curve within an image domain and influences it to deform around a shape. The deformation of an active contour model occurs by imposing internal and external forces on the curve. Where the internal force acts as a smoothness constraint and the external force advances the contour to a shape’s edge. Generally, active contour models optimize these forces in an energy minimization approach,
but models can also add additional energy terms to their objective function. These energy terms leverage the intensity statistics of ECHO images to segment contours within the cardiac chambers. There have been many approaches to propose external energy functions to find an optimal contour, examples include using optical flow to segment the LV [65], gradient vector flow [99], and balloon models [27]. Furthermore, Mishra et al. proposed to segment the LV frame-by-frame, by using the contour from the previous frame to initialize the active contour in the next frame [66]. The active contour function employed, used an additional energy term to describe the non-linear mapping of the intensity gradient. Alternatively, Mignotte and Meunier used a shifted Rayleigh distribution to create an external energy term that modelled the LV’s gray level statistics in Parasternal long axis image [64]. The authors suggested using the Rayleigh distribution to overcome ECHO noise instead of intensity gradient features, since Wagner et al. had shown fully developed speckle follows the Rayleigh statistical distribution model. As an alternative, de Alexandria et al.’s active contour approach consisted of representing the contour’s external energy term by modelling a region’s intensity information in a 1D Hilbert transform [33]. In doing so, they proposed a radial active contour technique, pSnakes for LV segmentation. Their promising method leveraged the fact that RF beams diverge from a single point on the probe, enabling the use of polar coordinates to represent intensity and filter out image noise.

Another modification of the active contour is the geometric active contour method [23]. This is based on the level-set method [73] and curve evolution theory, which allows a curve to evolve or split based on topological changes. In this method, the evolution of a curve is independent of parametrization, and can be represented as a level-set function. The level-set function is a computationally costly function that can evolve a boundary with topological changes based on region-based intensities or edge-based features [73]. Level-sets are considered as an alternative to active contours for ECHO segmentation, and Yan and Zhuang was the first to consider using level-sets for LV segmentation by applying the traditional fast
marching algorithm [100]. Yan and Zhuang improved the algorithm by replacing the level-set speed term [100]. This term was originally based on local image gradient, but was modified to incorporate average energy of the whole curve. This was done to protect the speed term from being influenced by noise. Yan and Zhuang investigated an alternative level-set framework, which combined intensity gradient edge constraints and a region intensity distribution term to automatically delineate a closed boundary curve [100]. Their method was applied to 2D slices of 3DE data with good results. Leveraging an image’s intensity distribution was also explored by Sarti et al., who also incorporated intensity ECHO information into a level-set formulation. Conversely, Sarti et al. used the Rayleigh model of speckle, instead of the intensity gradient for the prior feature [83]. This choice in prior by Sarti et al. to incorporate the statistical distribution of gray levels was shown to aid in overcoming the known ECHO low signal/noise ratio for LV segmentation. Dydenko et al.’s level-set method also assumed a Rayleigh intensity distribution, which performed segmentation and tracking via a level-set function that was constrained by gray level image statistics and a shape prior [39].

Overall, variants of active contours and level-sets can be grouped together as deformable models. Deformable models have the advantage of not requiring a training step, being able to easily alter a model with additional energy terms in their objective function and incorporate shape priors constraints (seen below). However, deformable models are at a disadvantage when medical images are noisy, the endocardium boundary has protrusions and the required initialization is not close to the region of interest. Therefore, the increasingly more common strategy is to combine prior knowledge of the shape of the object and intensity descriptor for segmentation.

2.5.2 Model Fitting Techniques

Using statistical priors, based on a learned shape or the geometrical assumptions of the heart, help overcome analyzing ECHOs with excessive noise or missing tissue. The statistical shape modelling techniques that include:
shape priors, Active Shape Model (ASM), Active Appearance Model (AAM) or joint ASM/AAM models can be categorized by their shape prior restrictions.

Previous literature on shape prior restriction was extensively studied as it was shown to improve the accuracy and reliability of ECHO segmentations [37]. Using geometric models, a chamber’s anatomy can be represented through a set of parametric equations, requiring few tuning parameters and did not require training. However, geometric models are not well suited for complex shapes because as the complexity increases, so does the computational cost to align the model. Using a geometrical model, Hamou and El-Sakka first segmented the LV in a 2D B-mode ECHO using an external energy gradient vector flow snake [43]. The snake was trained using two, third order hyperbolas to better represent the ventricle in systole and diastole. To aid intensity or edge-based functions that failed on imperfect ECHOs, several authors further exploited the LV’s shape as a truncated ellipse to create a prior model of the expected ventricle shape. Alessandrini et al. addressed ECHO segmentation with a geometrically constrained model, but for myocardium tissue in the SAX view [2]. Alessandrini et al. using a level-set framework model that consisted of two ellipses represented by 10 parameters to perform segmentation [2]. Recently, Dietenbeck et al. also embedded a geometrical shape prior into their proposed level-set framework for AP4 segmentation [37]. They approximated the myocardium using a geometric model with two hyperquadics, allowing asymmetric shape modeling in any view. The shape prior was then combined with a thickness term that allowed for joint segmentation of endocardium and epicardial borders.

Another way to build shape restricted priors is to used a learned shape model from annotated a priori LV data, allowing a target image to be matched with its corresponding model. This was previously performed using either a mean contour curve [24, 25] or probabilistic maps [81]. Chen et al. created a mean contour curve shape prior by utilizing the LV contour of an annotated database to segment the epicardial and endocardial borders [24].
This method utilized the distance between the active contour and the prior model to create a new energy term for their level-set framework. Chen et al. extended their prior model to incorporate an intensity profile with the mean annotated LV curve [25]. This allowed the intensity profile along multiple segmentations to be compared to the prior intensity profile, which was used to select the best segmentation.

Cootes and Taylor developed an alternative technique to describe shape priors, using PCA on parametric contours of face outlines to obtain the main axis of variation [28]. This technique became a common method to obtain a shape prior from a database by capturing the main shape components of manually contoured images, while discarding redundant information. Leventon et al. applied this PCA technique to 2D LV ECHO data, but used the signed distance function of the image contours to represent the reference shape, instead of parametric geometric contours. Additionally, the same shape prior representation proposed by Leventon et al. [56] was adopted by Tsai et al. to calculate the parameters needed to minimize their energy functional for segmentation of the 2D LV data [90].

Cootes et al. also introduced the Point Distribution Model (PDM), an alternative way to create a shape constrained prior learned from a training set of manually drawn contours [29]. Cootes et al.’s proposed shape prior was a combination of a mean shape of the contour points and, using PCA, a model of the main modes of shape variation within the dataset. The PDM has become a standard in medical image segmentation, where shape priors aid in interpreting noisy images. The development of the PDM led to the ASM, which Cootes et al. used to represent the variation of manual LV contours [29]. The ASM is a statistical model of the shape of an object, which is constrained by the PDM to only vary in ways witnessed within the training database. This prior shape knowledge was represented within a probabilistic frameworks, such as a Gaussian distribution [29] or mixture model [28]. While using ASM priors in endocardial segmentation is advantageous due to its ability to handle intensity variations [29], ASM requires a point-to-point correspondence when finding parameter values that properly fit the
model to a new image. Additionally, a level-set variant of the ASM was introduced by Rousson and Paragios [81] to avoid a Gaussian distributed prior shape, which was applied to the LV data by Paragios and Deriche [74]. In an attempt to improve the ASM model, an extension to include intensity profile information was investigated to develop the AAM [30]. The AAM shares similarities to the ASM mode, but includes the intensity variations of the image too. By combining both shape and intensity data, Cootes et al. introduced a new method of matching statistical models of appearance to images, which also models appearance texture [30]. The AAM model was additionally improved upon by Bosch et al. by adding temporal information, using PCA to learn shape prior of ECHO LV segmentations for each position within a cine of images [15]. Furthermore, Bosch et al.’s AAM + motion model did not assume standard Gaussian distribution of image intensity, and instead used non-linear intensity normalization to match the intensity distribution of the images. The normalization proved to be beneficial to the LV segmentation, qualitatively increasing the quality of their endocardium segmentation. A limitation of the AAM method is new clinical images are assumed to have similar appearance and tissue property variations to those the model trained upon. This led to other extensions to include motion information [42] and an AAM plus temporal information (Active Appearance Motion Model (AAMM)) for 3D segmentation [67]. Mitchell et al.’s AAMM was capable of segmenting ECHO temporal image sequences [67]. Previously, Zhou [102] questioned if the characterization of the LV’s endocardium can be accurately represented by a linear model, such as the linear appearance model in Cootes et al.’s AAM. Non-linear methods have been proposed, citing the need from variability of training sets derived from different patients, sonographers, and ultrasound machines. Furthermore, the literature suggests that the ASM proposed by Cootes et al. [29] is effective, but lacks a good one-to-one point feature criteria [102]. Zhou proposed a non-linear LV segmentation machine called a shape regression machine to overcome the mentioned issues [102]. Their proposed shape regression approach was shown to overcome blurred boundaries in B-mode ECHO and
could handle missing LV boundaries too. Their shape regression machine used statistics of the shape, appearance, and anatomy to construct a model.

