IMAGE BASED COMPUTATIONAL MODELING OF INTRACARDIAC FLOWS

By

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ABSTRACT

With continuous advancements in four-dimensional medical imaging technologies, increasing computational speeds, and widespread availability of high performance computing facilities, computational modeling of intracardiac flows is becoming increasingly viable and has the potential to become a powerful non-invasive diagnostic tool for the diagnosis and treatment of cardiovascular disease. The motive of the current study is to develop a modeling framework that facilitates image-based analysis of intracardiac flows in health as well as disease and to use this framework to gain fundamental insights into intracardiac hemodynamics.

A procedure is developed for constructing computational fluid dynamics (CFD) – ready models from in vivo imaging data. The key components of this procedure are the registration and segmentation of the 4D data for several (~20) key frames, template based mapping to ensure surface grid conformality and high-fidelity simulations using a sharp-interface immersed boundary solver. A physiologically representative, kinematic model of the mitral valve is also developed for use in these simulations.

As a precursor, a comprehensive quantitative validation of the flow solver is performed using experimental data in a simple model of the left ventricle. A quantitative comparison of the phase-averaged velocity and vorticity fields between the simulation and the experiment shows a reasonable agreement. The detailed assessment of this comparison is used to identify and discuss the key challenges and uncertainties associated in conducting such a validation study.

The vast majority of computational investigations of intracardiac flows have focused either on the left or the right ventricles while the corresponding atria were modeled in
highly simplistic ways. However, the impact of this simplification on the hemodynamics of the ventricular filling has not been clearly understood. Additionally, the surface of the ventricle has been assumed to be smooth although it is well known that the left ventricle is highly corrugated with surface protrusions or trabeculae and papillary muscles extending deep into the ventricular cavity. Hence, separate studies were conducted to understand the effect of complex atrial flows on the intraventricular flow development and also to understand and quantify the impact of the trabeculae and papillary muscles on ventricular hemodynamics.

Results indicate that the trabeculae and papillary muscles significantly impact ventricular flow resulting in a deeper penetration of the mitral jet into the ventricle during filling. These anatomical features are also found to produce a “squeezing” effect that enhances apical washout. It is also demonstrated that the complex flow dynamics developed inside the left atrium have minimal influence on the flow inside the left ventricle, which is primarily governed by the mitral valve leaflets configuration. The complex vortical structures inside the left atrium are rapidly dissipated due to the complex interaction of multiple vortex rings leading to breakup, annihilation and enhanced viscous dissipation so that the flow is smoothly streamlined as it enters the mitral orifice and produces a near-uniform velocity profile at the level of the mitral annulus. The implications of these findings on the modeling of the intra-ventricular flows are also discussed.

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Readers: Richard George, M.D.

Joseph Katz, Ph.D.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>LV</td>
<td>Left Ventricle</td>
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<tr>
<td>LA</td>
<td>Left Atrium</td>
</tr>
<tr>
<td>MV</td>
<td>Mitral Valve</td>
</tr>
<tr>
<td>PMs</td>
<td>Papillary Muscles</td>
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<tr>
<td>PVs</td>
<td>Pulmonary Veins (left/right)</td>
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<td>CCT</td>
<td>Cardiac Computed Tomography</td>
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<td>CMRI</td>
<td>Cardiac Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>IB</td>
<td>Immersed Boundary</td>
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<tr>
<td>LDDMM</td>
<td>Large Deformation Diffeomorphic Mapping Method</td>
</tr>
<tr>
<td>CMM</td>
<td>(Doppler) Color M-mode</td>
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<tr>
<td>$u_i$</td>
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<td>Fluid density</td>
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<td>$\kappa$</td>
<td>Diffusivity of passive scalar</td>
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<tr>
<td>$\Delta V$</td>
<td>Change in ventricular volume</td>
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<tr>
<td>$T$</td>
<td>Cardiac cycle time</td>
</tr>
<tr>
<td>$Q$</td>
<td>Flow rate or rate of change of ventricular volume</td>
</tr>
<tr>
<td>Re</td>
<td>Reynolds number</td>
</tr>
<tr>
<td>Wo</td>
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<tr>
<td>$\Lambda_E$</td>
<td>Vortex formation number (E-wave)</td>
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<td>Symbol</td>
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<td>Schmidt number (for passive scalar)</td>
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<td>Peak area-averaged velocity through the mitral annulus</td>
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<td>$D_{MO}$</td>
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<td>$\lambda_{ci}$</td>
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<td>KE</td>
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CHAPTER 1. INTRODUCTION

1.1. Motivation & Background

1.1.1. Trends in cardiovascular disease (CVD)

Cardiovascular disease (CVD) forms the leading causes of death in United States—more than the deaths due to cancer and accidents combined together (Go et al., 2014). Although improved diagnostics and treatment options have decreased the overall mortality over the last couple of decades, other trends in CVD point towards a troubling future. The CVD was found to have a very strong positive correlation with people over 45 years (see Figure 1-1A) and it is projected that by 2030, at least 50% of the population would fall in this age group (Figure 1-1A). CVD is also strongly correlated to other factors associated with marked excess mortality such as obesity, diabetes, and high levels of BP and cholesterol (Go et al., 2014). While the 2014 study on heart disease update indicated that currently about 35% of US adults (age >20 years) are obese and about 8% are diabetic, trends suggest that the prevalence of diabetes and obesity is increasing dramatically with time and by 2030, about 40% would be clinically obese and about 16% would be diabetic. At the same time, the projected national expenditure on heart related diseases could be over a whopping trillion dollars by 2030 (Go et al., 2014). As most of these costs are attributed to the costly invasive treatment options, it is necessary to develop improved, reliable and economical non-invasive diagnostic methods by bringing together the various disciplines of medicine, engineering, and technology.
1.1.2. Trends in computing

One way to counteract these negative trends in CVD is the favorable trend in computing as dictated by Moore’s law (Schaller, 1997). Faster and cheaper computations are being enabled today due to increased clock-speeds, heterogeneous computing, enhanced memory-bandwidth and data transfers together with virtualization and cloud computing. The computational demand of a typical flow simulation inside a left ventricle employing a spatial resolution of about 10 million grid points and about 10,000 time steps per cardiac cycle is of the order of ExaFLOPS. However, the current supercomputers which operate in the range of PetaFLOPS require excessive times that are impractical for clinical deployment of such simulations (Figure 1-1B). From Moore’s law, it is very likely that Exascale computing could be realized in about a decade from now and at a cost that might not be excessive. These trends have already begun to be realized with the recent advent of GPUs and MICs providing supercomputing performance on a desktop PC which is necessary for real-time diagnosis and therapy.
Thus, it is important to understand that computer-based modeling aided by advances in medical imaging provides a promising future in terms of cost-effective diagnosis and treatment of cardiac diseases. At the same time, a necessary framework has to be developed with relevant tools and diagnostic metrics in order to make simulation-based diagnosis and surgical planning viable for heart related diseases.

1.1.3. **Heart – multiphysics modeling and complexities**

Figure 1-2. Multiphysics modeling of heart and the interplay across these various disciplines.

The human heart is a highly complex organ, the functioning of which implicates multiple physical domains (Figure 1-2). Electrophysiology translates the electrical activity at the cellular level into the macroscale mechanical motion of the heart tissue which is then governed by the cardiac tissue (solid) mechanics. The complex fluid dynamics exhibited by the blood within the heart chambers due to high Reynolds numbers is further complicated by the flow-structure interaction between the blood and
the heart walls and the atrio-ventricular valves. Additionally, the biochemical activity within the blood plasma prevents it from forming clots while hemoacoustics is another promising area of modeling so that effective tapping of heart sounds and murmurs could enable improved auscultation-based diagnosis of heart disease. However, it is the complex interplay between each of these discrete physical domains that gives rise to several issues in terms of both the physical modeling and properties as well as other computational related issues.

While the application of CFD to modeling of vascular flows (i.e., modeling blood flows through vessels to and from the heart) is relatively well-established, the computational modeling of cardiac hemodynamics (i.e., modeling blood flow in heart chambers such as the atria and ventricles) has not found significant clinical application yet due to the various complexities associated with these models. Some examples of the former that have greatly progressed the simulation based therapeutic approach are the functional diagnosis of blood flow in coronary arteries developed by Heartflow Inc. (Taylor, Fonte and Min, 2013), optimization of Fontan surgical procedure (Long et al., 2012; Kung et al., 2013) and Kawasaki disease treatment (Sengupta et al., 2012). However, the latter comprising cardiac hemodynamics has various challenges due to the complex large scale motion of the heart chambers (atria and ventricles) undergoing significant volume change and deformation, complex flow-induced dynamics around the atrio-ventricular valves and the high Reynolds number transitional flow produced in the ventricular cavity. The present work aims to address these issues systematically using computational fluid dynamics modeling and medical imaging.
1.2. Literature review

Cardiovascular flows has been studied over the past three decades using both computational and experimental methods, continuously providing newer insights into the flow patterns and transport phenomena. The earliest analysis was primarily conducted using simplified canonical shapes and by applying simplified boundary conditions both in simulations and experiments (Bellhouse, 1972; Reul, Talukder and Muller, 1981; Thomas and Weyman, 1992; Taylor et al., 1996; Vierendeels et al., 2000; Baccani et al., 2002; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Long et al., 2003; Long et al., 2008) (Doenst et al., 2009; Schenkel et al., 2009; Krittian et al., 2010; Zheng et al., 2012; Seo and Mittal, 2013). Most of the focus of these studies has been on investigating single chamber models such as either the left ventricle (LV) or right ventricle (RV) only (Taylor et al., 1996; Vierendeels et al., 2000; Baccani et al., 2002; Long et al., 2003; Pasipoularides et al., 2003; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Pedrizzetti and Domenichini, 2005; Long et al., 2008; Schenkel et al., 2009) (Doenst et al., 2009; Krittian et al., 2010; Le and Sotiropoulos, 2012; Zheng et al., 2012; Seo and Mittal, 2013; Seo et al., 2014) while multi-chamber interaction has been very limited in scope. An exception to this is the seminal modeling studies of Peskin et al. (Peskin, 1972; Peskin, 1977; McQueen, Peskin and Yellin, 1982; McQueen and Peskin, 1989; Peskin and McQueen, 1989) which were for a multi-chamber heart model. More recently, advances in medical imaging have led to the development of more realistic heart models (4D, four-chamber) (Mihalef et al., 2011; Le and Sotiropoulos, 2012; Chnafa, Mendez and Nicoud, 2014; Lim et al., 2014), inclusion of atrio-ventricular valves (Seo et al., 2014), detailed surface geometry of the
atria and ventricle (Kulp et al., 2011), etc. The following paragraphs provide a review of the previously reported works on understanding blood flows in heart chambers beginning with simplified ventricular models to more complex image-based heart models.

Laboratory experiments have been also performed using simplified models of LV providing fundamental insights into the hemodynamics of intraventricular flows. Observations on intraventricular flow patterns were made in the seminal works of Bellhouse et al. (Bellhouse and Bellhouse, 1969; Bellhouse, 1972) who demonstrated the formation of a vortex ring at the distal ends of the bileaflet mitral valve (MV) and conjectured that the dynamics of the valve closure rely on forces produced by this vortex ring. However, this was later contradicted by Reul et al. (Reul, Talukder and Muller, 1981) whose experimental study showed that vortices are only partially responsible for closing the mitral valve during mid-diastole; whereas, the development of an adverse pressure gradient at the end of filling is responsible for the final closure of the valve. More recently, MV leaflets were found to significantly influence the LV filling pattern using a laboratory ventricular model (Charonko et al., 2013). In particular, it is argued that the ventricular vortex formed at the MV tips, previously thought to be a passive by-product, instead acts as a virtual channel and reduces convective losses in driving the flow towards the apex. It is argued that this leads to an efficient mass transfer enhancing the function of LV as a suction pump; whereas, any impairment of this mechanism could lead to eventual heart failure. Other experiments have also been performed using simplified LV models to further characterize intraventricular flow (Kheradvar and Gharib, 2009; Fortini et al., 2013) and investigate the effects of prosthetic mitral valves (Querzoli, Fortini and Cenedese, 2010; Vukčević et al., 2012).
Computational modeling of intracardiac flows is influenced by several factors: the type of boundary treatment (prescribed wall motion vs. fluid-structure interaction); geometry (axisymmetric such as semi-prolate spheroid vs. image-based realistic anatomy, two dimensional vs. three dimensional); and flow boundary conditions (prescribed flow profiles vs. pressure driven). For instance, Peskin et al. (Peskin, 1977) and McQueen et al. (McQueen, Peskin and Yellin, 1982) were the first to numerically elucidate flow patterns in a two-dimensional ventricle using the immersed boundary (IB) method which was earlier developed by Peskin (Peskin, 1972). Briefly, this method employs a fixed Cartesian grid to solve for the flow inside a body whose wall is represented by elastic fibers immersed in the background fluid grid. The fibers are modeled as linear springs; the force of these fibers is transmitted to the fluid using a discrete delta function and these fibers move with the local fluid velocity. Although this method has the advantage of avoiding complex remeshing, smooth approximation of the discrete delta function leads to a diffused boundary representation and thereby, lowers the accuracy in resolving the near-wall hemodynamics. This methodology was extended later to simulate three-dimensional flow inside a model LV (McQueen and Peskin, 1989; Peskin and McQueen, 1989).

More than a decade later, Vierendeels et al. (Vierendeels et al., 2000; Vierendeels, Dick and Verndock, 2002) conducted another two-dimensional axisymmetric study of intra-ventricular flows using an Arbitrary Lagrangian-Eulerian (ALE) approach while applying physiological boundary conditions derived from lumped element models (Georgiadis, Wang and Pasipoularides, 1992; Thomas and Weyman, 1992; Watanabe et al., 2004; Pasipoularides, 2010). Cheng et al. (Cheng, Oertel and Schenkel, 2005) have
attempted to simulate the filling dynamics of left ventricle in a prolate-spheroidal geometry, by modeling the flow using ALE approach and the structural dynamics is modeled using finite element method assuming a time varying Young's modulus of the heart wall. Commercial solvers such as ADINA-FSI solver have been used in their study; but it is noted that the constitutive law for myocardium is quite complex (Guccione and McCulloh, 1993; Guccione, Waldman and McCulloh, 1993; Gurev et al., 2011; Trayanova, 2011). Several other numerical studies have assumed a semi-prolate-spheroidal LV in addition to other approximations on the expansion and contraction of the ventricle (Baccani et al., 2002; Domenichini, Pedrizzetti and Baccani, 2005; Pedrizzetti and Domenichini, 2005; Domenichini et al., 2007; Pedrizzetti, Domenichini and Tonti, 2010; Zheng et al., 2012; Seo and Mittal, 2013; Seo et al., 2013; Choi, Vedula and Mittal, 2014).

Despite these simplifying assumptions, these studies have provided useful insights into the flow physics of the left ventricle in both health and disease. For instance, Pedrizzetti et al. (Pedrizzetti and Domenichini, 2005) reported that the asymmetry of the blood flow in a normal ventricular flow is associated with minimum energy dissipation around physiological conditions while the pumping work load increased by at least 10% due to cardiac diseases or valvular replacement. This computational assessment obtained using simplified ventricular model is also in-line with the qualitative arguments provided by Kilner et al. (Kilner et al., 2000) using clinical phase-contrast MR data sets. However, it was later argued by Watanabe et al. (Watanabe, Sugiura and Hisada, 2008) and Seo et al. (Seo and Mittal, 2013) using more detailed computational investigations that the asymmetric redirection of momentum between filling and ejection associated with
physiological ventricular flow patterns does not preserve any significant part of kinetic energy because the dissipation of kinetic energy is only a negligible fraction of the total pressure work done by the ventricle. This type of flow pattern does, however, ensure an effective mixing and ‘washout’ of the ventricular blood. Further, Seo et al. (Seo et al., 2013) has developed a multiphysics framework of the ventricular model by including hemoacoustics into the modeling procedure and developed metrics based on virtual echocardiography and phonocardiogram for improved auscultation-based diagnosis of hypertrophic obstructive cardiomyopathy (HOCM).

With continued improvements in the spatial and temporal resolution of cardiac imaging modalities such as cardiac magnetic resonance imaging (CMRI) and cardiac computed tomography (CCT), there has been a gradual shift in the cardiac hemodynamics research community towards more realistic and even patient-specific models of the heart (Pasipoularides et al., 2003; Saber et al., 2003; Doenst et al., 2009; Schenkel et al., 2009; Krittian et al., 2010; Tang et al., 2010; Kulp et al., 2011; Mihalef et al., 2011; Le and Sotiropoulos, 2012; Toger et al., 2012) (Chnafa, Mendez and Nicoud, 2014; Lim et al., 2014). Computational models of the left ventricle have been created out of CMRI images although these models are still simplified without much surface details such as the papillary muscles (PMs) or the ventricular trabeculae (Saber et al., 2003; Doenst et al., 2009; Schenkel et al., 2009). Earlier models also did not account for separate inclusion of valves but mimicked their presence using time varying boundary conditions (Saber et al., 2003; Doenst et al., 2009; Schenkel et al., 2009). However, subsequent models have improved segmentation and registration procedures using high resolution CCT image data that have also accounted for additional complexities due to
ventricular surface detail such as trabeculae and realistic mitral valve modeling based on imaging data (Kulp et al., 2011; Mihalef et al., 2011; Chnafa, Mendez and Nicoud, 2014). Although CCT provides excellent spatial resolution (~0.5mm), CMRI suffers from poor through-plane resolution (~8mm) while the in-plane resolution is of the same order as the CCT. However, the temporal resolution of both CCT and CMRI is relatively low and in this regard, 4D-echocardiography is another promising imaging modality owing to its high temporal resolution, lack of radiation hazard, low cost, and allows instant validation against simultaneous clinical measurements. A notable implementation of an echo-based right ventricular model for flow analysis was performed by Pasipoularides (Pasipoularides et al., 2003).

In most of the image-based ventricular flow modeling approaches, significant amount of effort is spent on semi-automatic image segmentation and registration and hence, efforts are being made more recently to fully automate these processes (Zheng et al., 2008; Kulp et al., 2011; Mihalef et al., 2011; Lim et al., 2014). A promising effort along this direction was made by Dillard et al. (Dillard et al., 2014) who have developed methods to compute the blood flow directly from the medical images using level set based methods and hence, obviating the need for manual intervention while creating CFD-ready models from medical images. However, this has been developed for arterial or vascular flows while more studies are to be conducted and validated for the more complex cardiac flows.

1.3. Limitations of previous studies

Despite making significant advances in the field of computational modeling of cardiac flows and gaining newer sights into intraventricular flow development and blood
transport phenomena, there are several aspects that are still not clear. While some of these are related to the computational modeling of intracardiac flows, others are more fundamental in terms of intraventricular flow development and the various factors influencing it.

1.3.1. Quantitative validation

Despite the fact that computational modeling of intraventricular flows is now relatively well established, no study has, to our knowledge, focused on a comprehensive quantitative validation of such flows. Some previous studies either compare gross features such as global ejection fraction (EF, defined as the ratio of ejected blood volume or stroke volume (SV) to that of the end diastolic volume (EDV)) while some others make qualitative comparisons of observed flow and vortex patterns. For instance, Saber et al. (Saber et al., 2003) and Schenkel et al. (Schenkel et al., 2009) made qualitative comparisons of their computed results (obtained using a commercial CFD software, STAR-CD) with velocity fields reconstructed from two-dimensional CMRI data sets for healthy hearts. Qualitative comparisons of computed velocity and vorticity fields with experimental data have also been made by Domenichini et al. (Domenichini et al., 2007) and Doenst et al. (Doenst et al., 2009). The former has used a patient-specific model generated from cine MR to validate their model, while the latter performed validation using a simplified laboratory model. Recently, Krittian et al. (Krittian et al., 2010) compared intraventricular flow patterns and ventricular wall deformation between in vivo MRI data, laboratory experiment and a CFD-FSI based simulation using the Karlsruhe heart model (KaHMo, (Krittian et al., 2010)). However, they noted experimental limitations in obtaining realistic ejection fractions and Reynolds numbers; in addition, the
comparison was very much qualitative in nature (Krittian et al., 2010). Therefore, it is necessary to quantitatively validate the solver as a precursor to conducting patient-specific simulations of cardiac flows.

1.3.2. **Effect of left ventricular trabeculae and papillary muscles**

The left ventricular (LV) endocardium, that represents the innermost lining of the ventricle in direct contact with blood, is not smooth. Instead, the surface is highly corrugated with surface protrusions extending into the LV cavity (Pasipoularides, 2010). These surface protrusions or trabeculae are usually formed on the ventricular free wall extending helically from the base to the apex of the LV (Boyd et al., 1987) and comprise about 12-17% of LV by mass (Papavassiliu et al., 2005; Fernandez-Golfin et al., 2009; Jacquier et al., 2010). Most of the previous studies have focused on quantifying the size and mass of these trabeculae in health and disease (Chin et al., 1990; Papavassiliu et al., 2005; Fernandez-Golfin et al., 2009; Jacquier et al., 2010). These anatomical studies, however, do not address the very intriguing question regarding the function and effect of the trabeculae, especially viz-a-viz the dynamics of the blood flow in the left ventricle. It is well known that rough walls promote transition to turbulence and increase pressure loss. As such virtually all vessels of a healthy cardiovascular system including the right atrium, the left atrium, the aorta, and the systemic arteries and veins, have smooth inner walls. Why then does the left-ventricle, which is the arguably the most critical component of the cardiovascular system, have such a rough endocardium? In addition to the possible increase in pressure loss associated with this, the trabeculae introduce small interstitial spaces that would seem to increase the possibility of local flow stagnation and increase thrombogenic risk.
Interestingly, Pasipoularides (Pasipoularides, 2010) conjectured that the trabeculae enhance the ability of the left ventricle to “squeeze” the fluid from the apical region during systole (ejection). Serrani et al. (Serrani, Costantino and Fumero, 2013) employed a finite-element model to simulate the electromechanically driven contractions for highly simplified models of LV, and this study suggested that the trabeculae aid ventricular ejection by producing higher stroke volumes at low atrial pressures. Recently, Kulp et al. (Kulp et al., 2011) examined the effect of trabeculae on ventricular flow by simulating blood flow inside an LV model derived from high resolution 4D CT data. By comparing two models which had precisely the same trabecular structure but different apical contraction, they noted that the model with the reduced apical contraction had more stagnant flow in the apical region (Kulp et al., 2011). Since reduced apical contraction is expected to enhance apical stasis, irrespective of the presence or absence of trabeculae, it is not clear what this comparison implies with respect to the effect of the trabeculae on the ventricular hemodynamics.

1.3.3. **Effect of left atrium on ventricular flow development**

The vast majority of cardiac computational models to date have been single-chamber models which have focused either on the left or the right ventricles, while the corresponding atria were modeled in highly simplistic ways, mostly through varying inflow boundary conditions (Vierendeels et al., 2000; Long et al., 2003; Pasipoularides et al., 2003; Saber et al., 2003; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Long et al., 2008; Doenst et al., 2009; Schenkel et al., 2009; Le and Sotiropoulos, 2012) (Zheng et al., 2012; Seo and Mittal, 2013). However, the left atrium (LA) has a complex structure (Al-Saady, Obel and Camm, 1999; Stefanadis, Dernellis
There are four inlets to the LA – two from the left pulmonary veins (LPVs) connected to the left lung positioned lowly near the mitral orifice and two more inlets from the right pulmonary veins (RPVs) connected to the right lung positioned higher with respect to the LA cavity. Additionally, there is a highly distensible and trabeculated muscular sac positioned inferomedially near the mitral orifice (MO), called the left atrial appendage (Al-Saady, Obel and Camm, 1999). While one end of the left atrial appendage (LAA) is open to the LA cavity, the apical end is closed. The unique morphology of LAA presents a key hemodynamic challenge for the blood to get smoothly “washed” out of this closed sac without any clot formation.

