NON-INVASIVE ASSESSMENT OF AORTIC COARCTATION SEVERITY USING COMPUTATIONAL FLUID DYNAMICS

by

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Abstract

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Aortic coarctation (CoA) is a congenital cardiovascular disease characterized by an abnormal narrowing of the proximal descending aorta, which can result in serious morbidity and complications after treatment. The severity of CoA is quantified by the blood pressure drop across the stenotic coarctation lesion, and intervention is recommended if the pressure drop exceeds 20 mmHg [1]. The clinical gold standard to obtain the pressure drop is catheterization, which is however an invasive procedure with a 1 in 1,000 risk of patient death or serious injury [2].

In the thesis, we propose an image-guided computational fluid dynamics (CFD) method for non-invasive assessment of CoA severity. The method first reconstructs the geometry of the aorta and surrounding vessels from medical images, and then solves the Navier-Stokes equations numerically to estimate the pressure drop across the CoA. The obtained values are compared against the pressure drop measured in-vivo with catheterization and with Doppler echocardiography. A limitation of earlier CFD studies on CoA is that they considered only a handful of patients. In this thesis, the proposed method is applied to 18 adult cases, in order to obtain a more representative assessment of its accuracy and reliability. The Cohen’s kappa statistic test shows a 0.64 inner-rate agreement between the CFD method and catheterization, indicating that CFD has the potential of becoming a non-invasive alternative to catheterization for the estimation of CoA severity.
Acknowledgements

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Chapter 1

Introduction

1.1 Aortic Coarctation

Cardiovascular diseases are the leading causes of death and disability worldwide. The Coarctation of the Aorta is a relatively common cardiovascular condition, accounting for 5% to 8% of all congenital heart diseases [3]. CoA causes a stenosis or a constriction in a position of the aorta (usually in the descending aorta), which reduces the quantity of blood flowing from the aortic valve to the descending aorta. The root cause of CoA remains still not known. Although some congenital heart defects are related to a genetic issue, CoA occurs sporadically in most of cases (not family correlated), and can be diagnosed during infancy or adulthood [4]. Figure 1.1 shows a typical structure of CoA in the descending aorta, with the left panel showing an illustration from Mayo Clinic [5] and the right panel showing a CT angiographic image of CoA.

The immediate impact from CoA is the overload of heart because of the narrowing. To provide sufficient blood through the aorta to the rest of the body, the heart has to pump harder and this can eventually lead to increased blood pressure, a disease known as hypertension. For infants and young children, severe CoA could lead to a maldevelopment of heart and even cause death. For elder children and adults, CoA is associated with long-term cardiovascular abnormalities, including bicuspid aortic valve, arch hypoplasia, intracardiac shunts, and subaortic stenosis [6].

1.2 CoA interventional treatment

The recommended time for performing CoA correction is in infancy or early childhood, especially for those children with critical coarctation who are at risk of heart failure and death if the ductus arteriosus is closed. Early treatment can also help to prevent the development of chronic systemic hypertension and other complications [7]. The aim of interventional treatment is to repair the narrowing at the CoA site, which relieves the workload of heart and decreases the blood pressure in the aorta.
1.2.1 Treatment options

Surgical repair

Since the first successful surgical repair of coarctation being recorded in 1944 by Crafoord and Nylin [8] in Sweden, the surgical treatment has been developed and widely used for decades. The types of surgical treatment include resection with end-to-end anastomosis, patch aortoplasty, bypass graft insertion across the area of coarctation and Subclavian flap aortoplasty [9]. Figure 1.2 shows these 4 types of surgery. The surgical repair is the preferred treatment of infants and early children with an up to 98 percent survival rate at a follow-up of 4.8 years of age [10]. In elder children and adults, however, complications are common that require long-term follow up, as will be discussed in Sec. 1.2.2.

Endovascular repair

Balloon angioplasty is another type of interventional treatment, which has been used for opening narrowed arteries for more than 30 years [11]. The angioplasty technique puts a long, thin tube with a small balloon on its top inside the aorta, inflates the balloon at the coarctation section to increase the artery diameter of narrowing. Figure 1.3 shows the Balloon angioplasty technique for coarctation repair. Compared to surgical repair, the endovascular repair is an effective treatment with easier application and significantly lower cost (58% less). However, the risks of recoarctation and aneurysm formation are greater based on the clinical observation [13].

1.2.2 Long-term cardiovascular complications and surveillance

Long-term complications can occur after treatment, either with surgical or endovascular repair. The most common complications are arterial hypertension, recoarctation and ascending aortic aneurysm.
Other complications like coronary artery disease, bicuspid aortic valve, mitral valve anomalies, infective endocarditis or cerebral aneurysms have also been investigated in clinical research [9]. Therefore, all coarctation patients, whether repaired or not, should be monitored with long-term congenital cardiology follow-up because of the cardiovascular complications discussed above. From the American College of Cardiology and American Heart Association (ACC/AHA) 2008 Guidelines [1], follow-up monitoring should include: (i) systemic hypertension; (ii) imaging of the coarctation repair site at intervals of 5 years or less; (iii) periodic echocardiography to assess the function of bicuspid aortic valve, ascending aorta and ventricle; (iv) cranial imaging for evaluating intracranial aneurysms. Long-term surveillance is important for detecting the complications and hence increasing the survival rate.

1.3 Clinical assessment of CoA

According to the ACC/AHA guidelines for adults with coarctation [1], the assessment of the severity of CoA is by measuring the systolic pressure drop across the site of CoA. Intervention is recommended if the peak-to-peak difference is over 20 mmHg. The current gold standard for the measurement of the pressure drop is cardiac catheterization, which is an invasive procedure where one inserts one or two catheters\(^1\) into a patient’s arm, neck or upper thigh. The catheter(s) is then manually guided into the vessels until the desired location is reached. For CoA assessment, the pressure sensors in the catheter(s) are positioned before and after the CoA narrowing. Figure 1.4 shows the angiography of a patient undergoing catheterization [14]. The catheterization technique is currently the most reliable method to measure the pressure drop across the CoA. However, its drawbacks, such as invasiveness and

\(^{1}\)A catheter is a long, flexible and thin tube that has multiple uses, including measuring pressure in-vivo at some desired locations in the patient’s vessels.
ionizing radiation exposure, are considerable as well. Although catheterization is a relatively low-risk procedure, it still results in a 1 in a 1,000 risk of patient death or serious injury [2]. From a financial perspective, the cost of catheterization (over $7000 in the US [15]) is another issue that should be taken into consideration.

Non-invasive methods for estimating pressure drop in the aorta have been investigated extensively. In clinical practice, Doppler echocardiography has been implemented as an alternative to catheterization. This method uses ultrasound technology to examine the speed and direction of blood flow in heart and vessels by analyzing the pulse-wave or continuous-wave Doppler effect. Aortic flow information such as pressure half-time, mean velocity and mean of peak gradient are available with the echocardiography measurement [16]. The advantage of using Doppler echocardiography for CoA assessment is that it is a non-invasive procedure, which does not expose patients to significant risks. At the same time, an echocardiography exam costs $1000 to $3000 in the US [17], which is also cheaper than catheterization. However, Doppler echocardiography does not work well for elder children and adults due to the posterior location of descending aorta [18]. More importantly, Doppler echocardiography tends to overestimate the pressure drop [19], especially for severe CoA where the narrowing is relatively small and the pressure drop is high. The overestimation comes from the conversion of kinetic to potential energy downstream of the stenotic aortic valve in pressure recovery with simplified Bernoulli’s equation [20]. Because of the accuracy limitations of Doppler echocardiography, catheterization is the current gold standard for assessing the CoA severity.

In this thesis, we will compare the results from the proposed CFD approach to both catheterization and Doppler echocardiography, using the former as gold standard. Our comparison, presented in Chapter 4, will confirm that Doppler echocardiography tends to overestimate the pressure drop across the CoA.
1.4 Imaging-guided computational fluid dynamics

Computational fluid dynamics uses numerical techniques to solve the Navier-Stokes equations and study the behavior of fluids (liquids and gases). With the development of numerical methods and computer-aided techniques, CFD has been widely used in physics and engineering for countless tasks, including aircraft/automobile design, HVAC (heating, ventilation, and air conditioning) building, Chemical/Petrochemicals research, and oil and gas exploration [21]. In recent years, CFD-based techniques have been also increasingly used in bioengineering and in medicine, to study complex physiological flows and related biological phenomenon [22, 23].

Computational fluid dynamics has significant advantages. A numerical approach is able to find solutions for complex problems that have no analytic solution, and also provides flow information that may otherwise be hard to measure in practice. Furthermore, with scientific visualization tools, fluid flows can be effectively visualized, facilitating their analysis. Finally, CFD simulations are particularly useful for design and optimization purposes, that often require large parametric sweeps to properly explore the design/optimization space.

However, the limitations of CFD are not negligible as well. The accuracy of a CFD simulation is constrained by the faithfulness of the underlying mathematical model, which typically involves some simplifications of physical reality. Moreover, even if the model itself may be quite adherent to reality, its coefficients may be hard to determine experimentally, and introduce an uncertainty in the solution. Finally, CFD simulations for realistic problems can be very time and memory consuming.

The applications of CFD to cardiovascular medicine are rapidly increasing. Computational techniques have been applied to investigate many pathologies, such as coronary artery disease, valve prostheses, aortic/cerebral aneurysm, pulmonary hypertension, heart failure and congenital heart disease [23]. Computational fluid dynamics is generally regarded as a very promising approach to improve how we understand and treat cardiovascular diseases. This speculation is motivated by several considerations. Firstly, CFD simulations are potentially able to provide a very significant amount of hemodynamic information,
much more detailed than the information one can retrieve with in-vivo procedure such as catheterization. Secondly, CFD simulations can provide this information in a non-invasive way, lowering risks and costs. Finally, CFD simulations can be used to study hemodynamics in hypothetical/future conditions, while imaging and in-vivo procedures can offer an hemodynamic insight only for the patient in its current state. This ability can be potentially used to investigate medical treatments before they are actually performed, and optimize them on a patient-specific basis.

The application of CFD for hemodynamic studies typically involves two steps. In the first step, the anatomical information about the patient’s vessels of interest is extracted from medical images, typically obtained with computed tomography (CT) or magnetic resonance imaging (MRI). Then, the vascular model is imported into a CFD simulator for volumetric mesh generation and blood flow simulation. The finite element method (FEM) is often used to solve the three-dimensional incompressible Navier-Stokes equations in the reconstructed patient vessels. CFD simulators solve numerically the Navier-Stokes equation in order to compute blood pressure and velocity, resolved over time and over space.

1.5 CFD modeling of aortic coarctation

In recent decades, CFD-based modeling were applied to study the hemodynamics in patients with CoA to assess the severity of CoA. To simplify the spatial complexity of vascular region, models of various orders, from 0-D to 3-D, have been proposed [23, 24, 25]. Among these researches, Itu et al. proposed a CFD-based approach for the noninvasive hemodynamic assessment of pre- and post-operative CoA patients with 1-D CFD modeling [18]. Coogan et al. studied cardiac workload associated with various types of aortic obstruction using 3-D CFD simulations [26]. They also studied the effects of stent-induced aortic stiffness on cardiac workload and blood pressure with 3-D CFD simulations [27]. LaDisa et al. investigated the potential sources of morbidity caused by CoA with a procedure combining clinical image data and CFD modeling under both resting and non-resting condition [28]. Olivieri et al. studied the hemodynamics of various shaped aortic arches following surgical repair to analyze the reason of the association between certain aortic arch shapes and high morbidity rates [29].

A limitation of previous studies is that they considered a limited patient population, typically restricted to no more than five cases. This limitation is the main motivation behind this thesis, that aims at performing a larger study in order to better understand how accurate and reliable is a CFD-based approach to estimate CoA severity. While initially we aimed at a population of 40 CoA patients, some unforeseen difficulties in accessing the clinical data from an institutional database forced us to restrict the study to 18 patients, which is still quite higher than previous studies performed to date.

