

Aortic Biomechanics: From Images to Modeling

by

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Abstract

The aorta, the largest blood vessel in the human body, deliver nutrients and oxygen via its branch vessels. Because of this critical role, aortic diseases, such as aneurysm and dissections, are leading causes of morbidity and mortality worldwide. The blood flow patterns and mechanical properties of the aorta are central to aortic function and linked to cardiovascular disease. Medical imaging and computational simulations have been widely used to study these fundamental aspects of the aorta.

This thesis investigates aortic biomechanics through two approaches: imaging analysis technique and fluid-structure interaction (FSI) modeling. Both approaches employed nonlinear rotation-free shell formulations. While shell models are widely used for their computational efficiency, a systematic evaluation of their accuracy and efficiency compared to 3D solid models has been lacking. We performed a comparison and found that the rotation free shell formulations offer an effective compromise between computational efficiency and accuracy for vascular biomechanics.

Aortic stiffness is both heterogenous and anisotropic. However, existing non-invasive imaging techniques generally characterize the aorta as isotropic, being limited by the inability to extract multi-axial strain from medical images. Vascular Deformation Mapping (VDM) was adapted to quantify 3D displacement of the aorta between the diastole and systole from medical images. We demonstrated that VDM enables a rigorous characterization of 3D aortic root motion across various patient groups.

Proper application of VDM requires careful calibration and validation. During the deformable image registration process in VDM, penalty parameters are used to optimize image alignment. The principal challenge in the parameter calibrating process is the lack of a ground truth for 3D displacement throughout the entire aorta. We calibrated the penalty parameters for VDM using physics-based synthetic data. These calibrated parameters effectively reduced errors in 3D displacement.

FSI models were used to study the aorta, with a particular focus on aortic dissection. Using a clinical example of dynamic obstruction, we developed an idealized FSI model of type B aortic dissection and solved it using the Arbitrary Lagrangian–Eulerian (ALE) method. Our model successfully reproduced clinical findings, showing that dynamic obstruction occurs as systemic blood pressure increases. Our results showed that relatively small pressure differences between true lumen and false lumen are sufficient to displace the intimal flap, inducing dynamic obstruction. However, limitations of the ALE approach were identified, including high computational cost for fluid re-meshing and mesh distortion under large structural motions. This motivated the development of a more efficient FSI solver using the Immersed Boundary Method (IBM).

The primary contribution of this thesis is the development of a novel IBM formulation for cardiovascular simulations. Importantly, while most existing IBM implementations are restricted to structured grids and primarily pair with finite volume or finite difference methods, our approach extends the IBM framework to unstructured finite element meshes. Our method enables the flexible modeling of complex cardiovascular geometries, such as those encountered in aortic dissection. Two existing solvers were coupled using a direct forcing IBM algorithm: CRIMSON for fluid dynamics and a nonlinear rotation-free shell formulation for thin structures. A new IBM formulation was validated on two 3D benchmark problems involving thin structures. We established a pipeline for patient-specific aortic dissection modeling. Starting from medical imaging data, we generated 3D aorta and 2D intimal flap geometries. With appropriate boundary conditions derived from patient data, we performed the first patient-specific IBM-based simulation of aortic dissection.

Chapter 1 Introduction

The aorta is the largest blood vessel in the human body. It begins at the heart, at a region known as the aortic root, and passes through the chest as the thoracic aorta and the abdomen as the abdominal aorta. The aorta is composed of three layers. The tunica intima is the innermost layer and consists of endothelial cells and smooth muscle tissue. It regulates the blood flow and clots. The tunica media, which is the middle layer, consists of smooth muscle cells, elastin and collagen. This layer enables the aorta to expand and contract, helping to maintain a consistent blood supply to the rest of the body throughout the cardiac cycle. The tunica adventitia is the outermost layer and primarily consists of collagen, which helps preserve the structural integrity of the aorta [1].

Two fundamental aspects of aortic function – the blood flow pattern and the mechanical properties of the aortic wall – are intricately linked to cardiovascular health and disease. Blood flow patterns include parameters such as flow rate, shear stress, and blood pressure [2]. These patterns can change dynamically in the short term, in response to activities such as exercise, and in the long term, in association with aortic growth, aging, and diseases [3], [4]. The blood flow rate can change several-fold under different conditions. However, the mean blood pressure usually varies by only about 10 - 20% [2]. Abnormal blood flow can contribute to the development of diseases, such as thrombosis or malperfusion, and at the same time is influenced by diseases such as stenosis.

One of the most important properties of the aorta is its stiffness, as it serves as both a marker and a contributor to aortic diseases. Aortic stiffness is both heterogeneous, meaning it has different values in different regions along the aorta, and anisotropic, indicating distinct stiffness patterns in the axial and circumferential directions [5], [6], [7], [8]. These properties arise from the various protein components within the aortic wall. For example, the orientation of the collagen fibers is a major factor determining the anisotropic property [9]. Aortic stiffness has been recognized as an important indicator of vascular health [10], [11]. Typically, older patients or those with aortic diseases exhibit stiffer aortas [12], [13]. Understanding the different directional stresses and corresponding strains is important, as the aorta is in constant motion due to the combination

of cyclic loading and unloading with its mechanical coupling to the contractile left ventricle myocardium.

As the primary conduit for oxygen-rich blood, the aorta delivers essential nutrients and oxygen to entire body tissues through its extensive network of branch vessels. Because of this critical role, aortic diseases, such as aneurysm, aortic dissection, and Marfan syndrome, are major causes of morbidity and mortality worldwide [14], [15]. Additional details on these conditions are provided in Section 1.1 Aortic diseases. For this reason, studying the aorta is of paramount importance in both clinical and research contexts. The biomechanics of the aorta have been investigated with recent advancements in imaging (Section 1.3) and computational modeling (Section 1.4). In this thesis, we investigated aortic biomechanics using two approaches: imaging analysis technique and fluid-structure interaction (FSI) modeling.

1.1 Aortic diseases

1.1.1 Aortic dissection

Aortic dissection occurs when blood enters space within the aortic wall through the tear at the tunica intima (see Figure 1.1). This blood flow separates the original aortic lumen into two channels: the true lumen (TL), which is the original passageway, and the false lumen (FL), which is newly created. The thin structure between TL and FL is called intimal flap. The intimal flap is thin and flimsy, as it originates from the tunica intima. As a result, the intimal flap can move dynamically in response to even small pressure differences between TL and FL [16].

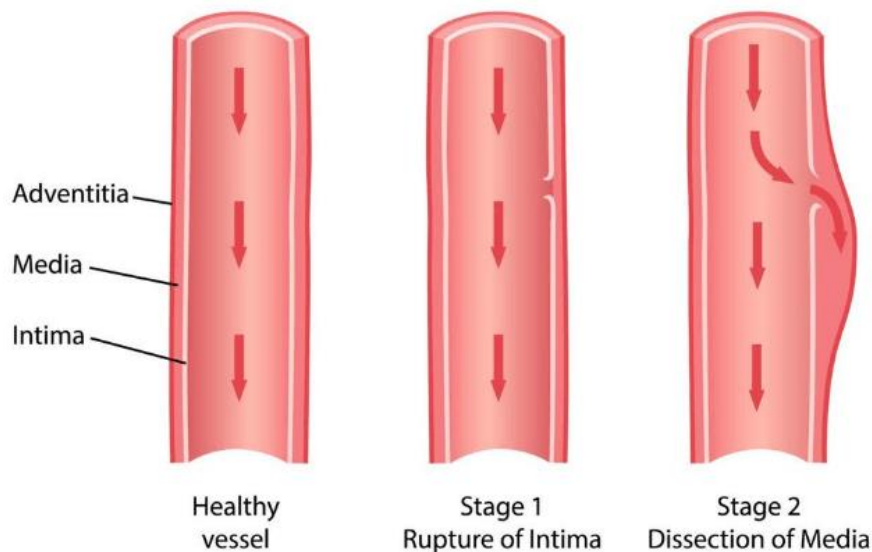


Figure 1.1. Stages of aortic dissection. Figure from [17].

Depending on the starting location of the aortic dissection, it is categorized as type A, involving the ascending aorta, and type B, which only involves the descending aorta (see Figure 1.2). Population-based studies have estimated that aortic dissection occurs at a rate of 3–4 cases per 100,000 people per year [18], [19]. Among all patients with aortic dissection, 30-40 % are classified as type B [20]. Type A aortic dissections have high mortality, with rates reaching up to 50% within the first 48 hours. In most cases, emergency surgery is necessary for treatment. Type B aortic dissections have a lower mortality rate of 5-10% and are typically treated with medication [21]. Endovascular stent is performed in certain cases, and fenestration procedures are also conducted [22].

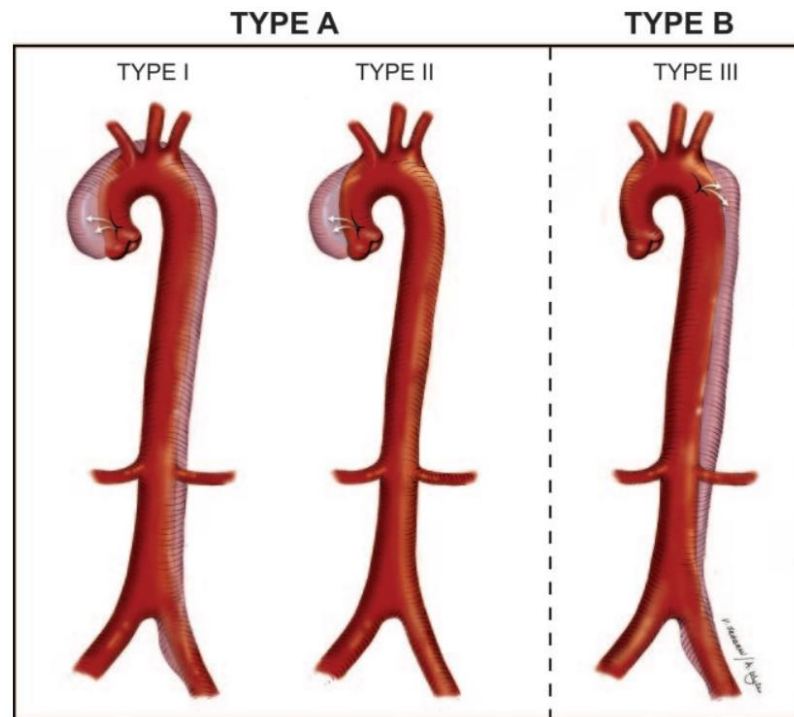


Figure 1.2. Classification of aortic dissection. Figure from [23]. Type A aortic dissection is categorized as type I, when dissection starts in the ascending aorta and extends into the descending aorta, and type II, when dissection is limited to the ascending aorta.

1.1.2 Aortic aneurysm

An Aortic aneurysm is an enlargement or ballooning of the aorta. Figure 1.3. compares normal and aneurysmal aortas. An aortic aneurysm is diagnosed based on the diameter of the aorta. It is defined as a 50% increase above the normal aortic size for a given age and body mass [24]. Depending on its location, an aortic aneurysm is categorized as an abdominal aortic aneurysm, when it occurs in the abdomen, or a thoracic aortic aneurysm, when it occurs in the chest.

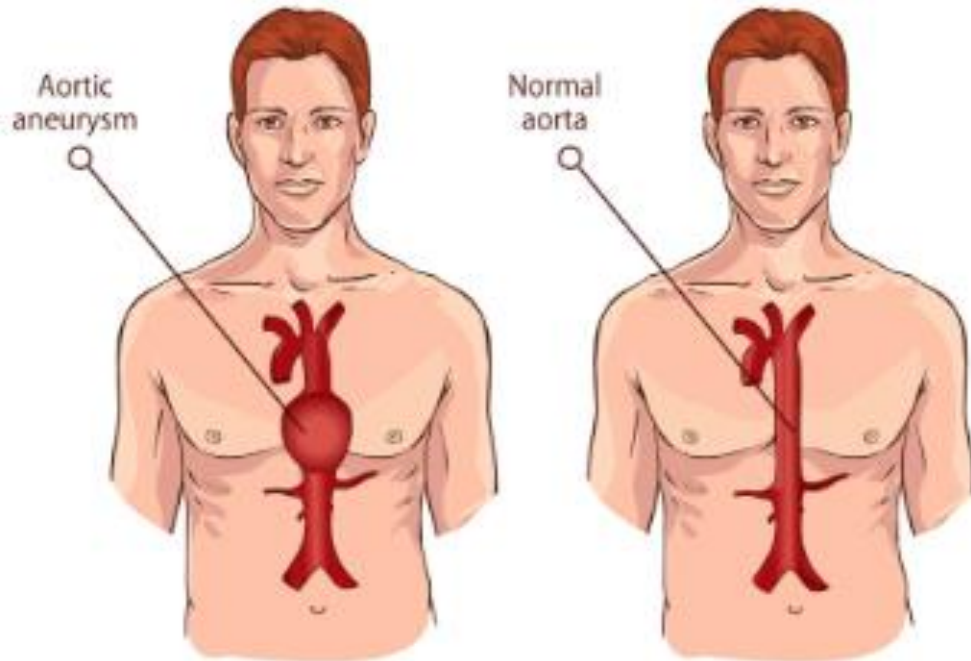


Figure 1.3. Comparison between normal and aneurysmal aortas. Figure from [25].

Most of the time, aortic aneurysms do not have specific symptoms until rupture, which can cause sudden chest or abdominal pain [26]. Contributing factors of aortic aneurysm include age, high blood pressure, and atherosclerosis. In United States, abdominal aortic aneurysm occurs in around 9% of adults older than 65 years old and more common in men [27]. Typically, small aortic aneurysms are managed by controlling risk factors, such as using blood pressure medications and encouraging smoking cessation. However, when an aneurysm becomes larger and ruptures, open surgical or endovascular repairs are necessary [28], [29].

1.1.3 Marfan syndrome

Marfan syndrome is a genetic disorder that affects connective tissue caused by a mutation in the genes such as fibrillin-1 [30]. Patients with Marfan syndrome typically present with long arms and legs, eye abnormalities, and cardiovascular complications. The aortic problems associated with Marfan syndrome include aortic enlargement (especially near the aortic root), aortic insufficiency, and an increased risk of aortic dissection [31]. Figure 1.4 illustrates aortic enlargement from Marfan syndrome. Diagnosis usually begins with an assessment of family history and is confirmed through physical examination, eye examination, and genetic testing [32]. Marfan syndrome occurs in approximately 1 in every 3,000 to 5,000 individuals [33].

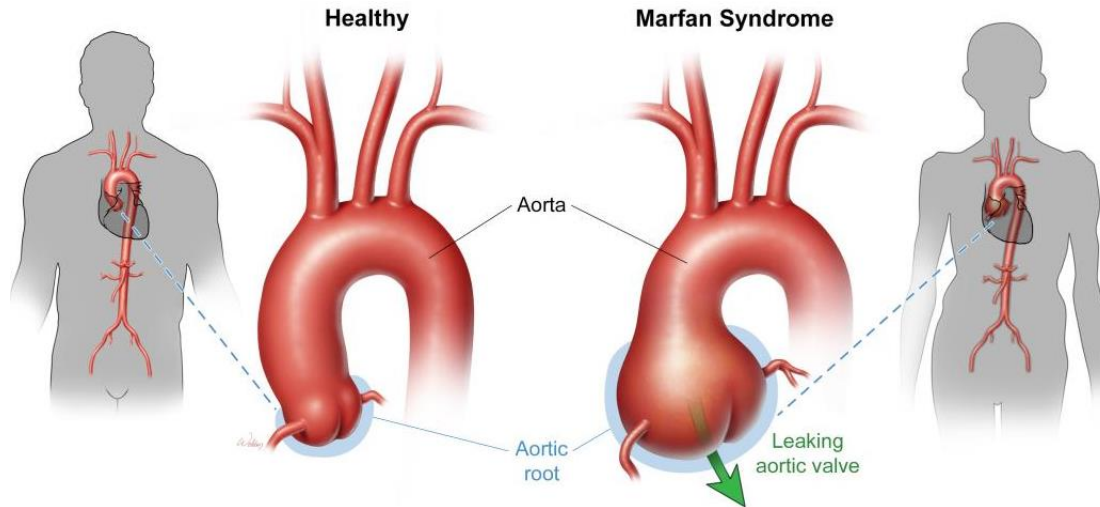


Figure 1.4. Comparison between healthy and Marfan syndrome aortas. Figure from [34].

The treatment of Marfan syndrome primarily focuses on managing symptoms and preventing complications. Medications, such as beta blockers, are prescribed to slow aortic dilation and reduce the risk of dissection and rupture [35]. Surgical aortic replacement is considered when aortic enlargement exceeds the threshold for increased risk of rupture [36].

1.2 Impact of hemodynamic and mechanical properties of the aorta on aortic disease

Aortic diseases are closely associated with the hemodynamic and mechanical properties of the aorta. First, hemodynamic parameters such as blood pressure, flow, and wall shear stress are related to cardiovascular diseases. For example, high blood pressure increases the risk of aortic dissection and aneurysm. Additionally, abnormal flow in the aorta can alter endothelial permeability, leading to weakening of the aortic wall. Low velocity is also closely linked to thrombosis formation. Second, the mechanical properties of the aorta, such as stiffness and thickness, greatly impact blood pressure and play major roles in diseases such as hypertension, aneurysm, and aortic dissection. Aortic wall stiffening and weakening can both cause and result from increased blood pressure. Figure 1.5 illustrates the impact of the hemodynamic and mechanical properties of the aorta on aortic dissection. Three aortic dissection cases with different false lumen (FL) conditions are presented: patent, partial thrombus, and full thrombus. Among these cases, the partial thrombus condition shows the highest mean arterial pressure and may result in the most severe outcome [37].

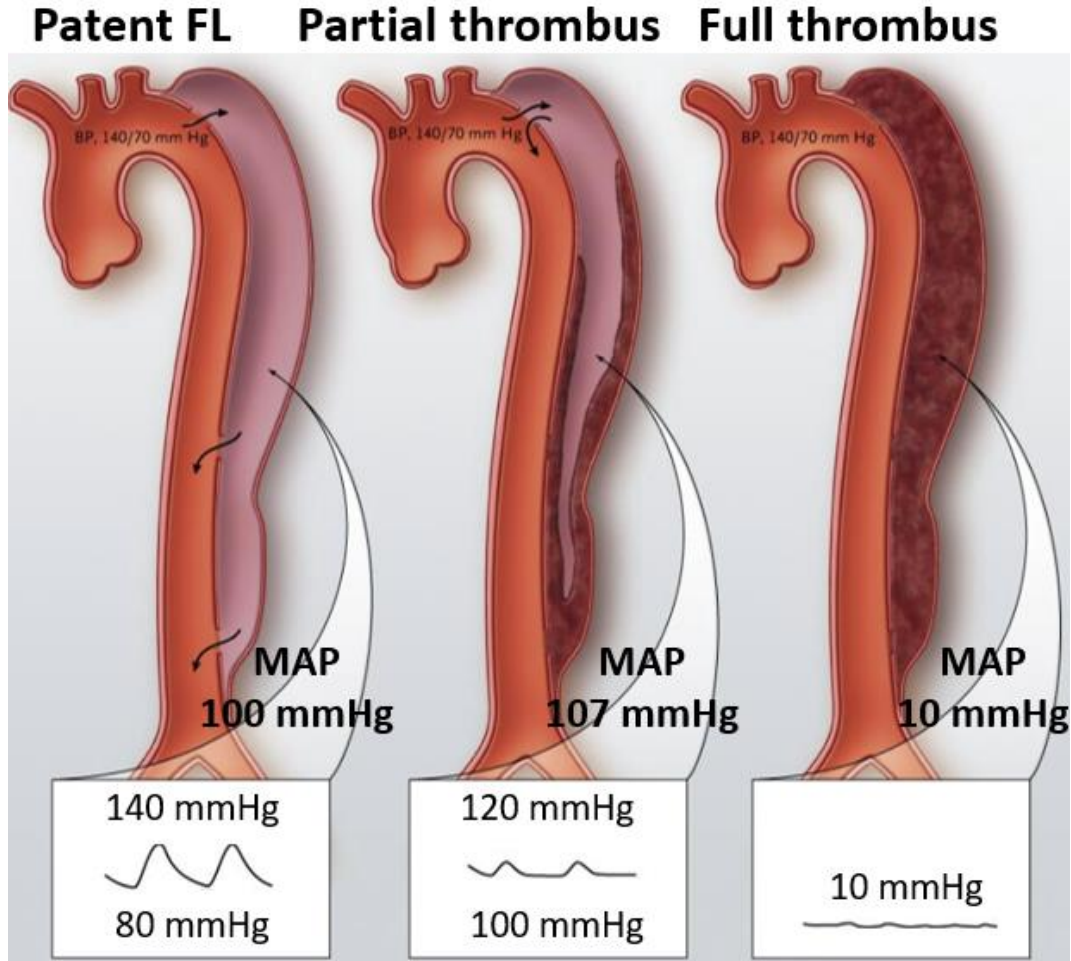


Figure 1.5. Three aortic dissection cases with different false lumen patency. FL: false lumen. MAP: mean arterial pressure. Figure from [37].

Hemodynamic and mechanical properties of the aorta are associated to partial thrombus aortic dissection case. Abnormal flow in the aortic dissection contributes to thrombosis formation in the FL. This thrombosis may block the exit tears at the intimal flap, causing impaired outflow and further increasing mean arterial pressure in the FL. Elevated blood pressure in turn increases wall tension, which may cause stiffening and weakening of the aortic wall. Eventually, this region of the aorta may enlarge, resulting in aneurysm, re-dissection, or rupture. This process can be repeated over time.

This example shows the importance of studying the hemodynamic and mechanical properties of the aorta. By understanding how these factors interact and contribute to disease progression, clinicians and researchers can better identify risk patients, develop effective interventions, and design improved treatment strategies. Medical imaging and computational simulations have been used to study the hemodynamic and mechanical properties of the aorta.

1.3 Medical imaging for the thoracic aorta: computerized tomography angiography

Various techniques have been used to visualize the aorta for diagnosis and management of aortic diseases. Widely used imaging modalities include X-ray angiography, echocardiography, angiography, computerized tomography angiography (CTA), and magnetic resonance imaging [38], [39], [40]. Among different image techniques, CTA is the most commonly used technique for studying the thoracic aorta [38]. CTA involves the injection of an iodine-based contrast material through a vein to enhance the visibility of the blood vessel lumen. Special X-ray equipment acquires images from multiple angles, and computer post processing is then used to reconstruct 3D images of the aorta. CTA is fast (entire scan takes several seconds) and widely available in most of the emergency rooms. CTA offers high quality images (~ 0.5 mm) of extensive segments of the aorta. However, because CTA used ionizing radiation, its use is limited in pregnant women and for repeated scans. Additionally, image quality can be affected by patient movement or the presence of calcifications, which may introduce noise or artifacts.

CTA has been widely used in studies of various aortic diseases, such as aortic aneurysm and dissection [41], [42]. Figure 1.6 shows CTA images of aortas with aortic aneurysm and dissection. There are two major applications of CTA in aortic disease assessment. First, CTA is critical for detecting disease by measuring aortic size or identifying the presence of an intimal flap. This information guides treatment decisions, including surgical repair, stenting, or medication management. Second, CTA enables measurement of aortic deformation in long and short terms. Over the long term, disease progression or postoperative prognosis can be monitored by measuring aortic growth. Aortic growth is obtained by comparing sequential CTA scans taken several years apart, ensuring that images are captured at the same phase of cardiac cycle to avoid the deformation from aortic motion. The magnitude of aortic deformation in this context is typically several millimeters. In the short term, aortic motion can be evaluated using Electrocardiogram (ECG)-gated CTA during the cardiac cycle (so called dynamic CTA), with the interval between images being less than seconds. Deformation is focused near the aortic root because of the left ventricle motion. The magnitude of aortic deformation in this context is around 10 mm. Aortic motion measured in this way can serve as an indicator of aortic health [43]. Dynamic CTA can also capture aortic valve or intimal flap motion during the cardiac cycle.

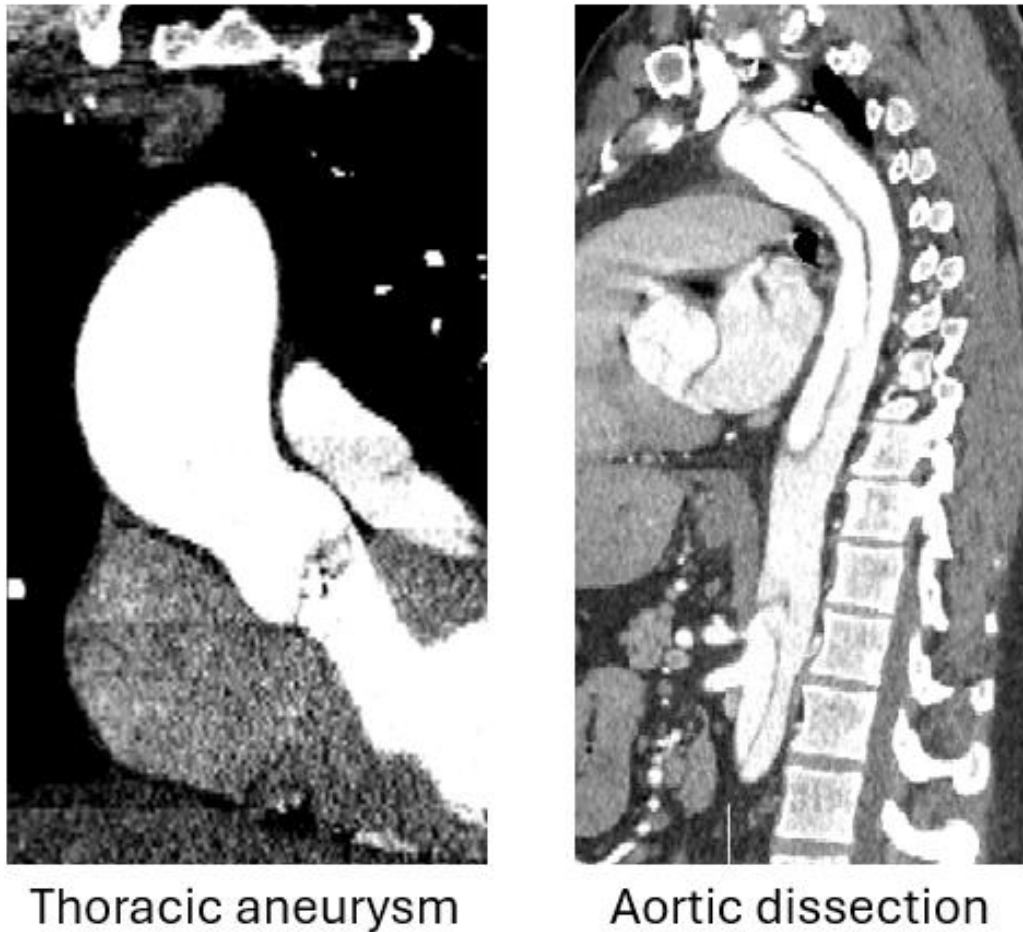


Figure 1.6. Computerized tomography angiography images of aortic disease. Left: thoracic aortic aneurysm and right: aortic dissection.

1.3.1 Medical imaging analysis examples

Figure 1.7 shows examples of medical imaging analysis. Panel (a) illustrates the evaluation of aortic strain using echocardiography [38]. In this study, aortic diameters were measured at two different regions, the aortic root and the middle of the ascending aorta, during diastole and systole. Aortic stiffness was then estimated using these measured diameters and the patient's blood pressure. However, the measurements were obtained from 2D images, which limits the analysis. Additionally, this method can only estimate circumferential aortic deformation and stiffness. Panel (b) shows the measurement of aortic root motion using MRI [39]. This study defined 1D aortic root motion by comparing the position of the aortic valve annular plane in diastole and systole. As a result, the analysis loses information about the full 3D aortic motion.

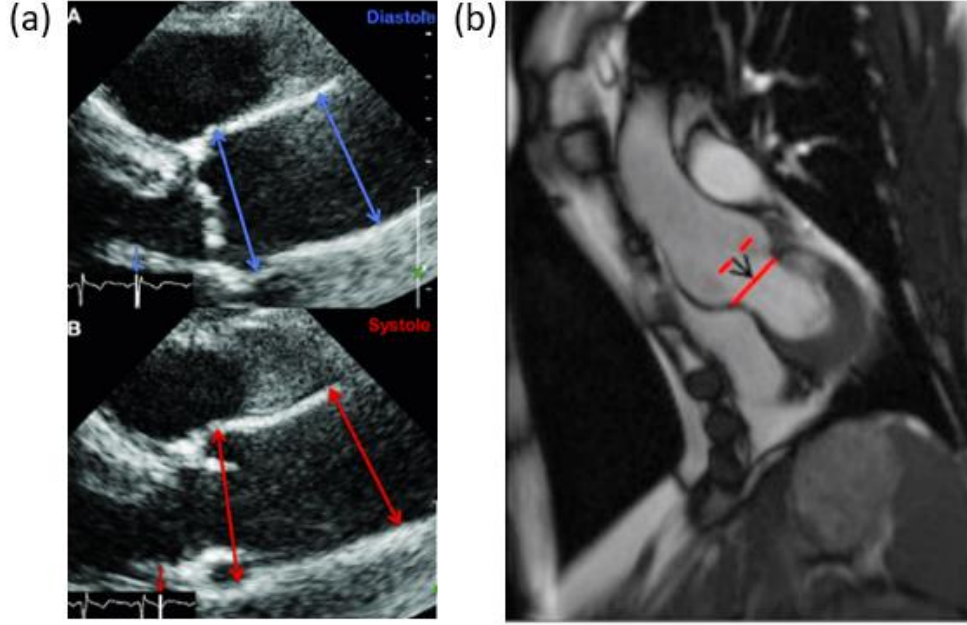


Figure 1.7. Examples of the medical imaging analysis. (a) Evaluation of circumferential directional aortic strain using echocardiography and (b) measurement of aortic root motion using MRI. Figure from [38] and [39] for panel (a) and (b), respectively.

1.4 Computational modeling of the aorta

Advances in imaging techniques, numerical methods, and computing resources have enabled patient-specific computational simulation of the aorta [44]. Computational simulations are used to study the physical behavior of the aortic blood flow, the aortic wall, and structures immersed in the flow, in both healthy and diseased states. Aortic computational simulations include (1) fluid, (2) solid, and (3) fluid-structure interaction (FSI) simulations.

1.4.1 Fluid simulations

Fluid simulation solves blood flow through aorta. It solves the incompressible Navier-Stokes equations. Vector forms of these equations are:

$$\rho_f \frac{\partial \vec{v}_f}{\partial t} + \rho_f \vec{v}_f \cdot \nabla \vec{v}_f = -\nabla p + \mu_f \nabla^2 \vec{v}_f \quad (1.1)$$

$$\nabla \cdot \vec{v}_f = 0 \quad (1.2)$$

,where $\vec{v}_f$ represents the fluid velocity, p is the kinematic pressure, ρ_f is the fluid density, and μ_f is the fluid viscosity. Computational fluid dynamics (CFD) models are used to solve these equations. In CFD, three numerical methods are commonly employed: the finite difference

method, the finite volume method, and the finite element method (FEM). Some researchers have used the finite difference [45] and the finite volume [46], [47] methods in aortic simulations. However, the FEM is often preferred for patient-specific simulations due to its ability to accurately handle complex geometries and diverse material properties, as well as its flexibility in implementing customized boundary conditions. There are open-source software FEM-based packages, which facilitate patient-specific blood flow simulations: CRIMSON (www.crimson.software) [48] and SimVascular (www.simvascular.org) [49]. Commercial software, such as COMSOL, is also widely used.

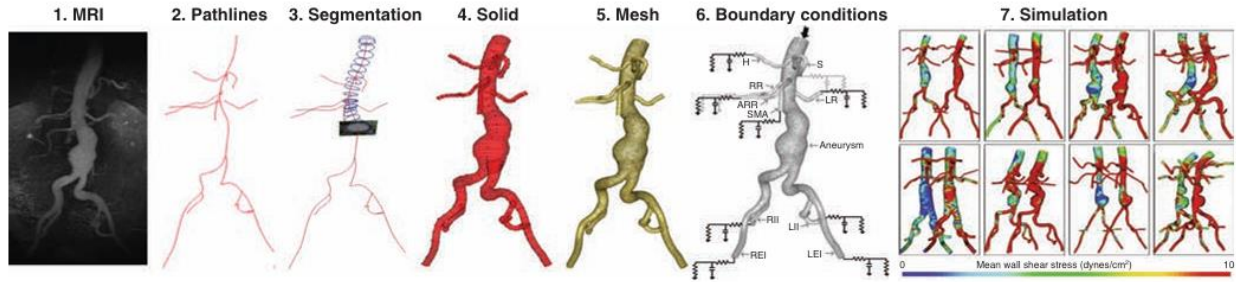


Figure 1.8. Patient-specific model processing pipeline from medical image to 3D aortic CFD simulation results.
Figure from [2].

Figure 1.8 illustrates a typical patient-specific modeling pipeline using an example of an abdominal aortic aneurysm case. The process begins with obtaining medical images, from which a centerline is generated through the center of the aortic lumen. Along this centerline, 2D segmentations of vessel lumen are performed. Using 3D volume rendering and blending techniques, a 3D solid model is reconstructed from the centerline and 2D segmentations. This 3D configuration is then discretized using unstructured mesh elements. Proper boundary conditions, derived from patient data, are applied to enable flow simulation with a FEM solver. Through appropriate postprocessing, the CFD simulation yields physiological solutions such as velocity, pressure, and wall shear stress throughout the entire fluid domain. Patient-specific CFD models have been used to study various aortic disease [2]: abdominal aortic aneurysms [50], pulmonary arteries [51], cerebral aneurysms [52], aortic coarctation [53], and aortic dissection [54].

1.4.1.1 Fluid simulation state-of-the-art examples

CFD simulations have been used to investigate the hemodynamics in aortic dissection with different conditions. Figure 1.9 panel (1) shows one of the velocity results of the aortic dissection study [54]. This study developed several patient-specific CFD models of aortic dissection to study

how changes in the intimal flap, such as its removal or varying the number of connecting tears between the TL and FL, affect blood flow. Comparisons were made between the dissected aorta and a healthy version with the intimal flap virtually removed. Localized increases in velocity, pressure, and wall shear stress were observed, especially in the narrowed true lumen and at the primary entry tear.

Figure 1.9 panel (2) shows the research on thrombosis formation in aortic dissection [55]. This study introduces CFD models that predict thrombus formation and growth in the FL of patients with type B aortic dissection, which is a key factor influencing outcomes. The model evaluates factors like shear rate, blood residence time, and platelet distribution using transport equations. Its predictions matched clinical observations, highlighting the impact of aortic geometry on thrombosis. The model operates efficiently, making it practical for clinical use and potentially valuable in guiding decisions about early intervention in patients at higher risk of FL thrombosis.

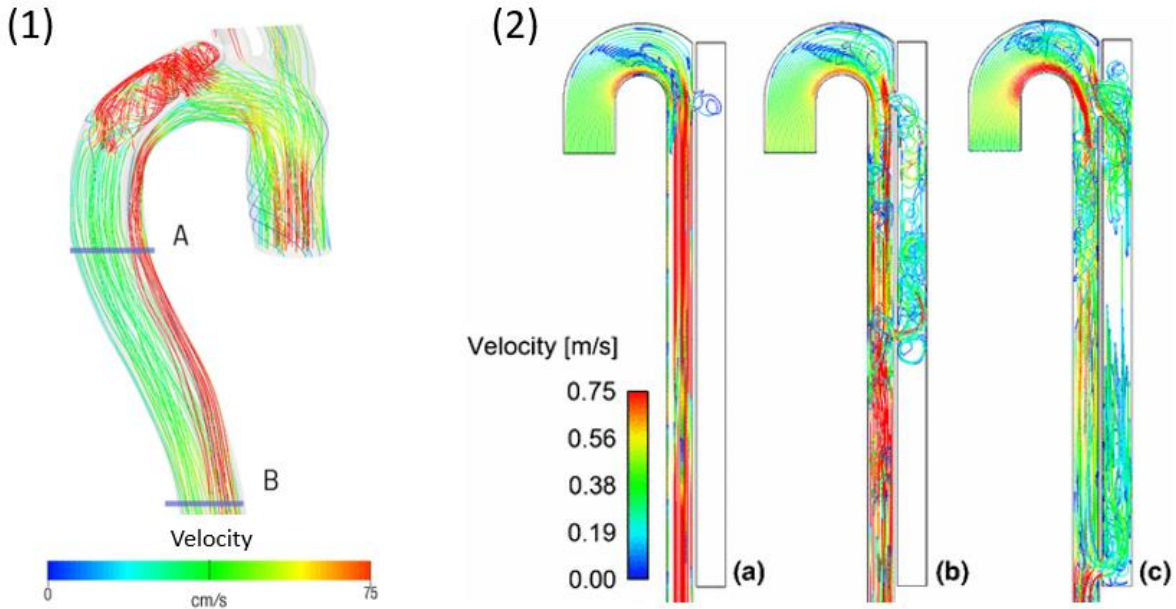


Figure 1.9. Two research using CFD on aortic dissection which studied: (1) effect of intimal flap and tear, and (2) thrombosis formation. Figure from [54] and [55] for panel (1) and (2), respectively.

1.4.2 Solid simulations

Aortic solid simulation models how the aortic wall deforms in response to external forces, such as pulsatile pressure during the cardiac cycle and mechanical loads, e.g., heart motion. This approach solves the Elasto-dynamic equation. The vector form of this equation is:

$$\rho_s \frac{\partial^2 \vec{u}_s}{\partial t^2} = \nabla \cdot \vec{\sigma} + \vec{f}_s \quad (1.3)$$

,where $\vec{u}_s$ represents the solid displacement, ρ_s is the solid density, $\tilde{\sigma}$ is the Cauchy stress tensor, and $\vec{f}_s$ is the external force. The FEM is preferred for solid simulations, as it was initially developed for structure analysis. The FEM can effectively handle the complex aortic geometries and material behavior of aortic wall tissue. Furthermore, FEM uses variational and energy-based formulations, which naturally align with the fundamental principles of structural mechanics, making it highly effective for predicting deformation, stress, and strain in solid materials. Some research groups have developed and used in-house code for aortic structure simulations [56], [57].

The relationship between the Cauchy stress tensor and stretch, which is defined as the spatial derivative of displacement, is established through prescribed constitutive models. The simplest model assumes a linear relationship between stress and strain. However, because the aortic wall is composed of various materials, such as elastin and collagen, it exhibits nonlinear mechanical properties [58], [59]. As a result, nonlinear constitutive models are widely used for modeling the aorta [60]. Depending on specific assumptions regarding aortic properties, such as isotropic vs anisotropic and homogenous vs heterogenous, various constitutive models have been used. For example, the incompressible Neo-Hookean model assumes that the aorta is isotropic. The strain energy density function, W , for this model is

$$W = C(I_1 - 3) \quad (1.4)$$

where I_1 is the first principal invariant of the right Cauchy–Green deformation tensor and C is a material parameter. In contrast, the four-fiber model assumes that the aorta is anisotropic with elastin and four different collagen fiber families. The strain energy density function, W , for this model is

$$W = c(I_1 - 3) + \sum_{k=1}^4 \frac{c_1^k}{4c_2^k} [e^{c_2^k[(\lambda^k)^2 - 1]^2} - 1] \quad (1.5)$$

where c, c_1^k, c_2^k are material parameters and λ is stretch. Material parameters are obtained from experiments. Patient-specific solid models have been used to study various aortic diseases: atherosclerosis [61], [62], rupture [63], and aneurysm [64]. A comprehensive review of aortic solid computational simulation models can be found in [65].

1.4.2.1 Solid simulation state-of-the-art example

Figure 1.10 illustrates the results from the research which used solid simulation to find a correlation between aortic wall components and stress [56]. This study presents a computational framework for patient-specific modeling of abdominal aortic aneurysm growth. The solid model used medical images and an inverse optimization method to set healthy aortic material properties before simulating aneurysm development by inducing elastin degradation in different patterns. Solid simulation results highlighted how elastin damage, aneurysm shape, and collagen turnover affect wall stress and expansion rates. Stress and expansion matched areas of collagen concentration due to tissue remodeling processes. The framework showed promise for future use in predicting individual patient aortic aneurysm development and mechanical behavior using patient-specific imaging data.

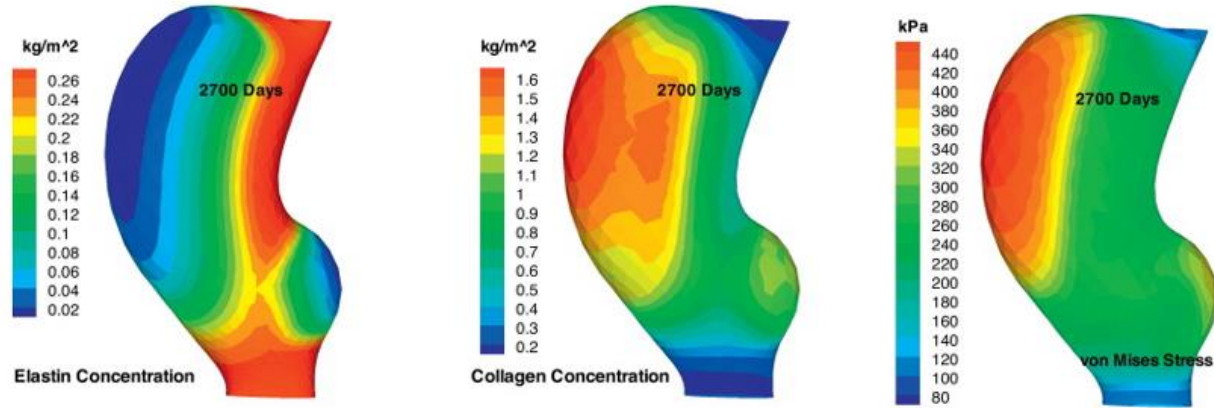


Figure 1.10. Elastin and collagen concentration along with von Mises stress distributions. Figure from [56].

1.4.3 Fluid-structure interaction simulations

In the aorta, FSI simulations are used in two scenarios: (1) modeling aortic wall motion in respect to blood flow and (2) simulating the motion of thin structures immersed in blood flow, such as the aortic valve or intimal flap. In both scenarios, the blood flow influences the motion of the structures, and the motion of these structures, in turn, affects the blood flow. Different FSI formulations have been employed in cardiovascular simulations. Here, we introduce three FSI formulations: Arbitrary Lagrangian-Eulerian, Immersed boundary method, and Coupled Momentum Method.

The Arbitrary Lagrangian–Eulerian (ALE) formulation solves fluid problems in a moving frame that follows the motion of the solid structure (see Figure 1.11 bottom meshes). The moving frame is determined by solving the solid mechanics problems using an arbitrary constitutive model.

At the fluid-solid interface, both velocity and tractions are matched to ensure coupling between fluid and solid problems. Consequently, the ALE formulation solves the fluid, solid and fluid mesh problems at each time step. While the ALE method provides accurate solutions at the interface, it is computationally expensive, particularly for cases involving large deformations. Additionally, mesh distortion may occur in the fluid region between two solid surfaces. ALE methods have been used for simulations involving deformable aortic walls [66], [67], aortic valves [68], and aortic dissections [69], [70].

The immersed boundary method (IBM) was introduced by Peskin for aortic valve simulation[71]. This approach does not require the re-meshing and facilitates handling complex and large structural motions (see Figure 1.11 top meshes). Boundary conditions at the fluid-solid interface are enforced through additional body forces in the Navier-Stokes equations near the solid domain. Since the solid boundary does not conform to the fluid grid, IBM requires additional interpolation or smoothing to integrate the boundary forces with the fluid solver. IBM methods have been successfully used in simulations of the aortic valve [72], [73].

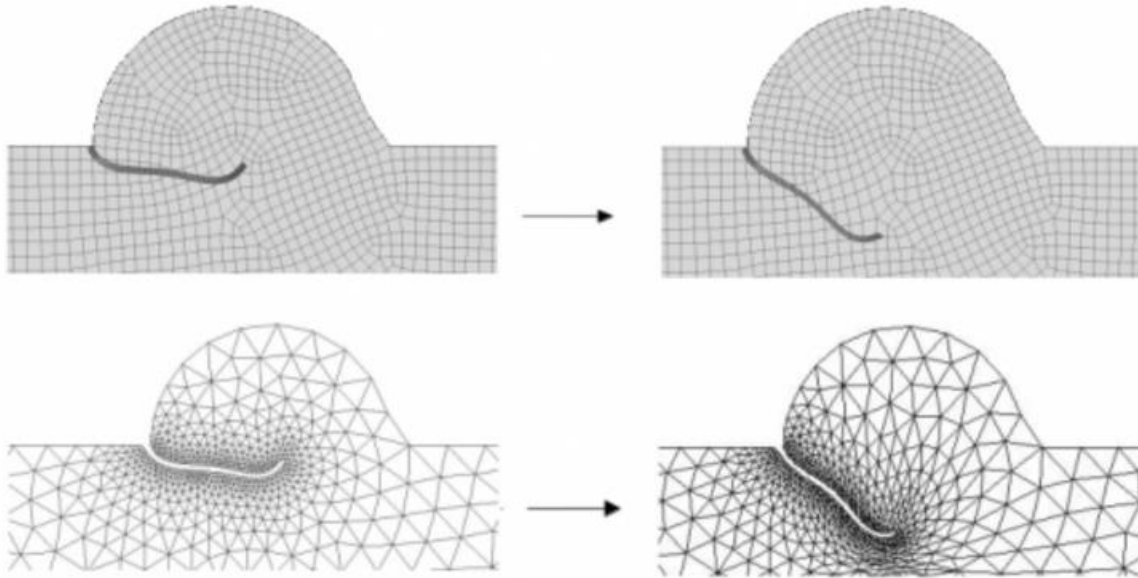


Figure 1.11. Fluid meshes at two different time steps, illustrating changes due to solid structure motion. Top: Immersed boundary method. Bottom: Arbitrary Lagrangian–Eulerian. Figure from [74].

The Coupled Momentum Method (CMM) was introduced by Figueroa [75] for FSI simulations involving deformable aortic walls. In CMM, the solid problem is embedded into the variation form of the fluid via a fictitious body force. This force is used to calculate traction at the fluid-solid interface. CMM has been applied in cardiovascular simulations for both humans [76] and animals [77].

1.4.3.1 Fluid-structure interaction simulation state-of-the-art example

Figure 1.12 shows patient-specific aortic dissection simulation results using ALE method [70]. This study introduces a framework for simulating aortic dissection, capturing the complex interactions between vessel deformation, blood flow, pressure, and wall shear stress in patient-specific models. The model used ALE method and distinct material properties for the vessel wall and dissection flap. Patient-specific anatomy and imaging data guided the simulations, which matched physiological deformation and flow patterns seen in 4D flow MRI. Results of this study showed that reduced intimal flap stiffness greatly increases its movement, decreases wall shear stress, reduces pressure differences between lumens, and lowers true lumen flow. This highlighted the critical importance of accurately modeling dissection flap mobility in patient-specific FSI simulations.

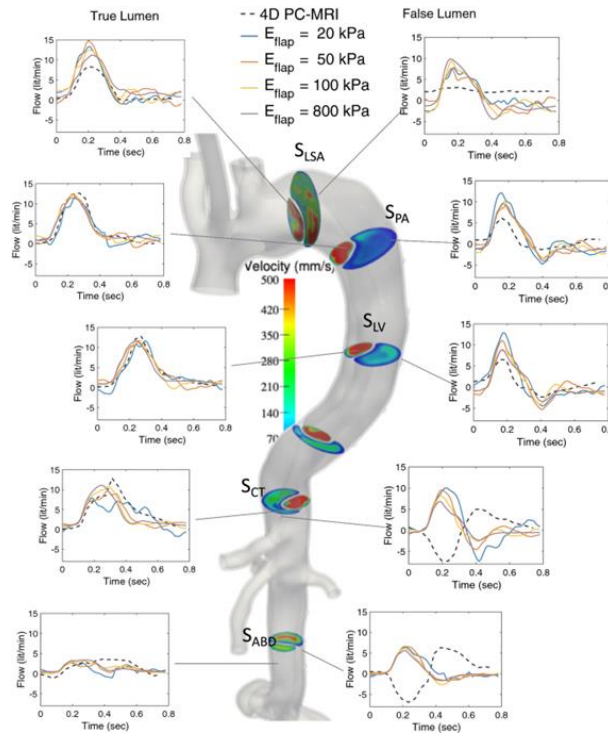


Figure 1.12. Fluid-structure interaction simulation on patient-specific aortic dissection model. Model was solved with ALE method. Figure from [70].

1.5 Background

1.5.1 Vascular deformation mapping

As medical imaging techniques have advanced, it has become increasingly possible to obtain medical images with improved spatial and temporal resolution. However, the methods used to extract quantitative data from these images have not changed significantly. Even though

advanced medical imaging can provide comprehensive information on 3D aortic deformation, in most cases, simple metrics such as aortic diameter [78], [79] or 1D measurements (axial direction) of aortic root motion [80], [81] are still commonly used in aortic studies.

Vascular deformation mapping (VDM) is a validated image analysis technique based on deformable image registration of two ECG-gated CTA scans [82], [83]. 3D segmented masks of the aortic lumen, obtained using a machine learning algorithm, serve as the input data for VDM. VDM enables precise assessment of changes in the entire 3D aortic geometry between two CTAs. It was originally developed to map and quantify aortic growth over several years by comparing baseline and follow-up sequential CTAs. It has demonstrated superior millimeter-level measurement accuracy compared to manual clinical assessment [84].

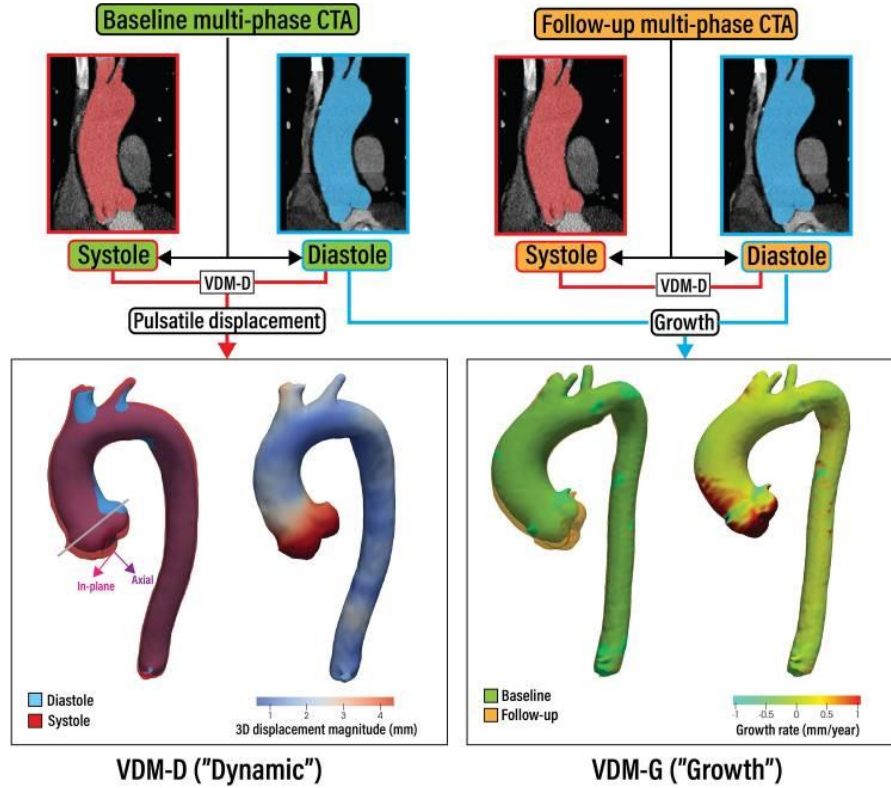


Figure 1.13. Schematic overview of VDM-D (dynamic) and VDM-G (growth). Figure from [86].

More recently, VDM has been adapted to quantify 3D pulsatile displacement of the aorta between diastole and systole using dynamic CTAs [12]. This application allows for detailed, patient-specific evaluation of multi-directional aortic root motion and changes in the cross-sectional area of the aorta. VDM applied to sequential CTAs is termed VDM-G ("growth"), while its application to dynamic CTAs is termed VDM-D ("dynamic"). Figure 1.13 compares VDM-D and VDM-G. Recent studies have utilized both VDM-G and VDM-D to explore the relationship

between aortic motion and growth rated in various aortic diseases such as in patients with aortic aneurysm or those undergoing thoracic endovascular aortic repair [85], [86].

1.5.2 CRIMSON

CardiovasculaR Integrated Modelling and Simulation (CRIMSON) is an open-source software framework for cardiovascular integrated modeling and simulation [48]. CRIMSON is specifically designed to solve patient-specific cardiovascular flow simulation. The main pipeline of CRIMSON includes: (1) vessel segmentation from medical images, (2) generating 3D geometries from the centerline and 2D segmentations, (3) discretizing the 3D geometry with unstructured mesh elements, (4) designing and applying proper boundary conditions, (5) solving Navier-Stokes equation with FEM based solver, and (6) post-processing and visualizing hemodynamic solutions.

CRIMSON Flowsolver, which is based on PHASTA, can be installed on high-performance computing systems with a message passing interface (MPI) parallel package. It was validated as scalable to tens of thousands of computing cores [87]. CRIMSON supports cardiovascular research-specific boundary conditions such as prescribed pulsatile flow, resistance-compliance-resistance (RCR), and both rigid and deformable wall models. CRIMSON can be used for a range of applications, including cardiovascular disease research, surgical planning, medical device evaluation, and non-invasive diagnostics. Furthermore, CRIMSON incorporates FSI solvers including the CMM and IBM (upcoming feature).

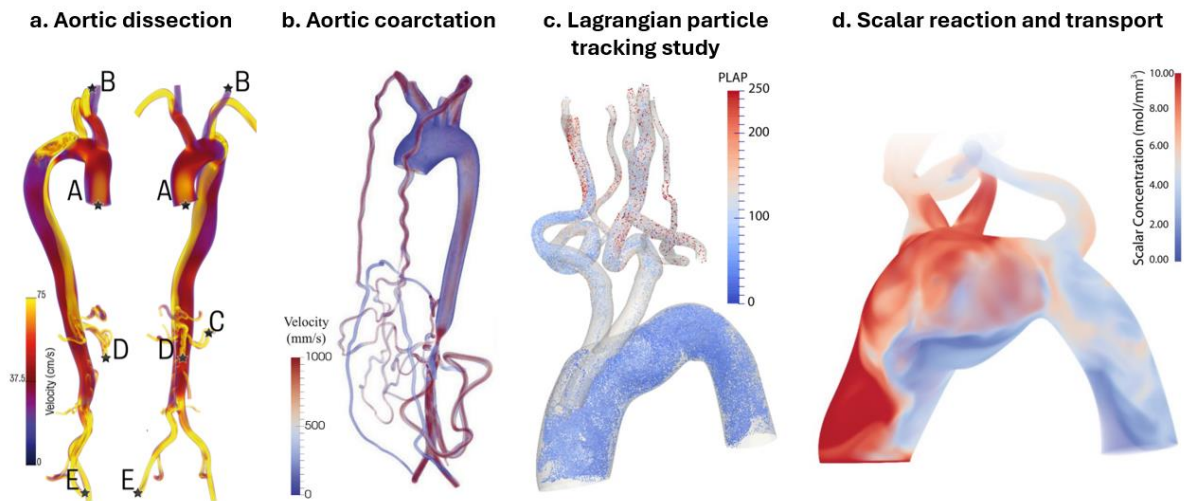


Figure 1.14. Examples of aortic studies using CRIMSON. Figures from A: aortic dissection [54], B: aortic coarctation [88], C: Lagrangian particle tracking applied on the aorta [48], and D: scalar reaction and transport study [48].

CRIMSON has been used for various aortic disease studies such as aortic dissection [54], aortic coarctation [88], and aortic aneurysm [89]. In addition, its features have supported aortic research involving Lagrangian particle tracking [90] and scalar reaction & transport [91]. Figure 1.14 presents solutions from different studies conducted using CRIMSON.

1.5.3 Nonlinear rotation-free shell

In cardiovascular models, most of the structural components, such as the aortic wall, aortic valves, and intimal flap, have a small thickness-to-length ratio. Based on Kirchhoff-Love theory, membrane models allow 3D structural problems to be simplified by solving them on a 2D middle surface while accounting for thickness, thereby significantly reducing computational cost [92]. Membrane models have become a popular choice for modeling thin biological structures [93]. However, because membrane models cannot capture bending stiffness, they may lead to numerical buckling in complex geometries [94]. The aorta, with its complex geometry and connections to side vessels, presents such challenges.

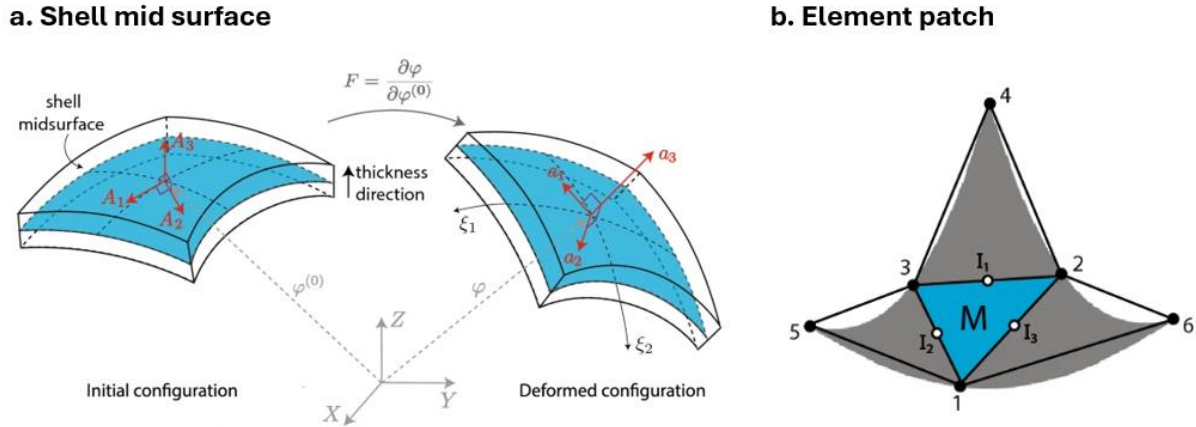


Figure 1.15. Schematic drawing illustrates the (a) shell mid surface in the initial and deformed configurations and (b) element patch comprising a master element and three adjacent elements. Figure recreated from [97].

Shell models, which also follow Kirchhoff-Love theory, can capture bending stiffness but are computationally more expensive due to the inclusion of an additional rotation degree of freedom. Figure 1.15 (a) shows how a shell formulation utilizes the mid-surface of a thin solid structure, along with basis vectors in both the initial and deformed configurations. To avoid these additional degrees of freedom, a rotation-free shell formulation has been developed [95]. This approach computes both membrane and bending behavior using only displacement degrees of freedom for a triangular element and its three neighboring elements, as shown in Figure 1.15 (b).

Recently, this nonlinear rotation free shell formulation has been adapted and validated for cardiovascular studies [56]. Shell formulations have also been successfully implemented in the FSI problems with its advantage of smaller computational cost [96]. A study demonstrating the efficiency and accuracy of a rotation-free shell formulation, compared to 3D solids, is presented in Chapter 2.

1.6 Objective and structure of the thesis

1.6.1 Objective of the thesis

Despite advances in medical imaging techniques and computational modeling methods, gaps and limitations remain in the field. First, although medical images provide 3D aortic configurations and allow for the measurement of 3D aortic deformations, the kinematic analysis of these images has been limited to characterizing aortic deformation in 1D, for example focusing only on circumferential diameter growth or axial aortic root motion (see Section 1.3.1). More sophisticated techniques are needed to assess 3D aortic deformation from dynamic 3D images.

Second, computational simulations, particularly FSI models, have been used to study the dynamic motion of the intimal flap in aortic dissection (see section 1.4.3.1). However, patient-specific FSI models are computationally expensive, especially when they are solved with ALE method. Furthermore, FSI models have not yet been applied to specific complications associated with the aortic dissection. Computationally efficient FSI models are needed to solve problems and applied to various complications.

The objective of thesis is to study the aorta using both medical imaging analysis techniques and computational modeling to address these limitations with two primary aims. Aim 1 is assessment of the 3D aortic deformation during cardiac cycle using medical image analysis techniques. Aim 2 is development of computationally efficient FSI models for aortic dissection.

1.6.2 Structure of the thesis

This thesis explores the biomechanics of the aorta through two main approaches: (I) the use of advanced medical imaging techniques, VDM, to extract 3D aortic deformation; and (II) the implementation and development of computational FSI models for aortic dissection.

Prior to presenting these two main parts, we establish the efficiency of the nonlinear rotation-free shell formulation, which is one of the key methods applied throughout both parts I

and II. Chapter 2 presents a systematic comparison between the rotation-free shell formulation and 3D solid models.

Part I, covered in Chapters 3 and 4, focuses on advanced image analysis. In Chapter 3, we apply VDM to dynamic CTA data to extract 3D pulsatile motion of the aortic root across a range of patient groups, including non-aneurysmal, TAA, Marfan syndrome, and post-stent repair cases. Chapter 4 details the calibration of deformable image registration parameters in VDM-D, leveraging physics-based synthetic data for improved accuracy.

Part II comprises Chapters 5, 6, and 7, and presents the computational modeling of aortic dissection. Chapter 5 discusses the modeling of dynamic obstruction using the ALE method. In this work, we identified the limitations of ALE. These findings motivate the development of an efficient FSI solver using IBM. Chapter 6 introduces a novel IBM formulation for modeling aortic dissection, the primary methodological contribution of this thesis. In Chapter 7, we apply this new IBM approach to create a patient-specific aortic dissection model.

Finally, Chapter 8 summarizes the main findings and discusses directions for future research.

1.7 Bibliography

- [1] S. Y. Ho, “Structure and anatomy of the aortic root,” *European Journal of Echocardiography*, vol. 10, no. 1, 2009, doi: 10.1093/EJECHOCARD/JEN243,.
- [2] C. A. Figueroa, C. A. Taylor, and A. L. Marsden, “Blood Flow,” *Encyclopedia of Computational Mechanics Second Edition*, 2017, doi: 10.1002/9781119176817.ecm2068.
- [3] H. G. Bogren et al., “The function of the aorta in ischemic heart disease: A magnetic resonance and angiographic study of aortic compliance and blood flow patterns,” *Am Heart J*, vol. 118, no. 2, pp. 234–247, Aug. 1989, doi: 10.1016/0002-8703(89)90181-6.
- [4] D. N. Ku, “Blood flow in arteries,” *Annu Rev Fluid Mech*, vol. 29, no. Volume 29, 1997, pp. 399–434, Jan. 1997, doi: 10.1146/ANNUREV.FLUID.29.1.399/CITE/REFWORKS.
- [5] J. P. Vande Geest, M. S. Sacks, and D. A. Vorp, “Age Dependency of the Biaxial Biomechanical Behavior of Human Abdominal Aorta,” *J Biomech Eng*, vol. 126, no. 6, pp. 815–822, Dec. 2004, doi: 10.1115/1.1824121.
- [6] J. P. Vande Geest, M. S. Sacks, and D. A. Vorp, “The effects of aneurysm on the biaxial mechanical behavior of human abdominal aorta,” *J Biomech*, vol. 39, no. 7, pp. 1324–1334, Jan. 2006, doi: 10.1016/J.JBIOMECH.2005.03.003.

- [7] J. F. Rodríguez, C. Ruiz, M. Doblaré, and G. A. Holzapfel, “Mechanical stresses in abdominal aortic aneurysms: Influence of diameter, asymmetry, and material anisotropy,” *J Biomech Eng*, vol. 130, no. 2, Apr. 2008, doi: 10.1115/1.2898830/452499.
- [8] M. Asgari, N. Latifi, F. Giovanniello, H. D. Espinosa, and M. Amabili, “Revealing Layer-Specific Ultrastructure and Nanomechanics of Fibrillar Collagen in Human Aorta via Atomic Force Microscopy Testing: Implications on Tissue Mechanics at Macroscopic Scale,” *Adv Nanobiomed Res*, vol. 2, no. 5, p. 2100159, May 2022, doi: 10.1002/ANBR.202100159.
- [9] T. C. Gasser, S. Gallinetti, X. Xing, C. Forsell, J. Swedenborg, and J. Roy, “Spatial orientation of collagen fibers in the abdominal aortic aneurysm’s wall and its relation to wall mechanics,” *Acta Biomater*, vol. 8, no. 8, pp. 3091–3103, Aug. 2012, doi: 10.1016/J.ACTBIO.2012.04.044.
- [10] R. H. Mackey et al., “Correlates of aortic stiffness in elderly individuals: a subgroup of the cardiovascular health study,” *Am J Hypertens*, vol. 15, no. 1, pp. 16–23, Jan. 2002, doi: 10.1016/S0895-7061(01)02228-2.
- [11] J. L. Cavalcante, J. A. C. Lima, A. Redheuil, and M. H. Al-Mallah, “Aortic Stiffness: Current Understanding and Future Directions,” *J Am Coll Cardiol*, vol. 57, no. 14, pp. 1511–1522, Apr. 2011, doi: 10.1016/J.JACC.2010.12.017.
- [12] T. Kim et al., “Three-Dimensional Characterization of Aortic Root Motion by Vascular Deformation Mapping,” *Journal of Clinical Medicine* 2023, Vol. 12, Page 4471, vol. 12, no. 13, p. 4471, Jul. 2023, doi: 10.3390/JCM12134471.
- [13] S. F. Vatner, J. Zhang, C. Vyzas, K. Mishra, R. M. Graham, and D. E. Vatner, “Vascular Stiffness in Aging and Disease,” *Front Physiol*, vol. 12, p. 762437, Dec. 2021, doi: 10.3389/FPHYS.2021.762437/XML/NLM.
- [14] E. M. Isselbacher, “Diseases of the Aorta,” *Essential Cardiology: Principles and Practice: Second Edition*, pp. 681–690, 2005, doi: 10.1007/978-1-59259-918-9_37.
- [15] A. Pinard, G. T. Jones, and D. M. Milewicz, “Genetics of Thoracic and Abdominal Aortic Diseases: Aneurysms, Dissections, and Ruptures,” *Circ Res*, vol. 124, no. 4, pp. 588–606, Feb. 2019, doi: 10.1161/CIRCRESAHA.118.312436/ASSET/A7362B6F-82C6-418E-A44F-B46E514F38DF/ASSETS/IMAGES/LARGE/588FIG04.JPG.
- [16] T. Kim et al., “A Computational Study of Dynamic Obstruction in Type B Aortic Dissection,” *J Biomech Eng*, vol. 145, no. 3, Mar. 2023, doi: 10.1115/1.4056355/1152231.

