Sources of Error in Image-based Computational Fluid Dynamics Modeling of Common Carotid Arteries

by

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Department of Mechanical and Industrial Engineering
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Abstract

Magnetic resonance imaging is often used as a source for reconstructing vascular anatomy for the purpose of computational fluid dynamics (CFD) analysis. We recently observed large discrepancies in such image-based CFD models of the normal common carotid artery (CCA) derived from contrast enhanced MR angiography (CEMRA). A novel quantitative comparison of velocity profile shape of N=20 cases revealed an average 25% overestimation of velocities by CFD, attributed to a corresponding underestimation of lumen area in the CEMRA-derived geometries. We hypothesized that this was due to blurring of edges in the images caused by dilution of contrast agent during the relatively long elliptic centric CEMRA acquisitions, and confirmed this with MRI simulations. CFD simulations incorporating realistic inlet velocity profiles and non-Newtonian rheology had a negligible effect on velocity profile skewing, suggesting a role for other sources of error or modeling assumptions.
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Chapter 1  
Introduction

1.0 Introduction

Cardiovascular diseases are known to be the leading cause of death in North America. They are defined as diseases and injuries of the cardiovascular system: the heart, the blood vessels of the heart, and the system of blood vessels (veins and arteries) throughout the body and within the brain. Among various types of cardiovascular diseases, stroke is the third leading cause of death in United States.

Strokes can be classified into two categories: i) ischemic stroke, and ii) hemorrhagic stroke. Ischemic stroke occurs when a blood vessel that supplies blood to the brain is blocked by a blood clot. This may happen in two ways: a) A clot may form in an artery that is already very narrow, known as thrombotic stroke; b) A clot may break off from another place in the blood vessels of the brain, or from some other part of the body, and travel up to the brain, known as embolic stroke. A hemorrhagic stroke occurs when a blood vessel in part of the brain becomes weak and ruptures, causing blood to leak into the brain. In some cases, defects in the blood vessels of the brain may make this more likely.

Based on Heart Disease and Stroke Statistics published by American Heart Association, cardiovascular disease accounted for 811,940 or 32.8% of all deaths in 2008, among which 162,388 or 20% were caused by strokes. Of all strokes, 87% were ischemic strokes and the remaining 13% were hemorrhagic strokes. The direct and indirect cost of stroke in 2008 was $34.3 billion, and the mean expense per person for stroke care in 2007 was estimated at $7,657. The mean lifetime cost of ischemic stroke in the United States is estimated at $140,048 per person.

Due to the high death rates and treatment costs, particularly associated with ischemic strokes, it is of significance in clinical studies and trials to investigate the parameters causing this phenomenon.
1.1 Atherosclerosis: Definition and Physiology

As described previously, the ischemic strokes occur as a result of plaques or blood clots that block blood supply to the brain. Deposits of cholesterol and plaque accumulate at an injury in the inner lining of an artery. The hardening of these deposits leading to the occlusion of the arterial lumen is known as atherosclerosis. Atherosclerosis may begin as early as the teen years and may remain symptomless for decades. Apart from age, certain traits, or habits may raise the chances of developing atherosclerosis. These risk factors include: smoking, obesity, diabetes mellitus, physical inactivity, high blood pressure and high cholesterol and genetic theory, all of which can play a role in the formation and progression of the disease.

Although the exact cause of atherosclerosis is unclear, it is thought to be caused by repeated subtle injury to the thin layer of cells that line the interior surface of the blood vessel (i.e. endothelium). This is due to various stress mechanisms such as physical stress induced from disturbed blood flow, inflammatory stress from the immune system, and chemical abnormalities in the blood vessel. As shown in Figure 1, the damaged area inside of the arterial wall begins to accumulate substances travelling in the blood stream. Once inside the arterial walls, substances such as cholesterol, fats, and cellular waste products become susceptible to oxidization and initiate an inflammatory reaction. In response to endothelial cells signaling damage, the body’s immune system sends specialized white blood cells, called monocytes, from blood stream to the injured arterial wall. These monocytes transform into macrophages to absorb the oxidized fatty acid forming specialized foam cells and accumulate to form plaques.

![Figure 1: The development of arterial atherosclerosis occurs when deposits of cholesterol and plaque accumulate at an injury in the inner lining of an artery. As the deposits harden and occlude the arterial lumen, blood flow to distant tissues decreases and a clot becomes lodged, completely blocking the artery. Image Source: umm.edu](image-url)
As the plaque increases in size with time, the arterial wall begins to thicken and harden. The smooth muscle cells in the arterial wall multiply and travel to the surface of the atherosclerotic plaque to form a firm, fibrous cap on top of the plaque. With time, this cap breaks open releasing plaque debris or more commonly, small blood clots, into the blood stream, which travel downstream and lodge into small brain vessels. This results in limited blood supply or nutrition to the neighboring brain tissues causing stroke.

1.2 Wall-Shear-Stress: Relation to Atherosclerosis

The fluid motion within the arterial system causes mechanical stresses, which by definition, is force per unit area. As shown in Figure 2, the perpendicular and tangential components of this force provide values for tensile or compressive stresses, and shear stresses, respectively. If this shear stress occurs in proximity of the vessel wall, it is known as Wall Shear Stress (WSS). Mathematically, WSS is equal to the spatial gradient of blood velocity, known as the shear rate, and blood viscosity, which is dependent on the hematocrit and fibrinogen content and decreases non-linearly with increasing shear rate.