2.5.3 Radio Frequency Techniques

The above referenced proposed information approaches are based on the analysis of B-mode ECHO images; however, some authors [10, 11] proposed using RF, a potentially more informative source than the envelope of the ECHO image. Bernard et al. formulated the segmentation problem using the generalized Gaussian distribution statistics of the RF signal, which was used within a Maximum Likelihood framework to delineate the myocardium [10]. Bernard et al. extended this work by showing that RF can also reliably describe a chamber’s blood pool and tissue area via a Generalized Gaussian distribution [8, 9]. However, the assumption that image intensities represented by RF can be modelled by a Gaussian distribution has not been validated against a range of intensities found in clinical B-mode data. As such, it has been shown that the gamma distribution can better describe the envelope of the RF in several studies [16, 87]. Tao et al. compared the validity of RF representation by gamma distribution by comparing it against Weibull, normal, and log-normal distributions on cardiac images [87]. Recently, Bui et al. used local gamma distributions in the data term of a level-set energy function to perform segmentation within 2D and 3D simulated ultrasound images, outperforming previous local Gaussian methods [17].

Validation of Literature

Regarding the validation of the segmentation techniques reviewed, we have summarized the main contributions for LV endocardial segmentation techniques. We present this information in Table 2.4 along with their modality, ROI, view, size of the validation dataset and validation results. Most methods were evaluated by their Mean Absolute Distance (MAD) between the expert segmentation results and their methods’ contours. However, some
papers have provided global errors of EF or LV mass error. Point to surface distance or MAD are usually within the range of 1-3mm for 2DE/3DE.

### 2.6 Commercial Products

Currently, both semi-automatic and fully automatic 2D and 3D cardiac measurements have been commercially explored by Philips, Siemens, GE Healthcare, TomTec, DiACardio and TeraRecon. The most prominent cardiac suites are Philip’s QLab™ (Philips Healthcare, Netherlands) and Siemen’s Syngo™ (Siemen’s Healthcare, Germany), TomTec’s Image-Area™ platforms (TomTec, Germany) and GE Healthcare’s CardiacIQ Suite™ (GE Healthcare, United Kingdom), with their features listed below in Table 2.5. All suites provide automatic methods for quantifying a wide suite of parameters determined from ECHO, with the goal to increase patient throughput, while improving accuracy and workflow efficiency. Currently, VGH cardiologists use a Philip’s Qlab™ plugin to manually perform their measurements. British Columbia (BC) Children’s Hospital performs their measurements using Siemen’s Syngo™ base platform for manual delineation of their 2D data.
Table 2.4: Validation of 2D ECHO image sequence on the LV endocardium.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Reference</th>
<th>Year</th>
<th>View</th>
<th>Number of Patients</th>
<th>Validation Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D</td>
<td>Wolf et al. [98]</td>
<td>2002</td>
<td>Transphogeal</td>
<td>20</td>
<td>LV Endocardial error: 3.4 ± 2.3 mm</td>
</tr>
<tr>
<td>2D</td>
<td>Bosch et al. [15]</td>
<td>2002</td>
<td>AP4</td>
<td>129</td>
<td>LV Endocardial error: 3.54 ± 1.62 mm</td>
</tr>
<tr>
<td>2D</td>
<td>Lin et al. [58]</td>
<td>2003</td>
<td>Long-Axis</td>
<td>24</td>
<td>LV Endocardial error: 1.64 ± 0.5 mm</td>
</tr>
<tr>
<td>2D</td>
<td>Sarti et al. [83]</td>
<td>2005</td>
<td>AP4</td>
<td>15</td>
<td>LV Endocardial error: 1.6 ± 1.8 mm</td>
</tr>
<tr>
<td>2D</td>
<td>Georgescu et al. [40]</td>
<td>2005</td>
<td>AP4</td>
<td>206</td>
<td>N/A</td>
</tr>
<tr>
<td>3D</td>
<td>Angelini et al. [3]</td>
<td>2005</td>
<td>Long Axis</td>
<td>10</td>
<td>Absolute Error for EF: 4.6%</td>
</tr>
<tr>
<td>2D</td>
<td>Yue and Tagare [101]</td>
<td>2008</td>
<td>Short-Axis (Phantom)</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>2D</td>
<td>Zhou [102]</td>
<td>2010</td>
<td>AP4</td>
<td>527</td>
<td>LV Endocardial error: 2.2 pixels</td>
</tr>
<tr>
<td>3D</td>
<td>Zhu et al. [103]</td>
<td>2010</td>
<td>Long Axis View</td>
<td>11 (Canine)</td>
<td>LV Endocardial error: 1.4 ±</td>
</tr>
<tr>
<td>3D</td>
<td>Leung et al. [55]</td>
<td>2010</td>
<td>Short-Axis</td>
<td>35</td>
<td>LV Endocardial error: 1.19 ± 0.47</td>
</tr>
<tr>
<td>2D</td>
<td>Dietenbeck et al. [37]</td>
<td>2012</td>
<td>AP4 &amp; AP2</td>
<td>20</td>
<td>AP4 Dice: 0.93 AP2 Dice: 0.89</td>
</tr>
<tr>
<td>2D</td>
<td>Carneiro et al. [22]</td>
<td>2012</td>
<td>AP4</td>
<td>12</td>
<td>N/A</td>
</tr>
<tr>
<td>2D</td>
<td>Cao et al. [19]</td>
<td>2014</td>
<td>AP4</td>
<td>10</td>
<td>LV DICE: 0.71</td>
</tr>
</tbody>
</table>
### Table 2.5: Commercial cardiac suite feature comparison.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Qlab\textsuperscript{TM}</th>
<th>Syngo\textsuperscript{TM}</th>
<th>Image-Arena\textsuperscript{TM}</th>
<th>CardiacIQ\textsuperscript{TM}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto 2D LV border detection</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Auto 2D LA border detection</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auto 2D right ventricle border detection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auto 2D Motion Strain &amp; Stress</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Auto 3D LV EF</td>
<td>√</td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Auto 3D right ventricle volume</td>
<td></td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Auto 3D Motion Strain &amp; Stress</td>
<td>√</td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Vendor Independent</td>
<td></td>
<td></td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 3

Materials

The proposed framework for automatic analysis of the left atrium uses the datasets described below. Software applications interfacing with these databases are also briefly described.