- [17] “Aortic Dissection | My Vascular Health.” Accessed: Aug. 06, 2025. [Online]. Available: <https://myvascularhealth.org/vascular-education/aortic-dissection/>
- [18] I. Meszaros, J. Morocz, J. Szlavi, J. Schmidt, L. T.- Chest, and undefined 2000, “Epidemiology and clinicopathology of aortic dissection,” Elsevier, Accessed: Aug. 07, 2022. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0012369215350844>
- [19] B. Yang, H. J. Patel, D. M. Williams, N. L. Dasika, and G. M. Deeb, “Management of type A dissection with malperfusion,” *Ann Cardiothorac Surg*, vol. 5, no. 4, pp. 265–274, 2016, doi: 10.21037/acs.2016.07.04.
- [20] J. Black, W. M.-. P. T. (ed): UpToDate, undefined Waltham, undefined MA, and undefined 2021, “Clinical features and diagnosis of acute aortic dissection,” *uptodate.com*, Accessed: Aug. 06, 2025.
- [21] P. G. Hagan et al., “The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease,” *jamanetwork.com*, vol. 283, no. 7, pp. 897–903, 2000, Accessed: Aug. 06, 2025.
- [22] B. Yang et al., “Endovascular Fenestration/Stenting First Followed by Delayed Open Aortic Repair for Acute Type A Aortic Dissection with Malperfusion Syndrome,” *Circulation*, vol. 138, no. 19, pp. 2091–2103, Nov. 2018, doi: 10.1161/CIRCULATIONAHA.118.036328/SUPPL_FILE/SUPPLEMENTALMATERIAL_FINAL.PDF.
- [23] A. C. Braverman, “Acute aortic dissection: Clinician update,” *Circulation*, vol. 122, no. 2, pp. 184–188, Jul. 2010, doi: 10.1161/CIRCULATIONAHA.110.958975/SUPPL_FILE/CIR200591VIDEO2.AVI.
- [24] A. M. Booher and K. A. Eagle, “Diagnosis and management issues in thoracic aortic aneurysm,” *Am Heart J*, vol. 162, no. 1, pp. 38-46.e1, Jul. 2011, doi: 10.1016/J.AHJ.2011.04.010.
- [25] “Familial Thoracic Aortic Aneurysm and Dissection.” The Marfan foundation.
- [26] N. Sakalihasan, R. Limet, and O. D. Defawe, “Abdominal aortic aneurysm,” *Lancet*, vol. 365, no. 9470, pp. 1577–1589, Apr. 2005, doi: 10.1016/S0140-6736(05)66459-8/ASSET/20C11997-DD5F-4B52-A652-C7F4B4F01E46/MAIN.ASSETS/GR9.JPG.
- [27] N. L. Weintraub, “Understanding Abdominal Aortic Aneurysm,” *N Engl J Med*, vol. 361, no. 11, p. 1114, Sep. 2009, doi: 10.1056/NEJMCIBR0905244.

- [28] J. Golledge, “Abdominal aortic aneurysm: update on pathogenesis and medical treatments,” *Nature Reviews Cardiology* 2018 16:4, vol. 16, no. 4, pp. 225–242, Nov. 2018, doi: 10.1038/s41569-018-0114-9.
- [29] T. Miyake and R. Morishita, “Pharmacological treatment of abdominal aortic aneurysm,” *Cardiovasc Res*, vol. 83, no. 3, pp. 436–443, Aug. 2009, doi: 10.1093/CVR/CVP155.
- [30] D. Attias et al., “Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in marfan syndrome and related disorders,” *Circulation*, vol. 120, no. 25, pp. 2541–2549, Dec. 2009, doi: 10.1161/CIRCULATIONAHA.109.887042/ASSET/0DF694D6-DF2D-41D0-9676-7F0988FC0A99/ASSETS/GRAPHIC/10FF3.JPEG.
- [31] A. W. Den Hartog et al., “Aortic disease in patients with Marfan syndrome: Aortic volume assessment for surveillance,” *Radiology*, vol. 269, no. 2, pp. 370–377, Nov. 2013, doi: 10.1148/RADIOL.13122310/ASSET/IMAGES/LARGE/RADIOL.13122310.TBL5.JPEG.
- [32] R. E. Pyeritz and V. A. McKusick, “The Marfan Syndrome: Diagnosis and Management,” *New England Journal of Medicine*, vol. 300, no. 14, pp. 772–777, Apr. 1979, doi: 10.1056/NEJM197904053001406/ASSET/AEEAC9C6-BEC2-4306-AF33-B801D670E256/ASSETS/IMAGES/LARGE/NEJM197904053001406_T1.JPG.
- [33] D. M. Milewicz, H. C. Dietz, and D. C. Miller, “Treatment of aortic disease in patients with Marfan syndrome,” *Circulation*, vol. 111, no. 11, Mar. 2005, doi: 10.1161/01.CIR.0000155243.70456.F4/ASSET/89DCAD56-489A-45A9-B60C-502D0A1DF0E2/ASSETS/GRAPHIC/16FF3.JPEG.
- [34] “Aortopathy, Valvular Heart Disease Research | BCM.” Accessed: Aug. 06, 2025.
- [35] A. Williams, S. Davies, A. G. Stuart, D. G. Wilson, and A. G. Fraser, “Medical treatment of Marfan syndrome: a time for change,” *Heart*, vol. 94, no. 4, pp. 414–421, Apr. 2008, doi: 10.1136/HRT.2006.109454.
- [36] V. Deleeuw, A. De Clercq, J. De Backer, and P. Sips, “An overview of investigational and experimental drug treatment strategies for marfan syndrome,” *J Exp Pharmacol*, vol. 13, pp. 755–779, 2021, doi: 10.2147/JEP.S265271.
- [37] Tsai, Thomas T., et al. "Partial thrombosis of the false lumen in patients with acute type B aortic dissection." *New England Journal of Medicine* 357.4 (2007): 349-359.

- [38] S. D. Singh, X. Y. Xu, J. R. Pepper, C. Izgi, T. Treasure, and R. H. Mohiaddin, "Effects of aortic root motion on wall stress in the Marfan aorta before and after personalised aortic root support (PEARS) surgery," *J Biomech*, vol. 49, no. 10, pp. 2076–2084, Jul. 2016, doi: 10.1016/J.JBIOMECH.2016.05.011
- [39] Goudot, Guillaume, et al. "Aortic wall elastic properties in case of bicuspid aortic valve." *Frontiers in physiology* 10 (2019): 299.
- [40] B. J. Holloway, D. Rosewarne, and R. G. Jones, "Imaging of thoracic aortic disease," *Br J Radiol*, vol. 84, no. Spec Iss 3, p. S338, Dec. 2011, doi: 10.1259/BJR/30655825.
- [41] A. T. Vertinsky, N. E. Schwartz, N. J. Fischbein, J. Rosenberg, G. W. Albers, and G. Zaharchuk, "Comparison of Multidetector CT Angiography and MR Imaging of Cervical Artery Dissection," *American Journal of Neuroradiology*, vol. 29, no. 9, pp. 1753–1760, Oct. 2008, doi: 10.3174/AJNR.A1189.
- [42] Y. Kato et al., "Application of three-dimensional CT angiography (3D-CTA) to cerebral aneurysms," *Surg Neurol*, vol. 52, no. 2, pp. 113–122, Aug. 1999, doi: 10.1016/S0090-3019(99)00062-2.
- [43] T. Kim et al., "Three-Dimensional Characterization of Aortic Root Motion by Vascular Deformation Mapping," *Journal of Clinical Medicine* 2023, Vol. 12, Page 4471, vol. 12, no. 13, p. 4471, Jul. 2023, doi: 10.3390/JCM12134471.
- [44] C. A. Taylor and C. A. Figueroa, "Patient-specific modeling of cardiovascular mechanics," *Annu Rev Biomed Eng*, vol. 11, no. Volume 11, 2009, pp. 109–134, Aug. 2009, doi: 10.1146/ANNUREV.BIOENG.10.061807.160521/CITE/REFWORKS.
- [45] H. Suito, T. Ueda, and D. Sze, "Numerical simulation of blood flow in the thoracic aorta using a centerline-fitted finite difference approach," *Jpn J Ind Appl Math*, vol. 30, no. 3, pp. 701–710, Nov. 2013, doi: 10.1007/S13160-013-0123-3/METRICS.
- [46] A. Fatahillah, A. L. Anggraini, and S. Setiawani, "Numerical analysis of blood flow in abdominal aortic aneurysm using finite volume method," *Desimal: Jurnal Matematika*, vol. 5, no. 2, pp. 131–142, Aug. 2022, doi: 10.24042/DJM.V5I2.9928.
- [47] Y. A. Algabri, S. Rookkapan, and S. Chatpun, "Three-dimensional finite volume modelling of blood flow in simulated angular neck abdominal aortic aneurysm," *IOP Conf Ser Mater Sci Eng*, vol. 243, no. 1, p. 012003, Sep. 2017, doi: 10.1088/1757-899X/243/1/012003.

- [48] C. J. Arthurs et al., “CRIMSON: An open-source software framework for cardiovascular integrated modelling and simulation,” *PLoS Comput Biol*, vol. 17, no. 5, p. e1008881, May 2021, doi: 10.1371/JOURNAL.PCBL1008881.
- [49] A. Updegrove, N. M. Wilson, J. Merkow, H. Lan, A. L. Marsden, and S. C. Shadden, “SimVascular: An Open Source Pipeline for Cardiovascular Simulation,” *Ann Biomed Eng*, vol. 45, no. 3, pp. 525–541, Mar. 2017, doi: 10.1007/S10439-016-1762-8/FIGURES/14.
- [50] A. S. Les et al., “Quantification of hemodynamics in abdominal aortic aneurysms during rest and exercise using magnetic resonance imaging and computational fluid dynamics,” *Ann Biomed Eng*, vol. 38, no. 4, pp. 1288–1313, Apr. 2010, doi: 10.1007/S10439-010-9949-X/FIGURES/14.
- [51] B. T. Tang, T. A. Fonte, F. P. Chan, P. S. Tsao, J. A. Feinstein, and C. A. Taylor, “Three-dimensional hemodynamics in the human pulmonary arteries under resting and exercise conditions,” *Ann Biomed Eng*, vol. 39, no. 1, pp. 347–358, Jan. 2011, doi: 10.1007/S10439-010-0124-1/FIGURES/7.
- [52] D. M. Sforza, C. M. Putman, and J. R. Cebral, “Hemodynamics of cerebral aneurysms,” *Annu Rev Fluid Mech*, vol. 41, no. Volume 41, 2009, pp. 91–107, Jan. 2009, doi: 10.1146/ANNUREV.FLUID.40.111406.102126/CITE/REFWORKS.
- [53] J. F. Ladisa et al., “Computational simulations for aortic coarctation: Representative results from a sampling of patients,” *J Biomech Eng*, vol. 133, no. 9, Sep. 2011, doi: 10.1115/1.4004996/466558.
- [54] D. Dillon-Murphy, A. Noorani, D. Nordsletten, and C. A. Figueroa, “Multi-modality image-based computational analysis of haemodynamics in aortic dissection,” *Biomech Model Mechanobiol*, vol. 15, no. 4, pp. 857–876, Aug. 2016, doi: 10.1007/S10237-015-0729-2/FIGURES/4.
- [55] Menichini, Claudia, Zhuo Cheng, Richard GJ Gibbs, and Xiao Yun Xu. "Predicting false lumen thrombosis in patient-specific models of aortic dissection." *Journal of The Royal Society Interface* 13, no. 124 (2016): 20160759.
- [56] Zeinali-Davarani, S., and S. Baek. "Medical image-based simulation of abdominal aortic aneurysm growth." *Mechanics Research Communications* 42 (2012): 107-117.
- [57] D. Ambrosi et al., “Perspectives on biological growth and remodeling,” *J Mech Phys Solids*, vol. 59, no. 4, pp. 863–883, Apr. 2011, doi: 10.1016/J.JMPS.2010.12.011.

- [58] J. D. Humphrey, “MECHANICS OF THE ARTERIAL WALL: REVIEW AND DIRECTIONS,” *Critical Reviews*; in *Biomedical Engineering*, vol. 23, no. 1–2, pp. 1–162, 1995, doi: 10.1615/CRITREVBIOSEDENG.V23.I1-2.10.
- [59] J. D. Humphrey and G. A. Holzapfel, “Mechanics, mechanobiology, and modeling of human abdominal aorta and aneurysms,” *J Biomech*, vol. 45, no. 5, pp. 805–814, Mar. 2012, doi: 10.1016/J.JBIOMECH.2011.11.021.
- [60] G. A. Holzapfel and R. W. Ogden, “Constitutive modelling of arteries,” *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, vol. 466, no. 2118, pp. 1551–1597, Jun. 2010, doi: 10.1098/RSPA.2010.0058;PAGEGROUP:STRING:PUBLICATION.
- [61] H. M. Loree, R. D. Kamm, R. G. Stringfellow, and R. T. Lee, “Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels.,” *Circ Res*, vol. 71, no. 4, pp. 850–858, 1992, doi: 10.1161/01.RES.71.4.850.
- [62] R. T. Lee, H. M. Loree, and M. C. Fishbein, “High stress regions in saphenous vein bypass graft atherosclerotic lesions,” *J Am Coll Cardiol*, vol. 24, no. 7, pp. 1639–1644, Dec. 1994, doi: 10.1016/0735-1097(94)90168-6.
- [63] G. C. Cheng, H. M. Loree, R. D. Kamm, M. C. Fishbein, and R. T. Lee, “Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: A structural analysis with histopathological correlation,” *Circulation*, vol. 87, no. 4, pp. 1179–1187, 1993, doi: 10.1161/01.CIR.87.4.1179;WGROU:STRING:PUBLICATION.
- [64] D. H. J. Wang, M. S. Makaroun, and D. A. Vorp, “Noninvasive estimation of wall strength distribution in human abdominal aortic aneurysm,” *asmedigitalcollection.asme.org* DHJ Wang, MS Makaroun, DA Vorp ASME International Mechanical Engineering Congress and, 2001•asmedigitalcollection.asme.org, vol. 51, 2001, Accessed: Aug. 08, 2025.
- [65] D. A. Steinman, D. A. Vorp, and C. R. Ethier, “Computational modeling of arterial biomechanics: Insights into pathogenesis and treatment of vascular disease,” *J Vasc Surg*, vol. 37, no. 5, pp. 1118–1128, May 2003, doi: 10.1067/MVA.2003.122.
- [66] A. Leuprecht, S. Kozerke, P. Boesiger, and K. Perktold, “Blood flow in the human ascending aorta: a combined MRI and CFD study,” *Springer* A Leuprecht, S Kozerke, P Boesiger, K Perktold *Journal of engineering mathematics*, 2003•Springer, vol. 47, no. 3–4, pp. 387–404, Dec. 2003, doi: 10.1023/B:ENGI.0000007969.18105.B7.

- [67] P. Le Tallec, J. M.-C. methods in applied mechanics and, and undefined 2001, “Fluid structure interaction with large structural displacements,” ElsevierP Le Tallec, J MouroComputer methods in applied mechanics and engineering, 2001•Elsevier, Accessed: Jun. 03, 2025.
- [68] J. De Hart, G. W. M. Peters, P. J. G. Schreurs, and F. P. T. Baaijens, “A three-dimensional computational analysis of fluid–structure interaction in the aortic valve,” *J Biomech*, vol. 36, no. 1, pp. 103–112, Jan. 2003, doi: 10.1016/S0021-9290(02)00244-0.
- [69] A. Qiao, W. Yin, and B. Chu, “Numerical simulation of fluid–structure interaction in bypassed DeBakey III aortic dissection,” *Comput Methods Biomech Biomed Engin*, vol. 18, no. 11, pp. 1173–1180, Aug. 2015, doi: 10.1080/10255842.2014.881806;SUBPAGE:STRING:FULL.
- [70] K. Bäuml et al., “Fluid–structure interaction simulations of patient-specific aortic dissection,” *Biomech Model Mechanobiol*, vol. 19, no. 5, pp. 1607–1628, Oct. 2020, doi: 10.1007/S10237-020-01294-8/FIGURES/12.
- [71] C. S. Peskin, “The immersed boundary method,” *Acta Numerica*, vol. 11, pp. 479–517, Jan. 2002, doi: 10.1017/S0962492902000077.
- [72] A. Gilmanov, T. B. Le, and F. Sotiropoulos, “A numerical approach for simulating fluid structure interaction of flexible thin shells undergoing arbitrarily large deformations in complex domains,” *J Comput Phys*, vol. 300, pp. 814–843, Nov. 2015, doi: 10.1016/J.JCP.2015.08.008.
- [73] I. Borazjani, L. Ge, F. S.-J. of C. physics, and undefined 2008, “Curvilinear immersed boundary method for simulating fluid structure interaction with complex 3D rigid bodies,” ElsevierI Borazjani, L Ge, F SotiropoulosJournal of Computational physics, 2008•Elsevier, Accessed: Jun. 03, 2025.
- [74] A. M. Bavo, G. Rocatello, F. Iannaccone, J. Degroote, J. Vierendeels, and P. Segers, “Fluid-Structure Interaction Simulation of Prosthetic Aortic Valves: Comparison between Immersed Boundary and Arbitrary Lagrangian-Eulerian Techniques for the Mesh Representation,” *PLoS One*, vol. 11, no. 4, p. e0154517, Apr. 2016, doi: 10.1371/JOURNAL.PONE.0154517.
- [75] C. A. Figueroa, I. E. Vignon-Clementel, K. E. Jansen, T. J. R. Hughes, and C. A. Taylor, “A coupled momentum method for modeling blood flow in three-dimensional deformable arteries,” *Comput Methods Appl Mech Eng*, vol. 195, no. 41–43, pp. 5685–5706, Aug. 2006, doi: 10.1016/J.CMA.2005.11.011.

- [76] N. Xiao, J. D. Humphrey, and C. A. Figueroa, “Multi-scale computational model of three-dimensional hemodynamics within a deformable full-body arterial network,” *J Comput Phys*, vol. 244, pp. 22–40, Jul. 2013, doi: 10.1016/J.JCP.2012.09.016.
- [77] F. Cuomo, J. Ferruzzi, J. D. Humphrey, and C. A. Figueroa, “An Experimental–Computational Study of Catheter Induced Alterations in Pulse Wave Velocity in Anesthetized Mice,” *Ann Biomed Eng*, vol. 43, no. 7, pp. 1555–1570, Jul. 2015, doi: 10.1007/S10439-015-1272-0/FIGURES/6.
- [78] A. Hager et al., “Diameters of the thoracic aorta throughout life as measured with helical computed tomography,” *J Thorac Cardiovasc Surg*, vol. 123, no. 6, pp. 1060–1066, Jun. 2002, doi: 10.1067/MTC.2002.122310.
- [79] L. A. Pape et al., “Aortic diameter ≥ 5.5 cm is not a good predictor of type A aortic dissection: Observations from the International Registry of Acute Aortic Dissection (IRAD),” *Circulation*, vol. 116, no. 10, pp. 1120–1127, Sep. 2007, doi: 10.1161/CIRCULATIONAHA.107.702720/ASSET/F45899D2-C82E-444B-BF8B-F8F8695D0B35/ASSETS/GRAPHIC/10FF2.JPEG.
- [80] S. D. Singh, X. Y. Xu, J. R. Pepper, C. Izgi, T. Treasure, and R. H. Mohiaddin, “Effects of aortic root motion on wall stress in the Marfan aorta before and after personalised aortic root support (PEARS) surgery,” *J Biomech*, vol. 49, no. 10, pp. 2076–2084, Jul. 2016, doi: 10.1016/J.JBIOMECH.2016.05.011.
- [81] C. J. Beller, M. R. Labrosse, M. J. Thubrikar, and F. Robicsek, “Role of Aortic Root Motion in the Pathogenesis of Aortic Dissection,” *Circulation*, vol. 109, no. 6, pp. 763–769, Feb. 2004, doi: 10.1161/01.CIR.0000112569.27151.F7/ASSET/7F00F1B9-2571-4765-91E7-4EA1704D7223/ASSETS/GRAPHIC/16FF6.JPEG.
- [82] N. S. Burris et al., “Vascular Deformation Mapping for CT Surveillance of Thoracic Aortic Aneurysm Growth,” *Radiology*, vol. 302, no. 1, pp. 218–225, Jan. 2022, doi: 10.1148/RADIOL.2021210658/ASSET/IMAGES/LARGE/RADIOL.2021210658.FIG6.JPEG.
- [83] N. S. Burris, B. A. Hoff, H. J. Patel, E. A. Kazerooni, and B. D. Ross, “Three-Dimensional Growth Analysis of Thoracic Aortic Aneurysm With Vascular Deformation Mapping,” *Circ Cardiovasc Imaging*, vol. 11, no. 8, p. e008045, Aug. 2018, doi: 10.1161/CIRCIMAGING.118.008045/SUPPL_FILE/CIRCCVIM_CIRCCVIM-2018-008045_SUPP2.PDF.

- [84] Z. Bian, J. Zhong, J. Dominic, G. E. Christensen, C. R. Hatt, and N. S. Burris, “Validation of a robust method for quantification of three-dimensional growth of the thoracic aorta using deformable image registration,” *Med Phys*, vol. 49, no. 4, pp. 2514–2530, Apr. 2022, doi: 10.1002/MP.15496.
- [85] N. Tjahjadi et al., “Three-dimensional characterization of ascending aortic strain, motion and growth in patients undergoing thoracic endovascular aortic repair,” *JVS Vasc Sci*, vol. 6, p. 100293, Jan. 2025, doi: 10.1016/J.JVSSCI.2025.100293.
- [86] N. S. Tjahjadi et al., “Three-dimensional assessment of ascending aortic stiffness, motion, and growth in ascending thoracic aortic aneurysm,” *European heart journal. Imaging methods and practice*, vol. 3, no. 1, Jan. 2024, doi: 10.1093/EHJIMP/QYAE133.
- [87] M. Zhou et al., “Cardiovascular flow simulation at extreme scale,” *Comput Mech*, vol. 46, no. 1, pp. 71–72, Dec. 2010, doi: 10.1007/S00466-009-0450-Z/METRICS.
- [88] C. Tossas-Betancourt et al., “Computational analysis of renal artery flow characteristics by modeling aortoplasty and aortic bypass interventions for abdominal aortic coarctation,” *J Vasc Surg*, vol. 71, no. 2, pp. 505–516.e4, Feb. 2020, doi: 10.1016/J.JVS.2019.02.063.
- [89] P. Youssefi, R. Sharma, ... C. F.-B. medical, and undefined 2017, “Functional assessment of thoracic aortic aneurysms—the future of risk prediction?,” *academic.oup.com* P Youssefi, R Sharma, CA Figueroa, M Jahangiri *British medical bulletin*, 2017•*academic.oup.com*, vol. 121, pp. 61–71, 2017, doi: 10.1093/BMB/LDW049/24331739/LDW049.PDF.
- [90] T. M. Van Bakel et al., “A computational analysis of different endograft designs for Zone 0 aortic arch repair,” *European Journal of Cardio-Thoracic Surgery*, vol. 54, no. 2, pp. 389–396, Aug. 2018, doi: 10.1093/EJCTS/EZY068.
- [91] S. R. Lynch, N. Nama, Z. Xu, C. J. Arthurs, O. Sahni, and C. A. Figueroa, “Numerical considerations for advection-diffusion problems in cardiovascular hemodynamics,” *Int J Numer Method Biomed Eng*, vol. 36, no. 9, p. e3378, Sep. 2020, doi: 10.1002/CNM.3378;WGROU:STRING:PUBLICATION.
- [92] T. Belytschko, W. Liu, B. Moran, and K. Elkhodary, *Nonlinear finite elements for continua and structures*. 2014. Accessed: Jun. 01, 2025.
- [93] A. Bonito, R. H. Nochetto, and M. Sebastian Pauletti, “Parametric FEM for geometric biomembranes,” *J Comput Phys*, vol. 229, no. 9, pp. 3171–3188, May 2010, doi: 10.1016/J.JCP.2009.12.036.

- [94] M. Lenz, D. J. G. Crow, and J. F. Joanny, “Membrane Buckling Induced by Curved Filaments,” *Phys Rev Lett*, vol. 103, no. 3, p. 038101, Aug. 2009, doi: 10.1103/PHYSREVLETT.103.038101/FIGURES/3/MEDIUM.
- [95] F. G. Flores and E. Oñate, “Improvements in the membrane behaviour of the three node rotation-free BST shell triangle using an assumed strain approach,” *Comput Methods Appl Mech Eng*, vol. 194, no. 6–8, pp. 907–932, Feb. 2005, doi: 10.1016/J.CMA.2003.08.012.
- [96] A. Nitti, J. Kiendl, A. Reali, and M. D. de Tullio, “An immersed-boundary/isogeometric method for fluid–structure interaction involving thin shells,” *Comput Methods Appl Mech Eng*, vol. 364, p. 112977, Jun. 2020, doi: 10.1016/J.CMA.2020.112977.
- [97] N. Nama, M. Aguirre, J. D. Humphrey, and C. A. Figueroa, “A nonlinear rotation-free shell formulation with prestressing for vascular biomechanics,” *Sci Rep*, vol. 10, no. 1, pp. 1–17, Dec. 2020, doi: 10.1038/S41598-020-74277-5;SUBJMETA=1041,166,639,705,985;KWRD=APPLIED+MATHEMATICS,BIOMEDICAL+ENGINEERING.

Chapter 2 A Systematic Comparison of Membrane, Shell, and 3D Solid Formulations for Nonlinear Vascular Biomechanics

This chapter is adapted from a manuscript currently in preparation for submission¹.

2.1 Introduction

Computational methods to simulate cardiovascular biomechanics in three-dimensional (3D) models of arteries have attracted significant interest owing to their applications in disease research, medical device design, and surgical planning [1],[2],[3],[4],[5],[6],[7]. Computational models have utilized various representations of the vascular wall which has been modeled, with varying degrees of detail, as either a 3D solid or a two-dimensional (2D) structure (membrane or shell). The latter choice has been motivated by the low ratio of wall thickness to radius exhibited by most arteries and veins as well as the presence of residual stresses, rendering them suitable to a 2D representation. Nonetheless, each of these approaches has its advantages and disadvantages concerning computational efficiency, accuracy, and ease of implementation.

In general, 3D solid models offer excellent accuracy, straightforward implementation, and flexibility to easily incorporate arbitrary constitutive material models [8]. They have been extensively employed both for the solid mechanics analysis of arterial wall [1],[9],[10],[11],[12] and fluid-structure analyses [13,14,15]. However, 3D solid models employing low-order interpolation present significant challenges concerning various locking phenomena and difficulty in generating good quality meshes for thin geometries. Specifically, generating a sufficiently good mesh (i.e. with appropriate aspect ratio of mesh elements) for thin geometries requires a finer in-plane mesh, leading to significant increases in degrees of freedom. This challenge can, in principle, be circumvented via the use of higher-order interpolation in 3D solid formulations. However, such formulations are typically undesirable for vascular applications owing to their associated numerical instabilities and high computational cost.

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To circumvent these challenges, 2D manifold representations of the vessel wall have been proposed. Earlier works have employed a membrane representation of the vessel wall and highlighted its significantly lower computational cost. For example, the vessel wall has been modeled as either a linear [16] or a nonlinear membrane [17],[18],[19],[20],[21]. More recently, various shell models have been employed to incorporate the bending stiffness of the vessel wall [22],[23],[24],[25],[26]. While shell theory is a mature field in nonlinear mechanics [27],[28],[29],[30],[31], adaptation of these theories for vascular biomechanics is largely restricted to shell formulations that employ the Kirchhoff-Love theory. In particular, we note the recent stress resultant shell formulation employed by Kim [22] (in the context of heart valve leaflets), the isogeometric formulation by Tepole [23], and our recent work using a rotation-free shell formulation [26]. We also note that subject-specific geometric models are typically obtained from medical images, where a direct assessment of vessel wall thickness is difficult. Consequently, construction of a 3D volumetric geometric model of the vessel wall entails the creation of a surface mesh that is then extended radially to obtain a 3D solid mesh. In this context, 2D representations of vessel wall offer another advantage over 3D models by avoiding the need for this additional pre-processing step.

Nevertheless, despite the widespread use of 2D models of vascular walls, there is limited understanding of the relative advantages and disadvantages of their performance against 3D solid formulations [8],[32]. To the best of our knowledge, there has been no comprehensive comparison of these approaches in the context of vascular biomechanics for complex subject-specific geometries and biologically relevant material models. Consequently, the modeling choice often relies on intuition and preference, with unclear consequences of choosing one approach over the other.

Another issue that introduces differences between 2D and 3D models concerns the handling of incompressibility. Typically, 3D models do not enforce incompressibility exactly to avoid the introduction of a Lagrange multiplier. Instead, they enforce near incompressibility. By contrast, 2D representations of vessel wall enforce incompressibility exactly by expressing through-the-thickness quantities in terms of in-plane quantities. The consequences of this difference in handling of incompressibility conditions are unclear.

Here, we address this gap in the literature by presenting a systematic comparison of three different approaches of modeling the nonlinear mechanics of the vascular wall. The first is a

nonlinear membrane model used previously by Lu *et al* [17] for cerebral aneurysms. The second is a nonlinear, rotation-free shell model, originally proposed by Onate and Flores [33], and recently adapted for biomechanics by Nama *et al* [26]. The third is a nonlinear 3D solid model, where we consider two different implementations employing wedge (or triangular prismatic) elements with linear and quadratic interpolation, which will be referred to as P1 and P2 models respectively [34],[35],[36],[37].

The outline of rest of the article is as follows: In Section 2.2, we briefly describe each formulation with an emphasis on assumptions concerning through-the-thickness variations of kinematic quantities. We also highlight differences in handling the incompressibility condition among these approaches. We then describe our strategy to obtain 3D solid wedge elements from the 2D midsurface triangular elements to ensure a consistent comparison among different formulations. In Section 2.3, we contrast results across the different formulations. We first consider an idealized cylindrical geometry to compare results of each formulation against the axisymmetric theory and investigate the performance of different formulations as a function of wall thickness to radius ratio. We also compare the performance of different formulations in idealized arterial bifurcation with regionally varying wall thickness. We then compare results for subject-specific mouse geometry with regionally varying material properties and wall thickness. Lastly, we provide a brief discussion of our results in Section 2.4.

2.2 Theoretical formulation

For each of the three basic formulations, we consider the mapping of a point within a neighborhood of the body from its initial configuration to any deformed configuration. Subsequently, we utilize this mapping to construct the deformation gradient tensor and right Cauchy-Green tensor. These expressions are then employed to define the elastic strain energy for the two constitutive models considered.

Below, Greek subscripts or superscripts take values $\{1,2\}$ while Latin subscripts or superscripts take values $\{1,2,3\}$. We follow Einstein's index notation where a repeated symbol denotes a summation, unless stated otherwise; x and X denote a point in the continuum in current and initial configurations, respectively, while φ and $\varphi^{(0)}$ denote a point on the midsurface of the continuum in current and initial configurations, respectively.

2.2.1 Kinematics

2.2.1.1 Membrane formulation

Consider the nonlinear membrane formulation, previously employed by Lu *et al* [38] for cerebral aneurysms. Membrane formulations represent the simplest modeling choice for the vessel wall and describe the kinematics via mid-surface quantities [39].

Consider a mapping between point $\varphi^{(0)}$ and point φ , both belonging to the membrane surface. The surface is parameterized by convective coordinates ξ^α ($\alpha = 1, 2$) which yield a basis of two covariant vectors in the tangent planes of the initial and deformed configurations

$$B_\alpha = \frac{\partial \varphi^{(0)}}{\partial \xi^\alpha}, b_\alpha = \frac{\partial \varphi}{\partial \xi^\alpha} \quad (2.1)$$

The corresponding contravariant vectors can be obtained as follows

$$B_\alpha = B^{\alpha\beta} B_\beta, b_\alpha = b^{\alpha\beta} b_\beta \quad (2.2)$$

where $B^{\alpha\beta} = B^\alpha \cdot B^\beta$ and $b^{\alpha\beta} = b^\alpha \cdot b^\beta$. Following Gruttman and Taylor [39], we introduce an orthonormal basis in the material configuration; in this case the covariant and contravariant components of the referential stress and strain tensors are identical, thereby simplifying the implementation. To this end, we define

$$A_3 = A^3 = \frac{B_1 \times B_2}{||B_1 \times B_2||}, A_1 = A^1 = \frac{B_1}{||B_1||}, A_2 = A^2 = A_3 \times A_1 \quad (2.3)$$

with associated coordinates s_α indirectly defined as

$$A_\alpha = A^\alpha = \frac{\partial \varphi^{(0)}}{\partial s_\alpha} \quad (2.4)$$

We remark that this orthonormal basis is introduced for mathematical convenience and ease of implementation and is not strictly necessary to describe the membrane formulation. Similarly, the basis vectors (not necessarily orthonormal) at a position φ of a point on the membrane surface in the current configuration can be defined as

$$a_\alpha = \frac{\partial \varphi}{\partial s_\alpha} \quad (2.5)$$

Figure 1(A) shows the initial and deformed configurations of the vessel wall midsurface, and the corresponding basis. The in-plane deformation gradient can be defined as

$$\bar{F} = \frac{\partial \varphi}{\partial \varphi^{(0)}} = \frac{\partial \varphi}{\partial s_\alpha} \otimes \frac{\partial s_\alpha}{\partial \varphi^{(0)}} = a_\alpha \otimes A^\alpha \quad (2.6)$$

Correspondingly, the in-plane right Cauchy-Green tensor is obtained as

$$\bar{C} = a_{\alpha\beta} A^\alpha \otimes A^\beta \quad (2.7)$$

where $a_{\alpha\beta}$ denotes the metric in the current configuration

$$a_{\alpha\beta} = a_\alpha \cdot a_\beta \quad (2.8)$$

We remark that the membrane strain can be described completely without requiring an explicit reference to the underlying 3D deformation. Nonetheless, it is useful to view the midsurface deformation as components of the 3D motion. Neglecting the transverse shear strain, the corresponding 3D deformation gradient can be written as

$$F = a_\alpha \otimes A^\alpha + \lambda_3 a_3 \otimes A_3 \quad (2.9)$$

where $\lambda_3 = h/H$ denotes the thickness stretch with h and H being the current and initial thickness of the membrane. Accordingly, the 3D right Cauchy-Green tensor is

$$C = a_{\alpha\beta} A^\alpha \otimes A^\beta + \lambda_3^2 A_3 \otimes A_3 \quad (2.10)$$

with

$$C_{ij} = \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & 0 \\ 0 & 0 & \lambda_3^2 \end{bmatrix} \quad (2.11)$$

where C_{33} is obtained via plane stress and incompressibility conditions. This allows the Jacobian determinant to be expressed as

$$J = \sqrt{\det(C)} = J_0 \lambda_3 \quad (2.12)$$

where $J_0 = \sqrt{\frac{|a_{\alpha\beta}|}{|A_{\alpha\beta}|}}$ denotes the in-plane Jacobian determinant. Equation (2.12), in combination with the incompressibility condition

$$J = 1 \quad (2.13)$$

yields

$$\lambda_3 = J_0^{-1} \quad (2.14)$$

This coupling of out-of-plane components with the in-plane metrics ensures satisfaction of the incompressibility constraint. This approach enables us to employ general 3D constitutive models by relating 3D strain quantities to their in-plane counterparts, as described in Section 2.2.2.

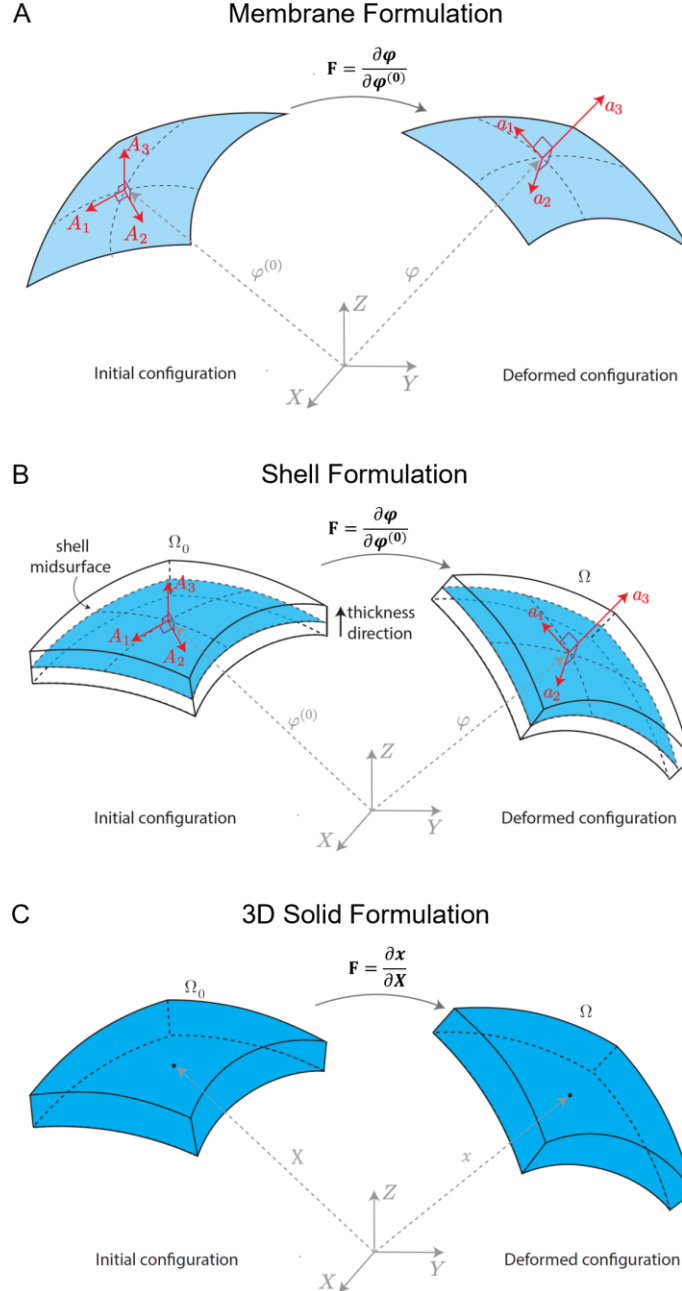


Figure 2.1. Schematic drawing illustrates the basis vectors in the initial and deformed configuration for the three formulations.

2.2.1.2 Rotation-free shell formulation

Next, we describe the rotation-free shell formulation, originally proposed by Onate and Flores [33] and recently adapted for biomechanics by Nama *et al* [26]. This shell formulation employs the Kirchhoff hypothesis of straight and normal cross-sections and describes the kinematics of the vessel wall via its midsurface and associated normal vector. Below, we provide a brief overview of this formulation and refer the reader to our earlier work [26] for a more detailed description.

Consider Figure 2.1(B) where a point $\varphi^{(0)}$ is mapped to point φ , with both belonging to the shell midsurface. Similar to the membrane formulation described above, and following Gruttmann and Taylor [39], we define an orthonormal basis corresponding to a point with associated coordinates s_α on the shell midsurface in the initial configuration as

$$A_\alpha = \frac{\partial \varphi^{(0)}}{\partial s_\alpha} \quad (2.15)$$

with the unit normal vector to the midsurface

$$A_3 = \frac{A_1 \times A_2}{||A_1 \times A_2||} \quad (2.16)$$

Again, as noted earlier in the discussion of membrane formulation, this orthonormal basis is introduced for mathematical convenience and ease of implementation and is not strictly necessary to describe the shell formulation. Similar to the initial configuration, the basis vectors (not necessarily orthonormal) at a position φ of a point on the shell midsurface in the current configuration can be defined as

$$a_\alpha = \frac{\partial \varphi}{\partial s_\alpha}, a_3 = \frac{a_1 \times a_2}{||a_1 \times a_2||} \quad (2.17)$$

These definitions allow us to express the positions, X and x , of a general point in the initial and the deformed configuration, respectively, as

$$X = \varphi^{(0)} + \xi_3 A_3 \quad (2.18)$$

$$x = \varphi + \xi_3 \lambda_3 a_3 \quad (2.19)$$

where $\xi_3(-\frac{H}{2} < \xi_3 < \frac{H}{2})$ denotes the perpendicular distance of the point to the midsurface with H being the shell thickness in the reference configuration and $\lambda_3 = h/H$ denotes the thickness stretch with h and H being the current and initial thickness. We note that the thickness stretch

represents an additional unknown quantity that is obtained by the use of incompressibility and plane stress conditions, as described in Section 2.2.2.1.

The basis vectors, $G_\alpha = \frac{\partial X}{\partial s_\alpha}$, at a general point in the shell continuum can be expressed in terms of midsurface basis vectors as

$$G_\alpha = A_\alpha + \xi_3 A_{3,\alpha} \quad (2.20)$$

$$G_3 = A_3 \quad (2.21)$$

where $(\cdot)_{,\alpha}$ denotes the partial derivative of a quantity with respect to s_α . The covariant metrics are obtained as

$$G_{\alpha\beta} = A_{\alpha\beta} + 2\xi_3 \kappa_{\alpha\beta}^{(0)} + \xi_3^2 A_{3,\alpha} \cdot A_{3,\beta} \quad (2.22)$$

$$G_{\alpha 3} = G_{3\alpha} = A_\alpha \cdot A_3 + \xi_3 A_{3,\alpha} \cdot A_3 = 0 \quad (2.23)$$

$$G_{33} = A_{33} = 1 \quad (2.24)$$

where $A_{\alpha\beta}$ are the components of the covariant metrics (first fundamental form) in the initial configuration given as

$$A_{\alpha\beta} = A_\alpha \cdot A_\beta \quad (2.25)$$

and $\kappa_{\alpha\beta}^{(0)}$ are the components of the curvature (second fundamental form) of the midsurface in the initial configuration given as

$$\kappa_{\alpha\beta}^{(0)} = \frac{1}{2} (A_\alpha \cdot A_{3,\beta} + A_\beta \cdot A_{3,\alpha}) \quad (2.26)$$

We linearize strain through the thickness and therefore neglect the quadratic term in equation (2.22) to obtain [40]:

$$G_{\alpha\beta} = A_{\alpha\beta} + 2\xi_3 \kappa_{\alpha\beta}^{(0)} \quad (2.27)$$

Similarly, using the basis vectors in the current configuration $g_\alpha = \frac{\partial x}{\partial s_\alpha}$, the metrics in the current configuration are

$$g_{\alpha\beta} = a_{\alpha\beta} + 2\xi_3 \kappa_{\alpha\beta} \quad (2.28)$$

with

$$a_{\alpha\beta} = a_\alpha \cdot a_\beta, \quad \kappa_{\alpha\beta} = \frac{1}{2}(a_\alpha \cdot a_{3,\beta} + a_\beta \cdot a_{3,\alpha}) \quad (2.29)$$

Given our choice of orthonormal basis in the initial configuration, the metrics $A_{\alpha\beta}$ are equal to the components of the 2X2 identity tensor. Therefore, for surfaces with non-zero curvature in initial configuration, the presence of the term $2\xi_3\kappa_{\alpha\beta}^{(0)}$ in Equation (2.27) implies that the metrics $G_{\alpha\beta}$ are not equal to the components of the identity tensor, indicating a non-zero deformation even in the initial configuration. To mitigate this issue, we follow the approach by Flores and Onate [41] to replace the curvature $\kappa_{\alpha\beta}$ by relative curvature $\chi_{\alpha\beta} = \kappa_{\alpha\beta} - \kappa_{\alpha\beta}^{(0)}$ in equations (2.27) and (2.28). Accordingly, we approximate the covariant metrics in the current configuration as

$$g_{\alpha\beta} = a_{\alpha\beta} + 2\xi_3\chi_{\alpha\beta} \quad (2.30)$$

We remark that this approximation, while not strictly necessary, facilitates the use of standard constitutive material models (e.g., equation (2.30)) by enforcing that the metrics in initial configuration are components of unit tensor.

Using the basis vectors defined in equations (2.20) and (2.21) and their counterparts in the deformed configuration, g_i , the deformation gradient is

$$F = \frac{\partial x}{\partial X} = \frac{\partial x}{\partial s_\alpha} \otimes \frac{\partial s_\alpha}{\partial X} = g_i \otimes G^i \quad (2.31)$$

and the right Cauchy-Green tensor is

$$C = F^T F = g_{ji} G^i \otimes G^j \quad (2.32)$$

Here, the transverse components $g_{\alpha 3} = g_{3\alpha} = 0$ since $g_\alpha \cdot g_3 = 0$. Furthermore, equation (2.32) indicates that the covariant components of the right Cauchy-Green tensor and the metrics in the deformed configuration are identical. However, since $g_{33} = a_3 \cdot a_3 = 1$ this equation does not reflect the change in shell thickness. Consequently, to account for the radial (thickness) deformation, equation (2.32) needs to be replaced by [40]

$$C = C_{ji} G^i \otimes G^j \quad (2.33)$$

with

$$C_{ij} = \begin{bmatrix} g_{11} & g_{12} & 0 \\ g_{21} & g_{22} & 0 \\ 0 & 0 & C_{33} \end{bmatrix} \quad (2.34)$$

where C_{33} is obtained via plane stress and incompressibility conditions. This allows the Jacobian determinant to be expressed as

$$J = \sqrt{\det(C)} = J_0 \sqrt{C_{33}} \quad (2.35)$$

where $J_0 = \sqrt{\frac{|a_{\alpha\beta}|}{|A_{\alpha\beta}|}}$ denotes the in-plane Jacobian determinant. Equation (2.35), in combination with the incompressibility condition

$$J = 1 \quad (2.36)$$

yields

$$C_{33} = J_0^{-2} \quad (2.37)$$

This coupling of out-of-plane components with the in-plane metrics ensures satisfaction of the incompressibility constraint.

2.2.1.3 Continuum formulation

Next, we describe a 3D nonlinear continuum formulation. Referring to Figure 2.1(C), let $\Omega_0 \subset R^3$, be an open, bounded and connected domain which represents the reference (or undeformed) configuration of the vessel wall. The deformation of the body Ω_0 is defined through the mapping $\phi: \Omega_0 \rightarrow R^3$ that links a material point from the reference configuration $X \in \Omega_0$ to a point in the deformed configuration $x \in \Omega$ according to $x = \phi(X)$ and $\Omega = \phi(\Omega_0)$. Associated with the mapping ϕ the deformation gradient tensor F and the right Cauchy-Green tensor C are defined as

$$F = \frac{\partial x}{\partial X}, \quad C = F^T F \quad (2.38)$$

We remark that, in contrast to the membrane and shell formulations that enforce the incompressibility constraint exactly at the continuum level, the chosen continuum displacement-based formulation enforces quasi-incompressibility (see Section 2.2.2.1 for further details).

We further note that, as opposed to the shell and membrane formulations, the 3D formulation requires no assumptions concerning through-the-thickness variation of kinematic

quantities other than those implicit in the choice of spatial interpolation. The strategy for the generation of the solid discretization as well as the different spatial interpolations considered for the 3D continuum formulation are discussed later in Section 2.2.3.

2.2.2 Constitutive models

Next, we describe the two different constitutive models considered. The expressions for the elastic strain energy provided below are standard representations of these constitutive models; however, these expressions are typically modified by introducing Lagrange multipliers or penalty terms (i.e. volumetric energy contributions) to enforce the incompressibility condition, as described in Section 2.2.2.1.

Mooney-Rivlin: The elastic strain energy for a Mooney-Rivlin model (commonly used to represent elastomers) is

$$\psi_{el} = c_1(I_C - 3) + c_2(II_C - 3) \quad (2.39)$$

where c_1, c_2 are the material parameters and I_C, II_C are the first and second principal invariants of the right Cauchy-Green tensor C given as

$$I_C = \text{tr}(C), \quad II_C = \frac{1}{2}[\text{tr}(C)^2 - \text{tr}(C^2)] \quad (2.40)$$

For the special case of $c_2 = 0$, this model reduces to the neo-Hookean model.

Four-fiber family model: The four-fiber family model characterizes the arterial wall as a composite structure comprising an elastin-dominated isotropic matrix, four families of embedded collagen fibers, and passive smooth muscle (circumferentially oriented along with one collagen family). The elastic strain energy is [42],[43],[44]

$$\psi_{el} = \frac{c}{2}(I_C - 3) + \sum_{k=1}^4 \frac{c_1^k}{4c_2^k} [e^{c_2^k[(\lambda^k)^2 - 1]} - 1] \quad (2.41)$$

where c_1, c_2^k, c_3^k are the material parameters, I_C is again the first invariant of the right Cauchy-Green tensor and $\lambda^k = \sqrt{M^k \cdot CM^k}$ is the stretch experienced by the k-th fiber family that is oriented along the direction $M^k = [0, \sin \alpha_0^k, \cos \alpha_0^k]$ in the reference configuration. The four-fiber families are considered to be aligned along $\alpha_0^1 = 0^\circ$ (axial family), $\alpha_0^2 = 90^\circ$ (circumferential family) and $\alpha_0^{3,4} = \pm \alpha_0$ (symmetric diagonal families), where α_0 is a free parameter. The four-fiber family model has recently been recommended as the first choice

constitutive model to simulate arterial deformations that lie outside the range of experimental tests [45] and has been extensively employed to describe the behavior of both human and murine arterial tissue [44],[45].

2.2.2.1 Enforcement of incompressibility and plane stress

In this section, we briefly discuss the strategies to enforce incompressibility constraint for each formulation considered in this work. Additionally, we discuss the plane stress condition employed in the membrane and shell formulations.

Membrane formulation: Here, we follow the strategy suggested by Lu *et al* [17] where the membrane deformation is viewed as components of a 3D motion. The corresponding 3D version of the in-plane right Cauchy-Green tensor, equation (2.7), is expressed as

$$\bar{C} = a_{\alpha\beta} A^\alpha \otimes A^\beta + \lambda_3^2 A_3 \otimes A_3 \quad (2.42)$$

where $\lambda_3 = h/H$ denotes the thickness stretch with h and H the current and initial thickness of the membrane, and A_3 denotes the unit normal vector to the membrane surface. Using equation (2.7) and (2.42), the 3D Jacobian determinant can be expressed as

$$J = \sqrt{\det(C)} = \bar{J} \lambda_3 \quad (2.43)$$

where $J_0 = \sqrt{\frac{|a_1 \times a_2|}{|A_1 \times A_2|}}$ denotes the in-plane Jacobian determinant. The incompressibility constraint is enforced by setting $J = 1$, which in combination with equation (2.43), yields

$$\lambda_3 = 1/\bar{J} \quad (2.44)$$

This allows us to express the 3D strain invariants in terms of the in-plane invariants (2.7), as

$$I_C = \bar{I}_C + \bar{II}_C^{-1}, \quad II_C = \bar{I}_C \bar{II}_C^{-1} + \bar{II}_C \quad (2.44)$$

Therefore, the 3D right Cauchy-Green tensor (equation (2.42)) and consequently, the elastic strain energy (equations (2.39) and (2.41)) can be completely described in terms of in-plane quantities. Furthermore, it can be shown that, under a plane stress condition, the in-plane components of the second Piola-Kirchhoff stress are given as $S^{\alpha\beta} = 2 \frac{\partial \psi_{el}(C)}{\partial a_{\alpha\beta}}$. We refer the reader to Lu *et al* [17] for further details on constitutive modeling in membrane formulation.

Rotation-free shell formulation: Here, we follow the strategy in [26],[46] where incompressibility is enforced by augmenting the elastic strain energy function $\psi_{el}(C)$ with a constraint term using a Lagrange multiplier p as

$$\psi = -p(J - 1) + \psi_{el}(C) \quad (2.47)$$

Here, we again follow the same arguments as above to express the thickness stretch $\lambda_3 = h/H$ in terms of in-plane quantities, as in equation (2.44). Furthermore, the additional unknown p introduced in equation (2.47) can be determined using a plane stress condition [40]. Following Kiendl *et al* [40], we first derive the 3D components of the second Piola-Kirchhoff stress tensor while considering p to be a function of C_{ij} as

$$S^{ij} = 2 \frac{\partial \psi}{\partial C_{ij}} = 2 \frac{\partial \psi_{el}}{\partial C_{ij}} - 2 \frac{\partial p}{\partial C_{ij}} (J - 1) - 2p \frac{\partial J}{\partial C_{ij}} \quad (2.48)$$

Using the plane stress condition $S^{33} = 0$, with equations (2.35), (2.36), (2.357), we obtain

$$p = 2 \frac{\partial \psi_{el}}{\partial C_{33}} C_{33} \quad (2.49)$$

A more detailed description of this strategy can be found in Kiendl *et al* [40] and our recent work [26].

3D continuum formulation: It proves convenient computationally to modify equation (2.39) as

$$\psi_{el} = c_1(I_C - 3) + c_2(II_C - 3) - 2(c_1 + 2c_2) \ln J \quad (2.50)$$

Similarly, for the four-fiber family model in equation (2.41), let

$$\psi_{el} = \frac{c}{2}(I_C - 3) + \sum_{k=1}^4 \frac{c_1^k}{4c_2^k} [e^{c_2^k[(\lambda^k)^2 - 1]^2} - 1] - c \ln J \quad (2.51)$$

where the last term in above equations (2.50) and (2.51) represents appropriate contributions to ensure the absence of deformation. With regards to incompressibility, there are various possibilities to enforce it. One approach is to enforce full incompressibility, as in equation (2.47), by introducing a Lagrange multiplier p that weakly enforces $J = 1$. However, for the 3D continuum formulation, this entails the use of a mixed formulation with finite element spaces for both displacements and the Lagrange multiplier p which comply with the *inf-sup* or LBB condition [47]. Therefore, in this work, it proves convenient computationally to employ a displacement-

based formulation where the incompressibility of the material is relaxed and enforced in a penalty-type manner by adding a volumetric term $U(J)$ [48]

$$\psi = \psi_{el} + U(J), \quad U(J) = \frac{\lambda}{2}(J - 1)^2 \quad (2.52)$$

with a sufficiently large value of λ yielding a good approximation of the incompressibility of the material, with $\lambda \approx 10^2 \times 2(c_1 + c_2)$ for the model in equation (2.50) and $\lambda = 10^2 \times c$ for the model in equation (2.51).

2.2.3 Discretization

To compare the performance of different formulations under the closest possible conditions, we chose a particular finite element discretization for the continuum formulation. Specifically, the solid mesh consists of wedge (or triangular prismatic) elements [34] generated by performing an extension of the midsurface triangular elements used for the membrane and shell formulations. This process comprises three steps: (1) Computation of the normal vector in the undeformed configuration, A_3 at each node within every element, (2) Generation of continuous distribution of A_3 across elements by local averaging, and (3) Extension of triangular elements along the continuous normal vectors A_3 , both inwards and outwards of the midsurface. This process is summarized in Figure 2.2.

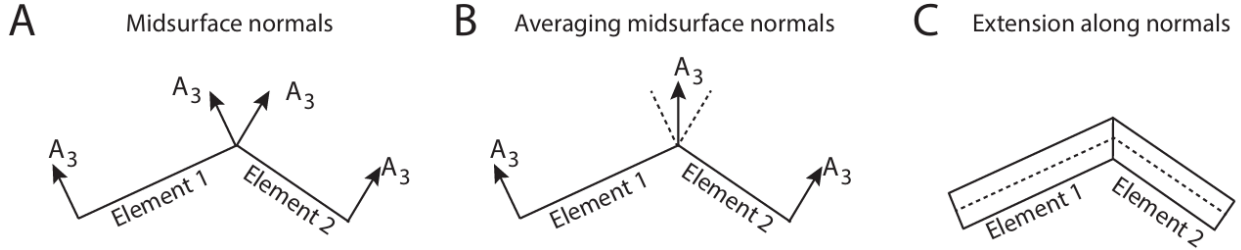


Figure 2.2. Generation of a solid mesh using extrusion of the midsurface mesh.

Figure 2.3 shows the results of this extrusion strategy, applied on a midsurface mesh of a cylinder to generate a solid cylindrical geometry. Here, the resulting solid geometry has been clipped to reveal the initial midsurface mesh.

We consider two different implementations for the 3D solid model. The first implementation, referred to as P1 wedge, utilizes linear interpolation both in-plane and through-the-thickness, while the second implementation utilizes quadratic interpolation both in-plane and through-the-thickness, and is referred to as P2 wedge. The difference in interpolation order results in a different number of degrees of freedom per element. Specifically, both the membrane and the

(rotation free) shell formulations employ linear triangular elements to represent the midsurface plane, resulting in 9 degrees of freedom per element. In contrast, the P1 wedge formulation employs a linear wedge element with six nodes, which results in 18 degrees of freedom per element. Lastly, the P2 wedge formulation employs a quadratic interpolation of displacement both in-plane and through-the-thickness, resulting in 54 degrees of freedom per element (see Figure 2.3).

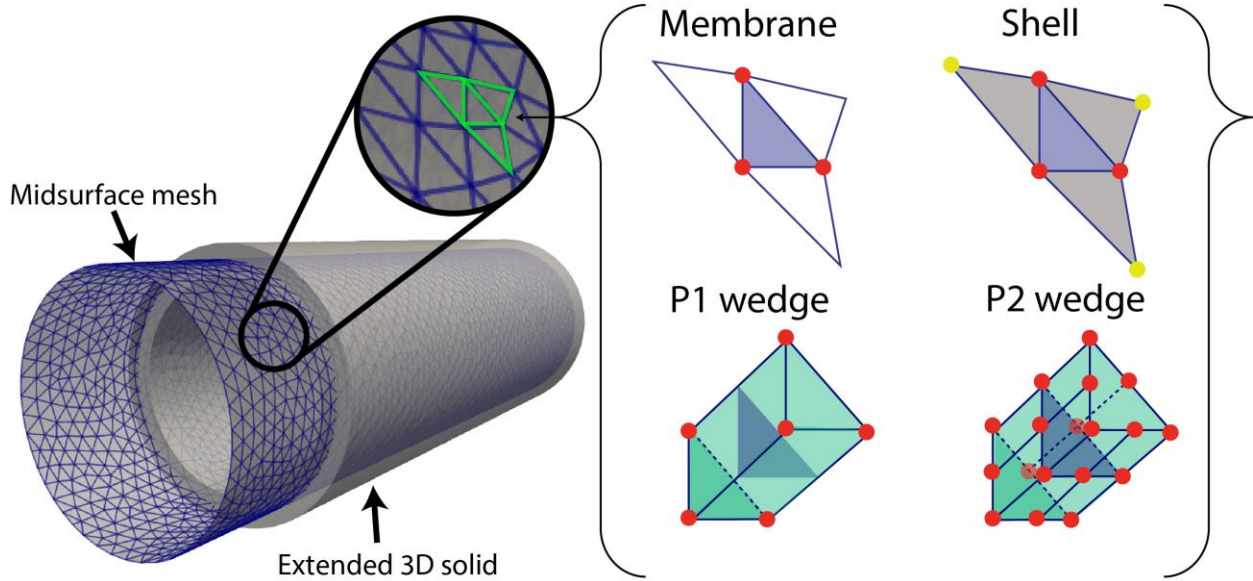


Figure 2.3. Extension of the midsurface mesh of a cylinder to generate a 3D solid cylindrical geometry. The resulting solid geometry has been clipped to reveal the initial midsurface mesh. The number of nodes per element for each formulation are denoted by solid red circles. The yellow circles represent the nodes in the neighboring patch of the nonlinear shell.

2.3 Results

The performance of the different formulations is demonstrated in three different geometries (see Figure 2.4): (A) a cylindrical geometry, (B) an idealized arterial bifurcation model comprising of a main artery and an orthogonal side branch, and (C) a mouse-specific aortic model featuring three branches from the arch. These examples have been carefully chosen to introduce increasing degrees of complexity, both in terms of geometry and material properties. In addition, a rigorous analysis of convergence rates, relying on analytical solutions for axisymmetric and plate geometries, is presented in Section 2.3.1. The effect of axial pre-stretch is also studied on the cylindrical geometry in Section 2.3.2.1.

Figure 2.4 summarizes the degree of complexity considered for each example. Specifically, in terms of geometrical complexity, the first example represents the simplest idealized cylindrical

model. The second example introduces a bifurcation in the geometry while still employing idealized cylindrical representations of individual vessels. The third example considers a subject-specific arterial model featuring multiple branches. Similarly, in terms of material properties, the first example represents the simplest case with uniform material properties and wall thickness. The second example employs uniform material properties with regionally varying wall thickness. The third example considers subject-specific, regionally-varying values for both material properties and wall thickness. In addition, the second and third examples consider external tissue support conditions. The second case employs uniform external tissue support value, while the third example used regionally varying values. The different formulations implemented using different programming languages across different platforms, and simulations were performed using different computers, hence a direct comparison of the wall clock time would be meaningless.

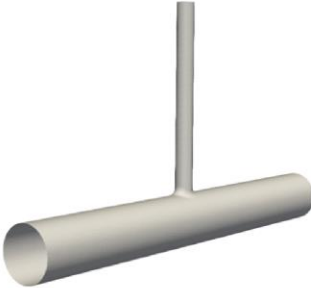
	Cylinder	Bifurcation	Mouse-specific
Geometry			
Material model	Four-fibers	Four-fibers	Four-fibers
Regionally varying Thickness	No	Yes	Yes
Regionally varying Properties	No	No	Yes
External Tissue Support	No	Yes (homogenous)	Yes (heterogenous)

Figure 2.4. Schematic illustration of the three geometries and respective modeling choices compared in this work: (A) a cylindrical geometry, (B) an idealized bifurcation model comprising a main artery and an orthogonal side branch, and (C) a mouse-specific aortic model featuring multiple branches.

Therefore, the total number of degrees of freedom serves as a surrogate for their relative computational costs. Noting this, Table 2.1 lists the resulting number of degrees of freedom for

each geometry for different formulations. The degrees of freedom for each geometry and model were determined from mesh-independence studies.

Table 2.1. Degrees of freedom for each geometry for different formulations.

Geometry	Membrane	Shell	P1 wedge	P2 wedge
Cylinder	8,601	8,601	17,202	102,420
Bifurcation	-	48,945	97,890	568,134
Mouse-specific	-	63,843	127,686	764,865

2.3.1 Convergence rate

A convergence analysis was performed to assess the impact of mesh refinement on the results obtained from the different formulations. Two alternative canonical problems are selected to demonstrate the expected orders of convergence of each formulation before establishing comparisons for a common problem of interest: 1) a thin plate with $10\text{mm} \times 10\text{mm} \times 0.43\text{mm}$ dimensions for the 3D formulations (P1 and P2 wedge), and 2) a cylindrical tube with midsurface radius $R = 8.6\text{mm}$, axial length $L = 60\text{mm}$, and thickness-to-radius ratio $H/R = 0.25$ for the 2D formulations (membrane and rotation-free shell). Meshes for both geometries are refined only in the in-plane direction. This choice ensures a fair comparison among the different models. The error is calculated as the L2 norm of the discrepancy between the simulation results and the analytical solutions. The analytical solution of the thin plate problem is described in Appendix A. The axisymmetric solution described in Section 2.3.2 is used for the analytical solution of the cylindrical tube.

Figure 5 shows results of the convergence analysis on displacement and stress. 3D formulations exhibit second- and third-order convergence rates in displacement for the P1 and P2 wedge, respectively. For the stress, first- and second-order convergence rates were obtained for the P1 and P2 wedge, respectively. These are expected convergence rates for linear and quadratic interpolations. Both membrane and rotation-free shell formulations showed near second-order convergence rates for the displacement. These convergence rates are consistent with previous studies using a rotation-free shell formulation [49]. As for the stress field, both membrane and shell formulations demonstrated near-second order convergence rates (1.88 and 1.87, respectively).