1.6 Thesis outline

The purpose of the thesis is to develop a medical image guided CFD approach for the assessment of CoA severity, and evaluate its accuracy on a patient population larger than previous studies. The thesis is organized in the following sequence:

- In Chapter 2, we present the clinical data considered in this study, and the workflow used to reconstruct the vessels geometry from medical images. The clinical data includes medical images, inlet flow rate, and systolic/diastolic pressure. The pipeline for creating the 3-D model for CFD simu-
lations consists of image preprocessing, intermediate surface reconstruction, centerline extraction and volumetric mesh generation.

- In Chapter 3, the computational framework of cardiovascular hemodynamics simulation is explained. The finite element method is used for solving the incompressible Navier-Stokes equations in a 3-D domain using the open-source software SimVascular [30].

- In Chapter 4, a post-processing pipeline and a discussion of the CFD results are presented. Pressure drop measurements computed with CFD are compared to in-vivo measurements performed with catheterization and Doppler echocardiography.
Chapter 2

Medical Image Processing

2.1 Clinical Data

The patient population considered in this thesis consists of 18 patients (6 female, mean age 41 ± 12.8 years) with a history of CoA. The clinical data were provided by Dr. Andrew Crean from the Toronto General Hospital. Ten (56%) patients had native and eight (44%) had post repaired CoA. A significant pressure gradient (higher than 20 mmHg) was found in 14 (78%) patients, according to catheterization. The clinical data available for each patient include the raw medical images, the patient’s age and sex, his/her blood pressure, and the pressure drop measured with catheterization and Doppler echocardiography.

2.1.1 Medical Images

Medical imaging techniques, such as computer tomography and magnetic resonance imaging, are largely in use for cardiovascular diagnosis and treatments. In our case, CT or MR imaging was perfomed on each patient as part of routine clinical procedures. The CT images were acquired using a 320-row detector CT scanner (Aquilion One Vision; Toshiba Medical Systems Corp., Tokyo, Japan). Scan parameters for the thoracic CT angiography were: detector collimation: 320 x 0.5 mm; tube current: 300 to 500 mA; tube voltage: 100 to 120 kV; gantry rotation time: 270 ms; and temporal resolution: 135 ms. Prospective electrocardiogram gating was used, covering 70% to 99% of the R-R interval. The MRI images were performed in parasagittal orientation with spatial resolution = 0.9-1.1mm x 1.0-1.1mm x 1.2-2.4mm. Images were acquired between 19 and 24 seconds after the post-injection of 0.15-0.2 mmol/kg gadobutrol (Bayer Healthcare, Berlin, Germany), using bolus triggering in the ascending aorta. The original CT/MRI images available in this thesis were stored with the Digital Imaging and Communications in Medicine (DICOM) format. The orientations of anatomic planes are shown in Figure 2.1.

1The DICOM is a standard for handling, storing, exchanging and transmitting information in medical imaging, first developed by American College of Radiology and National Electrical Manufacturers Association in 1985, and now administered by the Medical Imaging and Technology Alliance.
2.1.2 Inlet Blood Flow

Since a CFD simulation of large portions of the cardiovascular system has a prohibitive computational cost, one usually restricts the CFD computational domain to a region of interest. Any vessel crossing the boundaries of this region is therefore truncated, leading to "terminals" that we can refer as inlets and outlets [32]. At every inlet and outlet, a boundary condition must be applied to model, indirectly, the role of the circulation outside of the region of interest. In the thesis, we used blood flow data implemented at the inlet to represent the blood pumped from heart as the input of the CFD model, which is detailed in Chapter 3.

2.1.3 Blood Pressure

Blood pressure is another essential parameter for hemodynamics simulation. The patient-specific systolic and diastolic blood pressure (SBP, DBP) are utilized for setting up outlet boundary conditions before the simulation, which is discussed in Chapter 3.

2.1.4 Overview of Clinical Data

Table 2.1 summarizes the clinical data for the 18 patients considered in this thesis. The MRI and CT columns indicate the source of medical imaging, the blood pressure column indicates the systolic and diastolic pressure, and the pressure drop measurement from catheterization and Doppler echocardiography are displayed in the last two columns, respectively. Note that some Doppler echocardiography measurements were not provided. One may also notice that the numeration of the cases is not contiguous. This is because more than 40 CoA cases were initially included in the study. About half of them were randomly selected to develop and test the computational model, and are those included in this thesis. The other half of the cases was reserved for a blind validation of the final method. Since the
### Clinical Data List

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>MRI</th>
<th>CT</th>
<th>Age</th>
<th>Gender</th>
<th>Blood Pressure (mmHg)</th>
<th>Catheterization (mmHg)</th>
<th>Doppler Echo (mmHg)</th>
</tr>
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<td>6</td>
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<td>22</td>
<td>F</td>
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<td>&lt;10</td>
<td>30</td>
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<tr>
<td>8</td>
<td>X</td>
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<td>65</td>
<td>F</td>
<td>177/90</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>10</td>
<td>X</td>
<td></td>
<td>40</td>
<td>M</td>
<td>140/70</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>X</td>
<td></td>
<td>39</td>
<td>M</td>
<td>109/56</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>X</td>
<td></td>
<td>44</td>
<td>F</td>
<td>190/100</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>16</td>
<td>X</td>
<td></td>
<td>23</td>
<td>M</td>
<td>130/70</td>
<td>24</td>
<td>54</td>
</tr>
<tr>
<td>18</td>
<td>X</td>
<td></td>
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</tr>
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<td>X</td>
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<tr>
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<td>X</td>
<td></td>
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<td>X</td>
<td></td>
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<td>M</td>
<td>130/80</td>
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<td>35</td>
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<td></td>
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<td>F</td>
<td>160/80</td>
<td>50</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Table 2.1: Summary of the clinical data associated with the patient population considered in this thesis.

Relevant clinical data for this second set of cases is still unavailable, we have not been able to include them in this thesis.
2.2 Image Processing Pipeline

In this section, we discuss the pipeline that was used to extract the three-dimensional geometry of the aorta and its surrounding vessels from the CT/MRI images. The pipeline starts from the medical images and leads to a volumetric mesh suitable for CFD simulations. A flow chart of the pipeline is shown in Figure 2.2.

Figure 2.2: The medical image processing pipeline.
Chapter 2. Medical Image Processing

2.2.1 Preprocessing

Medical images from CT or MRI technique contain the anatomic information of organs, vessel, tissues and bones within the scanning region of the human body. The CT and MRI images are in gray scale, assuming the value of air or background being around -1000 (black), water and soft tissues around 0 (gray), and solid structures like bones around 1000 (white). During the acquisition process, noise is inevitably introduced. Quantum noise in CT and acoustic noise in MRI are the major obstacles of high-quality imaging. Figure 2.3a shows a slice of an MR imaging of a patient in the sagittal plane. One can notice the presence of noise from the granularity of the image. During the extraction of the 3D geometry from medical images, noise can lead to artifacts like those shown in Figure 2.3b, which shows the geometry of the aorta reconstructed from the MRI images. Imaging noise must be therefore reduced with a suitable filtering procedure prior to geometrical reconstruction. Even in absence of noise, geometrical reconstructions typically still contain some undesired features caused by the tissues and bones that surround the vessels of interest. Therefore, as part of the pipeline, a proper filtering procedure is needed before attempting to reconstruct the surface of the vessels.

Preprocessing consists of two procedures. Firstly, the DICOM frames are compressed and reorganized into a single MetaHeader file to ease subsequent manipulations. Secondly, noise is reduced with a suitable filtering method so that the structure of aorta can be distinguished from the surrounding tissues and organs.

DICOM image extraction

For practical convenience, we converted the DICOM images from the institutional database of the Toronto General Hospital from DICOM format to MetaHeader format. A single DICOM file contains only one slice of the images in one of the anatomy planes. After the format conversion, the series of slices are stored into a single meta file, while all the information is maintained. Moreover, it is also possible to extract a subvolume containing the region of interest while discarding the unnecessary data from the original DICOM images. Reducing the image size saves a significant amount of time when implementing
segmentation and mesh generation, especially for small vessels such as coronary arteries. This step can be performed either by the software 3DSlicer [33] with graphic user interface, or by vmtk [34] with the script vmtkimagewriter.py. For the sake of automation, we performed this operation using some custom-made scripts that call vmtk functions.

**Filtering**

The purpose of filtering is to reduce noise and enhance the blood vessel structure for segmentation. In the thesis, we used a vessel enhancement filter, or called Frangi filter [35], with vmtk. The vessel enhancement filter is based on the analysis of the eigenvalues of Hessian matrix to detect which geometrical structures can be regarded as tubular. The Hessian matrix in the point \( x \) at scale \( \sigma \), \( H_\sigma(I, x) \), can be derived using the convolution of the second derivative of Gaussian function \( G(\cdot) \) and the image \( I(\cdot) \).

\[
H_\sigma(I, x) = \frac{\partial^2 I_\sigma}{\partial x^2} = I(x) \ast \frac{\partial^2 G_\sigma(\cdot)}{\partial x^2}
\]

(2.1)

where \( I(x), x \in \mathbb{R}^3 \) is the 3D array of gray scale intensities and \( G_\sigma \) is a Gaussian function with standard deviation \( \sigma \) [36].

The decomposition of the local second-order structure of the image results in three eigenvalues (\( |\lambda_1| \leq |\lambda_2| \leq |\lambda_3| \)) [36]. In particular, eigenvalues of isotropic structures are all negative, while tubular structures feature two negative and one zero eigenvalue [35], with the assumption that background is dark (intensity < 0) and vessels are bright (intensity > 0).

The vesslesness function, \( V_F \), proposed by Frangi et al. [35], is defined as

\[
V_F(\lambda_1, \lambda_2, \lambda_3) = \begin{cases} 
(1 - \exp\left(\frac{-R_a^2}{2\sigma^2}\right)) \exp\left(-\frac{R_b^2}{2\sigma^2}\right) (1 - \exp\left(-\frac{S^2}{2\sigma^2}\right)), & \lambda_2 < 0 \text{ and } \lambda_3 < 0 \\
0, & \text{otherwise}
\end{cases}
\]

(2.2)

where \( R_a, R_b \) and \( S \) are values for distinguishing between tube/plate-like structures, blob-like structures and background, defined as

\[
R_a(\lambda_1, \lambda_2, \lambda_3) = |\lambda_2|/|\lambda_3|, \quad R_b(\lambda_1, \lambda_2, \lambda_3) = |\lambda_1|/|\lambda_2\lambda_3|, \quad S(\lambda_1, \lambda_2, \lambda_3) = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}
\]

(2.3)

and \( \alpha_F, \beta_F, \gamma_F \) are user-defined parameters for the sensitivity of the Frangi filter. In the thesis, \( \alpha_F, \beta_F, \gamma_F \) are set to be 0.5, 0.5 and 5.0, respectively. Tubular structures like vessels are associated with negative eigenvalues like \( 0 \approx |\lambda_1| \ll |\lambda_2| \approx |\lambda_3| \). Therefore, for tubular structure, \( R_a \approx 1, R_b \approx 0 \) and \( S \gg 0 \), which specifies a relatively maximum value of the vesselness function, \( V_F \).

The script vmtkimagevesselenhancement.py of vmtk was used in this work to apply the vessel enhancement filter to the images. Figure 2.4 shows the medical images of one patient with coarctation highlighted within the yellow circle that in the left panel is the original image while in the right panel is the image enhanced by Frangi filter. The images are visualized with the script vmtkimageviewer.py.

### 2.2.2 Segmentation

Segmentation is the process of dividing an image into regions with similar features like gray level, texture and brightness. In the segmentation of medical images, methods based on gray level are well studied. Examples include the histogram features based amplitude segmentation, edge based segmentation and region-based segmentation [37]. With these approaches, the contour of blood vessels such as the aorta
can be distinguished while the remaining uninteresting structures and regions are filtered out. In this project, a level sets segmentation approach, which is one kind of edge based segmentation method, is used iteratively through the ascending aorta, the arch with the descending aorta and the supra-aortic vessels. Note that the output of segmentation is a medical image in MetaHeader format as well.