3.1 Ethics

To evaluate the 6,993 studies that were acquired from routine cardiology care, we went through an ethics approval process from Clinical Medical Research Ethics Board of Vancouver Coastal Health (VCH) (H13-02370) and consultation from the VCH Information Privacy Office. Throughout the analysis, a rigorous process of data anonymization, de-identification and data encryption was followed based on the guidelines recommended by the VCH Privacy Office. All of the ECHO and patient information (age, sex, height, weight and related health issues) are assigned a non-identifying alpha-numeric code that ensures the risk of re-identification of participants from the acquired data is low. The data was encrypted and password protected using TrueCrypt™ (TrueCrypt.Org, Czech Republic), a software that has been independent audited that concluded no significant flaws were present1.

1https://opencryptoaudit.org/reports/TrueCrypt_PhaseJI_NCC_OCAP_final.pdf
3.2 Echocardiography Data

For the purposes of this thesis, a large database that reflected a wide range of patient morphology and pathology was required. By interfacing with VGH’s Cardiology clinic, more than 7,000 ECHO studies were acquired. Each study contained a patient’s ultrasounds that were requested by a physician. All obtained ultrasound ECHO images were from retrospective studies performed at VGH. To access these ultrasound studies, the cardiology department’s Xcelera™ database was interfaced, allowing information to be downloaded pertaining to patient follow-ups, emergency, and investigational ECHO studies. At VGH, ECHO information are primarily acquired from Philips iE33™ or the portable GE Vivid q™ ultrasound machines. The Digital Imaging and Communications in Medicine (DICOM) studies obtained from these devices were cached and uploaded to VGH’s cardiology department’s Xcelera™ server. Once the ECHO information was uploaded, the information was then accessible via an Xcelera™ workstation terminal.

3.2.1 Echo Lab Software

The Xcelera™ ultrasound software allows both cardiologists and sonographers to access all saved ECHO studies within a Graphical User Interface (GUI) interface. The software also acts as a server that accepts DICOM images from Philips US machines and stores it. The Xcelera™ software functions by acting as a traditional DICOM viewer for medical staff, plus it incorporates advanced features for sonographers and cardiologists. For instance, within the software suite there is an image measurement module that allows cardiac measurements to be drawn directly on medical images and saved for future examination. The measurement module is manual and has no automatic segmentation features for LV and LA segmentation. Sonographers use the measurement package to measure a LA’s area and major axis in both the AP4 and AP2 view. These measurements are then manually input into the Filemaker™ database, which then calculates the patient’s LA volume.
The Xcelera™ software operates by maintaining two separate databases. It downloads the ECHO information from the ultrasound machines and writes this information to two of its own mySQL instances, echo and xcelera. Xcelera™’s echo database stores all the manual segmentation information made on an image, and xcelera stores patient information keys, which allows studies to be reopened with the correct measurements attached. Meaning, whenever measurements are performed within the software suite, the measurements are saved to the echo database with a unique identifier. This identifier key is also stored on in the xcelera database, which has an additional identifier to link each particular ultrasound. The two databases work together using a key matching method to store large amount of data. For the purposes of this thesis, we only use the Xcelera™ database to obtain ECHOS, segmentation labels and major axis coordinates. Xcelera™ (Philips Healthcare, Netherlands)’s database relationship chart can be found in the appendix and it’s role in the context of saving a routine ECHO can be seen in Figure 3.1.

**Figure 3.1:** A diagram designed to show the relation between the Echo, Xcelera and Filemaker databases in the context of a routine cardiology study.
3.2.2 Data Acquisition and Pre-Processing

To perform the data acquisition, the following steps were taken with the help of VGH’s Information Technology (IT) team:

1. Replicated and anonymized Xcelera™ (Philips Healthcare, Netherlands)’s mySQL instance.

2. Installed the new mySQL instance on a computer located at Vancouver Coastal Health’s IT department.

3. Queried the mySQL database to return all studies that contained segmentation information.

4. Copied all available ECHO studies from VGH’s Picture Archiving and Communication System (PACS) system with segmentations that were not archived.

Once all of the data had been acquired, each ultrasound study ECHO information was then matched with its corresponding segmentation information, which was then reconfigured into MATLAB™ (Mathworks Inc. MA, USA) structures. Ultrasound images were matched with their correct segmentation using a unique study identification key. Each saved structure contained the volume ECHO information, manufacturer name, filename, date of study, Medical Record Number (MRN), DICOM header information, segmentation coordinates and the segmentation frame number for both AP4 and AP2 views. Each ECHO volume was then anonymized by applying a 2D rectangular black-out region to the US header that was burned into the image with confidential information. Furthermore, since LA segmentations were performed using the LV measurement module in Xcelera™ (Philips Healthcare, Netherlands), LA ECHO studies had to be visually separated from studies with LV segmentations to ensure the correct data was used.

For this thesis, the data acquired from VGH was filtered by the US machine type. The data acquired in this work was all from Philip’s ultrasound machines. Reasons for this include the majority of complete ECHO studies were performed with this manufacturer, imaging quality of this machine
rendered the most favourable ECHO images of the anatomy, and measurements were quantitatively considered as more reliable by VGH sonographers with this machine. The ECHO data used was also normalized to ensure equal pixel spacing between the images as pixel spacing between two unique studies was variable due to configuration settings and different operators. The mean pixel spacing was $0.364 \pm 0.06$ mm and $0.386 \pm 0.05$ mm for the AP4 and AP2 views, respectively. Each AP4 image was resized to have a pixel spacing of 0.605 mm and a pixel spacing of 0.658 mm for AP2 images (Figure 3.2).

### 3.3 Patient Measurements

All patient measurements are stored on VGH’s FileMaker\textsuperscript{TM} Pro 6 database. Sonographers are required to manually enter all their findings from an ECHO
study along with their patient’s personal information. A brief overview of the patient characteristics and general statistics within the database can be seen in Tables 3.1 and 3.2.

Table 3.1: Patient ECHO data characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Male Age</td>
<td>66 ± 16 years</td>
</tr>
<tr>
<td>Average Female Age</td>
<td>65 ± 16 years</td>
</tr>
<tr>
<td>Average Total Age</td>
<td>66 ± 16 years</td>
</tr>
<tr>
<td>Average Male BSA</td>
<td>1.96 ± 0.22</td>
</tr>
<tr>
<td>Average Female BSA</td>
<td>1.69 ± 0.20</td>
</tr>
<tr>
<td>Average Total BSA</td>
<td>1.83 ± 0.25</td>
</tr>
<tr>
<td>Average Male LA Volume</td>
<td>39.5 ± 15.03 mL</td>
</tr>
<tr>
<td>Average Female LA Volume</td>
<td>37.84 ± 14.92 mL</td>
</tr>
<tr>
<td>Average Total LA Volume</td>
<td>38.72 ± 15.00 mL</td>
</tr>
<tr>
<td>Normal EF dysfunction (65±10%)</td>
<td>71.5%</td>
</tr>
<tr>
<td>Lower Limits EF dysfunction (50-65%)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Mild EF dysfunction (50±10%)</td>
<td>4.7%</td>
</tr>
<tr>
<td>Mild-Moderate EF dysfunction (35-50%)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Moderate EF dysfunction (35±10%)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Moderate-Severe EF dysfunction (20-35%)</td>
<td>2.1%</td>
</tr>
<tr>
<td>Severe EF dysfunction (≤20%)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Male Studies</td>
<td>3566</td>
</tr>
<tr>
<td>Female Studies</td>
<td>3134</td>
</tr>
<tr>
<td>Unspecified Gender Studies</td>
<td>317</td>
</tr>
<tr>
<td>Number of Studies</td>
<td>7017</td>
</tr>
<tr>
<td>Number of Unique Patients</td>
<td>5943</td>
</tr>
<tr>
<td>Number of Followup Studies</td>
<td>1074</td>
</tr>
</tbody>
</table>

3.3.1 FileMaker Software

Filemaker™ is a relational database program that allows users with minimal technical knowledge to create a GUI with a backend database. This software fills a niche role within the cardiology department. Instead of using Xcelera™ (Philips Healthcare, Netherlands)’s cardiology suite, the custom Filemaker™ was created to allow advanced searching by not only
Table 3.2: Filemaker™ database data characteristics

<table>
<thead>
<tr>
<th>Distribution of Diastolic Dysfunction (DD)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Distribution of normal DD</td>
<td>16%</td>
</tr>
<tr>
<td>Total Distribution of mild DD</td>
<td>14%</td>
</tr>
<tr>
<td>Total Distribution of moderate DD</td>
<td>4%</td>
</tr>
<tr>
<td>Total Distribution of severe DD</td>
<td>1%</td>
</tr>
<tr>
<td>Total Distribution of indeterminate DD</td>
<td>14%</td>
</tr>
<tr>
<td>Total Number of Sonographers</td>
<td>120</td>
</tr>
<tr>
<td>Total Number of Cardiologists</td>
<td>6</td>
</tr>
</tbody>
</table>

MRN, but by patient physiology as well. This allows Filemaker™ to be a valuable teaching tool, as physicians can retrieve studies based on certain keywords.

