PREFACE

The major cause of death worldwide is cardiovascular diseases (CVDs). In 2016, approximately 17.9 million people died because of CVDs which represents 31% of the global death. Out of these, 85% of deaths are due to heart attack or stroke. 75% of deaths due to CVDs occur in mid-income and low-income countries. One in 4 deaths in India is now because of CVDs with ischemic heart disease and stroke, responsible for >80% of burden on healthcare system. Recognition of CVDs is the first and most important step in the treatment and management of the patients by the healthcare system. Timely diagnosis of cardiovascular disease plays a vital role in the effective management of high-risk patients. Early diagnosis of heart disease not only helps in providing adequate life-saving therapeutic intervention but also reduces the load on the healthcare system. Increased risk of death due to CVDs demands for accurate, rapid, sensitive, and reliable, affordable detection systems.

Several diagnostic modalities are developed for heart function analysis like biomarker monitoring. Broadly, cardiac function analysis modalities can be subdivided into Image-based systems, Signal based systems, and biomarker-based systems. Imaging techniques include but are not limited to Cardiac Magnetic Resonance Imaging (CMRI), Echocardiography, and Computed tomography. Signal Processing techniques include Phonocardiography (PCG) and Electrocardiography (ECG) while Biomarker based techniques include detection of cardiac-specific biomarkers detection like troponins (cTnI, cTnT, Myoglobin, etc.). Biomarkers specific to the heart are established to be identifiers of CVDs whose concentration varies as the physiological and pathological condition of the cardiac environment varies.

Several biomarkers are identified for CVDs within blood serum or plasma such as Cardiac Troponins, NT-proBNP, C-reactive protein (CRP), Myoglobin, etc. Several techniques have been developed for the early diagnosis of stroke and other CVDs. Techniques such as surface plasmon resonance (SPR), immunoassays, enzyme-linked immunosorbent assay (ELISA), surface-enhanced Raman spectroscopy (SERS), field-effect transistor-based methods, and liquid chromatography are commonly used for the quantification of biomarkers. Drawbacks of these methods include sample-specific preparation, long processing time, and the requirement of central laboratories. Recently, the main focus has been on point-of-care tests (POCT) for portability, small sample size, fast detection, and high accuracy.

In first phase of the work, biomarker-based detection of CVDS is explored using spectroscopy methods. Biomarkers are small molecules that can be quantified and help in the prognosis of the heart condition. Concentration above a certain value for biomarkers represents the changes of occurring of cardiac event in near future or certain heart condition is developed recently. Several spectroscopic methods had been used by different research groups still limitations exist in the method. Major limitations are:

- Method specific and tedious sample preparation
- Long processing and result time
- Requirement of central lab
- Lack of standardization
- Lack of prognosis capabilities and lower detection of limit

Spectroscopy based methods are proved to require no sample preparation method with faster results, and higher detection accuracy. UV-Vis, Raman, and Fourier transform infrared Spectroscopy is mainly investigated in this work for label-free detection of cardiac biomarker Cardiac Troponin I (cTnI). UV-Vis spectroscopy provided a SPR quenching phenomenon when biomarker is conjugated with gold nanoparticles. The 530 nm SPR peak of gold nanoparticles vanished as the concentration of cTnI is increased above certain level. The conjugation of cTnI with gold nanoparticles are further visualized using TEM images. The initial Raman signal for gold conjugated cTnI provided a hint of low concentration detection of the biomarker using multivariate signal processing but the results were initial and no conclusive inference can be drawn. The occurrence of global pandemic and shutdown of the institutes caused the postponement of the project and no further verification can be carried out as sample procurement and instrument handling is highly affected by the global situation. Further, the application of double density dual tree complex wavelet transform is also evaluated and observed that the method is not only able to remove the spikes from the spectroscopy signals but also have better denoising capabilities compared to other state-of-the-art denoising methods.

In the second phase of this work, Image based cardiac diagnosis is investigated mainly focusing on cardiac MR images. Cardiac Magnetic resonance imaging is considered the gold standard for non-invasive cardiac function analysis due to its 3D capabilities and high spatiotemporal resolution. It had been already proved to be an invaluable tool in the diagnosis of complex cardiomyopathies. Cardiac Magnetic resonance not only helps in the visualization of cardiac anatomy but also allows to know the functional behavior of the heart. Clinical implications of cardiac MRI are:

- Quantify coronary blood flow
- Measurement of ventricular volumes, wall thickness, and other parameters.
- Quantify myocardial infarction size.
- Myocardial viability
- Measure blood flow in the myocardium

Cardiac function analysis provides several information related to heart structure and helps in the diagnosis of several pathological conditions like hyper cardiomyopathy. But to accurately extract this information from cardiac function analysis-based modalities especially MRI, accurate segmentation is of the utmost importance. Despite several hardware and software advancements in recent years, several limitations exist like the requirement of ground truth, Image intensity and contrast inhomogeneity, and others. Major difficulties in Image-based diagnosis, regarding MRI, are as:

- Poor contrast between myocardium and surrounding structures
- Brightness heterogeneities in LV and RV chamber due to blood flow
- Presence of trabeculae and papillary muscles with intensity similar to the myocardium
- Inherent noise due to motion and heart dynamics
- Shape and intensity variability of heart structures
- Presence of banding artifact

These problems in the cardiac MR images makes the physicians difficult to do inference regarding the clinical conditions. To augment them, automated segmentation of the images is carried out which is further used to extract features to classify the patient as a normal or abnormal. To do so, accurate segmentation of the images is required for which a transfer learning-based method, a modified U-Net network, and a cascaded model is proposed. Results showed that the methods proposed are well-performed and the cascaded model paved a way to go from supervised learning to unsupervised learning thus removing the need of ground truth which is a hectic task.

The principal objective of the thesis is to improve methods of cardiac diagnostic by improving two of the most used aspects: Image-based diagnosis and Spectroscopy based diagnosis. In this view, this thesis aims to full fill the following objectives like design and optimization of Raman probe for Cardiac troponin I detection, validation of the use of spectroscopic methods in Cardiac troponin I detection, spectral signal processing to extract more accurate and quantitative information from the signal, development of an algorithm for more accurate segmentation of CMRI to improve feature extraction for diagnosis of the cardiac pathological condition, and to pave a way towards unsupervised segmentation of cardiac images to exploit the availability of vast unannotated biomedical image data for better diagnosis.