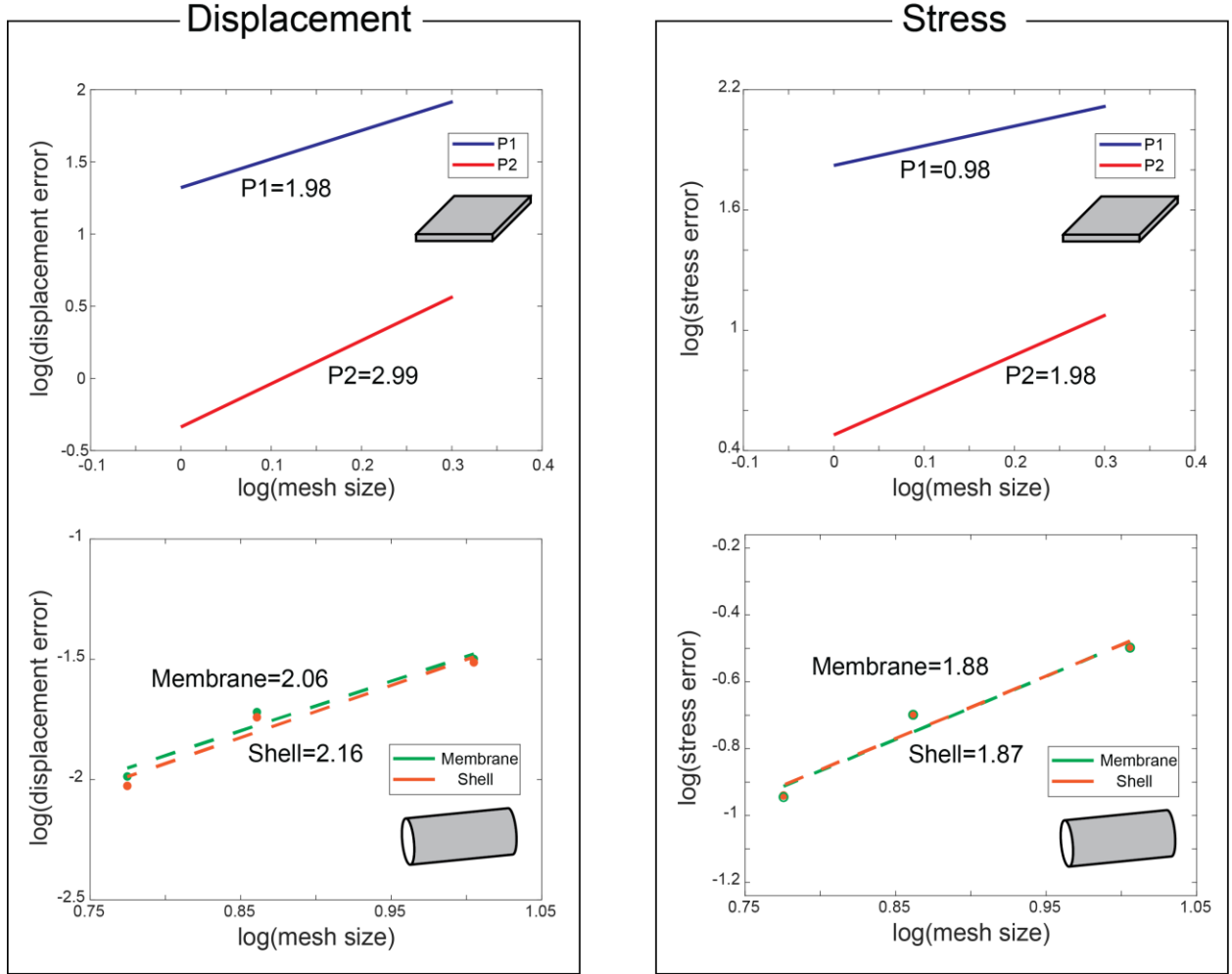


Figure 2.5. Convergence analysis results for displacement and stress. Plots are log scale and contain slopes of each formulation's trend lines.

2.3.2 Cylindrical geometry

First, we compare the performance of different formulations against the well-known axisymmetric solution for a cylindrical tube. Details of this solution can be found elsewhere [5],[50]. This solution provides, in the most general case, the static mechanical response of a thick axisymmetric tube under combined distension, extension. We consider it a cylindrical tube with midsurface radius $R = 8.6mm$ and axial length $L = 60mm$. To assess the performance of different formulations for increasing wall thickness-to-radius ratio, we consider different biomechanics-focused values of $H/R = 0.05, 0.10, 0.15, 0.20$ and 0.25 , while keeping the midsurface radius fixed. The wall is characterized by a four-fiber family model with the material parameters listed in Appendix Table B.1. For the purpose of this example, the tube is subjected to an internal pressure of $80 mmHg$, ($10.66 kPa$) while the ends of the tube are held fixed at an

axial stretch of 1.0 (the effect of axial stretch greater than 1.0 is studied in section 3.2.1.) while allowing changes in the radial direction. The comparison is performed in the mid-plane slice along the axial direction. The axisymmetric solution is taken to be the true solution and is compared against the solutions obtained from four different implementations: membrane, shell, P1 wedge, and P2 wedge.

Figure 2.6 (A-E) shows the cross section of the cylindrical tube for the five different thickness-to-radius ratios considered. Figure 2.6 (F-T) presents plots of the following three different metrics versus pressure: midsurface radius (Figure 2.6 (F-J)), first invariant of Green-Lagrange strain tensor (Figure 2.6 (K-O)), and circumferential Cauchy stress (Figure 2.6 (P-T)). For $H/R = 0.05$, all four models yield good agreement with the axisymmetric solution. 2D formulations perform slightly better than the 3D formulations with maximum differences of 1.38%, 1.08%, 2.59%, and 2.2% for the membrane, shell, P1 wedge, and P2 wedge implementations, respectively. As the wall thickness increased, differences between the membrane, shell, and P1 wedge and the axisymmetric solution became more pronounced. The P1 wedge was more sensitive to changes in the thickness-to-radius ratio than the membrane and shell. The P2 wedge yielded good agreement with the axisymmetric solution for all thicknesses. For $H/R = 0.25$, the P1 wedge solution yielded 10.67% smaller displacement, 20.8% lower first invariant of Green-Lagrange strain tensor, and 19.2% lower circumferential stress, compared to the axisymmetric solution. Membrane and shell solutions exhibited smaller deviations from the axisymmetric solution, with maximum differences for displacement of 6.4% and 4.6%, respectively. The P2 wedge solution yielded the best agreement with the axisymmetric solution, with a maximum displacement difference of 1%.

Note that all the numerical formulations employed an unstructured, non-axisymmetric mesh that might have introduced differences from the axisymmetric solution. Nonetheless, these results indicate that the 2D formulations (membrane and shell) perform better than the linear continuum formulation (P1 wedge) for the same surface mesh as the wall thickness increased. This is an interesting finding, given that the P1 wedge solution was obtained with twice the number of degrees of freedom compared to the 2D formulations. In contrast, the P2 wedge formulation, using the highest number of degrees of freedom, yielded the best agreement with the axisymmetric solution, except for the thinnest geometry ($H/R = 0.05$).

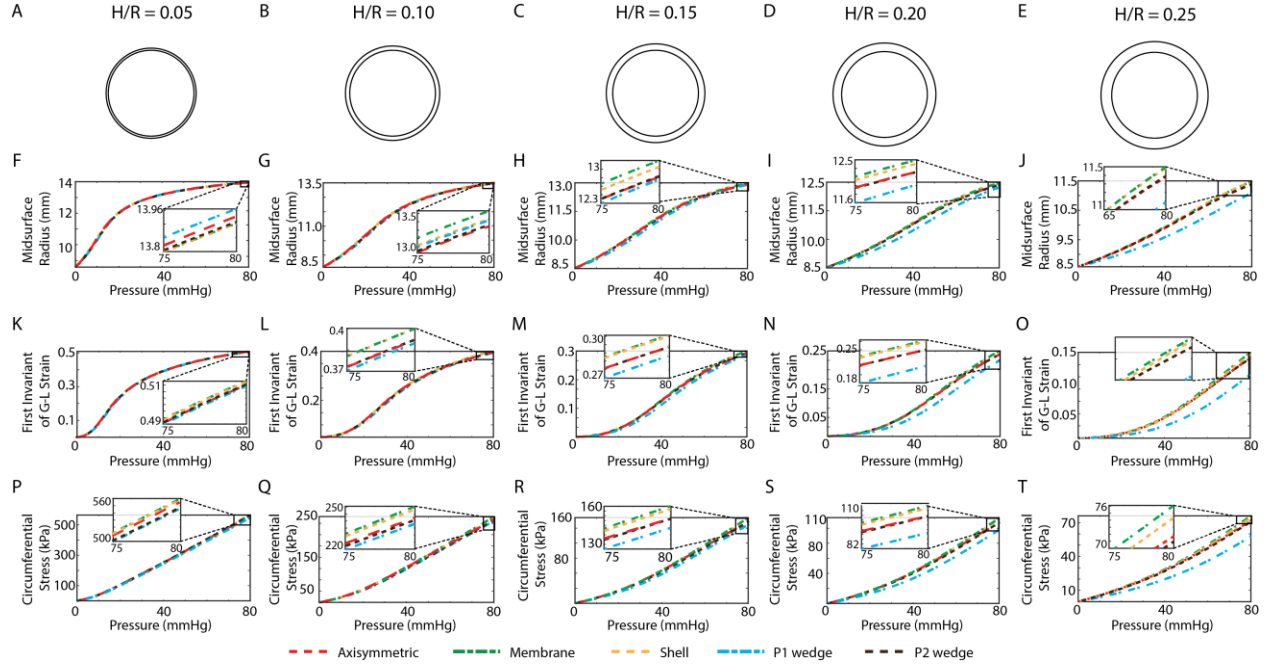


Figure 2.6. (A-E) Cross-sections of the cylindrical tube for three different thickness-to-radius ratios. (F-J), (K-O), and (P-T) compare the evolution of midsurface radius, first invariant of Green-Lagrange strain tensor, and circumferential Cauchy stress, respectively, with pressure for all formulations against the axisymmetric solution.

2.3.2.1 Axial pre-stretch

All in-vivo vessels are axially pre-stretched with the presence of intramural elastin [51]. Axial pre-stretch of human arteries is nearly 1.4 and is important both for the mechanobiological state and providing structural stability [52]. In this study, an extension-stretch loading scenario is used to analyze the effect of pre-stretch on the different formulations. We use cylindrical geometry from Section 2.3.2 with thickness-to-radius ratio of 0.05. The axisymmetric solutions with axial stretches of 1.0 and 1.4 are taken to be the true solution. Figure 2.7 (A) shows the loading condition we used: pressurization to 10 *mmHg* (1.33 *kPa*), followed by an extension to an axial stretch of 1.4 at constant pressure, and a subsequent pressurization to 80 *mmHg* (10.66 *kPa*). During entire loading condition, both ends of the cylinder are allowed to move in the radial direction (radial rollers). Same four-fiber family model and material parameters in Section 2.3.2. are used.

Figure 2.7 (B) shows the deformed configuration, obtained using the P2 wedge formulation at 80 *mmHg* (10.66 *kPa*) pressure and a 1.4 axial stretch. Figure 2.7 (C-F) presents plots of the four different metrics (C: midsurface radius, D: first invariant of Green-Lagrange strain tensor, E: axial Cauchy stress, and F: circumferential Cauchy stress) versus pressure at the mid-plane slice (yellow dotted ring in Figure 2.7 (B)). All four models yield good agreement with the axisymmetric solution. For the midsurface radius and the first invariant of Green-Lagrange strain tensor, the

largest error for all four formulations is less than 1%. For the axial and circumferential Cauchy stress, 2D formulations yield 2% higher stress than the axisymmetric and 3D formulations. As we found that all four formulations can cope with axially pre-stretch, we used fixed ends boundary condition for next two examples.

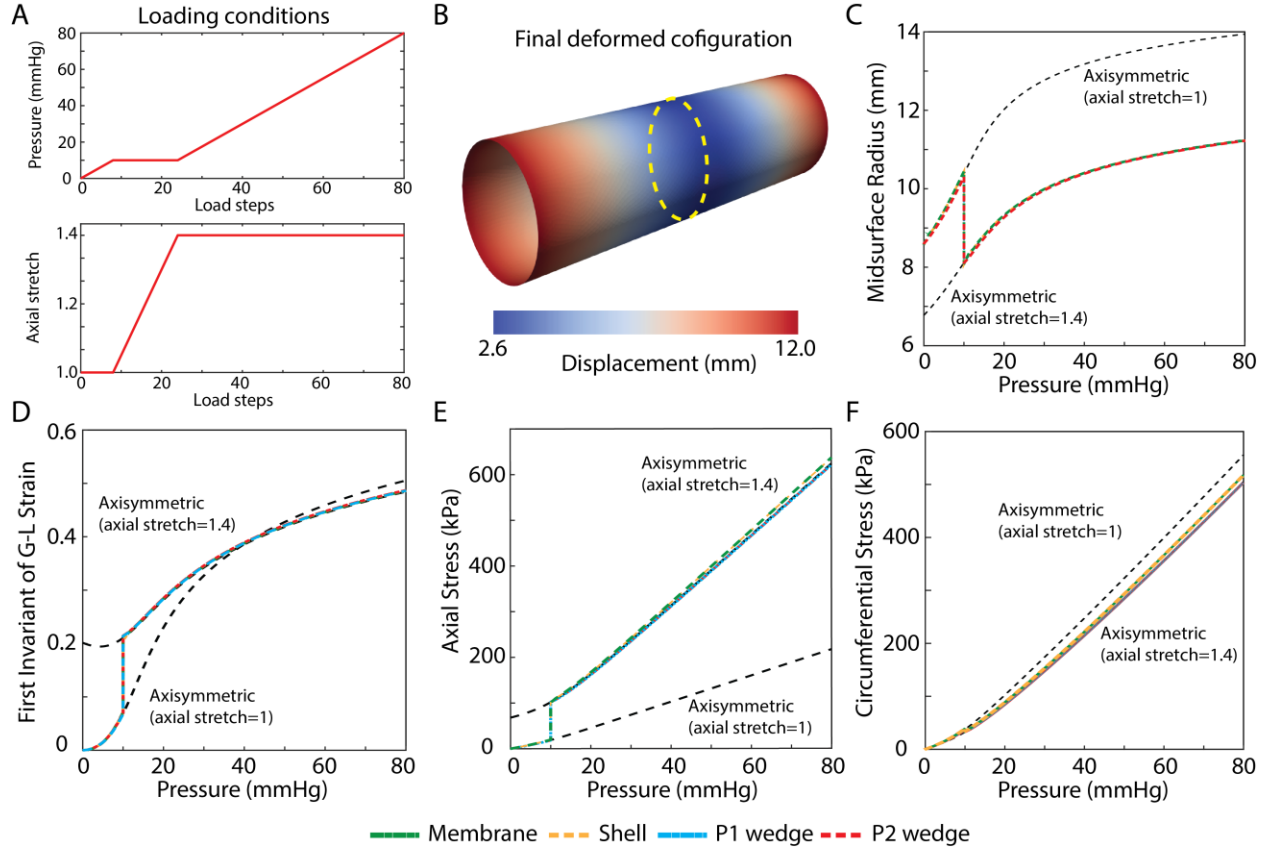


Figure 2.7. Axial pre-stretch for a cylindrical tube. (A) Shows the loading conditions. (B) Final P2 deformed configuration at 80 mmHg. Yellow ring shows the mid-plane slice along the axial direction where panel C-F calculated. (C-F) compare the evolution of midsurface radius, first invariant of Green-Lagrange strain tensor, axial and circumferential Cauchy stress, respectively, with pressure for all formulations against the axisymmetric solution.

2.3.3 Idealized bifurcation geometry

Next, we considered an idealized bifurcation model comprising a main artery and a side branch. The main vessel is a cylinder with radius 0.6 mm , while the side branch is a cylinder with radius 0.2 mm . To avoid a sharp intersection, the two branches are blended via a fillet with radius 0.2 mm . We refer to the region surrounding the intersection of the two branches as the 'blend region'. Wall thickness was taken to be 10% of the local radius, resulting in a wall thickness of 0.06 mm and 0.02 mm for the main vessel and the branch, respectively, with a smooth variation of thickness in the blend region. Therefore, this example introduces two additional geometrical complexities compared to cylindrical geometry: (a) a bifurcation region due to the presence of a

side branch and (b) regionally varying thickness due to different thickness of the main artery and the side branch. We used a four-fiber material model for the vessel wall with the same material parameters used in Section 2.3.2. In this example, we used homogeneous material parameters for the entire vessel surface. We pressurized this geometry to 80 mmHg (10.66 kPa) with fixed ends boundary conditions. As illustrated in our prior work [26], it is crucial to include the effect of surrounding tissue via external tissue support boundary conditions to avoid non-physiological deformations and buckling of the arterial wall. Therefore, we modeled the effect of external tissue via an imposed traction on the outer wall, $\sigma a_3 = -k_s u$, where k_s is the coefficient associated with simplified elastic response of the external tissue. For the current example, we used $k_s = 10^5 \text{ g}/(\text{mm}^2 \text{s}^2)$. The mesh size is taken to be 0.06 mm for the main vessel, 0.04 mm for the side branch, and 0.01 mm for the blend region. Small mesh size is chosen for the blend region to help convergence. The membrane formulation failed to converge for this example, likely due to its inability to handle bending mode deformations in the blend region. Consequently, the comparison for this case is performed only among shell, P1 wedge, and P2 wedge formulations.

Figure 2.8 (A) shows the displacement in the final deformed configuration, obtained using the P2 wedge formulation, with maximum displacement observed near the bifurcation. Figure 8 (I) compares the final deformed configuration in plane I, obtained using shell, P1 wedge, and P2 wedge formulations. Figure 2.8 (I) also includes the corresponding unloaded configuration to indicate the extent of deformation. The shell formulation shows good agreement with the P2 wedge formulation. This result shows that the shell formulation matches wedge formulations well on the blend region from the bifurcation. Figure 2.8 (II) and (III) compare the solution from different formulations at location II and III in Figure 2.8 (A), respectively. We plot the evolution of three different metrics with pressure: midsurface radius, first invariant of Green-Lagrange strain tensor, and circumferential Cauchy stress. These plots show that the solutions from the shell formulation match well with P2 wedge at both locations II and III. The maximum errors between the shell and P2 wedge formulations in location II are 0.4, 5.8, and 2.3% for midsurface radius, first invariant of Green-Lagrange strain tensor, and circumferential Cauchy stress, respectively. The maximum error between the shell and P2 wedge formulations in location III are 0.4, 2.4, and 3.4% for midsurface radius, first invariant of Green-Lagrange strain tensor, and circumferential Cauchy stress, respectively.

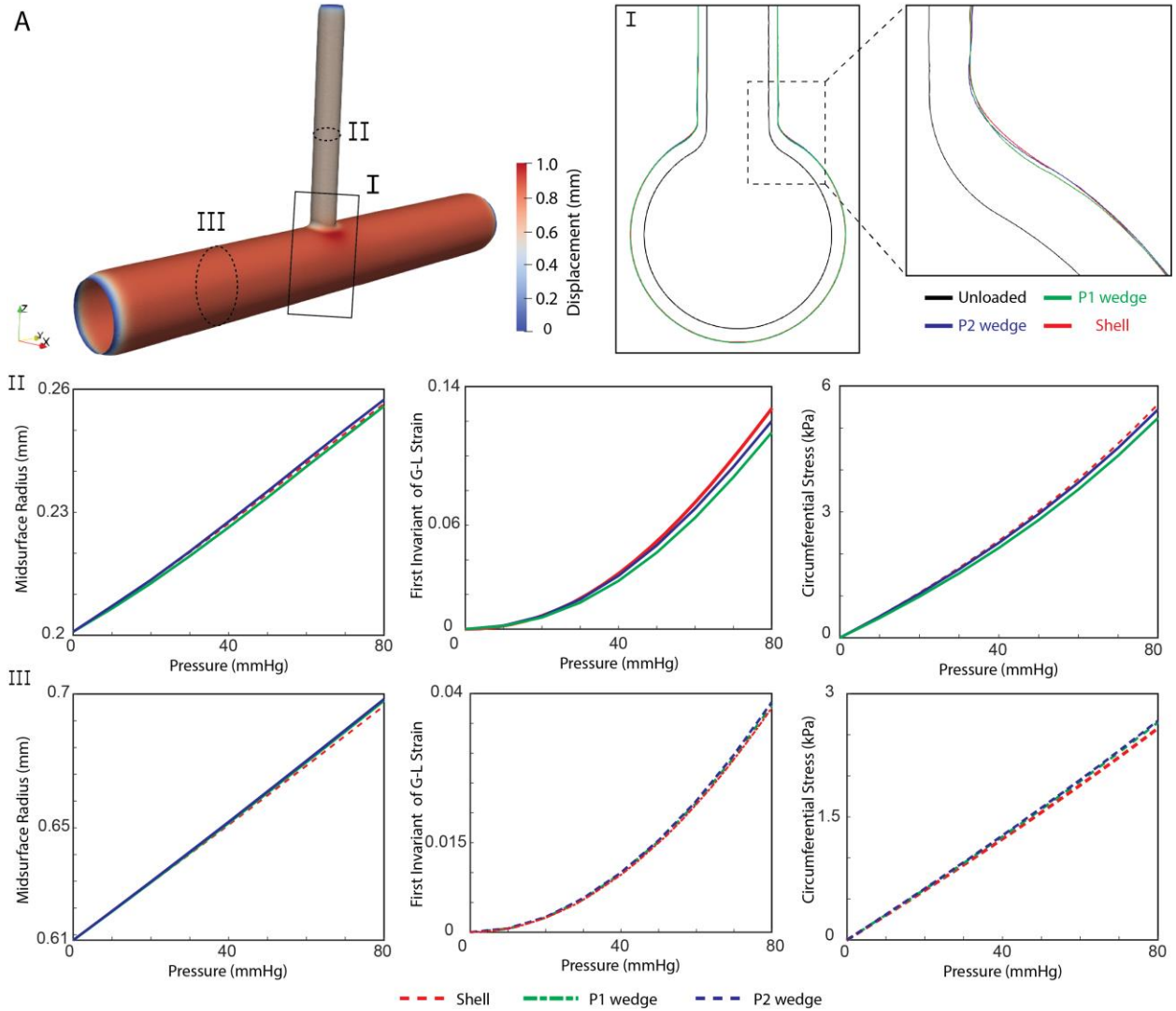


Figure 2.8. Comparison of shell, P1 wedge, and P2 wedge formulations for an idealized bifurcation geometry. (I) shows the unloaded and final configuration from the shell, P1 wedge, and P2 wedge formulations. (II) and (III) compare the evolution of midsurface radius, first invariant of Green-Lagrange strain tensor, circumferential Cauchy stress with pressure for two different locations.

This analysis revealed two significant findings: (1) The membrane formulation is unsuitable for general biomechanical analysis due to its inability to handle the bending mode deformation observed in geometries with branches, (2) the shell formulation yields a good agreement with P2 wedge formulation, despite using only 8.4% of the degrees of freedom (see Table 2.1).

2.3.4 Mouse-specific geometry

Next, we compare the different formulations in a mouse-specific anatomy featuring three upper branches. The anatomy was obtained via non-invasive *in vivo* micro-CT and has been

employed in our previous work [53]. We model the aortic wall via a four-fiber family material model with regionally varying material parameters and wall thickness distribution using experimental data (See Appendix Table B.2). The external tissue support boundary condition with $k_s = 1.2 \times 10^5 \text{ g}/(\text{mm}^2 \text{ s}^2)$ and $k_s = 3.0 \times 10^5 \text{ g}/(\text{mm}^2 \text{ s}^2)$ are used for the main aorta and side vessels to prevent non-physiological deformations and buckling of the arterial wall. These values are initially chosen based on our previous work [53] and are calibrated to avoid wrinkling patterns in the P2 wedge formulation (see Appedix D). Referring to Figure 2.4, this example introduces several additional complexities compared to previous examples by considering regional variations of material properties and wall thickness as well as the external tissue support. We subject this aortic geometry to pressurization of 80 mmHg (10.66 kPa) with fixed ends boundary conditions.

Figure 2.9 A shows the volume rendered geometric model and associated skeleton, obtained from the micro-CT data for a 20-week-old wild-type mouse. Figure 2.9 B shows displacements in the final deformed configuration obtained using the shell formulation. Panels I, II, and III in Figure 2.9 C compare the final deformed midsurface configuration obtained using different formulations at locations I, II, and III in Figure 2.9 B, respectively. The corresponding unloaded configuration of the midsurface has also been included to indicate the extent of deformation during the pressurization. The deformed configuration predicted by both the shell and P1 wedge formulation agreed well with the P2 wedge formulation at all three locations. Panel III of Figure 2.9 C shows that the deformation at the blend and side vessel is lower than the main aorta because of using large external tissue support value. This result also demonstrates that the shell formulation matches the 3D wedge formulations well in the blend region of the subject-specific geometry.

Next, we compared shell, P1, and P2 formulations in terms of various kinematic metrics at the locations I and II indicated in Figure 2.9 B. We plot the evolution of three different metrics: midsurface displacement, first invariant of Green-Lagrange strain tensor, and circumferential Cauchy stress with pressure, at locations I (mid row) and II (bottom row). The maximum error between the shell and P2 wedge formulations in location I (main aorta) are 0.3, 3.1, and 3.7% for midsurface radius, first invariant of Green-Lagrange strain tensor, and circumferential Cauchy stress, respectively. The maximum error between the shell and P2 wedge formulations in location II (smallest side vessel) are 0.5, 9.8, and 7.4% for midsurface radius, first invariant of Green-

Lagrange strain tensor, and circumferential Cauchy stress, respectively. These results show that the errors are larger at the smaller vessel than the main aorta. Nonetheless, despite this discrepancy, the results from all formulations agree reasonably well with each other.

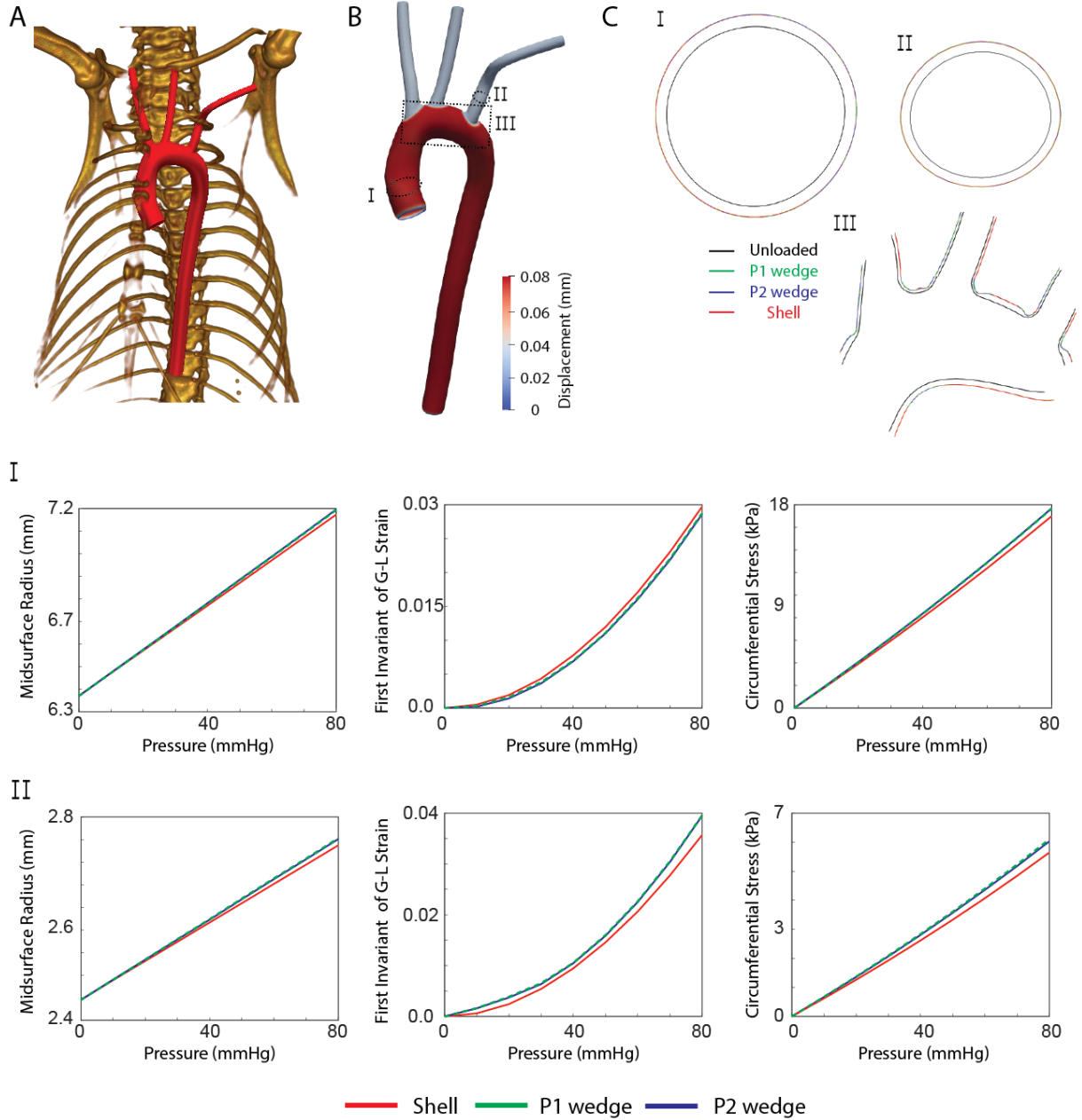


Figure 2.9. Comparison of shell, P1 wedge, and P2 wedge formulations for a mouse-specific geometry. (A) Volume rendered geometric model of the aortic anatomy of a 20-week old wild-type female mouse. (B) plot of the final deformed configuration obtained via shell formulation (c) enlarged versions comparing the deformed configurations predicted by three formulations at locations I, II, and III. Middle (I) and the bottom (II) row plot the comparison of the evolution of midsurface radius, first invariant of Green-Lagrange strain tensor, circumferential Cauchy stress with pressure.

Overall, given that the shell formulation uses only 16.7% and 8.4% of degrees of freedom compared to the P1 wedge and P2 wedge formulation, respectively, (see Table 2.1) our results suggest that the shell formulation represents a computationally superior alternative, considering a balance between cost and accuracy, to the 3D wedge formulations. We also found that the shell formulation is less sensitive to bulking and wrinkling than the 3D wedge formulations. Finally, as noted in the Introduction, the shell formulation offers another advantage over 3D models by avoiding the need for creating an extended mesh from the medical imaging data.

2.4 Discussion and conclusions

We compared three different nonlinear formulations for vascular biosolid mechanics; moreover, for the 3D solid formulation, we considered two different implementations employing wedge elements with linear and quadratic interpolation, referred to as P1 wedge and P2 wedge formulations, respectively. We compared results in three geometries having increasing degrees of complexity: (a) a cylindrical model, (b) an idealized bifurcation model comprising a main artery and a side branch, and (c) a mouse-specific arterial model featuring three branches. To ensure fair comparisons, the solid mesh was generated via an extension of the triangular mesh elements used for 2D formulations to obtain wedge (or triangular prismatic) elements.

An important consideration for the 3D formulations is their ability to satisfy the incompressibility condition, through a penalty parameter k in the volumetric term $U(J)$, see equation (2.52). To study the impact of this parameter, a sensitivity analysis was conducted for both P1 and P2 wedge formulations. Details of this sensitivity analysis are given in Appendix C.

For cylindrical geometry, we compared the solution from the four implementations against the well-known axisymmetric solution, for five different thickness-to-radius ratios. For the thin wall case ($H/R = 0.05$), all formulations agreed well with the axisymmetric solution; 2D formulations performed slightly better than the 3D formulations with maximum differences of 1.38%, 1.08%, 2.59%, and 2.2% for the membrane, shell, P1 wedge, and P2 wedge implementations, respectively. However, as wall thickness increased relative to the radius ($H/R = 0.25$), the P1 wedge solution deviated significantly from the axisymmetric solution. The membrane and shell formulations outperformed the P1 wedge solution and yielded results within 6.4% and 4.6%, respectively, of the axisymmetric solution. The P2 wedge formulation provided the best agreement with the axisymmetric solution, with differences of less than 1%. Two important considerations for the thinnest tissue scenario ($H/R = 0.05$): 1) P2 is not necessarily

the best formulation because it fails to ensure incompressibility exactly unless a mixed Lagrange multiplier approach is pursued [48] and may introduce instability across the thickness [54],[55] and 2) the shell outperforms the membrane, which is known to be unstable in the presence of wrinkling [56], and P1, which is inaccurate and shows potential risk of locking (see Appendix C) despite using twice the number of degrees of freedom.

Next, we compared results from different formulations in an idealized bifurcation model comprising of a main artery and a side branch, with regionally varying wall thickness. The membrane formulation failed to converge for this example, likely due to its inability to handle bending mode deformations in geometries with branches. This observation indicates that a nonlinear membrane formulation is inappropriate for general vascular biomechanical analyses of complex geometries that routinely feature vessel bifurcations. Among the remaining formulations (shell, P1 wedge, and P2 wedge), the shell solution captured the P2 wedge solution with good accuracy (maximum error of 6%) as well as the P1 wedge solution (maximum error of 4.5%). Again, these results point to the effectiveness of shell formulations for vascular biomechanics, given that it requires only 17% and 8.4% of the degrees of freedom for P1 wedge and P2 wedge formulations, respectively.

Lastly, we compared results from the shell, P1 wedge, and P2 wedge formulations for a mouse-specific arterial model featuring three branches, while incorporating regional variations of material properties and wall thickness as well as external tissue support. Results from the different formulations agreed reasonably well, with the shell solutions yielding maximum differences of 7.4% relative to the P2 wedge solution. Given that the shell formulation employs 8.4% degrees of freedom than the P2 wedge formulations (see Table 2.1), these results again highlight the efficacy of shell formulations, considering a balance between cost and accuracy.

One limitation of this study is the absence of residual stress in the formulations. Residual stress exists in in-vivo vessels in the absence of externally applied loads, such as pressure and surrounding external tissue, and non-uniformly distributed through thickness [57]. Residual stress is important to get natural stress-free configuration [58]. However, it is difficult to support 2D formulations which do not have physical thickness. Also, we need the vessel opening angle, extension, or radially cut dimension from experiment to implement in 3D formulations [58]. For this reason, we do not include residual stress in our formulations.

In this study, external tissue support techniques are implemented to avoid non-physiological deformations, wrinkling, and buckling of the arterial wall, especially for the 3D wedge formulations. The external tissue support acts on the outer surface of the vessel wall in 3D formulations, while it acts on the wall midsurface in the shell formulation. From a practical perspective, this implies that the choice of external tissue support parameters must be formulation-specific, to match the dynamic deformation data, if available.

Overall, our results indicate that shell formulations represent an effective compromise between the computational cost and accuracy for vascular biomechanics. Furthermore, given the lack of rotational degrees of freedom, the shell formulation is ideally-suited to serve as the structural model in fluid-structure interaction frameworks and fluid-solid-growth models for vascular biomechanics. We are currently utilizing the shell formulation to develop a strongly coupled, monolithic, computationally efficient, nonlinear fluid-structure interaction framework in the open-source software CRIMSON [59] via an adaption of the Coupled Momentum Method [16] to large displacements and nonlinear material models. Given the computational efficiency and accuracy of the shell formulation, this framework promises to provide a computationally efficient, yet accurate, alternative to the current fluid-structure interaction formulations that employ a 3D representation of the vessel wall [60],[61].

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2.5 Appendix

2.5.1 A. Analytical solution of the thin plate problem

In this section, we demonstrate the p-order of accuracy of the wedge finite element formulations as a function of the finite element approximation space. Towards that goal, an ad-hoc test problem is constructed [62]. such that a smooth solution is guaranteed. The following displacement field u^{exact} is considered

$$u^{exact} = [AX_1^3 \quad BX_2^3 \quad CX_3^3 + X_1^3]^T \quad (2.53)$$

with A=1.2, B=1.3, C=1.5. The corresponding deformation gradient tensor is

$$F^{exact} = \frac{\partial x^{exact}}{\partial X} = \frac{\partial(u^{exact} + X)}{\partial X} = \begin{bmatrix} 1 + 3AX_1^2 & 0 & 0 \\ 0 & 1 + 3BX_2^2 & 0 \\ 3X_1^2 & 0 & 1 + 3CX_3^2 \end{bmatrix} \quad (2.54)$$

We consider the following Neo-Hookean strain energy density,

$$W = \frac{\mu}{2}(F:F) - \mu \log \det F \quad (2.55)$$

with $\mu = 1$. The corresponding first Piola-Kirchhoff stress tensor is

$$p^{exact} = \frac{\partial W}{\partial F} \Big|_{F^{exact}} = \mu F^{exact} - \frac{\mu}{\det F^{exact}} H^{exact} \quad (2.56)$$

Where $H = (\det F)F^{-T}$. The volumetric force in mechanical equilibrium with the exact first Piola-Kirchhoff stress tensor P_{exact} is

$$f_0 = -DIV \, p^{exact} \quad (2.57)$$

An explicit expression for f_0 can be obtained using the chain rule as follows

$$f_0 = -DIV \, p^{exact} = - \left(\frac{\partial p^{exact}}{\partial F} \Big|_{F^{exact}} \right)_{iljj} \frac{\partial (F^{exact})_{j,j}}{\partial X_i} \quad (2.58)$$

The non-zero term of the third order tensor $\partial F / \partial X$ are

$$\frac{\partial F_{11}}{\partial X_1} = 6AX_1; \quad \frac{\partial F_{22}}{\partial X_2} = 6BX_2; \quad \frac{\partial F_{33}}{\partial X_3} = 6CX_3; \quad \frac{\partial F_{21}}{\partial X_1} = 6X_1; \quad (2.59)$$

and the stiffness tensor $\partial p^{exact} / \partial F$ is obtained as follows

$$\begin{aligned}
& \left(\frac{\partial P^{exact}}{\partial F} \right)_{F^{exact}} \Big|_{iljj} \\
& = \mu I_{iljj} + \frac{\mu}{\det F^{exact2}} (H^{exact})_{il} (H^{exact})_{jj} \\
& \quad - \varepsilon_{ijpq} \varepsilon_{jppq} I_{ilpp} \left(\frac{\mu}{\det F^{exact}} F^{exact} \right)_{qq}
\end{aligned} \tag{2.60}$$

where $I_{iljj} = \delta_{ij}\delta_{il}$ and ε represents the third order alternating tensor or Levi-Civita tensor. In addition, Dirichlet boundary conditions compatible with the displacement field must be provided,

$$u = u^{exact}; \text{ on } \partial_D \Omega_0 \tag{2.61}$$

as well as a traction t_0 on the Neumann portion of the boundary $\partial_N \Omega_0$.

2.5.2 B. Material parameters for the four-fiber family constitutive model

Table 2.2. Material parameters for validation with axisymmetric theory. These parameters correspond to the material parameters for a human descending aorta reported in reference [43].

c (kPa)	c_1^1 (kPa)	c_2^1	c_1^2 (kPa)	c_2^2	$c_1^{3,4}$ (kPa)	$c_2^{3,4}$	α_0 (deg)
37.20	4.68e-6	2.97e-7	2.9e-5	1.68e-5	28.16	3.48	43.88

Table 2.3. Material parameters of the four-fiber constitutive model for wild type mouse for different aortic wall segments denoted by ATA- Ascending Thoracic Aorta, DTA-Descending Thoracic Aorta, SAA-Suprarenal Abdominal Aorta, IAA-Infrarenal Abdominal Aorta, and CCA-Common Carotid Arteries [43].

Wall	c (kPa)	c_1^1 (kPa)	c_2^1	c_1^2 (kPa)	c_2^2	$c_1^{3,4}$ (kPa)	$c_2^{3,4}$	α_0 (deg)
ATA	20.99	18.50	0.026	18.91	0.062	4.90	0.410	40.7
DTA	12.74	25.10	0.170	14.36	0.062	0.43	1.935	23.3
CCA	5.05	20.59	0.054	7.66	0.044	0.02	1.522	34.1

2.5.3 C. Sensitivity analysis for incompressibility terms in the 3D formulations

In the P1 and P2 wedge 3D formulations, a penalty parameter k is introduced in the volumetric term to enforce the incompressibility condition. We calibrated this parameter using the cylindrical geometry problem described in Section 2.3.2 of the main manuscript. Different values of penalty parameters were tested: 10, 100, 1,000, and 10,000. Figure 2.10 shows the pressure-radius results for the P1 and P2 wedge. For the P2 wedge, results show consistent solutions across the different k values. However, the P1 wedge shows large discrepancies between low and high k values. These

discrepancies, apparent for larger penalty terms, indicate the presence of volumetric locking. Based on these results, we used the value of $k = 100$ for the penalty parameter.

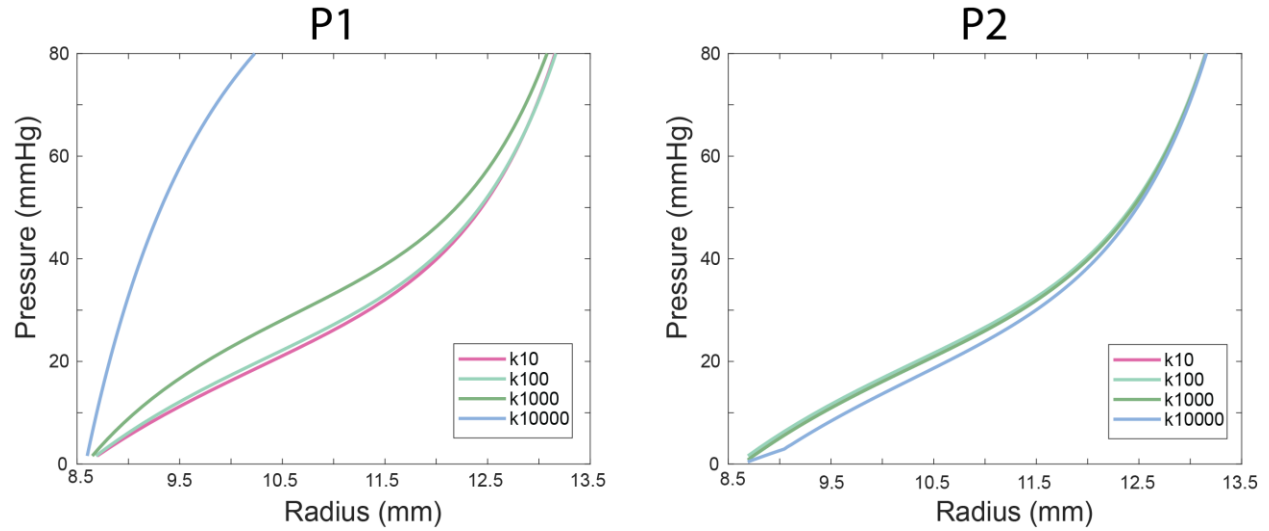


Figure 2.10. Sensitivity analysis for incompressibility term in the 3D formulations.

2.5.4 D. Wrinkling pattern in the P2 wedge formulation

In the mouse-specific geometry, the P2 wedge formulation made wrinkling patterns at the side vessels and at the end of the main aorta under high pressure when small external tissue support values were used ($k_s = 0.6 \times 10^5 \text{ g}/(\text{mm}^2\text{s}^2)$ and $k_s = 1.5 \times 10^5 \text{ g}/(\text{mm}^2\text{s}^2)$) for the main aorta and side vessels, respectively). Figure 2.11 shows the P2 wedge results at four different pressure values: 50 mmHg (6.66 kPa), 60 mmHg (8.00 kPa), 70 mmHg (9.33 kPa), and 80 mmHg (10.66 kPa). Wrinkling patterns begin to appear around 60 mmHg and become increasingly severe and widespread at 80 mmHg. These patterns are only observed in the P2 wedge formulation and do not occur in the rotation-free shell or P1 wedge formulations. Increasing the external tissue support value helps to prevent the formation of wrinkling. The final external tissue support values are $k_s = 1.2 \times 10^5 \text{ g}/(\text{mm}^2\text{s}^2)$ and $k_s = 3.0 \times 10^5 \text{ g}/(\text{mm}^2\text{s}^2)$ for the main aorta and side vessels, respectively.

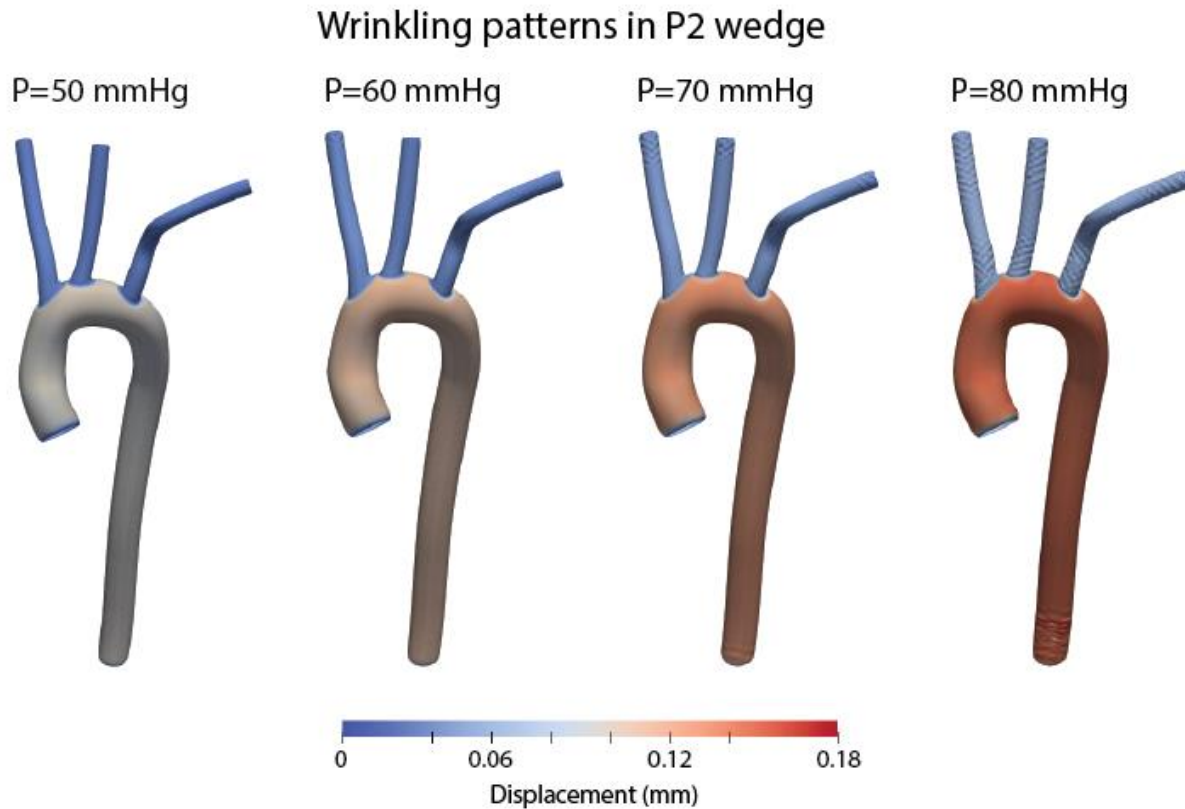


Figure 2.11. Wrinkling patterns in P2 wedge with not enough external tissue support value.

2.6 Bibliography

- [1] C. Lally, F. Dolan, P. Prendergast, Cardiovascular stent design and vessel stresses: a finite element analysis, *Journal of biomechanics* 38 (8) (2005) 1574–1581.
- [2] C. A. Figueroa, S. Baek, C. A. Taylor, J. D. Humphrey, A computational framework for fluid–solid–growth modeling in cardiovascular simulations, *Computer methods in applied mechanics and engineering* 198 (45-46) (2009) 3583–3602.
- [3] J. D. Laubrie, J. S. Mousavi, S. Avril, A new finite-element shell model for arterial growth and remodeling after stent implantation, *International Journal for Numerical Methods in Biomedical Engineering* 36 (1) (2020) e3282.
- [4] M. L. Raghavan, D. A. Vorp, M. P. Federle, M. S. Makaroun, M. W. Webster, Wall stress distribution on three-dimensionally reconstructed models of human abdominal aortic aneurysm, *Journal of vascular surgery* 31 (4) (2000) 760–769.
- [5] J. D. Humphrey, *Cardiovascular solid mechanics: cells, tissues, and organs*, Springer Science & Business Media, 2013.

- [6] S. A. Maas, B. J. Ellis, G. A. Ateshian, J. A. Weiss, Febio: finite elements for biomechanics, *Journal of biomechanical engineering* 134 (1) (2012).
- [7] T. Kim, P. A. J. van Bakel, N. Nama, N. Burris, H. J. Patel, D. M. Williams, C. A. Figueroa, A computational study of dynamic obstruction in type b aortic dissection, *Journal of Biomechanical Engineering* 145 (3) (2023) 031008.
- [8] P. Wriggers, R. Eberlein, S. Reese, A comparison of three-dimensional continuum and shell elements for finite plasticity, *International Journal of Solids and Structures* 33 (20-22) (1996) 3309–3326.
- [9] B. J. Doyle, A. Callanan, T. M. McGloughlin, A comparison of modelling techniques for computing wall stress in abdominal aortic aneurysms, *Biomedical engineering online* 6 (1) (2007) 1–12.
- [10] H. Weisbecker, D. M. Pierce, G. A. Holzapfel, A generalized prestressing algorithm for finite element simulations of preloaded geometries with application to the aorta, *International journal for numerical methods in biomedical engineering* 30 (9) (2014) 857–872.
- [11] M. Liu, L. Liang, W. Sun, A new inverse method for estimation of in vivo mechanical properties of the aortic wall, *Journal of the mechanical behavior of biomedical materials* 72 (2017) 148–158.
- [12] F. Riveros, S. Chandra, E. A. Finol, T. C. Gasser, J. F. Rodriguez, A pull-back algorithm to determine the unloaded vascular geometry in anisotropic hyperelastic passive mechanics, *Annals of biomedical engineering* 41 (4) (2013) 694–708.
- [13] J.-F. Gerbeau, M. Vidrascu, P. Frey, Fluid–structure interaction in blood flows on geometries based on medical imaging, *Computers & Structures* 83 (2-3) (2005) 155–165.
- [14] C. M. Colciago, S. Deparis, A. Quarteroni, Comparisons between reduced order models and full 3d models for fluid–structure interaction problems in haemodynamics, *Journal of Computational and Applied Mathematics* 265 (2014) 120–138.
- [15] Y. Bazilevs, M.-C. Hsu, Y. Zhang, W. Wang, X. Liang, T. Kvamsdal, R. Brekken, J. Isaksen, A fully-coupled fluid-structure interaction simulation of cerebral aneurysms, *Computational Mechanics* 46 (1) (2010) 3–16.
- [16] C. A. Figueroa, I. E. Vignon-Clementel, K. E. Jansen, T. J. Hughes, C. A. Taylor, A coupled momentum method for modeling blood flow in three-dimensional deformable arteries, *Computer methods in applied mechanics and engineering* 195 (41-43) (2006) 5685–5706.

- [17] J. Lu, X. Zhou, M. L. Raghavan, Inverse method of stress analysis for cerebral aneurysms, *Biomechanics and modeling in mechanobiology* 7 (6) (2008) 477–486.
- [18] S. Kyriacou, J. Humphrey, C. Schwab, Finite element analysis of nonlinear orthotropic hyperelastic membranes, *Computational Mechanics* 18 (4) (1996) 269–278.
- [19] A. J. Gil, Structural analysis of prestressed saint venant–kirchhoff hyperelastic membranes subjected to moderate strains, *Computers & structures* 84 (15-16) (2006) 1012–1028.
- [20] A. J. Gil, J. Bonet, Finite element analysis of prestressed structural membranes, *Finite Elements in Analysis and Design* 42 (8-9) (2006) 683–697.
- [21] A. J. Gil, J. Bonet, Finite element analysis of partly wrinkled reinforced prestressed membranes, *Computational Mechanics* 40 (2007) 595–615.
- [22] H. Kim, J. Lu, M. S. Sacks, K. B. Chandran, Dynamic simulation of bioprosthetic heart valves using a stress resultant shell model, *Annals of biomedical engineering* 36 (2) (2008) 262–275.
- [23] A. B. Tepole, H. Kabaria, K.-U. Bletzinger, E. Kuhl, Isogeometric kirchhoff–love shell formulations for biological membranes, *Computer methods in applied mechanics and engineering* 293 (2015) 328–347.
- [24] X. Zhou, M. L. Raghavan, R. E. Harbaugh, J. Lu, Patient-specific wall stress analysis in cerebral aneurysms using inverse shell model, *Annals of biomedical engineering* 38 (2) (2010) 478–489.
- [25] C. Martin, W. Sun, J. Elefteriades, Patient-specific finite element analysis of ascending aorta aneurysms, *American Journal of Physiology-Heart and Circulatory Physiology* 308 (10) (2015) H1306–H1316.
- [26] N. Nama, M. Aguirre, J. D. Humphrey, C. A. Figueroa, A nonlinear rotation-free shell formulation with prestressing for vascular biomechanics, *Scientific Reports* 10 (1) (2020) 17528.
- [27] M. Bischoff, K.-U. Bletzinger, W. Wall, E. Ramm, Models and finite elements for thin-walled structures, *Encyclopedia of computational mechanics* (2004).
- [28] J. J. Remmers, G. N. Wells, R. d. Borst, A solid-like shell element allowing for arbitrary delaminations, *International Journal for Numerical Methods in Engineering* 58 (13) (2003) 2013–2040.

- [29] S. Hosseini, J. J. Remmers, C. V. Verhoosel, R. De Borst, An isogeometric solid-like shell element for nonlinear analysis, *International Journal for Numerical Methods in Engineering* 95 (3) (2013) 238–256.
- [30] S. Hosseini, J. J. Remmers, C. V. Verhoosel, R. De Borst, An isogeometric continuum shell element for non-linear analysis, *Computer Methods in Applied Mechanics and Engineering* 271 (2014) 1–22.
- [31] T. J. Hughes, E. Carnoy, Nonlinear finite element shell formulation accounting for large membrane strains, *Computer Methods in Applied Mechanics and Engineering* 39 (1) (1983) 69–82.
- [32] K.-K. Chen, Comparison of shell and solid models for corner fill in tube hydroforming, in: *AIP Conference Proceedings*, Vol. 712, American Institute of Physics, 2004, pp. 1083–1088.
- [33] E. Oñate, F. G. Flores, Advances in the formulation of the rotationfree basic shell triangle, *Computer methods in applied mechanics and engineering* 194 (21-24) (2005) 2406–2443.
- [34] O. C. Zienkiewicz, R. L. Taylor, J. Z. Zhu, *The finite element method: its basis and fundamentals*, Elsevier, 2005.
- [35] S. Yamakawa, K. Shimada, Converting a tetrahedral mesh to a prism– tetrahedral hybrid mesh for fem accuracy and efficiency, *International journal for numerical methods in engineering* 80 (1) (2009) 74–102.
- [36] S. Afazov, A. Becker, T. Hyde, Mathematical modeling and implementation of residual stress mapping from microscale to macroscale finite element models, *Journal of manufacturing science and engineering* 134 (2) (2012).
- [37] K. Meftah, L. Sedira, A. Ayadi, A six-node prismatic solid finite element for geometric nonlinear problems in elasticity, *Mathematics and Computers in Simulation* 182 (2021) 143–164.
- [38] J. Lu, X. Zhou, M. L. Raghavan, Inverse elastostatic stress analysis in pre-deformed biological structures: demonstration using abdominal aortic aneurysms, *Journal of biomechanics* 40 (3) (2007) 693–696.
- [39] F. Gruttmann, R. Taylor, Theory and finite element formulation of rubberlike membrane shells using principal stretches, *International Journal for Numerical Methods in Engineering* 35 (5) (1992) 1111–1126.

- [40] J. Kiendl, M.-C. Hsu, M. C. Wu, A. Reali, Isogeometric kirchhoff–love shell formulations for general hyperelastic materials, *Computer Methods in Applied Mechanics and Engineering* 291 (2015) 280–303.
- [41] F. G. Flores, E. Onate, Improvements in the membrane behaviour of the three node rotation-free BST shell triangle using an assumed strain approach, *Computer Methods in Applied Mechanics and Engineering* 194 (6-8) (2005) 907–932.
- [42] J. Eberth, L. Cardamone, J. Humphrey, Evolving biaxial mechanical properties of mouse carotid arteries in hypertension, *Journal of biomechanics* 44 (14) (2011) 2532–2537.
- [43] S. Roccabianca, C. Figueroa, G. Tellides, J. Humphrey, Quantification of regional differences in aortic stiffness in the aging human, *Journal of the mechanical behavior of biomedical materials* 29 (2014) 618–634.
- [44] J. Ferruzzi, M. J. Collins, A. T. Yeh, J. D. Humphrey, Mechanical assessment of elastin integrity in fibrillin-1-deficient carotid arteries: implications for marfan syndrome, *Cardiovascular research* 92 (2) (2011) 287–295.
- [45] F. Schroeder, S. Polzer, M. Slařansk’y, V. Man, P. Sk’acel, Predictive capabilities of various constitutive models for arterial tissue, *Journal of the mechanical behavior of biomedical materials* 78 (2018) 369–380.
- [46] J. Kiendl, K.-U. Bletzinger, J. Linhard, R. W’uchner, Isogeometric shell analysis with kirchhoff–love elements, *Computer Methods in Applied Mechanics and Engineering* 198 (49-52) (2009) 3902–3914.
- [47] D. Boffi, F. Brezzi, M. Fortin, et al., *Mixed finite element methods and applications*, Vol. 44, Springer, 2013.
- [48] G. A. Bonet, J., R. Wood, *Nonlinear Solid Mechanics for Finite Element Analysis: Statics*, Cambridge university press, 2016.
- [49] M. Behzadinasab, M. Alaydin, N. Trask, Y. Bazilevs, A general-purpose, inelastic, rotation-free kirchhoff–love shell formulation for peridynamics, *Computer Methods in Applied Mechanics and Engineering* 389 (2022) 114422.
- [50] G. A. Holzapfel, T. C. Gasser, R. W. Ogden, A new constitutive framework for arterial wall mechanics and a comparative study of material models, *Journal of elasticity and the physical science of solids* 61 (1-3) (2000) 1–48.

- [51] P. Dobrin, T. Canfield, S. Sinha, Development of longitudinal retraction of carotid arteries in neonatal dogs, *Experientia* 31 (11) (1975) 1295–1296.
- [52] L. Cardamone, A. Valentin, J. Eberth, J. Humphrey, Origin of axial prestretch and residual stress in arteries, *Biomechanics and modeling in mechanobiology* 8 (2009) 431–446.
- [53] F. Cuomo, J. Ferruzzi, P. Agarwal, C. Li, Z. W. Zhuang, J. D. Humphrey, C. A. Figueroa, Sex-dependent differences in central artery haemodynamics in normal and fibulin-5 deficient mice: implications for ageing, *Proceedings of the Royal Society A* 475 (2221) (2019) 20180076.
- [54] R. Poya, R. Sevilla, A. J. Gil, A unified approach for a posteriori highorder curved mesh generation using solid mechanics, *Computational Mechanics* 58 (2016) 457–490.
- [55] R. Poya, R. Ortigosa, A. J. Gil, Variational schemes and mixed finite elements for large strain isotropic elasticity in principal stretches: Closedform tangent eigensystems, convexity conditions, and stabilised elasticity, *International Journal for Numerical Methods in Engineering* 124 (16) (2023) 3436–3493.
- [56] K. Lu, M. Accorsi, J. Leonard, Finite element analysis of membrane wrinkling, *International Journal for numerical methods in engineering* 50 (5) (2001) 1017–1038.
- [57] Y. C. Fung, What are the residual stresses doing in our blood vessels?, *Annals of biomedical engineering* 19 (1991) 237–249.
- [58] J. D. Humphrey, S. L. Delange, An introduction to biomechanics, *Solids and Fluids, Analysis and Design*. Springer, Heidelberg (2004).
- [59] C. J. Arthurs, R. Khlebnikov, A. Melville, M. Marčan, A. Gomez, D. Dillon-Murphy, F. Cuomo, M. Silva Vieira, J. Schollenberger, S. R. Lynch, C. Tossas-Betancourt, K. Iyer, S. Hopper, E. Livingston, P. Youssefi, A. Noorani, S. Ben Ahmed, F. J. H. Nauta, T. M. J. van Bakel, Y. Ahmed, P. A. J. van Bakel, J. Mynard, P. Di Achille, H. Gharahi, K. D. Lau, V. Filonova, M. Aguirre, N. Nama, N. Xiao, S. Baek, K. Garikipati, O. Sahni, D. Nordsletten, C. A. Figueroa, Crimson: An open-source software framework for cardiovascular integrated modelling and simulation, *PLOS Computational Biology* 17 (5) (2021) 1–21.
- [60] M. Bathe, R. Kamm, A fluid-structure interaction finite element analysis of pulsatile blood flow through a compliant stenotic artery, *Journal of biomechanical engineering* 121 (4) (1999) 361–369.
- [61] J. Hron, M. M’adl’ik, Fluid-structure interaction with applications in biomechanics, *Nonlinear analysis: real world applications* 8 (5) (2007) 1431–1458.

[62] R. Ortigosa, A. J. Gil, C. H. Lee, A computational framework for large strain nearly and truly incompressible electromechanics based on convex multi-variable strain energies, *Computer Methods in Applied Mechanics and Engineering* 310 (2016) 297–334.

Chapter 3 Three-Dimensional Characterization of Aortic Root Motion by Vascular Deformation Mapping

This chapter is adapted from a peer-reviewed publication of this work:

<https://doi.org/10.3390/jcm12134471>².

3.1 Introduction

Current guidelines for management of aortic diseases such as thoracic aortic aneurysm (TAA) and aortic dissection largely focus on maximal diameter as a primary metric of disease severity and risk [1,2]. Aortic diameter is an inherently static metric, typically performed in diastole [3]. However, the aorta is in constant motion due to the combination of cyclic loading and unloading, and its mechanical coupling to the contractile left ventricle (LV) myocardium. Electrocardiogram (ECG) gated computed tomography angiography (CTA) affords the opportunity to visualize motion of the thoracic aorta through-out the cardiac cycle, and is capable of depicting such dynamic aortic root motion in a three-dimensional (3D) manner [4]. Abnormalities in aortic root motion have been proposed to be a potential risk factor for disease progression and complications in thoracic aortic disease [5-8].

Previous studies have characterized aortic root motion from dynamic imaging and have incorporated this data into methods to estimate wall stresses in the ascending thoracic aorta (ATAA). However, some studies have used idealized aortic models rather than patient-specific anatomy [5]. Furthermore, most techniques used to extract and quantify aortic root motion are based on 2D imaging and thus lack a comprehensive description of the multi-directional components of aortic root motion [5-9]. An accurate, 3D assessment of cyclic motion of the ATAA could have significant implications for estimating mechanical properties of the aorta, informing computational simulations, endovascular device design, and importantly refining diameter-based assessment of disease severity.

² The authors of this manuscript are: Taeouk Kim, Nic S. Tjahjadi, Xuehuan He, JA van Herwaarden, Himanshu J. Patel, Nicholas S. Burris, and C. Alberto Figueroa.

Vascular Deformation Mapping (VDM) is a validated medical image registration technique which allows for comprehensive assessment of the degree and extent of growth mapping of the aorta (VDM-G: VDM growth) [10-12] using longitudinal CTA data acquired at two different points during clinical surveillance. However, when applied to dynamic CTA data (i.e., time-resolved CTA), VDM allows for 3D assessment of the aortic deformation throughout the cardiac cycle (VDM-D: VDM dynamic).

The objective of this study is to utilize VDM-D to accurately quantify aortic root motion in a 3D manner, using patient-specific data in a cohort of patients with various manifestations of TAA disease (i.e., sporadic and Marfan syndrome(MFS)) as well as non-aneurysmal controls. The structure of this paper is as follows: First, we will provide a brief introduction to the technical aspects of the VDM-D and introduce the aortic root motion metrics studied in this paper, namely: total displacement, area ratio and distensibility, axial tilt, and aortic rotation. The results section will present these metrics for the different patient groups, including their relationship with age and left-ventricular/aortic root (LV/Ao) angle. The paper will conclude with a discussion of the results for the different aortic root metrics, in particular their dependency with age, as well as the limitations of the study.

3.2 Materials and methods

3.2.1 Study population

All procedures were approved by the local institutional review board with a waiver of informed consent obtained for this retrospective study and were Health Insurance Portability and Accountability Act-compliant. Electronic medical records search software was used to identify patients aged 18 years and older with a clinical diagnosis thoracic aortic aneurysm (TAA), either sporadic or associated with MFS, with available high-quality, retrospectively electrocardiography-gated CTA data. For comparison, we also identified a cohort of patients with available retrospective CTA data that had non-aneurysmal thoracic aortic dimensions (i.e., maximal diameter <40 mm) as well as a group of patients who had undergone prior open surgical repair of their aortic root and/or ascending aorta. Exclusion criteria were non-ECG-gated acquisition, suboptimal thoracic aortic enhancement (< 250 Hounsfield unit), image slice thickness > 2.5mm, or significant motion/respiratory artifacts preventing accurate delineation of the aortic wall and thus accurate registration in VDM analysis. At random, 51 patients meeting these criteria, divided

over 4 groups: non-aneurysmal, sporadic TAA (referred to as “TAA” henceforth), MFS (referred to as “Marfan” henceforth) and ascending graft repair (referred to as “repair” henceforth), were included in this study. Patient demographics and clinical characteristics were collected through medical chart review. Maximum diameter measurements of the thoracic aorta were collected from clinical radiology reports. Peak systolic and end-diastolic phases of the ECG-gated CTA imaging were selected and extracted using OsirixMD [13]. The angle between the aortic annulus and the mitral annulus (LV/Ao angle) was also measured using OsirixMD for each patient. Figure 3.1 depicts the definition of LV/Ao angle adopted in this study, namely the angle (ϕ) between two lines perpendicular to the aortic and mitral annuli, respectively.