The software operates by allocating four main tabs for each ECHO study. The tabs Front Page, Valves/PA, Aorta/Atria/Shunts Pericardium are the only pages filled out by the sonographer. There are check boxes and empty values for their report. The last tab, LV/RV/Conclusions is filled out by the cardiologist after reviewing the first three tabs and the ECHO images.

3.3.2 Data Acquisition & Data Pre-processing

Data acquisition from Filemaker™ was performed by first exporting the database into a Comma-Separated Values (CSV) file, where each row represented one study and each column represented a unique field. This method of export was the only method available at the time of retrieving data for this thesis. This CSV file was then imported into MATLAB™ (Mathworks Inc. MA, USA) using its bulk importer tool, which was required to import over 207020 rows and over 450 columns. The imported file was saved as a matrix sorted by study date. Once the import process was complete, a for-loop was used to match a patient’s MRN and date of study in both the ECHO study previously gathered and the measurements obtained from the Filemaker™ database. Specific measurements that were matched to each MATLAB™ (Mathworks Inc. MA, USA) structure includes LA volume, MR severity,
Figure 3.3: (Left) Distribution of left atrial volume for each gender in the dataset. (Right) Distribution of index atrial volume within the dataset.

DD level, filling pressure and BSA. The distribution of LA volume from the gathered studies has been plotted in Figure 3.3 and an example image with its corresponding segmentation can be see in Figure 3.4.
Figure 3.4: An example AP4 ECHO from the database with it’s corresponding sonographer’s LA segmentation information. The LA’s centroid has also been identified using the center of weight from the ground truth.
Chapter 4

Methods

The proposed joint information framework for ECHO analysis consists of four phases of view processing, segmentation, and LA volume estimation and disease detection. The objective of view preprocessing is to automatically differentiate between AP4 and AP2 views and pinpoint the LA anatomy. In the segmentation phase, we estimate the LA boundary in both AP4 and AP2 views. In the volume estimation and disease classification phase, we use the segmentation result to estimate the LA volume and also, detect and classify MR severity. In the following, we provide details for each phase.

![Diagram](image)

**Figure 4.1:** Overview of the components of the framework. First, a preprocessing step is performed on the acquired echo data to identify and crop the left atrium region for the following segmentation phase. Next, simultaneous echo segmentation, volume estimation evaluation and MR disease labels are estimated from localized apical views.
4.1 View Preprocessing

The proposed view preprocessing phase, as seen in Fig. 4.2, automatically separates AP4 and AP2 views for the subsequent segmentation phase and determines the ROI defining the anatomical location of the LA. In a training step, we use PCA on a data set of AP4 and AP2 views given its computational efficiency and low memory requirements. This allows us to reconstruct each view from the linear combination of orthogonal basis functions. The score vectors of such reconstructions along with the LA segmentation contours are then used in the testing step to perform apical view classification and ROI selection on a new ECHO image. In the subsequent phase for a new query image, the following two steps are followed:

Apical view classification

The image is first labeled as either exclusively AP4 or AP2. This is achieved by projecting the query image, using PCA, in the space that is spanned by AP4 and AP2 orthogonal basis functions, and then computing the score vectors in each space. Subsequently, the L2 norm between the score vectors and those stored for all training data, is computed. The image resulting in
the smallest norm determines the associated view and closest match to the query image.

### 4.1.1 ROI Localization

To determine a region of interest containing LA in either the AP4 or AP2 view, we use the binary clinical LA segmentation associated with the closest match image to estimate the centroid of LA. Subsequently, a fixed-size bounding box, which was determined heuristically from the training data and is associated with the largest appearance of LA in the data, is centered on the estimated LA coordinates. We further refine the estimation of LA location through an intensity-based registration, where the fixed image is the ROI in the query image, and the moving image is the average mean intensity of all LA appearances with the same bounding box dimensions in the training data. We use an affine transform and mutual information as the similarity metric to perform the registration.
Figure 4.4: A schematic diagram of the LA segmentation, volume estimation and disease detection phases. During training, patients are grouped into clusters based on their LA appearance similarity. Subsequently, a jICA model is generated for each subgroup, and two SVM classifiers are trained. One SVM classifier is used to select the closest model to the query image and another performs disease classification. During testing, the jICA mixing coefficients from the reconstruction of image intensity maps in apical views are used to determine LA segmentation contours, compute LA volume, and assign the disease label for an unseen image.

4.2 LA Segmentation

The LA ROIs are used within a machine learning framework to segment the LA. In the training step, we cluster the LA contours as labelled by experts in the clinical data to sets of similar shapes, where a jICA model is constructed for each cluster (sec. 4.2.2). Subsequently, a segmentation SVM classifier is trained on the mixing coefficients (see Section 4.2.2) associated with each cluster. In the testing step, we project a query image on to these models to perform segmentation and choose the optimal model using SVM. A schematic of the LA segmentation phase is provided in Fig. 4.4.
4.2.1 Training: Patient Grouping

The clustering is performed to create detailed models of the main anatomical variations. Initially, we use PCA on the binary LA contours in both AP4 and AP2 views to compute score vectors of the training data: 1) We rigidly align the contours by their centroid and assume the contours’ corresponding orientation is consistent across the dataset based on clinical guidelines; 2) We quantize the contour points in polar coordinates. Using the center of gravity of each contour, we sub-sample the contour at 1° sampling interval to convert the contour to a set of points; 3) We perform PCA on the point-set across the training data and determine the principal modes of variation [31]. Subsequently, we divide the distribution of scores for the first principal component to \( N \) subgroups, determined experimentally.

4.2.2 Training: Joint Model Generation

For each subgroup, we use jICA to train a model that captures the joint space of LA regions of interest and their corresponding segmentation. We assume that there is a relation between the intensity variation in ROIs of LA in ECHO, and their binary clinical segmentation. This is not an unreasonable assumption since sonographers use the contrast of the boundary intensity against the blood pool to draw the LA contours. The input observations to jICA are the combined intensity information of both apical views (AP4 and AP2), along with their binary clinical segmentation. jICA can be used to identify any joint set of independent sources that describe the inter-relation between intensity and binary contours. Considering the generative model

\[
X = AB
\]

where \( X = [I_{AP4}, I_{AP2}, S_{AP4}, S_{AP2}] \) is the observation matrix of intensity information, \( I_{AP4} \) and \( I_{AP2} \), in an ROI containing LA in each apical view (converted to a vector form), and the corresponding segmentation, \( S_{AP4} \) and \( S_{AP2} \). \( A \) is a matrix of mixing coefficients (also referred as ICA loading parameters, or the modulation profile). \( B \) is the matrix of joint sources and
Figure 4.5: Schematic of the jICA method. The observation matrix $X$ is made by concatenating AP4 and AP2 intensity and segmentation pixels in ROIs that contain the LA in each apical view. jICA maximizes the independence among the constructed joint sources $B$, assuming that they share the same mixing coefficient matrix $A$.

has the form of $B = [B_1, B_2, B_3, B_4]$, where $B_1$ and $B_2$ are the independent sources for intensity information, and $B_3$ and $B_4$ are the independent sources for segmentation information in AP4 and AP2 apical views, respectively. The aim of jICA is to find the matrix $W = A^{-1}$ so that the estimation $U = WX$ is close to $B$ [18]. We use a MATLAB implementation of jICA available online\(^1\). A schematic of the jICA approach is shown in Fig. 4.5.