![Figure 2: Shear stress model in context of blood vessels. (A) Direction of force acting on the surface determines whether stress is tensile, compressive, or shear, (B) Wall-shear-stress (WSS), product of wall-shear-rate and viscosity, arises due to velocity difference in adjacent layers of blood flow at the vessel walls. Proximal to vessel walls, velocity increases linearly with distance and thus is equal to difference in velocity divided by distance. Image and caption adapted from Slager et al. [1] ](image-url)
There is substantial evidence that WSS is related to initiation, progression and development of atherosclerosis [1] [2] [3]. Endothelial cells (ECs) lining the artery walls sense this WSS and, in a feedback control loop, adapt the arterial dimensions to blood flow [4]. High WSS, acting for example on the flow divider of an arterial bifurcation, are thought to be atheroprotective. However, locations of average low WSS are prone to development of atherosclerosis. Figure 3 shows, in a chronological order, the process leading to the development of atherosclerotic plaques in arterial bends in presence of these low WSS [2]. The growth of such atherosclerotic lesion can itself alter the flow and, as a result, the WSS patterns on the endothelium. The narrow luminal spacing due to the presence of severe stenosis causes a pressure drop and increased velocity, which can create a flow separation zone immediately downstream, much like a jetting effect across the stenosis. This separation zone has similar characteristics to the prelesional sites.

**Figure 3:** Locations of low wall-shear-stress region, generally the inner wall of arterial bends, are prone to plaque build-up or wall thickening. The dotted red lines show the high shear region, and the solid blue line shows the low shear stress region. (A) Curved, healthy artery with global shear stress distribution, (B) In presence of atherosclerotic risk factors, atherosclerosis develops at low shear stress locations at the inner curve of the artery. The plaque-free wall (PFW) remodels to maintain a normal lumen, which in turn maintains the shear stress difference between the inner and outer curves to prolong lipid accumulation. (C) High-shear stress stimulates outward remodeling at the remaining small area of plaque-free-wall, which can become inadequate to maintain lumen preservation. Increased wall-shear-stress is experienced by upstream cap shoulder and low wall-shear-stress is experienced by downstream shoulder. Image and caption adapted from Slager et al. [1]
susceptible to WSS induced changes, and thus lesion-induced disturbed flow may further the growth of the lesion [3].

In addition to WSS induced atherosclerotic plaques in bends, there are certain anatomical regions, such as arterial branches and bifurcations that are also susceptible to atherosclerosis. As shown in Figure 4, downstream of arterial bifurcations, the flow departs from a unidirectional pulsatile shear stress, and creates flow-separation zones that are characterized by oscillatory shear stress, flow reversal and, in some cases, turbulence. These regions, unlike the undisturbed adjacent regions, are susceptible to development of atherosclerosis. Carotid artery bifurcation is one of these regions, and therefore is prone to development of atherosclerotic plaques [3]. Considering the risk of stroke associated with rupture of carotid plaques, it is of great clinical significance to investigate the WSS patterns and their relation to atherosclerosis.

Figure 4: Flow separation at arterial bifurcations is proatherogenic, in which complex transient vortices form and dissipate. This disturbed flow region is characterized by low average shear stress, varying gradients of shear stress, oscillatory flow, and multidirectional secondary flows. High shear stresses, as long as below approximately 40 N/m² range, are atheroprotective. Image and caption adapted from Davies et al. [3]
1.3 Carotid Bifurcation: Region of Disturbed Flow

As discussed previously, atherosclerosis is related to wall-shear-stresses and commonly develops at arterial bifurcations, branches and bends. One such bifurcation is the carotid bifurcation. As shown in Figure 5, carotid arteries are the main conduits for blood flow from heart to the brain. The left common carotid artery (CCA) branches from the aortic arch, and the right typically from the brachiocephalic artery off the arch. The left and the right CCA eventually bifurcate into an internal carotid artery (ICA), which supplies blood to the brain, and an external carotid artery (ECA), which feeds the rest of the head.

Carotid bifurcations have been the subject of intense hemodynamics studies owing to the preferential development of atherosclerosis at this site. As has been described previously, high shear stress regions are atheroprotective whereas low shear stresses are associated with atherosclerosis. In context of carotid bifurcation, the flow through the CCA is unidirectional and the WSS are within the physiological range. However, as the flow enters the bulbic region of the ICA and ECA, as shown in Figure 6, it creates flow-separation zones causing flow reversal, oscillatory shear stresses (OSS), and low average WSS, all of which have previously been shown to be proatherogenic.

![Figure 5: Both left and right common carotid arteries bifurcate into internal carotid artery and external carotid artery, supplying blood to the brain and rest of the head respectively. Image source: texasheartinstitute.org](image-url)
1.4 Image-Based Computational Fluid Dynamics: Predicting Hemodynamics in Carotid Bifurcations

In order to correlate complex hemodynamics factors, such as WSS and OSS, with atherosclerosis in carotid bifurcations, we need to acquire three dimensional (3D) velocity fields. Although imaging techniques, such as 4D Phase-Contrast Magnetic Resonance Imaging (PCMRI), can be used to obtain 3D velocity data, the coarse spatial resolution acquired significantly limits the flow analyses. Prolonging the scan times to achieve sufficient spatial resolution to accurately compute relevant hemodynamic quantities have precluded them from routine human studies [5].

Alternatively, image-based computational fluid dynamics (CFD) has proven to be a reliable and practical tool for studying time varying 3D blood flow patterns in patient-specific carotid bifurcations. High resolution carotid geometry is obtained from MRI of the patient, and discretized into smaller but regular elements. Assuming the shape of the velocity field within
these elements, we can solve the governing \textit{Navier-Stokes} equation at the \textit{nodes} connecting the elements, and extract important hemodynamic quantities such as WSS and OSS [6]. In the following two sections, we will provide the necessary imaging, and CFD background needed to perform computational hemodynamics of carotid bifurcations.