The complexity of the LA structure is further accentuated by its three-fold function during a cardiac cycle (Stefanadis, Dernellis and Toutouzas, 2001; Appleton and Kovacs, 2009; Ho, Cabrera and Sanchez-Quintana, 2012). The LA acts as a conduit passage during early ventricular filling (E-wave) when the ventricle passively relaxes and establishes a low pressure in its cavity driving the atrial flow through the mitral valve. During atrial filling (A-wave), the LA acts as a contractile booster pump forcefully delivering the blood into LV. Further, the LA acts as a reservoir during ventricular systole and fills with blood from the pulmonary veins when the mitral valve is completely closed. However, despite the complex anatomy of LA, in practice, it is usual to replace the LA with a pipe or to mimic its presence by providing suitable time-dependent velocity profiles and inflow boundary conditions. But, the impact of this simplification on the ventricular flow development is still not well understood.
1.4. **Current objectives**

In view of the limitations in the previous research efforts and with an eventual goal of developing a CFD-based solver to analyze patient-specific heart function, the present research aims to achieve the following objectives:

**Objective 1: Perform quantitative validation of the flow solver**

Our first step is to quantitatively validate the hemodynamic flow solver using a simplified laboratory LV model. Our numerical solver is based on a sharp-interface IB method (Mittal and Iaccarino, 2005; Mittal et al., 2008; Seo and Mittal, 2011), which has been validated for canonical flows (Mittal et al., 2008) as well as complex flows such as flow past fish fins (Dong et al., 2010) and flapping insect wings (Zheng, Hedrick and Mittal, 2013). The laboratory model of the left ventricle employed here has already been used earlier for investigation of intraventricular flows (Querzoli, Fortini and Cenedese, 2010; Espa et al., 2012; Vukčević et al., 2012; Fortini et al., 2013). We make quantitative comparisons of computed phase-averaged velocity and vorticity profiles for this LV model and use this to assess the limitations and challenges associated with conducting such simulations.

**Objective 2: Develop a computational framework for image-based modeling of cardiac flows**

After performing validation of the hemodynamic flow solver with experimental data, we develop a framework for image-based computational flow modeling of intracardiac flows. This involves a series of steps such as medical image acquisition, segmentation and registration, mitral valve modeling, CFD simulation using the validated flow solver,
analysis and post-processing to derive metrics relevant for clinical diagnostics or to gain fundamental insights into cardiac flows.

**Objective 3: Study the effect of trabeculae and papillary muscles on ventricular hemodynamics**

In this study, the effect of trabeculae on ventricular hemodynamics is examined with a study design that is different from that of Kulp et al. (Kulp et al., 2011). We perform CFD simulations for two different models of the LV derived from high resolution CT data. The first model is a trabeculated LV (TLV) model that includes trabeculae and papillary muscles whereas the second models is a smooth LV (SLV) model where papillary muscles are “excised” and the trabeculae smoothened out during model construction. The use of these two models, which are differentiated almost exclusively by the trabeculae, is expected to provide a more clear delineation of the role of trabeculae on the LV hemodynamics. The previously validated flow solver is employed to perform CFD simulations and the impact of trabeculae on flow propagation, viscous dissipation and ventricular washout is assessed using a number of metrics. In particular, we compare the flow field by visualizing the three-dimensional vortex structures, examine the phase-averaged velocity field along orthogonal long-axis planes and compare kinetic energy related metrics in the ventricular cavity as well as the apical volumes. The effect of trabeculae on the apical washout phenomenon is investigated using “virtual” ventriculography or dye visualization by solving the scalar transport equation.

**Objective 4: Investigate the effect of left atrium on intraventricular flow development**
The objective of the present study is twofold: first, to examine and quantify the effect of the kinematics of flow in the LA on diastolic flow patterns in the LV; and second, to use these simulations to determine the level of fidelity needed in modeling the LA, in studies that are focused on LV flow dynamics. The study design employed here is to compare two LV models, one that includes a physiological LA and the one that does not. In the first model, high resolution imaging data from 4D CT has been used to reconstruct the major chambers of the left heart (LA, LV, and Aorta (Ao)) while the latter model includes only the LV and Ao, with the LA being modeled as a simple pipe created by extruding the mitral orifice along its axis. The mitral valve modeling methodology is based on previously reported prescribed kinematics approach (Ranganathan et al., 1970; Seo et al., 2014) using the leaflet angles measured from the present 4D CT data. High resolution blood flow simulations were performed in these two models by solving the incompressible Navier-Stokes equations using the validated IB method based flow solver. Ventricular flow patterns are compared between these two models using various flow-based metrics and the corresponding differences are quantified. These results are then used to develop insights into the atrial flow and the effect of intra-atrial fluid dynamics on the flow patterns developed in the ventricle.
CHAPTER 2. COMPUTATIONAL FRAMEWORK FOR IMAGE BASED MODELING OF CARDIAC FLOWS

A typical framework for conducting 4D (three spatial dimensions and time) image-based patient-specific simulations of cardiac flows (flows in chamber of the heart, i.e., atrial and ventricles) is presented in Figure 2-1. The procedure begins with obtaining patient-specific anatomical data for the heart via in vivo medical imaging modalities such as Echocardiography, Cardiac Magnetic Resonance imaging (CMRI), or Cardiac Computed Tomography (CCT). The 4D medical images are then processed through a series of steps such as image segmentation and registration to generate a dynamic (moving) computational model of the heart for the flow simulation. At this point, one should also account for modeling the mitral valve given the spatio-temporal limitations to accurately resolve the leaflets directly from the medical images. Once the time-resolved, dynamic 3D CFD-ready heart model has been constructed, the flow simulation is performed by solving the Navier-Stokes equations for incompressible flows. The solver employed in the present research is based on the immersed boundary (IB) method described in Mittal et al. (Mittal et al., 2008; Seo and Mittal, 2011) that employs a Cartesian grid ideally suited for complex moving boundary problems such as the cardiac flows investigated here. Further, the data obtained from these simulations is validated against clinical measurements (Doppler ultrasound measurements or velocity patterns from phase-contrast MRI) or validated through in vitro experiments to obtain high fidelity. Finally, the simulation data is analyzed for clinically relevant metrics such as flow velocities and propagation, wall shear stress and residence times, pressure gradients,
etc. or could also be used for analysis and address fundamental research questions. The following sections describe each stage of the framework in more detail.

**Figure 2-1.** A typical computational framework for patient-specific simulation of cardiac flows

### 2.1. Medical imaging

In principle, the 4D medical images could be acquired through any imaging modality such as Echo, Cardiac MRI, or Cardiac CT-scans. However, the first challenge associated with patient-specific cardiac flow simulation is to ensure that the spatio-temporal resolution of these images is adequate for an accurate representation of the dynamic (moving) 3D heart model. Echocardiography provides excellent temporal resolution (30-100 Hz) which is particularly useful when resolving the rapid movements of structures such as valve leaflets (see Figure 2-2a). This high temporal resolution is typically
obtained in 2D echocardiography while 3D volumetric ultrasound sequences are limited to 20 volumes per second; although, newer methods are being devised to increase this frame rate (Perrin et al., 2012). However, the lower effective spatial resolution in ultrasound images and low signal to noise ratio makes it difficult to clearly resolve fine scale features such as the ventricular trabeculae.

Figure 2-2. (a) Apical four-chamber view of a heart obtained using echocardiography. (b) Axial slice of human heart obtained using 4D Cardiac MRI. (c) Axial slice of human heart imaged using 4D contrast-enhanced Cardiac CT.

On the other hand, modalities such as Cardiac MRI and Cardiac CT provide excellent spatial resolution. Cardiac MRI has an in-plane resolution of 1.5 mm X 1.5 mm, but more limited through-plane resolution of 8 mm (see Figure 2-2b) while CT is capable of high isotropic spatial resolution on the sub millimeter scale (~0.5 mm, see Figure 2-2c). Cardiac MRI has the advantage of higher temporal resolution (30-50 msec) while temporal resolution in Cardiac CT depends on the scanning system (50-200 msec). These are orders-of-magnitude lower than the temporal resolution required for the flow simulation (~10³-10⁴ phases per cardiac cycle) and appropriate interpolation methods need to be employed to create CFD-ready models and therefore, is the first bottleneck in patient-specific cardiac flow modeling. The quality of Cardiac CT can be further
enhanced by contrast-injection which enables clear delineation of lumen and ventricular boundaries including fine structural details such as the trabeculae and papillary muscles; thus, making it ideal for 4D endocardial boundary detection for subsequent computational modeling. On the other hand, larger acquisition times and phase-averaging of multiple beats during Cardiac MRI addition to coarse through-plane resolution pose challenge to extract accurate endocardial motion; although, the in-vivo 4D velocity measurements obtained using phase-contrast MRI could be used for clinical validation.

2.2. Model construction

The procedure for transforming medical images to CFD-ready models is a key contribution of the current work.

2.2.1. Heart model segmentation

The volume images acquired during medical imaging are then subjected to filtering using mean or median filter for noise reduction and contrast enhancement (Rangayyan, 2004) until the blood lumen is clearly distinguished from the tissue. Subsequently, image segmentation is performed to extract the regions of interest (i.e., blood lumen in the chambers of the heart). Depending on the image quality and resolution, the degree of human intervention varies during image segmentation and virtually in no case, can this be fully automated within the pipeline. A number of groups have been working on this aspect and have made significant progress in extracting the blood lumen for subsequent flow modeling. Within the classification of medical image segmentation techniques, region growing methods, parametric active contours (or snakes), and geometric active contours (level set based methods) are generally used for cardiac segmentation
In the present work, segmentation is performed using dynamic region growing algorithm (Rangayyan, 2004) in the commercial software (Mimics, Materialise Inc) owing to the excellent resolution in the Cardiac CT data sets. A result due to such segmentation performed on one of the CT data sets is shown in Figure 2-3 with indicated chambers of the heart and other key anatomical structures.

Figure 2-3. Chambers of heart and other key anatomical features. Figure shows blood lumen extracted from contrast-enhanced Cardiac CT data using region-growing segmentation method. LA/RA: left/right atrium; LV/RV: left/right ventricle; LPVs/RPVs: left/right pulmonary veins; Ao; Aorta; PA: pulmonary artery; LAA: left atrial appendage; MV: mitral valve

2.2.2. Mitral valve (MV) modeling

Mitral valve is unique among all other cardiac valves. The vortices formed on the leaflets of this bileaflet valve assist ventricular filling (Charonko et al., 2013) and also was recently shown to promote “looped flow” in the ventricle that enhances apical washout (Seo et al., 2014). Therefore, inclusion of a relatively accurate model of the
mitral valve is essential to reproducing key features of the ventricular flow. However, as seen in Figure 2-2 and Figure 2-4b the leaflets cannot be clearly delineated due to poor contrast around the thin leaflets in the Cardiac CT data sets. Therefore, we follow an approach presented in (Seo et al., 2014) using a simple prescribed kinematics but physiologically representative valve model. The morphology of the MV has been characterized in Ranganathan et al. (Ranganathan et al., 1970) from a database of about 50 volunteers who had no history of mitral valve disease. The model that was employed in the present study is based on these measurements and is shown in Figure 2-4a. Both anterior (AL) and posterior (PL) leaflets are indicated in Figure 2-4a separated by the commissural axis. One can immediately notice that the present model is a reasonable generalization of the physiological MV with detailed surface geometry such as the scallops present on the posterior leaflet (Ranganathan et al., 1970). Figure 2-4b also depicts a flattened cylindrical projection of the MV with the maximum lengths of each leaflet denoted as $L_{AL}$ and $L_{PL}$, respectively.

Since the MV deforms throughout the cardiac cycle, we have employed a prescribed kinematics valve model without any fluid structure interaction (FSI). This is primarily due to the additional computational cost involved in performing a full FSI simulation. Furthermore, there is still an incomplete understanding of the constitutive model for the extremely complex deformation of the MV and its tissue properties; hence, inclusion of an FSI-based model would introduce additional uncertainties in the simulation results. In the current procedure, we employ a prescribed kinematics model of the mitral valve wherein, the angles made by each of the leaflets with respect to the base of the MV ($\theta_{AL}$, $\theta_{PL}$) are measured from the CT data along an axial slice as shown in Figure 2-4b and is
smoothly distributed across the span of the leaflets (Seo et al., 2014). Although the present model is highly simplified in both its geometry and motion, this viable approach was shown to be a reasonable physiological representative that accurately captures the ventricular flow dynamics of particular interest (Seo et al., 2014).

Figure 2-4. (a) Isometric view and flattened cylindrical projection of the mitral valve whose geometry is based on Ranganathan et al. (Ranganathan et al., 1970). (b) Measurement of mitral valve (MV) leaflet angles with respect to the base or mitral annulus plane with the highlighted left atrium (LA) and left ventricle (LV) in the background. AL: anterior leaflet; PL: posterior leaflet; L\textsubscript{AL}, L\textsubscript{PL}: maximum lengths of AL and PL.

2.2.3. Surface registration and interpolation

The extracted lumen due to image processing and segmentation of the 4D volume imaging data (section 2.1) is represented as a set of triangulated surfaces for each frame over the entire cardiac cycle. However, since each of these volume frames has been processed independently, it is not necessarily guaranteed that the generated triangulated surface maintains the same mesh topology across all the frames. Instead, each surface will most likely have different number of nodes, order of numbering and connectivity. Therefore, it is necessary to register each of these surfaces to a chosen “template” and
create a smooth mapping across all the frames to be able to prescribe this moving surface as a time-dependent kinematic boundary condition for the flow solver.

Figure 2-5. (a) Schematic of volume registration of each “target” cardiac phase with respect to the “template” using large deformation diffeomorphic metric mapping (LDDMM, (Glaunes, Trouve and Younes, 2004; Ardekani et al., 2012)) method. (b) An example mapping of end-systolic state (template, red) with the end-diastolic state (target, blue) using LDDMM.

This mapping can in-principle be accomplished by a variety of surface matching algorithms (McInerney and Terzopoulos, 1995; Salvi et al., 2007; Santamaria, Cordon and Damas, 2011); but, methods such as iterative closest point (Besl and McKay, 1992) and elastic deformation algorithms (Bajcsy and Kovacic, 1989) are not diffeomorphic and are only suited for small local deformations. However, the reconstructed cardiac surfaces of interest in the present model undergo significant change in volume and large deformations. As a matter of fact, the ventricular volume changes by almost 100% of its end-systolic volume during the entire cardiac cycle. Therefore, we employ a diffeomorphic registration algorithm known as Large Deformation Diffeomorphic Metric
Mapping (LDDMM, (Miller, Trouve and Younes, 2002; Beg et al., 2005)). A brief description of the algorithm is provided in Appendix A and the readers are referred to Glaunes et al., (Glaunes, Trouve and Younes, 2004) and Ardekani et al., (Ardekani et al., 2012) for more details on the implementation and the underlying mathematics of the LDDMM algorithm.

A schematic of the surface registration is shown in Figure 2-5a where the “template” is registered to each of the “target” frames (T₁, T₂ ... Tₙ₋₁, Tₙ) using LDDMM to produce the corresponding mapping (M₁, M₂...Mₙ₋₁, Mₙ) during the cardiac cycle. Here N represents the total number of volume frames available in the 4D imaging data and is typically about, N≈20 volume frames per cardiac cycle. Since LDDMM can conveniently support large deformations, one can perform this mapping in parallel where the template is registered with each of the target frames, independently. This is in contrast to other local deformation methods where the output of each mapping is used as a template for the subsequent frame in a sequential manner. In the present study, we have chosen end-systolic state to be the template. An example mapping of the template registered to the end-diastolic state is presented in Figure 2-5b. Initially, one can clearly identify the mismatched regions between the template (red) and the target (blue) especially regions around the left atrial appendage (LAA), left atrium (LA), the lateral side of left ventricle (LV) and the outflow tract (left frame, Figure 2-5b). However, a reasonable agreement between these two surfaces can be seen in the final mapping (right frame, Figure 2-5b) after deforming the template by LDDMM. Currently, it takes about an hour for each mapping on a personal computer with about 52,852 triangular elements on each surface;
but, an efficient parallel implementation of the same can bring this down to a couple of minutes.

Figure 2-6. Dynamic motion of the mitral orifice: (A) Time variation of cross-sectional area of mitral annulus; (B) Schematic of the parameters characterizing the dynamic motion of mitral annulus; (C) Time variation of the displacement of the centroid of the mitral annulus (translation, $\lambda$) during diastole; (D) Time variation of the displacement of the annular ring with respect to the cross-sectional plane passing through the centroid ("warp", $\delta$) during diastole.

We have employed a similar registration procedure for the mitral valve as well because the mitral valve is not fixed at a definite position during the cardiac cycle. Instead, the orifice deforms changing its annular area, undergoes translation and tilt while moving away from the apex. In fact, though counter-intuitive, it is the mitral orifice that recedes away from the ventricular apex during filling whereas the apex is almost stationary (Appleton and Kovacs, 2009; Charonko et al., 2013). Some of these metrics
have been measured in the current 4D CT dataset and are presented in Figure 2-6. The time variation of the cross-sectional area of the mitral orifice (MO) is shown in Figure 2-6A and it is noted that the maximum change in the area during the cardiac cycle is about 18% of the end-systolic state. Further, the dynamic motion of the mitral valve is also characterized in terms of the linear displacement of the centroid (λ) and the displacement of the annular ring with respect to the cross-sectional plane passing through the centroid that represents the “warp” of the mitral annulus. A schematic of these measurements is shown in Figure 2-6B while the measured data is shown in Figure 2-6C and Figure 2-6D for the centroid displacement, λ and annulus warp, δ, respectively during diastole. Although, the presented data represents only an integral first order estimate of the mitral annulus deformation, the data confirms that the annulus indeed undergoes significant deformation during the cycle and underscores the need for a registration similar to the ventricular endocardium.

The LDDMM mapping of the mitral valve is performed with fully opened leaflets before prescribing the kinematic deformation of the leaflets because registering fully opened leaflets results in faster convergence and produces lesser distortion than mapping the valve subsequent to imposing its kinematics. It is to be noted that the end-systolic mitral orifice configuration (in terms of orifice position and size) with fully opened leaflets is used as the template for LDDMM mapping.

As noted earlier, the temporal resolution of the state-of-the art CT scanners (about 20 beats per cycle) is two or more orders of magnitude lower than the CFD requirements of about $10^3$-$10^4$ time steps for a cardiac cycle. Hence, we interpolate the triangulated surfaces in time subsequent to performing LDDMM registration that ensures one-to-one
correspondence between the surface nodes and also preserves mesh topology. This smooth interpolation allows one to extract the triangulated surface at any time instant during the cardiac cycle and hence can be prescribed as a moving wall boundary condition to the flow solver. In the present study, a periodic cubic spline interpolation of the position coordinates of these surfaces in time is performed which ensures continuity of both velocity and acceleration while retaining the periodicity of the cardiac cycle as well.

2.3. Governing equations and CFD solver

It is widely accepted that blood flows in major chambers of the heart can be modeled as Newtonian flow while the non-Newtonian behavior of blood has to be taken into account for small vessels such as capillary flows. Hence, the governing equations for the cardiac flows are the viscous, incompressible, Navier-Stokes equations given by,

\[
\frac{\partial u_j}{\partial x_j} = 0
\]  

\[
\frac{\partial u_i}{\partial t} + \frac{\partial (u_i u_j)}{\partial x_j} = -\frac{1}{\rho} \frac{\partial p}{\partial x_i} + \nu \frac{\partial}{\partial x_j} \frac{\partial u_i}{\partial x_j}
\]

where \( i, j = 1, 2, 3 \) represent the coordinate directions, \( u_i \) are the flow velocity components, \( p \) is the static pressure of the fluid, \( \rho \) and \( \nu \) are the fluid density and kinematic viscosity, respectively. The simulations employ a previously developed immersed boundary solver ViCar3D, and the key components of the solver are described here.

In ViCar3D, the above equations (Eqns. (2-1), (2-2)) are discretized using a second-order, cell-centered, collocated grid arrangement of the primitive variables, \( u_i \) and \( p \). A
central-difference scheme is used to discretize the viscous terms and a linear combination of the second-order central and upwind schemes is employed for the convection terms (Ghias, Mittal and Dong, 2007). Both terms are treated implicitly using a second-order Crank-Nicolson method to eliminate the viscous stability constraint. A variant of the second-order fractional-step method proposed by Zang et al. (Zang, Street and Koseff, 1994) is used to solve the above governing equations (Eqns. (2-1), (2-2)) on a non-body-conformal Cartesian grid. Briefly, the solution methodology consists of three sub-steps: in the first step, the solution is advanced by solving the advection-diffusion equation (Eqn. (2-3)) to obtain an intermediate velocity field ($u_i^*$). Subsequently, a conjugate gradient based BiCGSTAB method (Van der Vorst, 1992) with Jacobi preconditioner is employed to solve the pressure Poisson equation (PPE, Eqn. (2-4)) to obtain the pressure correction ($p'$). Finally, the velocity fields are updated using the corrected pressure (Zang, Street and Koseff, 1994; Mittal et al., 2008) while the cell-centered velocity ($u_i$) and face-centered velocity ($U_i$) fields are updated separately (Eqns. (2-5), (2-6)).

$$\frac{u_i^* - u_i^n}{\Delta t} = \frac{1}{2} \left( - \frac{\partial(U_j u_i)}{\partial x_j} + \nu \frac{\partial}{\partial x_j} \frac{\partial u_i}{\partial x_j} \right)^* + \frac{1}{2} \left( - \frac{\partial(U_j u_i)}{\partial x_j} + \nu \frac{\partial}{\partial x_j} \frac{\partial u_i}{\partial x_j} \right)^n$$ (2-3)

$$\frac{1}{\rho} \frac{\partial}{\partial x_j} \frac{\partial p'}{\partial x_j} = - \frac{1}{\Delta t} \left( \frac{\partial U_i^*}{\partial x_i} \right)$$ (2-4)

$$u_i^{n+1} = u_i^* - \frac{\Delta t}{\rho} \left( \frac{\partial p'}{\partial x_i} \right)_{cc}$$ (2-5)

$$U_i^{n+1} = U_i^* - \frac{\Delta t}{\rho} \left( \frac{\partial p'}{\partial x_i} \right)_{fc}$$ (2-6)

where, $\delta$ is the central differencing operator. It is noted that this separate update of cell-centered (cc) and face-centered (fc) velocity fields has been shown to achieve
discrete mass-conservation to machine zero by Zang et al. (Zang, Street and Koseff, 1994). Additionally, this approach has the advantage of having the simplicity of non-staggered grid, cell-centered approach. The present simulations employ about 30% second-order upwinding to control numerical dispersion errors as explained in Ghias et al. (Ghias, Mittal and Dong, 2007).

The flow solver employs a sharp-interface immersed boundary (IB) method based on the multi-dimensional ghost-cell methodology (GCM) described in Mittal et al. (Mittal and Iaccarino, 2005; Mittal et al., 2008; Seo and Mittal, 2011) well suited for flows associated with complex moving and deforming bodies. Immersed boundaries are represented by surface meshes with triangular elements and these boundaries are immersed in a Cartesian grid that covers a cuboidal domain (see Figure 2-7a). Further mathematical treatment of GCM and the implementation of the boundary conditions can be found in Mittal et al. (Mittal et al., 2008; Seo and Mittal, 2011). The velocity boundary conditions on the endocardial surface is given by the 4D kinematic heart model constructed by the method described in the previous section (2.2). These boundary conditions on the endocardial surface are imposed by a multi-dimensional ghost cell method (Mittal et al., 2008) as shown in Figure 2-7b. The boundary condition on the body-intercept point is satisfied by imposing the value on the ghost cell. The value at the ghost cell is obtained from the image point which is computed by the interpolation of the values on the surrounding fluid cells. Further details regarding this method can be found in Mittal et al. (Mittal et al., 2008; Seo and Mittal, 2011).
Figure 2-7. (a) Triangulated surface of a two chamber model of the left heart immersed into the background Cartesian volume grid. Chambers include left atrium (LA), left ventricle (LV) and a portion of outflow tract. (b) Schematic of the ghost cell method for the immersed boundary treatment.