The joint sources of $B$ are generated by the logistic InfoMax ICA algorithm [7], which is based on a neural network that uses mutual information minimization to output the number of sources specified.

We generate a jICA model for each patient sub-group we have determined in our data using PCA analysis. After training, we do not store the original intensity or segmentation data. The training data knowledge is stored within the compact jICA sources, allowing us to perform segmentation quickly and with reduced memory.

\(^1\)mialab.mrn.org/software
4.2.3 Training: Segmentation SVM Classification

The concatenated jICA mixing coefficient matrices $A_i, i = 1, \ldots, N$ and their associated patient subgroups are used to train a segmentation SVM classifier. This classifier maps the concatenated mixing coefficients to subgroup labels $1, \ldots, N$. Out of the $N$ segmentation contours derived from jICA models, we aim to choose the most accurate segmentation, which by definition is the segmentation that best matches (based on the highest Quantitative Dice Index (DICE) value) between the estimated and gold standard segmentations. Furthermore, the DICE similarity metric is defined below [36]. Where $\alpha$ and $\beta$ are the estimated and gold standard segmentations:

$$DICE = \frac{2|\alpha \cap \beta|}{|\alpha| + |\beta|}$$

(4.2)

4.2.4 Testing: LA Segmentation Based on Each jICA Model

The process to generate a segmentation from a query image is a fast matrix operation to solve the system of equations $U = WX$, to determine $W$ so that $U$ is the closest approximation of $B$. Since the query image only contains the intensity information, the system of equations will only optimize for $W$ by considering the intensity sub-matrices of $U$ and $X$. Since the mixing coefficients in $A = W^{-1}$ are the same for the intensity and binary segmentation sources, we can use the computed coefficients from the intensity maps to efficiently compute an estimated segmentation probability map of the LA contour in each view. Subsequently, we use a post-processing step to convert the estimated map to a final segmentation using a threshold calculated during the training phase. The threshold is determined experimentally on the training folds to maximize the overlap between the estimated LA segmentation and their gold-standard clinical segmentation.
4.2.5 Testing: Final LA Segmentation

To determine which of the $N$ segmentation to choose from, we use the segmentation SVM classification. Based on the estimated concatenated mixing coefficient matrix $A$ from the query image, the classifier outputs the label of the patient subgroup that best represents the LA boundary.

4.3 Volume Estimation

The atrium volume estimation is calculated by analyzing the final segmentation for both apical views. We calculate the estimated volume by using the preferred standard Area-Length 2D method:

$$V_{LA} = \frac{8}{3\pi} \times \frac{(A_{4C} \times A_{2C})}{\min(L_{4C}, L_{2C})}. \quad (4.3)$$

This technique uses the apical chamber areas ($A_{4C}, A_{2C}$) and the atrium long-axis length ($L$) [53]. Clinically, the LA long-axis dimension is defined as the distance perpendicular from the center of the mitral valve annulus to the apex of the atrium. However, in practice, we have observed that the major axis varies slightly from perpendicular to account for unusual anatomy.

To account for this variation, we fit an ellipsoid to the LA segmentation in each apical view, and calculate the length of its major axis. We use this length to estimate $L$ for both views.

4.4 Disease SVM Classifier

The framework is also used to train a heart disease classifier to learn the association between image intensity and its segmentation, with a disease label. We use mitral regurgitation as a proof of concept to distinguish two types of mitral regurgitation disease labels: healthy (without MR) and moderate/severe MR. We sought to demonstrate this by classifying two types of patients, those without MR (healthy) and those with moderate or severe MR. We design our classification pipeline to analyze the mixing coefficients from the reconstruction with each jICA model, which produces a concate-
nated matrix of jICA mixing weights. The concatenated matrix of jICA mixing weights and disease labels are used to train the disease SVM classifier. During testing when a diseased or healthy patient is introduced to the framework, we input the estimated concatenated matrix of jICA mixing weights into the trained SVM and estimate their MR disease label. A schematic diagram of this process is shown in Fig. 4.4.

4.5 Diastolic Function

In the previously mentioned methods, from raw ECHO images, we calculate volume information and separate healthy from moderately disease MR levels without any additional information. However, we add an additional process to our framework to supplement clinical knowledge. We incorporate standard measurements performed by a sonographer that are routinely performed during a clinical examination protocol to diagnose diastolic dysfunction. In a standard ECHO examination there are over 100 common measurements to extract correlation from. We reduce this feature set to only encompass the relevant features necessary for diastolic dysfunction. We used the mRMR feature selection algorithm [76], commonly used to determine pairing of genes and phenotypes, to remove redundant features. We use mRMR to maximize the joint distribution between the feature set (S) and the disease label (c); reducing m features, $x_i$, to a compact set of 15 features, seen in (Table 4.1). Where the mRMR criterion (4.6) is a combination of maximum relevance (4.4) and minimum redundancy (4.5) of the feature set $S$ and the target class $c$.

$$\max D(S,c), D = \frac{1}{|S|} \sum_{x_i \in S} I(x_i; c) \quad (4.4)$$

$$\min R(S), R = \frac{1}{|S|^2} \sum_{x_i, x_j \in S} I(x_i; x_j) \quad (4.5)$$

$$\max \phi(D,R), \phi = D - R \quad (4.6)$$
Where the mRMR criterion (4.6) is a combination of maximum relevance (4.4) and minimum redundancy (4.5) of the feature set $S$ and the target class $c$. (4.4) approximates $\max D(S,c)$ using the mean of all mutual information between clinical measurements and the target disease label. Due to the nature of the maximum relevance term (4.4), discovered features could be highly dependent amongst each other. This is fixed by the minimum redundancy term (4.5), which removes highly dependent features while minimally affecting the discriminative power of the features. The mRMR criterion is relevant to apply in echocardiography due to high correlation between features and reducing the number of redundant features that clinicians need to measure. This reduced feature set was then used to train a multi-label SVM classifier from over 10,000 patient records to perform classification of diastolic function and LV filling pressure.
Table 4.1: A subset of common ECHO measurements features

<table>
<thead>
<tr>
<th>Continuous Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter of ascending aorta</td>
</tr>
<tr>
<td>The fraction of outbound blood pumped from the heart (EF)</td>
</tr>
<tr>
<td>Posterior wall Thickness at end-diastole (PWd)</td>
</tr>
<tr>
<td>Passive mitral inflow velocity LV filling (E)</td>
</tr>
<tr>
<td>Active filing with atrial systole (A)</td>
</tr>
<tr>
<td>Mitral annular velocities of passive LV filling (E’)</td>
</tr>
<tr>
<td>The fraction of mitral inflow / mitral annular velocity (E/E’ Ratio)</td>
</tr>
<tr>
<td>Length of the sinuses within the valsalva</td>
</tr>
<tr>
<td>Diameter of the inferior vena cava (IVC)</td>
</tr>
<tr>
<td>Fraction of the PWd and LV end diastolic diameter (RWT)</td>
</tr>
<tr>
<td>Right Ventricle diameter in diastole (RVd)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discrete Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral regurgitation severity</td>
</tr>
<tr>
<td>Tricuspid regurgitation severity</td>
</tr>
<tr>
<td>Level of output of left ventricle</td>
</tr>
<tr>
<td>Aortic regurgitation severity</td>
</tr>
<tr>
<td>Left ventricle mass index</td>
</tr>
<tr>
<td>Right ventricle function</td>
</tr>
</tbody>
</table>
Chapter 5