### 1.5 Introduction to Magnetic Resonance Angiographies

Magnetic Resonance Angiography (MRA) is an MRI-based technique to generate images of arteries, such as carotid, aortic and renal arteries, to evaluate them for stenosis, occlusion or aneurysms. MRI makes use of the fact that our bodies contain a lot of water molecules, each consisting of two hydrogen nuclei or protons. As shown in Figure 7, when a patient is placed inside the strong magnetic field of an MRI scanner, the hydrogen protons align themselves in the direction of this magnetic field. A radio-frequency current is briefly activated to produce a varying electromagnetic field with just the right frequency, known as the resonance frequency, to be absorbed by the protons causing the spins to flip in the magnetic field. When the electromagnetic field is deactivated, the spins begin to relax while generating a radio frequency signal, which is measured with the receiver coil, and described by two relaxation times of the components of the magnetization, namely $T_1$ (longitudinal) and $T_2$ (transverse). This relaxation occurs until the protons revert to their thermodynamic equilibrium state and the net

![Figure 7](https://example.com/imaio.png)

**Figure 7:** Abundant water molecules in human body can be aligned in presence of a magnetic field. (A) Hydrogen nuclei have magnetic properties called nuclear spin, and behave like tiny rotating magnets represented by vectors, (B) The direction of these vectors are randomly oriented and sum of all the spins gives null net magnetization, (C) When a large magnetic field ($B_0$) is applied, more spins align (parallel) with the field than against it (anti-parallel) resulting in a net magnetization aligned with $B_0$. Imaging Source: imaios.com
magnetization becomes re-aligned with the statically applied magnetic field. Protons in different tissues return to their equilibrium state at different relaxation rates, and, as a result, creating a contrast between different types of body tissue, a property that can be exploited for the purpose of visualization.

There exists a variety of MRA techniques to visualize the vasculature, but they are generally classified into Flow Dependent Angiography methods (FDA) and Flow Independent Angiography methods (FIA). The former takes advantage of the fact that the blood is flowing compared to the static neighbouring tissues. FDA methods can be further categorized into Phase-Contrast MRA, which utilizes phase differences to distinguish blood from static tissues, and Time-of-Flight (TOF) MRA that relies on the fact that flowing blood will experience fewer radio-frequency current excitations than static tissues when imaging a thin slice. The FIA method is generally divided into contrast-enhanced MRA techniques, where a contrast agent is injected to alter the properties of blood from neighbouring tissues resulting in high quality images, and non-contrast enhanced techniques, which exploits the $T_1$ and $T_2$ properties, and chemical shift of different tissues of the voxel to generate the images. The two technique used in our studies are TOF MRA and Contrast Enhanced MRA, and are discussed in the following two subsections.

1.5.1 Time-of-Flight Magnetic Resonance Angiography

TOF MRA makes use of the through-plane blood flow to highlight blood vessels of the patient against a comparatively suppressed stationary background, and thus eliminating the need for intravenous contrast administration. This process is shown in Figure 8. Depending on the region of interest in the body, the TOFMRA can be implemented in two-dimensional sequential multi-slice format, known as 2D TOFMRA, or three-dimensional volume slab format, known as 3D TOFMRA. For the purpose of our studies, we will briefly describe the latter, but readers are encouraged to read about the former from many resources available online.

The 3D TOF-MRA is preferable for evaluation of detailed arterial anatomy because very thin digital slices or partitions are possible. However, the downside is that 3D TOFMRA can be time-consuming and, depending on desired spatial resolution and coverage, can take between 5 to 10 minutes. Due to this reason, the applications are usually restricted to vascular structures such as head and the neck, which are easier to immobilize during the acquisition. The breathing motion artifact is another reason why 3D TOFMRA is restricted to these regions.
There are two main limitations related to the 3D TOFMRA, namely flow-related enhancements and in-plane saturation. If the time between the radio frequency excitation pulses, known as repetition time (TR), is short, fresh spins will have insufficient time to enter the slice resulting in poor vascular contrast. This is known as flow-related enhancements, and can be partially eliminated through effective use of pre-saturation. The in-plane saturation occurs when the vessel is oriented largely within the image slab or the flow has complex re-circulation zones much like in the stenosis regions, causing the blood to become saturated, thus making it difficult to identify the vascular structure.

Three-dimensional TOFMRA has long been the technique of choice for non-invasive imaging of head and neck arteries [7] [8] [9]. Carotid arteries, the focus of our work, have particularly been most receptive to 3D TOFMRA. Carotid arteries, on average, have moderately high flow rates and predominantly superoinferior orientation, making it possible to acquire axial multi-slab acquisitions. It is feasible to ask patients to hold their heads still for relatively longer scan times to acquire high-resolution images. Also, head-neck surface coils dedicated for 3D TOFMRA are widely available to support parallel acquisition, and maximize the signal-to-noise-ratio (SNR).

**Figure 8:** In 3D time-of-flight (TOF) MRA, the stationary tissue signals are saturated and as the blood flows through the explored zone, it creates stronger signal than that of the saturated ones making it possible to visualize the artery. Image Source: imaios.com
1.5.2 Contrast-Enhanced Magnetic Resonance Angiography

Contrast-Enhanced MRA (CEMRA) has been one of the most powerful and valuable tools in MRI in recent years. This technique involves the intravenous administration of bolus of Gadolinium (Gd)-based contrast agent, which significantly heightens the signal intensity of blood compared to the nonvascular background tissue, resulting in angiograms with high contrast-to-noise-ratio (CNR). Even though the cost associated with the use of contrast agent in 3D CE-MRA is higher compared to non-contrast-based techniques, such as 3D TOFMRA, many other advantages make it an attractive option for clinical applications.

In comparison to TOFMRA, where it was difficult to image in the plane of the vascular anatomy, this technique is not dependent on flow as the contrast mechanism, allowing slices to be acquired in any orientation desired or to tailor the examination to patients’ anatomy. The paramagnetic agent is able to prevent the in-plane artifact and saturated flow that are common in TOFMRA, allowing for a greater anatomical coverage using fewer slices. As the pulse sequence is much faster in comparison with 3D TOFMRA and can be acquired as a breath-hold scan, artifacts associated with respiratory motion are minimized. Although best images result when the patients are able to hold their breath, this technique still provides better diagnostic images in comparison to TOFMRA even if the scans are acquired with free breathing.