**Level sets segmentation**

The level sets method uses active contours\(^2\) and has been widely utilized for image segmentation. The segmentation problem can be reduced to finding curve(s) that enclose the regions of interest, and the idea of level sets is a kind of deformable model in which the deformable surface is not represented by a set of points and triangles, but rather described by a 3-D function, which is flexible with respect to the topology of the object to be segmented [38]. Given a two-dimensional image \(I_0\), we can create a level set function \(\phi(x, y)\) to describe a contour \(C\) as [39]

\[
C = \{(x, y) \mid \phi(x, y, t) = 0\}
\]

(2.4)

The value of function \(\phi(x, y)\) inside and outside the region of the curve is explicitly defined as [39]

\[
\begin{cases}
\phi(x, y) > 0, & \text{inside the contour} \\
\phi(x, y) = 0, & \text{at the contour} \\
\phi(x, y) < 0, & \text{outside the contour}
\end{cases}
\]

(2.5)

With the criterion of level set function, complicated contours can be easily represented. A geometric active contour model based on the mean curvature motion is defined as [40]

\[
\begin{cases}
\frac{\partial \phi}{\partial t} = |\nabla \phi| \text{div}(\frac{\nabla \phi}{|\nabla \phi|}), & t \in (0, \infty), \ x, y \in \mathbb{R}^2 \\
\phi(x, y, 0) = \phi_0(x, y), & x, y \in \mathbb{R}^2
\end{cases}
\]

(2.6)

\(^2\)The concept of active contour is useful for detecting the contour of an object (e.g. a vessel) from the background.
where \( \text{div}(\nabla \phi(x, y)/|\nabla \phi(x, y)|) \) is the curvature of the level-curve of \( \phi \) passing through the point \((x, y)\), and \( \phi_0 \) is the initial level set function. The solution of (2.6) in vmtk is performed by the script `vmtklevelsetsegmentation.py`. Vmtk provides 4 initialization types, including colliding fronts, fast matching, threshold and isosurface method. The initialization is a procedure that specifies the general target region and the range of intensity within the target region to the iterator. The selection of initialization type depends on the application scenario. In this project, we choose the colliding fronts method for its fast speed and good fitting to tubular structures with larger diameter such like the aorta.

Colliding fronts method

The colliding fronts method requires the user placing two target seeds \( P_1 \) and \( P_2 \) interactively on the image as the initial position of the fronts. Then, the two fronts will propagate from each seed with speed proportional to the image intensity until they collide against each other. \( T_i(x), i = 1, 2 \) denotes the travel time of one front originating from \( P_i \) with velocity \( I(x) \), and satisfies the Eikonal equation [41] for \( i = 1, 2 \)

\[
|\nabla T_i(x)| = \frac{1}{I(x)} \tag{2.7}
\]

and the initial condition is

\[
\phi_0(x) = \nabla T_1 \cdot \nabla T_2 \tag{2.8}
\]

The numerical solution of (2.7) can be efficiently done by upwind finite differences with fast marching method [42]. The region where the two fronts propagate through will be the deformable model [34]. The tricky part of this method is the initialization, including the selection of seeds and setting thresholds. A bad initialization could result in a positive value of \( \phi_0 \), which denotes that the two fronts propagated in the same direction preventing convergence. In this thesis we created the segmentation section by section, starting from the ascending aorta and ending up in the descending aorta. The lower and upper threshold we used are 100 and 700, within which the intensity specifies a vessel structure distinguished from air (\(< 0\)) and bones/artifacts (\(> 1000\)).

The procedure of level sets segmentation is shown in Figure 2.5. The left figure shows the intermediate segmentation of the coarctation section, while the right figure shows the final level sets segmentation. These images were created with `vmtklevelsetsegmentation` and visualized by `vmtkimageviewer`.

2.2.3 Intermediate Surface Reconstruction

Once level set segmentation is complete, a polygonal surface can be generated to approximate the anatomy of the vessels. In this thesis, we generate this surface using the marching cubes algorithm, which is available in the script `vmtkmarchingcubes.py` from vmtk.

Marching cubes method

The marching cubes method aims at generating a closed surface that encloses the region of interest, in our case the region identified by the level sets method [43]. The algorithm firstly discretizes the entire domain of the image with a cubic grid and gives each vertex a weight (generally the weight is the intensity from the image). Secondly, the program then goes over every cube to determine whether it is inside the level set segmentation by comparing the weight at its vertices with a user-defined reference value. If a
cube contains the edge of the segmentation, which means some corners are inside the segmentation while others are outside, the algorithm takes the corner to find the intersection points and connect them as the contour. The surface contoured by those points is the approximation of the original surface. Then the interpolation among the approximation surface of each slice is implemented to reconstruct the 3-D geometry structure.

The marching cube can be illustrated quite simply if we consider the 2D case. Figure 2.6 demonstrates the procedure of how marching cubes method finds the contour of the highlight region.

**Surface generation**

With the marching cubes method implemented in vmtk, we successfully generated the surfaces of the aorta and surrounding vessels for all patients. The reference value for the marching cubes algorithm should be taken from the intensity of level sets segmentation which distinguishes between the blood vessel and other structures in gray scale. The choice of reference value depends on the quality of image, and in this thesis we used values around 500.

Figure 2.7 shows the level sets segmentation and the surface generated from it. In Figure 2.7a, it is only the aorta structure being highlighted, while the contour is still rough. This is reflected in Figure 2.7b, which compares the reconstructed surface of the aorta (in cyan) with the initial reconstruction of the whole image, just after the level-set segmentation. We can observe that the work flow we discussed filtered out all the heart, bones, noise and all side branches, leading to a segmentation of only the aorta. Notably, the coarctation section is also well presented in the reconstruction.
Chapter 2. Medical Image Processing

(a) Domain discretization
(b) Vertices inside segmentation
(c) Intersect corners specify the edge
(d) An approximation of the surface contour

Figure 2.6: Marching cubes method for 2D surface approximation [44].

(a) Level sets segmentation.
(b) The generated surface (cyan).

Figure 2.7: Polygonal surface reconstruction from the level sets segmentation of case n. 6.
2.2.4 Surface Post-processing

The intermediate surface after reconstruction may still contain artifacts either from CT/MRI scan or reconstruction, such as unnecessary side branches, nodules, bumps or incorrect stenoses on the surface. These irregularities could result in the crashing of mesh generation and in an incorrect computational solution for the flow fields, such as the Wall Shear Stress (WSS). Therefore, it is necessary to employ post-processing on the intermediate surface before generating the 3-D volumetric mesh.

The purpose of implementing post-processing on the intermediate surface is to: firstly, specify the inlet and outlets by cutting off the closed surface at each outermost terminal. Secondly, remove some useless side branches along the descending aorta for reducing the entire computation cost. Lastly, smooth the surface by removing irregularities that were artificially introduced during the geometrical reconstruction.

Clipping

The script `vmtksurfaceclipper.py` in `vmtk` provides the method for surface clipping. The first step is to specify the inlet and outlets by clipping the closed surface at each outermost terminal of ascending aorta (AscAo), brachiocephalic artery (BA), left common carotid artery (LCC), left subclavian artery (LS) and descending aorta (DescAo). The second step is to cut out the useless branches along the descending aorta, artificial nodules and bumps. The clipping procedure is shown in Figure 2.8. The white box in the left figure is the surface clipper in which the surface would be cut out. The vessel wall in the right figure is after clipping, with one inlet and 4 outlet surfaces.

Smoothing

There is a fundamental difference between the segmented surface and the actual blood vessel. The segmented surface is an infinitely thin sheet, with inner intima and outer wall on the same surface. The real aorta, on the other hand, has a certain thickness and is composed in most cases of three different tissue layers, with the intima layer being the innermost smooth muscle layer. This means that although some non-uniformities can occur on the actual outer blood vessel wall, they are most likely not to be found at the intima layer. In another word, the reconstructed surface should be smooth enough. Surface non-uniformities such as bumps and intersections can cause unrealistic local artefacts along the surface wall, affecting the accuracy of near-wall quantities such as wall shear stress (WSS).

Before smoothing the surface, we first filled up holes and rifts caused by the procedure of clipping for avoiding introducing extra outlets on the surface wall. At the same time, the bumps and nodules should be flattened as well. These two steps can be finished similarly by remeshing the specific area needed to be reconstructed. Firstly, we selected the areas manually and used the `vtkSelectPolyData` class to determine the contour. Subsequently, the module `vmtksurfacecapper` in `vmtk` provides the function for adding caps to the holes of a surface and assigning an identifier to each cap for easy specification of boundary conditions. The capped area would be interpolated as flat surface, while the mesh on the edge of unselected area is also broken because of the selection. Therefore, the third step is to remesh the rest of surface with the `vmtkSurfaceRemeshing` class. Figure 2.9 shows a comparison of surface before and after bump flattening.

The script `vmtksurfacesmoothing.py` in `vmtk` provides two methods for surface smoothing. The unshrinking smoothing method proposed by Gabriel Taubin [45] modifies the coordinate values of each vertex $v$ using a windowed sinc function as interpolation kernel which maintains the shape of curve and
surface without shrinkage after smoothing. The other method, called Laplacian smoothing [46], modifies the coordinate of each vertex \( v \) according to an average of the connected vertices. In this thesis, we choose Laplacian method for surface smoothing.

**Laplacian smoothing method**

The major problem a smoothing method is going to solve is that: how to smooth a curve? The idea of the Laplacian smoothing algorithm is quite simple: the position \( P_i \) of vertex \( V_i \) is replaced with the average of the positions of adjacent vertices

\[
\begin{align*}
L(P_i) &= \frac{1}{|\text{Adj}(i)|} \sum_{j \in \text{Adj}(i)} P_j - P_i \\
\lambda L(P_i) &= P_i + \lambda L(P_i)
\end{align*}
\]

where \( L(P_i) \) is the Laplacian function and \( \lambda \) is the interpolation parameter. Figure 2.10 demonstrates the procedure of Laplacian smoothing on a curve.

There are two techniques to update the value \( P_i \). One is modifying all positions concurrently, and is called *simultaneous version*; the other one is updating each position immediately, which is named *sequential version*. The simultaneous method requires more memory for storing the old points, but leads to better results [46].

Note that without contour compensation, the surface is inevitably shrunk after Laplacian smoothing,
Figure 2.9: Surface smoothing with passband 0.5. Left panel: with bumps; right panel: without bumps.

depending on the smoothing degree. In the thesis, we set the value of relaxation and iteration numbers to be 0.1 and 25, respectively. As is shown in Figure 2.9, these values lead to a reasonable smoothing of the surface, without being too aggressive and eliminating actual anatomical details.

Figure 2.10: Laplacian smoothing procedure for a curve. Left panel: calculating Laplacian function for inner points; right panel: updating inner points to obtain a new curve.
2.2.5 Centerline Extraction

Vessel centerlines are paths that run approximately along the mid point of each vessel, and are needed for the generation of the surface mesh. Centerlines are defined as the weighted shortest path from inlets to outlets. The intersections of the centerlines identifies the junctions between three or more vessels. To extract centerlines from the reconstructed aorta surface, the concepts of medial axis and Voronoi diagram are used.

**Medial axis**

The medial axis is a geometrical entity dual to object surface. The medial axis $MA(\Omega)$ of an object $\Omega$ is defined as the locus of centers of maximal spheres inside $\Omega$

$$MA(\Omega) = \{ x \in \Omega | \exists \text{dir} n, \exists \epsilon > 0 : \forall \epsilon \in (0, \epsilon), DT(x) \geq DT(x \pm \epsilon n) \}, \quad \Omega \in \mathbb{R}^3$$

(2.10)

where $DT(x)$ is the distance transform, defined as the Euclidean distance from a point $x$ to the closest boundary point. Equation (2.10) denotes that for each medial axis point $x$ there exists a direction $n$ along which the distance transform $DT(x)$ presents a local maximum [47]. The computation of $MA(\Omega)$ for a continuous object such as blood vessel is very complex, and an analytical solution is not available for most cases. Approximations are taken with numerical methods, such as Voronoi diagrams.