Experiments

To evaluate the presented joint segmentation and labeling framework, we perform a 4-fold cross validation on 6,993 studies that were acquired from the routine cardiology care (see Table 3.1) with ethics approval from Clinical Medical Research Ethics Board of Vancouver Coastal Health. Throughout the analysis, a rigorous process of data anonymization, de-identification and data encryption was followed based on the guidelines recommended by the Vancouver Coastal Health Privacy Office. No special treatment was taken for handling pathological cases. We used the end-systolic frame of each acquired ECHO cine, its clinical LA segmentation contour for AP4 and AP2 views, and MR disease labels in the archival data as the gold standard. To normalize the data, images were scaled to the largest pixel resolution in the dataset. The choice of parameters for our framework is detailed in Sec. 5.1. The evaluation was performed with respect to the apical view classification (Sec. 5.2), the LA volume estimation accuracy (Sec. 5.4), the MR classification accuracy (Sec. 5.5), diastolic dysfunction and LV filling pressure classification (Sec. 5.6), and the computational complexity (Sec. 5.7).
5.1 Framework Parameters

For each phase of the framework, we have set global parameters for the mentioned methods above. In the offline phase, we stratify patients into one of seven groups (determined experimentally), based on the histogram bin their mixing coefficients belong in. The joint model was optimized using 7 patient subgroups. These seven sets of patient studies are used to train seven joint segmentation models using jICA. When using jICA, unlike PCA, choosing the number of components that are needed to best describe an observation matrix is not well defined and can affect results [61]. We follow the idea used in functional magnetic resonance imaging cognitive studies to estimate the number of optimal sources. There has been success using Minimum Descriptive Length (MDL) criterion [57] to estimate the number of sources. We use the local minimum from MDL information-theoretic criterion to determine the number of independent sources to represent the each model (Fig. 6.6). During SVM training, we use the The LIBSVM classifier toolbox to perform classification of the optimum segmentation model and MR labels. The SVM classifier’s hyper-parameters are tuned using all three training folds using a Gaussian Radial Basis Function (RBF) kernel. This resulted in the following parameters for model selection: $C= 4$ (regularization parameter), $\gamma = 0.125$. For MR selection, we train the classifier, using $C= 2$, $\gamma = 0.0625$, by grouping healthy and mild MR patients together in one set and patients with moderate and severe MR in another. We determined these parameters via an exhaustive search to maximize classification accuracy. During the online evaluation, we use a 4-fold cross validation (three folds for training, one fold for testing). In the localization process, the intensity based registration has a minimum step length of 0.025, maximum step length of 0.0425 and a limit of 300 iterations.

5.2 Apical View Classification

We perform an experiment on the validation dataset to determine the accuracy of view classification, using the known AP4 and AP2 labels as the
gold-standard. We report the classification accuracy available when detecting each view.

5.3 ROI Localization

The LA localization error was determined as the Euclidean distance between the calculated centroid location of the LA bounding box and its gold standard position in the validation data.

5.4 Segmentation and Volume Estimation of the LA

The accuracy of the LA volume estimation was determined as the Pearson correlation coefficient and the Sum of Squared Errors (SSE) compared to the clinical gold standard measurement. Note that a direct comparison of maximal atrium volume with 3D volume estimation was not possible, as our dataset had no 3D LA measurements. Furthermore, we investigated the influence of using a joint model (AP4+AP2) incorporating both apical views, compared to using only a single model for each apical view, on the segmentation accuracy.

5.5 MR Diagnostic Labels

In a cohort of 1007 patients, including 424 healthy patients and 583 moderate or more severe MR we generate the jICA model on the combined training sets obtained using a 4-fold cross validation to ensure stability of the generated joint components.

5.6 Diastolic Dysfunction and LV Filling Pressure

Furthermore, the framework’s component to predict diastolic dysfunction is performed by analyzing our large data access of 10490 patient measurement reports to provide database-guided recommendations. In our local hospital, the patient’s diastolic function grade distribution was found to be: normal (16%), mild (14%), moderate (4%), severe (1%) and indeterminate (14%).
To predict diastolic dysfunction we divided the reports into training (80%) and testing (20%) and trained a multi-set SVM classifier based on the features shown in Table 4.1. We use five-fold validation to test the stability of this trained SVM.

5.7 Time and Computational Complexity

Runtime was measured in seconds for four independent groups of computations run on a standard PC (Intel Core i7, 2.93GHz, 8GB RAM): 1) models and SVM classifier training; 2) left atrium localization; 3) estimation of the left atrial volume from segmentation; and 4) SVM classifier application for optimal model selection and disease labels. The framework assumes that there are two orthogonal ECHO inputs of the heart that are in adherence with the clinical standard AP4 and AP2 orientations. The computational complexities of the testing phase to be considered are using an affine intensity-based registration, two SVM classifiers, and PCA/jICA reconstruction.
Chapter 6

Results and Discussion

In this thesis, we have introduced a joint information framework for fast and computationally efficient ECHO analysis. The core of our method is the application of jICA on a combined data matrix of echo images and their corresponding segmentation labels for simultaneous LA segmentation in two apical ECHO views and MR disease detection. The framework is generic and can potentially be extended from 2DE to 3DE, as long as a large retrospective patient database is available. The flexibility and true power of the framework is seen by combining intensity and segmentation information into a unified space to reveal diagnosis labels from only ECHO image information. By using a multi-set jICA approach, we have introduced a framework capable of learning from the observable correlation between each ultrasound intensity pixel and the corresponding segmentation labels.

Additionally, outside of this framework, we have investigated feature selection to improve disease classification for diastolic dysfunction and LV filling pressure. By introducing two classifiers, which perform with good accuracy, we show potential to provide labels to prevent patient parameters from being labelled as indeterminate.
6.1 Apical View Classification and Localization

Applying our joint information framework to the analysis of n=6993 ECHO datasets, we achieved a view classification accuracy of 87% and 99%, for the AP4 and AP2 views, respectively. Compared to AP2 classification rate, the AP4 classification rate was likely lower due to the variable noise in the image, which could have reduced the visibility of the right ventricle and atrium, causing the AP4 to resemble the AP2 anatomical structure. In our framework, we assume that there is only one unseen AP4 and one unseen AP2 image, which allows us to accurately identify the AP2 image and classify the remaining image as the AP4.

Furthermore, we simultaneously determine the ROI defining the anatomical location of the LA. Our initial localization accuracy of the LA in the AP4 was $3.75 \pm 3.1$ mm and $4.37 \pm 3.3$ mm in the AP2 view (Figure 6.1). This accuracy was improved using a refinement affine registration step, achieving an ROI localization accuracy was $3.2 \pm 3.0$ mm in AP4 and $3.5 \pm 3.3$ mm in AP2 ECHOs (Figure 6.2).
Figure 6.2: Refined centroid estimation results for AP4 and AP2 using an affine intensity-based registration to an average LA appearance.

6.2 Segmentation and Volume Estimation of the LA

The computed volume of the LA resulted in a volume Pearson correlation coefficient of $R = 0.87$, a SSE of 12 mL (Figure 6.3), and an average DICE coefficient of 0.91 and 0.90 (AP4 and AP2, respectively) when compared to the clinical gold standard. On the other hand, using the single segmentation model yielded AP4 and AP2 DICE coefficients of 0.87 and 0.86, respectively (Figure 6.4). Figure 6.5 shows 10 example segmentation cases of both the AP4 and AP2. The joint model was optimized using 52 joint sources, unlike the single models, which both used 75 joint sources (Figure 6.6).

To the best of our knowledge, our validation dataset containing approximately 7,000 patients is the largest of its kind to date. While there are many segmentation methods specific to the left ventricle, segmentation of LA from ECHO data has been only recently reported in a small cohort of 10 patients on AP4 views [19]. We suspect that this is due to the high variability and the poor signal-to-noise ratio of LA in ECHO, as it is the farthest chamber away from the ECHO sweep. A recent report also confirms the challenges associated with LA segmentation in 3D Magnetic Resonance Imaging (MRI) and CT data [88]. On a limited dataset of 30 CT and 30 MRI images (divided into...
**Figure 6.3:** (Top and bottom): The correlations between estimated and gold standard LA volumes and the corresponding agreement between the manual and estimated methods are shown in the Bland-Altman plot.
Figure 6.4: Comparison of segmentation accuracies (measured by DICE coefficient) for segmentations only based on models constructed from a specific view (single model) and on models jointly derived from multiple apical (joint) views.