Even though CE-MRA has many advantages over TOFMRA, it is important to realize that these are greatly dependent on accurate timing of the contrast bolus. In particular, the following factors need careful consideration when dealing with CE-MRA acquisitions:

- Arrival of the contrast bolus in the vessel of interest must coordinate with the beginning of the image acquisition.
- Center of the imaging matrix, containing information about the contrast, must correspond with the peak period of the contrast enhancement.
- Smallest amount of Gd-based contrast agent, able to produce diagnostic quality images, must be used to minimize the risk to the patients while reducing the contrast-associated cost.
• Images must be designed to obtain high-resolution arterial data while minimizing unwanted venous enhancement. For example, since contrast is injected intravenously, we must wait until the contrast reaches carotid artery, but before jugular vein, before beginning the scan.

1.5.3 Comparison of 3D CE-MRA and 3D-TOF-MRA

An overview of the two most common MRA techniques, namely CE-MRA and TOF-MRA, has been presented in the previous section. This section explicitly provides the advantages and disadvantages, as listed in Table 1, to make it easier for the reader to compare the two techniques. It should be noted that each of these technique has its own strengths and weaknesses, and must be used according to the application at hand.

In context of our application in image-based CFD of carotid bifurcation, CEMRA has obvious advantage over TOFMRA. The recirculation zones in the bulbic region of the ICA causes in-plane saturation in TOFMRA acquisitions, and leads to difficulties in segmentation of the true lumen geometry for the purpose of image-based CFD. On the other hand, CEMRA is insusceptible to such saturation artifacts, and thus allows for the segmentation of the “true” lumen geometry. Moreover, CEMRA also provides a higher contrast-to-noise-ratio compared to

Table 1: Advantages and Disadvantages of 3D contrast-enhanced MRA (CE-MRA) and 3D Time-of-Flight (TOF) MRA [10]

<table>
<thead>
<tr>
<th></th>
<th>3D CE-MRA</th>
<th>3D TOF-MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Immune to saturation, that is intravascular signal is dependent upon contrast and not flow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Freedom from flow directional restrictions.</td>
<td>• Obviates the need for contrast administration</td>
</tr>
<tr>
<td></td>
<td>• High spatial resolution and contrast-to-noise-ratio.</td>
<td>• Pre-saturation pulses enable definition of flow direction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High Signal-to-noise-ratio (SNR)</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Inadequate contrast bolus timing may result in non-diagnostic studies</td>
<td>• Sensitive to through-plane and in-plane saturation</td>
</tr>
<tr>
<td></td>
<td>• Venous contamination</td>
<td>• Relatively long repetition time increases acquisition time</td>
</tr>
<tr>
<td></td>
<td>• Imaging matrix may not correspond to peak contrast enhancement</td>
<td>• Use of pre-saturation pulses may introduce pseudo-occlusion in regions of flow reversal</td>
</tr>
</tbody>
</table>
TOF-MRA, which makes the segmentation of carotid bifurcation much easier.

Now that we realize the benefits of using CEMRA over TOFMRA in image-based CFD of carotid bifurcation, in the next section, we provide the necessary background into MRI image formation, particularly in context of CEMRA; a concept necessary in understanding the work presented in the later sections.

1.5.4 MRI Image formation: The Physics Behind it All

The readout of the MRI signal is a mix of radio-frequency waves with different amplitudes, frequencies and phases, containing the spatial information. The signal is digitized and this information is filled into a data matrix. Radiologists most often refer to this matrix as *k-space*, whereas mathematicians know it as *Fourier Plane*. Considering the context of our work, we will adapt the former in the remaining sections. To obtain the spatial matrix from this *k*-space, we perform 2D *Inverse Fourier Transform* of the original matrix.

A Fourier Transform (FT) decomposes a signal into its frequency components. Intuitively, if all the frequency and phase information are available, we may reconstruct the original signal precisely, a technique known as the Inverse Fourier Transform (IFT). Since the MRI scanner actually obtains the frequency and phase, rather than the spatial, information of the region of interest, an IFT is needed to visualize the original image. In this section, we will briefly describe the relationship between the frequency and spatial domain, the different encoding techniques used to fill the *k*-space matrix, and their advantages and disadvantages, particularly for CEMRA applications.

The first step in decomposing any 2D image into its frequency components is to perform a 1D Fourier transform along one axis. Figure 9 shows this process for an arbitrary image, but same can be applied to any MRI image. The next step in 2D Fourier Transform is to perform another 1D Fourier Transform in the orthogonal direction on the result of the first one. Mathematically, this 2D Fourier Transform is defined by the following equation:
In the above equation, \( k_x \) and \( k_y \) are spatial frequencies in \( x \) and \( y \) direction, respectively, and \( G(k_x, k_y) \) corresponds to the 2D spectrum of \( g(x, y) \). Since images are digitized, the information obtained is in discrete quantities rather than as a continuous function. For this reason, the above equation needs to be reformulated in the form of a finite summation, known as Discrete Fourier Transform (DFT), and can be written as follows:

\[
G(k_x, k_y) = \frac{1}{NM} \sum_{x=0}^{N-1} \sum_{y=0}^{M-1} g(x, y) e^{-j2\pi \left( \frac{k_x x}{N} + \frac{k_y y}{M} \right)} dx dy
\]
In the above equation, \( N \) and \( M \) corresponds to the grid size in \( x \) and \( y \) direction of the spatial domain matrix. Now that we understand the process needed to decompose an image into its frequency component using forward FT, the inverse theory is much easier to grasp. In inverse FT, the frequency components, obtained from the MRI scanner, are used to reconstruct the original image through the use of following equation:

\[
G(k_x, k_y) = \sum_{k_x=0}^{N-1} \sum_{k_y=0}^{M-1} g(x, y) e^{j2\pi \left( \frac{k_x x}{N} + \frac{k_y y}{M} \right)} dx dy
\]

In the above equation, \( N \) and \( M \) correspond to the grid size in \( k_x \) and \( k_y \) direction of \( k \)-space matrix. Figure 10 shows the use of IFT to reconstruct the original image from frequency and phase information encoded in \( k \)-space.