**Voronoi diagrams**

The definition of Voronoi diagram of a point set $P$ is [48]

$$Vor(P) = \bigcup_{p \in P} \partial V(p)$$

(2.11)

where $V(p)$ is the Voronoi region of point $p$, defined as [48]

$$V(p) = \{ x \in \mathbb{R}^3 | dist(p, x) \leq dist(p, P) \}$$

(2.12)

and $\partial V(p)$ is the boundary. The Voronoi diagram is a combination of regions $V(p)$, where any point $x$ inside the region is closer to $p$ than to any other element of point set $P$. Therefore, given the point set $P$, the Voronoi diagram $Vor(P)$ can be associated with the ridges of the distance transform $DT(P)$ and finally used to identify the medial axis $MA(P)$ in 2.10 [47].

**Centerline computation**

With the Voronoi diagram, the centerline computation is equivalent to finding the minimal integral of the radius of maximal inscribed spheres from point $p_0$ to $x$ [49]

$$T(x) = \min_{\gamma \in \Gamma_{(p_0, x)}(MA(\Omega))} \int_{\gamma^{-1}(p_0)}^{\gamma^{-1}(x)} F(\gamma(t)) dt$$

(2.13)

where $\Gamma_{(p_0, x)}(MA(\Omega))$ is the set of all paths from $p_0$ to $x$ on the medical axis $MA(\Omega)$, and $F(x) = 1/R(x)$ is the cost function which represents the inverse of maximal inscribed sphere radius. $T(x)$ are the regions...
of equal weighted geodesic distance to \( p_0 \), and weighted geodesic paths are orthogonal to level sets of \( T(x) \). Therefore, the value of the directional derivative in the direction of geodesics is \( dT(\frac{\gamma}{\tau})^{-1} \), so that the solution of \( T(x) \) must also satisfy the Eikonal equation \([47]\) as

\[
|\nabla T(x)| = F(x), \ x \in MA(\Omega)
\]

Hence, the calculation of centerline is equivalent to solving the following ordinary differential equation with finite difference method

\[
\frac{d\gamma(t)}{dt} = -\nabla T(x), \ x \in MA(\Omega)
\]

The solution of \( \gamma(t) \) is the minimal result for (2.13) with boundary condition \( \gamma(0) = p_0 \) and \( \gamma(T) = p_1 \), where \( p_0 \) and \( p_1 \) are points on the two outermost surfaces of a tubular structure. The script \texttt{vmtk-centerlines.py} in \texttt{vmtk} solves (2.15) and is used for centerline computation in this project. Figure 2.11 shows the centerline and its Voronoi diagram. Note that to match with the surface mesh, the centerline curves are recommended to be remeshed according to the size of the surface mesh.

### 2.2.6 Volume Mesh Generation

As is introduced in Chapter 1, computational fluid dynamics is a non-invasive approach for patient-specific blood flow modeling. Numerical method for CFD analysis, such as finite volumes and finite elements method, require the discretization of the entire domain so as to solve the Navier-Stokes equations to compute flow fields such as velocity and pressure value at each vertex (also called node) of the mesh.

For blood vessels modeling, the geometry is always complex and can vary significantly from patient to patient. Therefore, a robust software for mesh generation is required. Mesh generation must be (i) compatible with various geometries; (ii) able to ensure that volumetric and surface mesh are continuous at the boundary layer; (iii) not very time-consuming. With this purpose, three major types of mesh for 3-D volumetric mesh generation are widely used: structured grids, unstructured grids and Hybrid grids. The structured and unstructured grids are different for the type of connectivity, while the hybrid grids is a combination of them. Figure 2.12 illustrates the difference between a structured and an unstructured mesh.
For structured grids, the regular connectivity allows the shape of cells to be quadrilateral (2D) or hexahedral (3D). However, for unstructured grids, triangular (2D) and tetrahedral (3D) cells are implemented since the shape of cells is required to be compatible with irregular connectivity. Figure 2.13 shows the shape of mesh element used in structured and unstructured grids [51].

In the thesis, we used the unstructured tetrahedral mesh available in vmtk, which employs triangles on the surface and tetrahedra in the enclosed volume.

**Unstructured tetrahedral volume meshing**

Unstructured meshing is an adaptive meshing technique for its irregular connectivity. Mesh points can be added, deleted, or moved during generation, with the connectivity list being updated simultaneously. In the meantime, tetrahedral cells are the most flexible type of mesh cells, which meets no topological confinement and is compatible to any complex geometries, such as those found in the human cardiovascular system.

In this thesis, we used vmtk and TetGen for unstructured tetrahedral mesh generation with the Delaunay triangulation method. The TetGen triangulation generator employs the Bowyer-Watson algorithm and the incremental flip algorithm [52], where points are inserted into the domain to form triangles and tetrahedras sequentially. TetGen takes Piecewise Linear Complexes (PLCs) as input domain, which describe the aorta surface of each patient in our study. Note that intersections are not allowed by PLCs and would cause TetGen to stop. Therefore, it is important to check the surface mesh for intersections before generation of the volumetric mesh. This procedure can be accomplished by...
The size of the volumetric mesh is determined to be fine enough for the sake of accuracy. We performed a study on case 8 for mesh refinement with the mesh size varying from 0.5 mm, 0.25 mm, 0.15 mm, and 0.1 mm, and we found that 0.15 mm is a reasonable value with good accuracy and acceptable CPU time and memory usage. Therefore, we took the mesh size to be 0.15 mm for all the cases in the thesis. Figure 2.14 shows the final unstructured tetrahedral meshing for case n. 6.
Chapter 3

Computational Framework

3.1 Introduction

In chapter 2, we presented the complete pipeline for creating a 3-D vascular model with volumetric mesh from its medical images, which is the first step for performing an hemodynamic simulation. In this chapter, we will introduce the computational framework of computational fluid dynamics, which is implemented to solve the Navier-Stokes equations in the 3-D domain of the reconstructed vascular structure.

3.2 Navier-Stokes equations

The Navier-Stokes equations, named after Claude-Louis Navier and George Gabriel Stokes, describe the motion of viscous fluid substance, including blood. Blood, in this thesis, is taken as an homogeneous and incompressible fluid with constant density and viscosity, regardless of the effect of formed elements in blood. At the same time, thermal and gravity effects are not considered as well [53]. With these assumptions, blood can be considered as a Newtonian fluid, where the fluid flow is dominated by the conservation laws of both mass and momentum, which can be described using the incompressible Navier-Stokes equations [54]

\[
\begin{cases}
\nabla \cdot \mathbf{u} = 0 \\
\rho \frac{\partial \mathbf{u}}{\partial t} + \rho (\mathbf{u} \cdot \nabla) \mathbf{u} - \mu \Delta \mathbf{u} + \nabla p = f
\end{cases}
\] (3.1)

where \( \mathbf{u} \) is velocity, \( p \) is pressure, \( \mu \) is viscosity, \( \rho \) is density and \( f \) is the given source.

The first equation in (3.1) is the continuity equation for incompressible fluid. The general continuity equation, presented in (3.2), stems from the principle of mass conservation, and relates the amount of mass entering or leaving a domain to the mass accumulation in the domain

\[
\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0
\] (3.2)

In the thesis, blood density is assumed to be constant \( (\rho = 0.00106 \text{ g/mm}^3) \), which means that the time derivative of density \( \rho \) is zero and there is no mass accumulation or loss in the system. Therefore, equation (3.2) reduces to \( \nabla \cdot \mathbf{u} = 0 \).
The second equation in 3.1 is the conservation of momentum, derived from the Cauchy momentum equation [54]

\[
\frac{\partial}{\partial t} (\rho u) + \nabla \cdot (\rho u \otimes u) = -\nabla \cdot p I + \nabla \cdot \tau + \rho g
\] (3.3)

where \( \tau \) is the deviatoric stress tensor and \( g \) is the acceleration (e.g. gravity and inertial accelerations). In this thesis, the assumption of incompressible fluid indicates that the Cauchy stress tensor satisfies the Stokes’ stress constitutive equation [54]

\[
\tau = \mu (\nabla u + \nabla u^T)
\] (3.4)

and hence the divergence of deviatoric stress tensor becomes

\[
\nabla \cdot \tau = \mu \nabla (\nabla u + \nabla u^T) = \mu \Delta u
\] (3.5)

where the Laplace operator \( \Delta = \nabla^2 \) is a second order differential operator, defined as the divergence \( (\nabla \cdot) \) of the gradient \( (\nabla f) \). For the convection term \( \nabla u \otimes u \) in (3.3), using vector analysis, it can be derived that

\[
\nabla u \otimes u = u^2 \nabla \rho + \rho u \cdot \nabla u + \rho u \nabla \cdot u = \rho u \cdot \nabla u
\] (3.6)

Applying the derivations (3.5) and (3.6) to (3.3), we finally have the conservation equation in (3.1).

### 3.3 Boundary conditions

Boundary conditions, as well as initial conditions, are needed to solve the Navier-Stokes equations (3.1) with a unique solution. The incompressible Navier-Stokes equations implemented in this thesis, are partial differential equations (PDEs) describing the boundary value problem of fluid field distribution inside the computational domain.

A qualitative illustration of the computational domain considered in this thesis is given in Figure 3.1. Navier-Stokes equations are used inside the volume of the aorta and surrounding vessels. This computational domain is then bounded by several surfaces, where a suitable boundary condition must be specified. The boundaries consist of the lumen surface (vessels wall), the inlet on the ascending aorta, and the outlets on the descending aorta and lateral branches.

#### 3.3.1 Boundary condition on vessel walls

The vessel wall is the lumen surface of the aorta. The vessel wall boundary represents the interface between the computational domain and the vessel wall, which plays an important role in the hemodynamics simulation. The real vessel wall is a layer of endothelial cells with finite thickness, which is too complex to model. In hemodynamics simulations, a simplification is implemented, and we treat the wall as an infinitely thin surface with either a traditional rigid wall assumption or a elastic wall assumption [53].

Under the rigid wall assumption, a no-slip (zero velocity) Dirichlet condition is applied on the surface, because the particles close to a surface do not move along with the flow when adhesion force is stronger than cohesion force.
Figure 3.1: Illustration of the portion of the cardiovascular system considered in this thesis, together with the boundary conditions that are used at each inlet and outlet [18].

For the elastic wall assumption, a fluid structure interaction (FSI) is applied between the computational domain and aortic wall. Under this circumstance, the aortic wall is modeled as a linear elastic material, which is deformable when stresses and strains are exerted on it. The coupled momentum method (CMM) [55] is used for modeling the effect of deformation, which applies the traction condition (Neumann) satisfying the following elastodynamic equation that describes the motion of the vessel wall elastodynamics in (3.7) that describes the motion of vessel wall

$$\rho^v \frac{\partial^2 u}{\partial t^2} = \nabla \cdot \sigma^v + f^v$$ (3.7)

where $u$ is the displacement field, $\rho^v$ is the vessel wall density, $f^v$ is the body force per unit volume, and $\sigma^v$ is the vessel wall stress tensor [55]. The FSI model allows the uniform or variable elastic modulus along the aortic wall, which is closer to the real circumstance [53]. In this thesis, we used the no-slip Dirichlet boundary condition on vessel wall for simplicity.