It is also important to formulate the various non-dimensional numbers that are relevant to the cardiac flows. The flow Reynolds number, $\text{Re} = \frac{U_m D_{MO}}{\nu}$, is defined based on the peak area-averaged flow velocity at the mitral orifice ($U_m$), diameter of the mitral orifice ($D_{MO}$) and kinematic viscosity of blood ($\nu$). Another important number that signifies the pulsatility in the flow is the Womersley number, $\text{Wo} = \frac{D_{MO}}{\sqrt{\nu T}}$ where $T$ is the duration of the cardiac cycle. Formation of the vortex ring at the tips of the mitral valve leaflets is now very well established (Bellhouse, 1972; Kilner et al., 2000; Pedrizzetti and Domenichini, 2005; Long et al., 2008; Pasipoularides, 2010; Mihalef et al., 2011; Le et al., 2012; Toger et al., 2012; Charonko et al., 2013; Seo and Mittal, 2013) and the optimality of this vortex formation in terms of efficient mass and momentum transfer is represented using a non-dimensional number called, the vortex formation number (Gharib et al., 2006). It is evaluated as, $\Lambda_E = \frac{V_d}{(A_{MO} D_{MO})}$, where $V_d$ is the
volume of the blood discharged through the mitral orifice during E-wave and $A_{MO}$ is the area of the mitral orifice (Gharib et al., 2006).

### 2.4. Flow metrics

A number of derived metrics associated with the computed flow field are used to investigate the various objectives of the present research. The three-dimensional vortical structures are visualized using $\lambda_c$ criterion, defined as the isosurfaces of the complex imaginary eigen values of the velocity gradient tensor (Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005). Physically, this represents the swirl strength or rotation of particles at a given point in space and these are visualized for a qualitative understanding of the complex three-dimensional vortical flow in the atrial and ventricular cavities at various phases of the cardiac cycle. Phase-time-averaged flow fields are plotted along two orthogonal planes aligned with the mitral axis and are compared between various models under consideration. In particular, velocity vectors are visualized superposed over color-maps of the magnitude of the flow velocity. These provide a qualitative understanding of the flow propagation, circulatory flow patterns in the ventricle, wall interaction especially due to ventricular trabeculae and also could be used to identify regions of low flow velocity (or stasis) with in the ventricular cavity which has implications for clot formation. In fact, clot formation is a function of both flow stasis and blood residence times usually found in wall-bounded recirculatory flows.

However, a detailed quantitative analysis is also essential to complement the qualitative understanding and explain any discrepancies, if any, between the various flow patterns under consideration. Phase-averaged velocity profiles are compared along various transverse segments of the orthogonal planes, aligned with the mitral axis, at
different phases of the cardiac cycle. The differences exhibited by these profiles are quantified using $L_1$ norm expressed as percentages of the reference velocity corresponding to the peak flow rate through the mitral orifice ($U_m$) in addition to the normalized peak differences.

Wall shear stress $\left( \tau_w = \mu \frac{\partial \bar{u}}{\partial n} \right)$ has a strong correlation with the residence time of blood and clot formation, where $\mu$ is the dynamic viscosity of the blood and $n$, the unit normal vector at the wall. Regions of low flow velocity and low strain rates such as near-wall vortices or the interstitial gaps between the trabeculae have tendency to form lumps of blood due to stasis and longer residence time of blood particles caught in these vortices. Magnitudes of time averaged wall shear stress (AWSS) and time variation of area-averaged ventricular surface shear stress ($\tau'_w$) are compared between the two models. These are defined as, $AWSS = \frac{1}{T} \left| \int_0^T \tau_w \, dt \right|$ and $\tau'_w = \frac{1}{S_{LV}} \iiint |\tau_w| \, dS_{LV}$ where, the time integral is performed during diastole while the surface area ($S_{LV}$) is the area of the left ventricular surface alone. It is to be noted that the shear stress is resolved along Cartesian directions before performing time integration as the element normal vector on the ventricular surface changes its orientation with time.

As indicated earlier, one key issue to be explored here is the effect of trabeculae on pressure losses inside the ventricle. In this regard, we compute metrics related to the energy budget such as volume averaged kinetic energy density $\left(KE_{LV}' = \frac{1}{2V_{LV}} \iiint \rho \bar{u}^2 \, dV\right)$ and rate of dissipation per unit volume.
\[
\Phi'_{LV} = \frac{1}{V_{LV}} \iiint 2\mu : \varepsilon dV,
\]
where \( \varepsilon \) is the deformation gradient or the strain rate tensor and \( V_{LV} \) is the volume of the ventricular blood, and compare these between the two models. Recent studies have indicated that the hemodynamics of a healthy heart are designed to ensure efficient washout of blood from all the corners of the ventricle (Watanabe, Sugiura and Hisada, 2008; Seo and Mittal, 2013; Seo et al., 2014); this is particularly true for the apical region of the ventricle which is furthest away from the mitral inlet and therefore, more prone to flow stasis. We examine the effect of trabeculae on washout and residence time via metrics such as the volume averaged kinetic energy of the blood in the apical region \( KE'_{Ap} \) where, \( KE'_{Ap} \) is computed in a way similar to \( KE'_{LV} \) except that the volume averaging is performed over the apical volume designated as the region below \( Z=4 \) cm level with reference to Figure 4-3.

To further isolate the effect of the trabeculae on apical washout, we also employ “virtual” ventriculography near the apical region of the ventricular cavity. This is accomplished by modeling the transport of a passive scalar initialized in the apical volume of the LV cavity at end-systole (see Figure 4-3c). This involves solving the scalar transport equation using the background flow velocity mimicking the process of contrast visualization. If \( \psi \) is the concentration of the passive scalar per unit volume, then its evolution is governed by the convection-diffusion equation,

\[
\frac{\partial \psi}{\partial t} + \vec{u} \cdot \nabla \psi = \nabla \cdot (\kappa \nabla \psi)
\]

where \( \kappa \) is the mass diffusivity coefficient which is typically very small \( (10^{-9} \text{m}^2/\text{s}) \) so that the Schmidt number (Sc), defined as the ratio of viscous diffusivity to mass
diffusivity is $Sc=3300$. The above equation is solved in the same immersed boundary setting as a post-processing step throughout the cardiac cycle. Additionally, quantitative metrics associated with the scalar field, \textit{i.e.}, the time variation of the mean scalar field $\left\langle \psi_{avg} \right\rangle = \frac{1}{V_{Ap}} \iiint \psi dV$ and the root mean square (RMS), $\left\langle \psi_{rms} \right\rangle = \sqrt{\frac{1}{V_{Ap}} \iiint \psi^2 dV}$ within the apical cavity are compared between the two models. While the spatial mean $\left\langle \psi_{avg} \right\rangle$ can be average washout, $\left\langle \psi_{rms} \right\rangle$ emphasizes pockets of high scalar concentration in the apical cavity and is indicative of mixing.

The color M-mode (CMM) of Doppler assessment of flow propagation velocity ($V_p$) is routinely used in clinical cardiology to assess ventricular diastolic function (Nagueh et al., 2009). As such, it is useful to assess the accuracy of the simulated flow via this modality. In clinical practice, the color M-mode is acquired by aligning the ultrasound probe in the direction from the ventricular apex to the mitral annulus and the principle of Doppler shift is used to estimate the flow velocity directed towards the apex along the entire long axis of the ventricle (Garcia et al., 1997; Nagueh et al., 2009). However, in the present computational study, we follow a procedure that has been used in previously reported studies (Vierendeels, Dick and Verdock, 2002; Seo et al., 2013; Seo et al., 2014) to create a “virtual” CMM using the simulation data. In this method, the longitudinal component of velocity along the mitral axis from base to apex is extracted directly from the simulation data. We note that this method of computing CMM based on computational modeling has not been validated; although, a qualitative comparison with a simple Doppler ultrasound model has been provided in Seo et al. (Seo et al., 2013).
The velocity information obtained from this virtual CMM is then plotted with time as abscissa and the distance from the base to apex as ordinate and appropriately color-coded. \( V_p \) is then determined by the slope of the first aliasing velocity (transition from blue to red on the color-map) where the aliasing limit is set to 50-70% of the maximal velocity spread distally 4cm into the LV cavity (Garcia et al., 1997). The ratio of \( V_p \) to the peak E-wave flow velocity (\( V_E \)) was shown to be a potential marker of diastolic dysfunction (Garcia et al., 1997; Vierendeels et al., 2000; Boeck et al., 2005). We analyze this metric to develop insights into the flow propagation from the mitral annulus into the ventricular cavity. In addition to this, we also probe the location of the core of the vortex ring superposed on the CMM. The slope of a linear fit to this curve represents the vortex propagation velocity, \( \omega_p \) which is also computed for comparison in the present analysis.
CHAPTER 3. VALIDATION OF THE SIMULATION OF VENTRICAL FLOWS

3.1. Introduction

Despite the fact that the computational modeling of intraventricular flows is now relatively well established, no study has, to our knowledge, focused on a comprehensive quantitative validation of such models (see sections 1.2 and 1.3.1). Saber et al. (Saber et al., 2003) and Schenkel et al. (Schenkel et al., 2009) have made qualitative comparison of their computed results with velocity fields reconstructed from two-dimensional MRI data sets for healthy hearts. Qualitative comparison of computed velocity and vorticity fields with experimental data has also been made by Domenichini et al. (Domenichini et al., 2007) and Doenst et al. (Doenst et al., 2009). The former has used a patient-specific model generated from cine MRI to validate their model, while the latter performed validation using a simplified laboratory LV model. Recently, Krittian et al. (Krittian et al., 2010) compared intraventricular flow patterns and ventricular wall deformation between in-vivo MRI data, laboratory experiment and a CFD-FSI based simulation employing the Karlsruhe heart model (Krittian et al., 2010). However, they noted experimental limitations in obtaining realistic ejection fractions and Reynolds numbers; in addition, the comparison was mostly qualitative in nature (Krittian et al., 2010).

With an eventual goal of developing a CFD-based method to analyze patient-specific heart function, our first step is to quantitatively validate the hemodynamic flow solver using a simple laboratory model of the left ventricle. Our numerical solver is based on a sharp-interface immersed boundary method (Mittal and Iaccarino, 2005; Mittal et al., 2008; Seo and Mittal, 2011), which has been described in section 2.3. The laboratory
model of the left ventricle employed here has already been used earlier for investigation of intraventricular flows (Querzoli, Fortini and Cenedese, 2010; Espa et al., 2012; Vukčević et al., 2012; Fortini et al., 2013). In the present study, quantitative comparisons of computed phase-averaged velocity and vorticity profiles for this simplified LV model are performed and the results are used to assess the limitations and challenges associated with conducting such simulations. The validated simulations are then used to analyze the intraventricular flow; the analysis is based on velocity and vorticity distributions as well as the flow wave propagation velocity (\(V_p\)) obtained using “virtual” color M-mode (CMM) echocardiography. We relate \(V_p\) with respect to the propagation of the vortex ring (\(\omega_p\)) which was earlier categorized in Vierendeels et al. (Vierendeels, Dick and Verndock, 2002).

### 3.2. Methods

#### 3.2.1. Experimental setup and parameters

The experimental measurements have been performed in the pulse duplicator shown in Figure 3-1a. This setup has been employed in previous studies (Querzoli, Fortini and Cenedese, 2010; Espa et al., 2012; Vukčević et al., 2012; Fortini et al., 2013) and therefore, we provide only a brief description here. The ventricle (labeled V in Figure 3-1a) is flexible and made of silicone rubber that allows easy optical access. The ventricle is secured on a 56mm diameter circular plate (Figure 3-1b) and connected to a constant head reservoir via two plexiglass tubes which serve as the mitral and aortic conduits. Two one-way hydraulic valves are mounted inside these conduits in order to simulate the function of native heart valves- the valve in the mitral conduit only allows flow into the ventricle (Querzoli, Fortini and Cenedese, 2010; Fortini et al., 2013) and the valve in the
aortic conduit opens outward to allow only outflow. The entire ventricular assembly is housed inside a transparent plexiglass rectangular tank (labeled T in Figure 3-1a). Changes in the volume of the ventricle are driven by moving the piston (labeled P in Figure 3-1a), which is driven by a linear motor (labeled M in Figure 3-1a). The linear motor is controlled by a personal computer by means of a speed-feedback servo-control and this allows for the control of the time-rate-of-change of the ventricular volume.

Figure 3-1. Experimental setup and configuration: (a) Schematic of the setup used in the experiment. (b) Simplified laboratory model of the left ventricle (LV) made of silicone
rubber used in the experiment. (c) Time variation of the change in volume of the ventricle (ΔV(ml)) with the indicated cardiac phases.

The procedure for 3D reconstruction of the ventricular flow used in the experiments is explained in detail in Fortini et al. (Fortini et al., 2013). The working fluid (distilled water) inside the ventricle is seeded with neutrally buoyant particles with a mean diameter of 30μm. A high-speed camera (Mikrotron3620, F = 250 frames/s, 1280x1024 pixel resolution) is triggered by the motor to capture images of the seeded flow at chosen time-instants during the cycle. The acquired images are then analyzed to estimate the velocity fields over a regular grid by means of a feature tracking algorithm (Querzoli, Fortini and Cenedese, 2010). A series of 2D measurements over parallel planes are extracted and used to reconstruct the 3D flow. The temporal and spatial resolutions of this acquisition are 4ms and 0.12 mm, respectively, and these are adequate to identify the vortical structures generated in the left ventricle and to follow their evolution during the cardiac cycle. Ventricular filling (diastole) is a biphasic phenomenon characterized by early filling (the “E-wave”) that corresponds to ventricular relaxation and a second peak (the “A-wave”) that is driven by the contraction of the left atrium. The interim phase, when the ventricle volume remains nearly constant, is referred to as “diastasis”. Filling is followed by ejection (systole). The experimental setup attempts to reproduce these key features of left-ventricular diastole and systole. In Figure 3-1c, the change in ventricular volume (ΔV(ml)) is plotted as a function of normalized time, $t^* = t/T$ where, T is the period for one cardiac cycle. The key phases in the cardiac cycle relevant to the present investigation are also shown in Figure 3-1c. The experiments are continued for 50 cardiac cycles and the data is phase-averaged over these cycles.
Figure 3-2. Details of the computational model employed in the current validation study. (a) Reference planes depicted along the top view of the model LV. (b) Images of the model LV acquired during experiment along A-A' and B-B' planes are enhanced (Gaussian filter) and thresholded for ventricular edge detection. (c) Reconstructed LV from the detected edges of A-A' and B-B' planes and approximating a circular cross-section axially. Nomenclature has been indicated for end-diastolic (EDV) and end-systolic (ESV) states. (d) Triangulated ventricle (124,340 elements) immersed into the background Cartesian grid.
3.2.2. Computational model of the laboratory left ventricle

The present computational LV model is generated using biplanar images from the experiment along two orthogonal directions, referred to as A-A' and B-B' in Figure 3-2a. These images are enhanced by filtering followed by thresholding and subsequently, the edges of the ventricle in each plane are detected from the zero-crossings of the second-derivative of the image intensities (Rangayyan, 2004) as shown in Figure 3-2b. Once the edges were detected along A-A' and B-B' planes, three-dimensional reconstruction is accomplished by fitting a circle at each axial plane. The center of the circle along each of these transverse planes is located at the intersection of A-A' and B-B' planes while the radius is determined by an average of the distances from the center to the detected edges. Figure 3-2c shows the reconstructed LV at end-diastole (EDV) and end-systole (ESV). The segmentation approach described above is carried out for 1500 frames during one cardiac cycle, resulting in a 4D (3D + time) reconstruction of the ventricular lumen. The surface of the LV model is represented by an unstructured grid with 124,340 triangular elements and this time-evolving surface is “immersed” into the Cartesian grid as shown in Figure 3-2c. The surface velocity is computed by differentiating the element coordinates in time and then prescribed to the solver as a time-dependent velocity (kinematic) boundary condition.

3.2.3. Uncertainty in ventricular model extraction

The above procedure is subject to two main sources of uncertainty and error. The first source of error arises from the thresholding of the lumen boundary. As it is clear from Figure 3-2b, the LV boundary appears as a pixelated region with a finite thickness due to imaging artifacts, and in principle, the position of the actual LV lumen could lie
anywhere in the thin white pixelated band. Analysis of these images shows the thickness of this pixelated band is up to 2.0 mm which is about 8% of the average LV radius. The second source of error is associated with the assumption of a circular cross-section at each axial location of the LV lumen and we note a maximum deviation of the mean radius from the outer edges of either A-A’ or B-B’ to be about 3% of the mean LV radius. A major consequence of the above errors is that they introduce spurious temporal gradients in the endocardial velocity and thereby, in the computed flow rate in and out of the LV. One way to alleviate this is to apply “smoothing” to the motion of the LV boundary; however, this introduces a number of ad-hoc parameters and also does not ensure that the resulting flow rate will match the flow rate in and out of the LV as measured at the mitral inflow and aortic outlet of the LV. The matching of this velocity, especially the inflow at the mitral annulus, is crucial in order to be able to conduct a successful validation of the simulations. A decision was therefore made to directly match the segmented volume with the integral of a “target” flow rate at the mitral annulus, and adjust the LV motion to be consistent with this flow rate.
Figure 3-3. Comparison between: (a) Input flow rate ($Q_{in}$ (motor)) and measured flow rate ($Q$). ($\Delta Q$) is the uncertainty in the measured flow rate prescribed to the simulation ($Q$) due to axisymmetric approximation. For clarity of comparison, the $\Delta Q$ curve is shifted by 20ml/s on the plot along the positive ordinate; (b) Volume of LV computed directly from the segmentation procedure ($V_0$) and the integral of “target” or measured flow rate at mitral inlet, $\int Qdt$.

### 3.2.4. Ventricular volume and flow rate

The “target” volume flow rate at the mitral annulus was initially chosen to be the rate-of-change of volume prescribed to the piston motor of the experiment ($Q_{in}$ (motor), dotted line in Figure 3-3a. However, simulations conducted using $Q_{in}$ (motor) as the target, produced vortex propagation speeds that were noticeably lower than those in the experiment. The flow rate was then estimated directly from the PIV measurements at the mitral annulus by using an average of the measurements along the A-A' and C-C' planes (see Figure 3-6a for planar configuration) assuming an axisymmetric flow; this flow rate profile is also shown in Figure 3-3a as a solid line ($Q$) and it is easily verified that the actual flow rate profile at the mitral inlet is significantly different from $Q_{in}$ (motor) in both amplitude and phase. For systole, the flow rate profile was estimated based on outflow measured at A-A' plane. An axisymmetric flow was then assumed for the
outflow as well and the contraction rate is multiplied by a factor (equal to the ratio of the total inflow to the integral of predicted systolic flow rate) to match the net inflow or stroke volume. Also shown in Figure 3-3a is the error ($\Delta Q$) associated with the assumption of axisymmetry at the mitral inflow. This is computed as the difference between the flow rates estimated from the profiles along the A-A' and C-C' planes and we note errors up to 11% of the peak diastolic flow rate. This error introduces inherent uncertainty into our computational model, and this needs to be kept in mind while making comparisons with the experimental data.

Figure 3-3b shows the time variation of the LV volume, $V_0$, obtained directly from the segmentation compared to the integral of the measured flow rate at mitral inlet (denoted as $\int Q dt$ on the plot). It is clear that there is a mismatch between the two and in fact, analysis indicates this mismatch is up to 5.3% of the mean LV volume. However, due to the incompressibility constraint, it is necessary that the two volumes have to match each other at each time-step; therefore, we accomplish this by adjusting the LV boundary at each time-step. To elaborate, we use an iterative procedure where the segmented volume of the ventricle ($V_0$ in Figure 3-3b) is modified at selected key frames to match this integral ($\int Q dt$). In this iterative process, the radius of the circular cross-section at each axial location of the segmented LV is changed until the LV volume matches the target volume within a prescribed tolerance. We have chosen 125 frames over one cardiac cycle to apply this volume-matching procedure and this enables us to obtain a reasonably smooth variation in the resulting flow rate curve. The iterative method converges rapidly for the current problem and a pseudo code for this procedure is provided as follows:
start
for n from 1 until no_key_frames do
  Determine target volume, \( V_T(n) \)
  Determine initial volume, \( V(n) \)
  Determine initial radius at each axial cross-section, \( R(k,n) \) of \( V(n) \)
repeat until convergence
  for k from 1 until no._axial_sections do
    Update radius, \( R(k,n) \) using relaxation parameter, \( \beta \) as,
    \[
    R(k,n) \leftarrow R(k,n) + \beta R(k,n)(V_T(n) - V(n))/V(n)
    \]
  end k – loop
  Determine modified volume, \( V(n) \) using new radius, \( R(k,n) \)
  check if convergence is achieved
end repeat
end n – loop
stop

The presence of valves is modeled in the simulations by opening and closing the far ends of the mitral and aortic annuli. During diastole, the mitral orifice is kept open by imposing a zero gradient on the velocity and a Dirichlet condition for pressure while the aorta is closed using a no-slip, no-penetration boundary condition. Conversely, during systole, the mitral annulus is closed while the aorta is opened by interchanging the aforementioned boundary conditions. For the sake of simplicity, the Dirichlet value for pressure at the inflow boundaries is set to 0; this will have no effect on the pressure gradients in the flow. It is to be noted that the phase-average in the simulations is computed over 5 cardiac cycles, while the experiment estimates the phase-average over 50 cycles. It is also noted that the phase-average in the simulations does not show any significant cycle to cycle variation beyond the first two cycles. The shorter duration of
phase-averaging in the simulations is due partly to the limitations of computational time and resources, and also to the fact that there is greater inherent uncertainty and cycle-to-cycle variation in the experiment compared to the simulation which necessitates additional filtering. Certain key non-dimensional parameters relevant to the present experimental validation study are indicated in Table 3-1.

Table 3-1. Key parameters used for the simplified laboratory left ventricle (LV) model.

<table>
<thead>
<tr>
<th>Re</th>
<th>Wo</th>
<th>SV (ml)</th>
<th>EF (%)</th>
<th>E/A</th>
<th>ΔE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3475</td>
<td>9.7</td>
<td>60.0</td>
<td>40.0</td>
<td>3.0</td>
<td>3.94</td>
</tr>
</tbody>
</table>

### 3.2.5. Grid convergence study

In order to ensure adequate spatial accuracy, numerical simulations have been performed on four different computational grids: (a) very coarse (64x64x128); (b) coarse (96x96x192); (c) medium (128x128x256); (d) fine (256x256x512). The size of the time-step (Δt) in the simulations is varied appropriately (0.0004T – 0.0001T) for each chosen grid so that the maximum Courant-Friedrichs-Lewy (CFL) number is about 0.3. Figure 3-4a shows a comparison of the profiles of the three velocity components along the mitral axis during the deceleration phase of the E-wave (t*=0.22) and Figure 3-4b shows a comparison of the total kinetic energy of the fluid in the LV cavity (excluding mitral and aortic channels) as a function of time for the chosen grids. Additionally, time variation of area-averaged wall shear stress (τw) is also compared for the chosen grids in Figure 3-4c. A reasonable convergence was achieved on the fine grid for this highly transitional flow. However, due to limitations of computational time and resources, we have computed the
flow on the fine grid only for one cycle. Hence, we use the fine grid only for understanding the flow and the vortical features while the medium grid is chosen for conducting simulations over multiple cycles and the phase-averaged data is used for comparison against the experiments.

Figure 3-4. Results due to grid convergence (Very Coarse - 64x64x128; Coarse - 96x96x192; Medium - 128x128x256; Fine - 256x256x512). (a) Comparison of velocity components along the centerline of the mitral orifice during deceleration of E-wave, $t^*=0.22$. (b) Time variation of the total kinetic energy in the LV cavity (excluding mitral and aortic channels) for all the chosen grids. (c) Time variation of area-averaged wall shear stress ($\tau'_w$) computed over the ventricular surface for the chosen grids.
3.3. Results and Discussion

3.3.1. Vortical features

The intraventricular flow field in the simplified laboratory LV model is visualized using 3D vortex structures identified by the $\lambda_{ci}$ criterion, which is defined as the imaginary part of the complex eigen values of the velocity gradient tensor (Chong, Perry and Cantwell, 1990; Jeong and Hussain, 1995; Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005). The isosurfaces of this quantity plotted in Figure 3-5 for $\lambda_{ci}=10s^{-1}$, are color-coded by the longitudinal component of velocity and the corresponding cardiac phase is also indicated in each frame as a highlighted circle on the flow-wave form. It is noted that during the first cycle, filling takes place into a static fluid chamber i.e., the fluid inside the ventricular model is initially stationary without any remnants.