10 training and 20 validation data cases, DICE coefficients were comparable to those we report in this work. The literature is unclear as to how accurate left atrial estimations are required to be, especially when compared to 3DE technology [44]. Furthermore, the European Society of Hypertension recommends that LA volumes should be thresholded at $34 \text{ ml/m}^2$ (a value that implies diastolic dysfunction) when defining an abnormal LA size for ECHO, MRI and CT.

The model selection in LA segmentation has a direct impact on the volume procured. Visual assessment of the first principal component used for patient clustering shows that this component is directly related to the LA size. A mismatched model has the potential to over- or under-estimate volumes as shown by the outliers in Figure 6.3. The segmentation SVM model selection failed in 8% of patient cases where the length of the major axis,
Figure 6.5: Example studies of estimated segmentation results (dashed).
derived from the segmentation of the AP4 and AP2 views, were not within 20% of each other, in accordance to clinical practice [48]. Within the failed cases set, 25% had been marked by physicians as having sub-optimal image quality, 15% had a gold standard major axis deviation of over 20%, and 3.5% had mitral valves prosthetics installed. We expect that the model selection could be improved by incorporating the assessment of additional standard ECHO views of the LA into the framework. To visualize the information from mixing coefficients used in the segmentation SVM classifier, we use tSNE [34] to visualize one fold of the high-dimensional AP4 dataset in Figure 6.8. Using the Barnes-Hut implementation of tSNE\(^1\), we visualize the dataset mixing coefficients through its dimensionality reduction technique. We can see the separation of the larger blood pools (bottom) compared to those with smaller LA size (top). We can also observe the high variability of the LA’s shape from circular to an oblong ellipsoid in Figure 6.8, demonstrating the difficulty of the model selection process. Furthermore, tSNE has grouped LA’s with shadowing due to mechanical valves together in the bottom right. The shape and appearance of special cases like these are hard to characterize and can mask the disease’s perceived severity.

\(^1\)https://lvdmaaten.github.io/tsne/
Figure 6.7: LA segmentations grouped in columns based on their first principal components. Clustering is done to improve accuracy, given the diversity of our large dataset.
Figure 6.8: t-SNE is used to visualize the separability of AP4 joint ICA reconstruction weights of a random subgroup of 400 patients. This approach models the high-dimensional space in a two-dimensional system, such that nearby images are have similar AP4 anatomy and dissimilar AP4 images are further away. Images highlighted in red are those with severely enlarged left atriums ($\geq 40 \text{ mL/m}^2$)
Figure 6.9: An example of LA shadowing in the ultrasound created by a mechanical mitral prosthesis valve.

6.3 MR Diagnostic Labels

We use our framework to also detect patients with moderate or severe MR which is among the most frequent valve diseases resulting in LA enlargement and ultimately in LV dysfunction. For classification of MR disease label, we achieved a classification accuracy of 82.3%, specificity of 70.6% and a sensitivity of 91.6% (Figure 6.10). Without proper treatment, symptomatic patients have an annual death rate of over 5% [20]. MR is mainly characterized by the reverse blood flow from the LV to the LA and is thus most commonly assessed with respect to its mechanism and severity using noninvasive color Doppler [108]. However, Doppler ECHO measurements are based on geometric assumptions of the regurgitant jet, increasing the potential for misclassification. Current observer variability in detecting MR using Doppler is reported to account for approximately 25% [4]. By using LA dynamics to detect MR before it becomes unmanageable, we introduced a useful tool that allows physicians to alleviate diastolic dysfunction and safely manage heart failure. The ability to detect if a patient suffers from moderate MR during a routine examination only using B-Mode ECHO imag-
The confusion matrix for the healthy-moderate/severe and corresponding metrics.

**Figure 6.10:** The confusion matrix for the healthy-moderate/severe and corresponding metrics.

<table>
<thead>
<tr>
<th>True Diagnosis</th>
<th>Predicted Diagnosis</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>p'</td>
<td>p 534</td>
<td>91.6%</td>
<td>70.1%</td>
<td>82.3%</td>
</tr>
<tr>
<td>n'</td>
<td>n 129</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n'</td>
<td>p 49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n'</td>
<td>n 295</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predicting is of high clinical importance because it provides a means to trigger further examination visits to follow up the development of the disease.

Using our framework, we can classify patients with moderate to severe MR disease purely based on B-Mode ECHO image information. To understand the inputs used to train the disease SVM classifier, we visualize the learned independent sources in Figure 6.11. Based on the highlighted areas of modulation in Figure 6.11, we conclude that the sources grow and shrink based on an unseen TTE’s ultrasound intensity information, thus capturing the size of the atrium. As a result, our disease SVM classifier is likely learning to discriminate between normal and enlarged left atriums for MR detection. Clinically, using this information as a classifier is appropriate since, regardless of Doppler grading, severe chronic MR does not exist without left atrial enlargement [79]. Additionally, we compare the abilities of the learned sources for the joint and single model for MR classification, however, the mixing weights reconstructed from either jICA modelling approach had no apparent advantage (Figure 6.12). Furthermore, we investigate the cases where we have misclassified patient labels. We compare patients who were labeled as False Positive (FP) and False Negative (FN) against the True Positive (TP) and True Negative (TN) features. First, within the FP and TN sets, we see that there is potential to misclassify larger patients with increased BSA, seen in Figure 6.14(A). This indicates that patients with an
**Figure 6.11:** Learned joint independent sources. Each source represents a region-specific modulation in the AP4 and AP2 image intensity and the associated clinical LA segmentations. Highlighted areas show areas with more than 60% modulation of the sources. These 15 joint sources were created from a joint ICA decomposition of AP4 and AP2 apical views from one of the patient sub-groups.

Overall enlarged anatomy should be more carefully screened after our classification. Secondly, we also compare the LA volume of patients within the TP and FN sets, and note the misclassified patients have a significantly decreased mean LA volume of 35 ml/m² (Figure 6.13(B)). This finding is of clinical interest, as patients with increased levels of chronic MR will have LA dilation ($\geq 36$ ml/m² [95]). Furthermore by investigating the surface area of the reguritant valve (Figure 6.15), we observe the FN group has decreased indexed annular area, suggesting these patients within the FN set could suffer acute MR. As chronic MR progresses over time, it enlarges the heart’s anatomy and the diameter of the mitral valve. Acute MR is not normally reflected in the LV and LA chamber, and can instead manifest with physical symptoms.
Figure 6.12: The ROC curve for the healthy-moderate/severe SVM classifier using a single and joint model. Mitral regurgitation is trained only on reconstructed weights of ECHO features from the estimation process.

6.4 Diastolic Dysfunction and LV Filling Pressure

We achieved a diastolic dysfunction classification accuracy of 95.1%, specificity of 95.6% and a sensitivity of 80.8% (Figure 6.16). For LV filling pressure classification accuracy, specificity and sensitivity were 96.8%, 96.4% and 97.1%, respectively. These results were achieved by using a subset of features chosen by the Minimum Redundancy Maximum Relevancy selection algorithm. With a preset number of cardiac feature parameters, the algorithm determined the parameters that were mutually far away from each other while still having a strong correlation to the classification label. Out of the most common 46 features determined by experts (found in Figure 4.1),
Figure 6.13: Visualization of influence regarding normalized body surface area (a) and LA volume (b) on False Positives and True Negatives for MR classification.

Figure 6.14: The affect of normalized body surface area (a) and LA volume (b) patient features on MR classification’s False Positives and True Negatives.
it was experimentally determined that the optimum number of parameters was 16 and 36, for diastolic dysfunction (Figures 6.1 and 6.17) and LV filling pressure prediction respectively. Indicating that there were numerous parameters that were redundant, such as AP4 and AP2 surface area calculations.