**Figure 10:** A two-dimensional Discrete Inverse Fourier Transform (IFT) is used to reconstruct an image from its frequency components. An image of this frequency component often only contains the magnitude (amplitude). However, in order to reconstruct the original image, both amplitude and phase information is needed. (A) The signals obtained from an MRI scanner, containing both amplitude (gray levels) and phase (color) information, known as \( k \)-space, (B) A magnitude image (represented by gray levels) of \( k \)-space, where pixel intensity defines the amplitude of frequency component, (C) The phase image (represented by color) of \( k \)-space, where color defines the phase of the frequency component, (D) The original image reconstructed by performing IFT of the frequency and phase components. Image Source: imaios.com
As true for all MRI, the low-spatial-frequency data is mapped in the central region of k-space, whereas the high-spatial-resolution data is mapped in the peripheries of k-space. Figure 11 shows how losing the high or low frequency data from k-space affects the spatial image. The low-spatial-frequency data, containing the information about the contrast and general shape of the image, have the highest amplitudes resulting in greatest changes in gray-levels. These changes spread over in the image and only give the general shape of the region of interest. The high-spatial-frequency data have lower amplitudes. They do not have an effect on the contrast or

**Figure 11:** The effect of low and high spatial-frequency data on the resulting image. (A) The top image shows the k-space containing complete frequency and phase information. The bottom image is obtained by taking the IFT of this k-space. (B) The top image shows a truncated k-space containing only the low frequency and phase information. The bottom image is obtained by taking the IFT of this k-space. It should be noted that the effect of taking out the high frequency and phase data from k-space has resulted in the loss of edge information in the spatial domain. (C) The top image shows a truncated k-space containing only the high frequency and phase information. The bottom image is obtained by taking the IFT of this k-space. It should be noted that the effect of taking out the low frequency and phase data from k-space has resulted in the loss of edge information in the spatial domain. Image Source: imaios.com

As true for all MRI, the low-spatial-frequency data is mapped in the central region of k-space, whereas the high-spatial-resolution data is mapped in the peripheries of k-space. Figure 11 shows how losing the high or low frequency data from k-space affects the spatial image. The low-spatial-frequency data, containing the information about the contrast and general shape of the image, have the highest amplitudes resulting in greatest changes in gray-levels. These changes spread over in the image and only give the general shape of the region of interest. The high-spatial-frequency data have lower amplitudes. They do not have an effect on the contrast or
the general shape but sharpens the image since they encode the edge information (rapid changes in image signal as a function of space). Thus, the farther away we are from the center of k-space, the higher is the spatial-frequency-information, and as a result, the better the spatial resolution.

In the previous section, we mentioned that careful consideration is needed when acquiring k-space, particularly when dealing with CEMRA. There are several ways to encode k-space data, each with its advantages and disadvantages, depending on the acquisition technique. The three most common encoding techniques are: 1) Sequential or linear encoding, 2) Centric Encoding, and 3) Elliptical-Centric Encoding. Figure 12 explains each of these encoding methods. In our studies of carotid bifurcations, where scans can be too long for the arterial first-pass, elliptical-centric encoding technique is preferred. This technique is particularly suitable for carotid bifurcations because we can fill the center of k-space during the first pass to maximize the contrast of our images, and can fill the peripheries afterwards to increase the resolution. Now that we have the necessary imaging background, we can move on to discuss the essential fluid dynamics and CFD needed to understand the hemodynamics of carotids arteries.

![Figure 12](image)

**Figure 12:** The three most common k-space encoding techniques are shown. (A) Sequential or Linear encoding: k-space is acquired from top to bottom, (B) Centric encoding: Central k-space is acquired at the beginning of the scan and peripheries are obtained afterwards. The timing of bolus is critical to avoid venous enhancements. (C) Elliptical-Centric: Central lines are acquired and completed within approximately 1/9th of the scan time. This technique allows from longer scan time to provide higher resolution data, and can decrease the effects of breathing artifacts and venous enhancements. This technique is commonly used for carotid acquisitions since these scans can be too long for arterial first-pass.
1.6 Introduction to Computational Fluid Dynamics

In order to obtain the hemodynamics quantities in regions prone to the development of atherosclerosis, we need the help of cost-effective and time-saving engineering modeling tools. These hemodynamics quantities can be derived from the unsteady three-dimensional velocity field using state-of-the-art computational fluid dynamics (CFD) techniques. Since CFD is such a vast field, it is not possible to cover all the details in this section. The goal of this section is to equip the reader with the basic understanding of fluid dynamics and CFD, while further details pertaining to our studies will be provided in the later chapter. The remaining section will discuss laminar and turbulent flow; Poiseuille and Dean flow; pulsatile flows, and briefly introduce the topic of CFD, particularly in context of flow in large arteries. This fundamental knowledge into analytical fluid dynamics is essential for us to ensure that CFD results agree with theory.