ECG-gated CTA examinations were performed on either 64- or 246-detector CTA scanners using helical (Lightspeed VCT or Discovery CT750HD; GE Healthcare) or axial (Revolution; GE Healthcare) acquisition modes. Dynamic CT imaging was acquired through the entire thoracic aorta, from lung apices to at least 2-cm below the celiac trunk.

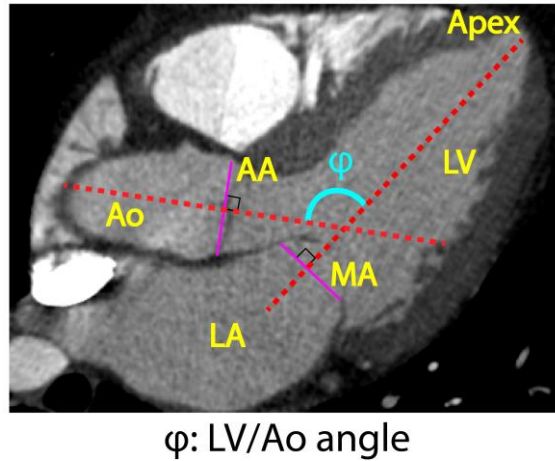


Figure 3.1. Definition of LV/Ao angle (ϕ) adopted in this study. LV: left ventricle, MA: mitral annulus, LA: left atrium, AA: aortic annulus, Ao: aorta. Purple lines indicate MA and AA. The LV/Ao angle (ϕ) is the angle between the lines perpendicular to the aortic and mitral annuli, respectively.

3.2.2 VDM

VDM employs b-spline deformable image registration techniques to quantify the 3D deformation of the aortic wall surface between two CTA images of a given subject. This approach has been previously applied to assess 3D aortic growth based on CTA images acquired at two time points spanning several years and has been validated in expert-rater and *in silico* phantom studies [10-12]. We refer to this growth-assessment technique as VDM-G.

In this study, the VDM concept is expanded to study 3D aortic deformation between the diastolic and systolic phases extracted from the dynamic CTA images. Therefore, instead of assessing 3D growth over a long period of time, the method quantifies 3D deformation over the cardiac cycle. We refer to this technique as VDM-D. Figure 3.2 illustrates the VDM-D workflow. First, the selected systolic and diastolic phase images are segmented using an in-house aortic segmentation neural network [14]. Next, rigid and deformable registrations were conducted to align the two segmentations. Registration accuracy is confirmed using a dual-channel plotting technique to assure alignment of the fixed diastolic and warped systolic configurations as previously described [10]. Lastly, the 3D displacement field resulting from the deformable registration is used to perform a vertex-wise de-formation of a triangulated mesh based on the diastolic configuration. The 3D displacement field between the diastolic and systolic aortic phases is amenable to performing engineering analysis of strains, stretches, as well and 3D motions of specific regions of the aorta, such as the aortic annulus.

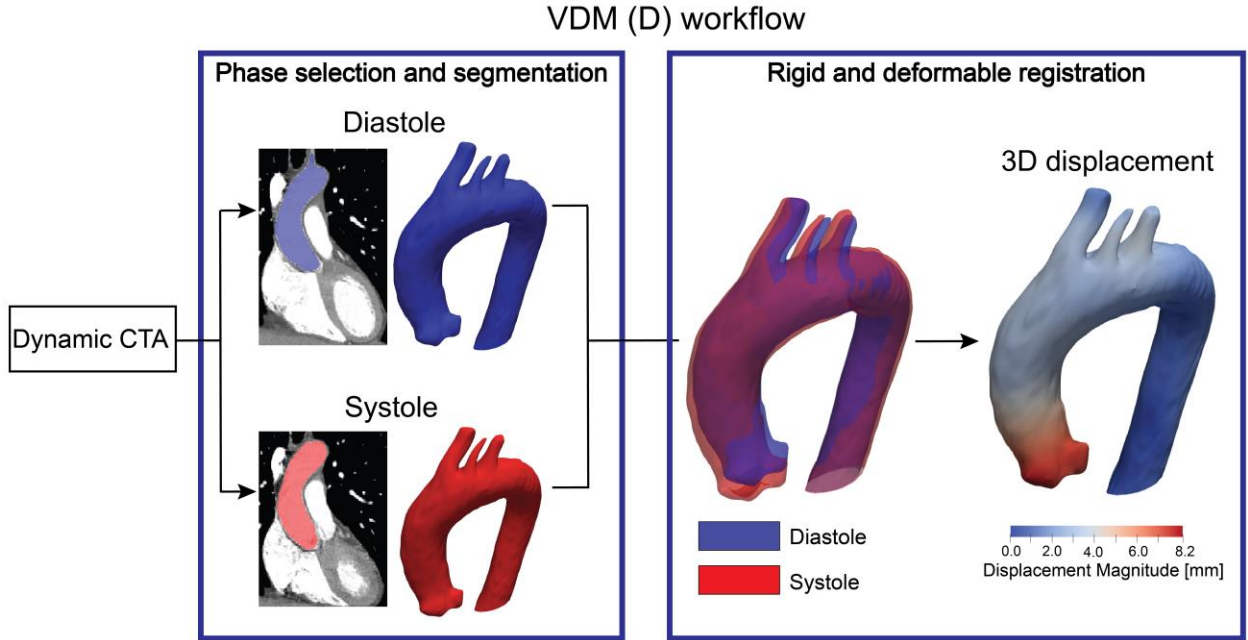


Figure 3.2. VDM workflow.

3.2.3 Metrics extracted from VDM-D

3.2.3.1 Defining a suitable location to study aortic root motion

VDM-D provides the 3D displacement from diastole to systole over the entire surface of the thoracic aorta. However, for the purpose of this study we extracted and analyzed aortic root motion at the sinuses of Valsalva, in a plane perpendicular to the aortic centerline. Specifically,

the analysis plane was placed at the level of the coronary arteries (i.e. coronary ostia) as this location provides a distinct anatomic feature for deformable registration during VDM-D (Figure 3.3a). A normal vector to this analysis plane was obtained via cross-product of in-plane unit vectors. The green and magenta arrows in Figure 3b show normal vectors to the analysis plane in diastole and systole respectively.

3.2.3.2 Displacement

Figure 3.3a represents the total, axial, and in-plane displacement vectors in 3D space. The total displacement (black arrow) was obtained by averaging the 3D displacement field as given by VDM-D over the entire analysis plane. The axial displacement (orange arrow) was defined as the projection of the total displacement vector in the direction of the diastolic normal vector (green arrow in panel b). Conversely, the in-plane displacement (purple arrow) was defined as the projection of the total displacement in the direction perpendicular to the diastolic normal vector. In addition, relative displacements in axial and in-plane directions can be defined as follows:

$$\text{Relative axial(in-plane) displacement} = \frac{\text{axial(in-plane)displacement}}{\text{total displacement}} \quad (3.1)$$

3.2.3.3 Distensibility and area ratio

Distensibility is a metric that reflects aortic stiffness, as it includes both changes in strain and pressure. Here, the ratio between diastolic and systolic analysis plane areas was obtained to calculate the distensibility (Figure 3.3c) using the following formula [15]:

$$\text{Distensibility}[10^{-3} \text{ mmHg}^{-1}] = \frac{A_{sys} - A_{dia}}{A_{dia}} \times \frac{1}{PP} = (\text{area ratio} - 1) \times \frac{1}{PP} \quad (3.2)$$

where A_{sys} and A_{dia} refer to the systolic and diastolic annulus areas, respectively, and PP is the pulse pressure. Area ratio is A_{sys}/A_{dia} .

3.2.3.4 Axial tilt and aortic rotation

The aortic root experiences a complex motion involving rotation and twisting around multiple axes due to its mechanical coupling with the contracting left ventricle. To characterize these complex rotations, in this paper we defined the following metrics:

Axial tilt α , defined as the angle between the diastolic (green arrow) and systolic (magenta arrow) normal vectors to their corresponding analysis plane areas (Figure 3.3b).

Aortic rotation θ , defined as the angle between two vectors from the centroid of the diastolic and systolic analysis plane areas, and a reference point such as the initial point of the centerline of the left coronary artery (Figure 3.3d). Here, the green arrow represents the reference diastolic vector, and the magenta arrow represents the projection of the reference systolic vector onto the diastolic annulus plane. This aortic rotation θ represents the cyclic twisting motion of the aorta.

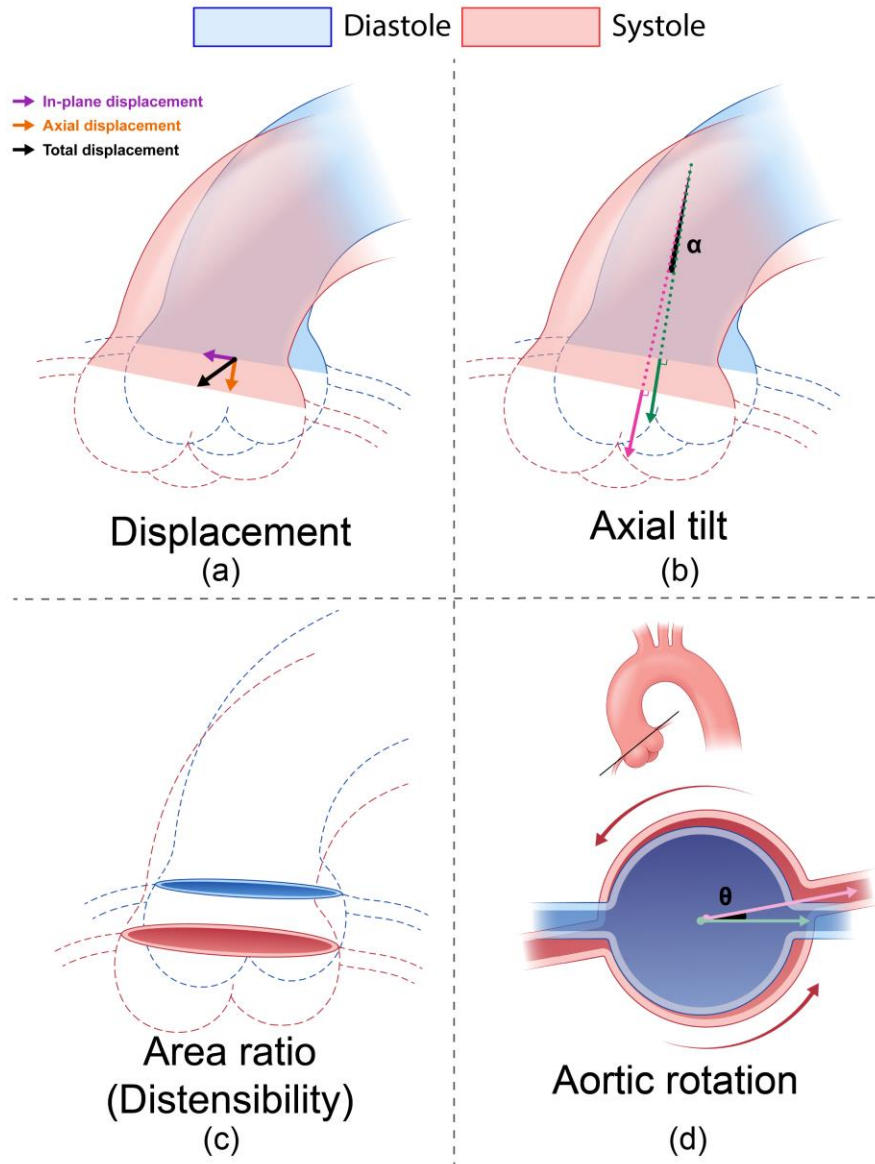


Figure 3.3. Four metrics of aortic root motion considered in this study, all calculated from 3D displacement extracted from VDM(D). (a) total, axial, and in-plane displacements, (b) axial tilt, (c) area ratio (distensibility), and (d) aortic rotation.

3.2.4 Statistical analysis

Due to the small sample size of the different groups considered in this study (~ 10 subjects per group), we could not assume normal distribution behavior for each group. Therefore, a Kruskal-Wallis test was performed to compare different groups [16]. A p-value < 0.05 was considered significant. Correlations between variables were assessed using linear regression. Again, a p-value < 0.05 was considered a strong correlation.

3.3 Results

3.3.1 Patient demographics

The 51 subjects included in this study were divided into 4 groups as follows: 13 non-aneurysmal, 15 TAA, 11 Marfan, and 12 repair. Patient demographics are shown in Table 3.1. Overall mean age was 55 ± 14.4 years old. Age distribution among the 4 groups is depicted in Figure 3.4 and Table 3.1. Age was significantly different between groups other than between Marfan and non-aneurysmal, with the repair group demonstrating the highest mean age (Figure 3.4). Mean systolic/diastolic and pulse pressures (the pressure difference between systole and diastole) were 127/71 mmHg and 56 mmHg, respectively, and did not differ across groups.

Table 3.1. Patient characteristics. TAA = thoracic aortic aneurysm, BP = blood pressure, HTN = hypertension, BAV = bicuspid aortic valve, AS = aortic stenosis, AI = aortic insufficiency, CAD = coronary artery disease, STJ = sinotubular junction, MAA = midascending aorta, LV/Ao angle = left-ventricular/aortic root angle.

Characteristic (n=45)	Non-aneurysmal (n=13)	TAA (n=15)	Marfan (n=11)	Repair (n=12)	P-value
Age [years]	48.6 ± 12.5	57.3 ± 9.5	43.1 ± 14.7	68.0 ± 9.0	< 0.01
Female (n)	6	5	6	2	-
BP systolic [mmHg]	130 ± 22	125 ± 19	125 ± 17	129 ± 11	0.86
BP diastolic [mmHg]	77 ± 15	68 ± 8	69 ± 10	71 ± 10	0.21
Pulse pressure [mmHg]	53 ± 12	56 ± 19	56 ± 14	58 ± 16	0.86
HTN (n)	8	8	7	6	-
BAV (n)	0	6	1	0	-
AS (n)	0	5	0	0	-
AI (n)	0	3	0	0	-
CAD (n)	2	2	0	3	-
Hyperlipidemia (n)	2	7	2	5	-
Diameter sinus [mm]	32 ± 4	43 ± 5	43 ± 6	36 ± 5	< 0.01
Diameter STJ [mm]	28 ± 3	43 ± 5	36 ± 6	32 ± 3	< 0.01
Diameter MAA [mm]	30 ± 4	45 ± 4	33 ± 4	32 ± 3	< 0.01
LV/Ao angle [degrees]	132.5 ± 9.5	134.4 ± 6.4	134.9 ± 7.4	126.4 ± 6.4	< 0.01

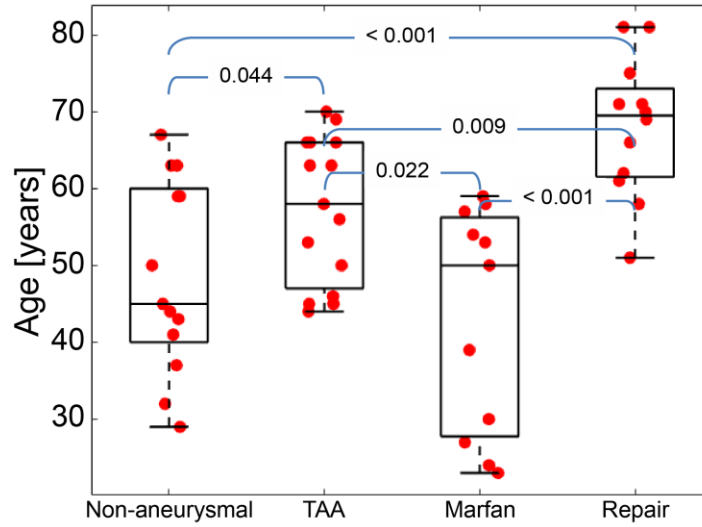


Figure 3.4. Age whiskers box plots for different groups. P-values are given at the top of the blue brackets.

TAA and Marfan groups demonstrated larger maximal sinus compared to the non-aneurysmal and repair groups (p-value < 0.001). Maximal diameter at the sinotubular junction (STJ) and mid-ascending aorta (MAA) was higher in the TAA compared to the other groups (p-value < 0.001), concordant with the predilection for MAA dilation in sporadic TAA. LV/Ao angle was lowest in the repair group.

3.3.2 Aortic root motion metrics

Figure 3.5 shows diastolic and systolic aortic geometries extracted from VDM-D, as well as the corresponding sinus contours at the analysis plane for representative subjects in each group (e.g., subject with motion patterns closest to the mean of the group). The 3D geometries and sinus contours demonstrate downwards (axial) motion and contour expansion in systole across all groups and subjects. In addition, in-plane motion was apparent for all subjects, although was lowest in the repair group. The non-aneurysmal and repair subjects show the largest and smallest axial displacements, respectively. The largest component of the aortic root motion in the repair subject was in the in-plane direction.

Table 3.2 and Figure 3.6 summarize the results for the aortic root motion metrics across all patients and groups. On average the repair group showed approximately 3.5 mm less total displacement than the other three groups; however, there was no significant difference between non-aneurysmal, TAA, and Marfan groups.

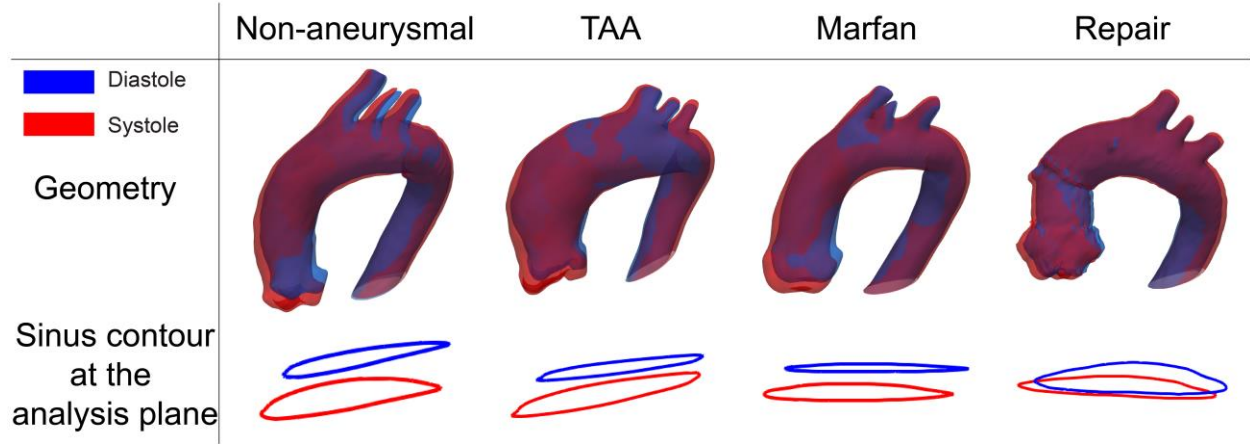


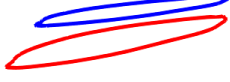
Figure 3.5. Diastolic (blue) and systolic (red) aortic geometries extracted from VDM(D), as well as the corresponding sinus contours at the analysis plane, for representative subjects in each group.

The Marfan group showed the largest heterogeneity in total displacement (range: 1.77 to 10.03 mm). In contrast, the repair group demonstrated the narrowest range of total displacements (range: 1.93 to 4.99 mm, Figure 3.6a).

The axial and in-plane displacements show similar trends as the total displacement. The repair group showed significantly smaller axial and in-plane displacement than the other groups (Figure 3.6b and c). Table 3.2 also summarizes the relative axial and in-plane displacements (i.e., the directional component normalized by the total displacement). The repair group showed smaller relative axial displacement and larger relative in-plane displacement than the other three groups (p -value < 0.01). The non-aneurysmal group is the only group showing larger relative axial displacement (0.72) compared to relative in-plane displacement (0.66).

There was no statistical difference in axial tilt between the four groups (Figure 3.6d). The repair group showed smaller aortic rotation values than the other groups (Figure 3.6e), but there was no statistical difference in rotation between non-aneurysmal, TAA, and Marfan groups. Figure 6f represents the distensibility results. Non-aneurysmal group showed higher median distensibility compared to the Marfan and repair groups, however, there was no statistical difference between non-aneurysmal and TAA groups. The TAA group displayed higher median distensibility compared to the repair group. The Marfan group shows the largest heterogeneity, with distensibility values ranging from 0.2 to $2.5 \cdot 10^{-3} \text{ mmHg}^{-1}$. In contrast, the repair group shows the smallest heterogeneity in distensibility, ranging from 0.4 to $1.3 \cdot 10^{-3} \text{ mmHg}^{-1}$.

Table 3.2. Aortic root metrics for different subject groups. Mean $\pm$ standard deviation. TAA = thoracic aortic aneurysm. Relative axial (in-plane) displacement = axial (in-plane) displacement/total displacement.

		Non-aneurysmal	TAA	Marfan	Repair
Sinus contour at the analysis plane (blue= diastolic, red= systolic)					
Displacement [mm]	Total	7.34 $\pm$ 1.69	7.14 $\pm$ 2.30	7.01 $\pm$ 3.09	3.60 $\pm$ 1.00
	Axial	5.20 $\pm$ 1.17	4.23 $\pm$ 2.27	4.84 $\pm$ 2.88	1.37 $\pm$ 1.14
	In-plane	4.98 $\pm$ 1.93	5.33 $\pm$ 2.32	4.79 $\pm$ 2.08	3.13 $\pm$ 1.06
Relative axial displacement		0.72 $\pm$ 0.14	0.58 $\pm$ 0.27	0.63 $\pm$ 0.21	0.38 $\pm$ 0.26
Relative in-plane displacement		0.66 $\pm$ 0.14	0.68 $\pm$ 0.25	0.73 $\pm$ 0.17	0.88 $\pm$ 0.17
Axial tilt [degree]		3.06 $\pm$ 2.06	2.79 $\pm$ 1.65	2.96 $\pm$ 0.83	3.83 $\pm$ 2.08
Aortic rotation [degree]		1.93 $\pm$ 1.35	1.92 $\pm$ 0.97	1.70 $\pm$ 1.02	1.03 $\pm$ 0.43
Distensibility [10^{-3} mmHg $^{-1}$]		2.21 $\pm$ 1.30	1.75 $\pm$ 0.37	1.34 $\pm$ 0.68	0.93 $\pm$ 0.26

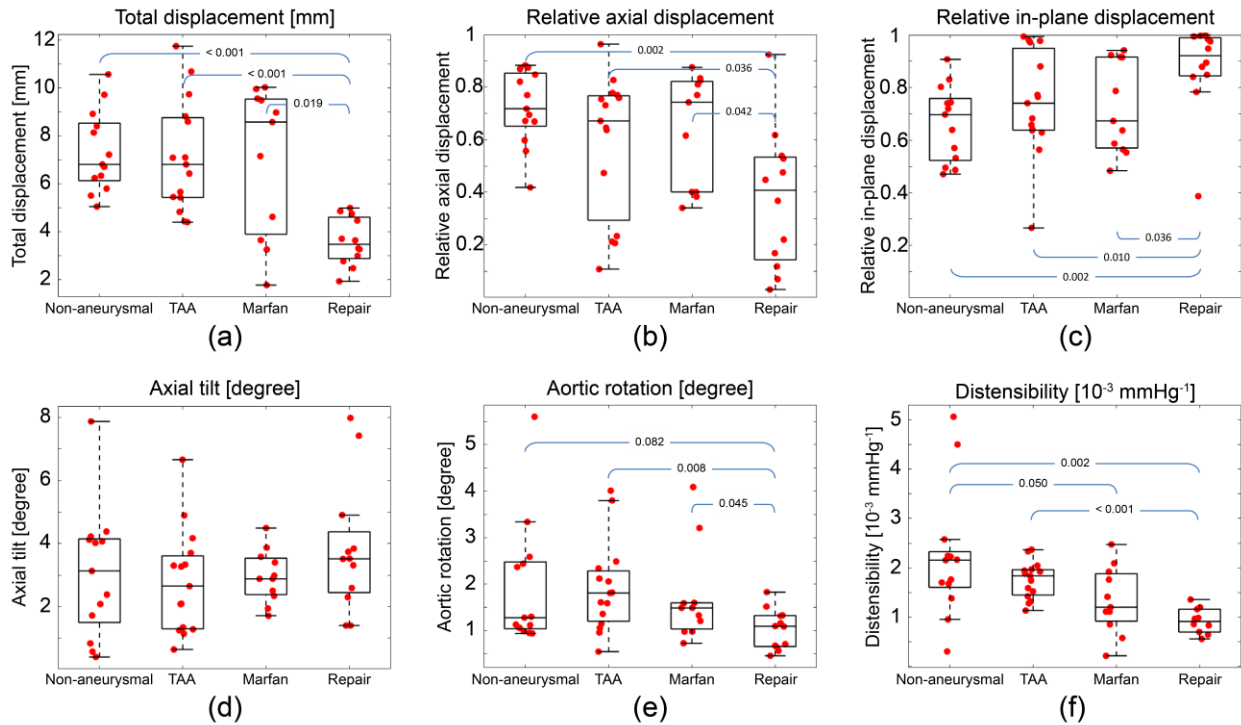


Figure 3.6. Whiskers box plots for the different subject groups. (a) total displacement, (b) axial displacement, (c) in-plane displacement, (d) axial tilt, (e) aortic rotation, and (f) distensibility. P-values are given at the top of the blue brackets.

3.3.3 Correlation with age

Figure 3.7 summarizes the correlation between age and total displacement (panel a), and distensibility (panel b) for each group. Although each group shows a negative correlation between

displacement and age, these correlations were weak-moderate and not statistically significant (Figure 3.7a). In contrast, there was a strong negative correlation between distensibility and age in the non-aneurysmal group, but not in the other groups. In a subgroup of young patients (< 40 years), distensibility was lower in Marfan compared to non-aneurysmal patients (1.73 vs. 4.04, p-value = 0.025).

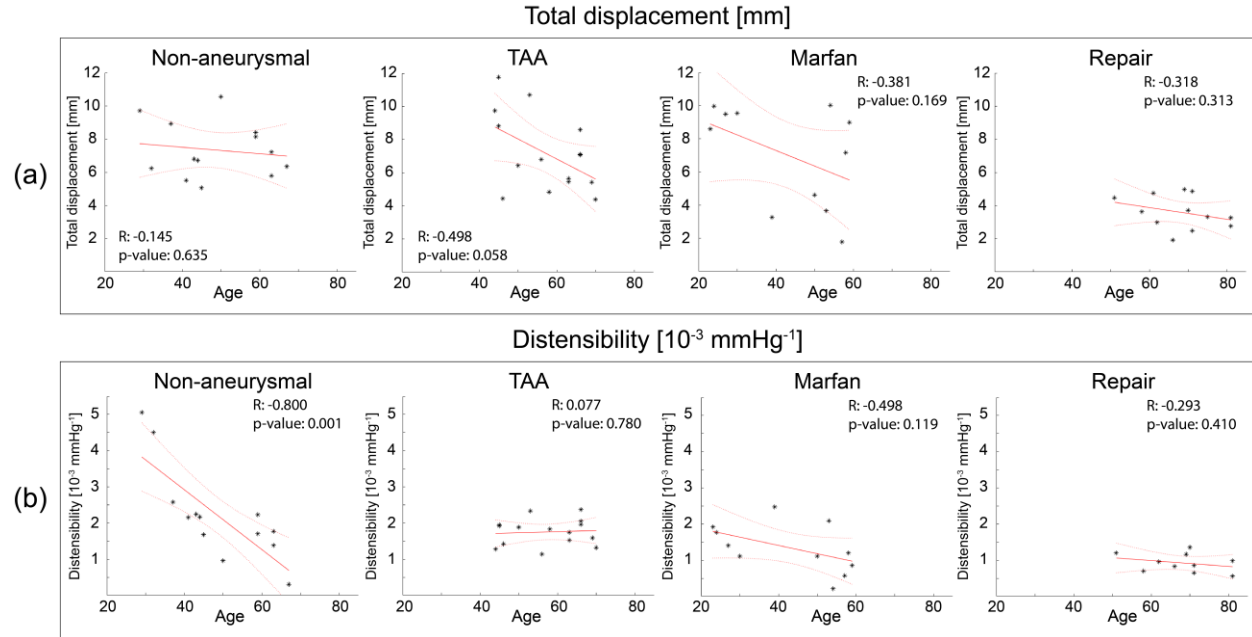


Figure 3.7. Scatter plots correlating (a) total displacement vs age and (b) distensibility vs age for the different subject groups. Solid and dotted red lines are fit and confidence bounds, respectively.

3.3.4 LV/Ao angle results

The LV/Ao angle (φ) represents the alignment between the aortic annulus and long-axis of the left ventricle (see Figure 3.1). The smaller this angle, the more perpendicularly oriented are the heart and the aorta. Figure 3.8a summarizes the distribution of LV/Ao angles for each group. The repair group shows an approximately 5-degree smaller LV/Ao angle than the other groups. There is no statistical difference between non-aneurysmal, TAA, and Marfan groups. Combining the results in Figure 3.4 and Figure 3.8a, we can appreciate that, in general, smaller LV/Ao angles are associated with older age.

Figure 3.8b and c illustrate the correlation between the LV/Ao angle and relative axial and in-plane displacements, respectively, for all subjects of all groups. Panel b shows that there is a strong positive correlation between LV/Ao angle and relative axial displacement. Conversely, Panel c shows a moderate negative correlation between LV/Ao angle and relative in-plane displacement.

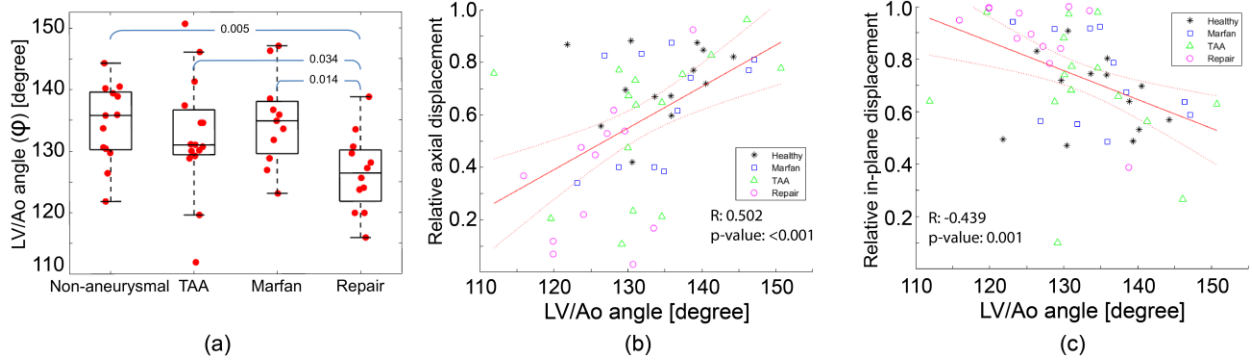


Figure 3.8. LV/Ao angle results. (a) whiskers box plots of LV/Ao angle for each group. P-values are given at the top of the blue brackets. (b) scatter plot correlating relative axial displacement and LV/Ao angle. (c) scatter plot correlating relative in-plane displacement and LV/Ao angle. Solid and dotted red lines are fit and confidence bounds, respectively.

3.4 Discussion

High level summary: In this study, 3D aortic root motion was characterized using dynamic CTA data and VDM-D analysis. Aortic root motion metrics such as axial and in-plane displacements, area ratio/distensibility, axial tilt, aortic rotation, and LV/Ao angles were extracted and compared for four different subject groups: non-aneurysmal, TAA, Marfan, and repair. Our results revealed differences in aortic root motion metrics, most notably between the repair group and other groups with native ascending aortas. The repair group showed the smallest aortic root displacement, aortic rotation and distensibility compared to other groups (Figure 3.6). There was no difference in axial tilt between groups. We also showed that there were moderate-strong correlations between LV/Ao angle and relative axial and in-plane displacements (Figures 3.8b & 3.8c).

Repair group: Table 3.2 and Figure 3.6 show that the repair group presents smaller and more homogeneous displacements and rotations than the other groups. These findings are consistent with previous studies, which reported decreased systolic downwards motion in aortic grafts [17], indicative of the higher graft stiffness relative to the native aortic tissue [18,19]. Distensibility was also lowest in the repair group, an expected finding given the very stiff properties of synthetic fabric of vascular grafts (Figure 3.6f) [20-22].

Marfan group: The Marfan group had the largest heterogeneity in displacement and distensibility (Figure 3.6), as well as in age (Figure 3.4). Such heterogeneity has been previously documented among patients with MFS [23]. While a pathogenic mutation in the fibrillin-1 gene is pathognomonic of MFS disease, it is well-recognized that large degrees of phenotypic heterogeneity exist between patients, an observation that aligns with the variability we observed

in root motion and mechanical metrics studied in this paper [24]. While these results need further conformation in larger cohorts, our preliminary findings suggest that VDM-D may be a useful tool for assessing the phenotypic severity of aortopathy in MFS in a patient-specific manner using available clinical CTA data.

Distensibility: Our results revealed that the Marfan and repair groups have lower aortic root distensibility than the non-aneurysmal and TAA groups, in alignment with prior reports [21,25]. Interestingly, we observed no statistical difference between non-aneurysmal and TAA groups (Figure 3.6f), in contrast with prior studies that have re-reported higher aortic stiffness in TAA compared to non-aneurysmal aortas [26-28]. This discrepancy may be explained by several factors. First, the location where aortic motion is extracted in our study is at the sinuses of Valsalva, which is different from the location of maximum aneurysm diameter in our TAA subjects, suggesting a potential gradient in distensibility (and therefore stiffness) from the aortic root to the aneurysm location in TAA subjects. This distensibility gradient can be appreciated in the diastolic and systolic aortic geometries of the TAA subject in Figure 3.5. While a clear difference between geometries is observed at the aortic root, these geometries are nearly identical at the maximum aneurysm diameter location. Secondly, we may have simply failed to capture a statistical difference in these groups owing to relatively small group sizes and the confounding effects of age on aortic stiffness in the non-aneurysmal group (Figure 3.7b).

LV/Ao angle: Previous studies have reported a negative correlation between age and LV/Ao angle [29,30] (e.g., the LV/Ao angle decreases with age). Our results are consistent with these studies (see Appendix A, Figure A1). To better understand the correlation between LV/Ao angle and root motion metrics, we examined relative aortic displacements normalized to total displacement given that LV/Ao angle would be expected to affect the directional proportion of root motion more so than its absolute degree (more reflective of the underlying aortic pathology). Further, normalizing the displacements allowed us to mitigate the relationship between age and aortic displacement, and therefore to directly compare all subjects across groups. In large LV/Ao angles, corresponding to a more parallel alignment between aorta the LV long axis, ventricular contraction and shortening results in an axial predominant root motion. However, as the LV/Ao angle becomes more perpendicular, the LV contraction is distributed to both axial and in-plane directions, with an increasing in-plane component.

Variation of metric with age: Previous studies have clearly demonstrated increasing aortic stiffness with aging [31-33]. Therefore, the negative correlation between age and distensibility (inversely related to stiffness) in the non-aneurysmal group (Figure 3.7b) is consistent prior results. However, the TAA, Marfan, and repair groups did not show significant correlations between distensibility and age. All three groups presented lower distensibility compared to the non-aneurysmal group. For instance, young (< 40 years) Marfan subjects had lower distensibility compared to non-aneurysmal patients (1.73 vs. 4.04, p-value = 0.025). However, we did not identify significant correlations between age and distensibility in the TAA or Marfan groups, suggesting that the effects of aortic stiffening related to these patient's aneurysmal disease supersedes the effects of age-related aortic stiffening. Finally, it is expected that the distensibility in the repair group low and independent of age due to very stiff nature synthetic graft.

Figure 3.7a shows that there is no strong correlation between age and aortic root displacement. Only the TAA group suggested a pattern of larger total displacements for younger subjects. However, this TAA group is highly heterogenous with 6 bicuspid aortic valve, 5 aortic stenosis and 3 aortic insufficiency patients. Unlike distensibility, which is dictated by aortic properties only, aortic root displacement results from the interactions between heart and aorta. Previous studies have reported that there is no significant correlation between age and LV ejection fraction [34,35]. Therefore, one could argue that aortic root motion is independent of age unless heart function is compromised.

Correlation with aortic diameter: Aortic diameter has been widely used as a clinical metric to assess aortic disease severity and progression [36-38]. However, numerous studies have demonstrated its poor predictive value [39-41]. Our results agree with these such studies, as we have observed no significant correlation between sinus diameter, distensibility, and aortic displacement (see Appendix A, Figure A2).

3.4.1 Displacement extraction comparison between 2D and 3D

Most studies thus far have characterized aortic root motion using 2D approaches [5,7-9,17,42,43]. However, extracting aortic root motion from 2D images, without accounting for the full 3D motion of the aorta, may provide a distorted assessment. Figure 3.9 illustrates diastolic (blue) and systolic (red) aortic geometries extracted from VDM-D for a non-aneurysmal subject. The motion is observed under two different views. View 1 shows that there is an axial (downward) motion and almost no in-plane motion. However, view 2 shows that there is both axial and in-

plane displacements. This is a simple demonstration of how a VDM-D analysis of dynamic CTA data can more fully capture 3D motion of the root compared to 2D approaches.

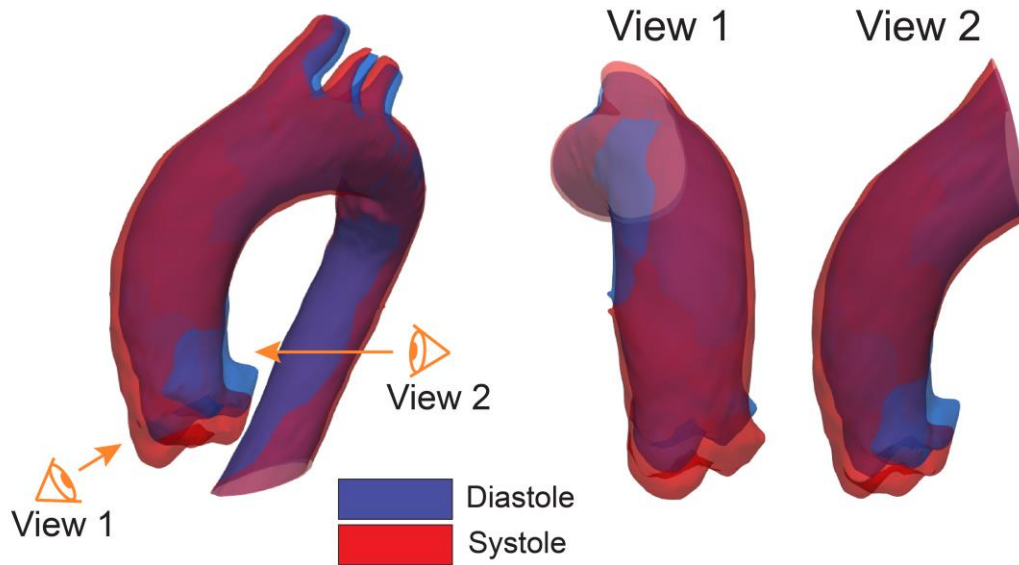


Figure 3.9. Diastolic (blue) and systolic (red) aortic geometries extracted from VDM-D for a non-aneurysmal subject. Two different 2D views provide different characterizations of aortic root motion.

3.4.2 Implications for aortic wall stress analysis

3D Aortic root motion extracted from VDM-D can be used to provide improved boundary conditions for aortic wall stress analysis [44]. A 3D assessment of root motion related to ventricular traction is important given that load-bearing elastin and collagen fibers have variable orientations within the aortic wall and thus different populations of these fibers will differentially bear loads depending on their directional orientation [45]. Most previous computational studies of ascending aortic stress hold the inlet boundary as fixed (no root motion) [46-50], and among the few studies have investigated the effect of aortic root motion on ascending aortic wall stress under simplified and unidirectional (e.g., axial) aortic root motion assumptions [5,7,51]. A recent study demonstrated that in-plane displacements contribute significantly to the stress level in the ascending aorta [8]. However, this study considered simplified, circumferentially uniform values of in-plane displacements extracted from 2D dimensional data. In reality, the aortic root has circumferentially variable in-plane and axial displacements, which can be fully quantified by VDM-D (see Figure 3.5). This 3D information could be used to define improved boundary conditions for aortic wall stress analysis.

3.4.3 Limitations

The small number of subjects per group is one limitation of this study, which may result in lack of strong correlations for some of the reported aortic root metrics in some of the subject groups. The composition of the TAA group was heterogenous, as one third of the patients had BAV, one third had aortic stenosis and one fifth had aortic insufficiency. These comorbidities may have an impact on aortic root motion. However, the primary objective of this study was to assess feasibility of VDM-D rather than provide a comprehensive assessment of metrics across different patient groups and characteristics. Future studies will expand the sample size of the TAA group and thus enable us to define sub-groups according to the presence or absence of valvular disease.

Additionally, the different patient groups had statistically significant differences in age. As expected, the TAA and repair groups were older than non-aneurysmal and Marfan groups (Figure 3.4). These trends therefore reflect the strong association between sporadic/degenerative TAA and age [52]. The Marfan group was youngest overall and had the largest variability in age (from mid 20s to nearly 60 years old), consistent with the well-known variability in phenotypes among Marfan patients [20]. Future studies using groups matched on age and other characteristics will be important to more fully understand the unique contribution of such factors on the described aortic root motion metrics.

3.5 Conclusions

VDM-D analysis of dynamic CTA data enables a rigorous characterization of 3D aortic root motion. This approach overcomes the limitations of previous methods, which focused solely on 1D axial motion. In this study, I developed a pipeline to extract aortic root motion from VDM-D results and defined the specific metrics used for analysis. Directional aortic displacements, area ratio and distensibility, axial tilt and aortic rotation can be extracted across a variety of TAA etiologies as well as in post-repair groups. Our results revealed differences in aortic root motion metrics, most notably between the repair group and other groups with native aortic tissue. The repair group was also the only group that showed a larger relative in-plane displacement than relative axial displacement, likely explained by the lowest (i.e., more perpendicular) LV/Ao angle in this group. The Marfan group showed the largest heterogeneity in aortic root displacement, distensibility and age, compatible with well-reported heterogeneity in this syndrome. The non-aneurysmal group showed a negative correlation between age and distensibility, consistent with widely reported age-related aortic stiffening; however, the effects of age-related stiffening were

blunted in sporadic TAA and Marfan groups. Additionally, our results demonstrated that the LV/Ao angle is an important determinant of the proportions of axial and in-plane displacements and thus should be included in future studies focused on dynamic assessment of the ascending aorta. Future studies can achieve more precise characterization of aortic motion across different patient populations, improving the accuracy of biomechanical modeling and personalized risk assessment. Lastly, 3D aortic root motion derived from VDM-D may be a useful method to better inform realistic, patient-specific boundary conditions in computational studies of aortic wall stress, work which is underway by our group.

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Institutional review board statement

All procedures were approved by the local institutional review board with a waiver of informed consent obtained for this retrospective study and were Health Insurance Portability and Accountability Act-compliant.

3.6 Appendix

Figure A1 presents the correlation between LV/Ao angle and age. Figure A2 presents the correlation between sinus diameter and (a) total displacement and (b) distensibility.

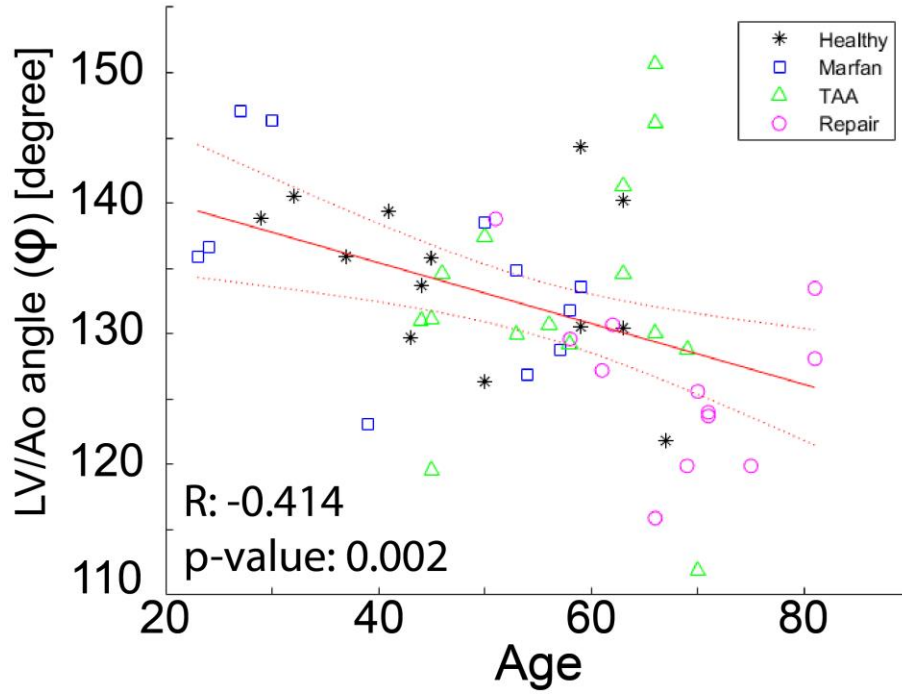


Figure 3.10. Scatter plot correlating LV/Ao angle and age. Solid and dotted red lines are fit and confidence bounds, respectively.

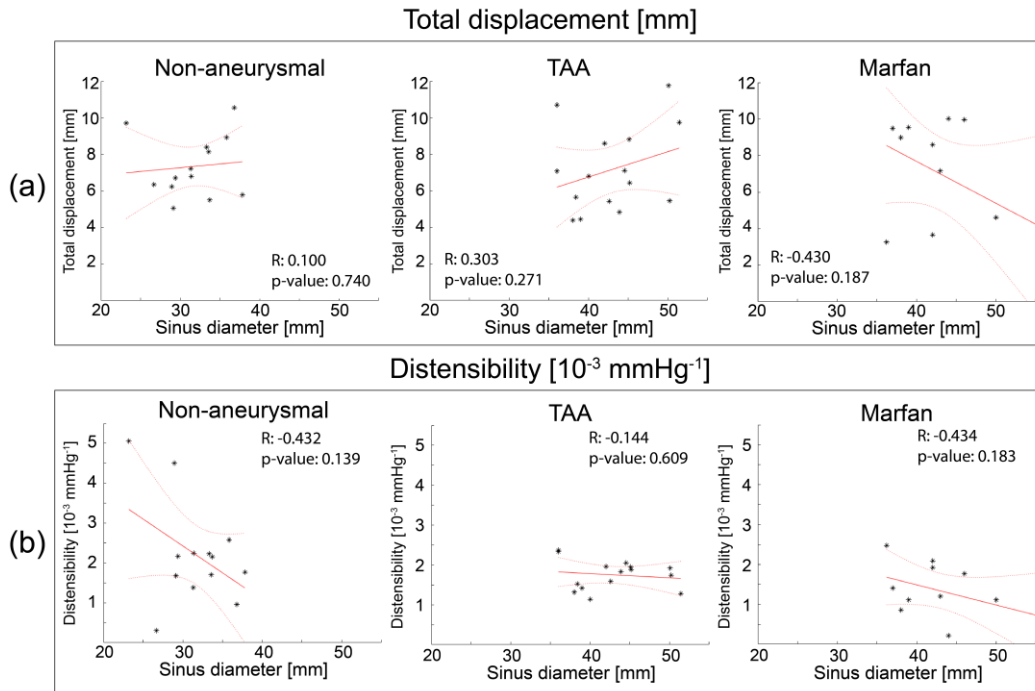


Figure 3.11. Scatter plot correlating (a) sinus diameter vs total displacement and (b) sinus diameter vs distensibility. Solid and dotted red lines are fit and confidence bounds, respectively.

3.7 Bibliography

- [1] Chau, K.H.; Elefteriades, J.A.J.P.i.c.d. Natural history of thoracic aortic aneurysms: size matters, plus moving beyond size. 2013, 56, 74-80.
- [2] Elefteriades, J.A.; Farkas, E.A.J.J.o.t.A.C.o.C. Thoracic aortic aneurysm: clinically pertinent controversies and uncertainties. 2010, 55, 841-857.
- [3] Freeman, L.A.; Young, P.M.; Foley, T.A.; Williamson, E.E.; Bruce, C.J.; Greason, K.L.J.A.A.J.R. CT and MRI assessment of the aortic root and ascending aorta. 2013, 200, W581-W592.
- [4] Desjardins, B.; Kazerooni, E.A.J.A.J.o.R. ECG-gated cardiac CT. 2004, 182, 993-1010.
- [5] Beller, C.J.; Labrosse, M.R.; Thubrikar, M.J.; Robicsek, F.J.C. Role of aortic root motion in the pathogenesis of aortic dissection. 2004, 109, 763-769.
- [6] Cutugno, S.; Agnese, V.; Gentile, G.; Raffa, G.M.; Wisneski, A.D.; Guccione, J.M.; Pilato, M.; Pasta, S.J.B. Patient-specific analysis of ascending thoracic aortic aneurysm with the living heart human model. 2021, 8, 175.
- [7] Singh, S.; Xu, X.; Pepper, J.; Izgi, C.; Treasure, T.; Mohiaddin, R.J.J.o.b. Effects of aortic root motion on wall stress in the Marfan aorta before and after personalised aortic root support (PEARS) surgery. 2016, 49, 2076-2084.
- [8] Wei, W.; Evin, M.; Rapacchi, S.; Kober, F.; Bernard, M.; Jacquier, A.; Kahn, C.J.; Behr, M.J.B.E.O. Investigating heartbeat-related in-plane motion and stress levels induced at the aortic root. 2019, 18, 1-15.
- [9] Kozerke, S.; Scheidegger, M.B.; Pedersen, E.M.; Boesiger, Heart motion adapted cine phase-contrast flow measurements through the aortic valve. 1999, 42, 970-978.
- [10] Burris, N.S.; Bian, Z.; Dominic, J.; Zhong, J.; Houben, I.B.; van Bakel, T.M.; Patel, H.J.; Ross, B.D.; Christensen, G.E.; Hatt, C.R.J.R. Vascular deformation mapping for CT surveillance of thoracic aortic aneurysm growth. 2022, 302, 218-225.
- [11] Burris, N.S.; Hoff, B.A.; Kazerooni, E.A.; Ross, B.D.J.T. Vascular deformation mapping (VDM) of thoracic aortic enlargement in aneurysmal disease and dissection. 2017, 3, 163-173.
- [12] Burris, N.S.; Hoff, B.A.; Patel, H.J.; Kazerooni, E.A.; Ross, B.D.J.C.C.I. Three-dimensional growth analysis of thoracic aortic aneurysm with vascular deformation mapping. 2018, 11, e008045.

- [13] Rosset, A.; Spadola, L.; Ratib, O.J.J.o.d.i. OsiriX: an open-source software for navigating in multidimensional DICOM images. 2004, 17, 205-216.
- [14] Zhong, J.; Bian, Z.; Hatt, C.R.; Burris, N.S. Segmentation of the thoracic aorta using an attention-gated u-net. In Proceedings of the Medical Imaging 2021: Computer-Aided Diagnosis, 2021; pp. 147-153.
- [15] Groenink, M.; de Roos, A.; Mulder, B.J.; Spaan, J.A.; van der Wall, E.E.J.T.A.j.o.c. Changes in aortic distensibility and pulse wave velocity assessed with magnetic resonance imaging following beta-blocker therapy in the Marfan syndrome. 1998, 82, 203-208.
- [16] Kruskal, W.H.; Wallis, W.A.J.J.o.t.A.s.A. Use of ranks in one-criterion variance analysis. 1952, 47, 583-621.
- [17] Izgi, C.; Nyktari, E.; Alpendurada, F.; Bruengger, A.S.; Pepper, J.; Treasure, T.; Mohiaddin, R.J.I.J.o.C. Effect of personalized external aortic root support on aortic root motion and distension in Marfan syndrome patients. 2015, 197, 154-160.
- [18] De Beaufort, H.W.; Conti, M.; Kamman, A.V.; Nauta, F.J.; Lanzarone, E.; Moll, F.L.; Van Herwaarden, J.A.; Auricchio, F.; Trimarchi, S.J.A.o.v.s. Stent-graft deployment increases aortic stiffness in an ex vivo porcine model. 2017, 43, 302-308.
- [19] Takeda, Y.; Sakata, Y.; Ohtani, T.; Tamaki, S.; Omori, Y.; Tsukamoto, Y.; Aizawa, Y.; Shimamura, K.; Shirakawa, Y.; Kuratani, T.J.C.J. Endovascular aortic repair increases vascular stiffness and alters cardiac structure and function. 2014, 78, 322-328.
- [20] Ioannou, C.; Stergiopoulos, N.; Katsamouris, A.; Startchik, I.; Kalangos, A.; Licker, M.; Westerhof, N.; Morel, D.J.E.j.o.v.; surgery, e. Hemodynamics induced after acute reduction of proximal thoracic aorta compliance. 2003, 26, 195-204.
- [21] Tremblay, D.; Zigras, T.; Cartier, R.; Leduc, L.; Butany, J.; Mongrain, R.; Leask, R.L.J.T.A.o.t.s. A comparison of mechanical properties of materials used in aortic arch reconstruction. 2009, 88, 1484-1491.
- [22] Spadaccio, C.; Nappi, F.; Al-Attar, N.; Sutherland, F.W.; Acar, C.; Nenna, A.; Trombetta, M.; Chello, M.; Rainer, A.J.J.o.c.t.r. Old myths, new concerns: the long-term effects of ascending aorta replacement with dacron grafts. Not all that glitters is gold. 2016, 9, 334-342.
- [23] Baumgartner, C.; Matyas, G.; Steinmann, B.; Baumgartner, D. Marfan syndrome--a diagnostic challenge caused by phenotypic and genetic heterogeneity. *Methods Inf Med* 2005, 44, 487-497.

- [24] Seo, G.H.; Kim, Y.-M.; Kang, E.; Kim, G.-H.; Seo, E.-J.; Lee, B.H.; Choi, J.-H.; Yoo, H.-W.J.M. The phenotypic heterogeneity of patients with Marfan-related disorders and their variant spectrums. 2018, 97.
- [25] van Andel, M.M.; de Waard, V.; Timmermans, J.; Scholte, A.J.; van den Berg, M.P.; Zwinderman, A.H.; Mulder, B.J.; Groenink, M.J.O.H. Aortic distensibility in Marfan syndrome: a potential predictor of aortic events? 2021, 8, e001775.
- [26] Kolipaka, A.; Illapani, V.S.P.; Kenyhercz, W.; Dowell, J.D.; Go, M.R.; Starr, J.E.; Vaccaro, P.S.; White, R.D.J.J.o.v.s. Quantification of abdominal aortic aneurysm stiffness using magnetic resonance elastography and its comparison to aneurysm diameter. 2016, 64, 966-974.
- [27] Perissiou, M.; Bailey, T.G.; Windsor, M.; Greaves, K.; Nam, M.C.; Russell, F.D.; O'Donnell, J.; Magee, R.; Jha, P.; Schulze, K.J.E.J.o.V.; et al. Aortic and systemic arterial stiffness responses to acute exercise in patients with small abdominal aortic aneurysms. 2019, 58, 708-718.
- [28] van Disseldorp, E.M.; Petterson, N.J.; van de Vosse, F.N.; van Sambeek, M.R.; Lopata, R.G.J.E.H.J.-C.I. Quantification of aortic stiffness and wall stress in healthy volunteers and abdominal aortic aneurysm patients using time-resolved 3D ultrasound: a comparison study. 2019, 20, 185-191.
- [29] Kwon, D.H.; Smedira, N.G.; Popovic, Z.B.; Lytle, B.W.; Setser, R.; Thamilarasan, M.; Schoenhagen, P.; Flamm, S.D.; Lever, H.M.; Desai, M.Y.J.H. Steep left ventricle to aortic root angle and hypertrophic obstructive cardiomyopathy: study of a novel association using three-dimensional multimodality imaging. 2009, 95, 1784-1791.
- [30] Swinne, C.J.; Shapiro, E.P.; Jamart, J.; Fleg, J.L.J.T.A.j.o.c. Age-associated changes in left ventricular outflow tract geometry in normal subjects. 1996, 78, 1070-1073.
- [31] Cuomo, F.; Roccabianca, S.; Dillon-Murphy, D.; Xiao, N.; Humphrey, J.D.; Figueroa, C.A.J.P.O. Effects of age-associated regional changes in aortic stiffness on human hemodynamics revealed by computational modeling. 2017, 12, e0173177.
- [32] Hickson, S.S.; Butlin, M.; Graves, M.; Taviani, V.; Avolio, A.P.; McEniery, C.M.; Wilkinson, I.B.J.J.C.I. The relationship of age with regional aortic stiffness and diameter. 2010, 3, 1247-1255.
- [33] O'Rourke, M.F.; Nichols, W.W.J.H. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. 2005, 45, 652-658.

- [34] Cain, P.A.; Ahl, R.; Hedstrom, E.; Ugander, M.; Allansdotter-Johnsson, A.; Friberg, P.; Arheden, H.J.B.m.i. Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study. 2009, 9, 1-10.
- [35] Port, S.; Cobb, F.R.; Coleman, R.E.; Jones, R.H.J.N.E.J.o.M. Effect of age on the response of the left ventricular ejection fraction to exercise. 1980, 303, 1133-1137.
- [36] de Wit, A.; Vis, K.; Jeremy, R.W.J.H., Lung; Circulation. Aortic stiffness in heritable aortopathies: relationship to aneurysm growth rate. 2013, 22, 3-11.
- [37] Nollen, G.J.; Groenink, M.; Tijssen, J.G.; Van Der Wall, E.E.; Mulder, B.J.J.E.h.j. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. 2004, 25, 1146-1152.
- [38] Vriz, O.; Driussi, C.; Bettio, M.; Ferrara, F.; D'Andrea, A.; Bossone, E.J.T.A.j.o.c. Aortic root dimensions and stiffness in healthy subjects. 2013, 112, 1224-1229.
- [38] Duprey, A.; Trabelsi, O.; Vola, M.; Favre, J.-P.; Avril, S.J.A.b. Biaxial rupture properties of ascending thoracic aortic aneurysms. 2016, 42, 273-285.
- [40] Pichamuthu, J.E.; Phillippi, J.A.; Cleary, D.A.; Chew, D.W.; Hempel, J.; Vorp, D.A.; Gleason, T.G.J.T.A.o.t.s. Differential tensile strength and collagen composition in ascending aortic aneurysms by aortic valve phenotype. 2013, 96, 2147-2154.
- [41] Vianna, E.; Kramer, B.; Tarraf, S.; Gillespie, C.; Colbrunn, R.; Bellini, C.; Roselli, E.E.; Cikach, F.; Germano, E.; Emerton, K.J.T.J.o.T.; et al. Aortic diameter is a poor predictor of aortic tissue failure metrics in patients with ascending aneurysms. 2022.
- [42] Weber, T.F.; Ganten, M.-K.; Böckler, D.; Geisbüsch, P.; Kauczor, H.-U.; von Tengg-Kobligk, H.J.E.j.o.r. Heartbeat-related displacement of the thoracic aorta in patients with chronic aortic dissection type B: quantification by dynamic CTA. 2009, 72, 483-488.
- [43] Rengier, F.; Weber, T.F.; Henninger, V.; Böckler, D.; Schumacher, H.; Kauczor, H.-U.; von Tengg-Kobligk, H.J.E.j.o.r. Heartbeat-related distension and displacement of the thoracic aorta in healthy volunteers. 2012, 81, 158-164.
- [44] Moireau, P.; Xiao, N.; Astorino, M.; Figueroa, C.A.; Chapelle, D.; Taylor, C.A.; Gerbeau, J.-F.J.B.; mechanobiology, m.i. External tissue support and fluid–structure simulation in blood flows. 2012, 11, 1-18.

- [45] Maeda, E.; Ando, Y.; Takeshita, K.; Matsumoto, T.J.S.R. Through the cleared aorta: three-dimensional characterization of mechanical behaviors of rat thoracic aorta under intraluminal pressurization using optical clearing method. 2022, 12, 8632.
- [46] Meierhofer, C.; Schneider, E.P.; Lyko, C.; Hutter, A.; Martinoff, S.; Markl, M.; Hager, A.; Hess, J.; Stern, H.; Fratz, S.J.E.H.J.C.I. Wall shear stress and flow patterns in the ascending aorta in patients with bicuspid aortic valves differ significantly from tricuspid aortic valves: a prospective study. 2013, 14, 797-804.
- [47] Nathan, D.P.; Xu, C.; Plappert, T.; Desjardins, B.; Gorman III, J.H.; Bavaria, J.E.; Gorman, R.C.; Chandran, K.B.; Jackson, B.M.J.T.A.o.t.s. Increased ascending aortic wall stress in patients with bicuspid aortic valves. 2011, 92, 1384-1389.
- [48] Nathan, D.P.; Xu, C.; Gorman III, J.H.; Fairman, R.M.; Bavaria, J.E.; Gorman, R.C.; Chandran, K.B.; Jackson, B.M.J.T.A.o.t.s. Pathogenesis of acute aortic dissection: a finite element stress analysis. 2011, 91, 458-463.
- [49] Di Martino, E.S.; Guadagni, G.; Fumero, A.; Ballerini, G.; Spirito, R.; Biglioli, P.; Redaelli, A.J.M.e.; physics. Fluid–structure interaction within realistic three-dimensional models of the aneurysmatic aorta as a guidance to assess the risk of rupture of the aneurysm. 2001, 23, 647-655.
- [50] Venkatasubramaniam, A.; Fagan, M.; Mehta, T.; Mylankal, K.; Ray, B.; Kuhan, G.; Chetter, I.; McCollum, P.J.E.J.o.V.; Surgery, E. A comparative study of aortic wall stress using finite element analysis for ruptured and non-ruptured abdominal aortic aneurysms. 2004, 28, 168-176.
- [51] Martin, C.; Sun, W.; Elefteriades, J.J.A.J.o.P.-H.; Physiology, C. Patient-specific finite element analysis of ascending aorta aneurysms. 2015, 308, H1306-H1316.
- [52] Schwarze, M.L.; Shen, Y.; Hemmerich, J.; Dale, W.J.J.o.v.s. Age-related trends in utilization and outcome of open and endovascular repair for abdominal aortic aneurysm in the United States, 2001-2006. 2009, 50, 722-729. e722

Chapter 4 Vascular Deformation Mapping Calibration with Physics Based Synthetic Data

This chapter is adapted from a manuscript currently in preparation for submission³.

4.1 Introduction

Aortic stiffness is both heterogeneous, meaning it has different values in different regions along the aorta, and anisotropic, indicating distinct stiffness patterns in the axial and circumferential directions [1], [2], [3], [4]. Aortic stiffness has been recognized as an important indicator of vascular health [5], [6]. Typically, older patients or those with aortic diseases, such as aortic dissection or Marfan's syndrome, exhibit stiffer aortas [7], [8], [9], [10], [11]. Numerous efforts have been made to estimate aortic stiffness. Some stiffness calibration efforts have relied on invasive approaches, whereby strips of aortic tissue from different regions are tested in both axial and circumferential directions [12], [13], [14], [15]. However, invasive methods have been limited because they require aortic tissue samples and can only be conducted in specific regions. As an alternative, non-invasive, dynamic image-based approaches have been used to quantify the aortic stiffness. However, non-invasive methods have been limited to characterizing the aortic tissue as isotropic and have thus been unable to discriminate stiffness between different spatial directions [16], [17], [18]. This limitation arises because these non-invasive methods either rely on 2D images or lack the techniques required to extract multi-axial strain from 3D dynamic images. The difficulty in obtaining multi-axial strain stems from the challenge of accurately capturing 3D deformation from these 3D images. More sophisticated techniques for assessing 3D aortic deformation from dynamic 3D images are needed to estimate multi-axial aortic stiffness.

Recently, vascular deformation mapping (VDM) successively characterized 3D aortic root motion using electrocardiogram (ECG)-gated computed tomography angiography (CTA) [7]. VDM was originally developed to assess the 3D growth of the aorta by using longitudinal CTA data acquired at two different times during clinical surveillance (VDM-G: VDM growth) [19],

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[20]. When VDM was applied to dynamic CTA data, it was able to assess the 3D aortic deformation over the cardiac cycle (VDM-D: VDM dynamic) [7]. Figure 4.1 shows the VDM-D workflow.