### 3.3.2 Inflow boundary condition

An inflow boundary condition is applied at the inlet of the ascending aorta in order to model the blood flow injected by the heart into the vasculature. This boundary condition consists of a given time-varying flow rate, which is usually non uniform in space, since the inlet velocity near the walls is quite lower than the velocity at the center. The general form of the profile is

$$u(r, t) = f(r) \hat{u}(t)$$ (3.8)
Figure 3.2: Hagen-Poiseuille ($\gamma = 2.0$ and $10.0$, blue line) and pulsatile Womersley ($W_o = 2.0$, $5.0$, $10.0$ and $20.0$, black line) profile.

where $f(r)$ can be modeled with either Hagen-Poiseuille or pulsatile Womersley profile [56],

$$
\begin{align*}
    f(r) &= \frac{r^2}{\gamma} \left( 1 - \left( \frac{r}{R} \right)^\gamma \right) \quad \text{Hagen-Poiseuille} \\
    f(r) &= \Re\left\{ \frac{\Lambda J_0(\Lambda) - J_0(\Lambda)}{\Lambda J_0(\Lambda) - 2J_1(\Lambda)} \right\} \quad \text{pulsatile Womersley}
\end{align*}
$$

(3.9)

where $r$ is the distance from the center of cross-section, $R$ is the maximum radius, $\gamma$ is the polynomial degree in the Hagen-Poiseuille expression, $\Re$ is the real part of a complex number, $J_0$ and $J_1$ are the zeroth and first order Bessel functions of first kind, and $\Lambda$ is defined as

$$
\Lambda = \left( \frac{j - 1}{\sqrt{2}} \right) W_o, \quad W_o = \sqrt{\frac{\omega}{\nu} R}
$$

(3.10)

where $j$ is the imaginary number, $\omega$ is the angular frequency and $W_o$ is the Womersley number, which specifies the velocity profile. For Womersley flow, the coefficient $W_o = 2$ is an approximation of a parabolic flow, while $W_o \geq 20$ specifies a plug-like flow. For Poiseuille flow, the coefficient $\gamma = 2$ corresponds to a parabolic flow while $\gamma \geq 10$ represents a plug-like flow. Figure 3.2 shows the inlet velocity profile of both Poiseuille and Womersley model. In this thesis, we imposed on the ascending aorta a parabolic Poiseuille flow profile ($\gamma = 2$).

The clinical data available for this retrospective study did not include any flow information, since such acquisition is not routinely performed as part of the standard of care for CoA patients. Therefore, we used the pulsatile flow rate in the ascending aorta provided as part of the 2nd CFD Challenge "Predicting Patient-Specific Hemodynamics at Rest and Stress through an Aortic Coarctation" from the 2013 International Conference on Medical Image Computing and Computer Assisted Intervention [57]. This flow rate
is shown in Figure 3.3, with the cardiac output\(^1\) being 3.71 L/min and heart rate being 47 beats/min. In a first set of CFD simulations, this flow was used for all patients, although this is not ideal since it neglects patient-specific conditions. An analysis of the obtained results from 15 cases (we selected 3 cases for validation, they are case n. 43, n. 45, and n. 46) showed that, with this patient-independent boundary condition, the pressure drop across the CoA was consistently underestimated for patients with either a low CoA degree or a large caliber of the ascending aorta.

We therefore performed a second set of simulations where we took into account some anatomical information from each patient, namely the area of the ascending aorta and the CoA severity based on the 15 experimental cases. We identified all cases where either:
* the area of the ascending aorta, measured at the inlet, is greater than 900 mm\(^2\);
* the CoA severity is less than 73%

For all these cases, the flow rate was amplified by a factor \(\alpha\) defined as

\[
\alpha = \frac{v_{\text{mean}} \cdot A_{\text{inlet}}}{Q_{\text{mean}}} \tag{3.11}
\]

where \(v_{\text{mean}}\) is the mean velocity in the aorta, which is 11 cm/s [58], \(A_{\text{inlet}}\) is the area at the inlet plane, and \(Q_{\text{mean}}\) is the mean flow rate defined as

\[
Q_{\text{mean}} = \frac{1}{t_p} \int_0^{t_p} q(t) dt \tag{3.12}
\]

where \(t_p\) is the period of one cardiac cycle, which was assumed to be 1.26 s for all cases.

The scaling factor (3.11) makes the average of the flow rate in the ascending aorta proportional to the aortic cross section. For the cases that do not satisfy one of the two conditions outlined above, we kept \(\alpha = 1.0\). Numerical results, that will be presented in Chapter 4, will show that this simple criterion to introduce some specificity to the inlet boundary condition helps to reduce the systematic tendency of the proposed computational method to underestimate the pressure drop.

---

\(^1\)The cardiac output is the amount of blood pumped by the heart per minute
3.3.3 Outflow boundary condition

The outflow boundary condition implemented at the outlet planes take into account the influence of the upstream and downstream vasculature on the blood flow in the vessels of interest. The most common boundary conditions used for partial differential equations (Dirichlet and Neumann), impose a prescribed pressure or velocity at the boundaries. Unfortunately, for cardiovascular simulations, they are not always viable. The foremost reason is that the time-varying flow field at the outflow boundary is usually hard to obtain, as it requires a simultaneous measurement of the waveform at each outlet [59]. If the transient flow data is not well-synchronized, boundary conditions may be incompatible with each other, for example they violate the principle of mass conservation, and lead to erroneous results or unstable simulations. In order to circumvent this issue, researches were conducted in the last decades [60, 59]. The alternative approach is to employ a one-dimensional lumped parameter model at each outlet to characterize the effect of upstream and downstream vasculature. The lumped parameter model imposes a relationship between the integral form of pressure $P$ and volumetric flow rate $Q$. The pressure prescribed on outlet plane is uniformly distributed in a weak formulation, which enforces the integral of pressure to be a constant value to satisfy the conservation law, instead of prescribing the pressure value at each boundary node like the Dirichlet or Neumann boundary conditions [53]. Example of lumped parameter models include the resistance boundary condition, the impedance boundary condition, and the Windkessel boundary condition, listed in order of increasing complexity.

**Resistance boundary condition**

The resistance boundary condition prescribes a relationship between flow and pressure at outlet in the form

$$p(t) = p_0 + Rq(t)$$

(3.13)

where $p(t)$ is the pressure, $q(t)$ is the flow rate at the outlet and $p_0$ is a pressure offsets, usually set to zero [53]. The resistance, $R$, is the only lumped parameter characterizing the upstream and downstream vasculature. On the one hand, as is with the simplest lumped parameter model, the resistance boundary condition has been widely used for flow simulations in 1-D [60, 61], 2-D and 3-D domains [62]. On the other hand, since the resistance is not frequency dependent, $p(t)$ is a linear function of $q(t)$ without any time lag, which is inconsistent with experimental results [63]. What is worse is that a flow rate fluctuation at any frequency is simultaneously transferred to a pressure oscillation, which could result in the instability of the numerical solution. Therefore, the resistance boundary condition is usually applied only in steady flow simulations. For more complicated situations, an impedance boundary condition can be employed for higher accuracy.

**Impedance boundary condition**

The impedance boundary condition is an upgraded boundary model from the resistance boundary condition, and imposes a relation between pressure and flow rate in the form

$$p(t) = p_0 + \frac{1}{T} \int_{t-T}^{t} z(t-\tau)q(\tau)d\tau$$

(3.14)

where $T$ is the cardiac cycle, $p(t)$ is the pressure, $q(t)$ is the flow rate at the outlet, and $z(t)$ is the
Chapter 3. Computational Framework

inversed Fourier Transform of the impedance function \( Z(\omega) \) as \( P(\omega) = Q(\omega)Z(\omega) \). The type of the kernel function, \( z(t) \), is depended on the application, while in general the Fourier Transform \( Z(\omega) \) is a low-pass filter where the high frequency component (\( \geq 5 \text{ Hz} \)) would be filtered out, which is consistent with the human body fundamental resonant frequency [64]. The most widely-used impedance model is the resistance-capacitance-resistance (RCR) model, also known as the Windkessel boundary condition.

Windkessel boundary condition

In the Windkessel model, an analogy with electric circuits is used as a reduced-order model for characterizing the downstream vasculature. The model is shown in Figure 3.4. The circuit consists of three elements including a proximal resistance \( R_p \), a capacitance \( C \) and a distal resistance \( R_d \). This model results in the following relation between pressure and flow rate [18]

\[
\frac{\partial p}{\partial t} = R_p \frac{\partial q}{\partial t} - \frac{p}{R_d \cdot C} + \frac{q(R_p + R_d)}{R_d \cdot C}
\] (3.15)

and the impedance \( Z \) can be derived as [65]

\[
Z(\omega) = R_p + \frac{R_d}{1 + j\omega CR_d}
\] (3.16)

\[
z(t) = R_p T \delta(t) + \frac{T}{C[1 - \exp(-\frac{t}{CR_d})]} \exp(-\frac{t}{CR_d})
\] (3.17)

where \( \omega \) is frequency and \( \delta(t) \) is the Dirac function.

![Figure 3.4: Windkessel (RCR) boundary condition model.](image)

In the thesis, we employed the Windkessel model for the outlet boundary conditions. The details of the model including determining the parameters are presented in the next session.

3.3.4 Estimation of outflow boundary models

As mentioned above, the outflow boundary condition in this thesis is implemented by the analog circuit with three-elements, \( R_p, C \), and \( R_d \). The values of the lumped parameters at each outlet can be estimated from the mean arterial pressure, the severity of the CoA, and the average flow rate at each outlet.
Coarctation severity degree

The coarctation section affects the flow distribution at outlets, especially in the descending aorta. Therefore, evaluating the coarctation degree is the foremost step for estimating the outflow lumped parameters. In this thesis, we defined the coarctation severity degree as

\[
CoA\text{ severity} = \left(1 - \frac{A_c}{A_r}\right) \times 100\%
\]

(3.18)

where \(A_c\) is the coarctation area defined as the minimum cross-section area at the coarctation section, and \(A_r\) is the average reference area defined as \(A_r = (A_{bef} + A_{aft})/2\), where \(A_{bef}\) and \(A_{aft}\) are the reference areas before and after the coarctation. The exact location used to measure these areas was estimated and provided by Dr. Crean together with the clinical data. Figure 3.5 shows the location of the two sections for case n. 6.

![Figure 3.5: The reference sections before and after the coarctation of case n. 6.](image)

Average flow rate

With the coarctation severity degree, the proportion of average descending flow \(Q_{desc}\) out of the total flow \(Q_{total}\) can be estimated by the linear regression in (3.19), which is plotted in Figure 3.6.

\[
Q_{desc} = \begin{cases} 
2.16 - CoA\text{ severity} & , \quad CoA\text{ severity} < 90\% \\
2.52 & \\
1.0 - CoA\text{ severity} & , \quad CoA\text{ severity} \geq 90\% \\
0.28 & 
\end{cases}
\]

(3.19)
Once the flow in the descending aorta is determined, the flow in the supra-aortic vessels is estimated based on their relative cross section \[67\] as

\[ Q_i = (Q_{total} - Q_{desc}) \cdot \frac{A_i}{\sum_{i=1}^{n} A_i} \tag{3.20} \]

where \( A_i \) is the outlet area of the supra-aortic branch \( i \) and \( n \) is the number of supra-aortic branches.