1.6.1 Laminar and Turbulent Flows

Depending on the Reynolds number, a dimensionless quantity defining the ratio of inertial to viscous forces, the fluid flow can be characterized as either laminar or turbulent. This dimensionless quantity was named after a British engineer, Osborne Reynolds, whose paper “On

![Figure 13: The flow past an elliptical object in a pipe. A) When the velocity is low, the fluid flows in a streamline pattern, called laminar flow. B) If the velocity is increased, while other parameters remain the same, the fluid flow becomes chaotic, called turbulent flow. Image Source: freshgasflow.com](image-url)
The dynamical theory of incompressible viscous fluids and the determination of the criterion marked a significant contribution in the field of fluid mechanics. The Reynolds number can be defined as:

\[
Re = \frac{\rho VD}{\mu} = \frac{2\rho}{\pi \mu} \frac{Q}{R}
\]

Where: 
- \(\rho\) = fluid density in kg/m\(^3\)
- \(V\) = fluid velocity in m/s
- \(D\) = pipe diameter in m
- \(\mu\) = fluid viscosity in Ns/m\(^2\)

Unless otherwise specified, \(V\) will be taken as the average velocity across the cross-section of the pipe. The Reynolds number helps us in determining the transition between laminar and turbulent flows. Laminar flows are highly organized along streamlines. However, as velocity increases, this organized behavior disappears and the flow becomes chaotic with random three-dimensional motion superimposed on the average flow velocity. This flow regime is characterized as being turbulent. If \(Re<2000\), the flow is considered to be laminar, and for circumstances under which \(Re>4000\), the flow is considered turbulent. The range between these two is known as the transition region. Figure 13 shows the visual characteristics of laminar and turbulent regimes for flow past an elliptical object in a pipe.

Although most blood flow in humans is laminar, having a \(Re\) of approximately 500 or less, it is possible for turbulence to occur when the flow rates are very high. For example, in highly conditioned athletes, turbulence can occur in the descending aorta. Pathological conditions, such as heart murmurs and stenotic heart valves, can also cause the flow to become turbulent.

1.6.2 Poiseuille and Dean Flows

Flow in most of the human body is considered to be laminar. Since our vascular geometries are tortuous, and pulsating, it is not possible for us to obtain an analytical solution to these laminar flows. However, what we can obtain, in some case, are analytical solutions to idealized geometries. These solutions also serve as benchmarking material to validate our computational tools. The two analytical solutions, most relevant to our studies, are obtained from Hagan-Poiseuille equation for a straight pipe, and Dean equation for a curved pipe.
Jean-Marie Poiseuille, a French physician and physiologist, empirically derived the famous Poiseuille’s law, also known as Hagen-Poiseuille Law due to additional experimental contributions of Gotthilf Heinrich Ludwig Hagen in 1839. This law describes a steady, incompressible, laminar, viscous flow of a Newtonian fluid in a rigid, cylindrical tube of constant cross-section [11]. Based on the resulting “parabolic” profile, as seen in Figure 14, it is noted that the velocity of a fluid particle traveling in the center of the tube is fastest, while the particles touching the wall of the tube are stationary. This is due to the viscous property of the fluid, where the adhesion forces between the fluid molecules and the solid wall become stronger than the cohesion forces between the neighboring molecules. The following equation defines the velocity of a fluid particle at any point in the cross-section as a function of radius:

\[
\nu(r) = \frac{2Q}{\pi R^4} (R^2 - r^2) = 2\bar{v} (1 - \left(\frac{r}{R}\right)^2)
\]

Where, 
- \( Q = \) flow rate in m\(^3\)/s
- \( R = \) radius of the pipe in m
- \( r = \) radial distance from the center of the pipe in m
- \( \nu = \) velocity at the defined radius in m/s

The wall shear stress (\( \tau_w \)), a risk factor for atherosclerosis, is defined by the following equation:

\[
\tau_w = 6 \mu \frac{2Q}{\pi R^4} \left(\frac{r}{R}\right)
\]

**Figure 14:** A steady, laminar, viscous, incompressible solution for a Newtonian fluid flow in a pipe with a constant cross-section derived from the Hagen-Poiseuille equation. a) A pipe with constant cross-section showing imaginary lamina. b) A cross section of the lamina showing movement of lamina at different speeds. Those closest to the walls are moving slowly while those near the center are moving faster. Image source: en.wikipedia.org.
\[ \tau_w = \frac{4Q}{\pi R^3} \]

In 1920, William Reginald Dean, a British mathematician and fluid dynamist, solved an approximate solution to the full Navier-Stokes equation for the steady, axially uniform flow for Newtonian fluids in toroidal pipes for very large curvatures. The Dean number is denoted by the symbol \( \text{De} \), and is defined as follows:

\[ \text{De} = \frac{\rho V D}{\mu} \sqrt{\frac{D}{2R_c}} = Re \sqrt{\frac{D}{2R_c}} \]

where, \( \text{De} \) = Dean number
\( D \) = Diameter in m
\( R_c \) = Radius of curvature in m
\( V \) = Fluid velocity in m/s²
\( \mu \) = Fluid viscosity in Ns/m²

The Dean number can be physically interpreted as the ratio of the square-root of the product between the centrifugal and inertial forces to the viscous forces. For axial flow in a toroidal pipe, an approximation exists for small Dean numbers (De<96), and is defined below [12]:

\[ \frac{W(r, \theta)}{2\bar{W}} = 1 - \left( \frac{r}{R} \right)^2 + \left( \frac{\text{De}}{96} \right)^2 \left[ \frac{19}{40} \left( \frac{r}{R} \right)^3 - \frac{3}{4} \left( \frac{r}{R} \right)^5 - \frac{1}{4} \left( \frac{r}{R} \right)^7 + \frac{1}{40} \left( \frac{r}{R} \right)^9 \right] \sin \theta \]

where, \( r \) = radial distance from the center of the pipe in cm
\( R \) = radius of the pipe in cm
\( \theta \) = Angular distribution of axial velocity for a given radial distance in radians \( \left( \tan^{-1} \frac{\nu}{\pi} \right) \)
\( \bar{W} \) = The mean velocity in cm/s

Figure 15 compares the Hagen-Poiseuille solution to Dean equation for increasing Dean numbers. The high velocity region is displaced away from the center of curvature and towards the wall of the pipe. Moreover, the secondary vortices, not shown in the diagram below, associated with the centrifugal forces also increase due to curvature.
1.6.3 Pulsatile Flows in Blood Vessels: The Womersley Number