Dynamic CTA and segmentation

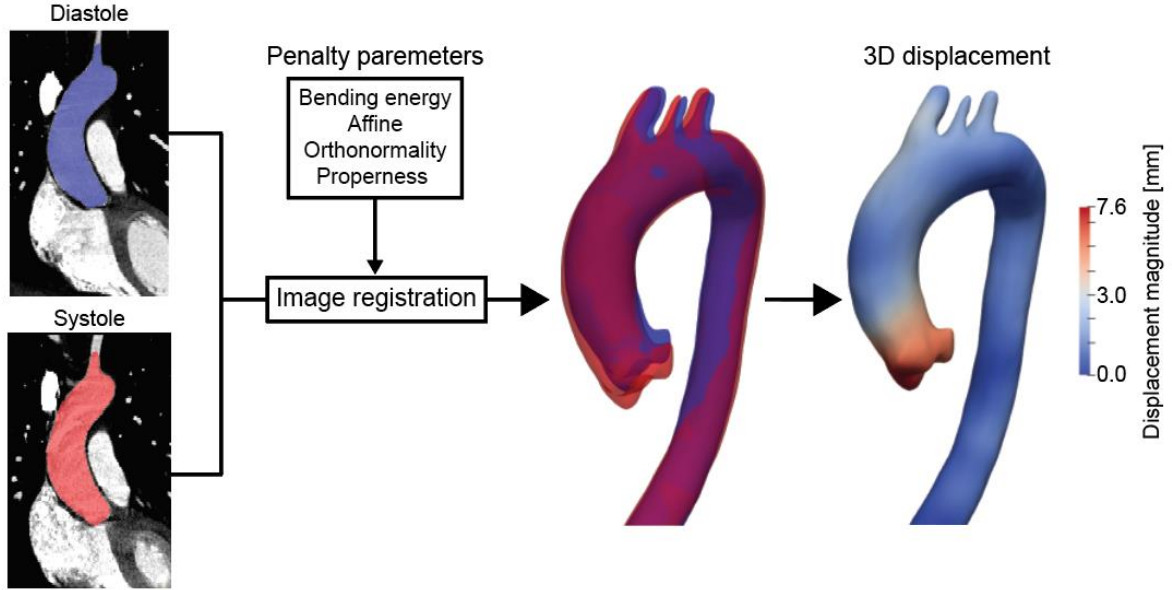


Figure 4.1. VDM-D workflow.

VDM performs nonrigid, deformable image registration to map two different images using the Elastix open-source software [21]. In Elastix, penalty parameters are employed to fine-tune image alignment and penalize non-physiological deformations. Staring et al. introduced penalty parameters that are capable of locally penalizing nonrigid image registration [22]. These parameters are called rigidity penalty terms and include bending energy, affine, orthonormality and properness. More details about these penalty parameters will be described in ‘Methods - 1. Rigidity penalty parameter’. Penalty parameters must be properly calibrated for different problems. These parameters were calibrated in VDM-G using in-silico phantom studies [23]. However, when using dynamic CTA to characterize aortic motion, these parameters need to be recalibrated due to significant differences between sequential and dynamic CTAs. Sequential CTA uses the same cardiac phase images to avoid deformation from aortic motion. Time between two images is several years. Deformation (growth) occurs across the aorta and is relatively small (~2 mm). In contrast, dynamic CTA uses diastole and systole images from a cardiac cycle. Time between two images is less than a second. Deformation (aortic motion) is focused near aortic root and is relatively large (~10 mm). Figure 4.2 presents the results from VDM-D using the penalty

parameters set for VDM-G. For comparison, ground truth results from the synthetic data are also included. More details about the synthetic data will be described in ‘Methods 4.2. Synthetic data generation’. It should be noted that small differences in 3D displacement can lead to significant discrepancies in an axial stretch (strain). In addition, the axial stretch from VDM-D without calibration shows non-physiological strip patterns. This example shows the necessity of recalibrating the penalty parameters for VDM-D.

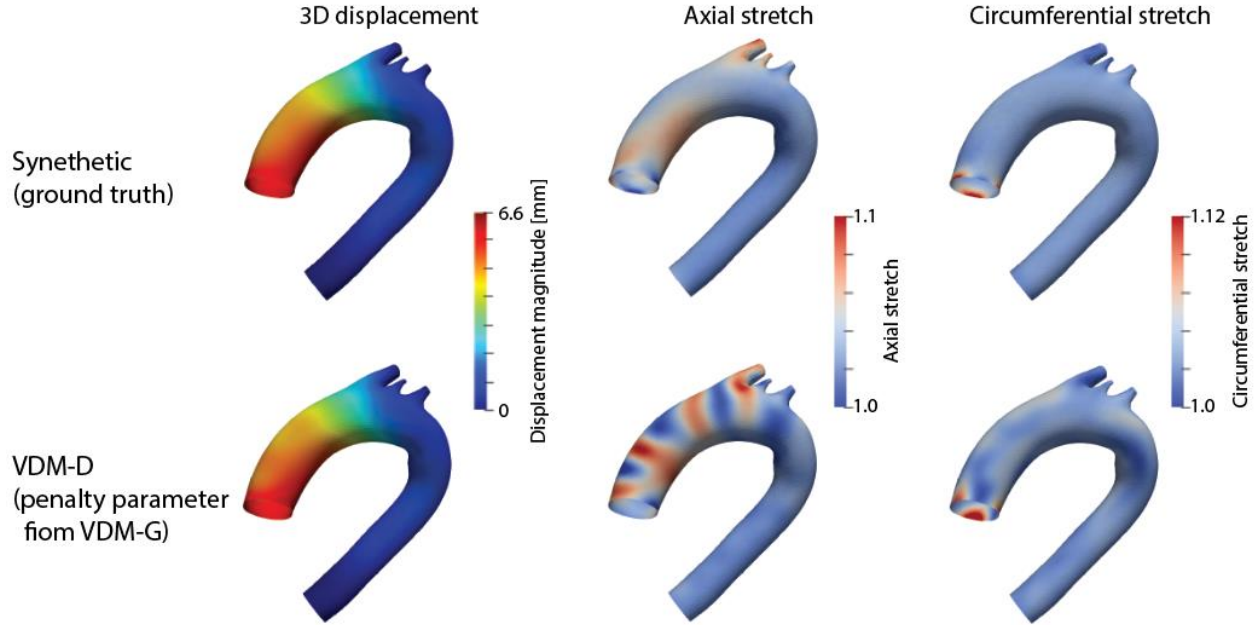


Figure 4.2. 3D displacement and multi-axial stretch analysis using synthetic data and VDM-D, employing penalty parameters derived from VDM-G.

The principal challenge in calibrating VDM-D penalty parameters is the absence of an established ground truth for 3D displacement across the entire aorta. Current methods for measuring aortic motion have been limited to either 1D aortic root motion measurement [24], [25] or 3D measurements at only specific points on the aorta [26], [27]. Aortic displacement from these methods is not enough to validate and calibrate the VDM-D. To address this issue, we generated synthetic data for aortic motion during cardiac cycle which can be used for calibrating VDM-D.

The goal of this work is to leverage VDM-D to estimate 3D aortic motion using dynamic CTA. The first step in this effort is to develop a pipeline to calibrate penalty parameters used in VDM-D and validate VDM-derived aortic motion over the cardiac cycle. Synthetic data on aortic motion for a total of 14 different aortas were used to calibrate penalty parameters in VDM-D.

4.2 Methods

4.2.1 Rigidity penalty parameter

VDM-D's registration algorithm minimizes the pixel-wise mutual information between the fixed diastolic image and the deformed systolic image. Four penalty parameters are utilized to constrain the optimization in the region of the image corresponding to the aorta. These parameters are: (1) bending energy (BE): penalizes sharp, unrealistic deformations, (2) affine constraint (AC): penalizes the second derivative of the deformation to enforce smoothness, (3) orthonormality constraint (OC): penalizes deviations of the deformation's Jacobian from orthonormality, encouraging the transformation to be rigid, and (4) properness constraint (PC): encourages volume preservation [22], [28]. Overall, BE encourages smooth deformation whereas the other three constraints encourage rigidity in the registration's deformation, leading to more realistic deformations [22].

Each penalty term has a weight term which determines its influence on the optimization. The range of weights tested are based on prior research [22] and our experiments: BE's weight was varied from 0 to 220, AC's weight from 0 to 550, OC's weight from 0 to 1.5, and PC's weight from 0 to 1.5. Combinations of weights were tested using a four-dimensional grid search scheme.

4.2.2 Synthetic data generation

4.2.2.1 Rotation-free shell

A non-linear rotation-free shell formulation, solved using the finite element method to produce 3D displacement over the aortic surface, was used to generate the synthetic data [29]. This formulation is validated and has been used to handle large deformations for applications in vascular biomechanics. An incompressible Neo-Hookean constitutive model was considered for the aortic wall, as it is suitable for describing the nonlinear stress-strain behavior under large deformations. Stiffness parameters used for this model are described in the following section 4.2.2.2. The density and thickness of aorta were set to 1000 kg/m^3 and 2.0 mm, respectively [30], [31]. Boundary conditions for the aortic model are presented in Figure 4.3 (a). For the inlet face, we prescribed patient-specific 3D aortic root motion [7], while the arch and outlet faces were fixed. Patient-specific blood pressure was applied inside of the aortic wall.

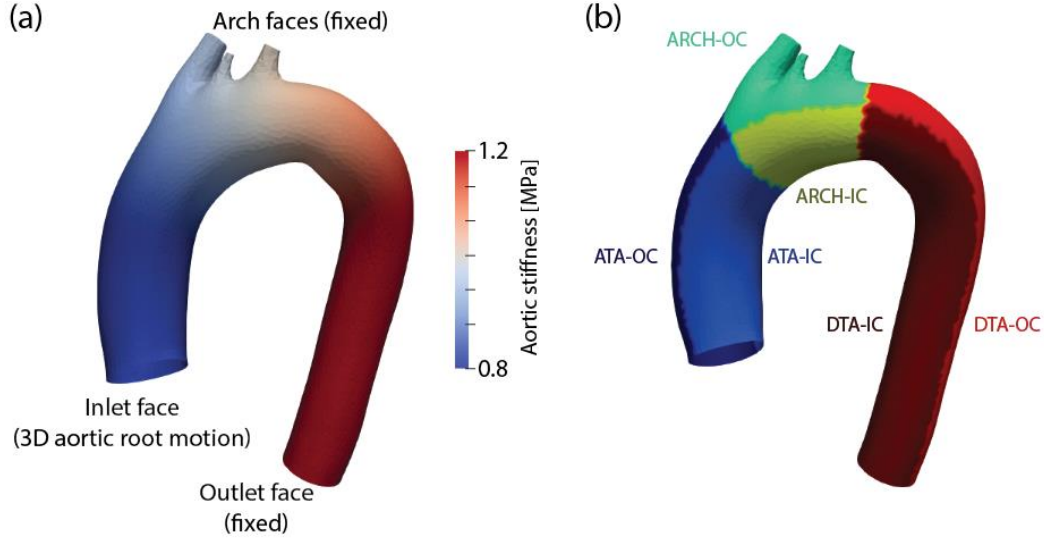


Figure 4.3. (a) Boundary conditions for synthetic data generation and heterogenous aortic stiffness. (b) Six subregions for the error calculation. ATA: ascending thoracic aorta, DTA: descending thoracic aorta, IC: inner curvature, and OC: outer curvature.

4.2.2.2 Population-based heterogenous aortic stiffness

The proper choice of aortic stiffness is important for dynamic aortic simulations. In this paper, we used population-based heterogeneous aortic stiffness values. Our cohort includes non-aneurysmal patients as well as those with thoracic aortic aneurysms (TAA) and Marfan syndrome (Marfan). Non-aneurysmal and TAA patients were classified based on a maximum diameter threshold of 40 mm, without any syndromic features and no family history of aortic diseases. The aortic diameter was collected from clinical radiology reports. Marfan patients were classified using the Ghent criteria, which incorporate aortic root dilatation and *FBN1* mutations in the diagnosis [36], [37].

To determine baseline stiffness, we first extracted age-based stiffness data for the ascending thoracic aorta (ATA) and descending thoracic aorta (DTA) from the literature, which reports both axial and circumferential stiffnesses for non-aneurysmal patients [32]. Since we employed an isotropic model, we averaged the axial and circumferential stiffness values. To adjust for TAA and Marfan patients, we applied stiffness ratios of 1.26 and 1.65 on the ATA stiffness, respectively, based on differences from non-aneurysmal patients [7]. ATA and DTA stiffness values were linearly interpolated on the aortic surface. Figure 4.3 (a) shows one example of the heterogeneous aortic stiffness values on the aortic surface. ATA and DTA stiffness values for each patient can be found in Table 4.1.

Table 4.1. Patient characteristics and aortic stiffness. BP: blood pressure and NA: non-aneurysmal.

	Age	BP [mmHg]	ATA stiffness [MPa]	DTA stiffness [MPa]	3D Root motion [mm]	Cluster
NA 1	65	107/61	0.834	1.152	7.1	1
NA 2	63	164/98	0.834	1.152	6.6	1
NA 3	32	100/62	0.386	0.737	8.6	1
TAA 1	66	139/78	1.05	1.152	6.9	1
TAA 2	43	116/73	0.486	0.737	3.0	0
TAA 3	75	142/77	1.05	1.152	3.8	0
TAA 4	67	124/85	1.05	1.152	4.8	0
TAA 5	64	110/72	1.05	1.152	6.5	1
TAA 6	69	131/85	1.05	1.152	7.0	1
Marfan 1	36	133/66	0.637	0.737	10.0	2
Marfan 2	64	114/66	1.376	1.152	3.0	0
Marfan 3	52	115/68	0.637	0.737	8.4	1
Marfan 4	42	96/54	0.637	0.737	11.1	2
Marfan 5	40	125/85	0.637	0.737	7.6	1

4.2.3 Synthetic image generation

A synthetic systolic image and mask were generated from the displacement field computed by the rotation-free shell model. An Elastic Body Spline (EBS) transformation was applied to the diastolic image using the vertices of the diastolic aortic surface and the synthetic systolic aortic surface as two sets of landmark points. EBS transforms the diastolic image into a synthetic systolic image by mapping corresponding landmark points to one another while interpolating intermediate points in a manner consistent with a physical model of a homogenous, isotropic 3D elastic body [33]. EBS transformation is applied using Elastix's Transformix program [21] with a Poisson ratio of 0.3.

4.2.4 Error calculation

To quantitatively evaluate the performance of VDM-D with different penalty parameters, we first calculate a 3D displacement error field by comparing the VDM-D result with the ground truth from the rotation-free shell model. Next, we define an appropriate error metric from the 3D displacement error field. Our error metric calculation involves three steps. (1) We define six subregions of the aorta to ensure equal contributions from all aortic surfaces. The aorta is first

segmented into three regions - ATA, arch, and DTA - based on side vessel configuration. Each of these regions is then further divided into two subregions: inner curvature (IC) and outer curvature (OC). Figure 3 (b) illustrates these six subregions, including ATA-IC, ATA-OC, ARCH-IC, ARCH-OC, DTA-IC, and DTA-OC. (2) For each subregion, we calculate the maximum displacement error, and the root mean square error to evaluate local and global errors, respectively. A subregion error is the average of these two errors. (3) The error for the aorta is calculated by averaging the six subregion errors. In summary, the error metric is defined as

$$Error\ metric = \frac{1}{6} \sum_{i=1}^6 \frac{MAX_i + RMSE_i}{2} \quad (4.1)$$

where i is a different region, MAX is the maximum displacement error, and RMSE is the root mean square error.

4.2.5 VDM-D penalty parameter calibration pipeline

Figure 4.4 shows our VDM-D penalty parameter calibration pipeline. (1) Synthetic data generation: We calculated a 3D displacement of the aorta from diastole to systole using the rotation-free shell formulation with an incompressible Neo-Hookean constitutive model. This defines the ground truth for our pipeline. (2) Synthetic image generation: we generated a synthetic systolic image and mask. The computed displacement field on the aortic surface from step (1) was interpolated through the 3D aortic volume to generate a synthetic systolic medical image and corresponding mask using the EBS transformation. (3) VDM-D analysis: the VDM-D with penalty parameters was run to calculate 3D displacement from the reference diastolic and the synthetic systolic images and their masks. (4) Error calculation: VDM-D displacements are compared against the computational ground truth, and the discrepancy was quantitatively calculated by using the error metric defined in section 4.2.4. Error calculation method. (5) Calibration of penalty parameters: we changed the penalty parameters based on the error. We repeated steps (3), (4), and (5) with different penalty parameters until we found a minimal error.

4.2.6 Patient data

All procedures were approved by the local institutional review board, and a waiver of informed consent was obtained for this retrospective study. The study was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Fourteen

patients, categorized into three groups (non-aneurysmal, TAA, and Marfan), were selected based on the availability of high-quality, retrospectively ECG-gated CTA data.

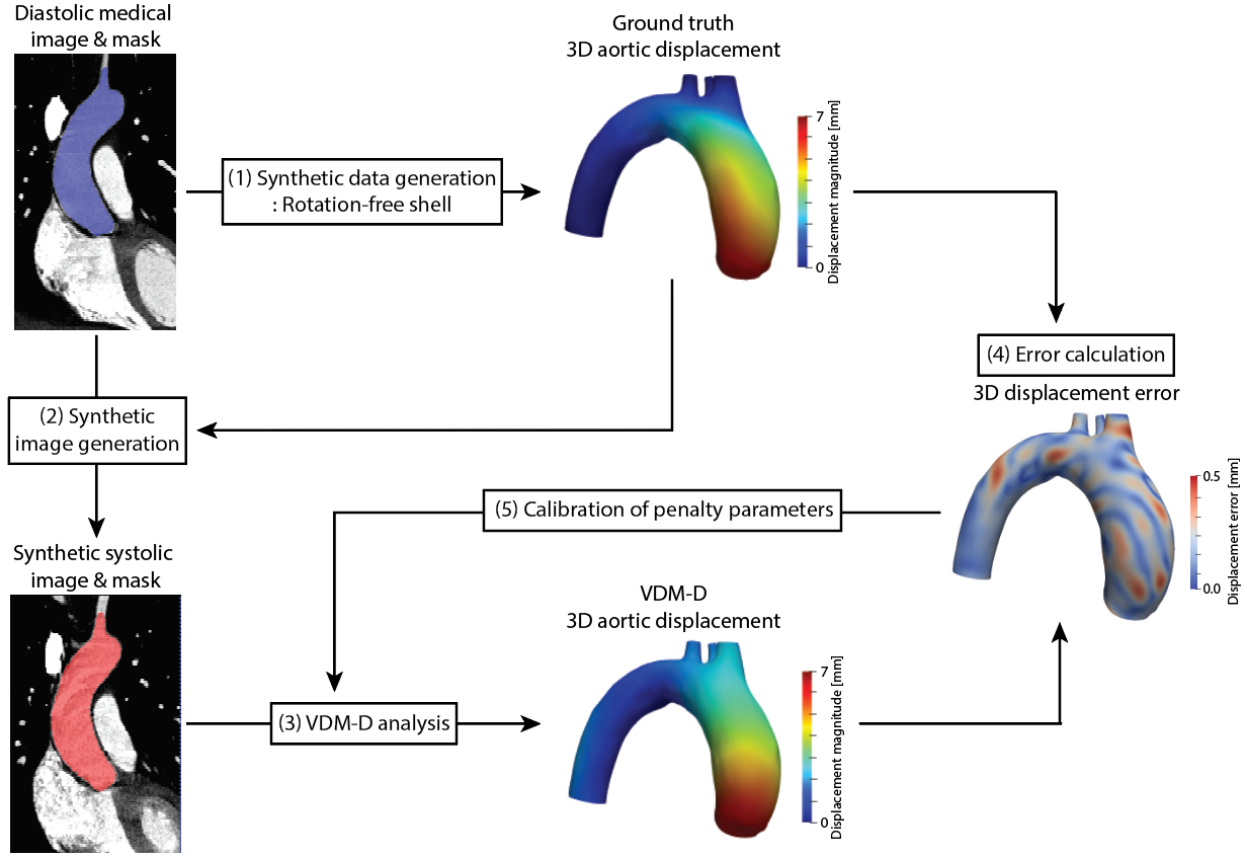


Figure 4.4. VDM-D penalty parameters calibration pipeline.

The peak systolic and end-diastolic phases of the ECG-gated CTA imaging were selected and extracted using an open-source software, OsiriX MD [34]. Dynamic CT imaging covered the entire thoracic aorta. Details of the patient data can be found in Table 4.1. There were 3, 6, and 5 patients from non-aneurysmal, TAA, and Marfan groups, respectively. Overall, the mean age was $55.4 (\pm 14.4)$. The average systolic and diastolic blood pressure were $122.6 (\pm 18.3)$ and $73.6 (\pm 11.9)$ mmHg, respectively. ATA and DTA stiffness values were calculated according to section 4.2.2.2 Population-based heterogeneous aortic stiffness. 3D root motion magnitude was measured as described in our previous publication [7].

4.2.7 Subject classification strategies

VDM-D penalty parameters were calibrated using three distinct grouping methods, leading to the identification of non-specific, disease-specific, and motion-specific penalty parameters. The non-specific penalty parameter was identified as the one that minimized error across all fourteen

patients. In contrast, disease-specific and motion-specific penalty parameters were tailored for each disease group (non-aneurysmal, TAA, and Marfan) and for each cluster divided by root motion, respectively. We employed the k-means clustering technique for classification based on root motion to avoid arbitrary thresholds when separating clusters [35]. K-means clustering is an algorithm that groups data points into K number of clusters, where each data point belongs to the cluster with the nearest average. In this study, we used 3 clusters. The cluster 0, 1, and 2 include patients with root motion less than 5 mm, between 5 and 9 mm, and larger than 9 mm, respectively. Each cluster includes 4, 8, and 2 patients. The clustering results can be found in Table 1. The penalty parameters for each group were determined by minimizing the error across the patients within that group.

4.3 Results

4.3.1 Penalty parameters

Table 4.2 shows the non-specific, disease-specific, and motion-specific penalty parameters obtained from our calibration pipeline. Overall, the ranges of calibrated penalty parameters are between 100-220, 0-350, 0.75-1.5, and 0.75-1.5 for the BE, AC, OC, and PC, respectively. While no specific trends are observed across different disease groups, there is a correlation between motion-specific penalty parameters and aortic root motion. Patient clusters with smaller aortic root motion require higher penalty values. For example, cluster 0 shows the largest penalty parameter values: BE/AC/OC/PC = 220/350/1.5/1.5, while cluster 2 shows the smallest penalty parameter values: BE/AC/OC/PC = 100/0/0.75/0.75.

Table 4.2. Non-specific, disease-specific, and motion-specific penalty parameters. NA: non-aneurysmal.

	Groups	BE	AC	OC	PC
Non-specific	-	140	0	0.75	1.5
Disease-specific	NA	100	350	0.75	0.75
	TAA	140	0	1.5	1.5
	Marfan	100	0	0.75	0.75
Motion-specific	Cluster 0	220	350	1.5	1.5
	Cluster 1	140	0	0.75	1.5
	Cluster 2	100	0	0.75	0.75

4.3.2 Error metric values with different penalty parameters

Figure 4.5 shows the error metric values (see section 4.2.4. Error calculation) without penalty parameters (represented by yellow bar) and with three different penalty parameter sets (represented by blue, red, and magenta bars for non-specific, disease-specific, and motion specific, respectively). Nearly all patients show that penalty parameters help reduce error compared to no penalty. The average errors across all patients are 0.211, 0.167, 0.164, and 0.163 for the no penalty, non-specific, disease-specific, and motion specific, respectively. Given that the motion-specific penalty parameters are obtained from the objective grouping method and result in the lowest error, our final choice among the grouping methods is the motion-specific penalty parameters. More details about the parameter choice will be described in section 4.3.2. Penalty parameter choice. From here, results using penalty parameters implies the use of motion-specific penalty parameters. The largest reduction in error metric achieved with penalty parameters, compared to no penalty, is 44.3% for patient 6. The average error reduction is 20.4%.

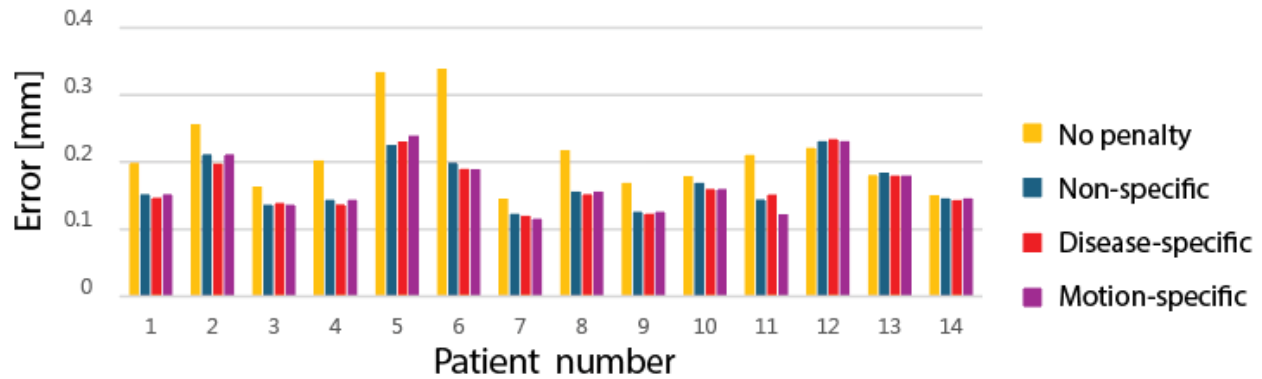


Figure 4.5. Error metric for each patient with different penalty parameters: no penalty, non-specific, disease-specific, and motion-specific.

4.3.3 Surface error plots with and without penalty parameters

Figure 4.6 illustrates the surface error plots, which show the 3D displacement error between ground truth from the rotation-free shell and VDM-D results, both without and with penalty parameters applied. Four aortas are presented: two representing the best cases (patient 5 and 6 from Figure 4.5) and two representing the worst cases (patient 12 and 13 from Figure 5). Two aortas from the best error improvement show that properly calibrated penalty parameters successively reduce high displacement errors. The largest error decreases from 0.74 mm to 0.31 mm for the first patient and 0.58 mm to 0.26 mm for the second patient. Physiologically spurious bands in error maps are also smoothed out by using penalty parameters (see second aorta of the best error improvement). Two aortas from the worst error improvement show relatively small displacement

error without penalty (maximum error of 0.24 mm and 0.38 mm) compared to the best error improvement aortas without penalty (maximum error of 0.74 mm and 0.58 mm). These aortas show no improvement or a slight increase in error with penalty application.

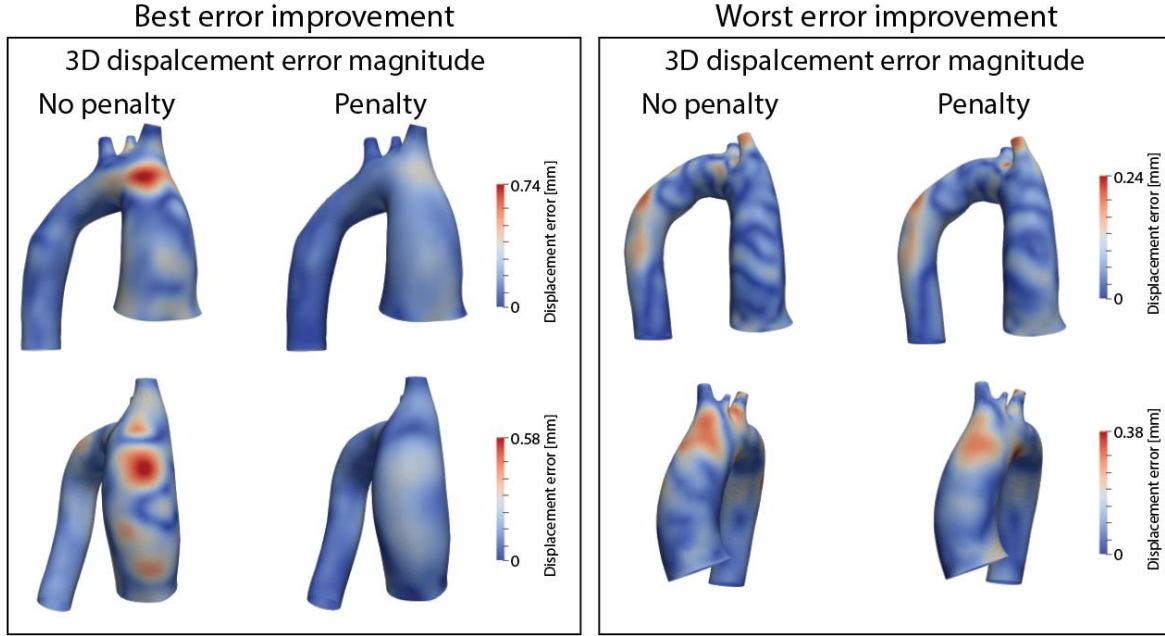


Figure 4.6. 3D displacement error analysis: comparison between scenarios with no penalty and with calibrated penalty, including the two most improved and two least improved error cases.

4.4 Discussion

4.4.1 Stretch comparison

Figure 4.7 compares 3D displacement and multi-axial stretch between the ground truth (derived from the rotation-free shell) and VDM-D results using different penalty parameter values. The axial direction is tangent to the centerline, while the circumferential direction is perpendicular to the centerline. The comparison between ground truth and VDM-D with uncalibrated penalty parameters emphasizes that even small errors in 3D displacement can result in large errors in multi-axial stretch, particularly in the axial direction (as indicated by the red star in Figure 4.6). Among the multi-axial aortic stretches, axial stretch derives from root motion, whereas circumferential stretch results from inflation due to blood pressure. The synthetic 3D displacement field in Figure 6 indicates that aortic deformation is primarily influenced by relatively large and complex root motion, rather than inflation. This complex motion challenges VDM-D's ability to accurately capture deformation without properly calibrated penalty parameters, resulting in a higher error in axial stretch compared to circumferential stretch.

The 3D displacement magnitudes at the red star are 4.62 mm for the ground truth and 4.64 mm for VDM-D with uncalibrated parameters. This minor difference of 0.02 mm results in a significant discrepancy in axial stretch values, which are 1.021 and 1.079, respectively. This sensitivity arises from the definition of stretch, which is a derivative of the 3D displacement in specific directions. With properly calibrated penalty parameters, the VDM-D results show a significant reduction in stretch discrepancy compared to the ground truth, particularly in the axial direction. The axial stretch at the red star region is 1.033 with calibrated penalty parameters. These results demonstrate that properly calibrated VDM-D effectively captures deformation from the root motion. The multi-axial strain obtained from non-invasive medical images can be used to estimate the multi-axial aortic stiffness.

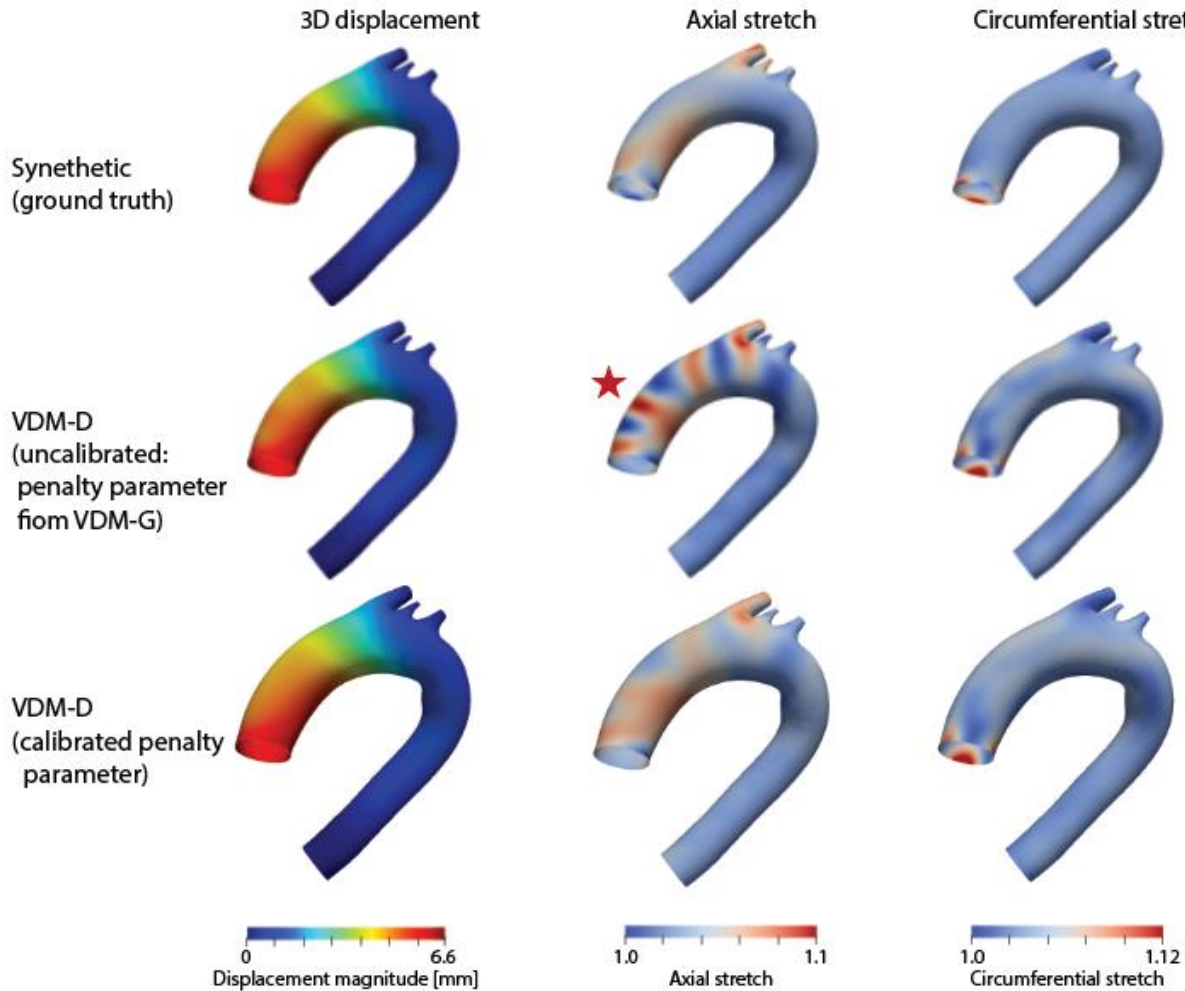


Figure 4.7. 3D displacement and multi-axial stretch comparison between ground truth and VDM-D results with different penalty parameter values: uncalibrated which used penalty parameters from VDM-G and calibrated using our pipeline.

4.4.2 Penalty parameter choice: disease-specific vs motion-specific

In this study, we used two different grouping methods: disease-specific and motion-specific. The disease-specific method categorized patients into non-aneurysmal, TAA, and Marfan groups. Again, non-aneurysmal and TAA patients were classified based on a maximum diameter threshold of 40 mm, without any syndromic features and no family history of aortic diseases. The aortic diameter was collected from clinical radiology reports. Marfan patients were classified using the Ghent criteria, which incorporate aortic root dilatation and FBN1 mutations in the diagnosis [36], [37]. The challenges of using maximum diameter for diagnosing TAA include inaccurate diameter measurement and the subjective choice of diameter threshold, which ranges from 40 to 60 mm [38], [39], [40], [41], [42]. This approach is dependent on the clinician's subjective judgment and leads to uncertainties in distinguishing between non-aneurysmal and TAA patients. Also, dynamic images can only capture the shape and motion of aorta, and not genetic disease. In contrast, root motion provides an objective metric. However, the primary challenge with using root motion for the patient classification is selecting the appropriate threshold between different groups. The k-mean clustering technique offers an objective threshold based on the given data. Since disease-specific and motion-specific penalty parameters showed similar performance (see Figure 5), we chose to use motion-specific method due to its more objective grouping approach. The similar performance of disease-specific and motion-specific penalty parameters may be attributed to the fact that the disease groups inherently exhibit different root motions in our cohorts. The average root motions for the non-aneurysmal, TAA, and Marfan groups are 7.4 (± 1.0), 5.3 (± 1.0), and 8.0 (± 3.1) mm, respectively (p-value: 0.063, using ANOVA test). This difference in root motion might already influence the values of disease-specific penalty parameters.

4.4.3 Correlation between penalty parameter and root motion

Motion-specific penalty parameters correlate with root motion, where clusters with smaller root motion need larger penalty parameter values (see Table 4.2). Smaller root motion results in more rigid deformation of aorta between diastole and systole. The penalty parameters we used in this study add rigidity to the deformable image registration. A larger rigidity penalty imposes a stronger constraint on deformation, favoring more rigid alignments, which is appropriate for the small root motion. In contrast, a lower rigidity penalty allows for more flexibility, enabling the registration algorithm to accommodate larger or more complex motions, including non-rigid deformations. This is useful when aligning images that undergo large changes in shape or when

there is significant motion like large root motion [43], [44]. This flexibility from using different penalty parameter values is particularly important for aortic image registration, as the thoracic aorta experiences a wide range of deformations influenced by root motion, varying with age and disease [7].

4.4.4 Correlation between error and root motion

The error also correlates with root motion. For in-depth analysis, we split the 3D root motion into axial and in-plane directions [7]. The axial motion is defined as the projection of the 3D root motion in the direction of the tangential of the centerline. Conversely, the in-plane motion is defined as the projection of the 3D root motion in the direction perpendicular to the centerline (see Figure 4.8). Different motion values are provided in Table 4.3. The average root motions are 6.79 (± 2.48), 5.41(± 2.13), and 4.41(± 1.78) mm, for the 3D, axial, and in-plane direction, respectively.

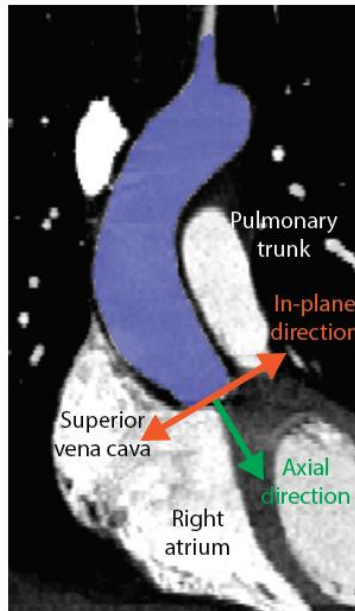


Figure 4.8. Axial and in-plane directions of the root motion with anatomies near aorta.

Figure 4.9 illustrates the nine different correlations between error and various root motions. Correlations between variables were assessed using linear regression. A p-value < 0.05 was considered indicative of a strong correlation. The ‘kruskalwallis’ and ‘fitlm’ functions in MATLAB were used for the Kruskal–Wallis test and linear regression, respectively. Plots (a), (b), and (c) show the correlations between errors from VDM-D without using penalty parameters and three types of root motion.

Table 4.3. 3D, axial, and in-plane root motions for all patients

	3D root motion [mm]	Axial root motion [mm]	In-plane root motion [mm]
NA 1	7.1	6.32	3.21
NA 2	6.6	5.81	4.72
NA 3	8.6	5.51	6.95
TAA 1	6.9	4.97	5.20
TAA 2	3.0	2.57	1.82
TAA 3	3.8	2.02	3.68
TAA 4	4.8	4.35	2.13
TAA 5	6.5	5.09	4.57
TAA 6	7.0	5.59	4.28
Marfan 1	10.0	8.06	7.81
Marfan 2	3.0	2.28	2.26
Marfan 3	8.4	7.38	4.51
Marfan 4	11.1	9.27	6.23
Marfan 5	7.6	6.56	4.44

There is a strong negative correlation with 3D root motion and axial motion, with p-values of 0.034 and 0.031, respectively, while no significant correlation is observed with in-plane motion. These results suggest that VDM-D without penalty parameters can effectively register two aortas with large deformations, while it does not have enough rigidity to accurately capture small deformations. These correlations are particularly strong in the ATA region (see Figure 4.3 (b)). Plots (d), (e), and (f) depict the correlation between errors, which were calculated only for the ATA region using VDM-D without penalty parameters, and three types of root motions. These plots demonstrate smaller p-values and larger magnitudes of R values than those in plots (a), (b), and (c). This indicates that the effect of root motion is stronger in the ATA than in the arch and DTA regions. In-plane root motion shows weaker correlations with error (p-values > 0.05) compared to 3D and axial root motions. This can be attributed to the relatively smaller magnitude on in-plane motion and its easier capture by VDM-D, as the aorta is surrounded by other structures such as the superior vena cava, right atrium, and pulmonary trunk in the in-plane direction (see Figure 4.8).

The correlations between error and root motion are gone with VDM-D results with properly calibrated penalty parameters. Plots (g), (h), and (i) illustrate the correlations between errors from VDM-D using penalty parameters and three types of root motion. No correlation is observed on

these results ($p\text{-value} > 0.05$). It demonstrates that the VDM-D with motion-specific penalty parameters can effectively capture both large and small deformations.

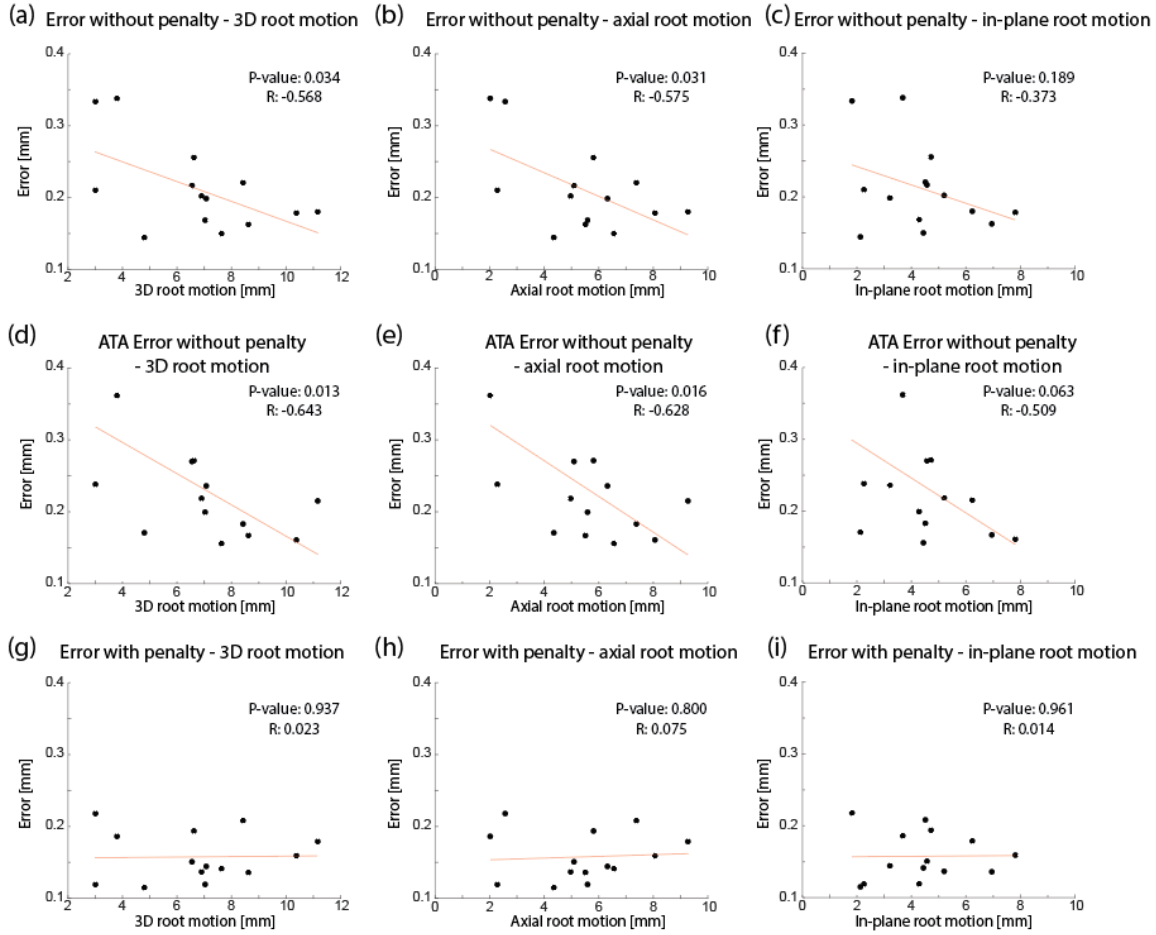


Figure 4.9. Correlations between errors and three types of root motion. (a), (b), (c): Error without penalty. (d), (e), (f): ATA Error without penalty. (g), (h), (i): Error with penalty. (Red line shows the line of the regression).

4.4.5 Homogenous penalty parameter

In this study, we implemented the homogenous penalty parameters. However, different aortic regions experience varied deformations. Figure 4.10 (a) shows the 3D displacement field on the aortic surface, where the ATA, arch, and DTA regions exhibit displacement ranges of 4~7 mm, 2~4 mm, and 0~2 mm, respectively. This variation in displacement distribution originates from root motion. In this study, we showed the correlation between optimal penalty parameters and aortic motion. Since we used homogenous penalty parameters on aorta with heterogenous motion, different regions exhibited different levels of error reduction. Figure 4.10 (b) demonstrates the 3D displacement error between the ground truth and VDM-D, both with and without penalty parameters. With penalty applied, the maximum displacement error in the ATA region decreased

from 0.346 mm to 0.181 mm (47% decrease), while the arch and DTA region decreased from 0.320 mm to 0.282 mm (11.8% decrease) and 0.225 mm to 0.200 mm (11.1% decrease), respectively. The penalty parameter tuned for large motion is effective for the ATA, where large deformation occurs, but shows lower performance in the arch and DTA regions, where relatively smaller deformation occurs.

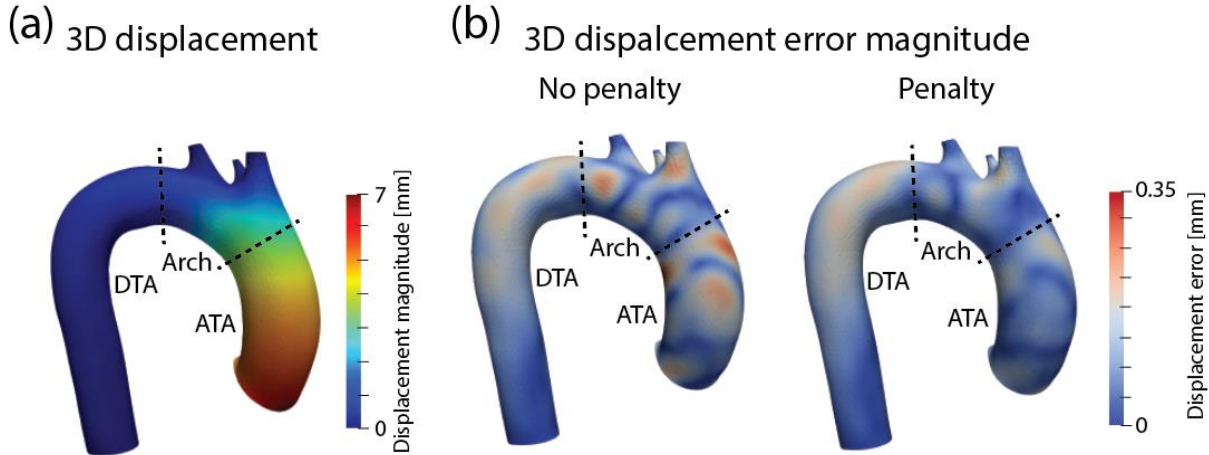


Figure 4.10. (a) 3D displacement and (b) 3D displacement error with and without penalty parameters for the ATA, arch, and DTA regions.

4.4.6 Limitations

One limitation of this study is the small number of subjects in our cohort. The thresholds used to categorize patients into motion-specific groups were determined using the k-means clustering technique. Because these thresholds (5 and 9 mm) were calculated based on a limited dataset, they may differ in larger, real-world cohorts. Additionally, the motion-specific penalty parameters for each cluster were calibrated with a small number of patients, which may not accurately represent broader populations. This study focused on the development of a penalty parameter calibration pipeline. Future studies will aim to expand the sample size, allowing for the determination of root motion thresholds and penalty parameters that are more representative of real cohorts.

The current VDM-D can only utilize homogeneous penalty parameters. However, our results demonstrate that the values of these parameters correlate with the magnitude of motion. Since the aorta exhibits heterogeneous motion, it is not feasible to find a single set of homogeneous penalty parameters that performs well across all aortic regions.

4.4.7 Future works

Aortic Stiffness Estimation: Once the 3D VDM-derived aortic displacement is available, it is possible to extract multi-axial aortic strain. Assuming a choice of non-linear and multi-axial constitute model, such as four-fiber family model [45], strains can be calculated using a nonlinear rotation-free shell and compared with VDM-derived strains over the entire aorta. This approach would make it possible to determine both axial and circumferential aortic stiffness in a non-invasive way.

4.5 Conclusion

In this study, we successfully calibrated penalty parameters for deformable image registration in VDM-D using physics-based synthetic data from the rotation-free shell formulation. I developed the VDM-D parameter calibration pipeline including synthetic data generation. By tailoring these parameters for each cluster categorized by root motion, we identified that clusters with smaller root motion require larger penalty parameters. These calibrated parameters effectively reduced errors in 3D displacement and multi-axial stretch. Our results demonstrate the importance of customized parameter settings in improving the accuracy of aortic deformation analysis. Multi-directional strain from VDM-D can be used for non-invasive estimation for anisotropic aortic stiffness.

4.6 Bibliography

- [1] J. P. Vande Geest, M. S. Sacks, and D. A. Vorp, ‘Age Dependency of the Biaxial Biomechanical Behavior of Human Abdominal Aorta’, *J Biomech Eng*, vol. 126, no. 6, pp. 815–822, Dec. 2004, doi: 10.1115/1.1824121.
- [2] J. P. Vande Geest, M. S. Sacks, and D. A. Vorp, ‘The effects of aneurysm on the biaxial mechanical behavior of human abdominal aorta’, *J Biomech*, vol. 39, no. 7, pp. 1324–1334, Jan. 2006, doi: 10.1016/J.JBIOMECH.2005.03.003.
- [3] J. F. Rodríguez, C. Ruiz, M. Doblaré, and G. A. Holzapfel, ‘Mechanical stresses in abdominal aortic aneurysms: Influence of diameter, asymmetry, and material anisotropy’, *J Biomech Eng*, vol. 130, no. 2, Apr. 2008, doi: 10.1115/1.2898830/452499.
- [4] M. Asgari, N. Latifi, F. Giovanniello, H. D. Espinosa, and M. Amabili, ‘Revealing Layer-Specific Ultrastructure and Nanomechanics of Fibrillar Collagen in Human Aorta via Atomic

- Force Microscopy Testing: Implications on Tissue Mechanics at Macroscopic Scale', *Adv Nanobiomed Res*, vol. 2, no. 5, p. 2100159, May 2022, doi: 10.1002/ANBR.202100159.
- [5] R. H. Mackey et al., 'Correlates of aortic stiffness in elderly individuals: a subgroup of the cardiovascular health study', *Am J Hypertens*, vol. 15, no. 1, pp. 16–23, Jan. 2002, doi: 10.1016/S0895-7061(01)02228-2.
- [6] J. L. Cavalcante, J. A. C. Lima, A. Redheuil, and M. H. Al-Mallah, 'Aortic Stiffness: Current Understanding and Future Directions', *J Am Coll Cardiol*, vol. 57, no. 14, pp. 1511–1522, Apr. 2011, doi: 10.1016/J.JACC.2010.12.017.
- [7] T. Kim et al., 'Three-Dimensional Characterization of Aortic Root Motion by Vascular Deformation Mapping', *Journal of Clinical Medicine* 2023, Vol. 12, Page 4471, vol. 12, no. 13, p. 4471, Jul. 2023, doi: 10.3390/JCM12134471.
- [8] S. F. Vatner, J. Zhang, C. Vyzas, K. Mishra, R. M. Graham, and D. E. Vatner, 'Vascular Stiffness in Aging and Disease', *Front Physiol*, vol. 12, p. 762437, Dec. 2021, doi: 10.3389/FPHYS.2021.762437/XML/NLM.
- [9] S. Sethi, O. Rivera, R. Oliveros, and R. Chilton, 'Aortic stiffness: Pathophysiology, clinical implications, and approach to treatment', *Integr Blood Press Control*, vol. 7, no. 1, pp. 29–34, May 2014, doi: 10.2147/IBPC.S59535.
- [10] J. A. Chirinos, P. Segers, T. Hughes, and R. Townsend, 'Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review', *J Am Coll Cardiol*, vol. 74, no. 9, pp. 1237–1263, Sep. 2019.
- [11] A. De Wit, K. Vis, and R. W. Jeremy, 'Aortic Stiffness in Heritable Aortopathies: Relationship to Aneurysm Growth Rate', *Heart Lung Circ*, vol. 22, no. 1, pp. 3–11, Jan. 2013, doi: 10.1016/J.HLC.2012.08.049.
- [12] S. Peterson et al., 'Regional differences in biomechanical properties of the ascending aorta in aneurysmal and normal aortas', *Biomech Model Mechanobiol*, pp. 1–13, Apr. 2025, doi: 10.1007/S10237-025-01941-Y/TABLES/8.
- [13] E. Durbak et al., 'Ex vivo biaxial load testing analysis of aortic biomechanics demonstrates variation in elastic energy distribution across the aortic zone zero', *Journal of Thoracic and Cardiovascular Surgery*, vol. 166, no. 3, pp. 701–712.e7, Sep. 2023, doi: 10.1016/j.jtcvs.2021.09.071.

- [14] T. Sigaeva, S. Polzer, R. Vitásek, and E. S. Di Martino, ‘Effect of testing conditions on the mechanical response of aortic tissues from planar biaxial experiments: Loading protocol and specimen side’, *J Mech Behav Biomed Mater*, vol. 111, p. 103882, Nov. 2020, doi: 10.1016/J.JMBBM.2020.103882.
- [15] D. Mohan and J. W. Melvin, ‘Failure properties of passive human aortic tissue. II—Biaxial tension tests’, *J Biomech*, vol. 16, no. 1, pp. 31–44, Jan. 1983, doi: 10.1016/0021-9290(83)90044-1.
- [16] P. Salvi et al., ‘Noninvasive Estimation of Aortic Stiffness Through Different Approaches: Comparison with Intra-Aortic Recordings’, *Hypertension*, vol. 74, no. 1, pp. 117–129, Jul. 2019
- [17] Y. Oishi, Y. Mizuguchi, H. Miyoshi, A. Iuchi, N. Nagase, and T. Oki, ‘A Novel Approach to Assess Aortic Stiffness Related to Changes in Aging Using a Two-Dimensional Strain Imaging’, *Echocardiography*, vol. 25, no. 9, pp. 941–945, Oct. 2008, doi: 10.1111/J.1540-8175.2008.00725.X.
- [18] M. Hrabak-Paar et al., ‘Variability of mri aortic stiffness measurements in a multicenter clinical trial setting: Intraobserver, interobserver, and intracenter variability of pulse wave velocity and aortic strain measurement’, *Radiol Cardiothorac Imaging*, vol. 2, no. 2, Apr. 2020, doi: 10.1148/RYCT.2020190090/ASSET/IMAGES/LARGE/RYCT.2020190090.TBL3.JPEG.
- [19] N. S. Burris, B. A. Hoff, H. J. Patel, E. A. Kazerooni, and B. D. Ross, ‘Three-Dimensional Growth Analysis of Thoracic Aortic Aneurysm With Vascular Deformation Mapping’, *Circ Cardiovasc Imaging*, vol. 11, no. 8, p. e008045, Aug. 2018, doi: 10.1161/CIRCIMAGING.118.008045/SUPPL_FILE/CIRCCVIM_CIRCCVIM-2018-008045_SUPP2.PDF.
- [20] N. S. Burris et al., ‘Vascular Deformation Mapping for CT Surveillance of Thoracic Aortic Aneurysm Growth’, *Radiology*, vol. 302, no. 1, pp. 218–225, Jan. 2022, doi: 10.1148/RADIOL.2021210658/ASSET/IMAGES/LARGE/RADIOL.2021210658.FIG6.JPEG.
- [21] S. Klein, M. Staring, K. Murphy, M. A. Viergever, and J. P. W. Pluim, ‘Elastix: A toolbox for intensity-based medical image registration’, *IEEE Trans Med Imaging*, vol. 29, no. 1, pp. 196–205, Jan. 2010, doi: 10.1109/TMI.2009.2035616.
- [22] M. Staring, S. Klein, and J. P. W. Pluim, ‘A rigidity penalty term for nonrigid registration’, *Med Phys*, vol. 34, no. 11, pp. 4098–4108, 2007, doi: 10.1118/1.2776236.

- [23] Z. Bian, J. Zhong, J. Dominic, G. E. Christensen, C. R. Hatt, and N. S. Burris, ‘Validation of a robust method for quantification of three-dimensional growth of the thoracic aorta using deformable image registration’, *Med Phys*, vol. 49, no. 4, pp. 2514–2530, Apr. 2022, doi: 10.1002/MP.15496.
- [24] S. D. Singh, X. Y. Xu, J. R. Pepper, C. Izgi, T. Treasure, and R. H. Mohiaddin, ‘Effects of aortic root motion on wall stress in the Marfan aorta before and after personalised aortic root support (PEARS) surgery’, *J Biomech*, vol. 49, no. 10, pp. 2076–2084, Jul. 2016, doi: 10.1016/J.JBIOMECH.2016.05.011.
- [25] J. A. Elefteriades, S. K. Mukherjee, and H. Mojibian, ‘Discrepancies in Measurement of the Thoracic Aorta: JACC Review Topic of the Week’, *J Am Coll Cardiol*, vol. 76, no. 2, pp. 201–217, Jul. 2020, doi: 10.1016/J.JACC.2020.03.084;PAGEGROUP:STRING:PUBLICATION.
- [26] C. J. Beller, M. R. Labrosse, M. J. Thubrikar, and F. Robicsek, ‘Role of Aortic Root Motion in the Pathogenesis of Aortic Dissection’, *Circulation*, vol. 109, no. 6, pp. 763–769, Feb. 2004, doi: 10.1161/01.CIR.0000112569.27151.F7/ASSET/7F00F1B9-2571-4765-91E7-4EA1704D7223/ASSETS/GRAPHIC/16FF6.JPEG.
- [27] X. Yuan, X. Kan, Z. Dong, X. Y. Xu, and C. A. Nienaber, ‘Nonsurgical Repair of the Ascending Aorta: Why Less Is More’, *Journal of Clinical Medicine* 2023, Vol. 12, Page 4771, vol. 12, no. 14, p. 4771, Jul. 2023, doi: 10.3390/JCM12144771.
- [28] D. Rueckert, ‘Nonrigid registration using free-form deformations: Application to breast mr images’, *IEEE Trans Med Imaging*, vol. 18, no. 8, pp. 712–721, 1999, doi: 10.1109/42.796284.
- [29] N. Nama, M. Aguirre, J. D. Humphrey, and C. A. Figueroa, ‘A nonlinear rotation-free shell formulation with prestressing for vascular biomechanics’, *Sci Rep*, vol. 10, no. 1, pp. 1–17, Dec. 2020, doi: 10.1038/S41598-020-74277-5;SUBJMETA=1041,166,639,705,985;KWRD=APPLIED+MATHEMATICS,BIOMEDICAL+ENGINEERING.
- [30] B. Mensel et al., ‘MRI-based determination of reference values of thoracic aortic wall thickness in a general population’, *Eur Radiol*, vol. 24, no. 9, pp. 2038–2044, May 2014, doi: 10.1007/S00330-014-3188-8/TABLES/4.
- [31] A. E. Li et al., ‘Using MRI to Assess Aortic Wall Thickness in the Multiethnic Study of Atherosclerosis: Distribution by Race, Sex, and Age’, *American Journal of Roentgenology*, vol.

182, no. 3, pp. 593–597, Nov. 2004, doi:

10.2214/AJR.182.3.1820593/ASSET/IMAGES/AD0331_04_EPS.JPEG.

[32] S. Roccabianca, C. A. Figueroa, G. Tellides, and J. D. Humphrey, ‘Quantification of regional differences in aortic stiffness in the aging human’, *J Mech Behav Biomed Mater*, vol. 29, pp. 618–634, Jan. 2014, doi: 10.1016/J.JMBBM.2013.01.026.

[33] M. H. Davis, A. Khotanzad, D. P. Flamig, and S. E. Harms, ‘A physics-Based coordinate transformation for 3-D image matching’, *IEEE Trans Med Imaging*, vol. 16, no. 3, pp. 317–328, 1997, doi: 10.1109/42.585766.

[34] A. Rosset, L. Spadola, and O. Ratib, ‘OsiriX: An open-source software for navigating in multidimensional DICOM images’, *J Digit Imaging*, vol. 17, no. 3, pp. 205–216, Sep. 2004, doi: 10.1007/S10278-004-1014-6/FIGURES/7.

[35] D. Pelleg and A. Moore, ‘Accelerating exact k -means algorithms with geometric reasoning’, pp. 277–281, Aug. 1999, doi: 10.1145/312129.312248.

[36] N. M. Ammash, T. M. Sundt, and H. M. Connolly, ‘Marfan Syndrome—Diagnosis and Management’, *Curr Probl Cardiol*, vol. 33, no. 1, pp. 7–39, Jan. 2008, doi: 10.1016/J.CPCARDIOL.2007.10.001.

[37] D. M. Milewicz et al., ‘Marfan syndrome’, *Nat Rev Dis Primers*, vol. 7, no. 1, pp. 1–24, Dec. 2021

[38] M. A. Coady et al., ‘What is the appropriate size criterion for resection of thoracic aortic aneurysms?’, *J Thorac Cardiovasc Surg*, vol. 113, no. 3, pp. 476–491, Mar. 1997, doi: 10.1016/S0022-5223(97)70360-X.

[39] E. M. Isselbacher, ‘Thoracic and abdominal aortic aneurysms’, *Circulation*, vol. 111, no. 6, pp. 816–828, Feb. 2005, doi: 10.1161/01.CIR.0000154569.08857.7A/ASSET/7D045A06-0730-4E2E-8A9F-B62156A68819/ASSETS/GRAPHIC/18FF12.JPEG.

[40] O. E. Dapunt et al., ‘The natural history of thoracic aortic aneurysms’, *J Thorac Cardiovasc Surg*, vol. 107, no. 5, pp. 1323–1333, May 1994, doi: 10.1016/S0022-5223(94)70054-0.

[41] J. A. Elefteriades and E. A. Farkas, ‘Thoracic Aortic Aneurysm: Clinically Pertinent Controversies and Uncertainties’, *J Am Coll Cardiol*, vol. 55, no. 9, pp. 841–857, Mar. 2010, doi: 10.1016/J.JACC.2009.08.084.

- [42] A. M. Booher and K. A. Eagle, ‘Diagnosis and management issues in thoracic aortic aneurysm’, *Am Heart J*, vol. 162, no. 1, pp. 38-46.e1, Jul. 2011, doi: 10.1016/J.AHJ.2011.04.010.
- [43] M. Wang and P. Li, ‘A Review of Deformation Models in Medical Image Registration’, *J Med Biol Eng*, vol. 39, no. 1, pp. 1–17, Feb. 2019, doi: 10.1007/S40846-018-0390-1/TABLES/2.
- [44] B. Glocker, A. Sotiras, N. Komodakis, and N. Paragios, ‘Deformable medical image registration: Setting the state of the art with discrete methods’, *Annu Rev Biomed Eng*, vol. 13, no. Volume 13, 2011, pp. 219–244, Aug. 2011, doi: 10.1146/ANNUREV-BIOENG-071910-124649/CITE/REFWORKS.
- [45] J. Ferruzzi, D. A. Vorp, and J. D. Humphrey, ‘On constitutive descriptors of the biaxial mechanical behaviour of human abdominal aorta and aneurysms’, *J R Soc Interface*, vol. 8, no. 56, pp. 435–450, Mar. 2011, doi: 10.1098/RSIF.2010.0299;WEBSITE:WEBSITE:RSJ-SITE;WGROUP:STRING:PUBLICATION.

Chapter 5 A Computational Study of Dynamic Obstruction in Type B Aortic Dissection

This chapter is adapted from a peer-reviewed publication of this work:

<https://doi.org/10.1115/1.4056355>⁴.

5.1 Introduction

5.1.1 Clinical background

Thoracic aortic dissection (TAD) is characterized by a disruption of the intima, which leads to delamination of the aortic wall and creation of a true lumen (TL) and a false lumen (FL) [1]. Population based studies have estimated that TAD occurs at a rate of 3-4 cases per 100,000 people per year [2,3]. TAD is commonly categorized using the Stanford classification, which distinguishes between type A aortic dissection, involving the ascending aorta, and type B aortic dissection (TBAD) which only involves the descending aorta [4]. One of the most dramatic complications of TAD is end-organ malperfusion, which is present in approximately 30% of type A aortic dissection and 20% of TBAD patients [5-7] and is associated with high morbidity and mortality [8-9]. Malperfusion is defined as inadequate flow to a vascular territory; if left untreated, it could result in malperfusion syndrome, which includes further complications such as tissue necrosis and end-organ dysfunction. Vessel malperfusion is caused by either dynamic obstruction, static obstruction, or a combination of both. Static obstruction occurs when the intimal flap extends into the branch vessel and causes fixed stenosis of the TL [10]. However, the pathophysiology of dynamic obstruction is more complex. Clinically, we have observed two main drivers of dynamic obstruction. One is the high-pressure-related collapse described in this paper. The second is the abrupt relief of outflow obstruction and increase of TL outflow observed after restoration of flow by aortoiliac stenting can impose collapse of the infrarenal aorta TL. Stenting that segment can in turn cause collapse of the TL supplying the celiac and superior mesenteric artery (SMA). Focused

⁴ The authors of this manuscript are: Taeouk Kim, Petrus Antonius Jacobus van Bakel, Nitesh Nama, Nicholas Burris, Himanshu Jagdish Patel, David M Williams, and C Alberto Figueroa.

on the first case, we hypothesized that dynamic obstruction is driven by FL pressure exceeding TL pressure, causing the flap to drape over the ostium of a branch vessel supplied by the TL and thus obstruct blood flow.

While dynamic obstruction has been reported in prior clinical studies, the factors driving this phenomenon remain unknown, largely due to the challenges of assessing pressure in TL and FL during dynamic obstruction, at a time when restoration of normal branch-artery perfusion pressures is the highest clinical priority. Computational simulations can be used to shed light into this phenomenon via in-silico investigations of the intimal flap motion and its relation to the pressure gradient across TL and FL.