The need for diastolic dysfunction classification is not only important because it is one of the criteria for diagnosing heart failure [75], but it’s prevalence in the elderly exceeds 40% [26]. Using the American Society of Echocardiography (ASE) 2009 guidelines, there are a set of specific parameters that must be met before further grading of the dysfunction can continue. In a 2010 study [26], it was found that 47% of 1369 ECHO studies could not be classified as they did not meet all of the ASE standards. Thus, being able to determine the grading of diastolic dysfunction, and contributing markers like LV filling pressure, is not an objective classification for elderly patients referred for ECHO. By incorporating a more fluid classification system, based on prior information, there is potential to better define the dysfunction severity of this group and prevent a high percentage of the population from being classified as indeterminate.
**Figure 6.16:** A diastolic dysfunction confusion matrix. Diastolic dysfunction is trained using 16 of the top clinical measurements routinely performed. We show a classification distribution heat map confusion matrix of diastolic dysfunction.

### 6.5 Time and Computational Complexity

Performing volume estimation, bi-plane segmentation and classification on a per-patient basis can be completed within 20 seconds, with the registration being the slowest step (approximately 13 seconds) (Figure 6.2). There is potential to decrease the registration time by running this step in a parallel processing code. However, at the time these experiments were conducted, the code was not optimized for speed performance.
Figure 6.17: Feature selection using mRMR comparing classification accuracy.
**Table 6.1:** Diastolic dysfunction mRMR ECHO measurements features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral Doppler measurement of the Mitral Annulus (Lat E’)</td>
<td></td>
</tr>
<tr>
<td>Septal Doppler measurement of the Mitral Annulus (Sep E’)</td>
<td></td>
</tr>
<tr>
<td>The mitral inflow Doppler E velocity/ E tissue Doppler velocity</td>
<td></td>
</tr>
<tr>
<td>Level of output of Left Ventricle</td>
<td></td>
</tr>
<tr>
<td>Diameter of Ascending Aorta</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation severity</td>
<td></td>
</tr>
<tr>
<td>Passive mitral inflow velocity LV filling (E)</td>
<td></td>
</tr>
<tr>
<td>Posterior wall Thickness at end-diastole (PWd)</td>
<td></td>
</tr>
<tr>
<td>Tricuspid regurgitation severity</td>
<td></td>
</tr>
<tr>
<td>Fraction of the PWd and LV end diastolic diameter (RWT)</td>
<td></td>
</tr>
<tr>
<td>Right Ventricle diameter in diastole (RVd)</td>
<td></td>
</tr>
<tr>
<td>Left Ventricle mass index</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation severity</td>
<td></td>
</tr>
<tr>
<td>Active filing with atrial systole (A)</td>
<td></td>
</tr>
<tr>
<td>Length of the sinuses within the valsalva</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation severity</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6.2:** Computational Time (Online)

<table>
<thead>
<tr>
<th>Process</th>
<th>Average Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centroid Estimation and LA Localization</td>
<td>2.4</td>
</tr>
<tr>
<td>Affine Image Registration</td>
<td>12.44</td>
</tr>
<tr>
<td>jICA Reconstruction and Post Processing</td>
<td>2.94</td>
</tr>
<tr>
<td>Segmentation SVM Classifier</td>
<td>0.07</td>
</tr>
<tr>
<td>Disease SVM Classifier</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Chapter 7

Conclusion

In this thesis, we proposed an extensible joint information framework for automatic estimation of cardiac parameters from TTE data by simultaneously segmenting AP4 and AP2 ECHO views, which are both required for volume calculations. We specifically focused on a large cohort of LA ECHO data, and leveraged the data’s diversity to generate a set of comprehensive models using ICA [18] that are capable of assisting in diagnosis. Our framework fused ECHO image intensity information and their segmentations from multiple 2DE views of the heart to automatically estimate clinical parameters and diagnostic labels. We segmented both AP4 and AP2 views simultaneously by using models within our framework that incorporated intensity information from both views. Using maximally independent basis functions to learn the observable patterns between intensity and the corresponding segmentation, we employed these patterns for LA volume estimation and, as a corollary objective, classification of individuals with chronic MR. The approach consisted of the following steps: 1) During training, using a joint independent component analysis of image intensity information, and the corresponding labels, associated with clinical measurements and diagnosis, to generate models that jointly describe the image and label space of those patients; 2) During evaluation, it segmented the anatomy of interest, and estimated the volume from simultaneous analysis of multiple anatomical
views in echo. 3) For diagnosis, it exploited the generated intensity-label joint patterns determined for each abnormal pathology group to classify new studies. Furthermore, we looked to reduce the number of indeterminate patients who are investigated for diastolic dysfunction and filling pressure; towards enabling standardized patient care.

In this work, with the investigated joint information framework focused on LA estimation and disease label analysis, we made the following contributions:

- Obtaining a largest of its kind dataset of ECHO information and patient parameters by interfacing and anonymizing VGH’s medical ECHO storage system and clinical database.

- Proposing a segmentation technique that jointly fuses information from multiple apical views to aid in overcoming the obstacles of segmenting the LA region.

- Investigating a new technique for classifying normal and moderate or more severe mitral regurgitation based on jICA reconstruction coefficients. Demonstrating the unique information provided by the jICA learned sources.

- Investigating the use of combining clinical parameters for analysis diastolic dysfunction and filling pressure to prevent indeterminate classification of patient measurements. Simulations showed the method could has potential to be used in parallel with traditional dysfunction and filling pressure classification.

### 7.1 Future Work

There is room for future work to improve the accuracy of this framework, namely, improving the patient grouping, enhancing the automatic localization process, and improving the segmentation SVM classification accuracy. Currently, patients are grouped based on their first-mode of variation from
PCA; that generally corresponds to the overall surface area. In the future, more complex models could be formed from our current database to incorporate age, body surface area and past medical history. This could be especially useful in cases where the LA cavity is severely deformed due to old age. Similarly, there is room to improve the localization process, as some ROIs did not contain the entire LA blood pool due to the intensity-based registration method. When performing volume estimation using ROIs containing LA, aligned based on the gold-standard segmentation of LA in the query image instead of using the intensity-based registration, we find our method achieves an improved Pearson correlation coefficient of 0.90 and a reduced SSE of 11 mL. This result suggests that developing a more accurate localization method could improve the framework.

Finally, the segmentation SVM model selection failed in 8% of patient cases where the length of the major axis, derived from the segmentation of the AP4 and AP2 views, were not within 20% of each other, in accordance to clinical practice [48]. Within the failed cases set, 25% had been marked by physicians as having sub-optimal image quality, 15% had a gold standard major axis deviation of over 20%, and 3.5% had mitral valves prosthetics installed. We expect that the model selection could be improved by incorporating the assessment of additional standard ECHO views of the LA into the framework.

Future work to improve MR classification could include incorporating Doppler information and the analysis of the entire ECHO sequence instead of only end-systolic views that we analyze in this work. The effectiveness of this approach has been recently demonstrated in 3DE data in a small patient study [96].

To conclude, while there are many left ventricle segmentation approaches available for use in echocardiography, we believe we are the first to propose a joint multi-view segmentation of LA and MR label analysis using B-mode intensity information. The flexibility and true power of the framework is seen by combining intensity information into a unified space to reveal diagnosis labels from only 2DE image information. The benefits advanced by
this unified framework are: 1) it can estimate the LA volume by learning the large anatomical diversity of patients witnessed in approximately 7,000 studies, or 14,000 images, and obtain results that have high correlation with clinical measurements; 2) It can create patient-specific models capable of identifying MR labels; and 3) Due to the low computational complexity of the framework, there is potential for our framework to be applied to portable ECHO machines that are frequently used in the emergency room and in rural clinics.
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