**Mean arterial pressure**

The mean arterial pressure (MAP) is defined as the average arterial pressure during a single cardiac cycle, and can be approximated using the easily measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) as \[18\]

\[ MAP \approx DBP + \left[ \frac{1}{3} + (HR \cdot 0.0012) \right] (SBP - DBP) \tag{3.21} \]

where \( HR \) is the heart rate (beats/s). The reason why MAP is so important is because it can be used to calculate the total distal resistance \( R_t \) in the RCR circuit model, with the expression

\[ MAP = Q_i \cdot (R_t)_i \tag{3.22} \]

where \( Q_i \) is the average flow rate through outlet \( i \) in the arterial circulation, \( (R_t)_i \) is the total distal resistance at outlet \( i \) as \( (R_t)_i = (R_p)_i + (R_d)_i \). With MAP and average flow, the value of the proximal and distal resistance at outlet \( i \) can be easily calculated \[27\]

\[ (R_p)_i = \alpha_{RCR}(R_t)_i \]

\[ (R_d)_i = (1 - \alpha_{RCR})(R_t)_i \tag{3.23} \]

where \( \alpha_{RCR} \) is a parameter requiring calibration for matching the clinical data. In the previous study \[68, 69, 70\], a value of \( \alpha_{RCR} \) between 0.06 and 1 is proposed, and we employed \( \alpha_{RCR} = 0.06 \) in this
thesis.
The value of capacitance $C_i$ at outlet $i$ can be estimated from the total resistance $(R_t)_i$ as well, using the expression

$$C_i = \frac{SV}{SBP - DBP} \approx \frac{\beta_{RCR}}{(R_t)_i}$$  \hspace{1cm} (3.24)$$

where $SV$ is the stroke volume, $\beta_{RCR}$ is a parameter for estimating the vessel compliance. In this thesis we take $\beta_{RCR}$ as 1.5 derived from $SV$.

**Pressure drop across the coarctation**

The coarctation of aorta introduces a pressure drop across the CoA site, which should be taken into consideration when estimating the resistance and capacitance of the Windkessel model at the outlet of the descending aorta. We used a pressure-drop model for evaluating the pressure drop across the CoA site [18]:

$$\Delta p(t) = K_v(\alpha_W) \cdot R_{vc}q(t) + \frac{\rho K_t}{4 A_0^2} \left( \frac{A_0}{A_c} - 1 \right)^2 |q(t)|q(t) + K_u L_u \frac{\partial q(t)}{\partial t} + K_c(\alpha_W) R_{vc} \bar{q}(t)$$ \hspace{1cm} (3.25)$$

where $K_v = 1 + 0.053 \cdot (A_c/A_0)\alpha_W^2$ is the viscous coefficient, $A_0$ is the average cross section area of the reference section, $A_c$ is the cross section area of CoA, $R_{vc} = \frac{8\mu}{\pi} \int_0^{L_c} \frac{1}{r(l)} dl$ is the viscous resistance, $L_c$ is the length of CoA section, $r(l)$ is the radius across the CoA site, $K_t = 1.52$ is the turbulence coefficient, $K_u = 1.2$ is the inerence coefficient, $L_u = \frac{\rho}{2} \int_0^{L_c} \frac{1}{r(l)} dl$ is the inerence, $K_c = 0.0018\alpha_W^2$ is the continuous coefficient and $\alpha_W$ is the Womersley number, and the time-varying flow rate $q(t)$ equals to $\frac{Q_{desc}}{Q_{total}} q_{asc}(t)$. The pressure drop consists of the viscous losses, the turbulent losses, the inertial effect and the continuous effect, respectively, where the turbulent losses are the dominant term. The maximum pressure $\delta P = \max_t|\Delta p(t)|$ can be taken for calculating the total resistance of outlet on the descending aorta as

$$(R_t)_{desc} = \frac{MAP - \delta P}{Q_{desc}}$$ \hspace{1cm} (3.26)$$

### 3.4 Numerical solution of the Navier-Stokes equations

With the boundary conditions set up, we are ready to solve the three-dimensional incompressible Navier-Stokes equations presented in section 3.1. This task can be performed with several methods, including finite difference method (FD), finite volume method (FVM), spectral method, and FEM. In this thesis, we take FEM as the numerical approach for the Navier-Stokes equations.

#### 3.4.1 Finite element method

The finite element method (FEM) is a numerical discretization tool for solving partial differential equations (PDEs) on complex geometries, especially when the analytical solution over the entire domain is not available. The main idea of FEM is discretizing the entire computational domain into a number of small subdomains and implementing trial functions on each subdomain. The FEM pipeline with a boundary-value problem includes:

1. Discretization of the entire domain into subdomains;
2. Selection of the interpolation functions (test functions) and weak formulation;
3. Formulation of the system of equations via Ritz or Galerkins method;
4. Solution of the system of equations.

**Discretization of the entire domain**

The discretization is the first and perhaps the foremost step in any finite element analysis because the manner in which the domain is discretized will affect the computer storage requirement, CPU time, and especially the accuracy of numerical result. In this step, the entire domain $\Omega$ is divided into $M$ subdomains $\Omega^e$ which are always referred to as *elements*. For a one-dimensional domain, the elements are always short segments to form (at least approximately) the original line; for a two-dimensional domain, the elements are often triangles (for irregular region) and rectangles (for regular region). In a three-dimensional problem, the domain can be discretized into tetrahedra, triangular prisms, or rectangular bricks. Figure 3.7 shows an example of these discretization schemes.

![Discretization schemes](image)

**Figure 3.7: A typical example of finite elements [71]**

The domain discretization is often considered as a preprocessing task because it can be completely separated from the other steps. In this thesis, the domain discretization is accomplished by the meshing procedure introduced in Chapter 2.

**Weak formulation**

The weak formulation is to convert the original equation $Lu = f$ into an integral form by inner product with a test function, $\psi$, as

$$
\int_{\Omega} (Lu) \psi \, d\Omega = \int_{\Omega} f \psi \, d\Omega \quad (3.27)
$$

where $L$ denotes any linear operator, including the differential operator that defines the Navier-Stokes equations. Function $u$ is the unknown, $f$ is the excitation term and $\Omega$ is the computational domain.

**Petrov–Galerkin method**

The Petrov–Galerkin method is used for obtaining approximation solutions of PDEs in a weak formulation. The idea of the Petrov-Galerkin method is to expand the unknown function through a suitable set of basis functions $\phi_j$ and solve the approximated value $u_j$ at each discretized node $j$ so that the
final solution \( u(r) \) can be interpolated from those values which satisfies the boundary conditions. We determine \( U_j = U(r_j) \) as the approximation value of \( u(r) \) at the node \( r_j \), the solution of \( u(r) \) can be interpolated by a linear combination of the basic functions \( \phi_j(r) \) as

\[
u(r) = \sum_{j=1}^{N} U_j \phi_j(r)
\]

(3.28)

where \( N \) is the number of nodes. The basis functions \( \phi_j(r) \) are required to be linearly independent to form a complete solution space. The most widely used one is the general linear piecewise basis function, which is a first order interpolation. For higher accuracy of the approximated solution, the quadratic, cubic and higher order interpolation can be implemented. The test function \( \psi(r) \), on the other hand, is also formed as a combination of the basis function \( \phi \), defined as

\[
\psi(r) = \sum_{i=1}^{N} \xi_i \phi_i(r)
\]

(3.29)

where \( \xi_i \) is the interpolation coefficient. For simplicity, we can assume that \( \psi(r) = \phi_i(r) \) for node \( i \).

Applying (3.28) and (3.29) to (3.27), the equation becomes

\[
\sum_{j=1}^{N} U_j \int_{\Omega} (L \phi_j(r)) \phi_i(r) \, d\Omega = \int_{\Omega} f(r) \phi_i(r) \, d\Omega, \quad i = 1, 2, ..., N
\]

(3.30)

The system of equations (3.30) can be written into the equivalent matrix form as

\[
K U = b
\]

(3.31)

where \( K \) is the stiffness matrix, \( U \) is the unknown vector, and \( b \) is the load vector [72], defined as

\[
K = \{a_{i,j}\}_{N \times N}, \quad \text{with} \quad a_{i,j} = \int_{\Omega} (L \phi_j(r)) \phi_i(r) \, d\Omega
\]

(3.32)

\[
U = (U_1, U_2, ..., U_N)^T
\]

(3.33)

\[
b = (b_1, b_2, ..., b_N)^T, \quad \text{with} \quad b_i = \int_{\Omega} f(r) \phi_i(r) \, d\Omega
\]

(3.34)

Therefore, the vector \( U \) can be calculated with matrix manipulation. With the value \( U \) at each node, the approximated solution of \( u(r) \) can be interpolated using (3.28).

Since using basis functions that span the entire domain leads to very costly projections, in the FEM one typically employs basis functions defined on subdomains, commonly referred to as elements. We can implement the Galerkin formulation on each element and then combine them together to form the matrix \( K \) and vector \( b \). Therefore the solution of \( u \) within an element \( e \) can be defined as

\[
u^e(r) = \sum_{j=1}^{n} U_j^e \phi_j^e(r)
\]

(3.35)

where \( n \) is the number of nodes in \( e \), \( U_j^e \) and \( \phi_j^e \) are the node value and basis function of \( e \), respectively. The equation set in \( e \) can be written to the matrix form
\[ K' U' = b' \]  

(3.36)

and the system of equations in (3.31) can be assembled by a summation over all elements and then an imposition of the stationarity requirement

\[ \sum_{e=1}^{M} \left( (K_e \{U_e\}) - \{b_e\} \right) = \{0\} \]  

(3.37)

where \( M \) is the number of elements in the entire domain. Then the equation can be solved as mentioned above.

### 3.4.2 SUPG formulation for incompressible N-S equations

The accuracy of standard Petrov–Galerkin approach implemented with FEM is of the order \( O(h^{k+1}) \), where \( h \) is the representative size of the elements and \( k \) is the polynomial degree of interpolation per element [71]. However, for convection-diffusion problems, which is quite common in hemodynamics, if the convection dominates the diffusion, the accuracy decreases rapidly, especially for coarse grids. For solving the convection-dominent flow, upwind methods in combination with FEM is proposed, and the most famous one is the streamline upwind Petrov-Galerkin method (SUPG) [73].

The SUPG introduces a test function \( \bar{\psi} \) defined as

\[ \bar{\psi} = \psi + p \]  

(3.38)

where \( \psi \) is the classical test function and \( p \) is a correction for upwind term, which is discontinuous over the elements. For incompressible Navier-Stokes equations defined on domain \( \Omega \in \mathbb{R}^3 \) with boundary \( \Gamma = \Gamma_D \cup \Gamma_N \). The Galerkin form \( G(w_i, q; v_i, p) \) of (3.1) can be derived as [53]

\[
G(w_i, q; v_i, p) = \int_{\Omega} \left\{ w_i (\rho \frac{\partial v_i}{\partial t} + \rho v_j v_{ij}) + w_{i,j} (-p \delta_{ij} + \tau_{ij} - q_i v_i) \right\} d\Omega \\
+ \int_{\Gamma_N} \left\{ w_i (p \delta_{in} - \tau_{in}) + q v_i \right\} d\Gamma = 0
\]  

(3.39)

where \( w \in W_h^k \) is the weight function and \( q \in P_h^k \) is the SUPG test function with \( k^{th} \) order. Under the stabilization condition, the weak form \( B(w_i, q; v_i, p) \) of (3.1) can be finally achieved

\[
B(w_i, q; v_i, p) = G(w_i, q; v_i, p) \\
+ \sum_{e=1}^{N_e} \int_{\Omega_e} \left\{ \tau_M (v_j w_{i,j} + q_i) L_i + \tau_C w_i v_{ij,j} \right\} d\Omega \\
+ \sum_{e=1}^{N_e} \int_{\Omega_e} \left\{ w_i \tilde{\nu}_j v_{i,j} + t \tilde{\sigma} \tilde{\nu}_j w_{i,j} v_{i,k} \right\} d\Omega = 0
\]  

(3.40)

where \( N_e \) is the number of elements, \( \tau_M \) and \( \tau_C \) is the stabilization parameter, \( L_i \) is the \( i^{th} \) momentum equation as [53]

\[ L_i = \frac{\partial v_i}{\partial t} + v_j v_{i,j} + p_i - \tau_{ij,j} \]  

(3.41)

The first term in (3.40) is the Galerkin formulation; the second term represents the momentum and
pressure stabilization; the third term characterizes compensation for the stabilization terms [53]. With the weak form, a generalized alpha timestepping scheme is implemented for time discretization.