5.1.2 Clinical example of dynamic obstruction

A 36-year-old hypertensive female in renal failure (blood pressure 170/80, creatinine 4.2 mg/dL) presented with TBAD. To correct hypertension, intravenous hydralazine and esmolol were administered. To determine whether there was a treatable anatomical cause of hypertension, angiograph and intravascular ultrasound examinations were performed. Intra-luminal blood pressure was assessed in the FL using an arterial catheter. Aortic root pressure was compared with abdominal aorta TL, visceral, and iliac artery pressures. Aortic root and abdominal TL pressures were both 90/50 and the TL was approximately $\frac{1}{4}$ of the total aortic cross-section (Figure 5.1A).

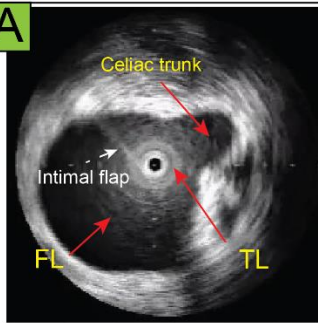
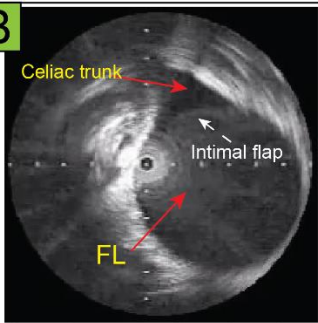
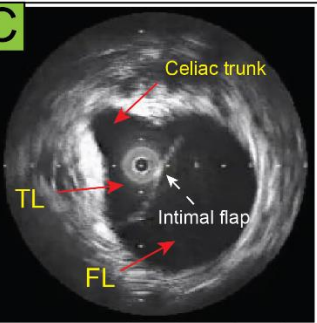
IVUS	A			B			C		
									
	TL Status		Patent TL	TL obstructed (Dynamic obstruction)			Recovered TL patency		
	Treatment		Esmolol infusion	Esmolol discontinued. Hypotension treated medically and patient intubated			Esmolol infusion resumed		
	Time [h:min]		19:14	20:40			20:53		
P [mmHg]		90/50		159/83				93/53	

Figure 5.1. Timeline of dynamic obstruction and blood pressure during baseline infusion of esmolol. (A) following discontinuation of esmolol and after intubation. (B) and after vasodilator infusion and esmolol resumption. (C) TL = true lumen, FL = false lumen, and P = abdominal aorta TL blood pressure.

No pressure deficits were present in the celiac trunk or SMA, renal artery systolic pressure deficits (compared to the aortic root and measured distal to dissection reentry tears) were 70 mm Hg on the right and 15 mmHg on the left. While the operators were preparing to stent the right renal artery, the patient became hypoxic and developed sinus bradycardia with oxygen saturation in the low 80s and a heart rate of 46 bpm. In view of impending respiratory arrest, esmolol was stopped, fluids were administered, and a medical code was called. The code team administered Romazicon (a sedative reversal agent) and atropine (to increase heart rate) and intubated the patient. After fluids and discontinuation of esmolol, cuff blood pressure rose to 110/50, further increasing to 200/102 after intubation. Intravascular ultrasound examination while abdominal aorta TL blood pressure was 159/83 demonstrated TL collapse with the intimal flap draped over and prolapsing into the ostia of the celiac trunk and SMA (Figure 5.1 B). Esmolol was subsequently restarted resulting in normalization of blood pressure (93/53 mmHg) and displacement of the flap away from the branch vessel ostia, re-establishing flow to the abdominal aorta TL, celiac trunk, and SMA (Figure 5.1 C).

5.1.3 Previous computational studies on the aortic dissection

No computational study has thus far investigated aortic dynamic obstruction and malperfusion. Previous contributions have been focused on characterizing complex hemodynamics in aortic dissection, often using patient-specific models with rigid wall assumptions. Some studies have investigated the effects of anti-hypertension medication on hemodynamic parameters [11,12]. Other studies have explored the factors determining FL thrombosis and retrograde aortic dissection [13,14]. Healthy and acutely dissected aortas were compared to understanding the effects of dissection geometry on aortic hemodynamics [15]. Other studies have focused on the effect of connecting tears, including tear size and location [16]. Re-entry tears were also found to have a large effect on pressure and flow distributions between the TL and FL [15]. Other anatomical risk factors such as curvature were also investigated for type B aortic dissection using idealized models [17]. Rigid wall models were also used to quantify the pressure difference between the TL and FL. This difference was found to be smaller than 20 mmHg in a patient-specific analysis [18].

A rigid wall representation of the intimal flap assumes fixed flap position, and therefore is unsuitable to relate flap motion with pressure gradient between TL and FL. Noting this, fluid-structure-interaction (FSI) models have been used in aortic dissection simulations to investigate

the effect of the intimal flap motion on hemodynamic parameters. Compared to analyses under rigid wall assumptions, FSI simulations are challenging because of the high complexity and computational cost of the problem, which deal with the coupled motion to the fluid and solid [19,20]. An FSI model with rigid intimal flap calculated a peak systolic 30 mmHg pressure difference between TL and FL [20]. Several studies focused on studying the differences in wall shear stress between rigid wall and FSI simulations [19,21].

Lastly, intimal flap motion was investigated in several studies. Several studies reported small flap displacements (0.15 – 1 mm) after imposing different levels of pressure difference between TL and FL [19,22,23]. More recently, another study investigated the impact of intimal flap material stiffness on flap displacement. Imposing a 5 mmHg pressure difference between TL and FL, flap displacement varied from 1.4 mm to 13.4 mm as the flap material stiffness varied from 20 kPa to 800 kPa, respectively [24].

However, to the best of our knowledge, no studies so far have investigated dynamic obstruction and malperfusion caused by flap motion.

5.1.4 Hypothesis and purpose

In this work, we aimed to investigate the biomechanical and hemodynamic factors driving dynamic obstruction in aortic dissection. The above clinical example showed that an increase in systemic blood pressure was associated with dynamic obstruction. Furthermore, pharmacologic management of systemic blood pressure resulted in restoration of TL patency. From a clinical perspective, it is not feasible to assess TL and FL pressure during dynamic obstruction. In this study, we hypothesized that relatively small pressure differentials between the TL and FL are sufficient to displace the flap and induce obstruction because of the highly compliant nature of the intimal flap, concurrent with a global increase in systemic blood pressure. To test this hypothesis, we developed an FSI model of dynamic obstruction in TBAD, whereby inducing dynamic changes in systemic blood pressure were triggered by altering FL outflow resistance.

5.2 Methods

5.2.1 Geometrical model

An idealized 3D geometrical model of a TBAD was constructed (Figure 5.2). The model consists of fluid and solid domains (noted in red and blue, respectively). The fluid domain consists of the aorta and main branch vessels. The uniform aortic diameter and length are 30 and 173 mm,

respectively. The model includes the ascending thoracic aorta, descending thoracic aorta, and abdominal aorta. The branch vessels include the brachiocephalic trunk (BCT), left common carotid artery (LCCA), left subclavian artery (LSA), and right and left renal arteries (RRA and LRA). BCT diameter is 10 mm. All other branch vessels have an 8 mm diameter. All branch lengths are 20 mm. The RRA is perfused by the TL and the LRA is perfused by the FL. Thus, from now on, we refer to the RRA and LRA branches as TR and FR branches, respectively.

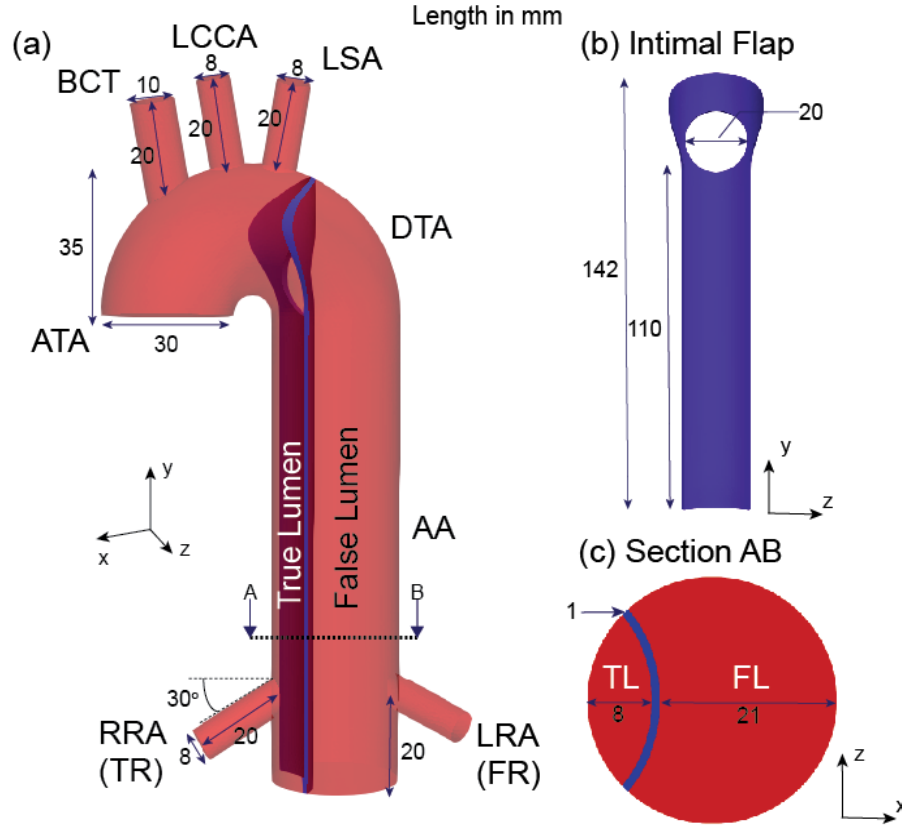


Figure 5.2. Idealized 3D geometrical model of a TBAD. Fluid and solid domains are depicted in red and blue, respectively. Dimensions in mm. ATA: ascending thoracic aorta, DTA: descending thoracic aorta, AA: abdominal aorta.

The solid domain represents the intimal flap (Figure 5.2 (b)). A single 20 mm diameter circular entry tear and no re-entry tears were assumed. The aortic walls were assumed to be rigid. The intimal flap has a 1mm uniform thickness and a total length of 142 mm. The flap has a constant curvature along the axial direction and divides the descending thoracic aorta and abdominal aorta into a TL and a FL with areas of 113 mm^2 and 570 mm^2 , respectively. The distance between the intimal flap and aortic wall of TL and FL are 8mm and 21 mm, respectively (Figure 5.2 (c)).

5.2.2 Governing equations and assumptions

Arbitrary Lagrangian-Eulerian formulation was used for the FSI simulation. Blood was modeled as an incompressible Newtonian fluid, and the intimal flap as a homogenous, isotropic, nearly incompressible Neo-Hookean material. A simple linear elasticity model does not make a good description of deformation with large strain. In order to analyze the large motion of the intimal flap during dynamic obstruction and decrease the computational cost, we used a Neo-Hookean model, which is a simple nonlinear elasticity model. The incompressible Navier-Stokes equations in a moving domain and the elasto-dynamics equations were simultaneously solved in COMSOL Multiphysics 5.6.1, rendering solutions for blood velocity v_{fluid} and pressure p , and intimal flap displacement u_{solid} . Using an Arbitrary Lagrangian-Eulerian formulation, the Navier-Stokes equations are written in a moving mesh that follows the motion of the intimal flap interface (body-fitted mesh). Mesh motion was solved in every time step assuming a Yeoh hyper-elastic constitutive model with boundary conditions that matched the motion intimal flap interface. Blood density ρ and dynamic viscosity μ were set to 1060 kg/m³ and 0.004 Pa·s, respectively. The strain energy density W_s for the intimal flap is:

$$W_s = \frac{1}{2}\mu(I_1 - 3) - \mu \ln(J) + \frac{1}{2}\lambda \ln(J)^2 \quad (5.1)$$

where I_1 is the first invariant of the right Cauchy-Green deformation tensor $\mathbf{C} = \mathbf{F}^T \mathbf{F}$, $J = \det(\mathbf{F})$ is the third invariant of the deformation gradient tensor $\mathbf{F}$, and μ and λ are Lamé parameters

$$= \frac{E}{2(1 + \nu)}, \quad \lambda = \frac{E}{3(1 - 2\nu)} \quad (5.2)$$

where E is the Young's modulus, and ν is the Poisson's ratio. Due to the lack of experimental data, in this study we assumed that the flap is less stiff than the thoracic aorta [25]. The rationale for this assumption is that the inner layer of the aortic wall from where the flap originates consists primarily of elastin fibers, which are more compliant than the collagen fibers more prevalent in outer layers of the aortic wall [26]. Therefore, given that the material stiffness of the descending thoracic aorta and abdominal aorta has been reported as 0.5 - 1 MPa and 1.5 - 2 MPa, respectively [25], we assumed a Young's modulus for the intimal flap of 0.1 MPa. The flap density was set to 1080 kg/m³ and its Poisson's ratio ν to 0.49.

5.2.3 Boundary conditions

A steady-state flow rate ($Q_{in}=6L/min$) boundary condition, mapped to a parabolic profile, was set at the inlet face of the aortic model. Pulsatility was neglected because the time scale of dynamic obstruction is several minutes (Figure 5.1), much longer than the time scale of a single cardiac cycle (~ 1 s). Flow rate conditions were prescribed at BCT, LCCA, and LSA vessel branches (outlets 1 – 3 in Figure 5.3) as a fixed % of the cardiac output: 16.6%, 8.5%, and 8.1%, respectively [27].

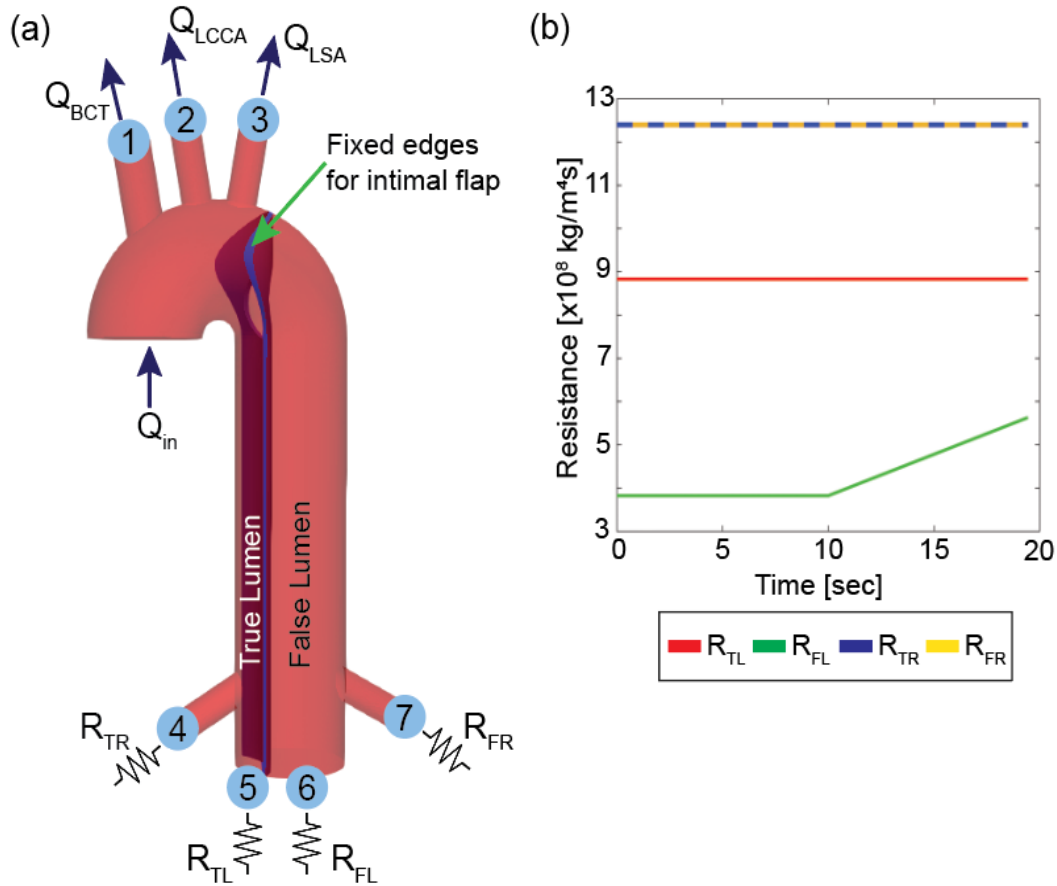


Figure 5.3. (a) Schematic of boundary conditions for the fluid and solid domains. (b) Imposed histories of outlet resistances.

Resistance outlet boundary conditions were set for the TR branch, FR branch, TL, and FL (outlets 4 - 7), (Figure 5.3 (b)). Initial resistance values for each branch were set as $R = \Delta P / Q$, based on $\Delta P = 94$ mmHg for outlets 4-7, and flow rates (Q) of $0.1 Q_{in}$ for TR and FR branches [27], $0.14 Q_{in}$ for TL, and $0.328 Q_{in}$ for FL. This ratio of flows in TL:FL assumes that, initially, 30% of the flow goes through the TL and 70% through the FL. While TR branch, FR branch, and TL resistances were kept constant over time, the FL resistance was dynamically controlled. After

10 seconds, a linear increase of FL resistance was imposed. The increase in FL resistance triggered both a systemic increase in blood pressure and also the intimal flap motion. Table 5.1 summarizes the resistance values used in the simulation. The outer aortic walls were assuming to be rigid.

Lastly, all edges of the solid domain were kept fixed, including the edge at the distal end of the flap, on the outflow face of the computational domain.

Table 5.1. Resistance values used in TR, FR, TL, and FL.

Outlet face	Outlet number	Resistance [$\times 10^8 \text{ kg/m}^4\text{s}$]
TR branch	4	12.40
FR branch	7	12.40
TL	5	8.83
FL	6	$\begin{cases} 3.82, & 0 < t < 10 \text{ s} \\ 0.192t + 1.9, & t > 10 \text{ s} \end{cases}$

5.2.4 Discretization and simulation

The fluid and solid domains were discretized using tetrahedral elements. A second order backward differentiation formula time integration method was used. Mesh independence studies were conducted using three different computational grids containing 0.34 M, 0.67 M, and 1.4 M elements. Convergence was achieved for the quantities of interest (for instance, maximum intimal flap displacement changed by only 4% between the 0.67M and 1.4M element meshes) for the 1.4 M element mesh, which consists of 1,363,198 fluid and 38,323 solid elements and 243,028 fluid and 11,217 solid nodes. FSI simulations were run using COMSOL Multiphysics 5.6.1. The simulation ran for 35 hours on 36 cores of Intel(R) Xeon(R) CPU E5-2699, 124 GB RAM, running Ubuntu 20.04.

5.3 Results

5.3.1 Intimal flap displacement

Figure 5.4 shows plots of intimal flap displacement at the Π plane ($y=18 \text{ mm}$, panel a) and Ω plane ($z=0 \text{ mm}$, panel b) at $t=0 \text{ s}$ and at time $t=19.44 \text{ s}$ (final time, corresponding to the start of dynamic obstruction of the TR branch). The Π plane corresponds to the position of maximum flap displacement for all time points of the simulation. At $t=0 \text{ s}$, the maximum flap displacement is 0.4 mm , TL and TR branch are fully patent, and the areas of TL and FL are 109 mm^2 and 574 mm^2 , respectively.

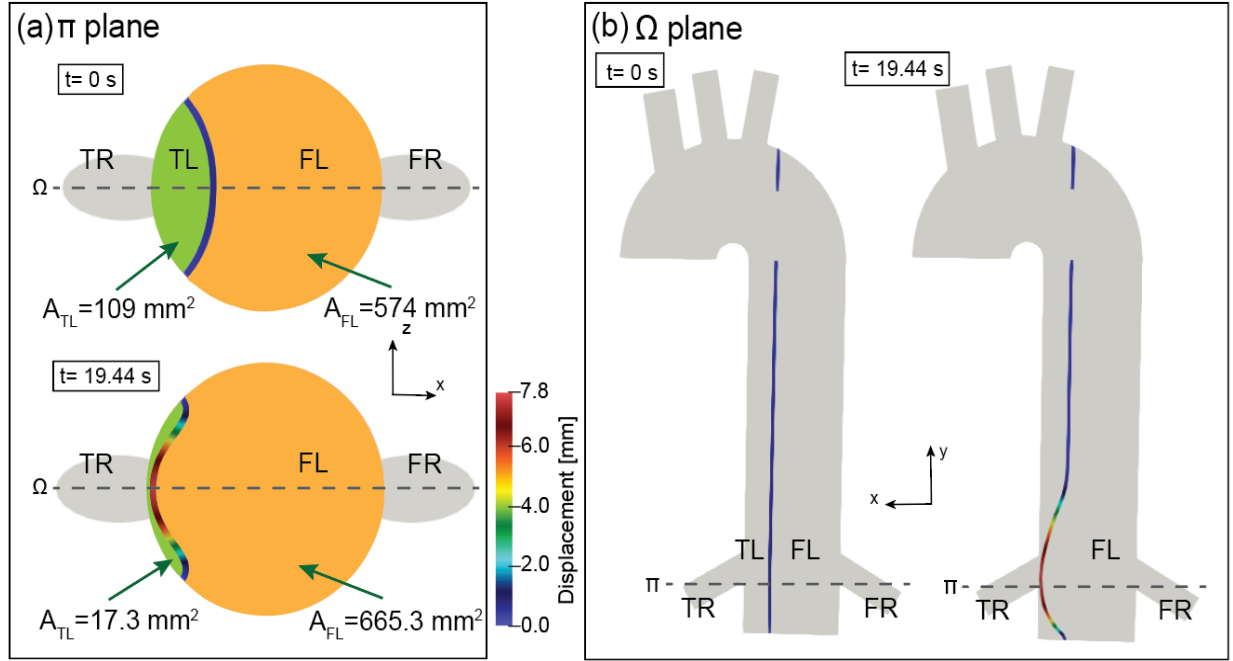


Figure 5.4. Intimal flap displacement at times $t=0$ and $t=19.44$ seconds at (a) Π plane ($y=18\text{mm}$) and (b) Ω plane ($z=0$ mm).

The prescribed dynamic increase in FL resistance increases FL pressure and thus induces a motion of the intimal flap towards the TL wall, ultimately resulting in dynamic obstruction of the TR branch. At the last time step of the analysis ($t=19.44$ s), the maximum intimal flap displacement is 7.8 mm, nearly identical to the initial distance between TL wall and intimal flap of 8 mm (see Figure 5.2 c). The TL and FL area at the final time step are 17.3 mm^2 and 665.3 mm^2 , respectively. The TL area reduction is 84%. Simulations of the intimal flap motion beyond the final time step ($t=19.44$ s) require incorporation of a contact model within our computational framework and were not considered in this study.

5.3.2 Pressure and velocity contours

Figure 5.5 shows contours of pressure (panel a) and velocity (panel b) at $t=0$ s and $t=19.44$ s. At $t=0$ s, mean inflow aortic pressure is 95.7 mmHg, and the pressure difference between FL and TL is smaller than 0.5 mmHg. A region of high pressure is apparent in the FL of the proximal descending aorta, where the high-velocity flow through the tear impinges against the FL wall.

The prescribed increase in FL resistance results in an increase of total systemic resistance and a corresponding increase in systemic blood pressure (since the cardiac output remains constant). The mean inflow aortic pressure at $t=19.44$ s is 115.3 mmHg. Simulation results therefore reproduce a global increase in pressure (from 95.7 mmHg to 115.3 mmHg) as the intimal

flap collapsed onto the TL and occluded the TR branch. This behavior is consistent with the clinical example reported in Figure 5.1.

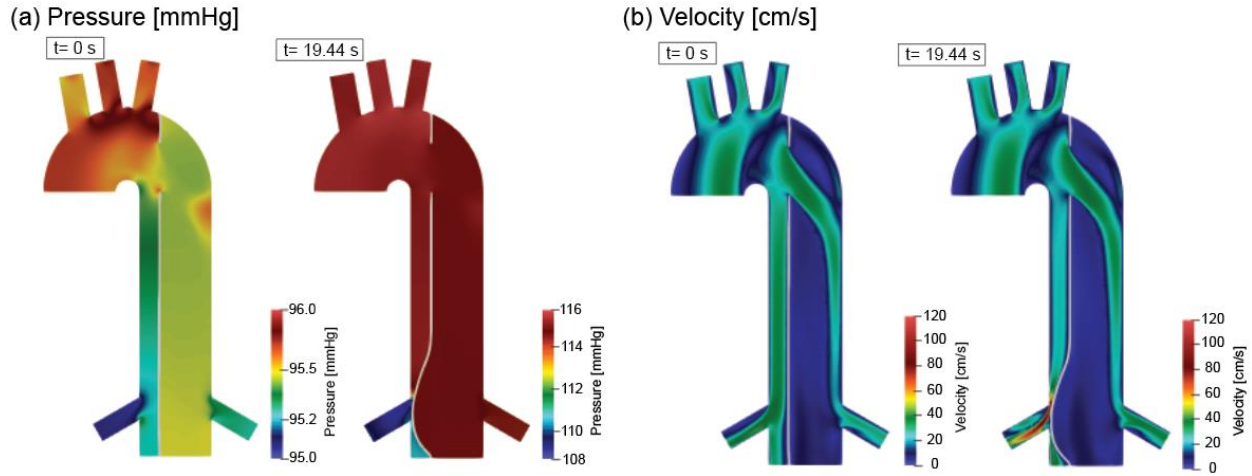


Figure 5.5. (a) Pressure and (b) velocity contour at $t=0$ and $t=19.44$ s.

Furthermore, as the FL resistance and global pressure increased, so did the pressure difference between FL and TL, from 0.5 mmHg at $t=0$ s, to 4.5 mmHg at $t=19.44$ s. This 4.5 mmHg pressure difference is only 3.9 % of the central aortic pressure (115.3 mmHg), and thus challenging to assess in vivo as dynamic obstruction unfolds.

At $t=0$ s, the maximum TL velocity is 42 cm/s. As the intimal flap moves towards the TL wall, the TL area decreases and its velocity increases. A maximum TL velocity of 118.5 cm/s occurs at the gap between the intimal flap and the TL aortic wall at time $t=19.44$ s. The velocity at the ascending thoracic aorta and upper branches remains relatively constant due to the fixed flow rate boundary conditions at BCT, LCCA, and LSA.

5.3.3 History of hemodynamic indices

Figure 5.6 shows temporal plots for resistance, blood pressure and flow rate at TL, FL, and TR and FR branches, in addition to pressure difference between FL and TL and maximum intimal flap displacement at the plane II. Temporal plots show three distinct stages: steady-state (0 – 10 s), development (10 – 19 s), and obstruction (19 – 19.44s). These stages are clearly appreciated in the FL-TL pressure difference (panel c).

During the steady-state stage, resistances at TL, FL, TR and FL are constant and therefore no dynamic changes are observed in the hemodynamics. During the development stage, FL resistance is increased linearly while keeping the other resistances fixed. The displacement of the intimal flap is limited during this stage (see panel e), from 0.4 mm at $t = 10$ s to 2.1 mm at $t = 19$

s. The pressure gradient between FL and TL also mildly increases during this stage, from 0.42 mmHg at $t = 10$ s, to 0.58 mmHg at $t=19$ s (panel c). Due to the prescribed increase in FL resistance, FL flow rate decreases from 1.99 to 1.62 L/min and flow rates through TL, and TR and FR branches increase (panel d).

During the obstruction stage, the intimal flap gets dramatically closer to the TL aortic wall: its displacement increases from 2.1 mm to 7.8 mm in just 0.44 s. At this point, the flap movement causes obstruction of the TL and the TR branch (see Figure 5.4). As a result of the obstruction, there is a sudden drop of pressure and flow rate in the TL and TR branch (Figure 5.6 panel b and d, respectively). Conversely, FL and FR branch flows increase. The increase in FL flow happens despite the continuous (imposed) increase in FL resistance. Pressure difference between FL and TL rapidly increases in the obstruction stage, from 0.58 mmHg at $t = 19$ s, to 4.5 mmHg at $t=19.44$ s (panel c).

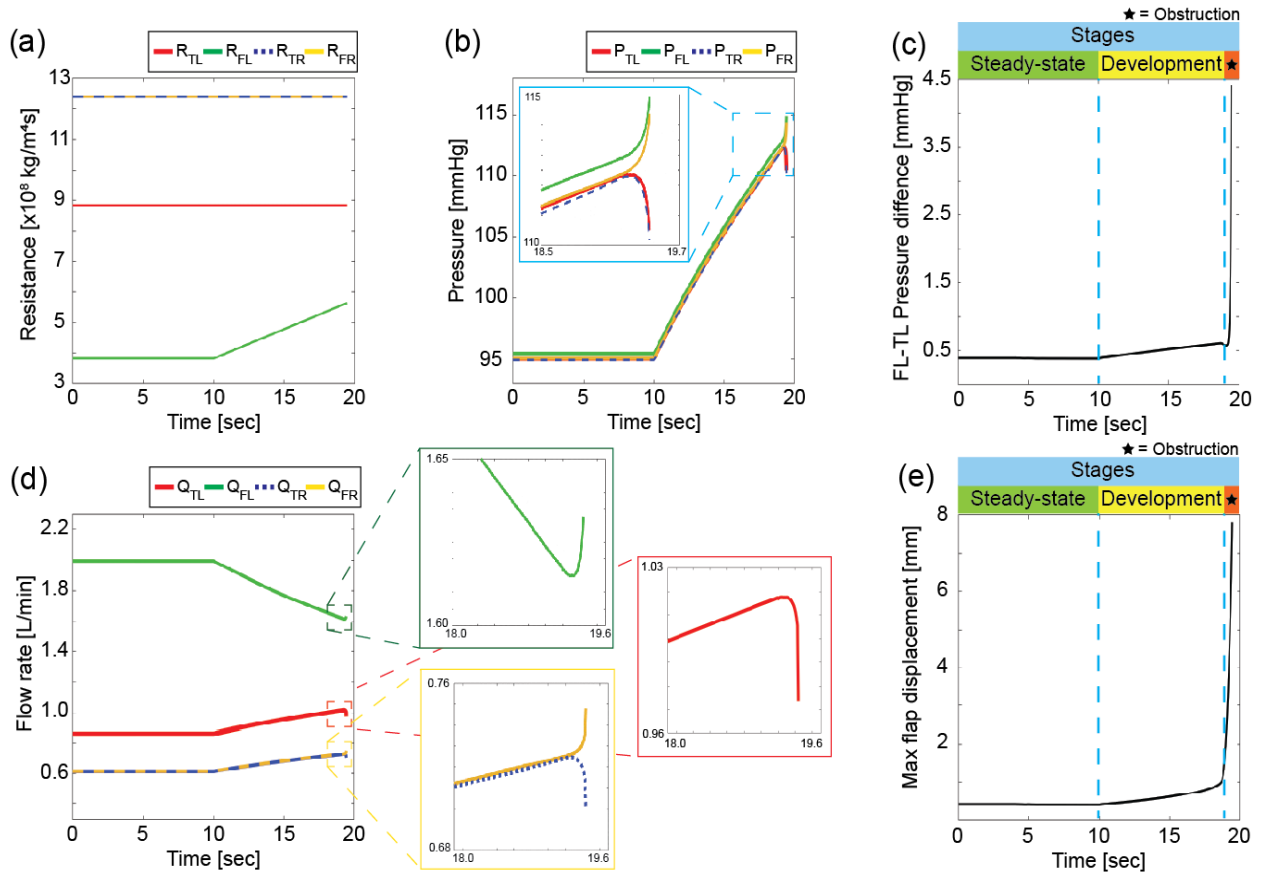


Figure 5.6. Time history of (a) resistance, (b) pressure, (c) pressure difference between TL and FL, (d) flow, and (e) maximum flap displacement. Resistance, pressure, and flow are given for TL, FL, TR and FR branches. Pressure difference between FL and TL is given at the aortic outlet, and maximum flap displacement is given at plane II.

5.4 Discussion

In this study, we have demonstrated that computational simulations can be used to understand the complex hemodynamics associated with dynamic obstruction in type B aortic dissection. Specifically, we performed a detailed characterization of both TL and FL hemodynamics which cannot be easily assessed *in vivo*. Our results have revealed that in our model dynamic obstruction occurred as mean systemic blood pressure increased from 95.7 mmHg to 115.3 mmHg (Figure 5.5 panel a). This behavior is consistent with the clinical example reported in Figure 1, where dynamic obstruction occurred as mean systemic blood pressure increased from 63.3 mmHg to 108.3 mmHg, although the exact transition pressure was not documented. Our clinical experience has shown that the transition-pressure window in patients has been as low as 75 mm Hg and as narrow as 10-15 mm Hg.

Our results have supported the hypothesis that relatively small pressure differences between FL and TL are sufficient to displace the flap to induce dynamic obstruction. Here, a maximum FL – TL pressure difference of 4.5 mmHg was obtained just prior to the complete TL obstruction. During most of the dynamic obstruction, the FL – TL pressure differences remained under 1 mmHg, and only in the instances just prior to obstruction did the pressure differences increase substantially.

Clinically, increases in central blood pressure may be triggered by a variety of mechanisms, including hypertension, partial thrombosis in the FL, hypoxia, changes in vasoactive medication administration, etc. [28-30]. In this simulation, these changes were reproduced by imposing an increase in FL resistance while keeping the cardiac output and other outflow boundary conditions (prescribed flows and resistances) constant.

Our results have shown that the final stage of dynamic obstruction was very sudden in nature, occurring over a short time (< 1 second, see Figure 5.6), consistent with the clinical understanding of this dramatic event. The TL remained patent as pressure differentials between FL and TL slowly changed until a threshold was reached and sudden obstruction occurred. This threshold for sudden obstruction may vary with the patients' age, vascular anatomy, and chronicity of the intimal flap.

We have often observed onset of dynamic obstruction in the abdominal aorta accompanied by TL collapse following correction of static obstruction of the aortoiliac segment. However, we submit that whatever the trigger for transient changes in hemodynamic conditions might be, such

as alterations in cardiac output, differential resistances in TL- and FL-supplied branch arteries or different number and size of connecting tears, etc., it only takes a relatively small pressure difference between FL and TL to induce intimal flap motion and ultimately TL obstruction. In this study, we have demonstrated the clear association between systemic changes in blood pressure and dynamic obstruction.

5.4.1 Material stiffness of the intimal flap

To date, no human or animal experimental studies have reported the material stiffness of the intimal flap. Previous computational studies used different assumptions: Alimohammadi 2015 [19], and Qiao 2015 [23] assumed the same material stiffness for intimal flap and aortic wall. Another study considered a wide range of material stiffness (0.02 – 0.80 MPa) and tried to match the flap displacement observed in the clinical images [24].

In this study we assumed that the flap is less stiff than the thoracic aorta [25]. This assumption is justified because the flap consists primarily of elastin fibers, which are more compliant than the collagen fibers more prevalent in outer layers of the aortic wall [26]. Also, the phenomenon of pressure-related TL collapse has only been observed clinically in days-old aortic dissections, in which the acute dissection flap is thin and flimsy. Dissection flaps in dissections weeks to months old are in various states of thickening due to fibrosis and have not been observed to behave in this same way. We have not observed dynamic obstruction in a single instance of chronic dissection.

Considering this, several simplifying assumptions were made to set the mechanical properties of the intimal flap. Material stiffness and thickness were assumed to be uniform along its length. The flap thickness was set to 1mm. As for the material stiffness, we considered values in the 0.07 – 0.50 MPa range. Ultimately, a 0.10 MPa value was used. This value enabled us to reproduce physiological changes in mean pressure over the course of the dynamic obstruction. When the flap stiffness was too low (~0.07 MPa), the dynamic obstruction was triggered at lower levels of pressure. Conversely, dynamic obstruction occurred at elevated levels of systemic blood pressure when the intimal flap material stiffness was large (~0.50 MPa). In reality, one would expect changes in material stiffness and thickness (and therefore in structural stiffness [31]) along the length of the flap.

5.4.2 Distal (0D) and geometric (3D) changes in vessel resistance

To understand the hemodynamic changes during dynamic obstruction, it is helpful to consider two types of resistances for each lumen: 1) the 0D distal resistance imposed via boundary conditions, and 2) the 3D geometrical resistance, which varies over time due to changes in cross-sectional area (see schematic in Figure 5.7). The 3D geometrical resistance can be evaluated as $R = \Delta P / Q$ for both TL and FL, where ΔP is the pressure differential between planes 1 and 2, and Q is the flow in each lumen. For each lumen, the total resistance is thus the sum of the 3D geometrical and the 0D distal components (see panel a of Figure 5.7).

During the steady-state (0 - 10 s) and development (10 - 19 s) stages, there is no significant changes in TL and FL 3D resistances (Figure 5.7 panel b). Therefore, the prescribed increase in FL 0D resistance causes a decrease in FL flow (Figure 5.6 panel d). In the obstruction stage (19 – 19.44 s), as the intimal flap moves towards the TL wall, significantly reducing the TL area, the 3D geometrical resistances change substantially: the 3D TL resistance increases six-fold, from 0.65×10^6 at $t = 19$ s, to $4.00 \times 10^6 \text{ kg/m}^4\text{s}$ at $t=19.44$ s (Figure 5.7 panel b). This increased 3D TL resistance is associated with a reduction in TL flow and an increased FL flow (Figure 5.6 panel d) despite the prescribed increase in FL 0D resistance.

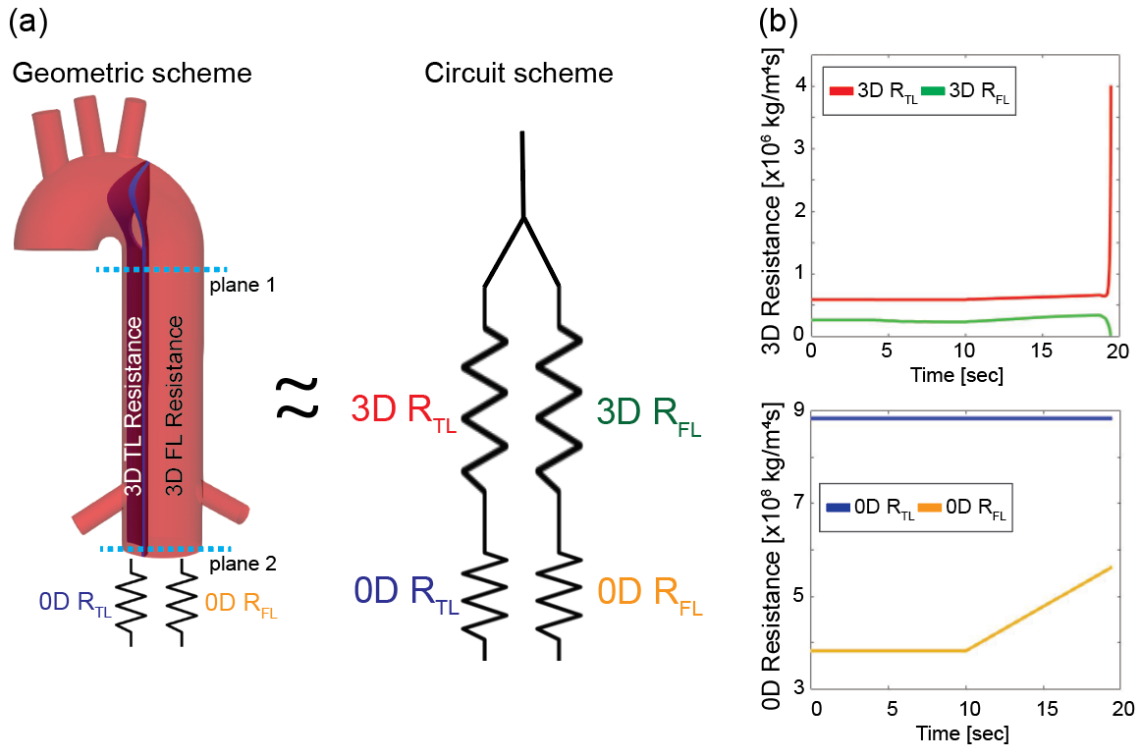


Figure 5.7. (a) Schematic decomposition of TL and FL resistance into a 3D geometric and a 0D distal components acting in series for each lumen. (b) Time history of 0D and 3D geometric TL and FL resistances.

This study underlines the relationship between alterations in peripheral vascular resistance (represented here by 0D circuits) and dynamic TL collapse. Optimal pharmacological management of these patients induces changes in peripheral vascular resistance that may impact the overall pressure levels in TL and FL and thus potentially trigger dynamic obstruction.

5.4.3 Auto-regulation of the branch vessels

In this study, flow to the upper branch vessels was assumed constant over time, and renal artery outflows were determined via fixed resistance boundary conditions. Both the cerebral and the renal circulations are heavily auto-regulated and thus have the capacity of maintaining flow over a wide range of systemic pressures [32-35]. Setting a fixed flow boundary conditions effectively achieved this behavior for the upper branch vessels. However, for the renal arteries, setting a fix flow condition was not a reasonable modeling choice as we wanted to study malperfusion during dynamic obstruction. As a result, both renal flows varied over time corresponding to the systemic blood pressure change (Figure 5.6). Future studies will expand on the work presented here by accounting for renal flow auto-regulation models, which attempt to maintain constant flow over a 90-170 mmHg range of systemic blood pressures [36].

5.4.4 Flow distribution between TL and FL

In this study, a 30:70 TL:FL flow ratio was assumed. Different flow ratios would impact the simulation results. With a 30:70 TL:FL flow ratio, dynamic obstruction occurred at systemic blood pressure of 115.3 mmHg. As more flow goes through the TL for a given TL:FL area ratio, the pressure drop between aortic root and distal TL increases, resulting in larger pressure differentials between FL and TL. We tested a 50:50 TL:FL flow ratio with the same geometry. Here, dynamic obstruction occurred at lower levels of systemic pressure (101.5 mmHg). Furthermore, the TL:FL ratio of flows and areas may vary considerably across patients. The ratios of TL:FL peak flows ranged from 0.5 to 2 in Dillon-Murphy 2016 [15] and Baumler 2020 [24], respectively. Both patients had larger FL than TL. Anatomical variation, such as different TL:FL area ratios, the size and number of initial and re-entry tears, and the patency of the FL can alter the TL:FL flow distributions across patients.

5.4.5 Limitations

Lack of a contact model: Due to a lack of contact model, simulations stopped at the time step ($t=19.44$ s) when the intimal flap nearly touched the TL wall. When contact occurs, the topology

of the fluid domain changes: the TL is no longer a continuous conduit, and contact forces between intimal flap and TL wall must be defined. These additional complexities were outside the scope of the current work, which was focused on describing the temporal response of dynamic obstruction in aortic dissection. In the future, will tackle this TL collapse using other FSI strategies relying on immerse-boundary formulations [37].

Lack of re-entry tears: In this study, we assumed no re-entry tears in the model. However, studies have shown that patients with aortic dissection have an average of 2-3 re-entry tears. The most common locations for re-entry tears are the descending aorta and the juxta-renal region [38,39]. Previous research showed the significant effects of re-entry tears on aortic dissection hemodynamics. A larger number of re-entry tears tends to equilibrate the pressure between TL and FL [15]. Based on this principle, dynamic obstruction can be treated by fenestration. Size and location of re-entry tears, such as near side branches, is also likely to impact dynamic obstruction.

Rigid aortic wall assumption: To reduce complexity and computational cost, we modeled the behavior of the aortic wall as rigid and only studied the FSI problem given by the interactions between flow in TL and FL and a deformable intimal flap. However, the aorta experiences relatively large deformation, even in patients with relatively stiffer vessels [35,40,41]. This deformability affects flow through TL and FL, which in turn will affect intimal flap motion. Compliant outer walls may impact the dynamics of flap motion due to the differential ability that TL and FL have to accommodate changes in blood volume as blood pressure changes. These changes may be important if pulsatility is considered in the FSI simulation. Here, the assumed steady-state flow conditions reduce the impact of this simplifying assumption. Future expansions on this work will account for aortic wall deformation.

Lack of pulsative flow: Non-pulsatile flow was used for this study because the time scale of dynamic obstruction is several minutes (Figure 5.1), much longer than the time scale of a single cardiac cycle (~ 1 s). However, under pulsatile conditions, the pressure difference between FL and TL will also be pulsatile and therefore the flap displacement may also exhibit a pulsatile component superimposed with the steady-state trend described in this work. Additionally, it is possible to for a transitional stage to occur whereby TL collapse happens only during systole, but not in diastole. This situation could only be studied by simulating dynamic obstruction under full pulsatile conditions.

Idealized anatomy: a highly simplified type B aortic dissection model was used for this study. More complex anatomical features such as vessel tortuosity and curvature, in addition to the number of re-entry tears, may affect dynamic obstruction. From a clinical perspective, it would be interesting to investigate whether there is a particular dissection anatomy prone to dynamic obstruction. Further work will involve correlating anatomical features such as entry tear size, tear location, aortic curvature, constellation of branch arteries compromised by static obstruction, etc.

5.5 Conclusion

An idealized FSI type B aortic dissection model was created to study dynamic obstruction. Our model succeeded in reproducing the clinical evidence supporting that dynamic obstruction occurs as mean systemic blood pressure increases. Our results showed that relatively small pressure differences between FL and TL are sufficient to displace the intimal flap to induce dynamic obstruction. Lastly, the final stage of dynamic obstruction occurred over a very short time (< 1 second), consistent with the clinical understanding of this dramatic event. To our knowledge, this study shows the first computational analysis of potential mechanisms driving dynamic obstruction in aortic dissection.

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5.6 Bibliography

- [1] Goldfinger, Judith Z., Jonathan L. Halperin, Michael L. Marin, Allan S. Stewart, Kim A. Eagle, and Valentin Fuster. "Thoracic aortic aneurysm and dissection." *Journal of the American College of Cardiology* 64, no. 16 (2014): 1725-1739.
- [2] Meszaros, Istvan, Jozsef Morocz, Jozsef Szlavi, Janos Schmidt, Laszlo Tornoci, Laszlo Nagy, and Laszlo Szép. "Epidemiology and clinicopathology of aortic dissection." *Chest* 117, no. 5 (2000): 1271-1278.
- [3] Peterss, Sven, Ahmed M. Mansour, Julia A. Ross, Irena Vaitkeviciute, Paris Charilaou, Julia Dumfarth, Hai Fang et al. "Changing pathology of the thoracic aorta from acute to chronic dissection: literature review and insights." *Journal of the American College of Cardiology* 68, no. 10 (2016): 1054-1065.

- [4] Daily, Pat O. "Management of acute aortic dissections." *Ann Thorac Surg* 10 (1970): 237-247.
- [5] Geirsson, Arnar, Wilson Y. Szeto, Alberto Pochettino, Michael L. McGarvey, Martin G. Keane, Y. Joseph Woo, John G. Augoustides, and Joseph E. Bavaria. "Significance of malperfusion syndromes prior to contemporary surgical repair for acute type A dissection: outcomes and need for additional revascularizations." *European journal of cardio-thoracic surgery* 32, no. 2 (2007): 255-262.
- [6] Fattori, Rossella, Thomas T. Tsai, Truls Myrmel, Arturo Evangelista, Jeanna V. Cooper, Santi Trimarchi, Jin Li et al. "Complicated acute type B dissection: is surgery still the best option? A report from the International Registry of Acute Aortic Dissection." *JACC: Cardiovascular Interventions* 1, no. 4 (2008): 395-402.
- [7] Suzuki, Toru, Rajendra H. Mehta, Hüseyin Ince, Ryozi Nagai, Yasunari Sakomura, Frank Weber, Tetsuya Sumiyoshi et al. "Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD)." *Circulation* 108, no. 10_suppl_1 (2003): II-312.
- [8] Jonker, Frederik HW, Himanshu J. Patel, Gilbert R. Upchurch, David M. Williams, Daniel G. Montgomery, Thomas G. Gleason, Alan C. Braverman et al. "Acute type B aortic dissection complicated by visceral ischemia." *The Journal of Thoracic and Cardiovascular Surgery* 149, no. 4 (2015): 1081-1086.
- [9] Fann, JAMES I., GEORGE E. Sarris, R. SCOTT Mitchell, NORMAN E. Shumway, EDWARD B. Stinson, PHILIP E. Oyer, and D. CRAIG Miller. "Treatment of patients with aortic dissection presenting with peripheral vascular complications." *Annals of surgery* 212, no. 6 (1990): 705.
- [10] Williams, David M., Do Yun Lee, Brian H. Hamilton, M. Victoria Marx, Dasika L. Narasimham, Sahira N. Kazanjian, Martin R. Prince, James C. Andrews, Kyung J. Cho, and G. Michael Deeb. "The dissected aorta: part III. Anatomy and radiologic diagnosis of branch-vessel compromise." *Radiology* 203, no. 1 (1997): 37-44.
- [11] Chen, Duanduan, Matthias Müller-Eschner, Drosos Kotelis, Dittmar Böckler, Yiannis Ventikos, and Hendrik von Tengg-Kobligh. "A longitudinal study of Type-B aortic dissection and endovascular repair scenarios: computational analyses." *Medical engineering & physics* 35, no. 9 (2013): 1321-1330.

- [12] Abazari, Mohammad Amin, Deniz Rafieianzab, M. Soltani, and Mona Alimohammadi. "The effect of beta-blockers on hemodynamic parameters in patient-specific blood flow simulations of type-B aortic dissection: A virtual study." *Scientific reports* 11, no. 1 (2021): 1-14.
- [13] Menichini, Claudia, Zhuo Cheng, Richard GJ Gibbs, and Xiao Yun Xu. "Predicting false lumen thrombosis in patient-specific models of aortic dissection." *Journal of The Royal Society Interface* 13, no. 124 (2016): 20160759.
- [14] Osswald, A., Christof Karmonik, J. R. Anderson, F. Rengier, M. Karck, J. Engelke, K. Kallenbach et al. "Elevated wall shear stress in aortic type B dissection may relate to retrograde aortic type A dissection: a computational fluid dynamics pilot study." *European Journal of Vascular and Endovascular Surgery* 54, no. 3 (2017): 324-330.
- [15] Dillon-Murphy, Desmond, Alia Noorani, David Nordsletten, and C. Alberto Figueroa. "Multi-modality image-based computational analysis of haemodynamics in aortic dissection." *Biomechanics and modeling in mechanobiology* 15, no. 4 (2016): 857-876.
- [16] Cheng, Zhuo, Celia Riga, Joyce Chan, Mohammad Hamady, Nigel B. Wood, Nicholas JW Cheshire, Yun Xu, and Richard GJ Gibbs. "Initial findings and potential applicability of computational simulation of the aorta in acute type B dissection." *Journal of vascular surgery* 57, no. 2 (2013): 35S-43S.
- [17] Ahmed, S. Ben, D. Dillon-Murphy, and C. A. Figueroa. "Computational study of anatomical risk factors in idealized models of type B aortic dissection." *European Journal of Vascular and Endovascular Surgery* 52, no. 6 (2016): 736-745.
- [18] Cheng, Zhuo, Nigel B. Wood, Richard GJ Gibbs, and Xiao Y. Xu. "Geometric and flow features of type B aortic dissection: initial findings and comparison of medically treated and stented cases." *Annals of biomedical engineering* 43, no. 1 (2015): 177-189.
- [19] Alimohammadi, Mona, Joseph M. Sherwood, Morad Karimpour, Obiekezie Agu, Stavroula Balabani, and Vanessa Díaz-Zuccarini. "Aortic dissection simulation models for clinical support: fluid-structure interaction vs. rigid wall models." *Biomedical engineering online* 14, no. 1 (2015): 1-16.
- [20] Bonfanti, Mirko, Stavroula Balabani, John P. Greenwood, Sapna Puppala, Shervanthi Homer-Vanniasinkam, and Vanessa Díaz-Zuccarini. "Computational tools for clinical support: a multi-scale compliant model for haemodynamic simulations in an aortic dissection based on

multi-modal imaging data." *Journal of The Royal Society Interface* 14, no. 136 (2017): 20170632.

[21] Qiao, Yonghui, Yujie Zeng, Ying Ding, Jianren Fan, Kun Luo, and Ting Zhu. "Numerical simulation of two-phase non-Newtonian blood flow with fluid-structure interaction in aortic dissection." *Computer methods in biomechanics and biomedical engineering* 22, no. 6 (2019): 620-630.

[22] Bonfanti, Mirko, Stavroula Balabani, Mona Alimohammadi, Obiekezie Agu, Shervanthi Homer-Vanniasinkam, and Vanessa Díaz-Zuccarini. "A simplified method to account for wall motion in patient-specific blood flow simulations of aortic dissection: Comparison with fluid-structure interaction." *Medical engineering & physics* 58 (2018): 72-79.

[23] Qiao, Aike, Wencong Yin, and Bo Chu. "Numerical simulation of fluid–structure interaction in bypassed DeBakey III aortic dissection." *Computer Methods in Biomechanics and Biomedical Engineering* 18, no. 11 (2015): 1173-1180.

[24] Bäumlér, Kathrin, Vijay Vedula, Anna M. Sailer, Jongmin Seo, Peter Chiu, Gabriel Mistelbauer, Frandics P. Chan, Michael P. Fischbein, Alison L. Marsden, and Dominik Fleischmann. "Fluid–structure interaction simulations of patient-specific aortic dissection." *Biomechanics and modeling in mechanobiology* 19, no. 5 (2020): 1607-1628.

[25] Roccabianca, S., C. A. Figueroa, G. Tellides, and Jay D. Humphrey. "Quantification of regional differences in aortic stiffness in the aging human." *Journal of the mechanical behavior of biomedical materials* 29 (2014): 618-634.

[26] Vlachopoulos, Charalambos, Michael O'Rourke, and Wilmer W. Nichols. *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*. CRC press, 2011.

[27] Lantz, B. M., J. M. Foerster, Daniel P. Link, and James W. Holcroft. "Regional distribution of cardiac output: normal values in man determined by video dilution technique." *American Journal of Roentgenology* 137, no. 5 (1981): 903-907.

[28] Hathcock, James J. "Flow effects on coagulation and thrombosis." *Arteriosclerosis, thrombosis, and vascular biology* 26, no. 8 (2006): 1729-1737.

[29] JOUPPILA, PENTTI, and PERTTI KIRKINEN. "Increased vascular resistance in the descending aorta of the human fetus in hypoxia." *BJOG: An International Journal of Obstetrics & Gynaecology* 91, no. 9 (1984): 853-856.

- [30] Goulopoulou, Styliani, and R. Clinton Webb. "Symphony of vascular contraction: how smooth muscle cells lose harmony to signal increased vascular resistance in hypertension." *Hypertension* 63, no. 3 (2014): e33-e39.
- [31] Humphrey, Jay D., David G. Harrison, C. Alberto Figueroa, Patrick Lacolley, and Stéphane Laurent. "Central artery stiffness in hypertension and aging: a problem with cause and consequence." *Circulation research* 118, no. 3 (2016): 379-381.
- [32] Ruland, Sean, and Venkatesh Aiyagari. "Cerebral autoregulation and blood pressure lowering." *Hypertension* 49, no. 5 (2007): 977-978.
- [33] Arthurs, Christopher J., Kevin D. Lau, Kaleab N. Asress, Simon R. Redwood, and C. Alberto Figueroa. "A mathematical model of coronary blood flow control: simulation of patient-specific three-dimensional hemodynamics during exercise." *American Journal of Physiology-Heart and Circulatory Physiology* 310, no. 9 (2016): H1242-H1258.
- [34] Lau, Kevin D., and C. Alberto Figueroa. "Simulation of short-term pressure regulation during the tilt test in a coupled 3D–0D closed-loop model of the circulation." *Biomechanics and modeling in mechanobiology* 14, no. 4 (2015): 915-929.
- [35] Figueroa, C. Alberto, Charles A. Taylor, and Alison L. Marsden. "Blood flow." *Encyclopedia of Computational Mechanics Second Edition* (2017): 1-31.
- [36] Ravera, Maura, Michela Re, Luca Deferrari, Simone Vettoretti, and Giacomo Deferrari. "Importance of blood pressure control in chronic kidney disease." *Journal of the American Society of Nephrology* 17, no. 4 suppl 2 (2006): S98-S103.
- [37] Peskin, Charles S. "The immersed boundary method." *Acta numerica* 11 (2002): 479-517.
- [38] Quint, Leslie E., Joel F. Platt, Seema S. Sonnad, G. Michael Deeb, and David M. Williams. "Aortic intimal tears: detection with spiral computed tomography." *Journal of Endovascular Therapy* 10, no. 3 (2003): 505-510.
- [39] Khojinezhad, Ali, Irwin Walot, Matthew J. Kruse, Tony Rapae, Carlos E. Donayre, and Rodney A. White. "Distribution of intimomedial tears in patients with type B aortic dissection." *Journal of vascular surgery* 52, no. 3 (2010): 562-568.
- [40] Taylor, Charles A., and C. A. Figueroa. "Patient-specific modeling of cardiovascular mechanics." *Annual review of biomedical engineering* 11 (2009): 109.
- [41] Cuomo, Federica, Sara Roccabianca, Desmond Dillon-Murphy, Nan Xiao, Jay D. Humphrey, and C. Alberto Figueroa. "Effects of age-associated regional changes in aortic

stiffness on human hemodynamics revealed by computational modeling." PLoS One 12, no. 3 (2017): e0173177.

Chapter 6 An Immersed Boundary Method Formulation for Aortic Simulation

This chapter is adapted from a manuscript currently in preparation for submission⁵.

6.1 Introduction

In human vessels, thin structures such as heart valves, vein valves, and aortic dissection flaps interact with blood flow. These structures are flexible and undergo large deformations, resulting in complex blood flow patterns during the cardiac cycle. Abnormal motions of these structures can lead to serious conditions, including aortic insufficiency, venous insufficiency, and dynamic obstruction [1], [2], [3]. The motions of these structures have been reported using various dynamic medical image techniques, such as CT, MR, and ultrasound [4], [5], [6]. These imaging methods are valuable for disease diagnosis and classification [7], [8], [9], [10]. However, relying solely on medical imaging makes it challenging to conduct an in-depth investigation into how these large motions affect physiological function and contribute to disease. Furthermore, blood flow data under such conditions are limited, given the constraints of clinical hemodynamic measurements [11], [12]. To address these challenges, computational simulations have been used to investigate the large and complex motions of thin structures and their impact on blood flow in vessels.

Fluid–structure-interaction (FSI) methods have been used in simulations of the aortic valve and aortic dissection to study the effect of the structure motions on hemodynamic parameters. FSI methods can be categorized by two main criteria: time coupling strategies and interface handling techniques [13], [14]. Regarding time coupling, FSI methods are classified into monolithic and partitioned approaches [14]. In the monolithic approach, fluid and structural equations are solved simultaneously as a single system. This ensures that the results for fluid and solid interactions are perfectly synchronized in time and unconditionally stable [15], [16]. However, the monolithic approach requires significant computational resources and complex solvers to form an integrated

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system with stabilization terms [17]. In contrast, the partitioned approach solves the fluid and structural domains separately, using distinct solvers for each. This separation introduces a time lag between fluid and solid solutions [14], [18]. To address this issue, an iterative process is employed, where fluid and structural applied multiple times until convergence is achieved at the end of each time step [19], [20]. Partitioned approaches offer greater flexibility, allowing the use of pre-existing solvers for fluid and structural domains with minor modifications [21].

Following the second categorized criteria, FSI methods differ in how they handle the interface between fluid and structural domains, classified into boundary-fitted (conforming mesh) and non-boundary-fitted (non-conforming mesh) methods. In boundary-fitted methods, the fluid problem is solved on a moving mesh that follows the motion of the solid. The Arbitrary Lagrangian–Eulerian (ALE) method is a prominent example [22]. It allows for strict imposition of boundary conditions at the fluid-solid interface and is particularly useful when the fluid boundary deforms with solid motion, as the fluid mesh can adapt to these changes. However, ALE methods require additional computational cost for re-meshing at each time step and may suffer from mesh distortion under large structural motions [23], [24]. ALE methods have been used for simulations of deformable aortic walls [25], [26], [27] and aortic dissection [28], [29], [30]. In contrast, non-boundary-fitted methods use a fixed grid for the fluid domain while representing the solid domain independently. Immersed Boundary Method (IBM) introduced by Peskin is the most representative example [31]. This approach does not require the re-meshing and facilitates handling complex and large structural motions [31], [32]. Boundary conditions at the interface are enforced through additional body forces in the Navier-Stokes equations near the solid domain. Since the solid boundary does not conform to the fluid grid, IBM requires additional interpolation or smoothing to integrate the boundary forces with the fluid solver. Various IBMs have been developed with different body force calculation and interpolation schemes, such as continuous forcing [31], [33] sharp interface [34] and direct forcing [35], [36]. IBM methods have been successfully used in aortic valve simulations [37], [38], [39].

The thin structures within vessels undergo large deformations over relatively short time scale, such as during the cardiac cycle (~ 1 second). These structures may also move into proximity and contact with other solid structures, like two valve leaflets in aortic valves during the diastole [40] or the dissection flap and the aortic wall in dynamic obstruction [30]. The ALE method is not suitable for these scenarios due to issues with poor mesh quality and mesh distortion [41]. In such

cases, IBM offers an attractive alternative, as it avoids the need for fluid re-meshing and effectively captures the dynamics interactions of thin structures.

In FSI simulations of biological tissues, it is important to use a robust and efficient structural model that accurately represents realistic deformations. While membrane models are a popular choice for modeling thin biological structures [42], [43], they fall short in capturing the bending behavior seen in thin structures undergoing large deformations. Shell formulations are particularly effective for analyzing solid domains with a small thickness-to-length ratio and pronounced bending. However, traditional shell formulations require an additional rotation degree of freedoms, which increase computational cost, for the bending behavior [44]. The rotation-free shell formulation saves computational resources by calculating both the membrane and bending behaviors using only displacement degrees of freedom. Shell formulations have been successfully implemented in the FSI problems. For example, Gilmanov et al. used a curvilinear IBM with a finite volume fluid solver and a rotation-free shell solid solver to simulate aortic valves [44]. Nitti et al. employed a direct forcing IBM with a finite difference fluid solver, coupled with an isogeometric analysis-based shell solver to model interactions between thin structure and incompressible flow [45]. Boustani et al. used a sharp interface IBM with a finite difference fluid solver and a shell solid solver [46]. However, all these implementations rely on structured fluid grids, limiting their capacity to handle complex geometrical fluid domains, such as patient-specific aorta geometries.

Finite elements method (FEM), which uses an unstructured grid, is a powerful tool for modeling fluid dynamics in cardiovascular systems [47], [48], [49]. For example, CRIMSON is an open-source, FEM-based software designed for cardiovascular simulations [50]. It employs unstructured tetrahedral elements and has been used in simulating various cardiovascular conditions, including aneurysm and aortic dissection [51], [52], [53]. Recently, Zhang et al. introduced FEM based IBM, so called immersed finite element method (IFEM) [54]. This method used FEM for both fluid and solid domains and implemented reproducing kernel particle method delta function for interpolation during fluid-solid interaction. However, they used a general 3D solid formulation. IFEM successively applied to simulations involving red blood cells, aortic stent, and heart models [55].

In this study, the partitioned approach is applied to IBM to utilize suitable and efficient solvers for both fluid and solid problems. Two promising pre-exist solvers are used: CRIMSON

for fluid domain and FEM based nonlinear rotation-free shell formulation for thin structure. The rotation-free shell formulation used here was specifically developed for vascular biomechanics simulations [56]. This formulation has been validated and used for the aorta simulations. We implemented direct forcing IBM [36] due to its compatibility with pre-existing solid solvers and low computational cost. By using predefined shape functions for the fluid FEM, we minimize the need for additional computational resources for interpolation at the fluid-solid interface. Both strong and weak time coupling schemes are implemented. To the authors' knowledge, this is the first IBM formulation that integrates an FEM fluid solver with a rotation-free shell solver to address the interaction between thin structures and incompressible flow. Our formulation is validated against two 3D problems involving thin structures. A simple valve-like model is used to investigate the effects of strong and weak coupling methods. Finally, we applied our formulation to solve an idealized type-B aortic dissection problem.

6.2 Methods

Notation: We use $\vec{a}$ and $\tilde{a}$ symbols to define quantities of the 3D vector and tensor, respectively. ∇ and ∇^2 denote the Gradient and Laplacian operators, respectively.

6.2.1 Fluid solver

The fluid problem is solved using CRIMSON [50]. It solves the incompressible Navier-Stokes and momentum equations using the finite element method (FEM). Vector forms of these equations are:

$$\rho_f \frac{\partial \vec{v}_f}{\partial t} + \rho_f \vec{v}_f \cdot \nabla \vec{v}_f = -\nabla p + \mu_f \nabla^2 \vec{v}_f + \vec{f} \quad (6.1)$$

$$\nabla \cdot \vec{v}_f = 0 \quad (6.2)$$

where $\vec{v}_f$ represents the fluid velocity, p is the pressure, ρ_f is the fluid density, μ_f is the fluid viscosity, and $\vec{f}$ is the body force. FEM can handle complex geometries compared to the finite volume and finite difference methods which require structured grids. The fluid domain is discretized using 3D unstructured tetrahedral elements. Meshing is conducted by MeshSim installed in CRIMSON. Generalized alpha method is used for time integration [57].