It has been well established that under normal resting conditions, a vortex ring is formed inside the human left ventricle during filling (Hong et al., 2008; Pasipoularides, 2010; Mihalef et al., 2011; Le and Sotiropoulos, 2012; Sengupta et al., 2012; Toger et al., 2012; Charonko et al., 2013; Seo and Mittal, 2013; Chnafa, Mendez and Nicoud, 2014). In line with this, we notice a strong vortex ring formed at the mitral orifice at the peak of E-wave in Figure 3-5A. The formation number of this E-wave vortex ring is $\Lambda_E=3.94$ and we observe that this strong vortex ring pinches off from the base of the LV and convects towards the apex. The trailing shear layers behind the vortex ring are nearly nonexistent and this is in alignment with the fact that the $\Lambda_E$ is very close to the “optimal” value of 4.0 (Gharib et al., 2006). Early in the vortex ring formation and propagation (Figure 3-5B), the ring interacts with the lateral wall of the ventricle causing it to tilt. Continued
interaction of the ring with the lateral wall leads to disruption of the vortex ring (Figure 3-5C) and a further tilting allows the left side of the vortex ring to fill up the central cavity of the ventricle (Figure 3-5C).

Figure 3-5. Time evolution of three-dimensional vortical structures of the intraventricular flow visualized using $\lambda_{ci}$-criterion (Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005) as the isosurfaces of imaginary part of complex eigen values of the velocity gradient tensor colored by the longitudinal component of velocity for value, $\lambda_{ci}=10$ s$^{-1}$ at the indicated times.

Subsequently, the vortex impinges on the right wall and disintegrates completely leading to the formation of smaller eddies that fill up the ventricular cavity (Figure 3-5D). From this point onwards, the flow exhibits traits of transition with a strong cascade of eddies of various length scales as evident in Figure 3-5D-G. However, due to the overall
circulation being established in the clockwise direction, the fluid inertia pushes these 
dissipating eddies towards the aorta by the end of diastasis (Figure 3-5E, Figure 3-5F).
Although the present model is very simplistic, flow features described here have also 
been identified in 4D patient-specific models (Mihalef et al., 2011; Le and Sotiropoulos,
2012; Toger et al., 2012; Chnafa, Mendez and Nicoud, 2014). Following this, the atrial 
filling due to A-wave produces a weak vortex near the mitral orifice which immediately 
interacts with the remnants of the E-wave vortex (Figure 3-5G). The weak A-wave vortex 
does not seem to play any role in re-energizing the dissipating eddies in the ventricular 
cavity. By the end of the filling, the stronger eddies which appeared during diastole seem 
to have been mostly dissipated. Systole ensues during which the fluid gets smoothly 
ejected through the outflow tract (Figure 3-5H) that acts as a “sink”. The vortex 
structures that remain at the end of the diastole get stretched and aligned with this 
outwardly directed flow.

3.3.2. Validation with experimental data

3.3.2.1. Velocity profiles comparison

Phase-averaged velocity profiles along the A-A' plane are compared between the 
simulation and the experiment at various phases of the cardiac cycle in Figure 3-6. The 
vertical component of velocity is plotted along three horizontal cross-sections (H₁, H₂, H₃) 
while the lateral component of velocity is plotted along three vertical cross-sections (V₁, 
V₂, V₃) of A-A' plane (see Figure 3-2a for plane configuration). The experimental data is 
shown as symbols while the numerical data is plotted using solid lines. A visual 
comparison of the two sets of profiles indicates that the simulation reproduces all the key 
features of the experimental velocity profiles reasonably well. Some general trends
observed are that the primary differences between the experimental and simulated flow profiles are in the vertical component of velocity in early- and mid- diastole and that these differences are mostly concentrated in the region near the lateral wall of the ventricle. It is also noted that the velocity profiles from the simulation are relatively smooth at all phases except for $t^* = 0.56$, where the simulation data are significantly “rounder” than the experimental ones.

Figure 3-6. Comparison of profiles of phase-averaged longitudinal (red) and lateral (blue) components of velocity between the computational data and that of the experiment (symbols) at various cross-sections of the LV along the A-A' plane (see Figure 3-2a) at the indicated non-dimensional times. Reference vectors in frames A and D correspond to 10 cm/s along each coordinate direction.
Quantitative comparisons of the velocity profiles are performed in Table 3-2 that shows error measured as the L₁ norm of the difference in the velocity profiles between the simulated and experimental data sets normalized by the peak area-averaged flow velocity through mitral orifice (Uₘ=15.5cm/s). This is computed for each of the designated sections on the A-A' plane and at the corresponding time as shown in Table 3-2. We notice that except for two profiles (H₁ at t*=0.172 and V₂ at t*=0.22, 0.28, 0.36), the difference between these datasets is less than 10% elsewhere. The highest error is 15% and this occurs for V₂ at t*=0.36. It should be noted that the uncertainty in the estimation of the diastolic flow rate (as described in section 3.2.4) is about 11% of the peak diastolic flow rate. Thus, the level of discrepancy between the two velocity profiles is very much in line with this inherent uncertainty in the modeling procedure.
3.3.2.2. Out-of-plane vorticity comparison

In Figure 3-7 and Figure 3-8, we compare contours of phase-averaged out-of-plane vorticity on A-A' and B-B' planes, respectively at the indicated non-dimensional times. The plots in the top row correspond to the simulation while the bottom row shows the corresponding plots for the experiment. A visual comparison indicates a reasonable agreement in the overall vorticity pattern between the simulation and the experiment at all these phases of the cardiac cycle on both these planes. In Figure 3-7, the comparison of the clockwise (blue/left contours) rotating vorticity is particularly good; the shape as well as the location of the clockwise vorticity matches well at these phases of diastole. On the other hand, the comparison between the counter-clockwise (red/right contours) rotating vorticity may be considered good only up to t*=0.22. At t*=0.28 it is noted that the shape of this vortex is not predicted well and at t*=0.36, the simulation does not accurately capture the location and size of this vortex. Beyond this phase in the cardiac cycle, the magnitude of the peak vorticity drops to exceedingly low values, thereby making a comparison of this quantity very difficult. The comparison of both clockwise and counter-clockwise vorticity agrees reasonably well along B-B' plane in terms of magnitude, phase and the location of the vortex as shown in Figure 3-8. However, a careful observation reveals a slight tilt of the vortex ring in the experiment (t*=0.22&0.28) while the simulation predicts a nearly symmetric vortex structure.
Figure 3-7. Comparison of the computed phase-averaged out-of-plane vorticity (top row) with the corresponding phase-averaged data from the experiment (bottom row) along the A-A' plane (see Figure 3-2a) at various non-dimensional times.

It was earlier noted that the majority of the larger differences in the two velocity profiles (Figure 3-6) are localized to the region near the right (or lateral) wall of the ventricle. This mismatch is clearly correlated with the mismatch of the portion of the vortex ring closer to the lateral wall as evident from Figure 3-7. It can be seen here that the right vortex decays faster in the simulation due to its interaction with the wall while it persists much longer in the experiment. This vortex-wall interaction is highly sensitive to the precise location and motion of the lateral wall relative to the inflow jet. Our assumption of a locally circular cross-section (sections 3.2.2, 3.2.3) as well as our method to match the ventricular volume to the measured flow rate (section 3.2.4) are expected to introduce discrepancies in the exact location of the ventricular walls and would modify the vortex-boundary layer interaction in this region.
Figure 3-8. Comparison of the computed phase-averaged out-of-plane vorticity (top row) with the corresponding phase-averaged data from the experiment (bottom row) along the B-B’ plane (see Figure 3-2a) at various non-dimensional times. The dark circle indicates the location of the core of the vortex used for computing ωp.

Furthermore, it is noticed from Figure 3-6A and Figure 3-6B that there is a horizontal shift in the mitral jet between the experiment and simulation, with the jet in the simulation being directed closer to the right wall. Given that the jet in the simulation is centered along the axis of the mitral annulus (Figure 3-6A), this implies that the difference is due to a slight jet tilt in the experiment from the centerline of the mitral annulus. A slight tilt in the mitral flow is also evident in the vorticity structure shown in Figure 3-8 along B-B’ plane. The cause for this tilt in the experiment is not clear but likely has to do with a slight asymmetry in the flow exiting the mitral inflow pipe that is not captured in the simulation. The leftward shift of the jet in the experiment provides a
larger area for the growth of the near-wall portion of the vortex ring and leads to a stronger counter-clockwise vortex in that region (Figure 3-7B-D).

![CMM for simulation](image1.png)  ![CMM for experiment](image2.png)

Figure 3-9. Comparison of “virtual” CMM between (a) simulation and (b) experiment for the present simplified LV model. \( V_p \) is measured by the slope of the thick yellow colored line while \( \omega_p \) is measured by the slope of the linear fit to the locus of the position of vortex ring indicated by symbols. Comparison between the numerical values is reported in Table 3-3.

### 3.3.2.3. Color M-mode and flow propagation

It is well known that early ventricular filling is a suction phenomenon during which the velocity increases from the base to apex and this can be captured clinically using color-coded Doppler M-mode (CMM) echocardiography. Such a “virtual” CMM is presented in Figure 3-9 for both computational and experimental data. CMM is plotted as color-maps of longitudinal component of velocity versus time along the mitral axis (see section 2.4). A comparison of the two shows that while the initial E-wave propagation is similar for the two data sets, the wave in the simulation propagates deeper (~9.7cm) into the LV than for the experiment (~9cm). This is also evident from Figure 3-6A-C from the velocity profiles for the sections, \( H_1-H_3 \). The CMM for the simulation also shows higher
fluctuations and reversed flow during diastasis and the A-wave (t* = 0.45 − 0.7) when compared to that of the experiment. The locus of the position of the vortex core (indicated in Figure 3-8 as a dark circle) is also superposed on the CMM plots in Figure 3-9 and it indicates that the vortex ring lags behind the flow for this LV model in both simulation and experiment.

Table 3-3. Comparison of metrics computed using “virtual” CMM shown in Figure 3-9

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simulation</th>
<th>Experiment</th>
<th>%Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_E$ (cm/s)</td>
<td>16.8</td>
<td>15.5</td>
<td>8.7</td>
</tr>
<tr>
<td>$V_P$ (cm/s)</td>
<td>5.6</td>
<td>5.1</td>
<td>8.3</td>
</tr>
<tr>
<td>$V_E/V_P$</td>
<td>3.0</td>
<td>3.0</td>
<td>0.3</td>
</tr>
<tr>
<td>$\omega_P$ (cm/s)</td>
<td>3.6</td>
<td>3.9</td>
<td>8.6</td>
</tr>
</tbody>
</table>

The velocity with which the strong E-wave flow propagates from the basal region into the ventricular cavity is called the “flow wave” propagation velocity ($V_p$). This is not equal to the velocity of the blood particles which, in fact, tend to move at much higher velocities within the vortex ring. Instead, it represents the delay in ventricular filling partly due to varying degree of expansion of the ventricle along its length together with the roll-up of the shear layer in the form of a vortex ring. Both $V_p$ and $\omega_p$ can be estimated from the slopes of the respective lines in the Figure 3-9 and these are reported in Table 3-3. Also reported in the table is the peak E-wave velocity ($V_E$) along the mitral axis at the basal level of the ventricle.

It is noted that the difference in $V_E$ between the simulation and experiment is about 8.7% of the experimental value. This is within the uncertainty of the flow rate as shown
in Figure 3-3 and discussed in section 3.2.4. It is interesting to note that the values of $V_p$ and $\omega_p$ are also different from the experiment by about 8-9%. Not surprisingly, the value of $V_E/V_p$, a quantity that is considered to have diagnostic significance (Garcia et al., 1997; Greenberg et al., 2001; Vierendeels, Dick and Verndock, 2002; Boeck et al., 2005), is matched very well between the experiment and the simulation (Table 3-3).

From Table 3-3, it is also clear that the propagation speed of the vortex ring ($\omega_p$) is lower than that of $V_p$ which is not in-line with the conclusion of Vierendeels et al. (Vierendeels, Dick and Verndock, 2002) that the vortex ring propagates at the same speed as that of the flow. However, their model assumes axisymmetric filling into a long and slender prolate-spheroidal shaped LV model, whereas, the present LV model has a low aspect-ratio with a large cavity at the center. Moreover, the filling takes place asymmetrically into this cavity from the mitral annulus; thus, allowing one side of the vortex to fill up the cavity while subjecting the other to wall interaction thereby, giving rise to this velocity difference.

3.4. Summary

A comprehensive quantitative validation of intraventricular flow between a highly resolved simulation and an experiment has been conducted. The major sources of modeling uncertainty are identified and quantified. Among these, the uncertainty in the estimation of the instantaneous flow rate as well as the non-axisymmetric nature of the mitral flow in the experiment was found to be the most significant. The phase-averaged velocity profiles and vorticity contours from the simulation were found to match reasonably well with the experiment given the uncertainty inherent in the modeling procedure. Flow-wave propagation velocity ($V_p$) and the ratio, $V_E/V_p$ computed from
“virtual” color M-mode (CMM) as well as the vortex propagation velocity showed a very good agreement between simulation and experiment. The study demonstrates the challenge of modeling the flow even in a relatively simple experimental model of the left ventricle, and underscores the need for continued quantitative validation to clearly understand the limitations of such simulations. The contents of this chapter have appeared in the paper titled, “Computational modeling and validation of intraventricular flow in a simple model of the left ventricle”, in vol. 28, issue 6 of Theoretical and Computational Fluid Dynamics Journal in 2014.
CHAPTER 4. EFFECT OF TRABECULAE AND PAPILLARY MUSCLES ON VENTRICULAR HEMODYNAMICS

4.1. Introduction

The left ventricular endocardium, that represents the innermost lining of the ventricle in direct contact with blood, is not smooth (Figure 4-1a). Instead, the surface is highly corrugated with surface protrusions extending into the left ventricular (LV) cavity (Pasipoularides, 2010). These surface protrusions or “trabeculae” are usually formed on the ventricular free wall extending helically from the base to the apex of the LV (Boyd et al., 1987). In addition to surface trabeculae there are also the papillary muscles (PMs), which are two large distinct muscular bundles protruding from the LV endocardium and therefore, can be considered as the largest trabeculae in the LV (Madu and D'Cruz, 1997). The PMs are connected to the mitral valve (MV) via chordae-tendineae and ensure a complete closure of the valve leaflets preventing any regurgitation of the ventricular blood back into the left atrium (LA) (Madu and D'Cruz, 1997).

Interestingly, the embryonic heart is a smooth annular tube made up of spongy interwoven fibers (Chin et al., 1990; Sedmera et al., 2000; Lee et al., 2013). At a later stage, the heart undergoes looping and a series of transformations that lead to the development of the heart chambers, the atrio-ventricular valves and papillary muscles (Sedmera et al., 2000). It is argued that the forces due to fluid shear and pressure gradient distribution have a significant role in inducing the mechano-transduction effects transforming the embryonic heart into a normal one (Hove et al., 2003; Scherz et al., 2008; Peshkovsky, Totong and Yelon, 2011; Lee et al., 2013). Subsequently, the spongy myocardial structures undergo compaction (Chin et al., 1990; Sedmera et al., 2000).
although an inner layer of this tissue remains intact in the form of solid endocardial trabeculae. However, if the normal process of compaction halts due to congenital defects, it results in the development of excessive trabeculations - a pathological disorder widely known as left ventricular non-compaction cardiomyopathy (LVNCC, (Chin et al., 1990)). Given this, a majority of studies have focused on quantifying the size and mass of these trabeculae (Chin et al., 1990; Papavassiliu et al., 2005; Fernandez-Golfin et al., 2009; Jacquier et al., 2010) and these studies indicate that in a healthy ventricle, the trabeculae comprise about 12-17% of the mass of the LV (Papavassiliu et al., 2005; Fernandez-Golfin et al., 2009; Jacquier et al., 2010). Clinical studies also indicate that the trabeculated LV mass measuring above 20% of the total LV mass is an indicator of LVNCC (Jacquier et al., 2010).

However, the anatomical studies presented earlier do not address the very intriguing question regarding the function and hemodynamic effect of the trabeculae, especially viz-a-viz the dynamics of the flow in the left ventricle. It is well known that rough walls promote early transition to turbulence and increase energy losses. As such, virtually all vessels of a healthy cardiovascular system including the right atrium, the left atrium, the aorta, and the systemic arteries and veins, have smooth inner walls. Why then does the left ventricle, which is, arguably, the most critical component of the cardiovascular system, have such a rough endocardium? In addition to the possible increase in pressure loss associated with this, the trabeculae introduce small interstitial spaces that would seem to increase the possibility of local flow stagnation and increase thrombogenic risk. The current study aims to explore these questions using computational fluid dynamics.
Interestingly, Pasipoularides (Pasipoularides, 2010) conjectured that the trabeculae enhance the ability of the left ventricle to “squeeze” the fluid from the apical region during systole (ejection). Serrani et al. (Serrani, Costantino and Fumero, 2013) employed a finite-element model to simulate the electromechanically driven contractions for highly simplified models of the LV, and this study suggested that the trabeculae aid ventricular ejection by producing higher stroke volumes at low atrial pressures. Recently, Kulp et al. (Kulp et al., 2011) examined the effect of trabeculae on ventricular flow by simulating blood flow inside an LV model derived from high resolution 4D CT data. By comparing two models which had precisely the same trabecular structure but different apical contraction (Kulp et al., 2011), they noted that the model with the reduced apical contraction had more stagnant flow in the apical region. Since reduced apical contraction is expected to enhance apical stasis irrespective of the presence or absence of trabeculae it is not clear what this comparison implies with respect to the effect of the trabeculae on the ventricular hemodynamics.

In the current study, we examine the effect of trabeculae on ventricular hemodynamics with a study design that is different from that of Kulp et al. (Kulp et al., 2011). We perform CFD simulations for two different models of the LV derived from high resolution CT data. The first model is a trabeculated LV (TLV) model that includes trabeculae and papillary muscles whereas the second model is a smooth LV (SLV) model where papillary muscles are ‘excised’ and trabeculae smoothened out during model construction. It is noted that the smooth LV models have been the norm in computational (Vierendeels et al., 2000; Baccani et al., 2002; Long et al., 2003; Watanabe et al., 2004; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Doenst
et al., 2009; Krittian et al., 2010) (Pedrizzetti, Domenichini and Tonti, 2010; Zheng et al., 2012; Seo and Mittal, 2013; Seo et al., 2013; Choi, Vedula and Mittal, 2014; Seo et al., 2014; Vedula et al., 2014) and benchmark experimental (Cenedese et al., 2005; Kheradvar et al., 2010; Charonko et al., 2013; Fortini et al., 2013) studies of LV hemodynamics whereas the trabeculated LV model have only been studied by Kulp et al. (Kulp et al., 2011). The use of these two models, which are differentiated almost exclusively by the trabeculae, is expected to provide a more clear delineation of the role of trabeculae on LV hemodynamics.

The solver used to conduct CFD simulations has been discussed in section 2.3 while the metrics used to compare the flow features have been presented in section 2.4. We assess the impact of trabeculae and papillary muscles on the flow propagation, viscous dissipation and ventricular washout using a number of metrics obtained from the simulations. In particular, we compare the flow field by visualizing the three-dimensional vortex structures, examine the phase-averaged velocity field along orthogonal long-axis planes and compare kinetic energy related metrics in both the ventricular cavity as well as the apical volumes. Additionally, the apical washout phenomenon is also investigated using “virtual” ventriculography or dye visualization by solving the scalar transport equation.

4.2. Methods

In section 2.2, we have discussed the methodology for computational modeling of intracardiac flows using 4D (three spatial dimensions + time) medical images. However, 4D medical images would be difficult to treat with registration methods when the ventricle has high level of structural detail such as trabeculae and papillary muscles as
noted earlier (section 2.2). At the same time, it is also possible that only 3D volume image data could be acquired only at a single cardiac phase because 4D medical image acquisition modalities are relatively expensive and are mostly available for patients with pathological conditions. Additionally, the template-based mapping used for registering the 4D volume frames (see section 2.2.3) would be rendered unnecessary while dealing with 3D images acquired at a single cardiac phase. This leads to reduced pre-processing efforts, although, additional modeling methods have to be employed to account for the dynamic motion of the ventricle. But, these simplified wall-motion models could be easily translated to the complex structural detail of the ventricle such as the ventricular trabeculae and papillary muscles which are, otherwise, very difficult to map using 4D registration methods. In the present section, we describe the modeling approaches for the 3D CT imaging data which will be used to understand the impact of trabeculae on the ventricular hemodynamics.

4.2.1. **Left ventricular model**

The present left ventricular model is extracted from a high resolution (0.43x0.43x0.5mm voxel resolution, 512x512x280 total voxels) CT scan (Toshiba 320 Aquilon One multi-detector CT scanner) of a normal heart as shown in the left frame of Figure 4-1a along with the highlighted regions of interest. Segmentation is performed using the dynamic region-growing algorithm (Rangayyan, 2004) in Mimics (Mimics, Materialise Inc.) commercial software and the segmented volume is shown in the right frame Figure 4-1a. Two distinct LV models are derived from this segmented volume using the surface-wrapping tool in Mimics (Mimics, Materialise Inc.) by providing the smallest detail (SD) and closing distance (CD) as the necessary input parameters. The SD
parameter represents the size of the smallest triangle on the newly created surface while CD represents the size of the largest gaps to be filled while creating the wrapped surface. The first model is the trabeculated LV model (TLV) that incorporates the trabeculae and papillary muscles to a resolution of about 1 mm (SD=0.8mm, CD=0.8mm). The second model is the smooth LV model (SLV) where surface features such as trabeculae or the papillary muscles are excised or smoothened out by using SD=3mm and CD=3mm.

It is noted that features at the limit of the scanner resolution (~0.5mm) are not necessarily well resolved due to motion artifacts associated with the temporal resolution of the scanner. However, even if the features in the CT image at the 0.5mm scale were assumed to be accurate, the grid required to adequately resolve the flow around these fine-scale features is currently untenable. Hence, the wrap parameters (SD and CD) for the TLV model are chosen such that we have a reasonably good representation of the trabeculae while at the same time, limiting the computational effort for these simulations. These models are shown in Figure 4-1b with the associated nomenclature. It is to be noted that since the focus here is to understand the effect of trabeculae on the ventricular flow, we follow the conventional approach (Long et al., 2003; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Doenst et al., 2009; Pedrizzetti, Domenichini and Tonti, 2010; Le et al., 2012; Seo and Mittal, 2013; Seo et al., 2013; Seo et al., 2014; Vedula et al., 2014) of using a simple model of the inflow from the atrium as shown in Figure 4-1b.

The variation in the cross-sectional area along the mitral axis from the apex to the mitral orifice (MO) is compared between the TLV and SLV models in Figure 4-1b. Although this comparison is presented here at mid-diastole, the trends remain similar.

- 67 -
across the cardiac cycle with at most a 1% deviation. It is evident that the maximum difference in cross-sectional area between the two models is about 10% at the mid-ventricular cavity level. While this alone is not expected to introduce any significant changes in the blood flow patterns, the general shape and location of the papillary muscles could significantly alter the flow due to development of boundary layers and wake vortices and recirculation zones. These features and the associated effect on ventricular blood transport are of particular interest to us in this study.
Figure 4.1. Left ventricular modeling: (a) Left ventricle model segmentation from volume CT data; (b) Computational left ventricular models used for the current investigation (TLV - trabeculated left ventricle; SLV - smooth left ventricle) along with the comparison of cross-sectional area along mitral axis between the two models; (c) Prescribed flow rate waveform (Q) and change in volume (ΔV) of the ventricular model with the indicated phases of the cardiac cycle. (LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract; MV: mitral valve; PMs: papillary muscles; AT: acceleration...
time; DT: deceleration time; E-wave: early filling; A-wave: atrial filling; IVC: isovolumic contraction; IVR: isovolumic relaxation.