The Poiseuille’s law previously described for incompressible, Newtonian fluid flows is only applicable to steady conditions, whereas the blood flow in large vessels is pulsatile in nature. Our aim is to introduce mathematical models that can take into account the pulsatile nature of blood flow. One of such models was introduced by J. R. Womersley, a physiologist at St. Bart’s Hospital in London. He solved the Navier-Stokes equations for sinusoidal and oscillatory, laminar, incompressible, viscous flows in a long straight tube to determine the ratio of the transient inertial forces to the viscous forces, famously known in biofluid mechanics as the Womersley number. The expression is as follows:

![Figure 15: Velocity profiles as approximated by the Dean equations.](www2.imperial.ac.uk)

Figure 15: Velocity profiles as approximated by the Dean equations. The case of De=0 is exactly equal to the standard Hagen-Poiseuille flow in a straight tube. An introduction of curvature and resulting increase in Dean number causes the peak velocity to increase and skew away from the center of curvature. As the Dean number increases, the approximation of the Dean equation breaks down. Image Source: www2.imperial.ac.uk
\[ \alpha = R \sqrt{\frac{\omega \rho}{\mu}} \]

where, 
- \( R \) = Radius of the pipe in m
- \( \omega \) = Angular frequency of the oscillations in rads/s
- \( \rho \) = Fluid density in kg/m\(^3\)
- \( \mu \) = Fluid viscosity in Ns/m\(^2\)

We can qualitatively describe the effect of Womersley number on the physical flow behavior. When the transient inertial forces are much smaller than the viscous forces (i.e. \( \alpha \ll 1 \)), or alternatively, when frequency of pulsation is much lower, the flow becomes fully-developed during each cycle, and shows the parabolic-shape representative of the Poiseuille’s law. In higher-frequency-flows (\( \alpha \gg 1 \)), the velocity profile is blunter close to the centerline of the blood vessel since the transient inertial forces become more important than viscous forces. However, viscous forces still dominate near the vessel wall, where the velocity is zero. Figure 16 shows the time-varying velocity profiles for increasing Womersley number.

**Figure 16:** The effect of Womersley number (\( \alpha \)) on the shape of the velocity profile. For low-frequency flows (low \( \alpha \)), parabolic velocity profile is dominant. For high-frequency-flows (high \( \alpha \)), the velocity profile is blunter near the centerline. Image source: http://www.buickj.myweb.port.ac.uk
1.6.4 Overview of Computational Fluid Dynamics

Computational Fluid Dynamics (CFD) can be used to simulate time-varying pulsatile flow in our arteries. One of the main steps involved in the process is to solve a set of equations, known as Navier-Stokes equations. The Navier-Stokes equations were formulated by a French mathematician, L. M. H. Navier (1758-1836), and an English mechanician G. G. Stokes (1819-1903). These second-order, nonlinear, partial differential equations govern the motion of incompressible Newtonian fluids, and can be written in the following form:

\[
\begin{align*}
X - \text{Momentum: } \rho \left( \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= - \frac{\partial p}{\partial x} + \mu \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + \rho \ddot{g}_x \\
Y - \text{Momentum: } \rho \left( \frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) &= - \frac{\partial p}{\partial y} + \mu \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) + \rho \ddot{g}_y \\
Z - \text{Momentum: } \rho \left( \frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) &= - \frac{\partial p}{\partial z} + \mu \left( \frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right) + \rho \ddot{g}_z \\
\end{align*}
\]

\[
\text{Continuity: } \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0
\]

In order to solve these equations, the geometry of interest is divided into small elements and these equations are discretized and solved over each element to obtain the three-dimensional velocity field. The discretization of these continuous equations generally poses a trade-off between accuracy and stability, and if done properly, can equate to carefully performed experiments. Since the purpose of this subsection was to give a brief overview of the topic, the relevant details about the mesh generation, discretization schemes, and solution procedures will be discussed in later chapters.

The previous two sections have provided us with the necessary background into medical imaging and fluid dynamics. Integration of these two can be used to perform patient-specific computational hemodynamics of carotid arteries. The next section will discuss this image-based CFD technique.
1.6.5 Image-Based CFD of Carotid Arteries

In the previous section, we described that equation of fluid motion, when discretized properly, can be used to simulate blood flow in arteries of patients. To perform such simulations, we require patients’ geometry as the domain, and flow rate as the boundary conditions for the CFD solver. In context of our work, the patient data was acquired as part of the National Institute of Health (NIH)-sponsored VALIDATE (Vascular Aging – The Link That Bridges Age to Atherosclerosis) initiative, from which CEMRA was used to segmented carotid arteries. Also, as part of the VALIDATE initiative, 2D cine phase contrast MRI (PCMRI) were obtained approximately 0.5cm above, and 1.5cm below the carotid bifurcation, from which flow rates were extract and used as boundary conditions for the CFD solver.

**Figure 17:** Carotid geometries are segmented from CEMRA and boundary conditions are obtained from 2D cine PCMRI slice, acquired above and below the carotid bifurcation. The geometries and boundary conditions are used in the CFD solver to obtain 3D velocity fields.
1.7 Thesis Objectives and Scope

Computational hemodynamics is widely used in the scientific community to obtain risk factors for cardiovascular diseases, such as atherosclerosis, and treatment options. Carotid bifurcation has received much attention in clinical research due to its predilection for atherosclerosis. Although many studies have combined CFD with patient-specific carotid geometries in order to obtain clinically relevant quantities, there has been a lack of validation, and as a result, a lack of thorough analyses of the sources of errors that arise from such validation studies.