3.5 Hemodynamics simulation

In the thesis, an open-source computational fluid dynamics software, SimVascular (Stanford University, simvascular.github.io) [30], is utilized as the fluid solver for the patient-specific hemodynamics simulations. The flow solver of SimVascular uses the open-source PHASTA (Parallel, Hierarchical, Adaptive, Stabilized, Transient Analysis) code [74] to solve the three-dimensional incompressible Navier-Stokes equations in an arbitrary domain. SimVascular allows the flow solver to run either on a single core or multiple cores with the Message Passing Interface (MPI). We simulated the blood flow within two cardiac cycles, since we performed a study on case n. 8 with 4 cardiac cycles and we found that the pressure drop is converged after the first cycle. The entire simulation for each one of 18 cases took from 36 to 48 hours with 8 cores on the SciNet [76] cluster, depending on the mesh size of each case.

SimVascular requires the user to specify the hemodynamics parameters to the flow solver, including the blood density \( \rho \), viscosity \( \mu \), number of time steps, time step size, body force, and boundary conditions. Note that the time step, \( \Delta t \), should satisfy the CFL condition for a stable solution as

\[
CFL = \frac{v \Delta t}{h}
\]  

(3.42)

where \( v \) is the average velocity, \( h \) is the spatial discretization parameter or finite element size. In the thesis, we take CFL to be slightly less than 1.0 for a balance of temporal and spatial discretization with \( v \approx 110\, mm/s \) and \( h \approx 0.15\, mm \). Therefore the maximum threshold of time step size is 0.00136 s, and we set \( \Delta t = 0.001\, s \) according to the CFL condition.
Chapter 4

Post-processing and Numerical Results

The medical image processing pipeline and computational framework proposed in Chapters 2 and 3 are applied in this chapter to 18 patients for non-invasively assessing the severity of CoA. In this chapter, firstly we discuss how pressure values were extracted from the raw CFD results in order to compute the pressure drop across the CoA. We also discuss how velocity streamlines can be generated, since they are useful to have a graphical insight on the simulation results. Then, we compare the pressure drops obtained from the proposed method against the in-vivo measurements obtained with catheterization and Doppler cardiography.

4.1 Pressure measurement

To calculate the pressure drop ($\Delta P$) across the CoA, we first need to compute the mean pressures $P_{bef}$ and $P_{aft}$ before and after the CoA, respectively. These pressures were calculated at the two locations indicated by the clinician. The maximum pressure difference $|P_{bef} - P_{aft}|_{max}$ over time is taken as the pressure drop used for assessing the CoA severity.

The measurement firstly finds the points at each reference plane which satisfy the following equation

$$|\bar{V}_{pc} \cdot \hat{n}| < \varepsilon$$ (4.1)

where $\bar{V}_{pc}$ denotes the vector pointing from the point $P$ to the center point $C$ of the reference section, and $\hat{n}$ represents the normal vector of the reference plane. In (4.1), $\varepsilon$ denotes a threshold and is set to be 0.01 mm in the thesis.

With the pressure value at each point, we can integrated over the cross section to obtain the average pressure

$$P_{mean} = \frac{1}{A_0} \sum_{e=1}^{N_e} \sum_{i=1}^{N_p^e} f(p_i^e) \cdot A_e$$ (4.2)

where $A_0$ is the reference area, $N_e$ is the number of elements, $N_p^e$ is the number of nodes within each element, and $A_e$ is the area of each element. The pressure $p_i^e$ at node $i$ of element $e$ is interpolated with
the function \( f(p) \) to form the mean pressure \( p^e \) of each element. In the thesis we chose a linear function \( f(p) = \frac{1}{N_p} \cdot p \) as the interpolation scheme.

The simulated pressure at reference planes for patient n. 8 is shown in Figure 4.1. For this patient, the pressure drop measured with catheterization is 20 mmHg. The maximum pressure difference over one cardiac period appears at \( t = 1.38 \) s with the value 17.15 mmHg, which is \(-2.85\) mmHg off the catheterization result. Figure 4.2 shows the simulated pressure \( P_{bef} \) and \( P_{aft} \) and the pressure drop \( \Delta P \) within one cardiac cycle of patient n. 8.

Figure 4.1: The pressure at reference sections at \( t = 1.38 \) s of case n. 8.

Figure 4.2: The pressure at reference planes and pressure drop of case n. 8.
4.2 Stream Tracing

A scalar field, such as the pressure mentioned above, represents the intensity of the physical quantities. On the other hand, the vector field, such as velocity, can be used to display the dynamic features of the moving fluid. Therefore, to visualize the blood flowing through the aorta and its supra-aortic branches, we generated the streamlines of the velocity field as well as its vector glyphs. A streamline denotes the path that a massless particle would flow through a vector field at an instant in time, which gives a graphical illustration of the structure of the vector field. The mathematic principle and scientific visualization of the streamlines are presented in the following subsections.

4.2.1 Streamlines

A streamline \( s \) can be defined through the solution to the following ordinary differential equation (ODE)

\[
\frac{\partial s(\tau)}{\partial \tau} = v(s(\tau), t_0), \quad s(0) = s_0
\]  

(4.3)

where \( v \) is the vector field (in the thesis is velocity), \( \tau \) is the pseudo-time used to generate the particle trajectory through the vector field at a given time \( t_0 \). The streamline starts at position \( s_0 \) and ends up at the boundary. Given a pseudo-time interval \( \Delta \tau \) at real time \( t_0 \), the new location \( s(\tau + \Delta \tau) \) can be found as

\[
s(\tau + \Delta \tau) = s(\tau) + \int_\tau^{\tau + \Delta \tau} v(s(t'), t_0) dt'
\]  

(4.4)

And therefore the full path would be

\[
s(\tau) = s(0) + \int_0^\tau v(s(t'), t_0) dt'
\]  

(4.5)

Equations (4.3) and (4.4) represent a typical inhomogeneous value problem, which can be solved numerically with several integration methods, including Euler’s method, Adam’s method, Runge-Kutta’s method, and many others. These methods differ in the number of steps (single or multi step) and in the explicit or implicit nature. In the thesis, we choose the Runge-Kutta method for its accuracy on higher-order streamlines.

The Runge-Kutta methods, developed by the German mathematicians C. Runge and M. W. Kutta, are a set of temporal discretization methods for the numerical solution of differential equations with different orders of accuracy. For the streamline equation (4.3), the temporal differential scheme can be implemented with different orders, derived from the expansion of Taylor series as

First Order (Euler):

\[
s_{k+1} = s_k + \Delta \tau v(s_k)
\]  

(4.6)

Second Order:

\[
\begin{align*}
s'_k &= s_k + \frac{1}{2} \Delta \tau v(s_k) \\
s_{k+1} &= s_k + \Delta \tau v(s'_k)
\end{align*}
\]  

(4.7)
Forth Order:

\[ K_1 = \Delta \tau v(s_k) \]
\[ K_2 = \Delta \tau v(s_k + K_1 \frac{\Delta \tau}{2}) \]
\[ K_3 = \Delta \tau v(s_k + K_2 \frac{\Delta \tau}{2}) \]
\[ K_4 = \Delta \tau v(s_k + K_3 \Delta \tau) \]
\[ s_{k+1} = s_k + \frac{1}{6} K_1 + \frac{1}{3} K_2 + \frac{1}{3} K_3 + \frac{1}{6} K_4 \] (4.8)

where \(v(s)\) is the steady velocity field at time \(t_0\). With the Runge-Kutta method, the streamline path \(s\) can be computed iteratively within the domain.

### 4.2.2 Streamline tracing and visualization

In the thesis, we generated streamlines with the stream trace filter in **Paraview** [75], which is an open-source software for scientific analysis and visualization. The velocity field and its corresponding streamlines at \(t = 1.38\) s for patient n. 8 are presented in Figure 4.3, where the pressure drop across the CoA reaches its maximum.

![Figure 4.3: Vector glyph (left panel) and streamlines (right panel) of velocity field at \(t = 1.38\) s.](image)

The velocity field was computed with the **SimVascular** flow solver by solving the incompressible Navier-Stokes equations. With the velocity data, the vector glyph field is created by the Glyph filter in Paraview, while the streamline is integrated using the forth order Runge-Kutta method with both forward and backward integration directions by the Stream Trace filter in Paraview. The Glyph filter places a glyph on each point with an orientation direction and scaled according to the magnitude of the field. The Stream Tracer filter seeds a vector field with \(s\) collection of points, and then traces those seed points through the steady vector field. In the thesis, the maximum streamline length is 700 mm, while the number of sampled points is 7000.
4.3 Results

The results we achieved in the thesis are presented and discussed in this section. The procedure of geometry reconstruction and meshing was performed with the pipeline proposed in Chapter 2, and the complexity of the obtained volumetric mesh for all 18 patients is reported in Table 4.1 with a fixed mesh size equal to 0.15 mm.

First we simulated the 18 cases using the general inflow rate from the 2nd CFD Challenge "Predicting Patient-Specific Hemodynamics at Rest and Stress through an Aortic Coarctation" from the 2013 International Conference on Medical Image Computing and Computer Assisted Intervention [57] (shown in Figure 3.3) and the Windkessel boundary conditions proposed in Chapter 3 with SimVascular. After the post-processing of retrieving the mean pressure at the reference sections, we obtained the pressure drop across the CoA section of each patient, as is displayed in Table 4.2. The pressure drop from CFD modeling is compared with the value measured by catheterization, and the mean error and standard deviation are $-10.5$ mmHg and $18.9$ mmHg, respectively. Note that for patient n. 6 and n. 18, the clinical record indicated "low" pressure drop, which usually means a pressure drop below 10 mmHg. Therefore, the error of these two cases is unavailable since we do not know exactly the gold standard.

We also evaluated the accuracy of Doppler echocardiography with catheterization, and the mean error and standard deviation are $18.3$ mmHg and $10.5$ mmHg, respectively. This shows that the CFD model tends to underestimate the pressure drop, while Doppler echocardiography tends to overestimate the pressure drop significantly.
Chapter 4. Post-processing and Numerical Results

Table 4.2: CoA information and pressure drop measured by CFD method with the general inflow rate and the comparison with catheterization and Echocardiography.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>CoA degree (%)</th>
<th>Blood Pressure (mmHg)</th>
<th>Catheterization Pressure drop (mmHg)</th>
<th>CFD Pressure drop (mmHg)</th>
<th>Error</th>
<th>Doppler Echo Pressure drop (mmHg)</th>
<th>Error</th>
</tr>
</thead>
<tbody>
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<td>177/90</td>
<td>20</td>
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<td>-2.8</td>
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<td>22</td>
</tr>
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<td>84</td>
<td>140/70</td>
<td>30</td>
<td>37.3</td>
<td>7.3</td>
<td>56</td>
<td>26</td>
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<td>65</td>
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<td>29</td>
<td>18.8</td>
<td>-10.2</td>
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<td>-5.0</td>
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<td>3.3</td>
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<td>42</td>
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<td>1.5</td>
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<td>49</td>
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<tr>
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<td>66</td>
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<td>145/60</td>
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<td>30.1</td>
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<tr>
<td>45</td>
<td>71</td>
<td>150/90</td>
<td>60</td>
<td>61.0</td>
<td>1.0</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>46</td>
<td>77</td>
<td>160/80</td>
<td>50</td>
<td>16.2</td>
<td>-33.8</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean error (mmHg)</th>
<th>-10.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard deviation (mmHg)</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>10.5</td>
</tr>
</tbody>
</table>

We did the regression analysis on the error from CFD and the pressure drop by catheterization, as is shown in Figure 4.4.

Note that for case n. 6 and n. 8 since the exact error is unknow, we didn’t include these two cases. From both Table 4.2 and Figure 4.4, we found that if we compare some case pairs, such as cases n. 38 and n. 41, or cases n. 36 and n. 38, they have very close CoA severity, and their CFD results are quite close as well. However, the catheterization measurement shows a significant difference between the paired cases. This fact has led us to explore the difference between them, and we found that the major difference is the inlet area at the ascending aorta. For those cases with a significant underestimation of pressure drop by CFD approach, what they have in common is that they all have a relatively large ascending aorta, a mild CoA and a high pressure drop by catheterization.