### 4.2.2. Modeling LV motion

In order to model the diastolic (filling) and systolic (ejection) phases of the cardiac cycle, the endocardial surfaces of the LV models are subjected to a prescribed motion over the cardiac cycle. Blood flow into and out of the left ventricle is plotted in Figure 4-1c (solid line, Q) while the change in volume (ΔV) which is essentially the integral of flow rate (Q) is also shown on the same plot as a dotted line with the indicated cardiac phases. Briefly, the cardiac cycle is divided into two phases- diastole or filling from mitral inlet into the LV cavity and systole or ejection of the ventricular blood through the left ventricle outflow tract (LVOT). Diastole is further divided into distinct phases- the E-wave corresponds to early filling due to passive relaxation of the ventricle, while the A-wave represents active filling due to atrial contraction. The interim phase during which there is no change in the LV volume is referred to as diastasis. Additionally, there are two other phases during which the volume of the ventricle remains constant- isovolumic contraction (IVC) and isovolumic relaxation (IVR). It is during these phases that the maximum pressure rise and fall occurs in the left ventricle without any change in the volume together with the closing and opening of the mitral valve, respectively. The duration of each of these phases of a representative flow waveform have been modeled using published data (Chung, Karamanoglu and Kovacs, 2004; Nagueh et al., 2009) as shown in Table 4-1 when the heart rate (HR) was chosen as 67bpm for a normal heart.
Table 4-1. Duration in milliseconds of various phases of the model cardiac cycle shown in Figure 4-1c. (AT: acceleration time; DT: deceleration time; IVC: isovolumic contraction; IVR: isovolumic relaxation)

<table>
<thead>
<tr>
<th>AT</th>
<th>DT</th>
<th>Diastasis</th>
<th>A-wave</th>
<th>IVC</th>
<th>Systole</th>
<th>IVR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>160</td>
<td>130</td>
<td>140</td>
<td>30</td>
<td>320</td>
<td>30</td>
<td>900</td>
</tr>
</tbody>
</table>

Table 4-2. Important flow-wave related parameters and non-dimensional numbers governing blood flow in the left ventricle

<table>
<thead>
<tr>
<th>E/A Ratio</th>
<th>Max. Q (E-wave)</th>
<th>Stroke Volume (SV)</th>
<th>End Diastolic Volume (EDV)*</th>
<th>Ejection Fraction (EF=SV/EDV)*</th>
<th>Heart Rate (HR)</th>
<th>Reynolds No. (Re)</th>
<th>Womersley No. (Wo)</th>
<th>Formation number, E-wave (Δε)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5</td>
<td>400 ml/s</td>
<td>76 ml</td>
<td>124 ml</td>
<td>0.61</td>
<td>5630</td>
<td>15.7</td>
<td>3.64</td>
</tr>
</tbody>
</table>

*values correspond to TLV model

The flow waveform is modeled using a simple harmonic oscillator model as described in (Kovacs Jr, Barzilai and Perez, 1987; McGuire et al., 1997) and the mathematical details are furnished in Seo et al. (Seo et al., 2014) and Appendix B. Local deformation of the ventricular model is based on the works reported by (Taylor et al., 1996; Seo et al., 2013; Seo and Mittal, 2013; Seo et al., 2014) where the ventricle undergoes expansion
and contraction with respect to a fixed focal point near the mitral orifice. The parameters relevant to the flow waveform are listed in Table 4-2 which are within the physiological range for normal human hearts (Nagueh et al., 2009; Zheng et al., 2012). In particular, the present model has an E/A ratio, defined as the ratio of peak E-wave and A-wave flow rates, as 1.5 while the stroke volume (SV), defined as the net flow discharge by the ventricle during a cardiac cycle, is 76ml. The end diastolic volume (EDV) of the TLV model is 124ml thereby, producing an ejection fraction (EF=SV/EDV) of 61%. However, the EF for SLV model is slightly lower than that of the TLV model because the same flow rate (Q in Figure 4-1c) is prescribed for the SLV model as well and therefore, it has identical stroke volume. However, the absence of trabeculae or papillary muscles in the SLV model increases its effective EDV to 132ml thereby reducing the overall ejection fraction to 57%. The 4% difference in EF is not expected to generate any significant differences in the measured quantities.

4.2.3. Mitral valve modeling

As noted in section 2.2.2, it is necessary to account for an accurate model of the mitral valve while modeling cardiac flows in determining accurate flow patterns in the ventricle (Charonko et al., 2013; Seo et al., 2014). However, none of the existing imaging modalities (echo, CCT or CMR) have the spatial and temporal resolution required to adequately resolve the motion of the valve leaflets. Hence, we choose to employ a kinematic model of the mitral valve using an approach that is similar in essence to that of previously published works (Kulp et al., 2011; Seo et al., 2014). In this approach the MV geometry is based on the work by Ranganathan et al. (Ranganathan et al., 1970) who characterized MV morphology from a database of about 50 normal volunteers, while the
motion of the leaflets is prescribed based on the measurement of leaflet angles from echocardiographic data. The morphology of the mitral valve employed in the current study is shown in Figure 2-4a providing a three-dimensional view (top) as well as a flattened cylindrical projection of the same (bottom). Overall, the present valve model is a reasonable prototype of the physiological normal mitral valve that captures surface details such as the scallops on the posterior leaflet. The area of the mitral orifice in the present model is about 5.8cm² while the lengths of anterior and posterior leaflets are LAL=2.1cm and LPL=1.25cm, respectively.

![Figure 4-2](image)

(a) Schematic of angle measurements
(b) Measured leaflet angles

Figure 4-2. Schematic of measurement of mitral valve leaflet angles (θ) with respect to the base of the ventricle; (c) Model of the mitral valve leaflet angles based on the measurements from echocardiographic data. (AL: anterior leaflet; PL: posterior leaflet; L_AL, L_PL: lengths of anterior and posterior leaflets measured from the base of the leaflets to the tip.

The model for mitral valve motion is created by measuring the angles made by the leaflets with the base of the LV along a 4-chamber view of the echocardiographic data (Figure 4-2a) and a smooth curve was fit as shown in Figure 4-2b. Immediately, one can notice that the leaflets not only do not completely close during diastasis (θ=45°) but also
do not open fully (max. \( \theta < 90^\circ \)). It is noted that the present study assumes that the leaflets motion is in phase with the mitral flow waveform and that the valve leaflets execute motion in such a way that the MV base is fixed to the orifice (Seo et al., 2014). Additionally, while performing the echocardiographic measurements, the orientation of the base of the leaflets adjusted such that the angles made by the leaflets with the base are nearly equal and the base is pointing towards the LV apex. Although the present model is simplified in terms of both the geometry and the motion, it was shown to be sufficient to produce correctly the overall features of the ventricular flow (Seo et al., 2014). Further details about the motion of the valve and its implementation have been discussed in Seo et al. (Seo et al., 2014) and Appendix C.

4.2.4. CFD-ready model and non-dimensional parameters

The TLV heart model used in the present study is discretized with about 32,168 triangular elements while the mitral valve is discretized using 19,920 elements. The entire surface is immersed in a Cartesian grid of size 6.3cm x 6.0cm x 13.0cm covered by a total of 256x256x512 (~33.5 million) cells (Figure 4-3a). However, we use this fine grid mesh to understand the complex three-dimensional vortical feature whereas to compute phase-averaged quantities over multiple cycles, we use a coarser mesh comprising 128x128x256 (~4.2 million) cells. The resolution is chosen based on the grid convergence study performed as a part of validation in section 3.2.5. The non-dimensional time step chosen for the present simulations is \( 1 \times 10^{-4} \) which results in about 10,000 time steps per cardiac cycle. Simulations are performed on Stampede high performance computing cluster (part of XSEDE program) with 512 CPU cores for 4 cardiac cycles and the computation for one cardiac cycle takes about 4 days on the finer...
mesh. Phase-averaging was performed across all the cardiac cycles and the comparison between the two computational models (TLV and SLV) is performed using the phase-averaged data. Orthogonal cross-sectional planes (A-A’) and (B-B’) are projected for subsequent analysis and comparison of hemodynamic data, as shown in Figure 4-3b.

(a) Immersed LV model  
(b) Cross-sectional planes

(c) Initial dye concentration

Figure 4-3. (a) Computational domain with immersed TLV model. (b) Orthogonal cross-sectional planes (A-A’ and B-B’) of the TLV model used for analyzing ventricular flow dynamics portrayed in both plan and elevation views. The atlas corresponding to the ventricular geometry is also depicted on A-A’ (septal/lateral) and B-B’ planes (anterior/posterior) along with the colored outline of the SLV model. (c) Initial dye concentration for TLV (left) and SLV (right) models. (ALPM: antero-lateral papillary muscle; PMPM: postero-medial papillary muscle)
Certain key non-dimensional numbers determine the hemodynamics inside the ventricle (see section 2.3) and are listed in Table 4-2. In particular, the flow Reynolds number (Re) for the present model is about Re=5630 while the Womersley number and vortex formation number during E-wave are Wo=15.7 and \( \Lambda_E=3.64 \), respectively. These numbers are determined based on the peak area-averaged flow velocity at the mitral orifice, \( U_m=69\text{cm/s} \), diameter of mitral orifice \( D_{MO}=2.7\text{cm} \) and kinematic viscosity of blood \( =3.3\times10^{-6}\text{m}^2\text{s} \) while the cardiac duration is \( T=0.9\text{s} \) (HR=67bpm).

4.3. Results

4.3.1. Vortex structures

Three-dimensional vortical structures are illustrated in Figure 4-4 and Figure 4-5 for both TLV and SLV models at various key phases of the cardiac cycle plotted as of isosurfaces of \( \lambda_{ci}=133.3\text{s}^{-1} \). Figure 4-4a and Figure 4-4b visualize the vortex structures along septal-lateral view for the TLV and SLV models, respectively while Figure 4-5a and Figure 4-5b depict vortex structures during early filling along anterior-posterior view in which both the papillary muscles could be distinctly seen on either side of the cavity. While the large-scales vortical features are similar for the two cases, as expected, trabeculae and PMs tend to “scramble” the vortices further and generate a more complex vortex topology (Figure 4-4 and Figure 4-5). Interestingly, the vortices in the TLV model exhibit a larger spread across the ventricular cavity as well as a deeper penetration \( (t^*=0.30) \) than the SLV model. This effect of the trabeculae could potentially increase washout and mixing in the ventricle and will be explored further in the following sections. The plot also suggest that the vortices in the TLV model dissipate faster at end-diastole
on account of their interaction with a relatively “rough” wall than for the SLV model ($t^* = 0.50$). The flow is described in greater detail highlighting the differences between the two models in the following paragraphs.

Figure 4-4. Three dimensional vortex structures visualized using $\lambda_{ci}$ criterion, defined by the imaginary eigen values of velocity gradient tensor ($\lambda_{ci} = 133.3 \text{s}^{-1}$) along septal-lateral view (see Figure 4-3b) at the indicated time instants. (a). TLV model; (b). SLV model.
Figure 4-5. Three dimensional vortex structures visualized using $\lambda_{ci}$ criterion, defined by the imaginary eigen values of velocity gradient tensor ($\lambda_{ci}=133.3s^{-1}$) along septal-lateral view (see Figure 4-3b) at the indicated time instants. (a). TLV model; (b). SLV model.

During early filling ($t^*=0.05$), a vortex ring pinches-off from the tips of the mitral valve leaflets and propagates towards the lateral wall owing to the asymmetry induced by the mitral leaflets- a phenomenon that is well established in previous studies (Bellhouse,
1972; Doenst et al., 2009; Le et al., 2012; Toger et al., 2012; Charonko et al., 2013; Seo and Mittal, 2013; Chnafa, Mendez and Nicoud, 2014; Seo et al., 2014). The present simulations indicate that the presence of scallops on the posterior leaflet together with its shorter length compared to the anterior leaflet causes the vortex structure to dissociate near the central scallop of the posterior leaflet and connect with the anterior vortex structure through cylindrical tube-like structures (Figure 4-5, t*=0.05). Subsequently, the vortex structure propagates towards the lateral wall and forms an intricate coil-like structure with several small tube-like vortices helically looping around a central core (t*=0.10). This helical looping of vortical structures is found to be more pronounced in the TLV model compared to the SLV model. The complex vortical structures formed during the acceleration phase of early filling get disrupted due to their interaction with the lateral wall during the deceleration phase (t*=0.15) and this generates several small scale vortices into the ventricular cavity. This effect seems to be more pronounced for the TLV model as seen in Figure 4-4 and Figure 4-5.

During diastasis (t*=0.30) when the ventricular volume does not change, the vortices fill up the ventricular cavity due to the inertia acquired during early filling. However, the penetration and spread of these vortices was found to be greater in the TLV model (Figure 4-4a at t*=0.30) than that of the SLV model (Figure 4-4b at t*=0.30). The atrial filling (A-wave, t*=0.50) also produces another vortex at the mitral valve tips but of much weaker strength and therefore, this vortex cannot reenergize the already decaying vortices formed during the preceded phase. Evidently, the dissipation of vortices is higher in the TLV model due to the fact that the trabeculae and PMs contribute to a more effective cascade from larger to smaller scale vortices, which are more prone to viscous
dissipation. As a result, only a few discrete eddies are seen during late atrial filling in the ventricular cavity in the TLV model compared to the SLV model ($t^*=0.50$). During systole, the ventricular cavity is mostly devoid of any vortical structures for both models with all the vortices concentrated near the entrance to, and inside the outflow tract.

4.3.2. Phase-time-averaged flow

The computed phase-time-averaged flow field during diastole and systole is compared along A-A’ and B-B’ planes between the two ventricular models in Figure 4-6. Velocity vectors superposed over the contours of velocity magnitude are shown in Figure 4-6 compared between the two models which exhibit significant differences. Time averaged flow during diastole along A-A’ plane for SLV model (Figure 4-6E) indicates a coherent clockwise rotating circulatory flow in the ventricular cavity that sweeps the fluid from the lateral wall to the septum (as indicated by arrows in Figure 4-6E). Though this coherence of the vortical flow is still retained for the TLV model, the velocity magnitude is markedly lowered near the mid-septal wall of the TLV model as indicated in Figure 4-6A. The flow pattern on the same plane also indicates that the high speed mitral inflow has an increased penetration into the apical region for the TLV model (Figure 4-6A) while a region of low velocity magnitude could be distinctly identified near the apex of the lateral wall for the SLV model (as pointed in Figure 4-6E). During systole (Figure 4-6B, Figure 4-6F), the differences in the flow pattern for the two models are quite small.

The flow pattern along the B-B’ plane (Figure 4-6C, D and Figure 4-6G, H) provide a clear picture of the interaction of the trabeculae and papillary muscles with the incoming blood flow. From Figure 4-6C, it is clear that the papillary muscles provide significant blockage to the mitral jet which has three consequences: first, the jet is forced away from
the larger postero-medial papillary muscle towards the anterior wall; the flow which is forced between the gap between the two sets of papillary muscles penetrated deeper into the apex and third, low-velocity circulatory flows patterns are created in the “wake” of the papillary muscles with the one downstream of the postero-medial papillary muscle being particularly large and noticeable (highlighted in Figure 4-6C). In contrast, for the SLV model in Figure 4-6G, there are no such circulatory patterns on this plane; the velocity varies gradually from the anterior to the posterior walls with mildly higher velocity on the posterior side. Furthermore, the jet does not penetrate as deep into the apex thereby creating a distinct region of flow stasis at the apex as indicated in Figure 4-6G.

During systole the flow behavior along B-B’ plane is similar to what has been observed along the A-A’ plane but noticeable differences could be identified between the two models. An interesting sweeping flow pattern is identified in the proximity of ventricular apex in Figure 4-6D where the blood flows towards the apex along anterior wall and sweeps back around the apex at high velocities along the posterior wall. Consequently, the flow under the postero-medial papillary muscle that was recirculating at end-diastole is now ejected at high velocities for the TLV model (highlighted in Figure 4-6D). However, the SLV model (Figure 4-6H) portrays an overall low velocity flow zone below the mid-papillary level wall during systole. Thus, there remains a layer of low velocity around the apex of the SLV model throughout the cardiac cycle. This implies that the trabeculae and papillary muscles act together to squeeze the trapped flow from their interstitial gaps and wakes during systole – a mechanism that is absent for a smooth ventricular wall (Pasipoularides, 2010).
Figure 4-6. Comparison of phase-time averaged velocity fields during diastole and systole between the TLV model (top), and the SLV model (bottom), along A-A' and B-B' planes as indicated (see Figure 4-3b). Color map represents contours of velocity magnitude while the velocity vectors are plotted at every 8th grid point along each direction.

4.3.3. Kinetic energy and viscous dissipation

Figure 4-7a and Figure 4-7b compare the volume-averaged kinetic energy density in the ventricular cavity \( KE'_{LV} \) and the apical region \( KE'_{AP} \), respectively for both TLV and SLV models while Figure 4-7c compares the rate of viscous dissipation \( \Phi'_{LV} \) between the two models as a function of time. As noted earlier in section 2.4, the apical
volume is designated as the region below \( Z=4 \text{cm} \) with reference to Figure 4-3. Evidently, \( KE'_{LV} \) is initially higher for the TLV model (peak difference \( \approx 10\% \)) during early filling while drops rapidly below the corresponding value of the SLV model during diastasis. This could be attributed to the very high rate of dissipation of kinetic energy (\( \approx 55\% \)) during early filling for the TLV model (Figure 4-7c) that eventually leads to a rapid decrease of kinetic energy during diastasis. This increased dissipation rate due to trabeculations was earlier qualitatively observed through the three-dimensional vortical structures in Figure 4-4 and Figure 4-5. It is noted that the differences in \( KE'_{LV} \) and \( \Phi'_{LV} \) are not very apparent between the two models during atrial filling and systole, although, early systole exhibits lower \( KE'_{LV} \) for the TLV model. Interestingly, the apical kinetic energy is consistently high for the TLV model during most of the cardiac cycle with differences being more prominent during diastasis and ejection which was earlier implicated in deeper inflow jet penetration for the TLV model in Figure 4-6.

Overall, the net viscous dissipation in the TLV flow is about 6mJ which is 55\% higher than that in the SLV models. While this is a large relative increase, the overall magnitude of the viscous dissipation is negligible compared to the approximately 0.8J (for stroke volume, \( SV=76\text{ml} \) operating at 80mmHg systolic pressure) pressure work associated with the human ventricle.
Figure 4-7. Comparison of volume-averaged (a) ventricular kinetic energy density, (b) apical kinetic energy density, (c) rate of viscous dissipation in the left ventricle between the TLV and SLV models. It is noted that the apical volume was measured as the region below $Z = 4\text{cm}$ for both the models (see Figure 4-3c).

4.3.4. **“Virtual Ventriculography”**

Dye visualization or “virtual” ventriculography inside the ventricle is modeled here using the transport phenomena of a passive scalar where the scalar is convected due to the background fluid velocity governed by the convection-diffusion equation (Eqn. (2-7)). This is used to understand the near-wall flow and in particular, to identify any regions of stagnant flows near the boundaries. In the present study, the scalar was originally initialized at the beginning of diastole within the apical cavity (designated as the region...
below \(Z=4\text{cm}\) level, see Figure 4-3c). The convection of this scalar out of the apex gives us a direct measure of apical washout between the two models.

\[\psi = 1\] in the apical cavity at \(t^*=0\) (region below \(Z=4\text{cm}\) level, see Figure 4-3c) and the transport phenomenon is modeled using the convection-diffusion equation.

Figure 4-8. Comparison of dye concentration (“virtual” ventriculography or dye visualization) of a passive scalar along B-B’ plane at end-diastolic and end-systolic phases between (a) TLV model and (b) SLV model. The scalar is initialized as, \(\psi = 1\) in the apical cavity at \(t^*=0\) (region below \(Z=4\text{cm}\) level, see Figure 4-3c) and the transport phenomenon is modeled using the convection-diffusion equation.
The distribution of scalar field along B-B’ plane is compared between the two models at the end-diastolic and end-systolic phases in Figure 4-8. By the end of diastole (Figure 4-8a), most of the dye concentration in the TLV model is contained only in the recirculation zone below the posterior papillary muscle that was earlier identified in the velocity distribution (Figure 4-6C). This seems to suggest that the trabeculae tend to enhance flow stagnation in the apical region. However, by the end of systole, the dye is very effectively ejected out from this end-diastolic recirculatory region for the TLV model which is consistent with the high ejection velocities identified in this zone earlier in Figure 4-6D. It is also interesting to note that there is some dye deposited near the anterior wall of the TLV model by end-systole, which could be attributed to the sweeping flow found in the proximity of the ventricular apex during systole (Figure 4-6D). On the other hand, the apical region of the SLV model (Figure 4-8b) is always associated with a high concentration of the dye which correlates with the low apical velocities identified previously in Figure 4-6E - Figure 4-6H.

The time variation of spatial mean \( \langle \psi_{\text{avg}} \rangle \) and RMS, \( \langle \psi_{\text{rms}} \rangle \) of the scalar field is compared between the TLV and SLV models in Figure 4-9a and Figure 4-9b, respectively. The differences between the two models in each of the quantities are also indicated on the plots at end-diastolic and end-systolic phases. It is noted that initially \((t*=0)\), both the mean and RMS are identically equal to unity. At end-diastole, \( \langle \psi_{\text{avg}} \rangle \) is higher for the TLV model which is consistent with the high scalar concentration in the apical recirculatory region depicted earlier in Figure 4-8a. However, the difference of \( \langle \psi_{\text{avg}} \rangle \) between the two models reduces significantly by the end of systole.
Figure 4-9. Comparison of the time variation of (a) mean scalar field distribution $\langle \psi_{avg} \rangle$ and (b) root mean square (RMS) of the scalar field $\langle \psi_{rms} \rangle$ between the TLV and the SLV models. The differences in each of these quantities at end-diastole and end-systole are also quantified as indicated. At $t^*=0$, both $\langle \psi_{avg} \rangle$ and $\langle \psi_{rms} \rangle$ are identically equal to unity.

This is primarily due to the increase of $\langle \psi_{avg} \rangle$ for the SLV model implying higher scalar distribution in the apical cavity for the SLV model and therefore, poor apical ejection. At the same time, the very little change in $\langle \psi_{avg} \rangle$ between end-diastolic and end-systolic states for the TLV model indicates that the TLV model has better apical ‘stroke’ without any significant accumulation of dye in the apical cavity during systole. On the other hand, pockets of high scalar concentration could be identified in the SLV model via the distribution of $\psi_{rms}$. Clearly, the slightly lower value of $\psi_{rms}$ for the TLV model at end diastole observed in Figure 4-9b is indicative of better mixing generated by the more energetic apical flow and flow fluctuations created by the trabeculae and papillary muscles.
4.4. Discussion

The ventricular endocardium has large-scale roughness, which are often ignored while modeling ventricular hemodynamics. The surface is highly corrugated with protrusions or trabeculae spreading helically along the lateral free wall from the base to the apex. Furthermore, the ventricular endocardium extends deep into the cavity in the form of papillary muscles connected to the mitral valve leaflets via chordae-tendineae whose primary function is to provide a complete closure of the valve during ventricular systole. However, the question arises as to whether valve closure is the only function of these muscles or if there are other important implications of these structures for the hemodynamics in the ventricle. On one hand, the large papillary muscles could be perceived as providing greater obstruction to the incoming blood flow and thereby increasing pressure losses; on the favorable side, the flow could be locally accelerated due to the area constriction created by the papillary muscles and that could potentially enhance the flow penetration into the apical cavity.

Secondly, it is also not clear if the ventricular trabeculae are the vestigial residues of the embryonic heart development or whether they have any role in the hemodynamic functioning of the left ventricle? However, it is well-known from the elements of fluid mechanics that surface “roughness” significantly alters the associated flow dynamics especially by producing local recirculatory flows, enhanced unsteadiness and increased dissipation. Despite making significant progress in understanding the morphology of the trabeculae and the papillary muscles (Boyd et al., 1987; Chin et al., 1990; Sedmera et al., 2000; Papavassiliu et al., 2005; Fernandez-Golfin et al., 2009; Jacquier et al., 2010), efforts towards understanding their impact on the ventricular hemodynamics have been
very minimal in their scope (Kulp et al., 2011). Pasipoularides (2010) suggested in his monograph (Pasipoularides, 2010) that the trabeculae and papillary muscles might enhance the ability of the LV to squeeze the fluid from the apical region during systole to overcome the inability of the ventricle to contract beyond a certain limit. Kulp et al. (Kulp et al., 2011) have simulated the interaction of the ventricular trabeculae with the blood flow inside an LV model constructed from 4D CT data and suggested that reduced apical contraction would make the interstitial recesses between the trabeculae more prone to flow stasis.