6.2.2 Solid solver

The solid structures in vessels, such as dissection flaps and valves, have a small thickness-to-length ratio. Membrane models allow us to simplify 3D structural problems by solving them on a 2D middle surface with thickness, thereby greatly reducing computational cost [58], [59]. However, membrane models are not capable of capturing bending stiffness, which can lead to numerical buckling in complex geometries [60], [61], [62]. Shell models can capture bending stiffness but are computationally more expensive due to the additional rotation degree of freedom. In this study, the solid problem is solved using a nonlinear rotation-free shell formulation for vascular biomechanics [56]. This formulation calculates both the membrane and bending behavior via displacement degrees of freedom for a triangular element and its three neighboring elements, making it a good fit for use in an efficient fluid-structure interaction framework. This method has been validated as capable of handling large deformations [56]. The nonlinear rotation-free shell formulation uses FEM to solve an Elasto-dynamic equation

$$\rho_s \frac{\partial^2 \vec{u}_s}{\partial t^2} = \nabla \cdot \vec{\sigma} + \vec{f}_s \quad (6.3)$$

where $\vec{u}_s$ represents the solid displacement, ρ_s is the solid density, $\vec{\sigma}$ is the Cauchy stress tensor, and $\vec{f}_s$ is the external force, such as gravity as a body force and pressure or contact force as a surface force.

Human aortic tissues have been considered as incompressible materials from a biomechanical perspective [63], [64]. Incompressible Neo-Hookean hyper-elastic constitutive model is implemented in this study. The strain energy density function, W , for this model is

$$W = C(I_1 - 3) \quad (6.4)$$

where I_1 is the first principal invariant of the right Cauchy–Green deformation tensor and C is a material constant. The solid domain is discretized using 2D unstructured triangular elements. Meshing is done with Gmsh, an open source finite element grid generator [65]. The generalized alpha method is used for time integration [66]. Among different choices of user-specified high-frequency dissipation, ρ_∞ , asymptotic annihilation case ($\rho_\infty = 0$) is used for the rotation-free shell formulation to annihilate the high-frequency response [57].

6.2.3 Fluid structure interaction

The fluid and solid domains are coupled using an IBM. In this study, we used two forces which enable the interaction between fluid and solid solvers. These forces ensure a kinematic and dynamic equilibrium between fluid and solid:

$$\text{Kinematic equilibrium : } \vec{v}_f = \vec{v}_s \text{ on the interface} \quad (6.5)$$

$$\text{Dynamic equilibrium : } \vec{\sigma}_f \cdot \vec{n} = \vec{f}_s \text{ on the interface} \quad (6.6)$$

where $\vec{v}_f$ and $\vec{v}_s$ are the fluid and solid velocities, $\vec{\sigma}_f$ is the fluid stress tensors, $\vec{n}$ is the normal vector to the interface, and $\vec{f}_s$ is the external force to the solid. The first force is an IBM body force, which ensures kinematic equilibrium. This force is applied as the body force in the Navier-Stokes equation (Equation 6.1). The second force is the hydrodynamic force, which ensures dynamic equilibrium. This force is used as the external force in the Elasto-dynamic equation (Equation 6.3). Details about these forces are described below.

6.2.3.1 IBM body force

An IBM with direct forcing, as introduced by Uhlmann [36], is used to calculate the IBM body force. In this work, the method is further extended to support computations on unstructured grids. This method enforces the no-slip condition ($\vec{v}_f = \vec{v}_s$) at the interface by adding a fictitious body force at the solid nodes of the interface. The following are the steps in the IBM body force calculation process:

- (a) The fluid elements which contain each solid node are searched. The fluid solutions at the four fluid node of the fluid tetrahedral element are interpolated into the solid node using FEM shape function (Figure 6.1 (a)):

$$\varphi_f(X_s) = \sum_{i=1}^4 \varphi_f(X_{f,i}) \cdot N_i \quad (6.7)$$

where φ_f is the fluid solution which is the velocity, pressure, and first and second derivative of the velocity. X_s and $X_{f,i}$ are solid and fluid node locations. N_i is the i-th linear shape function used for the FEM in CRIMSON. We are able to avoid additional computational costs for interpolation, by using these pre-defined FEM shape functions.

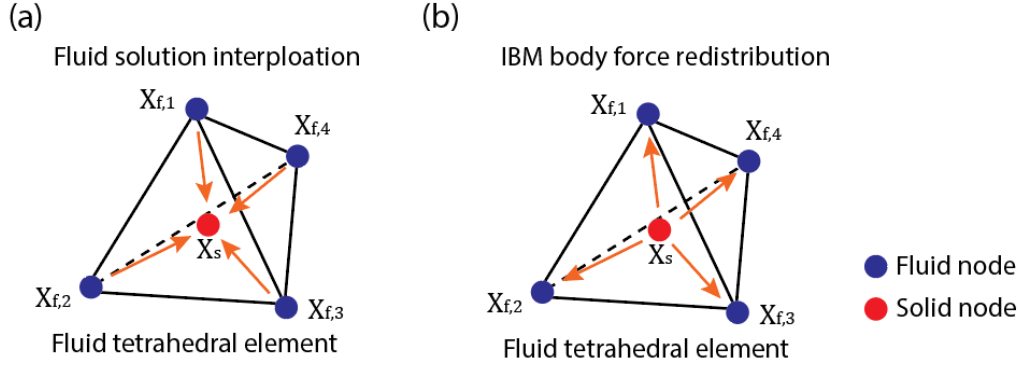


Figure 6.1. Interpolation using FEM shape functions. Interpolation (a) from fluid to solid and (b) from solid to fluid.

(b) IBM body force is calculated at the solid node as follows:

$$\vec{f}(X_s) = \rho_f \frac{\vec{v}_s(X_s) - \vec{v}_f(X_s)}{\Delta t} + \rho_f \vec{v}_f(X_s) \cdot \nabla \vec{v}_f(X_s) + \nabla p(X_s) - \mu_f \nabla^2 \vec{v}_f(X_s) \quad (6.8)$$

where $\vec{v}_s$ is the solid velocity and $\vec{v}_f$ is the fluid velocity, which is interpolated from the fluid nodes [36].

(c) The IBM body force calculated at the solid node is redistributed to the fluid nodes. This process is carried out in two steps. First, the IBM body force on the solid node is interpolated to the four fluid nodes using same FEM linear shape function used in Equation 6.7 (Figure 6.1 (b)):

$$\vec{f}(X_{f,i}) = c \cdot \vec{f}(X_s) \cdot N_i, \text{ where } i = 1 \text{ to } 4 \quad (6.9)$$

where c is the scaling factor used to impose the conservation of the total force acting on the fluid. We followed scaling factor calculation method introduced by Nitti *et al* [45]:

$$c = \frac{A_s \cdot h_f}{V_f} \quad (6.10)$$

where A_s is a local solid mesh area, h_f is a local fluid mesh size, and V_f is a local fluid mesh volume. If there is more than one solid node near the fluid element, the IBM body force from each solid node is accumulated.

Second, we used a diffusion equation to make a smooth distribution over the fluid domain. Re-using the FEM shape function for interpolation of the IBM force is convenient; however, there are stability and grid-dependence issues that must be addressed before it can be introduced as a source term in the fluid momentum equations. Traditionally, these issues were managed by diffusing the interface over a predetermined thickness, thereby

spreading the source term over that length scale [36], [45], [67]. Typically, this is accomplished by identifying the support region for each Lagrangian point and constructing a transfer function based on a chosen discretized Dirac delta function, such as the Peskin cosine function [31], or by using a moving least squares interpolation of a weighting function [68]. These approaches are practical for structured grids, but it becomes infeasible for the unstructured grids due to the high computational cost of locating Eulerian grid points with the support domain for each Lagrangian point. To avoid the computational cost of identifying Eulerian points in an unstructured grid, we adopted an approach inspired by Particle-Mesh methods [69]. After IBM force is distributed to the fluid nodes using FEM shape function, we solve a diffusion equation for each force component to smooth the force on the Eulerian grid over the prescribed length scale. The diffusion equation is:

$$\frac{\partial \vec{f}}{\partial \tau} = \nabla \cdot (D \nabla \vec{f}) \quad (6.11)$$

where D is the diffusivity and τ is a pseudo time. This vector diffusion equation evaluates the final IBM body force that appears in the fluid momentum equation. The smoothing length is set to $\sqrt{D\tau}$. This equation is discretized in (pseudo-) time using the backward Euler method and solved in a single time step with an iterative conjugate-gradient solver. The diffusion coefficient and time step size are selected so that the diffusive length scale matched the size of the supported domain. This method is robust and does not introduce oscillations as the immersed Lagrangian points move between Eulerian elements [69]. This method is also compatible with adaptively refined local grids. Final IBM body force is used for the body force $\vec{f}$ in Equation 6.1.

6.2.3.2 Hydrodynamic force

The hydrodynamic force for the open solid surface is calculated following the method of Nitti et al. [45]. They demonstrated that this method provides accurate results and effectively handles high pressure differences across the solid surface [70]. This method used two probe points to calculate the hydrodynamic force [68]. Figure 2 shows two probe points aligned along the normal direction of the solid surface, in opposite directions (n^+ and n^-). For convenience, we illustrate a 2D triangular fluid mesh and a 1D solid surface. The distance from the solid node to the probe point, h , is determined by the local fluid mesh size [71].

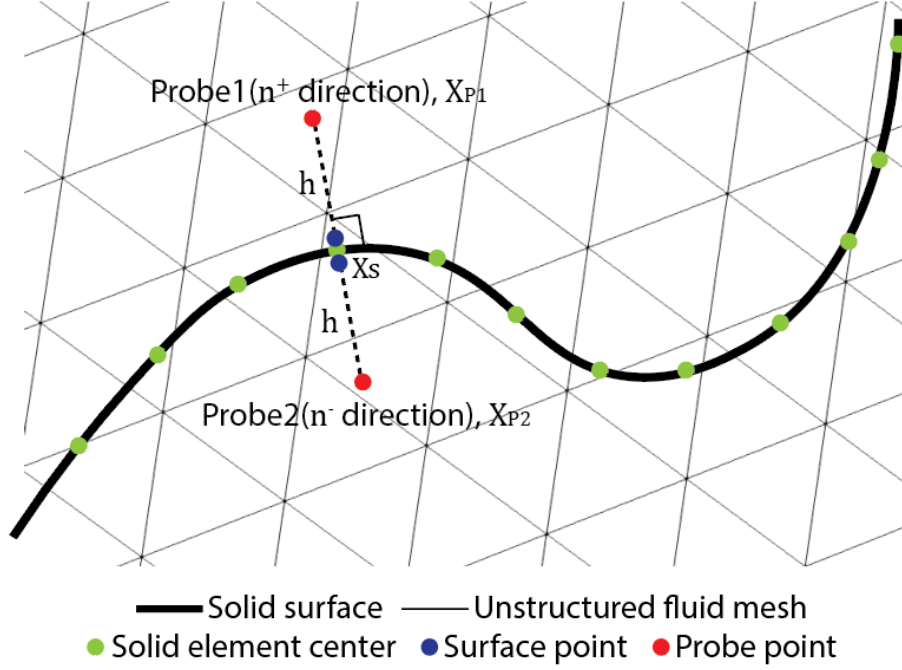


Figure 6.2. Hydrodynamic force calculation using two probe points.

The hydrodynamic force $\vec{F}$ with normal vector $\vec{n}$ and the fluid stress tensor $\vec{\sigma}_f$ is calculated as

$$\vec{F} = \vec{\sigma}_f \cdot A\vec{n} = [-p\vec{I} + \mu_f(\nabla\vec{v}_f + \nabla\vec{v}_f^T)] \cdot A\vec{n} \quad (6.12)$$

where $\vec{I}$ is an identity tensor and A is a fluid element area. For the open solid surface, this force is written by

$$\vec{F} = [-(p^+ - p^-)\vec{I} + \mu_f \{(\nabla\vec{v}_f + \nabla\vec{v}_f^T)^+ - (\nabla\vec{v}_f + \nabla\vec{v}_f^T)^-\}] \cdot A\vec{n} \quad (6.13)$$

The pressure at the surface point p^+ is calculated with a boundary layer equation which is derived from the momentum equation projected into the normal direction:

$$p^+ = p(X_s^+) = p(X_{P1}) + h \rho_f \frac{D\vec{v}_f(X_s)}{Dt} \cdot \vec{n}^+ \quad (6.14)$$

In this equation, the material derivative of the fluid velocity, $D\vec{v}_f/Dt$, is approximated by the solid node point acceleration $\vec{a}_f(X_s)$ [45]. The pressure and acceleration at the probe point and solid node is calculated by the same interpolation method using FEM shape function (Equation 6.7).

The fluid velocity changes linearly in space inside the boundary layer near the solid surface [72]. This ensures that the first derivative of the fluid velocity is the same at the solid node and the

corresponding probe points. With this assumption, the velocity derivative at the surface point is calculated by

$$(\nabla \vec{v}_f + \nabla \vec{v}_f^T)^+ = \nabla \vec{v}_f(X_{P1}) + \nabla \vec{v}_f(X_{P1})^T \quad (6.15)$$

The velocity derivative at the probe point is calculated by the same interpolation method using the FEM shape function (Equation 6.7). The hydrodynamic force $\vec{F}$ is used for the external force $\vec{f}_s$ in Equation 6.3.

6.2.4 Solid searching

Searching for solid points within an unstructured grid is a complex task and can be computationally expensive. The procedure for tracking the Lagrangian solid mesh as it moves within a partitioned unstructured Eulerian fluid tetrahedral mesh is described in this section. At the beginning of the simulation, as a preprocessing step, we identify the host fluid element for each solid point. Although this initial search requires scanning the entire fluid mesh and can be computationally demanding, it is only performed once.

Figure 6.3 illustrates the schematic of solid tracking method. The fundamental tracking algorithm is the Delaunay search, which involves evaluating the barycentric coordinates of a solid point relative to a fluid element [73]. If all barycentric coordinates are positive, the solid point lies within that fluid element. If any coordinate is negative, the point is in a fluid element that is located across the fluid element surface corresponding to the negative coordinate. Using fluid element neighbor connectivity, we move to the indicated neighboring element and repeat the inclusion test. The time step size is chosen to restrict the motion of the immersed solid. Consequently, solid points move no more than a few fluid elements per one time step. As a result, the searching procedure typically concludes in a few iterations, making it reliable and efficient in practice. This tracking scheme is applied separately to four sets of solid points: solid mesh nodes, two probe points, and solid element centers. The solid mesh nodes move according to the calculated kinematics and are tracked as previously described. Although solid element centers and probe points do not move independently, they are determined based on the updated positions of the solid mesh. As a result, they can still be reliably tracked using the same method, as their displacements remain small.

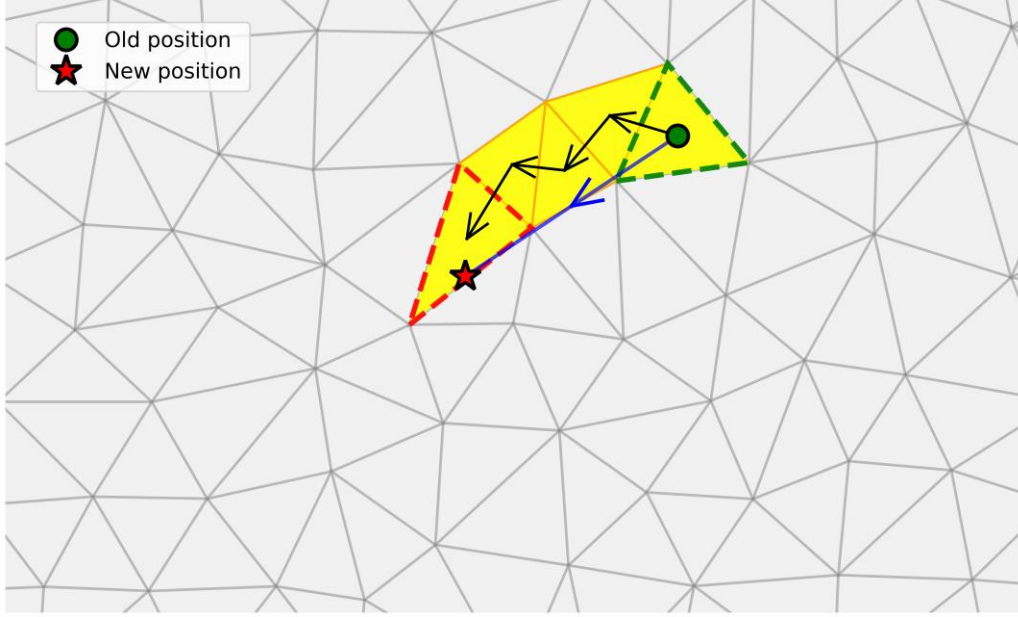


Figure 6.3. Schematic of a particle tracking method.

6.2.5 Time coupling scheme

Partitioned approach, which solves fluid and solid problems in a staggered manner, was used for time coupling. There are two coupling methods: weak (explicit/staggered/loose) and strong (implicit/iterative) coupling [19], [74]. Weak coupling solves the fluid and solid problems once per time step. This method is computationally efficient and has been successfully implemented in the field of aerodynamics [75], [76], [77]. However, numerical instability and degradation of temporal accuracy have been reported in cases with low solid-to-fluid density ratio ρ_s/ρ_f [78], [79], [80]. These issues arise from the added mass effect, whereby one of the pressure components of the hydrodynamic force acts as an extra mass in the solid equation [81], [82]. In contrast, strong coupling iteratively solves fluid and solid problems within a single time step until the coupled fluid and solid solutions converge to stable solutions. This method requires more computational cost but ensures stability and maintains kinematic and dynamic equilibrium at the end of each time step [20], [83]. An under-relaxation scheme has been used to reduce computational costs in the strong coupling [20], [79]. Both weak and strong coupling with the under-relaxation scheme were implemented in this study.

6.2.5.1 Strong & weak couplings

We use *BF*, *FS*, *HDF*, *SS*, and *UR* for the IBM body force calculation (section 6.2.3.1), fluid solver (section 6.2.1), hydrodynamic force calculation (section 6.2.3.2), solid solver (section

6.2.2), and under-relaxation (section 6.2.5.2) operators, respectively. $\overline{IBMbf}$ and $\overline{HDF}$ are IBM body force and hydrodynamic forces, respectively. λ denotes the under-relaxation coefficient. ε is the convergence tolerance with the value of 10^{-4} . Subscripts I denotes the intermediate value before applying the under-relaxation scheme. The predictor-corrector scheme is used for strong coupling.

Weak coupling

[Time loop, n]

- a. $\vec{v}_f[n], p[n], X_s[n], \vec{v}_s[n] \rightarrow BF \rightarrow \overline{IBMbf}[n+1]$
- b. $\vec{v}_f[n], p[n], \overline{IBMbf}[n+1] \rightarrow FS \rightarrow \vec{v}_f[n+1], p[n+1]$
- c. $\vec{v}_f[n+1], p[n+1], X_s[n] \rightarrow HDF \rightarrow \overline{HDF}[n+1]$
- d. $X_s[n], \vec{u}_s[n], \vec{v}_s[n], \vec{a}_s[n], \overline{HDF}[n+1] \rightarrow SS \rightarrow X_s[n+1], \vec{u}_s[n+1], \vec{v}_s[n+1], \vec{a}_s[n+1]$

Strong coupling

[Time loop, n]

Predictor

- a. $\vec{v}_f[n], p[n], X_s[n], \vec{v}_s[n] \rightarrow BF \rightarrow \overline{IBMbf}[predict]$
- b. $\vec{v}_f[n], p[n], \overline{IBMbf}[predict] \rightarrow FS \rightarrow \vec{v}_f[predict], p[predict]$
- c. $\vec{v}_f[predict], p[predict], X_s[n] \rightarrow HDF \rightarrow \overline{HDF}[predict]$
- d. $X_s[n], \vec{u}_s[n], \vec{v}_s[n], \vec{a}_s[n], \overline{HDF}[predict] \rightarrow SS \rightarrow X_s[predict], \vec{u}_s[predict], \vec{v}_s[predict], \vec{a}_s[predict]$
- e. *assign:* $X_s[k] = X_s[predict], \vec{v}_s[k] = \vec{v}_s[predict]$

Corrector

[iteration loop, k]

- f. $\vec{v}_f[n], p[n], X_s[k], \vec{v}_s[k] \rightarrow BF \rightarrow \overline{IBMbf}[k+1]$
- g. $\vec{v}_f[n], p[n], \overline{IBMbf}[k+1] \rightarrow FS \rightarrow \vec{v}_f[k+1], p[k+1]$
- h. $\vec{v}_f[k+1], p[k+1], X_s[k] \rightarrow HDF \rightarrow \overline{HDF}[k+1]$
- i. $X_s[n], \vec{u}_s[n], \vec{v}_s[n], \vec{a}_s[n], \overline{HDF}[k+1] \rightarrow SS \rightarrow X_{s,I}[k+1], \vec{u}_{s,I}[k+1], \vec{v}_{s,I}[k+1], \vec{a}_{s,I}[k+1]$
- j. $X_{s,I}[k+1], \vec{u}_{s,I}[k+1], \vec{v}_{s,I}[k+1], \vec{a}_{s,I}[k+1], \lambda[k] \rightarrow UR \rightarrow X_s[k+1], \vec{u}_s[k+1], \vec{v}_s[k+1], \vec{a}_s[k+1]$
- k. *check convergence:* $Max(\vec{u}_s[k+1] - \vec{u}_s[k]) < \varepsilon$
if YES, assign: $\vec{v}_f[n+1] = \vec{v}_f[k+1], p[n+1] = p[k+1],$
 $X_s[n+1] = X_s[k+1], \vec{u}_s[n+1] = \vec{u}_s[k+1], \vec{v}_s[n+1] = \vec{v}_s[k+1], \vec{a}_s[n+1] = \vec{a}_s[k+1]$
if No, assign: $X_s[k] = X_s[k+1], \vec{v}_s[k] = \vec{v}_s[k+1]$ and go back to step f.

6.2.5.2 Under-relaxation scheme

Strong coupling with iteration of simple weak coupling requires many iterations for convergence [82]. An under-relaxation scheme with Aitken acceleration technique [84] has been shown to reduce the number of iterations for convergence in each time step [20], [45], [85], [86]. In this study, we follow the under-relaxation scheme used by Nitti *et al* [45]. The under-relaxation operator UR conducts follow:

- (a) Calculate under-relaxation coefficient using Aitken method:

$$\lambda[k+1] = -\lambda[k] \frac{(\overrightarrow{a_{s,I}}[k] - \overrightarrow{a_s}[k-1]) \cdot \{(\overrightarrow{a_{s,I}}[k] - \overrightarrow{a_s}[k]) - (\overrightarrow{a_{s,I}}[k] - \overrightarrow{a_s}[k-1])\}}{\|(\overrightarrow{a_{s,I}}[k] - \overrightarrow{a_s}[k]) - (\overrightarrow{a_{s,I}}[k] - \overrightarrow{a_s}[k-1])\|^2} \quad (6.16)$$

The $\lambda[1]$ value for the first step is chosen by 0.3. The $\lambda[1]$ value for the proceeding time step uses the previous time step's final λ value.

- (b) Update acceleration with under-relaxation coefficient

$$\overrightarrow{a_s}[k+1] = \overrightarrow{a_s}[k] + \lambda[k+1](\overrightarrow{a_{s,I}}[k+1] - \overrightarrow{a_s}[k]) \quad (6.17)$$

- (c) Update velocity, displacement, and position using Newmark update formulations

$$\overrightarrow{v_s}[k+1] = \overrightarrow{v_s}[n] + \Delta t\{(1-\gamma)\overrightarrow{a_s}[n] + \gamma\overrightarrow{a_s}[k+1]\} \quad (6.18)$$

$$\overrightarrow{u_s}[k+1] = \overrightarrow{u_s}[n] + \Delta t\overrightarrow{v_s}[n] + \frac{1}{2}\Delta t^2\{(1-2\beta)\overrightarrow{a_s}[n] + 2\beta\overrightarrow{a_s}[k+1]\} \quad (6.19)$$

$$X_s[k+1] = X_s[n] + \overrightarrow{u_s}[k+1] \quad (6.20)$$

where γ and β are Newmark coefficients with values of 1.5 and 1.0.

6.3 Results and discussion

In this paper, we addressed four problems. The first problem is used to validate the calculation of hydro-dynamic forces. The second problem focuses on validating the FSI capabilities. The third problem examines a simplified aortic valve model to investigate strong and weak time coupling schemes. The final case solves an idealized type-B aortic dissection problem.

6.3.1 Validation case1: drag on the circular disk

Calculating hydro-dynamic forces on open solid surfaces is a crucial task in our algorithm. To ensure accuracy, we tested hydro-dynamic force calculation on a thin structure. We consider the problem of a circular disk immersed in uniform flow as illustrated in Figure 6.4. The rigid disk

with radius R is fixed inside the cylindrical domain. The center of the disk is located at the origin. The cylindrical domain extends from $-5R$ to $30R$ in the x -direction and has a radius of $12R$. Fluid domain consists of 11.7M uniform, unstructured tetrahedral elements, with element size of $0.02R$. Solid domain consists of 500 uniform triangular elements, with element size of $0.02R$. This setup is consistent with two previous computational simulations by Shenoy and Kleinstreuer [87] and Tian et al. [88]. The boundary conditions for the fluid domain are a uniform flow at the inlet face, a no-slip wall on the lateral wall, and zero pressure at the outlet face (Figure 6.4).

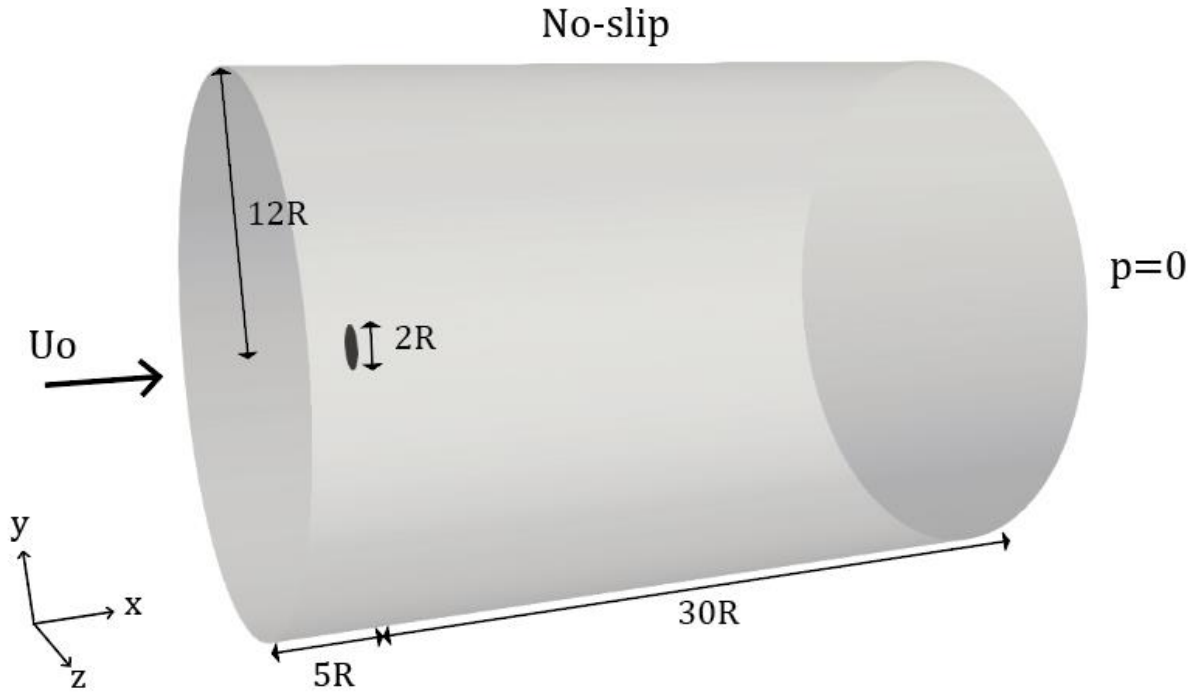


Figure 6.4. Schematic of the computational domain.

The drag coefficients of the disk at various Reynolds numbers are compared with results from previous experimental and computational studies. The drag coefficient of the disk, C_D , and Reynolds number, Re , are defined as follows:

$$C_D = \frac{F}{0.5\rho_f U_0^2 A}, \quad Re = \frac{\rho_f U_0 D}{\mu_f} \quad (6.21)$$

where ρ_f , U_0 , A , D , and μ_f are fluid density, uniform flow velocity, disk area (πR^2), disk diameter, and fluid viscosity, respectively. F is a hydro-dynamic force acting on the disk. Seven different Reynolds numbers are considered: 10, 21, 36, 54, 75, 90, and 107. Different Reynolds numbers are obtained by using different fluid densities while fixing the uniform velocity and viscosity. The drag coefficient is calculated under the fully developed fluid.

Figure 6.5 shows the drag coefficient of the disk for various Reynolds numbers ranging from 10 to 110. Reynolds numbers higher than 110 are not considered because the flow becomes unsteady and does not reach the fully developed stage [89]. The results from the present work are compared with the data from the experiment study by Roos & Willmarth [89], as well as computational simulation by Shenoy and Kleinstreuer [87] using CFX-10.0 (ANSYS Inc., 2005), and by Tian *et al.* [88] using their in-house code. All three studies consider a finite disk thickness of $0.2R$. Additionally, Tian *et al.* provide results for the zero-disk thickness (2D disk). In our study, the nonlinear rotation-free shell formulation uses a 2D mid-surface solid domain with zero thickness. The drag coefficient results from the present work show a good agreement with the simulation results for zero thickness across the entire Reynolds number range.

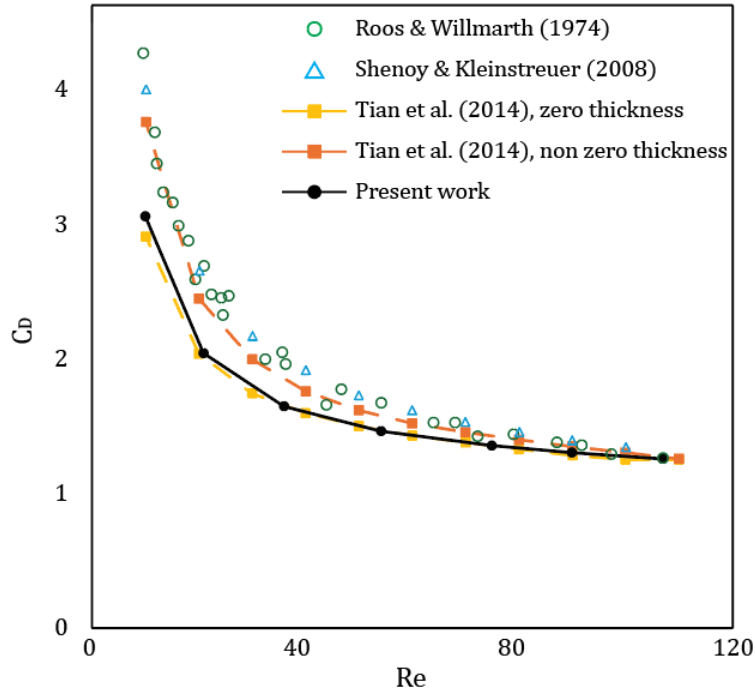


Figure 6.5. The drag coefficient (C_D) for various Reynolds numbers (Re).

6.3.2 Validation case 2: 3D flapping flag in a uniform flow

Flapping flag in a uniform flow problem, proposed by Huang and Sung [90], was considered to validate our FSI solver. This problem has served as a benchmark for validating previous IBM algorithms due to the large 3D displacements involved [45], [88]. Figure 6.6 panel (a) shows the schematic of the computational domains for this problem. A square flag with a length of L is located within a cylindrical domain. The center of the flag's leading edge is positioned at the origin. The cylindrical domain extends from $-2L$ to $8L$ in the y -direction and has a radius of

5L. Fluid domain consists of 2.1M nonuniform, unstructured tetrahedral elements, with the minimum element size of $0.02L$ near flag (see Figure 6.6 panel (b)). A nonuniform tetrahedral mesh is created using a mesh adaptation feature in CRIMSON. Solid domain consists of 5.8K uniform triangular elements, with element size of $0.02L$. This setup is consistent with two previous computational simulations by Huang & Sung [90] and Tian et al. [88]. The boundary conditions for the fluid domain include a uniform flow at the inlet face, a uniform velocity on the lateral wall, and zero pressure at the outlet face (Figure 6.6 panel (a)). The initial condition of fluid domain is U_0 velocity in y-direction. The leading edge of the flag is fixed, while the other three edges are free to move. Initially, the flag is tilted at an angle of 0.1π within the YZ plane, as illustrated in Figure 6.6 panel (b).

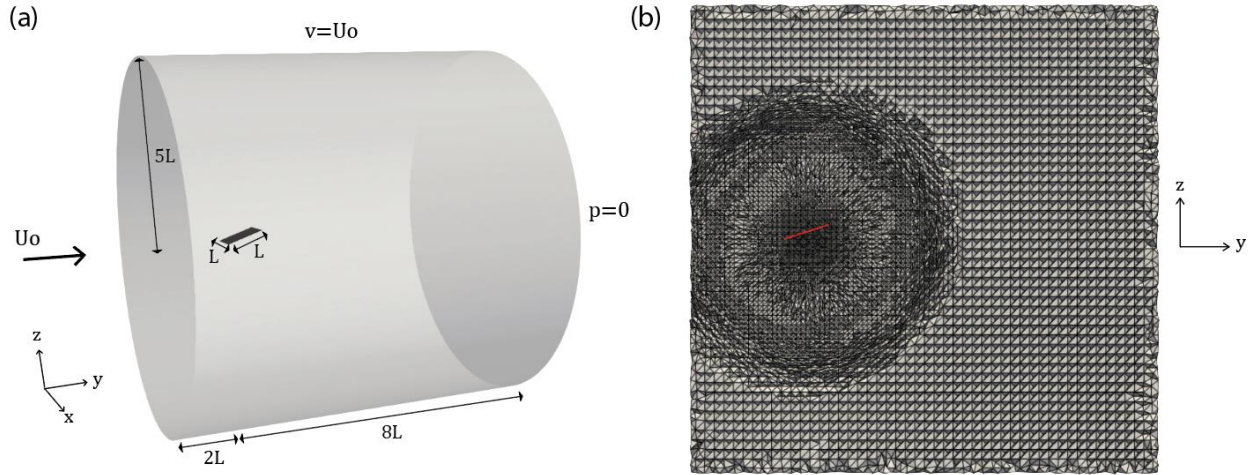


Figure 6.6. (a) Schematic of the computational domain and (b) ununiform, unstructured fluid mesh.

The Reynolds number is $Re = 200$. The mass ratio between fluid and solid is $\rho_s h / \rho_f L = 1.0$, where h is the flag thickness and uses for the parameters in the rotation-free shell formulation. Bending rigidity is defined and set as follows:

$$\frac{Eh^3}{12(1 - \nu_s^2)\rho_f U_0^2 L^3} = 0.0001 \quad (22)$$

where E and ν_s are an elastic modulus and Poisson's ratio of the solid. As we used incompressible Neo-Hookean constitutive model, Poisson's ratio is $\nu_s = 0.5$. A time step size of $\Delta t = 0.002L/U_0$ is chosen to ensure that the CFL number is less than 0.1.

Figure 6.7 panel (a) shows the velocity contours, highlighting the disturbed flow pattern that develops following the motion of the flag. Figure 6.7 panel (b) depicts the time history of the y-directional displacement of the middle point on the trailing edge of the flag. The result from the

present work is compared with the data from the two computational studies by Huang & Sung [90] and Tian et al. [88]. Present work shows a good agreement with previous data even they used different constitutive models, e.g., Saint Venant–Kirchhoff model.

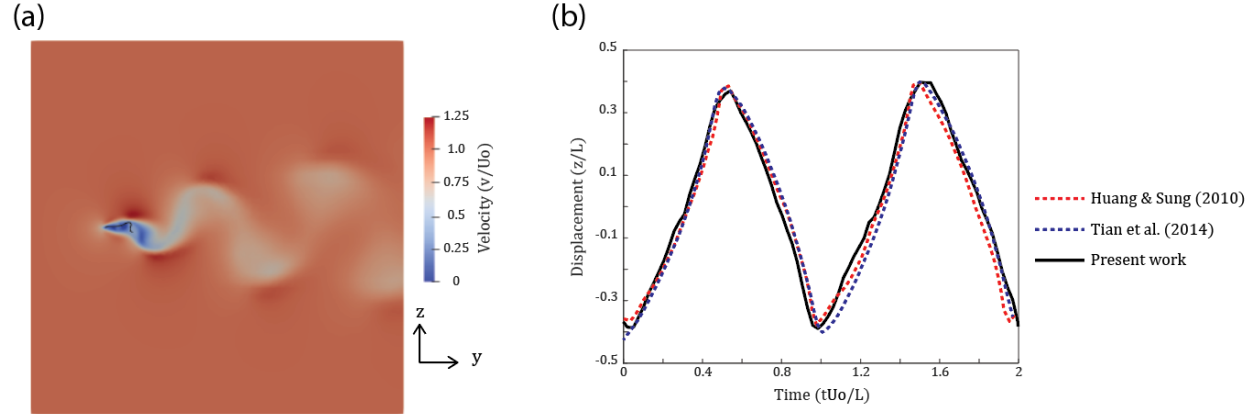


Figure 6.7. (a) Velocity contour at the y-z plane and (b) the z displacement at the middle of the trailing edge of the flag.

6.3.3 Strong & weak coupling comparison

The problem of a thin vertical obstacle structure in a cylindrical tube is considered to compare the performance of strong and weak time coupling schemes. The solid-to-fluid density ratio (ρ_s/ρ_f) has been identified as a key factor in selecting an appropriate coupling scheme, with strong coupling generally recommended when $\rho_s/\rho_f < 1$ [78], [79], [80]. To investigate this, we tested four different solid-to-fluid density ratios, $\rho_s/\rho_f = 0.5, 1, 10, \text{ and } 100$, by changing the solid density while keeping the fluid density constant, 000106 g/mm^3 . The fluid viscosity was 0.004 g/mm s . Both static and dynamic scenarios were considered to assess the efficacy of the weak and strong coupling schemes under different problems. The computational domain was identical for both scenarios. The vertical solid structure with a 10 mm width and height was located at the center of the cylindrical domain (see Figure 6.8). The thickness of the structure was 0.5 mm. The bottom edge was fixed while the other three edges are free to move. The cylindrical domain had a radius of 10 mm, and a length of 60 mm. Mesh independent studies were conducted using four different mesh sizes: 1 mm, 0.7 mm, 0.5 mm, and 0.3 mm with 120K, 360K, 970K, and 3.2M fluid elements, respectively. Convergence was achieved for the solid displacement at the final time step (maximum displacement difference by 0.7% between 0.5 mm and 0.3 mm mesh sizes). The following simulations were conducted with mesh size of 0.5 mm. Fluid domain consists of 970k

uniform, unstructured tetrahedral elements. Solid domain consists of 1,000 uniform triangular elements.

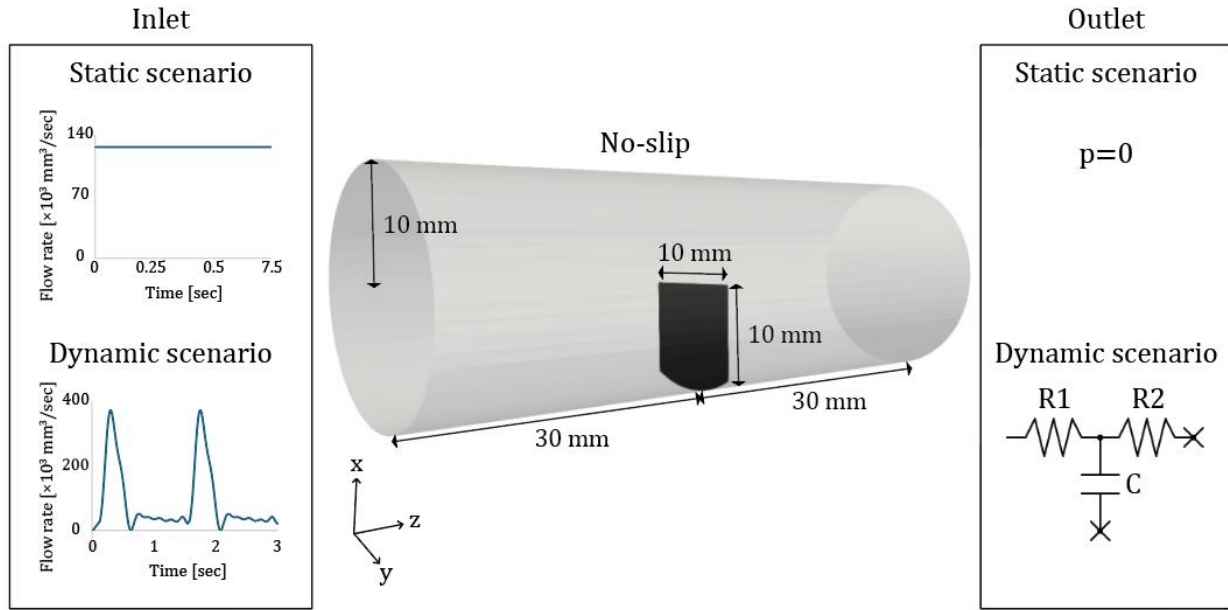


Figure 6.8. Schematic of the computational domain and boundary conditions for the static and dynamic scenarios.

6.3.3.1 Static scenario

First, we considered the static scenario. Constant flow and zero pressure boundary conditions were assigned at the inlet and outlet of the fluid domain, respectively (see Figure 8). The step size was set to $\Delta t = 0.005 \text{ sec}$ to ensure that the CFL number remained below 1. The simulation consists of 1,500-time steps, corresponding to a final time of 7.5 sec. The average Reynolds number was 2,000. The elastic modulus of the solid was set to 10^4 Pa .

Figure 6.9 presents the velocity contour on the XZ plane at the final time step for $\rho_s/\rho_f = 1$ using the strong coupling scheme. As the fluid moves toward the positive z-direction, the solid structure correspondingly deformed in the same direction.

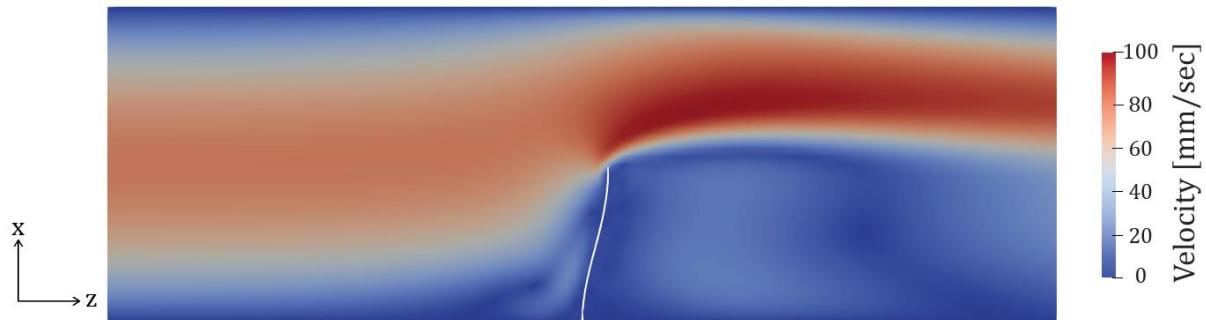


Figure 6.9. Velocity contour of static scenario with $\rho_s/\rho_f = 1$ using strong coupling.

Figure 6.10 shows the time history of the z-directional displacement of the middle point on the top edge of the solid structure. Panel (a), (b), (c), and (d) compare the z-directional displacement results obtained with weak and strong coupling schemes for $\rho_s/\rho_f = 0.5, 1, 10, 100$, respectively. In these plots, red and black lines represent the displacement results from strong and weak coupling schemes, respectively. For lower solid-to-fluid density ratios, the weak coupling scheme produced non-physical oscillations at an early time step ($\rho_s/\rho_f = 0.5$) and at a later time step ($\rho_s/\rho_f = 1$). By contrast, strong and weak coupling results showed good agreement for larger solid-to-fluid density ratios ($\rho_s/\rho_f = 10$ and 100). These results are consistent with previous studies and highlight the necessity of the strong coupling scheme for problems involving low solid-to-fluid density ratios ($\rho_s/\rho_f \leq 1$).

6.3.3.2 Dynamic scenario

Next, we considered the dynamic scenario. Pulsatile flow and three-element Windkessel boundary conditions were assigned at the inlet and outlet of the fluid domain, respectively (see Figure 8). R1, R2, and C values were assigned as $0.02 \text{ g/mm}^4\text{s}$, $0.17 \text{ g/mm}^4\text{s}$, and $66 \text{ mm}^4\text{s}^2/\text{g}$, respectively. Two cycles of pulsatile flow were simulated. The step size was set to $\Delta t = 5e^{-4} \text{ sec}$ to ensure that the maximum CFL number remained below 1. The simulation consists of 6,000-time steps, corresponding to a final time of 3 sec. The maximum and average Reynolds numbers were 5,000 and 1,000, respectively. The elastic modulus of the solid was set to $3 \times 10^5 \text{ Pa}$.

Figure 6.11 presents the same comparison as in Figure 6.10, but for the dynamic scenario. Unlike static scenario, strong and weak coupling results showed good agreement across all solid-to-fluid density ratios. This finding is consistent with the study by Borazjani et al [20]. They showed that the strong and weak coupling yield identical results for the heart valve simulation with complex cardiac flow. These results suggest that, in dynamic problems, if the weak coupling approach converges, it can be used even for small solid-to-fluid density ratios.

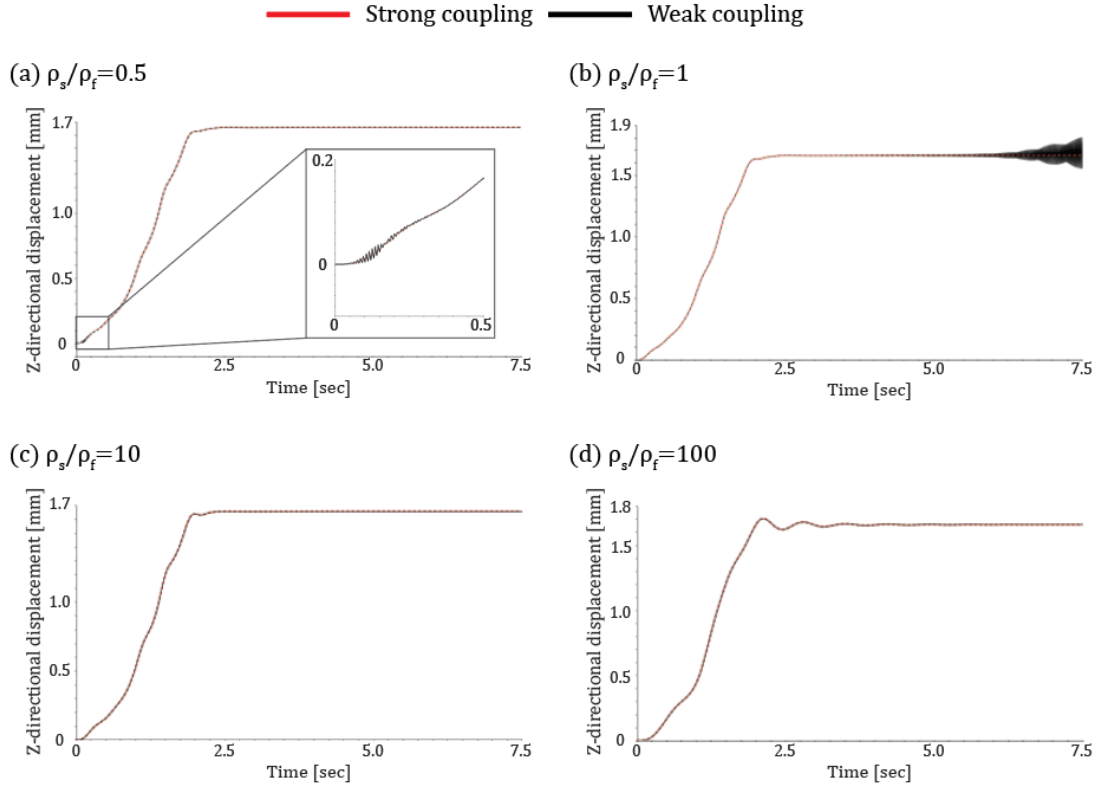


Figure 6.10. Static scenario. Strong vs weak coupling comparison.

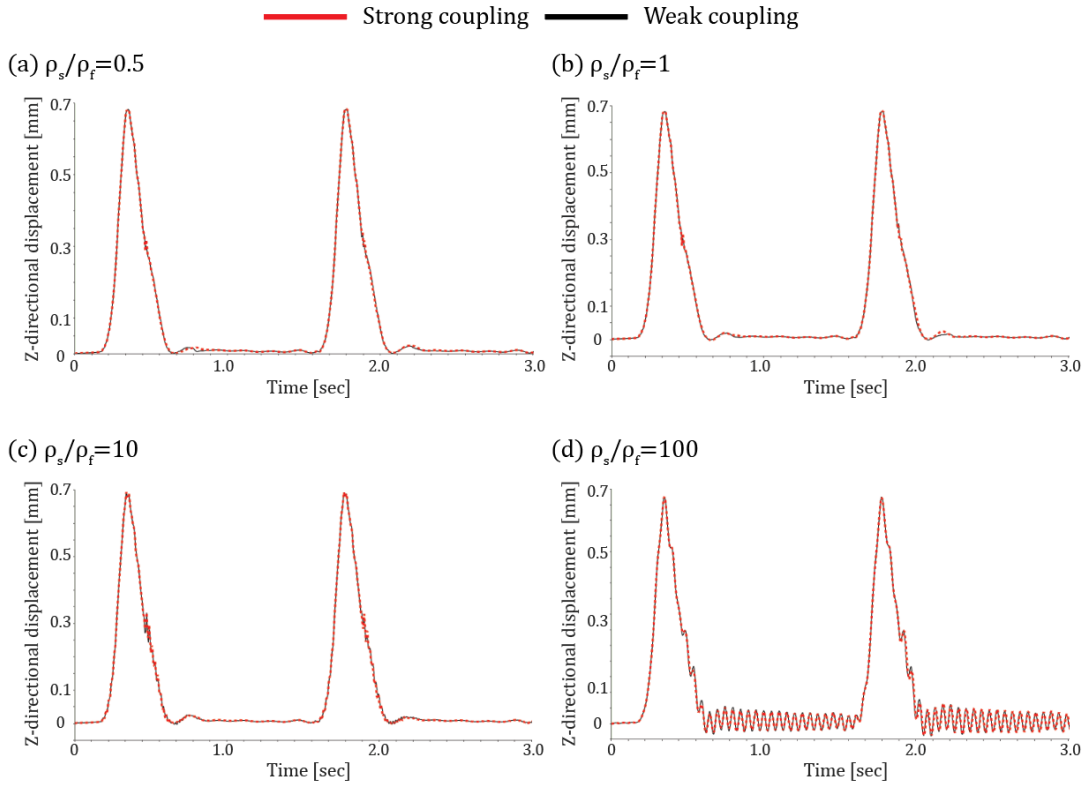


Figure 6.11. Dynamic scenario. Strong vs weak coupling comparison.

6.3.4 Idealized 3D type-B aortic dissection

In this example, an idealized 3D geometrical model of a 3D type-B aortic dissection was constructed (Figure 6.12 panel (a)). The fluid domain is the aorta with uniform diameter and length of 30 and 225 mm, respectively. Figure 6.12 panel (b) shows the solid domain which represents the intimal flap. The intimal flap has a 1 mm uniform thickness and a total length of 200 mm. An intimal flap has one 20 mm diameter circular entry tear and one 10 mm circular exit tear. The flap has a constant curvature along the axial direction and divides the descending thoracic aorta and abdominal aorta into a true lumen (TL) and false lumen (FL) with areas of 218 mm^2 and 489 mm^2 , respectively (Figure 6.12 panel (c)). The distance between the intimal flap and aortic wall of TL and FL are 9 mm and 21 mm, respectively. Mesh independent studies were conducted using three different mesh sizes: 1 mm, 0.7 mm, and 0.5 mm with 1.2M, 3.6M, and 9.5M fluid elements, respectively. Convergence was achieved for the maximum intimal flap displacement during the systole (maximum displacement difference by 0.98 % between 0.7 mm and 0.5 mm mesh sizes). The following simulations were conducted with mesh size of 0.7 mm. Fluid domain consists of 3.6M uniform, unstructured tetrahedral elements. Solid domain consists of 297K uniform triangular elements.

Prescribed pulsatile flow, no-slip, and three-element Windkessel boundary conditions were assigned at the inlet, lateral wall, and outlet of the fluid domain, respectively (see Figure 6.12 panel (a)). R_1 , R_2 , and C values were assigned as $0.023 \text{ g/mm}^4\text{s}$, $0.091 \text{ g/mm}^4\text{s}$, and $16.54 \text{ mm}^4\text{s}^2/\text{g}$, respectively. We simulated two cardiac cycles. For the solid, external edges which attached to the aortic wall were fixed while the tear edges were free to move.

The blood density and viscosity were set to 0.00106 g/mm^3 and 0.004 g/mm s , respectively. The intimal flap density was set to 0.00106 g/mm^3 . The material stiffness of the intimal flap has not been thoroughly reported. In this study we assumed that the intimal flap is less stiff than the aorta. This assumption is based on the fact that the intimal flap originates from the inner layer of the aortic wall. The inner layer consists primarily of elastin fibers, which are more compliant than the collagen fibers that are more prevalent in the outer layers of the aortic wall [91]. The material stiffness of the aorta has been reported to be $0.5 \sim 1 \times 10^6 \text{ Pa}$ [92]. Therefore, we assumed the elastic modulus of the intimal flap to be $2 \times 10^4 \text{ Pa}$. The step size was set to $\Delta t = 1e^{-4} \text{ sec}$ to ensure that the maximum CFL number remained below 1. The simulation consists of

27,000-time steps, corresponding to a final time of 2.7 sec. The maximum and average Reynolds numbers were 5,400 and 1,200, respectively.

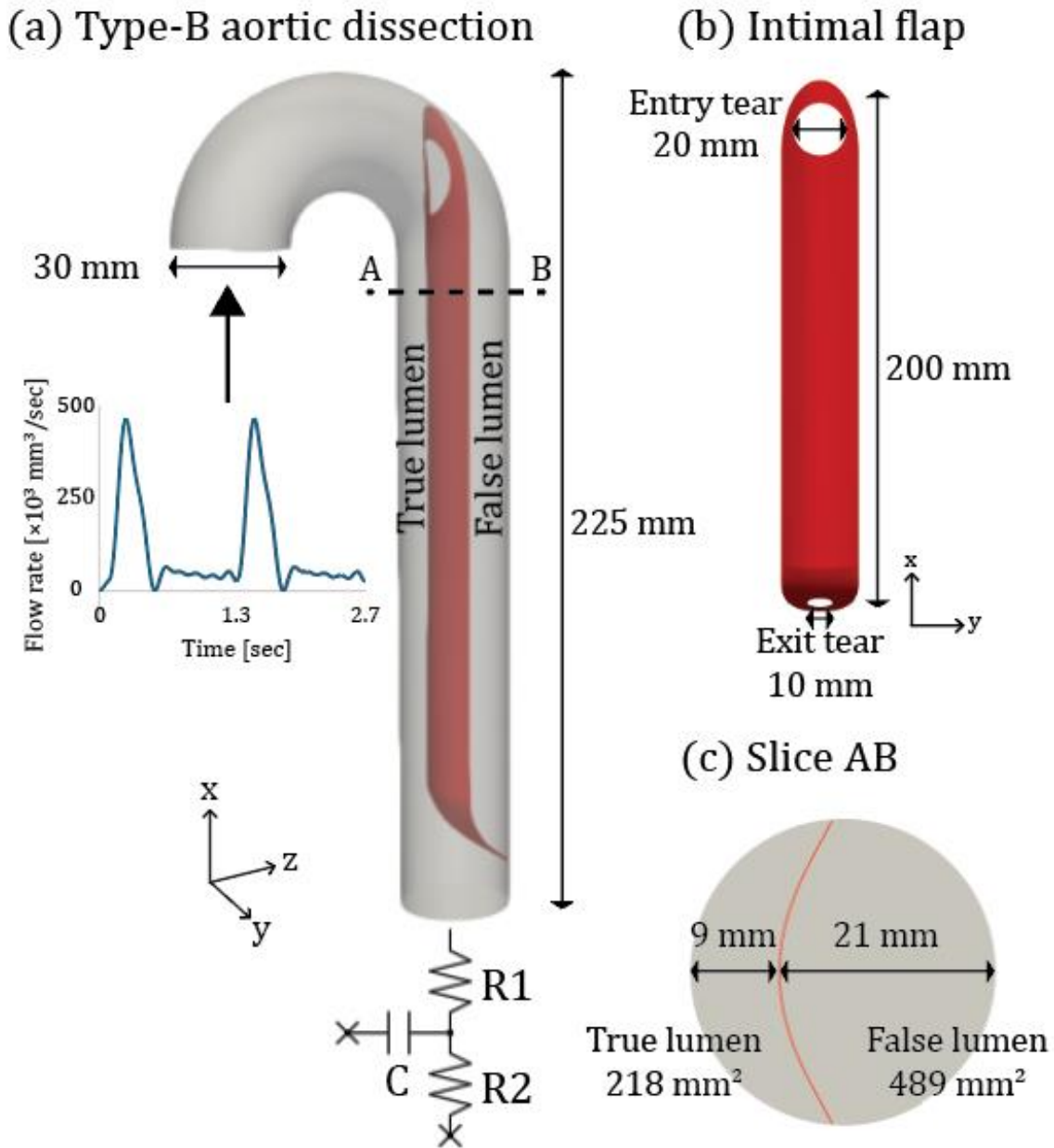


Figure 6.12. Schematic of the computational domain and boundary conditions for the idealized aortic dissection model.

Figure 6.13 shows the intimal flap displacement at diastole and systole. Panel (a) illustrates the 3D intimal flap configurations. As inlet flow increases during systole, the intimal flap deforms toward the FL (positive z -direction). The largest displacement (9.79 mm) occurs near the entry tear. Panel (b) shows the YZ plane at slice AB, which is 10 mm below the entry tear. In diastole, the maximum length between the intimal flap and the aortic wall are 9 mm and 21 mm for the TL

and FL, respectively. TL and FL cross section area are 218 mm^2 and 489 mm^2 , respectively. As the intimal flap deforms, the maximum length between the intimal flap and the aortic wall becomes 17.6 mm and 12.4 mm for the TL and FL, respectively. TL and FL cross section area are 386 mm^2 and 321 mm^2 , respectively. Panel (c) shows the intimal flap configurations of XY plane at mid slice.

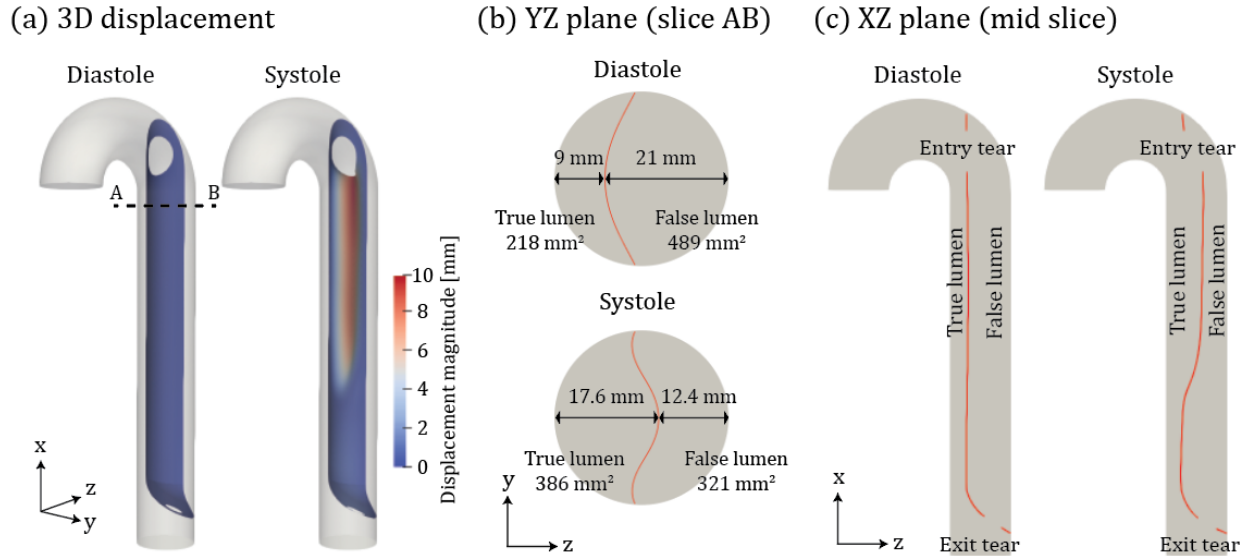


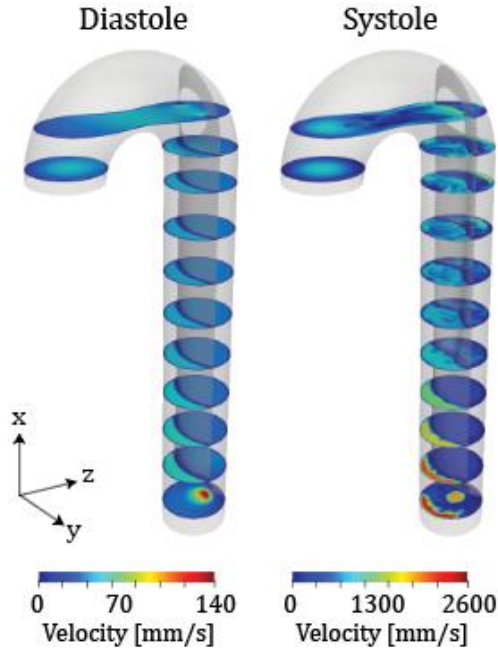
Figure 6.13. Intimal flap displacement on diastole and systole. (a) 3D displacement, (b) YZ plane (slice AB), and (c) XZ plane (mid slice).

Figure 6.14 shows velocity and pressure contours in different planes during diastole and systole. Panels (a) and (b) illustrate velocity distributions on various YZ plane slices and the XZ plane mid slice, respectively. During diastole, a high velocity ($\sim 140 \text{ mm/s}$) is observed at the exit tear, which is attributable to the relatively smaller area of the exit tear (314 mm^2) compared to the entry tear (78.5 mm^2). Additionally, the TL velocity ($\sim 70 \text{ mm/s}$) is higher than the FL velocity ($\sim 50 \text{ mm/s}$) near the distal region of the intimal flap, due to the smaller cross-sectional area.

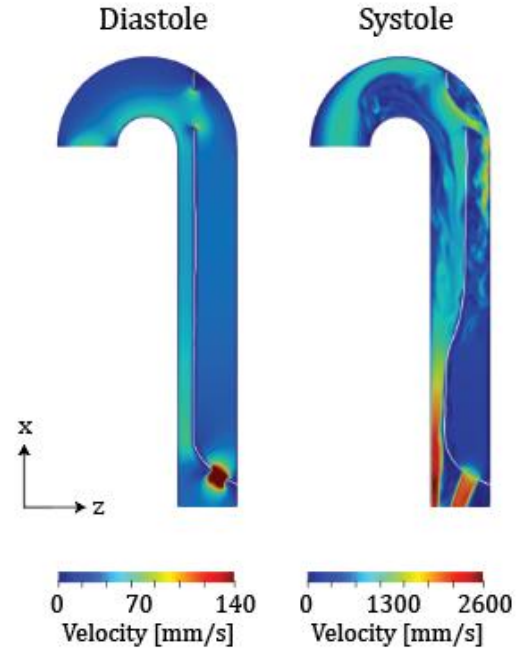
In systole, increased inflow raises the velocity through the entry tear to $\sim 1500 \text{ mm/s}$, directing the jet toward the FL side aortic wall (see Figure 6.14, panel (b), Systole). The velocity through the exit tear also increases significantly, reaching $\sim 2000 \text{ mm/s}$. As the intimal flap moves toward the FL, the proximal TL area increases. As a result, the TL velocity at this region shows a relatively moderate increase to $\sim 1000 \text{ mm/s}$, while the distal TL velocity increases sharply to 2600 mm/s with minimal intimal flap motion. During systole, large and rapid intimal

flap motion (within <0.5 seconds) leads to flow disturbances near the proximal part of the intimal flap in both the TL and FL.