Therefore, to solve the underestimation problem of the CFD method, we employed the criteria proposed in section 3.3.2 that modifies the flow rate imposed in the ascending aorta for those patients with a large ascending aorta and a mild CoA. This criterion was defined in (3.11) and the corresponding scaling factor $\alpha$ for the flow rate is shown in Table 4.3.
Figure 4.4: The error analysis of the CFD error and pressure drop from catheterization.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Inlet Area (mm²)</th>
<th>CoA degree (%)</th>
<th>α</th>
<th>Patient ID</th>
<th>Inlet Area (mm²)</th>
<th>CoA degree (%)</th>
<th>α</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>298</td>
<td>35</td>
<td>1.0</td>
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<td>1,213</td>
<td>78</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>1,011</td>
<td>73</td>
<td>1.0</td>
<td>30</td>
<td>300</td>
<td>49</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>1,533</td>
<td>84</td>
<td>1.0</td>
<td>34</td>
<td>1,366</td>
<td>72</td>
<td>2.840</td>
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<tr>
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<td>460</td>
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<td>1.0</td>
<td>36</td>
<td>882</td>
<td>66</td>
<td>1.0</td>
</tr>
<tr>
<td>15</td>
<td>688</td>
<td>69</td>
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<td>38</td>
<td>1,323</td>
<td>66</td>
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</tr>
<tr>
<td>16</td>
<td>527</td>
<td>75</td>
<td>1.0</td>
<td>41</td>
<td>1,505</td>
<td>69</td>
<td>2.732</td>
</tr>
<tr>
<td>18</td>
<td>970</td>
<td>62</td>
<td>1.165</td>
<td>43</td>
<td>374</td>
<td>69</td>
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<td>963</td>
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<td>1.120</td>
<td>45</td>
<td>418</td>
<td>71</td>
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</tr>
<tr>
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<td>1,172</td>
<td>42</td>
<td>1.727</td>
<td>46</td>
<td>825</td>
<td>77</td>
<td>1.0</td>
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</table>

Table 4.3: Inflow amplification factor α for equation (3.11).
We re-simulated the 18 cases with the modified patient-specific inflow rate. Table 4.4 displays the pressure drop computed by the modified CFD model and its comparison with catheterization. A significant improvement can be found in cases 20, 24, 34, 38 and 41, in which the pressure drop were significantly underestimated with the original inlet flow. Compared to catheterization, the mean error and standard deviation of the CFD method are $-2.8\, \text{mmHg}$ and $14.0\, \text{mmHg}$, respectively. The comparison shows that with the modified inflow boundary condition, the CFD method is much more accurate. The proposed method still, on average, tends to underestimate the pressure drop, mostly because of the significant underestimation ($> 30\, \text{mmHg}$) in 2 (11%) patients (patient ID: 20, 46). Due to this large discrepancy, these cases were investigated in depth, but a precise cause for this large mismatch could not be found. The two main hypothesis are that the boundary conditions are not well representative of the upstream and downstream circulation for these patients, or that a transcription error might have happened during the extraction and anonymization of the clinical data from the institutional database. If we exclude these two patients from Table 4.4, the mean error and standard deviation become $1.7\, \text{mmHg}$ and $7.2\, \text{mmHg}$, respectively, which means that in most cases (89%), the pressure drop obtained by the CFD method is very close to the reference pressure drop measured by catheterization.

We also did the regression analysis on the error from CFD with the patient-specific inflow data and the pressure drop by catheterization. as is shown in Figure 4.5.

Since CoA treatment guidelines recommend surgical intervention when the pressure drop is above 20 mmHg, it is interesting to investigate how frequently the proposed method correctly detects a pressure drop above these threshold. In Table 4.4, a significant pressure drop ($\geq 20\, \text{mmHg}$) was found in 14 (78%) patients by catheterization, and in 11 (61%) patients by the numerical simulation. In 15 (83%) patients, the CFD method was in agreement with catheterization. The agreement and disagreement between the two methods is summarized in Table 4.5. A good agreement between the two methods can be observed, since the Cohen’s kappa coefficient is 0.64, which indicates a fairly good agreement.
### Table 4.4: CoA information and pressure drop measured by CFD method with the patient-specific inflow rate and the comparison with catheterization and echocardiography.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>CoA degree (%)</th>
<th>Blood Pressure (mmHg)</th>
<th>Pressure drop (mmHg)</th>
<th>CFD</th>
<th>Error</th>
<th>Doppler Echo</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Catheterization</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>&lt;10</td>
<td>12.8</td>
<td>n/a</td>
<td>30</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>177/90</td>
<td>20</td>
<td>17.2</td>
<td>-2.8</td>
<td>42</td>
<td>22</td>
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<tr>
<td>10</td>
<td>84</td>
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<td>37.3</td>
<td>7.3</td>
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<td>11</td>
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<tr>
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<td>190/100</td>
<td>20</td>
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<td>-5.0</td>
<td>36</td>
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<td>145/80</td>
<td>&lt;10</td>
<td>10.7</td>
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<td>173/89</td>
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<td>142/80</td>
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<td>-1.0</td>
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<td>145/60</td>
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<td>30.1</td>
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<td>n/a</td>
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<td>150/90</td>
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<td>61.0</td>
<td>1.0</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
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<td>77</td>
<td>160/80</td>
<td>50</td>
<td>16.2</td>
<td>-33.8</td>
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<td>n/a</td>
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<table>
<thead>
<tr>
<th>Mean error (mmHg)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Standard deviation (mmHg)</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Table 4.4: CoA information and pressure drop measured by CFD method with the patient-specific inflow rate and the comparison with catheterization and echocardiography.

### Table 4.5: Agreement between the proposed CFD method and catheterization in detecting a pressure drop higher than 20 mmHg.

<table>
<thead>
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<th></th>
<th>Catheterization ≤ 20 mmHg</th>
<th>Catheterization &gt; 20 mmHg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFD ≤ 20 mmHg</td>
<td>5 (71%)</td>
<td>2 (29%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>CFD &gt; 20 mmHg</td>
<td>1 (9%)</td>
<td>10 (91%)</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (33%)</td>
<td>12 (67%)</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 4.5: Agreement between the proposed CFD method and catheterization in detecting a pressure drop higher than 20 mmHg.
Chapter 5

Conclusions

5.1 Summary

In the thesis, we proposed a non-invasive method for assessing the CoA severity using computational fluid dynamics guided by medical images. The severity of CoA is assessed by measuring the pressure drop across the CoA site. The proposed method reconstructs the aortic structure using the geometry information from the medical images and computes the fluid fields by numerically solving the 3-D incompressible Navier-Stokes equations with the finite element method. The pressure drop is calculated as the difference of pressure before and after the CoA site. The simulation result is then compared with catheterization and Doppler echocardiography to evaluate the accuracy of the CFD method.

We studied 18 patients with CoA severity degree varying from mild (35%) to severe (84%) using their patient-specific information including aortic geometry and SBP/DBP. We proposed an inflow model based on the general inflow data from information provided as part of a CFD challenge in the 2013 International Conference on Medical Image Computing and Computer Assisted Intervention [57] for the inlet boundary condition and implemented a Windkessel model [65] for the outlet boundary conditions. We used the open-sourced software SimVascular [30] for hemodynamics simulation, and we proposed a post-processing procedure for measuring pressure, velocity and other fluid fields in an automated way.

The comparison of pressure drop across CoA site between the catheterization and CFD method shows a good consistency. The mean error and standard deviation are $-2.8 \text{ mmHg}$ and $14.0 \text{ mmHg}$, respectively, which is better than the accuracy of Doppler echocardiography. For the 18 patients considered in this study, echocardiography resulted in a mean error and standard deviation of $17.5 \text{ mmHg}$ and $10.3 \text{ mmHg}$, respectively. The average error, quite higher than in the proposed method, confirms the known fact that echocardiography tends to overestimate the pressure drop in aortic coarctation. We also analyzed the ability of the proposed method to predict whether the pressure drop is lower or higher than $20 \text{ mmHg}$, and compared its predictions with catheterization. Above the $20 \text{ mmHg}$ threshold, intervention is recommended according to the ACC/AHA guidelines [1]. In 15 (83%) patients, the proposed CFD method provided an indication consistent with catheterization, overall resulting in a Cohen’s kappa coefficient of 0.64, which indicates a fairly good agreement.

The obtained results show that the image-guided CFD method can provide valuable clinical information about the severity of CoA without exposing patients to the risks and costs of invasive procedures like catheterization. More studies are however still in order to further investigate the reliability of a com-
putational approach, that in two cases out of 18 gave results far away from the gold standard, possibly due to the uncertainty in boundary conditions, or due to a transcription error in the anonymization of the clinical records, that we were not able to exclude.

5.2 Future work

Several directions could be explored along the lines drawn by this thesis in order to improve the accuracy, reliability and automation of the proposed method. These directions include better boundary conditions, improvements to the imaging processing flow, and the application to other cardiovascular diseases.

5.2.1 Patient-specific boundary conditions

In the proposed method, and in most studies on computational hemodynamics, a significant source of uncertainty is represented by boundary conditions, that are typically derived from literature data with only a limited adjustment based on patient-specific information. Advances in medical imaging techniques, such as 4D flow MRI, are opening a new opportunity to address this long-lasting issue. With 4D flow MRI, blood velocity can be imaged in-vivo, resolved over both time and space with a fair resolution. This functional information can then be used to derive patient-specific boundary conditions at the inlets and outlets of the region of interest. Since, in CoA simulations, inlets and outlets are defined on fairly large vessels, the current resolution of 4D flow MRI seems adequate to derive an accurate and reliable patient-specific boundary condition. Given the influence of boundary conditions on CFD results, this direction of improvement is one of the most compelling.

5.2.2 Improvements to the medical images processing pipeline

The medical image processing procedure plays a significant role in computational hemodynamics, since the accuracy of the simulation significantly depends on the quality of the anatomical reconstruction. Although we developed a well established pipeline for the whole procedure, the level sets segmentation step still requires significant manual guidance (seeds specification, intensity threshold selection, validation of the reconstruction against the original medical images). This issue is obviously an important roadblock towards clinical translation. Currently automated algorithms for vessels identification are mainly available for 2-D angiography images [77].

In addition to improvements to the existing methods for geometry reconstruction, advancements in machine learning may provide a complementary contribution to automating the extraction of anatomy from medical images. Many studies have shown that convolutional neural networks can be used for vessel segmentation with an accuracy close to human observation [78, 79, 80]. Advancements in geometrical reconstruction techniques can save a significant amount of time when preparing a hemodynamics simulation, and also make computational methods more user-friendly, facilitating clinical translation.

5.2.3 Application to other cardiovascular diseases

A remarkable feature of computational hemodynamics is its versatility and applicability to a wide range of cardiovascular studies. While this thesis focused on aortic coarctation, CFD can be applied to many other diseases, as confirmed by the rising number of publications in the general area of computational
hemodynamics. Examples include coronary arteries bypass graft, aortic aneurysm and Pulmonary hypertension. Recently, we have started applying the knowledge learned in this project to coronary arteries, in order to then investigate the mechanisms that lead to graft failure. With the hemodynamics simulations we can calculate a large number of hemodynamics parameters, such as wall shear stress and oscillatory shear index, and investigate their correlation to graft failure.

In comparison to aorta, coronary arteries are much thinner and more complicated, which makes the geometrical reconstruction more challenging. Nevertheless, the incidence and complications of coronary artery disease justifies this increased effort as it can eventually lead to benefits for the large number of patients around the world that suffer from coronary artery disease. As remarked earlier, the unavailability of patient-specific boundary conditions was a significant source of uncertainty in the study performed in this thesis. In the recently-started project on coronary arteries, 4D flow MRI will be used to extract boundary conditions from in-vivo measurements, hopefully leading to better accuracy and repeatability.
Bibliography