In the current study, computational modeling is used to study the effect of surface trabeculae on the hemodynamics of the left ventricular filling and ejection and thereby, address some of the questions raised above. This is achieved by simulating blood flows inside two different models of the left ventricle – a trabeculated ventricular model (TLV) which includes trabeculae and papillary muscles; and a smooth ventricular model (SLV) in which the ventricular surface is free from any surface features due to trabeculae. Both models are derived from a high resolution contrast-enhanced 3D CT scan of a normal human being and the study indicates that the surface trabeculae significantly impact the blood flow transport inside the left ventricle. Simulations were performed on a high resolution grid using a methodology that has been implemented before (Taylor et al., 1996; Kulp et al., 2011; Seo and Mittal, 2013; Seo et al., 2014) and a solver that has been comprehensively validated for the ventricular flows using experimental data (Vedula et al., 2014).

It is useful to note that the ventricular flow field obtained here generally correlates well with many of the previously reported studies. First, a vortex ring is observed to
pinch off from the tips of the mitral leaflets and propagates and impinges on the lateral wall (Figure 4-4 and Figure 4-5). This behavior has been well established in the past (Kilner et al., 2000; Pasipoularides, 2010; Mihalef et al., 2011; Sengupta et al., 2012; Toger et al., 2012; Chnafa, Mendez and Nicoud, 2014) although, the structure of the vortex characterized here is more complex with small tube-like vortices coiling around a central core. The vortex ring subsequently disintegrates and a clockwise circulatory flow pattern is produced in the ventricular cavity that sweeps the flow from the lateral wall along the apical region towards the septum (Kilner et al., 2000; Hong et al., 2008; Long et al., 2008; Faludi et al., 2010; Mihalef et al., 2011; Toger et al., 2012; Charonko et al., 2013; Seo and Mittal, 2013). Although this pattern of flow redirection was previously conjectured to be hydrodynamically efficient (Kilner et al., 2000; Pedrizzetti and Domenichini, 2005), later studies have indicated that the effect of the flow patterns on pumping efficiency is quite small and that it is mixing and washout that are more dependent on the intraventricular flow pattern, (Seo and Mittal, 2013; Watanabe, Sugiura and Hisada, 2008). Nevertheless, the present simulations capture the widely recognized ventricular looped flow dynamics accurately.

Qualitative understanding of the effects of trabeculae on the ventricular flow dynamics was facilitated through the visualization of the three-dimensional vortex structures as isosurfaces of $\lambda_{ci}$ (Figure 4-4 and Figure 4-5). The papillary muscles and the trabeculae increase the complexity of the vortex topology in the diastolic flow and also lead to increased dissipation in the flow for the TLV model. The time-averaged flow field along orthogonal cross-sections (Figure 4-6) indicated that the trabeculae and the papillary muscles enhance the penetration depth of the mitral inflow jet into the apical
region. This effect far exceeds what would be expected solely due to the approximately 10% area blockage in the mid-axial plane (see Figure 4-1b) associated with the papillary muscles. The results indicate that the blockage effect is accentuated by the formation of thick shear layer on the papillary muscles as well as the formation of a large region of recirculating flow in the wake of these muscles which also act as a virtual blockage to the flow, thereby guiding the mitral jet deeper into the apex. While the flow in these recirculation zones is fairly stagnant during diastole, it does not remain as such during systole as the papillary muscles come together and align to facilitate a better ‘squeezing’ of the apical region. On the contrary, the SLV model exhibits a stagnant region near the apical wall throughout the cardiac cycle.

The aforementioned effects are further confirmed using dye visualization or “virtual” ventriculography. These results reconfirm the presence of a stagnant apical flow in the SLV model throughout the cardiac cycle (Figure 4-8b) while the TLV model exhibits a high concentration of dye in the recirculatory region by end-diastole which gets ejected by the end of systole (Figure 4-8a). The kinetic energy of the fluid in the apical region is found to be consistently higher by about 13% for the TLV model compared to the SLV model which also supports the argument that trabeculae indeed provide deeper penetration of the inflow jet. Additionally, other global metrics such as ventricular kinetic energy and rate of dissipation were found to be enhanced in the presence of trabeculae (Figure 4-7). However, this increase in viscous dissipation is negligible compared to the net pressure work of the LV and therefore, trabeculae and papillary muscles have no measurable effect on the hydrodynamic efficiency of the ventricle.
It is useful to identify and understand the potential limitations and caveats of the present modeling approach. Firstly, the motion of the left ventricle modeled here is highly simplified and that could have implications on the predicted near-wall flow behavior. More realistic wall motion could be obtained from dynamic cardiac CT imaging where multiple (up to 20) images are extracted over a cardiac cycle. However, such 4D imaging is usually performed only for patients with pathologies and such data is not easily available for normal patients. Furthermore, extraction of the lumen out of 4D data requires additional preprocessing overhead in registering each key frame to the other using some template-based mapping to preserve mesh topology throughout the cardiac cycle (Chnafa, Mendez and Nicoud, 2014; Lim et al., 2014). However, given the relatively low temporal resolution available in dynamic CT (about 20 frames per cycle) such a mapping algorithm would not be able to match the level of surface detail that is of particular interest in the present study such as the trabeculae or the papillary muscles. Hence, the present study incorporates a ventricular model created from high resolution volumetric CT data and the motion is prescribed based on available data (Taylor et al., 1996; Seo et al., 2013; Seo and Mittal, 2013; Seo et al., 2014).

Secondly, there could be some uncertainty in the flow waveform modeled here (Figure 4-1c) and the various parameters associated with it (Table 4-1 and Table 4-2) such as the duration of each phase of the cardiac cycle, representation of the flow waveform using simple-harmonic oscillator model during filling, etc. However, given the limitations in obtaining 4D data and the associated overheads as discussed above, we have employed a waveform based on clinically accepted results (Kovacs Jr, Barzilai and Perez, 1987; McGuire et al., 1997; Nagueh et al., 2009). Further, the present study does
not account for a full patient-specific mitral valve model. Instead a kinematic valve model is incorporated based on morphology characterized by Ranganathan et al. (Ranganathan et al., 1970) and imparted a prescribed motion based on echocardiographic measurements (Seo et al., 2014). Ideally, a patient-specific mitral valve model extracted from the 4D imaging data should be employed with a full FSI-based computation to simulate the leaflets motion and deformation accurately. However, the spatio-temporal resolution limitations of the current image acquisition methods, and our less-than-complete understanding of the constitutive and structural properties of the mitral leaflets may not allow for such a simulation to be viable for now.

Lastly, the surface trabeculae may not be fully resolved in the present model. However, given the highly complex coupled nonlinear system of governing equations simulating the blood flow inside a complex moving system of ventricle and mitral valve leaflets, resolving the trabeculae on par with the image resolution is not viable at this time. More advanced algorithms for the proper treatment of highly complex immersed boundaries are necessary for such a simulation. Some recent efforts towards minimizing these limitations are made by Dillard et al. (Dillard et al., 2014) where level-set based meshless methods are being developed to solve for blood flows directly from medical images which would greatly simplify the preprocessing steps in the current model, especially when 4D imaging data would be available at a low cost. However, these methods have been demonstrated to be promising for arterial flows while further research has to be conducted to apply these techniques for intracardiac flows to deal with the complex motion of the heart chambers.
4.5. Summary

The impact of trabeculae and papillary muscles on the hemodynamics of the left ventricle has been investigated here using high resolution simulations employing an immersed boundary method based flow solver. The flow field is compared between the two different models of the left ventricle – the first model comprises a trabeculated endocardium (TLV) which includes trabeculae and papillary muscles; while, the second model is the smooth left ventricle (SLV) whose endocardium is devoid of any surface irregularities. The key conclusions of the current study are:

(a) While the presence of the trabeculae and papillary muscles significantly increase the viscous dissipation in the flow, the magnitude of this increase is negligible compared to the total pressure work associated with the left ventricle. Thus, the trabeculae and papillary muscles do not have any measurable effect on the overall hydrodynamic efficiency of the ventricle.

(b) While the papillary muscles seem to represent only a small (10%) area blockage to the mitral jet, this blockage is accentuated by the boundary layers that form on the papillary muscles as well as the recirculating flow in the wake of the muscles. These muscles act in concert to guide the mitral jet deeper into the apical region and energize the apical flow.

(c) In addition to a deeper penetration of the mitral jet, the other significant effect of the papillary muscles on the flow pattern observed here is the migration of the mitral jet from the posterior wall for the SLV to towards the anterior wall of the LV for the TLV. It is however not clear the degree to which, patient-specific variations in the morphology of the papillary muscles would modulate this effect.
(d) Overall, the net washout in the apical region as measured by the mean and RMS scalar concentration is similar in the two models indicating that the trabeculated endocardium is at least as effective as the smooth wall in minimizing flow residence time in the apical region. Given the more energetic apical flow and the slightly lower end-systolic RMS value of the TLV model, it may be argued that the trabeculae and papillary muscles might marginally reduce the risk of thrombogenesis.
CHAPTER 5. EFFECT OF FLOW PATTERNS IN LEFT ATRIUM ON VENTRICULAR FLOW DEVELOPMENT

5.1. Introduction

The left atrium (LA) has a complex structure (Al-Saady, Obel and Camm, 1999; Stefanadis, Dernellis and Toutouzas, 2001; Ho, Cabrera and Sanchez-Quintana, 2012). There are four inlets to the LA – two from the left pulmonary veins (LPVs) connected to the left lung positioned lowly near the mitral orifice (MO) and two more inlets from the right pulmonary veins (RPVs) connected to the right lung positioned higher with respect to the LA cavity. Additionally, there is a highly distensible and trabeculated muscular sac positioned inferomedially near the MO, called the left atrial appendage (LAA) (Al-Saady, Obel and Camm, 1999). While precise role of the LAA in the functioning of the heart and the atrium is not clear, it is prone to the generation of clots in conditions such as atrial fibrillation.

The complexity of the LA structure is further accentuated by its three-fold function during a cardiac cycle (Stefanadis, Dernellis and Toutouzas, 2001; Appleton and Kovacs, 2009; Ho, Cabrera and Sanchez-Quintana, 2012). The LA acts as a conduit passage during early ventricular filling (E-wave) when the ventricle passively relaxes and establishes a low pressure in its cavity driving the atrial flow through the mitral valve. During atrial filling (A-wave), the LA acts as a contractile booster pump forcefully delivering the blood into the left ventricle (LV). Further, the LA acts as a reservoir during ventricular systole and fills with blood from the pulmonary veins when the mitral valve is completely closed.
The complexity of the atrial hemodynamics has been the subject of a number of studies in the past (Fyrenius et al., 2001; Kilner et al., 2000; Park et al., 2013). In particular, Fyrenius et al. (Fyrenius et al., 2001) indicated that there is a huge disparity between the flow pathways of left and right pulmonary veins. The inflow from LPVs was indicated to form a rotational loop and is associated with longer pathways towards the mitral orifice although these veins are paradoxically located in proximity to the mitral annulus. On the other hand, the inflow from RPVs was found to be more aligned with the wall, with preserved velocity and direction before entering the mitral annulus. Additionally, it is also conjectured that the velocity distribution within and around the atrial vortices might produce a better ‘washing’ effect in LA and avoid intra-atrial flow stasis. Given the importance the functioning of the left-ventricle, the question as to how atrial flow patterns effect diastolic filling in the LV has also been brought up before. For instance, based on cardiac MR imaging, Kilner et al. (Kilner et al., 2000) suggested that asymmetric filling from the pulmonary veins generate sinuous asymmetric atrial flow pathways, and a complex rotational flow in the LA cavity, which tend to preserve the blood momentum towards the atrio-ventricular valves during ventricular diastole as well as systole.

Computational modeling has emerged as a powerful way of exploring some of these issues in cardiac hemodynamic (Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Pedrizzetti and Domenichini, 2005; Long et al., 2008; Schenkel et al., 2009; Krittian et al., 2010; Le and Sotiropoulos, 2012; Mangular et al., 2013; Seo and Mittal, 2013; Choi, Vedula and Mittal, 2014). Modeling approaches have been consistently improved by the inclusion of additional complexities (Domenichini et
al., 2007; del Alamo, Marsden and Lasherasa, 2009; Doenst et al., 2009; Tang et al., 2010; Kulp et al., 2011; Mihalef et al., 2011; Zheng et al., 2012; Seo et al., 2013; Hendabadi et al., 2013; Chnafa, Mendez and Nicoud, 2014) (Dillard et al., 2014) and these continue to provide new insights into the dynamics of blood flow in health and disease (Pedrizzetti and Domenichini, 2005; Watanabe, Sugiura and Hisada, 2008; Kulp et al., 2011; Le et al., 2012; Mangual et al., 2013; Seo and Mittal, 2013). The vast majority of cardiac computational models to date have however been single-chamber models (Vierendeels et al., 2000; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Long et al., 2008; Doenst et al., 2009; Schenkel et al., 2009; Krittian et al., 2010; Le and Sotiropoulos, 2012; Zheng et al., 2012; Seo and Mittal, 2013) which have focused either on the left or the right ventricles (Long et al., 2003; Pasipoularides et al., 2003; Saber et al., 2003; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Schenkel et al., 2009; Krittian et al., 2010) and in these models, the atria are modeled in highly simplistic ways; it is usual to replace the LA with a pipe or to mimic its presence by providing suitable time-dependent velocity profiles and inflow boundary conditions (Vierendeels et al., 2000; Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Long et al., 2008; Doenst et al., 2009; Schenkel et al., 2009; Krittian et al., 2010; Le and Sotiropoulos, 2012; Zheng et al., 2012; Seo and Mittal, 2013). However, the impact of this simplification on the ventricular flow development is still not well understood.

Long et al. (Long et al., 2003) have made initial attempts along this direction by investigating the effect of inflow boundary conditions on the ventricular flow. This is performed by changing the area of cross-section at the mitral orifice and providing
patches of hybrid velocity and pressure boundary conditions using commercial CFD software. Although, by itself the work is very interesting and lays the groundwork for the present investigation, there are several issues with this approach that does not provide a clear delineation of the impact of atrial flow on the ventricular flow. The mitral orifice is not fixed during a cardiac cycle as assumed in their work but instead changes its size, position and orientation during the cycle. Secondly, the presence of asymmetric leaflets was shown to aid left ventricular filling (Charonko et al., 2013) and to promote looped flow pattern in the LV (Seo et al., 2014) which was not included in their model; instead, the study tries to mimic the presence of valves using inflow boundary conditions. Finally, providing patches of zero gradient velocity and pressure might introduce spurious effects especially when applied on an inflow boundary that is very proximal to the mitral orifice which is considered fluid dynamically very “active”. It is not clear how much contribution would be to the physics of the problem and the observed consequences due to these spurious numerical errors. Moreover, commercial CFD packages are known to introduce high artificial dissipation that could have significant effect on the outcome.

The objective of the present study is therefore twofold: first, to examine and quantify the effect of the kinematics of flow in the LA on diastolic flow patterns in the LV, and second, to use these simulations to determine the level of fidelity needed in modeling the LA, in studies that are focused on LV flow dynamics. The study design employed here is to compare two LV models, one that includes a physiological LA and the one that does not (see Figure 5-2). In the first model, high resolution imaging data from 4D CT has been used to reconstruct the major chambers of the left heart (LA, LV, and Aorta (Ao)) following the methodology described in CHAPTER 2; while the latter model includes
only the LV and Ao, with the LA being modeled as a simple pipe created by extruding the mitral orifice along its axis (see Figure 5-2).

High resolution blood flow simulations were conducted in these two models by solving the incompressible Navier-Stokes equations (Eqns. (2-1), (2-2)) using immersed boundary method based solver as described in section 2.3. The mitral valve modeling methodology is based on previously reported prescribed kinematics approach (Ranganathan et al., 1970; Seo et al., 2014) using the leaflet angles measured from the present 4D CT data as described in section 2.2.2. Ventricular flow patterns are compared between these two models using various flow-based metrics and the corresponding differences are quantified. These results were then used to develop insights into the atrial flow and the effect of intra-atrial fluid dynamics on the flow patterns developed in the ventricle.

5.2. Methods

In order to investigate the effect of left atrium and the mitral valve on the intraventricular flow development, we employ the framework described in CHAPTER 2 to develop a computational model of the two chamber model of the left heart using high resolution 4D Cardiac CT images. The chambers comprise left atrium (LA), left ventricle (LV) and a portion of outflow tract in addition to the pulmonary veins (PVs) supplying inflow to the left atrium. The mitral valve (MV) is modeled using the previously reported simplified geometry (Ranganathan et al., 1970) and prescribed kinematics approach as discussed in section 2.2.2.
Figure 5-1. (a) Axial slice of contrast enhanced CT data with highlighted chambers of left heart. (b) Reconstructed chambers of left heart model from the volume CT (Figure 5-1a) with the indicated nomenclature. (c) Time variation of LV volume during the cardiac cycle. (d) Isometric view and flattened cylindrical projection of the mitral valve model (Ranganathan et al., 1970). (e) Measurement of mitral valve leaflet angles with respect to the base or mitral annulus plane as shown in Figure 5-1a. LPVs/RPVs: left/right pulmonary veins; LA: left atrium; LAA: left atrial appendage; MV: mitral valve; AL/PL: anterior/posterior leaflet; $L_{AL}$, $L_{PL}$: maximum lengths of AL and PL; LV: left ventricle; Ao: Aorta.

5.2.1. **Left heart and mitral valve models**

The computational model is based on a high-resolution 4D (3D space and time) CT scan of a normal human. The scanner employed is Toshiba 320 Aquilon One multidetector scanner (Toshiba Medical Systems Inc.) with a voxel resolution of about
0.43x0.43x0.5 mm³ (512x512x280 voxels) and the temporal resolution of 0.06s (20 volume frames per cycle). Each of these volume images is subjected to filtering using median filter for noise reduction and contrast enhancement (Rangayyan, 2004) until the blood lumen is clearly distinguished from the tissue. Subsequently, segmentation is performed using region growing algorithm (Rangayyan, 2004) in commercial software (Mimics, Materialise Inc). Figure 5-1a shows an axial slice of the CT data during mid-diastole with the chambers of the left heart highlighted while the reconstructed atrio-ventricular model is shown in Figure 5-1b. Apart from the left atrium (LA) and the left ventricle (LV), identified structures include the left pulmonary veins (LPVs), right pulmonary veins (RPVs), left atrial appendage (LAA), mitral valve (MV) and aorta (Ao). As mentioned earlier, the complexity of the LA anatomy can be appreciated from this figure. The time variation of the LV volume during the cardiac cycle is plotted using discrete symbols in Figure 5-1c. It is clear that errors associated with image acquisition, processing and segmentation generate noticeable spurious variation in the volume-time curve. A smooth spline is fit to these points as shown and this smooth variation is used for subsequent temporal interpolation between the key frames as described in the next section. The present model has an end-diastolic volume (EDV) of 210 ml and a stroke volume (SV, volume ejected by the LV in one cycle) of 90 ml which produces an ejection fraction (EF=SV/EDV) of 43% per cardiac cycle. While this EF is slightly lower than nominal values for a normal adult (which is typically about 55%), the reduced value is not expected to significantly change the ventricular fluid dynamics.

In the present study, the mitral valve is modeled as described in section 2.2.2. The morphology of the mitral valve is shown in Figure 5-2d that is based on previously
published data (Ranganathan et al., 1970; Seo et al., 2014) with the lengths of AL and PL measured to be \( L_{AL} = 2.7 \text{cm} \) and \( L_{PL} = 1.6 \text{cm} \), respectively from the CT data. As we know that the mitral valve cannot be fully open throughout the cycle and needs to be deformed with time, we have employed a prescribed kinematics model (Seo et al., 2014) without any fluid structure interaction (see section 2.2.2). In this procedure, the angles made by each of the leaflets with respect to the base of the mitral valve (\( \theta_{AL} \), \( \theta_{PL} \)) are measured from the CT data along the axial slice as shown in Figure 5-1a and is smoothly distributed across the span of the leaflets (Seo et al., 2014). Leaflet angle measurements obtained from the present CT data are shown in Figure 5-1e for both the leaflets. Although the present model is highly simplified in both geometry and motion, this is a viable approach that accurately captures the ventricular flow dynamics of particular interest.

Since the output of image processing and segmentation of 4D volume CT data is a set of triangulated surfaces for each of the 20 key frames over the entire cardiac cycle and that these surfaces do not maintain the same mesh topology across all the key frames, we perform a template-based surface registration as described in section 2.2.3 using the LDDMM method. A brief description of the algorithm is provided in Appendix A. Similar registration procedure is also applied for mitral valve as well as described in section 2.2.3. Subsequent to performing LDDMM registration, temporal interpolation is performed using periodic cubic splines, which ensures continuity of both velocity and acceleration while retaining the periodicity of the cardiac cycle (see section 2.2.3).
Figure 5-2. (a) Computational models used in the present investigation: (left) Physiological left heart model with anatomically correct LA, LV, and Aorta; (right) Simplified atrium model comprising physiological LV and Aorta while filling into LV takes place from a pipe created by outward extrusion of mitral orifice along its axis. Both these models have identical MV configuration as highlighted. (b) Computational domain with the physiological model immersed into it. (c) Orthogonal cross-sectional planes used for analysis of hemodynamic data. LA: left atrium; LV: left ventricle; MV: mitral valve; Ao: Aorta.

5.2.2. CFD-ready models and simulation parameters

Since the objective of the present study is to investigate the effect of atrial flow patterns on ventricular flow, we have created two different computational models – the
first model comprises a physiological left heart model with all the major chambers - LA, LV, and Aorta (left frame, Figure 5-2a) and in the second model, the atrium is replaced by a pipe (right frame, Figure 5-2a) via outward extrusion of the mitral orifice along its axis. It is to be noted that both these models have the same mitral valves included as a part of the LV. Hence, we have two models under investigation with near-identical behavior of the left ventricle, the mitral valve and the mitral annulus with only the atrium being different. A zero gradient velocity boundary condition is provided at all the open boundaries such as the pulmonary veins for the physiological model and at the pipe inflow for the simplified model. The outflow tract is fully closed during diastole and is opened using zero gradient velocity condition during systole for both these models; similarly, the mitral valve is fully closed during ventricular systole, thereby preventing any mitral regurgitation.

The heart model used in the present study is discretized with 52,852 triangular surface elements while the mitral valve is discretized using 12,000 elements. The entire surface is immersed in a Cartesian grid of size 11.5cm x 9.5cm x 15.8cm covered by a total of 384x256x256 (~25.2 million) cells (Figure 5-2b). The resolution is chosen based on the grid refinement study performed during experimental validation study (see section 3.2.5). The non-dimensional time step chosen in the present simulations is \(1 \times 10^{-4}\) which results in about 10,000 time steps per cardiac cycle. The flow Reynolds number based on peak diastolic area-averaged mitral velocity and mitral annulus diameter is about 2420 while the Womersley number based on mitral annulus diameter and cardiac cycle duration (~1.2 sec) is 19. Simulations are performed on Stampede high performance computing cluster (part of XSEDE program, TACC) with 512 CPU cores for 3 cardiac cycles and
the computation for one cardiac cycle takes about 3 days. Phase-averaging was performed across all the cardiac cycles and the comparison between the two computational models (physiological and simplified) is performed using this phase-averaged data unless otherwise mentioned explicitly. Orthogonal cross-sectional planes (A-A’) and (B-B’) are also projected for subsequent analysis and comparison of the hemodynamic data, as shown in Figure 5-2c.

5.3. Results

5.3.1. Flow patterns

5.3.1.1. Atrial flow and vortex topology

In this section, we describe the key features of the atrial flow patterns and vortex topology, especially with the aim of comparing them to previous data and to facilitate a deeper understanding of atrial vortex dynamics. Figure 5-3 shows streamlines, colored by the magnitude of velocity, in the atrial cavity during diastole (Figure 5-3A) and systole (Figure 5-3B) along two different views. In the left frame of Figure 5-3A, a complex looping of the flow ejected from the two LPVs during diastole could be identified while in the right frame of Figure 5-3A, this looping flow from the LPVs could be seen to be smoothly entering into the mitral orifice (MO). Additionally, the flow from the RPVs is seen entering the MO without any significant change in velocity or direction. The incoming flow from the RPVs is tightly confined between the LPVs’ generated circulatory flow in the LA and the outer periphery of the LA and takes a very direct, linear path to the mitral annulus; this observation is in general agreement with the in-vivo MR measurements of Fyrenius et al. (Fyrenius et al., 2001).
Figure 5-3. Flow field in left atrium visualized by streamlines colored by the magnitude of velocity during A. diastole and B. systole in two different views (left/right). RPVs: right pulmonary veins; LPVs: left pulmonary veins; MO: mitral orifice; LAA: left atrial appendage.