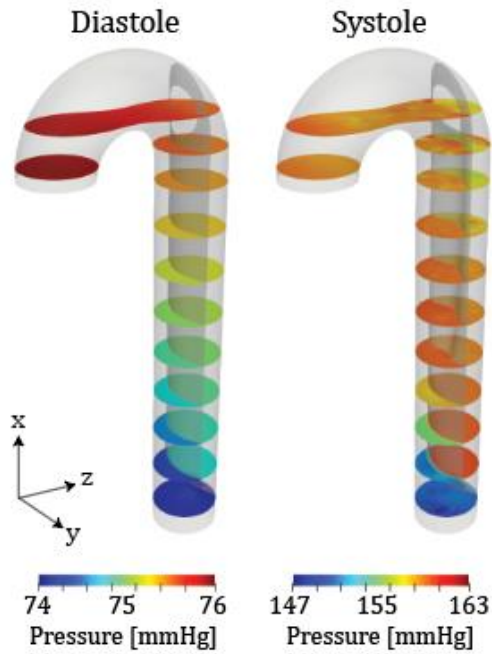
(a) YZ plane (various slices)



(b) XZ plane (mid slice)



(c) YZ plane (various slices)



(d) XZ plane (mid slice)

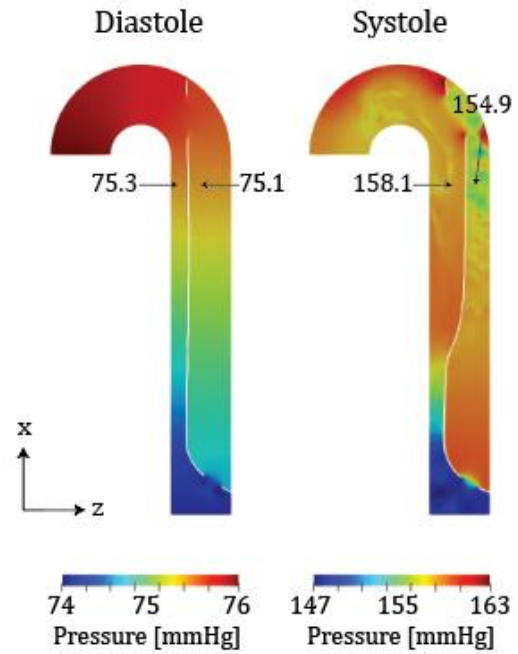


Figure 6.14. Velocity and pressure contour on the diastole and systole. Velocity: (a) YZ plane (various slices) and (b) XZ plane (mid slice). Pressure: (c) YZ plane (various slices) and (d) XZ plane (mid slice).

Figure 6.14 panels (c) and (d) illustrate pressure distributions on various YZ plane slices and the XZ plane mid slice, respectively. Blood pressure increases from 75 mmHg during diastole to 150 mmHg during systole. In diastole, the pressure difference between TL and FL is less than 1 mmHg. During systole, this pressure difference increases to ~ 4 mmHg and leads to large intimal flap motion in the proximal region. These pressure results are consistent with our previous findings in aortic dissection FSI model, which showed that even relatively small pressure difference between TL and FL are sufficient to induce movement of the intimal flap [30].

One limitation of this simplified model is that it includes only a single exit tear. In real cases of aortic dissection, there are often multiple exit tears. Blood flow through these tears can change the hemodynamics of aortic dissection, especially the pressure difference between TL and FL [53].

6.4 Conclusion

In this study, we developed an immersed boundary method formulation for cardiovascular simulations. Our approach couples two pre-existing solvers using direct forcing IBM framework: CRIMSON for fluid domain and FEM based nonlinear rotation-free shell formulation for thin structures. Both strong and weak time coupling schemes were implemented and applied on both static and dynamic problems with various fluid-to-solid density ratios. By using predefined shape functions for the fluid FEM, our method minimizes the need for additional computational resources for interpolation at the fluid-solid interface. To the best of our knowledge, this is the first IBM formulation that integrates an FEM fluid solver with a rotation-free shell solver, thereby providing a robust tool for simulating the interaction between thin structures and incompressible flow. The proposed method was validated using two 3D benchmark problems involving thin structures. As a demonstration of its applicability, we applied the method to an idealized type-B aortic dissection problem, showcasing its potential for future cardiovascular simulations.

6.5 Bibliography

- [1] G. J. Perry, F. Helmcke, N. C. Nanda, C. Byard, and B. Soto, "Evaluation of aortic insufficiency by Doppler color flow mapping," *J Am Coll Cardiol*, vol. 9, no. 4, pp. 952–959, Apr. 1987, doi: 10.1016/S0735-1097(87)80254-1.
- [2] R. T. Eberhardt and J. D. Raffetto, "Chronic venous insufficiency," *Circulation*, vol. 130, no. 4, pp. 333–346, Jul. 2014, doi: 10.1161/CIRCULATIONAHA.113.006898/ASSET/257A1A38-FE24-4CF1-B209-803005F863A9/ASSETS/GRAPHIC/333FIG07.JPEG.

- [3] G. M. Deeb, H. J. Patel, and D. M. Williams, "Treatment for malperfusion syndrome in acute type A and B aortic dissection: A long-term analysis," *Journal of Thoracic and Cardiovascular Surgery*, vol. 140, no. 6 SUPPL., pp. S98–S100, Dec. 2010, doi: 10.1016/j.jtcvs.2010.07.036.
- [4] C. J. Bennett, J. J. Maleszewski, and P. A. Araoz, "CT and MR imaging of the aortic valve: Radiologic-pathologic correlation," *Radiographics*, vol. 32, no. 5, pp. 1399–1420, Sep. 2012, doi: 10.1148/RG.325115727/ASSET/IMAGES/LARGE/115727FIG13C.JPEG.
- [5] "Venous Valves: Morphology, Function, Radiology, Surgery - R. Gottlob, R. May - Google Books." Accessed: Jun. 09, 2025. [Online].
- [6] R. R. Baliga et al., "The role of imaging in aortic dissection and related syndromes," *JACC Cardiovasc Imaging*, vol. 7, no. 4, pp. 406–424, 2014, doi: 10.1016/J.JCMG.2013.10.015;PAGEGROUP:STRING:PUBLICATION.
- [7] H. Jilaihawi et al., "A Bicuspid Aortic Valve Imaging Classification for the TAVR Era," *JACC Cardiovasc Imaging*, vol. 9, no. 10, pp. 1145–1158, Oct. 2016, doi: 10.1016/J.JCMG.2015.12.022;JOURNAL:JOURNAL:JCMG;ITEMPARENTTOPIC:TOPIC:CME>HAS-CME;PAGE:STRING:ARTICLE/CHAPTER.
- [8] H. Baumgartner et al., "Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography," *Eur Heart J Cardiovasc Imaging*, vol. 18, no. 3, pp. 254–275, Mar. 2017, doi: 10.1093/EHJCI/JEW335.
- [9] C. A. Nienaber et al., "Diagnosis of thoracic aortic dissection: Magnetic resonance imaging versus transesophageal echocardiography," *Circulation*, vol. 85, no. 2, pp. 434–447, 1992, doi: 10.1161/01.CIR.85.2.434;WGROUPE:STRING:PUBLICATION.
- [10] D. Spinelli et al., "Current evidence in predictors of aortic growth and events in acute type B aortic dissection," *J Vasc Surg*, vol. 68, no. 6, pp. 1925–1935.e8, Dec. 2018, doi: 10.1016/J.JVS.2018.05.232.
- [11] C. J. François et al., "Four-dimensional, flow-sensitive magnetic resonance imaging of blood flow patterns in thoracic aortic dissections," *J Thorac Cardiovasc Surg*, vol. 145, no. 5, pp. 1359–1366, May 2013, doi: 10.1016/J.JTCVS.2012.07.019.
- [12] J. J. M. Westenberg et al., "Mitral valve and tricuspid valve blood flow: Accurate quantification with 3D velocity-encoded MR imaging with retrospective valve tracking,"

- Radiology, vol. 249, no. 3, pp. 792–800, Dec. 2008, doi: 10.1148/RADIOL.2492080146/ASSET/IMAGES/LARGE/R08NV18T04X.JPEG.
- [13] “Computational Fluid-Structure Interaction: Methods and Applications - Yuri Bazilevs, Kenji Takizawa, Tayfun E. Tezduyar - Google Books.” Accessed: Jun. 09, 2025. [Online].
- [14] G. Hou, J. Wang, and A. Layton, “Numerical Methods for Fluid-Structure Interaction — A Review,” *Commun Comput Phys*, vol. 12, no. 2, pp. 337–377, Aug. 2012, doi: 10.4208/CICP.291210.290411S.
- [15] B. Hübner, E. Walhorn, and D. Dinkler, “A monolithic approach to fluid–structure interaction using space–time finite elements,” *Comput Methods Appl Mech Eng*, vol. 193, no. 23–26, pp. 2087–2104, Jun. 2004, doi: 10.1016/J.CMA.2004.01.024.
- [16] C. Michler, S. J. Hulshoff, E. H. van Brummelen, and R. de Borst, “A monolithic approach to fluid–structure interaction,” *Comput Fluids*, vol. 33, no. 5–6, pp. 839–848, Jun. 2004, doi: 10.1016/J.COMPFLUID.2003.06.006.
- [17] D. Kamensky, M. Hsu, D. Schillinger, ... J. E.-C. methods in, and undefined 2015, “An immersogeometric variational framework for fluid–structure interaction: Application to bioprosthetic heart valves,” ElsevierD Kamensky, MC Hsu, D Schillinger, JA Evans, A Aggarwal, Y Bazilevs, MS SacksComputer methods in applied mechanics and engineering, 2015•Elsevier, Accessed: Jun. 10, 2025. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0045782514004101>
- [18] C. Habchi et al., “Partitioned solver for strongly coupled fluid–structure interaction,” *Comput Fluids*, vol. 71, pp. 306–319, Jan. 2013, doi: 10.1016/J.COMPFLUID.2012.11.004.
- [19] W. Kim, I. Lee, and H. Choi, “A weak-coupling immersed boundary method for fluid–structure interaction with low density ratio of solid to fluid,” *J Comput Phys*, vol. 359, pp. 296–311, Apr. 2018, doi: 10.1016/J.JCP.2017.12.045.
- [20] I. Borazjani, L. Ge, F. S.-J. of C. physics, and undefined 2008, “Curvilinear immersed boundary method for simulating fluid structure interaction with complex 3D rigid bodies,” ElsevierI Borazjani, L Ge, F SotiropoulosJournal of Computational physics, 2008•Elsevier, Accessed: Jun. 03, 2025. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0021999108002490>

- [21] H. G. Matthies and J. Steindorf, "Partitioned strong coupling algorithms for fluid–structure interaction," *Comput Struct*, vol. 81, no. 8–11, pp. 805–812, May 2003, doi: 10.1016/S0045-7949(02)00409-1.
- [22] C. W. Hirt, A. A. Amsden, and J. L. Cook, "An arbitrary Lagrangian-Eulerian computing method for all flow speeds," *J Comput Phys*, vol. 14, no. 3, pp. 227–253, Mar. 1974, doi: 10.1016/0021-9991(74)90051-5.
- [23] M. S. Gadala, M. R. Movahhedy, and J. Wang, "On the mesh motion for ALE modeling of metal forming processes," *Finite Elements in Analysis and Design*, vol. 38, no. 5, pp. 435–459, Mar. 2002, doi: 10.1016/S0168-874X(01)00080-4.
- [24] A. Shamanskiy and B. Simeon, "Mesh moving techniques in fluid-structure interaction: robustness, accumulated distortion and computational efficiency," *Comput Mech*, vol. 67, no. 2, pp. 583–600, Feb. 2021, doi: 10.1007/S00466-020-01950-X/TABLES/2.
- [25] A. Leuprecht, S. Kozerke, P. Boesiger, and K. Perktold, "Blood flow in the human ascending aorta: a combined MRI and CFD study," *SpringerA Leuprecht, S Kozerke, P Boesiger, K PerktoldJournal of engineering mathematics*, 2003•Springer, vol. 47, no. 3–4, pp. 387–404, Dec. 2003, doi: 10.1023/B:ENGL.00000007969.18105.B7.
- [26] P. Le Tallec and J. Mouro, "Fluid structure interaction with large structural displacements," *Comput Methods Appl Mech Eng*, vol. 190, no. 24–25, pp. 3039–3067, Mar. 2001, doi: 10.1016/S0045-7825(00)00381-9.
- [27] M. Alishahi, M. M. Alishahi, and H. Emdad, "Numerical simulation of blood flow in a flexible stenosed abdominal real aorta," *Scientia Iranica*, vol. 18, no. 6, pp. 1297–1305, Dec. 2011, doi: 10.1016/J.SCIENT.2011.11.021.
- [28] A. Qiao, W. Yin, and B. Chu, "Numerical simulation of fluid–structure interaction in bypassed DeBakey III aortic dissection," *Comput Methods Biomech Biomed Engin*, vol. 18, no. 11, pp. 1173–1180, Aug. 2015, doi: 10.1080/10255842.2014.881806;SUBPAGE:STRING:FULL.
- [29] K. Bäumlér et al., "Fluid–structure interaction simulations of patient-specific aortic dissection," *Biomech Model Mechanobiol*, vol. 19, no. 5, pp. 1607–1628, Oct. 2020, doi: 10.1007/S10237-020-01294-8/FIGURES/12.
- [30] T. Kim et al., "A Computational Study of Dynamic Obstruction in Type B Aortic Dissection," *J Biomech Eng*, vol. 145, no. 3, Mar. 2023, doi: 10.1115/1.4056355/1152231.

- [31] C. S. Peskin, “The immersed boundary method,” *Acta Numerica*, vol. 11, pp. 479–517, Jan. 2002, doi: 10.1017/S0962492902000077.
- [32] Y. Kim, C. P.-P. of Fluids, and undefined 2007, “Penalty immersed boundary method for an elastic boundary with mass,” *pubs.aip.org*, Accessed: Jun. 10, 2025. [Online]. Available: <https://pubs.aip.org/aip/pof/article/19/5/053103/256858>
- [33] B. Griffith, C. P.-J. of C. Physics, and undefined 2005, “On the order of accuracy of the immersed boundary method: Higher order convergence rates for sufficiently smooth problems,” Elsevier, Accessed: Jun. 10, 2025. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0021999105000835>
- [34] R. Mittal, H. Dong, M. Bozkurtas, ... F. N.-J. of computational, and undefined 2008, “A versatile sharp interface immersed boundary method for incompressible flows with complex boundaries,” Elsevier R Mittal, H Dong, M Bozkurtas, FM Najjar, A Vargas, A Von Loebbecke *Journal of computational physics*, 2008 • Elsevier, Accessed: Jun. 12, 2025. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0021999108000235>
- [35] Y. Tseng, J. F.-J. of computational physics, and undefined 2003, “A ghost-cell immersed boundary method for flow in complex geometry,” Elsevier YH Tseng, JH Ferziger *Journal of computational physics*, 2003 • Elsevier, Accessed: Jun. 10, 2025. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0021999103004108>
- [36] M. Uhlmann, “An immersed boundary method with direct forcing for the simulation of particulate flows,” *J Comput Phys*, vol. 209, no. 2, pp. 448–476, Nov. 2005, doi: 10.1016/J.JCP.2005.03.017.
- [37] L. Ge and F. Sotiropoulos, “A numerical method for solving the 3D unsteady incompressible Navier–Stokes equations in curvilinear domains with complex immersed boundaries,” *J Comput Phys*, vol. 225, no. 2, pp. 1782–1809, Aug. 2007, doi: 10.1016/J.JCP.2007.02.017.
- [38] M. D. De Tullio, A. Cristallo, E. Balaras, and R. Verzicco, “Direct numerical simulation of the pulsatile flow through an aortic bileaflet mechanical heart valve,” *J Fluid Mech*, vol. 622, pp. 259–290, 2009, doi: 10.1017/S0022112008005156.
- [39] B. E. Griffith, X. Luo, D. M. McQueen, and C. S. Peskin, “Simulating the fluid dynamics of natural and prosthetic heart valves using the immersed boundary method,” *Int J Appl Mech*, vol.

1, no. 1, pp. 137–177, Mar. 2009, doi:

10.1142/S1758825109000113;WGROU:STRING:WSPC.

[40] M. Astorino, J. F. Gerbeau, O. Pantz, and K. F. Traoré, “Fluid–structure interaction and multi-body contact: Application to aortic valves,” *Comput Methods Appl Mech Eng*, vol. 198, no. 45–46, pp. 3603–3612, Sep. 2009, doi: 10.1016/J.CMA.2008.09.012.

[41] I. Zreid, R. Behnke, and M. Kaliske, “ALE formulation for thermomechanical inelastic material models applied to tire forming and curing simulations,” *Comput Mech*, vol. 67, no. 6, pp. 1543–1557, Jun. 2021, doi: 10.1007/S00466-021-02005-5/FIGURES/15.

[42] G. L. Nicolson, “The Fluid—Mosaic Model of Membrane Structure: Still relevant to understanding the structure, function and dynamics of biological membranes after more than 40 years,” *Biochimica et Biophysica Acta (BBA) - Biomembranes*, vol. 1838, no. 6, pp. 1451–1466, Jun. 2014, doi: 10.1016/J.BBAMEM.2013.10.019.

[43] A. Bonito, R. H. Nochetto, and M. Sebastian Pauletti, “Parametric FEM for geometric biomembranes,” *J Comput Phys*, vol. 229, no. 9, pp. 3171–3188, May 2010, doi: 10.1016/J.JCP.2009.12.036.

[44] A. Gilmanov, T. B. Le, and F. Sotiropoulos, “A numerical approach for simulating fluid structure interaction of flexible thin shells undergoing arbitrarily large deformations in complex domains,” *J Comput Phys*, vol. 300, pp. 814–843, Nov. 2015, doi: 10.1016/J.JCP.2015.08.008.

[45] A. Nitti, J. Kiendl, A. Reali, and M. D. de Tullio, “An immersed-boundary/isogeometric method for fluid–structure interaction involving thin shells,” *Comput Methods Appl Mech Eng*, vol. 364, p. 112977, Jun. 2020, doi: 10.1016/J.CMA.2020.112977.

[46] J. Boustani, M. F. Barad, C. C. Kiris, and C. Brehm, “An immersed boundary fluid–structure interaction method for thin, highly compliant shell structures,” *J Comput Phys*, vol. 438, p. 110369, Aug. 2021, doi: 10.1016/J.JCP.2021.110369.

[47] C. A. Taylor, T. J. R. Hughes, and C. K. Zarins, “Finite element modeling of blood flow in arteries,” *Comput Methods Appl Mech Eng*, vol. 158, no. 1–2, pp. 155–196, May 1998, doi: 10.1016/S0045-7825(98)80008-X.

[48] C. A. Taylor and C. A. Figueroa, “Patient-specific modeling of cardiovascular mechanics,” *Annu Rev Biomed Eng*, vol. 11, no. Volume 11, 2009, pp. 109–134, Aug. 2009, doi: 10.1146/ANNUREV.BIOENG.10.061807.160521/CITE/REFWORKS.

- [49] H. J. Kim, I. E. Vignon-Clementel, C. A. Figueroa, K. E. Jansen, and C. A. Taylor, “Developing computational methods for three-dimensional finite element simulations of coronary blood flow,” *Finite Elements in Analysis and Design*, vol. 46, no. 6, pp. 514–525, Jun. 2010, doi: 10.1016/J.FINEL.2010.01.007.
- [50] C. J. Arthurs et al., “CRIMSON: An open-source software framework for cardiovascular integrated modelling and simulation,” *PLoS Comput Biol*, vol. 17, no. 5, p. e1008881, May 2021, doi: 10.1371/JOURNAL.PCBI.1008881.
- [51] T. M. J. Van Bakel et al., “Cardiac remodelling following thoracic endovascular aortic repair for descending aortic aneurysms,” *European Journal of Cardio-Thoracic Surgery*, vol. 55, no. 6, pp. 1061–1070, Jun. 2019, doi: 10.1093/EJCTS/EZY399.
- [52] T. M. Van Bakel et al., “A computational analysis of different endograft designs for Zone 0 aortic arch repair,” *European Journal of Cardio-Thoracic Surgery*, vol. 54, no. 2, pp. 389–396, Aug. 2018, doi: 10.1093/EJCTS/EZY068.
- [53] D. Dillon-Murphy, A. Noorani, D. Nordsletten, and C. A. Figueroa, “Multi-modality image-based computational analysis of haemodynamics in aortic dissection,” *Biomech Model Mechanobiol*, vol. 15, no. 4, pp. 857–876, Aug. 2016, doi: 10.1007/S10237-015-0729-2.
- [54] L. Zhang, A. Gerstenberger, X. Wang, and W. K. Liu, “Immersed finite element method,” *Comput Methods Appl Mech Eng*, vol. 193, no. 21–22, pp. 2051–2067, May 2004, doi: 10.1016/J.CMA.2003.12.044.
- [55] W. K. Liu et al., “Immersed finite element method and its applications to biological systems,” *Comput Methods Appl Mech Eng*, vol. 195, no. 13–16, pp. 1722–1749, Feb. 2006, doi: 10.1016/J.CMA.2005.05.049.
- [56] N. Nama, M. Aguirre, J. D. Humphrey, and C. A. Figueroa, “A nonlinear rotation-free shell formulation with prestressing for vascular biomechanics,” *Sci Rep*, vol. 10, no. 1, pp. 1–17, Dec. 2020, doi: 10.1038/S41598-020-74277-5;SUBJMETA=1041,166,639,705,985;KWRD=APPLIED+MATHEMATICS,BIOMEDICAL+ENGINEERING.
- [57] J. Chung and G. M. Hulbert, “A Time Integration Algorithm for Structural Dynamics With Improved Numerical Dissipation: The Generalized- α Method,” *J Appl Mech*, vol. 60, no. 2, pp. 371–375, Jun. 1993, doi: 10.1115/1.2900803.

- [58] T. Belytschko, W. Liu, B. Moran, and K. Elkhodary, Nonlinear finite elements for continua and structures. 2014. Accessed: Jun. 01, 2025. [Online]. Available: <https://books.google.com/books?hl=en&lr=&id=BQpfAQAAQBAJ&oi=fnd&pg=PA21&dq=Nonlinear+Finite+Elements+for+Continua+and+Structures&ots=PVaEagpWTp&sig=mY-BTXHmcnEKXhh-jGvQer-4m70>
- [59] M. Bischoff, K.-U. Bletzinger, W. A. Wall, and E. Ramm, “Models and Finite Elements for Thin-Walled Structures,” *Encyclopedia of Computational Mechanics*, Aug. 2004, doi: 10.1002/0470091355.ECM026.
- [60] Z. Liu, W. Hong, Z. Suo, S. Swaddiwudhipong, and Y. Zhang, “Modeling and simulation of buckling of polymeric membrane thin film gel,” *Comput Mater Sci*, vol. 49, no. 1, pp. S60–S64, Jul. 2010, doi: 10.1016/J.COMMATSCI.2009.12.036.
- [61] E. Lac, D. Barthès-Biesel, N. A. Pelekasis, and J. Tsamopoulos, “Spherical capsules in three-dimensional unbounded Stokes flows: effect of the membrane constitutive law and onset of buckling,” *J Fluid Mech*, vol. 516, pp. 303–334, Oct. 2004, doi: 10.1017/S002211200400062X.
- [62] M. Lenz, D. J. G. Crow, and J. F. Joanny, “Membrane Buckling Induced by Curved Filaments,” *Phys Rev Lett*, vol. 103, no. 3, p. 038101, Aug. 2009, doi: 10.1103/PHYSREVLETT.103.038101/FIGURES/3/MEDIUM.
- [63] “Cardiovascular Solid Mechanics: Cells, Tissues, and Organs - Jay D. Humphrey - Google Books.” Accessed: Jun. 01, 2025. [Online]. Available: <https://books.google.com/books?hl=en&lr=&id=gwbSBwAAQBAJ&oi=fnd&pg=PA107&dq=Cardiovascular+Solid+Mechanics:+Cells,+Tissues,+and+Organs&ots=58IIMjsJID&sig=AbIfg2KJLv4q1dcPWxNsc9esjRY#v=onepage&q=Cardiovascular%20Solid%20Mechanics%3A%20Cells%2C%20Tissues%2C%20and%20Organs&f=false>
- [64] “Biomechanics: Mechanical Properties of Living Tissues - Y. C. Fung - Google Books.” Accessed: Jun. 01, 2025. [Online]. Available: <https://books.google.com/books?hl=en&lr=&id=yx3aBwAAQBAJ&oi=fnd&pg=PA1&dq=Biomchanics:+Mechanical+Properties+of+Living+Tissues&ots=fLknizUmrz&sig=ucGiAdYD7QZ8plv4Av7wtHSgiWI#v=onepage&q=Biomechanics%3A%20Mechanical%20Properties%20of%20Living%20Tissues&f=false>

- [65] C. Geuzaine and J. F. Remacle, “Gmsh: A 3-D finite element mesh generator with built-in pre- and post-processing facilities,” *Int J Numer Methods Eng*, vol. 79, no. 11, pp. 1309–1331, Sep. 2009, doi: 10.1002/NME.2579.
- [66] “Isogeometric Analysis: Toward Integration of CAD and FEA - J. Austin Cottrell, Thomas J. R Hughes, Yuri Bazilevs - Google Books.” Accessed: Jun. 01, 2025. [Online].
- [67] S. O. Unverdi and G. Tryggvason, “A front-tracking method for viscous, incompressible, multi-fluid flows,” *J Comput Phys*, vol. 100, no. 1, pp. 25–37, May 1992, doi: 10.1016/0021-9991(92)90307-K.
- [68] M. Vanella and E. Balaras, “A moving-least-squares reconstruction for embedded-boundary formulations,” *J Comput Phys*, vol. 228, no. 18, pp. 6617–6628, Oct. 2009, doi: 10.1016/J.JCP.2009.06.003.
- [69] R. W. Hockney and J. W. Eastwood, “Computer Simulation Using Particles,” *Computer Simulation Using Particles*, Mar. 2021, doi: 10.1201/9780367806934.
- [70] M. D. de Tullio and G. Pascazio, “A moving-least-squares immersed boundary method for simulating the fluid–structure interaction of elastic bodies with arbitrary thickness,” *J Comput Phys*, vol. 325, pp. 201–225, Nov. 2016, doi: 10.1016/j.jcp.2016.08.020.
- [71] P. Moin, J. K.-J. of fluid mechanics, and undefined 1982, “Numerical investigation of turbulent channel flow,” *cambridge.orgP Moin, J KimJournal of fluid mechanics*, 1982•cambridge.org, pp. 341–377, 2082, doi: 10.1017/S0022112082001116.
- [72] J. Yang and E. Balaras, “An embedded-boundary formulation for large-eddy simulation of turbulent flows interacting with moving boundaries,” *J Comput Phys*, vol. 215, no. 1, pp. 12–40, Jun. 2006, doi: 10.1016/j.jcp.2005.10.035.
- [73] E. P. Mucke, I. Saias, and B. Zhu, “Fast randomized point location without preprocessing in two-and three-dimensional Delaunay triangulations,” *Proceedings of the twelfth annual symposium on Computational geometry*, pp. 274–283, 1996, doi: 10.1145/237218.237396.
- [74] M. A. Fernández, “Coupling schemes for incompressible fluid-structure interaction: implicit, semi-implicit and explicit,” *SeMA Journal*, vol. 55, no. 1, pp. 59–108, Sep. 2011, doi: 10.1007/BF03322593/METRICS.
- [75] C. Farhat, K. G. van der Zee, and P. Geuzaine, “Provably second-order time-accurate loosely-coupled solution algorithms for transient nonlinear computational aeroelasticity,”

Comput Methods Appl Mech Eng, vol. 195, no. 17–18, pp. 1973–2001, Mar. 2006, doi: 10.1016/J.CMA.2004.11.031.

[76] R. D. Rausch, J. T. Batinat, and H. T. Y. Yangj, “Euler Flutter Analysis of Airfoils Using Unstructured Dynamic Meshes,” J. AIRCRAFT, vol. 27, no. 5, 1989, doi: 10.2514/3.25295.

[77] C. Farhat and M. Lesoinne, “Two efficient staggered algorithms for the serial and parallel solution of three-dimensional nonlinear transient aeroelastic problems,” Comput Methods Appl Mech Eng, vol. 182, no. 3–4, pp. 499–515, Feb. 2000, doi: 10.1016/S0045-7825(99)00206-6.

[78] S. Rugonyi, K. B.-C.-C. M. in E. and, and undefined 2001, “On finite element analysis of fluid flows fully coupled with structural interactions,” CiteseerS Rugonyi, KJ BatheCMES-Computer Modeling in Engineering and Sciences, 2001•Citeseer, vol. 2, no. 2, pp. 195–212, 2001, Accessed: Jun. 03, 2025.

[79] P. Le Tallec, J. M.-C. methods in applied mechanics and, and undefined 2001, “Fluid structure interaction with large structural displacements,” ElsevierP Le Tallec, J MouroComputer methods in applied mechanics and engineering, 2001•Elsevier, Accessed: Jun. 03, 2025.

[80] “Partitioned analysis approach of the transient coupled... - Google Scholar.” Accessed: Jun. 03, 2025.

[81] C. Förster, W. A. Wall, and E. Ramm, “Artificial added mass instabilities in sequential staggered coupling of nonlinear structures and incompressible viscous flows,” Comput Methods Appl Mech Eng, vol. 196, no. 7, pp. 1278–1293, Jan. 2007, doi: 10.1016/J.CMA.2006.09.002.

[82] P. Causin, J. F. Gerbeau, and F. Nobile, “Added-mass effect in the design of partitioned algorithms for fluid–structure problems,” Comput Methods Appl Mech Eng, vol. 194, no. 42–44, pp. 4506–4527, Oct. 2005, doi: 10.1016/J.CMA.2004.12.005.

[83] U. Küttler, M. Gee, C. Förster, A. Comerford, and W. A. Wall, “Coupling strategies for biomedical fluid-structure interaction problems,” Int J Numer Method Biomed Eng, vol. 26, no. 3–4, pp. 305–321, Mar. 2010, doi: 10.1002/CNM.1281.

[84] B. M. Irons and R. C. Tuck, “A version of the Aitken accelerator for computer iteration,” Int J Numer Methods Eng, vol. 1, no. 3, pp. 275–277, Jul. 1969, doi: 10.1002/NME.1620010306.

[85] U. Küttler and W. A. Wall, “Fixed-point fluid-structure interaction solvers with dynamic relaxation,” Comput Mech, vol. 43, no. 1, pp. 61–72, Feb. 2008, doi: 10.1007/S00466-008-0255-5/METRICS.

- [86] T. He, “On a Partitioned Strong Coupling Algorithm for Modeling Fluid–Structure Interaction,” <https://doi.org/10.1142/S1758825115500210>, vol. 7, no. 2, Apr. 2015, doi: 10.1142/S1758825115500210.
- [87] A. R. Shenoy and C. Kleinstreuer, “Flow over a thin circular disk at low to moderate Reynolds numbers,” *J Fluid Mech*, vol. 605, pp. 253–262, 2008, doi: 10.1017/S0022112008001626.
- [88] F. B. Tian, H. Dai, H. Luo, J. F. Doyle, and B. Rousseau, “Fluid–structure interaction involving large deformations: 3D simulations and applications to biological systems,” *J Comput Phys*, vol. 258, pp. 451–469, Feb. 2014, doi: 10.1016/J.JCP.2013.10.047.
- [89] F. W. Roos and W. W. Willmarth, “Some experimental results on sphere and disk drag,” <https://doi.org/10.2514/3.6164>, vol. 9, no. 2, pp. 285–291, May 2012, doi: 10.2514/3.6164.
- [90] W. X. Huang and H. J. Sung, “Three-dimensional simulation of a flapping flag in a uniform flow,” *J Fluid Mech*, vol. 653, pp. 301–336, 2010, doi: 10.1017/S0022112010000248.
- [91] W. Nichols, “McDonald’s blood flow in arteries,” *Theoretical, experimental and clinical principles*, vol. 67, pp. 321–337, 2005, Accessed: Jul. 14, 2025.
- [92] S. Roccabianca, C. A. Figueroa, G. Tellides, and J. D. Humphrey, “Quantification of regional differences in aortic stiffness in the aging human,” *J Mech Behav Biomed Mater*, vol. 29, pp. 618–634, Jan. 2014, doi: 10.1016/J.JMBBM.2013.01.026.

Chapter 7 Patient-Specific Aortic Dissection Model

In this chapter, we present the pipeline for creating a patient-specific aortic dissection FSI model using the IBM framework described in Chapter 6, illustrated with one example case.

7.1 Patient-specific aortic dissection model generation

Generating a patient-specific aortic dissection model from medical images is a complex task. To utilize the IBM formulation described in Chapter 6, a 3D volumetric model of the aorta, encompassing both the TL and FL, as well as a 2D surface representation of the intimal flap, is required. The model generation pipeline consists of 4 stages:

(1) The aorta model, which includes both TL and FL, is constructed using CRIMSON by following the pipeline described in Figure 1.6. Figure 7.1 shows the patient-specific aorta model from CTA images.

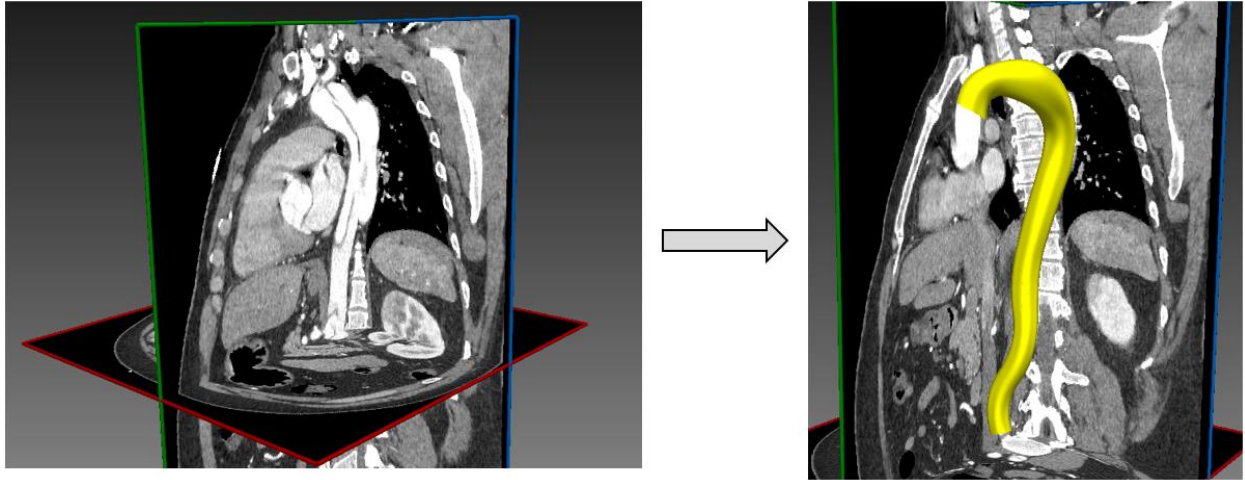


Figure 7.1. Aorta model from CRIMSON.

(2) To create the intimal flap model, 2D segmentation is first performed on image slices that are perpendicular to the path line following the intimal flap immersed in the aortic lumen. This segmentation process must be conducted on a sufficient number of slices to accurately capture both the complex geometry and the curvature variations along the path line. Figure 7.2 presents the results of the 2D segmentations, and the stack of segmented slices visualized in 3D space.

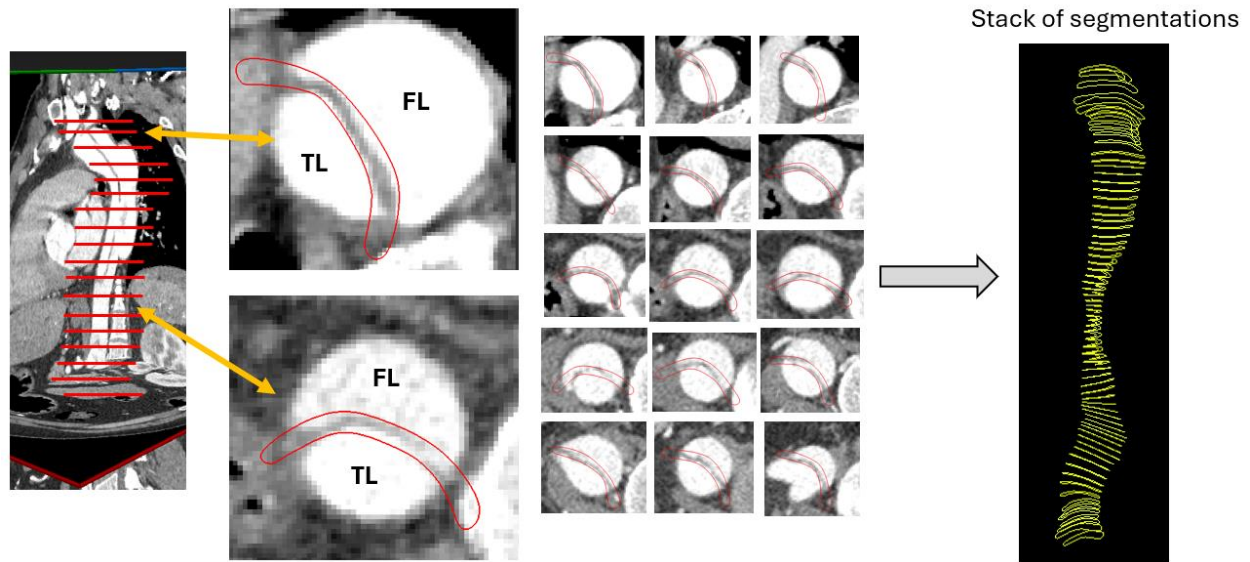


Figure 7.2. 2D segmentation of the intimal flap following the path line.

(3) The 3D volumetric intimal flap model is generated in CRIMSON by integrating the 2D segmentations along the path line and applying volume rendering techniques. Figure 7.3 illustrates the volume rendering of intimal flap.

Volume rendering of segmentations following centerline

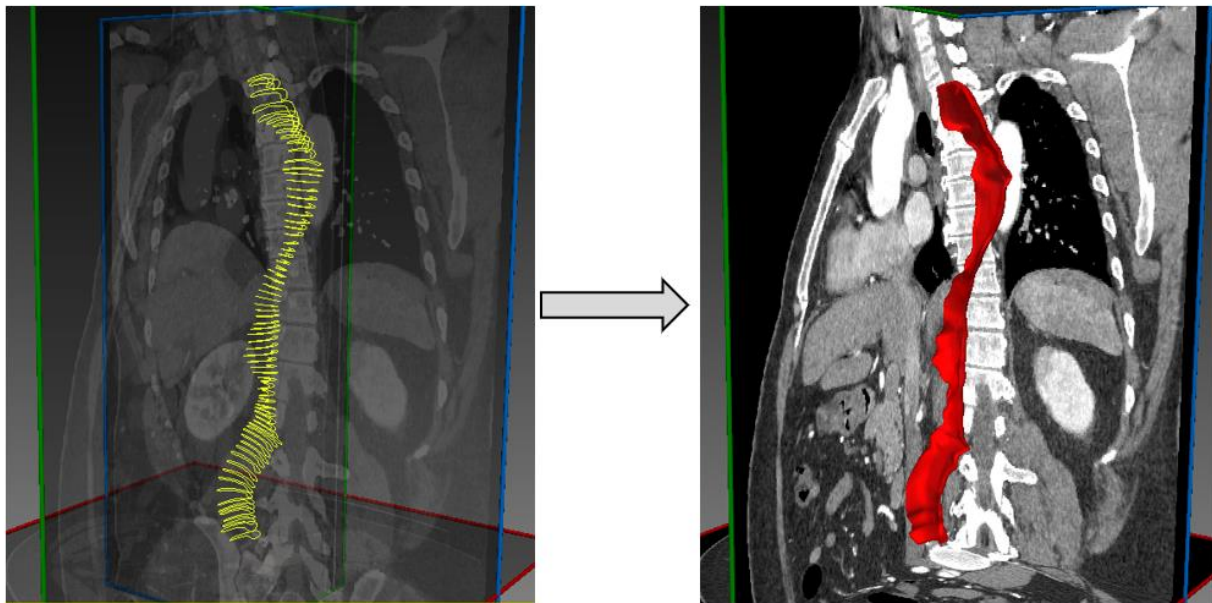


Figure 7.3. 3D intimal flap model generation using volume rendering.

(4) The 3D volumetric intimal flap model is converted to a 2D model using Gmsh software. Boolean operations, including intersection, union, and difference, are applied during this process.

Entry and exit tears are also created using Boolean operators. Figure 7.4 shows the final 2D configuration of intimal flap generated from 3D volumetric model.

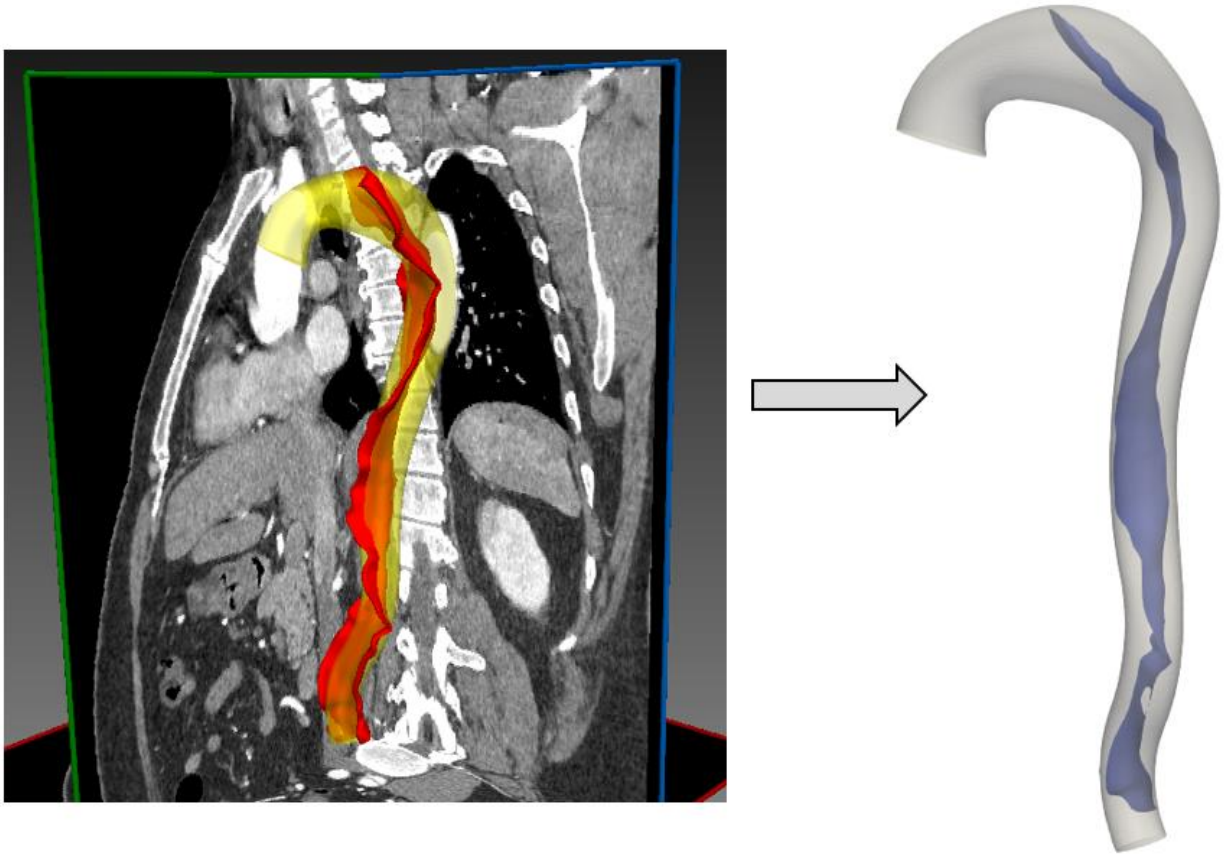


Figure 7.4. 2D intimal flap model generation using Gmsh.

7.2 Meshing and boundary conditions

7.2.1 Meshing

The 3D aorta configuration is discretized into a 3D uniform, unstructured tetrahedral elements using CRIMSON. The 2D intimal flap is discretized with a 2D uniform triangular elements using Gmsh. Fluid and solid elements are of the same size. Figure 7.5 shows the discretized aorta and intimal flap. The aorta mesh consists of 3.6M elements, while the intimal flap uses 2.7K elements.

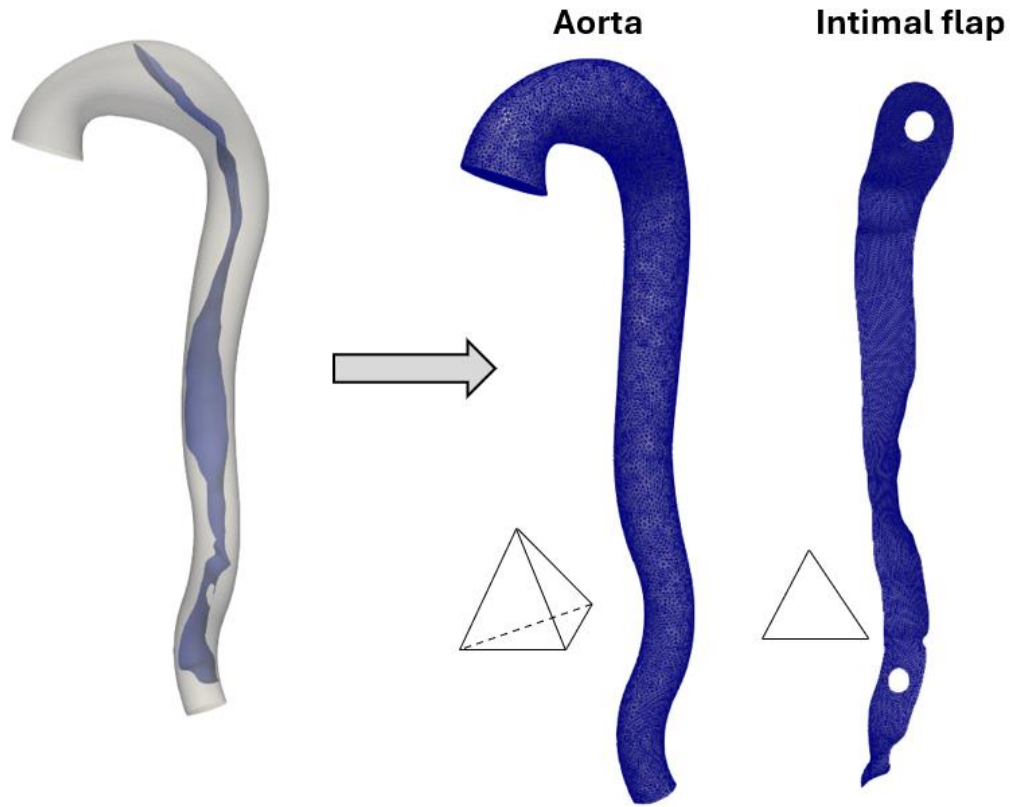


Figure 7.5. Discretized aorta and intimal flap. The aorta uses tetrahedral element, and intimal flap uses triangular element.

7.2.2 Boundary conditions

Figure 7.6 illustrates the boundary conditions assigned to the aortic dissection model. Prescribed pulsatile flow, no-slip, and three-element Windkessel boundary conditions were assigned at the inlet, lateral wall, and outlet of the fluid domain, respectively. R_1 , R_2 , and C values were calculated based on the mean flow and blood pressure. We simulated two cardiac cycles. For the solid, external edges which attached to the aortic wall were fixed while the tear edges were free to move. The blood density and viscosity were set to 0.00106 g/mm^3 and 0.004 g/mm s , respectively. The intimal flap density was set to 0.00106 g/mm^3 . The material stiffness of the intimal flap was set to 20 kPa .

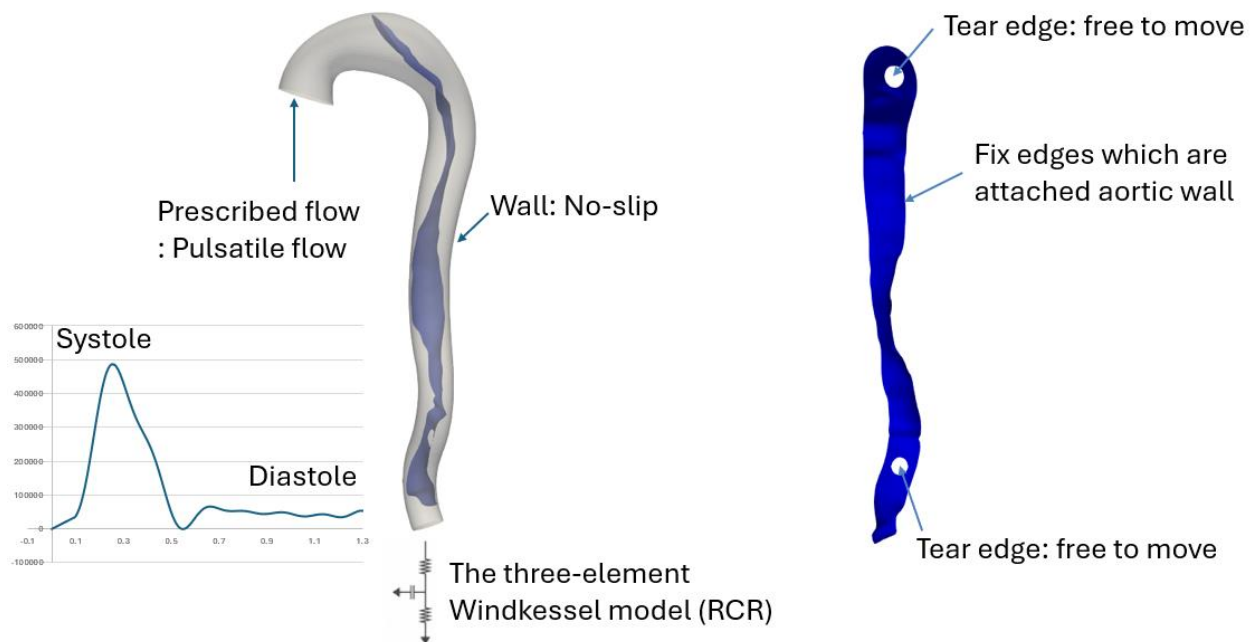


Figure 7.6. Boundary conditions of fluid (aorta) and solid (intimal flap) for the aortic dissection model.

7.3 Results

Figure 7.7 shows the systolic velocity contour of the patient-specific aortic dissection model on top of the CTA image. There is a jet at the entry tear and hit the FL side aortic wall. Overall, TL velocity is higher than FL velocity due to the smaller lumen area.

Figure 7.8 illustrates the pressure contour during diastole and systole. Blood pressure increases from 92 mmHg during diastole to 170 mmHg during systole. In diastole, the pressure difference between TL and FL is less than 1 mmHg. During systole, this pressure difference increases to ~5 mmHg and leads to large intimal flap motion in the proximal region. In this patient-specific model, the largest pressure difference is observed at the middle region of the intimal flap. As a result, largest intimal flap motion also occurs in this region. This location may be influenced by anatomical features of the aorta and the intimal flap. Additionally, the current model includes only one exit tear; the number and location of exit tears may affect the pressure distribution and overall results.

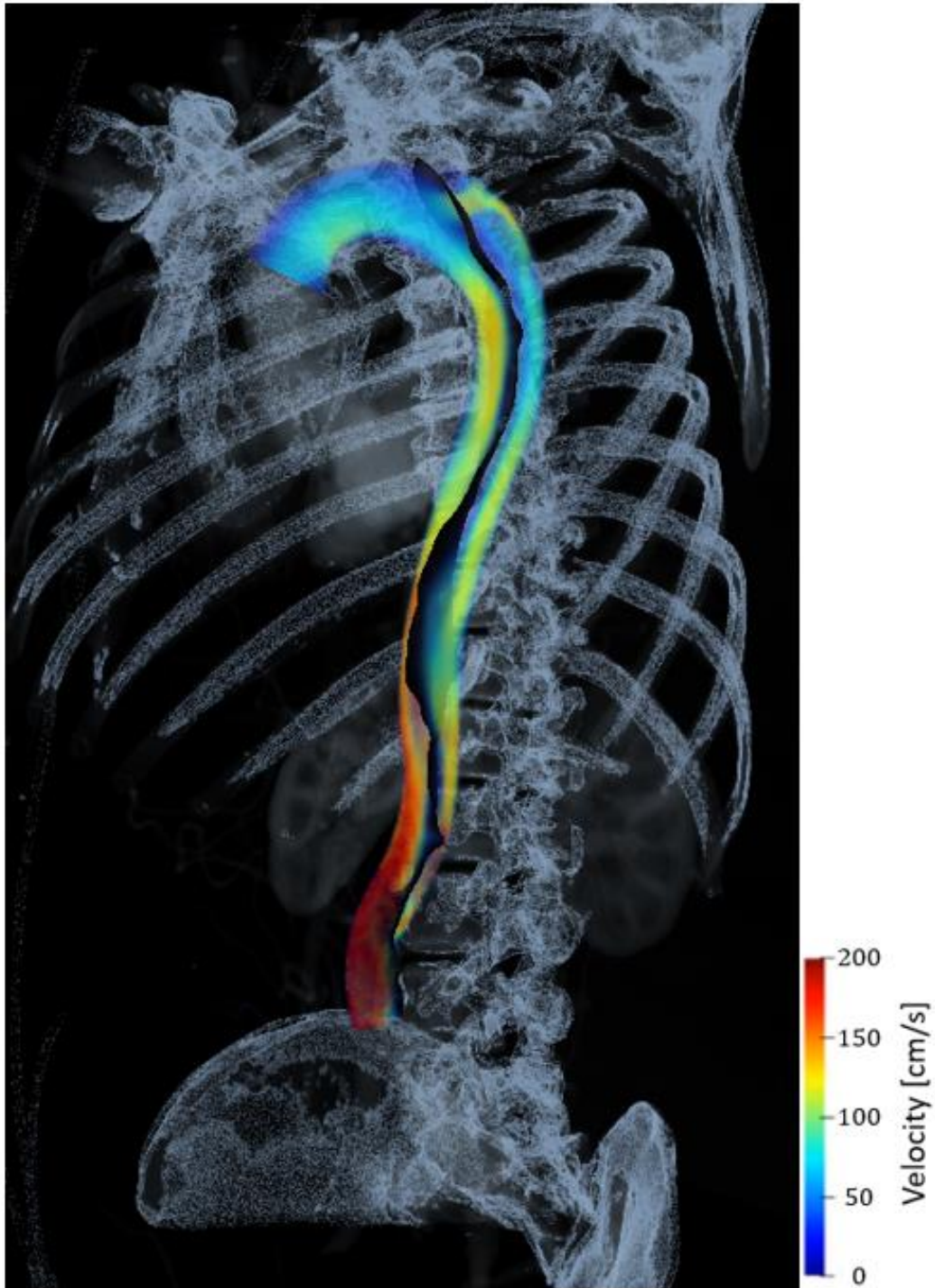
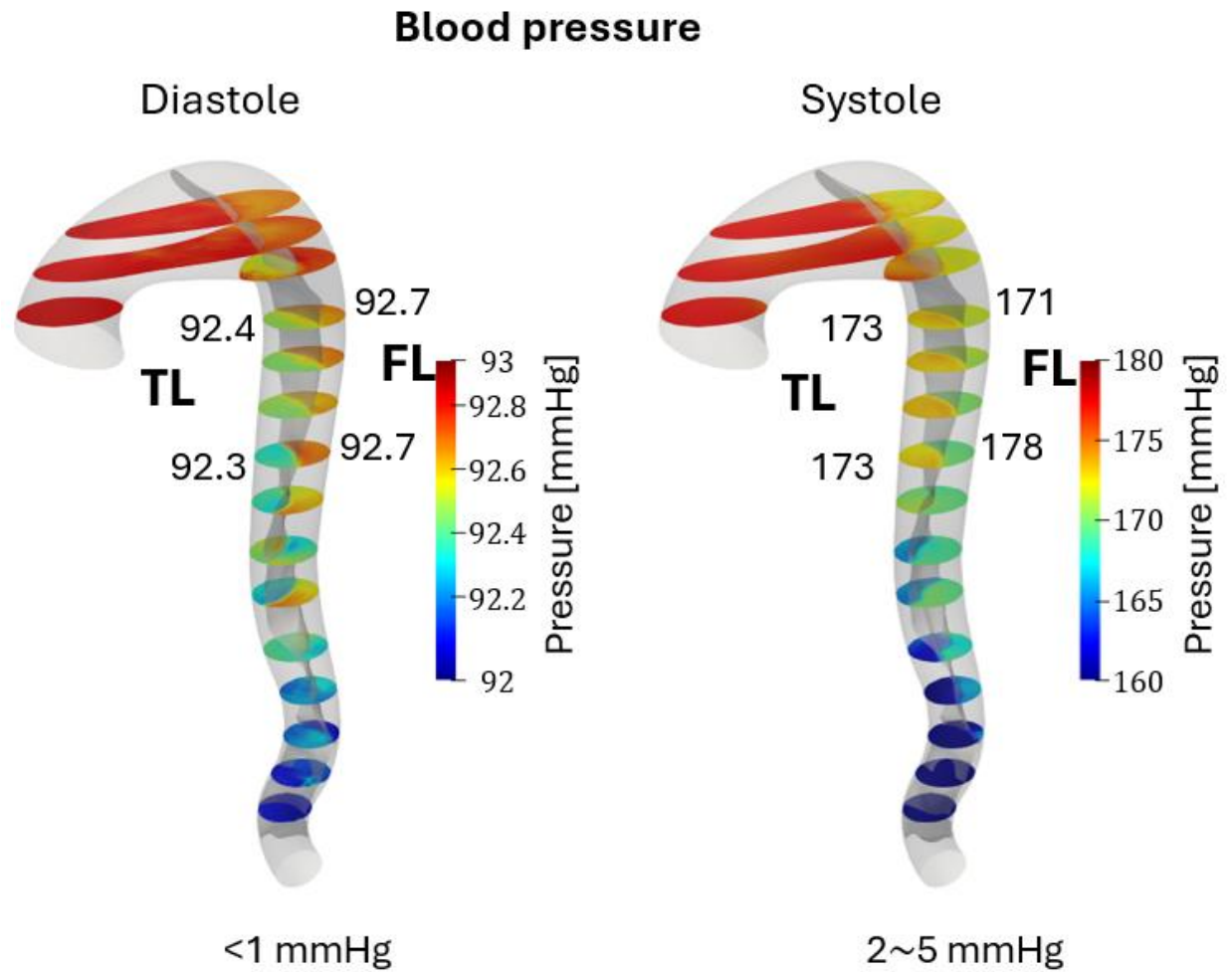


Figure 7.7. Velocity contour of patient specific aortic dissection model.



Pressure difference between TL and FL

Figure 7.8. Pressure contour of aortic dissection model during diastole and systole.

7.4 Conclusion

This chapter explains how to generate patient-specific aortic dissection model. This model was solved with new IBM method introduced in Chapter 6. I also showed the first patient-specific aortic dissection model results using IBM. Our model captured the dynamic intimal flap motion and hemodynamics in the aortic dissection, such as velocity distribution and pressure difference between TL and FL.

Chapter 8 Conclusion and Future Work

8.1 Conclusion

In this thesis, we studied the biomechanics of the aorta using two approaches. First, we demonstrated and applied an advanced technique, VDM, to extract the 3D motion of the entire aorta from CTA medical images. Second, we utilized a FSI algorithm to model the dynamic obstruction problem and developed a novel FSI algorithm that leverages the IBM for aortic dissection problems. We successfully implement this algorithm in a patient-specific aortic dissection model.

In both approaches, we used a nonlinear rotation-free shell formulation. In the VDM work, this formulation was used to generate synthetic data during parameter calibration process. For developing the IBM algorithm, a rotation free shell formulation was used for modeling thin structures immersed in the fluid domain. Despite the widespread use of shell formulations for their computational efficiency, a systematic comparison of these formulations' accuracy and performance in nonlinear vascular biomechanics has been missing. In this thesis, we addressed this gap by performing a comprehensive comparison between the rotation free shell formulation and 3D solid models. We compare results in both idealized and subject-specific mouse aortic geometries. Our results indicate that the rotation free shell formulations offer an effective compromise between computational efficiency and accuracy for vascular biomechanics. With these results, the shell formulation is particularly well-suited to serve as the structural model in fluid-structure interaction framework.

Despite significant advances in medical imaging techniques, the extraction of quantitative data from these images has not evolved substantially and still predominantly relies on simple metrics such as aortic diameter or general configuration of the aorta. VDM was originally developed to map and quantify aortic growth over time by comparing baseline and follow-up sequential CTAs using deformable image registration (VDM-G). In this thesis, VDM was adapted to quantify 3D pulsatile displacement of the aorta between diastole and systole using dynamic CTAs (VDM-D). We demonstrated that VDM-D analysis of dynamic CTA data enables a rigorous

characterization of 3D aortic root motion. Directional aortic displacements, area ratio and distensibility, axial tilt and aortic rotation can be extracted across various patient groups, including non-aneurysmal controls, patients with TAA, Marfan, and those post-repairs. Our results revealed notable differences in aortic root motion metrics, particularly between the post-repair group and other groups with native aortic tissue. Additionally, we identified the LV/Ao angle as an important determinant of the relative proportions of axial and in-plane displacements, suggesting that it should be included in future studies on dynamic assessment of the ascending aorta. 3D aortic root motion derived from VDM-D may serve as a valuable tool for informing realistic, patient-specific boundary conditions in computational studies of aortic wall stress.

Proper application of VDM-D requires careful calibration and validation using aortic data. During the deformable image registration process, penalty parameters are used to optimize image alignment and to penalize non-physiological deformations. However, until now, the penalty parameters employed in deformable image registration for VDM-D have not been systematically calibrated. The principal challenge in calibrating these parameters is the lack of a ground truth for 3D displacement throughout the entire aorta. In this thesis, we calibrated the penalty parameters for deformable image registration in VDM-D using physics-based synthetic data generated with the rotation-free shell formulation. By tailoring penalty parameters for each cluster categorized by root motion, we observed that clusters exhibiting smaller root motion required larger penalty values. These calibrated parameters effectively reduced errors in both 3D displacement and multi-axial stretches.

Next, we used computation simulations to model the aorta, with a particular focus on aortic dissection. Using a clinical example of dynamic obstruction, we developed an idealized FSI model of type B aortic dissection and solved it using ALE method with commercial software to study dynamic obstruction. Our model successfully reproduced clinical findings, demonstrating that dynamic obstruction occurs as mean systemic blood pressure increases. Our results showed that relatively small pressure differences between TL and FL are sufficient to displace the intimal flap, inducing dynamic obstruction. In addition, the final stage of dynamic obstruction took place over a very short time (< 1 second), consistent with the clinical understanding of this dramatic event. To our knowledge, this study shows the first computational analysis elucidating the potential mechanisms underlying dynamic obstruction in aortic dissection. However, we also identified limitations associated with the ALE method. Specifically, the need to solve the fluid mesh every

time step leads to high computational costs, and mesh distortion can occur between two solid structures when there is substantial structural deformation over a short time interval. These challenges provided the motivation to develop an efficient FSI solver using the IBM for modeling aortic dissection.

The primary contribution of this thesis is the development of an IBM formulation for cardiovascular simulations, with a particular emphasis on aortic dissection. Our approach couples two pre-exist solvers using a direct forcing IBM framework: CRIMSON for fluid problem and nonlinear rotation-free shell formulation for thin structure. Both strong and weak time coupling schemes were implemented and tested on both static and dynamic problems with various fluid-to-solid density ratios. By using predefined shape functions for the fluid FEM, our formulation minimizes the need for additional computational resources for interpolation at the fluid-solid interface. To the best of our knowledge, this is the first IBM formulation that integrates an FEM fluid solver with a rotation-free shell solver, thereby providing a robust tool for simulating the interaction between thin structures and incompressible flow. The proposed method was validated using two 3D benchmark problems involving thin structures. To demonstrate its applicability, the method was applied to an idealized type B aortic dissection model, highlighting its potential for future cardiovascular simulations.

As the final component of this thesis, we present a pipeline for making a patient-specific aortic dissection model. Starting from medical imaging data, we generated 3D aorta and 2D intimal flap geometries. With appropriate boundary conditions derived from patient data, we created and solved the first patient-specific aortic dissection model using IBM.

8.2 Future works

Future works for two main works covered in this thesis are envisioned. First, building on the VDM-D framework, we plan to develop non-invasive algorithms capable of estimating aortic stiffness which is both heterogenous and anisotropic. Current non-invasive methods for assessing aortic stiffness are limited to characterizing the aortic tissue as isotropic due to the lack the techniques required to extract multi-axial strain from 3D dynamic medical images. However, it is possible to extract multi-axial aortic strain from the 3D VDM-derived aortic displacement data. By adopting a non-linear and multi-axial constitute model, such as four-fiber family model, these strains can be computed using the nonlinear rotation-free shell formulation with the choice of aortic stiffness and compared with VDM-derived strains over the entire aorta. We can repeat this

process with different aortic stiffness values until we get a good agreement between computed and VDM-derived strains. This approach would make it possible to determine both axial and circumferential aortic stiffness in a non-invasive way.

The patient-specific aortic dissection model developed in this thesis can be further advanced to address more complex and clinically relevant scenarios. The current model includes only the main aorta as the fluid domain. Future iterations can incorporate side branches, allowing the intimal flap to extend into these vessels. In actual aortic dissection cases, the initial flap often involves both the main aorta and side branches, such as the renal or iliac arteries. Additionally, patient-specific models can be extended to include multiple exit tears, as the number and location of exit tears significantly affect the hemodynamics of aortic dissection. As an extension of this work, we can simulate the effects of fenestration as a treatment for aortic dissection, providing insights into the optimal location and size of fenestrations to support surgical decision-making.

To enhance model validation, we plan to utilize intravascular ultrasound (IVUS) data, which provides detailed measurements of intimal flap motion. This data will enable calibration of the model's intimal flap stiffness by matching simulated and IVUS-derived intimal flap motions. Comprehensive comparisons between patient-specific simulation results and clinical data, including IVUS, will be performed to further validate our models.

Finally, the IBM formulation developed in this thesis can be applied to a broader range of problems involving structures immersed in blood flow, such as simulations of aortic valve mechanics. Future work will involve incorporating contact models to accurately capture valve leaflet dynamics and other interactions within the cardiovascular system.