In Figure 5-3B, the streamlines in the atrial cavity during systole are visualized and these exhibit two distinct flow regimes in the atrial cavity similar to those seen during diastole. One is the complex vortex flow formed in the cavity due to the flow ejected out of LPVs while the flow from RPVs doesn’t seem to show significant interaction with this circulatory flow; instead it decelerates and forms an outer loop around this inner vortex flow due to LPVs. This shows that the flows from the right and left pulmonary veins filling the left atrial cavity behave very differently throughout the cardiac cycle. These effects have also been demonstrated earlier in Fyrenius et al. (Fyrenius et al., 2001) using in-vivo MR measurements. Thus, the overall flow pattern in the atrium is in line with what has been established in the literature.
Figure 5-4. Left atrial vortex dynamics and breakdown during ventricular systole. Vortex structures are visualized by $\lambda_{ci}$ criterion (imaginary part of complex eigen values of the velocity gradient tensor (Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005)) colored by the magnitude of velocity and the numbers indicate non-dimensional times.

Figure 5-4 shows the vortex structures inside the LA, visualized by the $\lambda_{ci}$ criterion (imaginary part of the complex eigen values of velocity gradient tensor (Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005)) and colored by the magnitude of velocity, during ventricular systole when the mitral valve is closed. As the atrial wall expands, four small vortex rings are ejected from the pulmonary veins (Figure 5-4A) and these are observed to propagate towards the center of the atrial cavity. We also note that the in-vivo, 2D echo-PIV based measurements of Park et al. (Park et al., 2013) also indicated the presence of small elliptic vortices in the atrial cavity of a normal heart and our results are, therefore, in line with these past observations.

The propagation of these vortex rings brings them into direct interaction (Figure 5-4B-D) with each other and this leads to vortex breakup and the formation of a large number of smaller vortex structures (Figure 5-4E-F) that dissipate rapidly over the next
few phases (Figure 5-4G-H). Collision of vortex rings at various inclination angles and their subsequent breakdown due to the non-uniform stretching and viscous dissipation has been studied extensively in the past (Lim, 1989) in a simplified experimental setup and it is interesting to observe this phenomenon occur in a realistic setting of the left atrium. The complexity of the present case is further accentuated due to the presence of four vortex rings colliding with each other at various angles, circumscribed by a moving wall.

It should be pointed out that in addition to the vortex breakup and viscous dissipation, vorticity annihilation between the vortex patches of opposite rotation is another key mechanism for the rapid diminishment of these vortices. The net result of all these combined effects of collision, annihilation and viscous dissipation is that the coherent vortex rings generated by the pulmonary veins at the beginning of ventricular systole have mostly disappeared by the beginning of ventricular diastole. Thus, as the mitral valve opens during diastole and the flow from the atrium is ejected into the ventricle, we expect there to be little in terms of convection of atrial vortices into the ventricle. Further discussion regarding atrio-ventricular vortex structures is presented in the following section.

**5.3.1.2. Atrio-ventricular vortex patterns**

Figure 5-5 shows instantaneous vortex structures during the 3rd cardiac cycle in the physiological model at the indicated time instants. Vortex structures are plotted as isosurfaces of $\lambda_{ci}$ ($\lambda_{ci} = 66.67$ s$^{-1}$) at all the instants and are colored using the magnitude of velocity. As previously reported (Le and Sotiropoulos, 2012; Seo and Mittal, 2013; Doenst et al., 2009; Chnafa, Mendez and Nicoud, 2014; Bellhouse, 1972; Charonko et al.,
2013; Toger et al., 2012), a vortex can be identified pinching off from the mitral leaflets during early diastole (t*=2.2) and it propagates towards the lateral wall. At the same time, the LA, which acts at this instance like as a passive conduit, is filled with vortex rings ejected from each of the pulmonary veins (LPVs and RPVs). Subsequently (t*=2.3), the diastolic ventricular vortex impinges onto the LV lateral wall and gets disrupted, giving rise to several small scale vortex structures. By this time, the vortices from the pulmonary veins in the LA interact with each other and disintegrate before being scattered in the atrial cavity. Furthermore, the flow advances into the LV cavity towards the apex due to fluid inertia and momentum gained during early filling (t*=2.4). On the other hand, the atrial vortices are found to rapidly dissipate in the atrial cavity. By the end of diastole (t*=2.5), the atrial contraction (where the atrium acts like a booster pump) produces distinct vortex rings in the LA and also generates another strong vortex ring in the LV. The movement of the vortices indicates an overall a clockwise circulatory flow pattern in the ventricular cavity by the end-diastole which has been observed by several investigators in the past (Kilner et al., 2000; Domenichini, Pedrizzetti and Baccani, 2005; Pedrizzetti and Domenichini, 2005; Watanabe, Sugiura and Hisada, 2008; Kheradvar et al., 2010; Sengupta et al., 2012; Seo and Mittal, 2013; Seo et al., 2014). These patterns will be clearly elucidated from the velocity vectors plots in the next subsection.
Figure 5-5. Three dimensional instantaneous vortical structures in the physiological model (see Figure 5-2a) visualized by $\lambda_{ci}$ criterion (imaginary part of complex eigen values of the velocity gradient tensor (Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005) and colored by the magnitude of velocity. Numbers indicate various non-dimensional times during the third cardiac cycle.

During systole ($t^*=2.6-2.9$), the flow from the ventricle is ejected out into the aorta through the outflow tract. Flow pattern inside the aorta is highly transitional with several discrete eddies ejected at high velocities. However, by the end of systole ($t^*=2.9$), the ventricular cavity is almost devoid of any vortical structures before the onset of the next cardiac cycle. On the other hand, the LA that acts as a reservoir with the mitral valve completely closed is refilled with vortices from the pulmonary veins during ventricular systole. Nevertheless, these vortices interact and dissipate towards the end of filling following which a fresh cycle is repeated again.
Figure 5-6. Three dimensional instantaneous vortical structures in the simplified model (see Figure 5-2b) visualized by $\lambda_{ci}$ criterion (imaginary part of complex eigen values of the velocity gradient tensor (Zhou et al., 1999; Chakraborty, Balachandar and Adrian, 2005) and colored by the magnitude of velocity. Numbers indicate various non-dimensional times during the third cardiac cycle.

Figure 5-6 shows vortex structures in the ventricle of the second model with a pipe replacing the atrium, at time instants identical to that in Figure 5-5. The plots do not indicate any significant differences between the intra-ventricular vortex structures for the two models despite the development of a complex three-dimensional vortical field in the LA of the physiological model. Only a few differences in terms of discrete small scale vortex structures scattered around the LV apex could be discerned in the physiological model. This seems to indicate that the complex flow patterns formed in the left atrium have minimal influence on the development of intraventricular hemodynamics.
5.3.1.3. **Averaged flow**

The phase-averaged flow field is compared in Figure 5-7 between the physiological model (Figure 5-7a) and simplified model (Figure 5-7b) along B-B’ plane at indicated key time instants during diastole (left, t*=0.3; right, t*=0.5). Whereas the phase-time-averaged flow field computed over entire diastole is compared in Figure 5-8 between the physiological (Figure 5-8a) and the simplified (Figure 5-8b) models along A-A’ (left) and B-B’ (right) planes. The flow field is visualized in terms of velocity vectors superposed over the contours of velocity magnitude as shown in the figures. Overall, no significant differences could be discerned from the velocity field comparison between the two models in the ventricular cavity not only at distinct time instants (Figure 5-7) but also with respect to the time averaged flow during diastole (Figure 5-8) despite producing significant differences in the upstream atrial flow. This is in agreement with our earlier observation made from the three-dimensional vortex structures (Figure 5-5 and Figure 5-6). Further, it is seen that the velocity vectors in the LA align themselves along the
mitral axis and converge smoothly towards the mitral valve (at $t^*=0.3$ in Figure 5-7a and Figure 5-8a) and this effect is explored in detail in later sections.

Figure 5-8. Comparison of phase-time-averaged velocity field during diastole between (a) physiological, and (b) simplified models along A-A’ plane (left) and B-B’ plane (right) (see Figure 5-2 for plane configuration).

It is interesting to note that two distinct flow regimes could be identified in the LA (as pointed in left frame, Figure 5-8a). On one side is a relatively lower velocity flow that smoothly loops from the LAA towards the mitral orifice filling up most of the LA cavity. On the other hand, the flow from RPV enters the mitral orifice at higher velocity. Both these streams merge as they approach the mitral orifice and accelerate through the mitral valve. In contrast, while the flow pattern in the pipe in Figure 5-8b is quite different and in line with what is expected of a pulsatile flow in a pipe, the flow pattern near the mitral orifice is quite similar to that observed above for the physiological LA model. This effect is also noticed in Figure 5-7a at $t^*=0.3$ and is attributed to the rapid increase in the flow velocity as it converges and streamlines itself before entering the mitral orifice and thereby, obtain a fairly uniform velocity profile at the mitral annulus.
It is noted that the ventricular flow pattern observed here is fairly consistent with the previously published literature (Kilner et al., 2000; Domenichini, Pedrizzetti and Baccani, 2005; Watanabe, Sugiura and Hisada, 2008; Kheradvar et al., 2010; Sengupta et al., 2012; Toger et al., 2012; Charonko et al., 2013; Seo and Mittal, 2013; Seo et al., 2014) where a strong jet emanating from the mitral orifice curls up at the leaflets, producing a vortex ring that impinges on the lateral wall producing a clockwise circulation in the ventricular cavity. While the LV flow patterns in both the models appear very similar, certain subtle differences could be recognized between the two averaged flow fields in the ventricular cavity. Due to the highly transitional nature of the flow subsequent to early vortex disruption in the ventricular cavity, the atrial vortex disruption is found to be markedly different between the two models (as indicated in Figure 5-7b at t*=0.5). A circular flow pattern could be found around the tip of the anterior mitral leaflet in the simplified model (Figure 5-8b, B-B' plane) while a straight upward flow with a slight tilt towards the anterior mitral leaflet is evident in the physiological model (Figure 5-8a).
5.3.1.4. Velocity profiles

While the previous two subsections provide a qualitative comparison of vortex structures and flow patterns between the two models, in this section, we provide a more quantitative comparison of the flow velocity in the two models. Figure 5-9 shows a comparison of the profiles of the longitudinal component of velocity along various transverse sections (H₁-H₁₂) of B-B’ plane between the physiological and the simplified models in. The plots shown here are for a single phase slightly beyond peak diastole ($t^*=0.3$) and the L₁ norm of the difference in these profiles between the two models is expressed in the plot as a percentage of the peak mitral flow velocity ($U_m=63\text{cm/s}$). This phase corresponds to the most energetic diastolic flow and therefore, this phase is most consequential to the development of diastolic flow patterns. Comparison at other phases
does not indicate any other interesting features and we therefore do not show the other phases here.

The plots indicate notable differences in the flow velocity profiles inside the LA cavity and the region proximal to the mitral orifice. Among all the velocity profiles, H1 records the highest deviation (14.3%) of physiological model with respect to the simplified model. This is attributed to the larger cross-sectional area of the physiological atrium at the level of H1 than that of the simplified model where the cross-sectional area is same as that of the mitral annular area. Hence, a diffused velocity profile that exhibits more spread and lower magnitude is found in the LA of the physiological model. However, as the flow is guided into reduced cross-section at H2 and H3, the flow gets streamlined and hence, “catches up” with that of the simplified model. Eventually, both the profiles become almost indistinguishable at the mitral orifice (H4). This argument is also supported by the gradual reduction in the L1 norm of the difference from 10.3% (H2) to 4.2% (H4). It is also noted that both the models produce a near-uniform velocity profile at the level of mitral orifice (H3 and H4).

The difference in the velocity profiles decreases further as the flow is guided through the mitral annulus by the valve leaflets at H5 and H6 with each profile contributing to a normalized difference of less than 3%. The asymmetric alignment of the mitral leaflets causing the anterior leaflet to have lesser opening than the posterior leaflet, skews the jet towards the lateral wall (H5-H7). After impingement, regions of reversed flow could be seen originating near the tips of the mitral leaflets (H7) due to vortex ring and the sharp peaks begin to diffuse across the section down into the ventricular cavity (H8-H9). Significant oscillations can be noticed in profile H7 away from the anterior leaflet for the
simplified model compared to physiological ones. The source of these oscillations are, however, precisely not clear although could perhaps be attributed to the transitional nature of the flow where small differences in leaflet motion could be eventually amplified. It is also noted that no significant difference in velocity field between the two models could be discerned around this region from Figure 5-7 at t*=0.3 in order to correlate these fluctuations.

Eventually, the flow decelerates and produces a diffused velocity profile that spreads towards the septal wall (H_{10}-H_{12}). Although the velocity profiles nearly overlap at the level of the mitral orifice (H_{3}-H_{5}), the same is not strictly reflected in the ventricular cavity. This could be due to small local differences in the geometry and motion of the ventricle and the valves between the two models as a result of diffeomorphic mapping. Additionally, small perturbations introduced in the LA could gradually amplify and manifest themselves in the ventricular cavity due to the highly transitional nature of the flow. Nevertheless, the profiles exhibit a maximum difference of 7.4% in the ventricular cavity despite the complex anatomy and the associated flow field developed in the atrial chamber.

5.3.2. Global ventricular flow metrics

In this section we compare a number of global metrics of ventricular flow in order to further establish the magnitude of the effect that the atrial flow has on ventricular hemodynamics.
Figure 5-10. Comparison of various quantitative metrics between the physiological and the simplified models: (a) $L_1$ norm of point-wise difference of each component of velocity normalized by peak mitral flow ($U_m=63\text{cm/s}$); (b) Volume averaged kinetic energy density ($KE'$) and rate of dissipation of energy per unit volume ($\Phi'$); (c) Time averaged wall shear stress (AWSS) where the averaging is performed during diastole; (d) Area averaged wall shear stress ($\tau'$). It is noted that only ventricular volume was considered while computing these quantitative metrics.

In Figure 5-10a shows the normalized $L_1$ norm of the point-wise difference of each component of the velocity field between the physiological model and the simplified model plotted as a function of time. The normalization was performed using the peak area-averaged mitral velocity, $U_m (=63\text{cm/s})$. While the maximum $L_1$ norm is about 10% of $U_m$ and occurs at the beginning of systole, no noticeable difference was found between
the two models for each component of the velocity field. During early diastole the norm of the difference is quite low (~2-3%) but it increases rapidly during peak diastole up to 5% when the vortex impinges the lateral wall and generates a cascade of eddies in the ventricular cavity. This sharp increase in errors could be attributed to the highly transitional nature of the flow and non-linear vortex interactions where small differences introduced in the atrial flow would get amplified. This trend of increase continues during the rest of the diastole although the rate of increase is very gradual. During systole, it is noted that the errors decrease monotonically in synchrony with the decay of vortices in the ventricular cavity and the flow ejection. However, the overall errors are lower than 10% throughout the cardiac cycle.

In Figure 5-10b is plotted the volume-averaged kinetic energy density (KE’) on the primary axis (lines) while the rate of dissipation of kinetic energy per unit volume (Φ’) is plotted on the secondary axis (symbols) as indicated. A reasonable match is produced in KE’ between the physiological and the simplified models which is consistent with the velocity comparison as described earlier. The L_1 norm of the difference between the two data sets was computed to be about 2.8% of the peak KE’ while the maximum deviation of the simplified model from that of the physiological model is about 10.5% which occurs during peak diastolic filling. Initially, the flow inside the ventricular cavity is almost at rest that translates to a negligible KE’ and then, the KE’ rises sharply during early filling producing distinct peaks corresponding to atrial filling and early systole before decaying to very low values. On the other hand, Φ’ which is evaluated using the derivatives of velocities shows higher differences during early diastole. The maxima of Φ’ for the simplified model differs from the physiological model by about 20% while the
overall $L_1$ is still kept low at 3.5% of the maximum $\Phi'$. The time variation of $\Phi'$ closely follows that of $KE'$ wherein initially $\Phi'$ is almost zero and sharply rises to peak during early diastole. Atrial filling produces another peak though not as pronounced as that of $KE'$.

A surface contour plot of the magnitude of the time averaged wall shear stress (AWSS) is plotted for the physiological (left) and the simplified (right) models in Figure 5-10c while the time variation of the area-averaged wall shear stress ($\tau'_w$) is compared in Figure 5-10d. Wall shear may be considered a proxy for near-wall residence time, which has implications for thrombogenesis. From Figure 5-10c, it is clear that although the overall shear distribution on the ventricular surface appears similar between the two models, certain regions of concentrated shear are apparent around the sites of vortex impingement on the lateral wall of the simplified model. In general, the lateral wall has relatively higher shear stress than the apical and the septal walls for both the models. This is consistent with our earlier observation of the impingement of the mitral jet on the lateral wall that could be produce high shear rates while the apical and the septal wall is smoothly washed by the circulatory flow at lower strain rates. Additionally, it is also evident that the “necks” of pulmonary veins in the LA are subjected to higher shear while negligible shear stress is noted elsewhere on LA including LAA. On the other hand, the shear stress is very much uniform on the extruded pipe of the simplified model consistent with a pipe flow with a Womersley velocity profile.

It is noted from Figure 5-10d that $\tau'_w$ of the simplified model deviates sharply from that of the physiological model during peak diastole although both the models exhibit unsteadiness during this regime and that the pattern of the oscillations is consistent
between the two models. The differences are somewhat smoothened subsequently but reappear before end-diastole although the deviation is relatively milder. During systole, the variation of $\tau'_w$ is almost similar between the two models. It is noted that the maximum difference in $\tau'_w$ between the two models is about 22% of the peak value while the $L_1$ norm of the difference is about 4% of the peak.

5.4. Discussion

In the present study, numerical simulations have been used to understand the role of the vortices and flow patterns in the left atrium (LA) on the diastolic ventricular flow patterns. Two distinct models are employed in this study: in the first model, medical imaging data is used to create a multi-chamber model of the left heart that includes LA, LV and Aorta; whereas in the latter, the LA is simplified while the other chambers (LV and Ao) are intact. The simplification of LA involves outward extrusion of the mitral orifice along its axis to form a pipe through which the filling takes place into the LV. As it is already proved that mitral valve has a significant role on ventricular fluid dynamics (Charonko et al., 2013; Seo et al., 2014), we include same MV models in both these models. The MV models employed here is a prescribed kinematics model (Seo et al., 2014) based on physiological data, which although not subject specific, is still expected to be a sufficiently reasonable representative of the physiological MV.

The primary focus of the study is on assessing the effect of atrial flow patterns and vortices on ventricular flow. The left ventricle is arguably the most important chamber of the mammalian heart since it provides much of the pumping power that drives blood to the body and is also the component of the heart that is most susceptible to consequential conditions such as various cardiomyopathies, myocardial infarction and valvular diseases.
Consequently a vast number of experimental and computational modeling studies of the heart have focused on the LV. These include the seminal experiments of Bellhouse et al. (Bellhouse, 1972; Bellhouse and Bellhouse, 1969) and the pioneering computational efforts of Peskin et al. (Peskin, 1972; Peskin, 1977; McQueen and Peskin, 1989; Peskin and McQueen, 1989) as well as the more recent experimental (Cenedese et al., 2005; Kheradvar and Gharib, 2009; espa et al., 2012; Charonko et al., 2013; Fortini et al., 2013) and computational modeling (Cheng, Oertel and Schenkel, 2005; Domenichini, Pedrizzetti and Baccani, 2005; Pedrizzetti and Domenichini, 2005; Long et al., 2008; Schenkel et al., 2009; Krittian et al., 2010; Le and Sotiropoulos, 2012; Mangual et al., 2013; Seo and Mittal, 2013; Choi, Vedula and Mittal, 2014) efforts. In most of these models that employed simplified laboratory ventricular models, it has been usual to model LA as a simplified pipe attached to the LV cavity at the mitral orifice. The recent advances in medical imaging have expanded the scope of modeling intra-ventricular flows from simple canonical shapes to complex image-based flow modeling strategies. These advances provide an opportunity to explore atrio-ventricular hemodynamic interaction and in particular, to assess the hemodynamic impact of the complex atrial flow on the ventricular flow patterns. The study design employed here is well suited to understand the coupling between atrio-ventricular hemodynamics.

The simulations presented here were conducted on a high resolution Cartesian grid comprising about 25.2 million cells. Flow simulations are carried out over three 3 complete cardiac cycles and the data has been phase-averaged over all the cycles before being used for analysis. Computed flow field has been visualized here using streamlines (Figure 5-3), three dimensional vortex structures (Figure 5-4, Figure 5-5 and Figure 5-6).
and averaged velocity field along cross-sectional planes (Figure 5-7 and Figure 5-8). It is noted that the ventricular flow field obtained here correlates very well with previous studies. Firstly, a uniform plug flow profile is seen near the mitral orifice which has been described by several researchers in the past (Kheradvar et al., 2010; Sengupta et al., 2012). Secondly, a vortex ring is seen to be pinched off from the tips of mitral leaflets which propagates and impinges on the lateral wall. This has also been well established in the past (Kilner et al., 2000; Pasipoularides, 2010; Mihalef et al., 2011; Sengupta et al., 2012; Toger et al., 2012; Chnafa, Mendez and Nicoud, 2014). Subsequently, the vortex ring disintegrates and a circulatory flow pattern is produced in the ventricular cavity that sweeps the flow from the lateral wall along the apical region towards the septum (Kilner et al., 2000; Hong et al., 2008; Long et al., 2008; Faludi et al., 2010; Mihalef et al., 2011; Toger et al., 2012; Charonko et al., 2013; Seo and Mittal, 2013; Seo et al., 2014). Although this pattern of flow redirection was previously conjectured to be hydro-dynamically efficient (Kilner et al., 2000; Pedrizzetti and Domenichini, 2005), later studies argued that this pattern contributes to enhanced mixing and apical washout than efficiency (Watanabe, Sugiura and Hisada, 2008; Seo and Mittal, 2013). Nevertheless, the present simulations capture the well-established ventricular looped flow dynamics accurately. It is noted that the present simulations not only predict the ventricular flow in consistent with the previous works but also the flow inside left atrium was computed in line with clinical measurements. For instance, velocity measurements in the LA performed by Fyrenius et al. (Fyrenius et al., 2001) using 3D phase contrast MRI data indicated that the flow from superior RPV is strained between the LA cavity flow and the
atrial wall while the flow from the LAA and the nearby LPV loops to enter the mitral orifice. These flow features are reproduced in the current study.

Vortex structures in the form of vortex rings in the left atrium are primarily produced from the pulmonary veins in the upper part of the atrial cavity and these structures undergo mutual interaction leading to a complex flow field (Figure 5-4 and Figure 5-5). The development of four vortex rings from each of the pulmonary veins at an angle to each other, circumscribed by a moving wall, leads to a non-uniform stretching and breakup of these vortex tings. This, coupled with vorticity annihilation and viscous dissipation, leads to a rapid decay of these vortices by the time ventricular diastole begins.

As the flow enters into the lower part of the atrial cavity, the gradual reduction in area causes the flow to be smoothly streamlined and become more regular similar to that of the pipe flow (velocity profiles H1-H4 of Figure 5-9). Further reduction in area at the mitral leaflets causes the flow to accelerate and subsequently impinge on the lateral wall of the LV (Figure 5-5). However, it is the dissipation of the atrial vortices due to vorticity annihilation and weakening of the core of the vortex leading to a vortex breakdown in the upper part of the atrial cavity that leads to regularization of flow in the lower part. This supports the observation made by Fyrenius et al. (Fyrenius et al., 2001) that the unique morphology of the left atrium enhances mixing and avoids stasis in the atrium; but at the same time leads to rapid dissipation of these vortices resulting in a near-uniform flow at the level of mitral orifice.

The simulation results indicate that the complex flow features in the atrium have an insignificant impact on the ventricular filling. 3D vortex structures (Figure 5-5 and Figure 5-6) and averaged velocity fields (Figure 5-7 and Figure 5-8) do not show any noticeable
differences between the simplified and the physiological atrium models. Velocity profiles plotted along the long-view plane (B-B’) indicate that the maximum difference in the velocity between the two models is at most about 10% of the peak mitral velocity (Figure 5-9). Comparison of kinetic energy (KE’), dissipation (Φ’) and surface shear (τ’_w) within the ventricular cavity also showed a similar overall trend between the two models with global differences less than 5% (Figure 5-10). However, during peak diastole when the flow is highly transitional, peak differences of up to 10% for KE’, 20% for Φ’, and 22% for τ’_w are observed (Figure 5-10). Given that viscous dissipation in the ventricle accounts for less than 1% of the total pressure work of the ventricle (Watanabe, Sugiura and Hisada, 2008; Seo and Mittal, 2013), the 20% difference in Φ’ is not energetically significant.

A recent study (Seo et al., 2014) has examined the effect of the mitral valve on ventricular flow patterns for a ventricular model that employed a pipe to model the left atrium. The physiological mitral valve model employed in this earlier study was very similar to the one used in the current study, and this study compared two cases: a case with no mitral valve and the one with the physiological mitral valve. The study found that the mitral valve produces significant changes not only in the filling velocity but also in the overall rotational motion, mixing and washout associated with the mitral jet. Coupled with the results of the current study, it may be concluded that the mitral valve model is far more essential for accurate modeling of the ventricular flow than a physiologically representative left-atrium.

In order to address this question, we have considered a case where the mitral valve has been removed from the physiological model while retaining all other features of it.
Simulations have been conducted for the blood flow in this new model in exactly the same way as was performed previously for the physiological model and the results have been compared in Figure 5-11.

Figure 5-11. Comparison of vortex structures (left) and phase-time-averaged velocity field along A-A’ and B-B’ planes (right) during late diastole (t*=0.4) between (a) physiological model with mitral valve; (b) physiological model without mitral valve.

Drastic differences in the ventricular vortex topology could be discerned from Figure 5-11 after the removal of the mitral valve from the physiological model. The vortex ring
is positioned closer to the mitral orifice throughout the cardiac cycle for the no-valve model and the flow does not penetrate as deep into the LV cavity. This is because the flow is not constrained between the asymmetric leaflets and hence, does not accelerate to higher velocities to produce a circulatory flow from the lateral wall to the septum sweeping through apex. It is interesting to note that the vortical structures obtained after exclusion of the mitral valve (Figure 5-11B) very much resembles the one described by Le et al. (Le and Sotiropoulos, 2012; Le et al., 2012) who have used 4D MRI images to extract the computational LV geometry with simplified atrium, but did not include MV in their model. This comparison therefore confirms the notion that the inclusion of mitral valve is essential to realizing a physiological flow pattern inside the ventricle.

The above observations have two important implications: first, they indicate that the morphology and physiology of the left atrium is designed so as to generate a highly regularized flow at the mitral annulus. From the point-of-view of cardiac physiology, this implies that small changes in the dynamics of the left atrium would not cascade into the functioning of the left ventricle which is, arguably, the most critical element of the cardiac pump. This suggests a certain level of inherent robustness in functioning of the left heart. The second implication is that simple models of the left atrium should suffice in computational or experimental studies where the phenomenon of interest is related to the ventricle or anything downstream of it. In our own study for instance, we have found that the model with the pipe-shaped left atrium requires 25% fewer computations than the physiological left atrium. For experimental models, this also implies that significant simplification could be made in the modeling of the left atrium. The inclusion of mitral
valve in these models is, however, very important to realize physiologically correct flow patterns in the left ventricle.

5.5. Summary

Numerical simulations have been used to elucidate the flow and vortex patterns in the left atrium and their effect on the dynamics of ventricular flows. Vortex topology in the left atrium is dominated by the generation and interaction of vortex rings from the four pulmonary veins. However, the vortex breakup, annihilation and viscous dissipation are observed to rapidly diminish the strength of these vortices. The flow pattern in the left atrium is characterized by a circulatory flow generated by the left pulmonary veins and a direct stream from the right-pulmonary veins to the mitral annulus. These patterns are in general agreement with previous studies (Kilner et al., 2000; Fyrenius et al., 2001; Park et al., 2013).

Due to the rapid dissipation of the vortices in the atrium, the flow through the mitral valve during ventricular diastole is highly regularized and a comparison of the physiological and pipe models of the left atrium showed that the overall differences in the ventricular flow velocity between the two models is limited to about 10% of the peak mitral flow velocity. This suggests that the morphology and physiology of the left atrium is designed so as enhance the robustness of the hemodynamics of the left ventricle. This also implies that significant simplification can be made in computational and experimental models that are focused on investigating ventricular hemodynamics.
CHAPTER 6. SUMMARY

A case has been made in the current study that computational modeling of intracardiac flows has the potential to significantly impact the diagnosis and treatment of cardiovascular disease non-invasively. High-fidelity image based modeling and simulation of cardiac flows enabled by the proliferation of four-dimensional medical imaging, continuously increasing computing speeds while simultaneously decreasing computational costs, presents an alternative non-invasive and cost-effective diagnostic method to counteract the increasing trends in the prevalence of cardiovascular disease. Current non-invasive diagnostics that predominantly rely on medical imaging alone could be significantly enhanced due to computational modeling of cardiac flows as it provides additional hemodynamic variables such as pressure field, accurate flow patterns, residence times, shear, etc. which complement the anatomical information available from the medical images. Modeling and simulations also present the cardiologist/cardiac surgeon with the possibility to optimize surgical interventions and carefully selecting the best treatment option in data-driven way rather than the heuristic approach that is the current norm.

However, real-time and bedside diagnosis of cardiovascular disease using patient-specific modeling is still far from realization due to a number of challenges involved. Some of these identified in the present study include: (a) the lack of rapid automatic methods to convert medical images into CFD-ready models; (b) high computational costs involved in performing flow simulations; (c) the need for improved valve modeling procedures; and (d) rapid validation of patient-specific computational models. Most of these challenges are attributed to the inherent complexity of cardiac flows which involve

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large scale motion and deformation of the wall chambers, complex geometries with very fine surface detail, strong fluid-structure interaction at the atrio-ventricular valves, high Reynolds number transitional flows in addition to the imaging artifacts and other cycle-to-cycle variabilities for certain pathological conditions. Nevertheless, the framework that has been developed here is more generic and further research that facilitates inclusion of multi-physics models such as electrophysiology and structural interaction, advanced image analysis algorithms that could automatically generate CFD ready models from medical images, valve models, and advanced computing technologies such as Graphical Processing Units (GPUs) and Many Integrated Core products (MICs), which could bring supercomputing performance to the desktop environment, could potentially transform the landscape towards real-time non-invasive diagnosis of cardiovascular disease through patient-specific simulations.

As a precursor to developing a CFD-based method to analyze patient-specific heart function, a comprehensive quantitative validation of intraventricular flow between a highly resolved simulation and an experiment was conducted. The major sources of modeling uncertainty are identified and quantified. Among these, the uncertainty in the estimation of the instantaneous flow rate as well as the non-axisymmetric nature of the mitral flow in the experiment was found to be the most significant. The phase-averaged velocity profiles and vorticity contours from the simulation were found to match reasonably well with the experiment given the uncertainty inherent in the modeling procedure. Flow-wave propagation velocity \( V_p \) and the ratio, \( V_E/V_p \) computed from “virtual” color M-mode (CMM) as well as the vortex propagation velocity showed a very good agreement between simulation and experiment. The study demonstrates the
challenge of modeling the flow even in a relatively simple experimental model of the left-ventricle, and underscores the need for continued quantitative validation to clearly understand the limitations of such simulations.

To understand the impact of surface trabeculae and papillary muscles, the flow field is computed in two models of the left ventricle – a smooth model devoid of any surface irregularities due to trabeculae and papillary muscles; secondly, a trabeculated wall which included trabeculae and papillary muscles. The flow field was found to be significantly different in the trabeculated model compared to the smooth model. Firstly, while the presence of the trabeculae and papillary muscles significantly increase the viscous dissipation in the flow, the magnitude of this increase is negligible compared to the total pressure work associated with the left ventricle. Thus, the trabeculae and papillary muscles do not have any measurable effect on the overall hydrodynamic efficiency of the ventricle. Secondly, while the papillary muscles seem to represent only a small (10%) area blockage to the mitral jet, this blockage is accentuated by the boundary layers that form on the papillary muscles as well as the recirculating flow in the wake of the muscles. These muscles act in concert to guide the mitral jet deeper into the apical region and energize the apical flow. Thirdly, in addition to a deeper penetration of the mitral jet, the other significant effect of the papillary muscles on the flow pattern observed here is the migration of the mitral jet from the posterior wall for the SLV to towards the anterior wall of the LV for the TLV. It is however not clear the degree to which, patient-specific variations in the morphology of the papillary muscles would modulate this effect. Lastly, the net washout in the apical region as measured by the mean and RMS scalar concentration is similar in the two models indicating that the trabeculated endocardium is
at least as effective as the smooth wall in minimizing flow residence time in the apical region. Given the more energetic apical flow and the slightly lower end-systolic RMS value of the TLV model, it may be argued that the trabeculae and papillary muscles might marginally reduce the risk of thrombogenesis.

Numerical simulations have been used to elucidate the flow and vortex patterns in the left atrium and their effect on the dynamics of ventricular flows. Vortex topology in the left atrium is dominated by the generation and interaction of vortex rings from the four pulmonary veins. However, the vortex breakup, annihilation and viscous dissipation are observed to rapidly diminish the strength of these vortices. The flow pattern in the left atrium is characterized by a circulatory flow generated by the left pulmonary veins and a direct stream from the right-pulmonary veins to the mitral annulus. These patterns are in general agreement with previous studies (Kilner et al., 2000; Fyrenius et al., 2001). Due to the rapid dissipation of the vortices in the atrium, the flow through the mitral valve during ventricular diastole is highly regularized and a comparison of the physiological and pipe models of the left atrium showed that the overall differences in the ventricular flow velocity between the two models is limited to about 10% of the peak mitral flow velocity. This suggests that the morphology and physiology of the left atrium is designed so as enhance the robustness of the hemodynamics of the left ventricle. This also implies that significant simplification can be made in computational and experimental models that are focused on investigating ventricular hemodynamics.
A. LDDMM mapping

In the LDDMM framework, the surfaces and curves are viewed as manifolds embedded in three-dimensional space, \( \mathbb{R}^3 \) and the deformation is a diffeomorphism, \( \varphi \) of \( \mathbb{R}^3 \). In other words, the mapping \( \varphi \) is a smooth one-one onto mapping with a smooth inverse. Therefore, it preserves the topology of the surfaces and avoids creating singularities or self-intersections of the computing grid even for large deformations. The diffeomorphisms are generated via flows of the differential equation,

\[
\frac{\partial \varphi(\bar{x},t)}{\partial t} = v(\varphi(\bar{x},t),t); \quad \varphi(\bar{x},0) = \bar{x}
\]

A. 1

for \( t \in [0,1] \), and \( \bar{x} \in \mathbb{R}^3 \). The vector field \( v \) belongs to a reproducing kernel Hilbert space (RKHS, \( V \)) (Aronszajn, 1950). The solution of the equation above for a given \( v \) is denoted by \( \varphi^v \). The registration algorithm minimizes a functional of the form,

\[
E(v) = \int_0^1 \|v(t)\|^2_v dt + D(\varphi^v(T,1),S)
\]

A. 2

where, the first term is the RKHS norm of \( v \), which controls the smoothness of the deformation, while \( D \) penalizes the disparity between the mapped template \( \varphi^v(T,1) \) and the target \( S \). For a triangulated surface template with nodes \( y(t) = (y_0(t),...,y_N(t)) \), the optimal velocity takes the form,

\[
v(y,t) = \sum_{k=0}^{N} K(y,x_k(t))\alpha_k(t)
\]

A. 3
where, $K$ is the kernel of $V$, $x_k(0) = y_k$ are the nodes of the template, and $x_k(t) = \varphi(y_k, t)$ is the deformed template at time $t$. The topology of the triangulated surface remains unchanged, and we only deform the nodes. The vector-valued function of time $\alpha(t) = (\alpha_0(t), \ldots, \alpha_N(t))$ is known as the momentum. The energy $E$ is therefore a functional of $\alpha$ and finding the optimal deformation $\varphi^\prime$ is equivalent to finding the optimal $\alpha$, which results in an optimal control problem. The algorithm used to minimize this cost functional is described in detail in Younes, 2010 (Younes, 2010). The disparity or mismatch $D$ between two surfaces is calculated using a mathematical formulation in which the triangulated surfaces are embedded in a RKHS (that is different from $V$). The RKHS norm is then used to measure the disparity (Glaunes, Trouve and Younes, 2004). The disparity between a surface and a set of cross sectional curves is defined as the sum of Euclidean distances from each point on the curve to the nearest point on the surface. Details for this formulation can be found in Ardekani et al. (Ardekani et al., 2012). Note that while this method appears similar to iterative closest point (ICP), unlike the latter, it guarantees that the deformation is a diffeomorphism.
B. Flow rate specification

The temporal parameters for the flow rate shown in Figure 4-1c and Table 4-1 are based on the data presented in Chung et al. (Chung, Karamanoglu and Kovacs, 2004). Essentially, the duration of any phase during the cardiac cycle is modeled as a function proportional to heart rate (HR) as well as inversely proportional to HR (Chung, Karamanoglu and Kovacs, 2004) as,

\[ D_p = B_p + M_{LP}HR + \frac{M_{IP}}{HR} \]  \hspace{2cm} B. 1

where, \( M_{LP} \) and \( M_{IP} \) are the direct and inverse proportionality constants and \( D_p \) is the duration of any cardiac phase (P) during the cardiac cycle. The constants have been statistically evaluated in Chung et al. (Chung, Karamanoglu and Kovacs, 2004) and when the heart rate is chosen as 67bpm for a normal heart at resting state (Nagueh et al., 2009), the duration of each phase of the cardiac cycle can be evaluated as shown in Table 4-1.

The flow rate waveform is evaluated based on the simple harmonic model (Kovacs Jr, Barzilai and Perez, 1987; McGuire et al., 1997) as described below. During acceleration time (AT), the flow rate \( Q_{AT} \) is given by,

\[ Q_{AT} = C_1 \exp(-C_2t) \sinh(t) \]  \hspace{2cm} B. 2

where,

\[ C_1 = \frac{Q_{peak}^E}{\exp(-C_2t_{peak}^E) \sinh(t_{peak}^E)}; \quad C_2 = \frac{1}{\tanh(t_{peak}^E)} \]  \hspace{2cm} B. 3

and \( Q_{peak}^E \) is the peak diastolic flow rate during E-wave. Similarly, the flow rate waveform during deceleration time (DT) is given by,
\[ Q_{DT} = \frac{Q_{peak}^E}{2} \left( 1 + \cos \left( \pi \frac{t - t_{peak}^E}{t_{end}^E - t_{peak}^E} \right) \right) \]  \quad \text{B. 4}

while the flow rate during diastasis, \( Q_{dias} \) is identically equal to zero. The waveform during atrial filling (\( Q_A \)) is given by,

\[ Q_A = \frac{Q_{peak}^A}{2} \left( 1 - \cos \left( 2\pi \frac{t - t_{st}^A}{t_{end}^A - t_{st}^A} \right) \right) \]  \quad \text{B. 5}

where, \( Q_{peak}^A \) is the peak diastolic flow rate during A-wave. Lastly, the flow rate during systole is specified using the cosine function as,

\[ Q_{sys}^a = \frac{Q_{peak}^{sys}}{2} \left( 1 - \cos \left( \pi \frac{t - t_{st}^{sys}}{t_{peak}^{sys} - t_{st}^{sys}} \right) \right) \]  \quad \text{B. 6}

and

\[ Q_{sys}^b = \frac{Q_{peak}^{sys}}{2} \left( 1 + \cos \left( \pi \frac{t - t_{peak}^{sys}}{t_{end}^{sys} - t_{peak}^{sys}} \right) \right) \]  \quad \text{B. 7}

where \( Q_{sys}^a \) and \( Q_{sys}^b \) are the flow rates during acceleration and deceleration of the contracting ventricle. The peak flow rate during systole, \( Q_{peak}^{sys} \) is computed as,

\[ Q_{peak}^{sys} = \frac{2(SV)}{(t_{end}^{sys} - t_{st}^{sys})} \]  \quad \text{B. 8}

where SV is the stroke volume during the cardiac cycle computed during diastole as,
In the present study, peak E-wave flow rate ($Q_{peak}^E$) and E/A-ratio (Table 4-1) are chosen initially to evaluate all the parameters described above and hence, the flow rate waveform. However, it is also noted that one can provide stroke volume (SV) and E/A ratio as inputs to model the flow rate waveform using the above expressions. Hence, we have $Q_{peak}^E = 400$ ml/s, E/A ratio=1.5, $Q_{peak}^A = 266.67$ ml/s and $Q_{peak}^{sys} = 478.33$ml/s with stroke volume SV=76.53 ml. The time instants $t_{st}^s=0.0s$, $t_{peak}^E = 0.09s$, $t_{end}^E = 0.25s$, $t_{st}^A = 0.38s$, $t_{end}^A = 0.52s$, $t_{st}^{sys} = 0.55s$, $t_{peak}^{sys} = 0.7s$, $t_{end}^{sys} = 0.87s$ correspond to beginning E-wave, peak E-wave, end E-wave, beginning A-wave, end A-wave, beginning systole, peak systole and end-systole, respectively as shown in Figure 4-1c.
C. Mitral valve angles modeling

Doppler echocardiography of the mitral valve indicates that the leaflets exhibit similar waveform as that of the transmitral flow itself (Bowman, Frihauf and Kov, 2004; Omran, Arifi and Mohamed, 2010). Measurements performed in the current study based on echocardiographic data (Figure 4-2a) also indicated that the leaflets motion resembles an ‘M’ shaped profile similar to the flow rate waveform. Therefore, the temporal variation of the leaflet angles, \( \phi \), as shown in Figure 4-2 is given by,

\[
\phi(t) = \begin{cases} 
\phi_i + C_1 \exp \left(-C_2(t-t_{st}^E)\sinh(t-t_{st}^E)\right) & t_{st}^E \leq t \leq t_{peak}^E \\
\phi_m + \frac{1}{2}(\phi_f - \phi_m) \left[ 1 + \cos \left( \frac{\pi}{t_{peak}^E - t_{st}^E} (t-t_{peak}^E) \right) \right] & t_{peak}^E \leq t \leq t_{end}^E \\
\phi_i + \frac{1}{2}(\phi_f - \phi_i) \left[ 1 - \cos \left( \frac{\pi}{t_{end}^A - t_{peak}^A} (t-t_{peak}^A) \right) \right] & t_{st}^A \leq t \leq t_{peak}^A \\
\phi_i + \frac{1}{2}(\phi_f - \phi_i) \left[ 1 - \cos \left( \frac{\pi}{t_{end}^A - t_{peak}^A} (t-t_{peak}^A) \right) \right] & t_{peak}^A \leq t \leq t_{end}^A \\
\phi_i & \text{else}
\end{cases}
\]

where, \( \phi_i = 20^\circ \), \( \phi_m = 45^\circ \), \( \phi_f = 80^\circ \) are the angles corresponding to the initial opening angle after leaflets coaptation, leaflets angles during mid-diastole or diastasis, and maximum opening angle, respectively. It is noted that the present leaflet motion model is in phase with the flow rate waveform assuming that the leaflets have very low inertia and also connected to avoiding introduction of another parameter in the model. The values of leaflet angles are based on the echocardiographic measurements (Figure 4-2) and are suitably modified to be fitted to the present computational model.
LIST OF REFERENCES


Taylor, C.A., Fonte, T.A. and Min, J.K. (2013) 'Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis', Journal of the American College of Cardiology, vol. 61, no. 22, pp. 2233-2241.


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**Research Interests**


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**Education**

- **Johns Hopkins University**, Baltimore, USA  
  Ph. D., Mechanical Engineering  
  Jan 2015

- **Indian Institute of Technology (I.I.T)**, Kanpur, India  
  M. Tech., Aerospace Engineering (Aerodynamics)  
  Jun 2009 (GPA – 3.91)

- **National Institute of Technology**, Tiruchirapalli, India  
  B. Tech., Mechanical Engineering  
  May 2007

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**Research Experience**

**Computational modeling of intracardiac flows, Johns Hopkins University**  
Aug ‘10 – Jan ‘15

- Developed a framework for 4D image-based modeling of blood flow in a two-chamber model of left heart. Collaborated with doctors at Johns Hopkins Medical Institutions and scientists from Computer Science Dept., JHU. This work complements medical imaging by providing 4D velocity and pressure distribution making significant progress towards simulation based diagnosis and treatment.

- Investigated the fluid dynamical impact of left atrium, mitral valve, ventricular trabeculae and papillary muscles on ventricular filling and transport. First of its kind analysis, this work provided a greater understanding of the transport phenomena in the ventricle.

- Comprehensively validated flow solver for hemodynamic simulations. Experiments were performed at University of Cagliari, Italy and a quantitative comparison showed excellent agreement between simulations and experiments.

- Work resulted in 8 peer-reviewed publications, 10 conference presentations.

- Strongly involved in code development and performance enhancement of flow solver (GPUs/MIC) with collaboration with computer scientists at George Washington University.

- Developed fully parallelized Navier-Stokes flows solvers and relevant CFD tools for post-processing. Technical knowledge was shared between the team.

- Dissertation: *Image-based Computational Modeling of Intracardiac Flows*

**DNS of high Reynolds number transitional flow, I.I.T. Kanpur**  

- Investigated effects of surface roughness and transition enhancement on flows over airfoils at high Reynolds numbers using DNS. Early transition was accurately predicted in consistent with previous experimental studies.

- Performed numerical simulations and stability analysis of lid-driven cavity flow. This work employs novel application of proper orthogonal decomposition for stability analysis.

- Analyzed numerical schemes using Fourier spectral analysis with respect to amplification and dispersion properties.

- Developed fully parallelized flow solver using highly accurate compact difference methods on body-conformal grids.

**Leading edge flow control past airfoil, N.I.T. Tiruchirapalli**  
Dec 2006 – May 2007

- Studied flow control due to a rotating cylinder at the leading edge of an airfoil.

- Flow simulations were performed using FLUENT commercial CFD software.
**Professional Experience**

**GE India Technology Center, Bangalore, India**  
*Heat transfer and Fluid Systems Design (HTFSD) Engineer*
- Contributed to HTFSD team by performing heat transfer and blade displacement analysis of various components in the high pressure compressor of GEnx-2B engine.

**Tridiagonal Solutions Private Limited, Pune, India**  
*CFD Engineer*
- Worked as an analyst and developer of OpenFOAM.
- Simulated and validated atmospheric flows over rough terrains using OpenFOAM and Fluent.
- Extended OpenFOAM solver abilities to account for roughness.

**Honors and Awards**
- **GE Foundation Scholar-Leader** scholarship awarded by the General Electric Foundation and Institute of International Education, 2008.
- Ranked 22nd among 150,000 in the common entrance test for undergraduate admission, 2003.

**Skills**
- Programming: Fortran¹, C¹, C++², Matlab¹, Linux Shell²
- Parallel computing: MPI¹, OpenMP¹, Intel MIC programming³, CUDA²
- Commercial CFD software: OpenFOAM¹, Fluent¹, CFX², Comsol², Star-CCM+³
- Post-processing: Tecplot¹, ParaView¹, VisIt², Ensight¹, Excel¹
- Image processing: Mimics¹, MIPAV¹, ITK-Snap²
- Computational Methods: Finite-Difference¹, Finite-Volume¹, Finite-Element¹, and Immersed Boundary Methods¹

Level of Expertise: 1 - strong; 2 - mid level; 3 - familiar;

**Selected Coursework**

**Professional Activities**
- Journal referee for Computers and Fluids journal.
- Teaching Assistant - duties involved preparing assignment solutions, grading, and consulting.
- Student member of American Physical Society (APS).

**Selected Publications**
- Mittal, R., Seo, J. H., **Vedula, V.,** et al., Computational modeling of cardiac hemodynamics: current status and future outlook, *J. Comput. Phys. (review article).*