Previous work performed by our group have shown good agreement between image-based CFD models of the carotid bifurcation, derived from black-blood MRI, and phase-contrast MRI (PCMRI) [6]. More recently, our group has based its image-based CFD models on 3D CE-MRA owing to their availability from large research studies of carotid disease, and the ease and reliability with which they can be digitally segmented. However, when comparing our CEMRA based CFD models of the CCA to PCMRI image of the same subject, we noticed two major discrepancies. i) CFD velocity levels were higher; ii) CFD velocity profile skewing tended to be greater. Our work aims to understand these differences arising from the validation study of CFD models of carotid arteries. More specifically, our goal is to:

1. Investigate the cause of higher velocity levels in CFD models and readjust these higher velocities to correct values.
2. Investigated the assumptions made in our CFD models to identify the cause of overly-skewed CFD velocity profiles

By investigating these two goals, we attempt to fulfill the primary objective of this thesis:

‘Preliminary exploration of sources of error in CE-MRA based CFD of carotid arteries’

In Chapter 2, we propose that CEMRA artifact causes area-reductions in our carotid geometries and, as a result, cause higher velocities in our CFD models. We attempt to correct for these higher velocities using a novel approach. In Chapter 3, we investigate the over-skewing in our velocity profiles, and relate that to assumptions of fully-developed inlet conditions and Newtonian rheology. We then use idealized geometries to show the influence of each on the shape of velocity profiles.
Chapter 2
Area-Reducing Artifact in CE-MRA of Common Carotid Arteries

2.0 Introduction

The carotid arteries are the main conduits for blood flow from the heart to the brain. The left common carotid artery (CCA) typically arises directly from the aortic arch and the right from the brachiocephalic artery off the arch. Both eventually bifurcate into an internal carotid artery (ICA), which feeds the brain, and an external carotid artery (ECA), which feeds the rest of the head. The carotid artery bifurcation has been the subject of intense study by image-based computational fluid dynamics (CFD) owing to the preferential development of atherosclerosis at this site, attributed to the presence of complex flows.

Our previous work in computational modeling of carotid bifurcations derived from black blood MRI have shown to be in good agreement with phase contrast MRI (PCMRI) [13]. More recently, our group has based its image-based CFD models on 3D contrast-enhanced MR angiograms (CEMRA), owing to their availability from large research studies of carotid disease, and the ease and reliability with which they can be digitally segmented [14]. However, when comparing our CEMRA-based CFD models of the CCA to cine PCMRI images of the same subjects, we noticed that CFD velocity levels were higher.

This chapter investigates the higher velocity levels observed in our CFD models. In particular, we compare the CFD velocity profiles against PCMRI data to show the presence of CFD velocity overestimations and, based on our deductions from the comparison, attribute this error to CEMRA. Later, we perform virtual MR simulations to attempt to confirm the source of this error, and finally introduce techniques to possibly correct our CFD models.

2.1 Validating our CFD models against PCMRI: Presence of Velocity Overestimations

To validate our studies, we compared the CFD models against the PCMRI slices from which the flow rates were derived. Firstly, we obtained an averaged CFD model for each patient by averaging the CFD velocities over the cardiac cycle. Likewise, we averaged the 32 PCMRI slices to obtain an average slice over the cardiac cycle. Then we extracted a 2D slice from our
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Figure 18: Counter plots of time-averaged CFD models are compared against the time-averaged PCMRI slices in the CCA, approximately one CCA-diameter below the carotid bifurcation, and in the ICA and ECA at approximately one CCA-diameter above the carotid bifurcation in 19 patients (refer to Figure 17). A two-dimensional slice from CFD model is extracted at the location where PCMRI slice was acquired in the patient. For each case, PCMRI and CFD slices are plotted at the same counter levels. A) The PCMRI slices at CCA, ECA and ICA have been shown. Lumen boundaries are not discernable in these images. An in-house gradient-based segmentation tool was employed to extract the flow rates B) The flow rates obtained from these PCMRI images were used in the CFD models. However, the velocity levels seen all of the CFD models is considerably higher when compared to the PCMRI slices, even though the flow rates are the same.
averaged CFD model at the location where the PCMRI slices was acquired in the patient. Figure 18 compares time-averaged CFD model against the corresponding time-averaged PCMRI slice at CCA, ECA and ICA. A visual comparison of the two slices shows that CFD velocity levels are consistently overestimated.

As described in the introduction to this chapter, the flow rates segmented from the PCMRI slices were used in our CFD models, and thus, we would expect the velocity levels to be comparable. Since CFD velocity levels are higher in all cases, as evident from Figure 18, a logical deduction is to assume that areas are underestimated in our CEMRA-derived geometries.

### 2.2 Area underestimation in CEMRA-derived Geometries

As shown from the comparison of CFD models against PCMRI in the previous section, CFD velocity levels are considerably higher due to possible underestimation of area in CEMRA-derived geometries used in our CFD models. In order to independently confirm the presence of this area-reduction in our CEMRA-derived geometries, we compared the TOFMRA with CEMRA for one patient. Figure 19 compares TOF and elliptical-centric CEMRA intensities along the center of the CCA for a representative VALIDATE participant. CCA was particularly chosen for the comparison due to absence of in-plane saturation artifact, caused by recirculation.

![Figure 19: CEMRA vs. TOF images from a VALIDATE participant, also showing image intensity profiles along the horizontal axis, with corresponding FWHM diameter measurements.](image)

30
zones, that pollutes the TOFMRA in ICA and ECA. Based on the full width half maximum (FWHM) criterion, comparable to a gradient-based segmentation approach, we notice that the CEMRA diameter is 14% smaller compared to TOF diameter. Such decrease in diameter would cause 30% area-underestimation and, as a result, equivalent velocity overestimation in our CFD models. We understand from this analysis and previous observation of velocity overestimation in our CFD models that there exists an artifact that causes the CEMRA areas to be underestimated. In the next section, we propose an explanation of the cause of such area-underestimations, and based on that, describe methods to investigate this artifact.

2.3 Cause of Area-Underestimation: Longer Scan Times

The presence of an area-reducing artifact is evident in our CEMRA derived geometries. However, our observations indicate the presence of an area-reducing artifact. Before proposing the cause of this artifact, we provide a brief overview of the CEMRA acquisition parameters used in our studies, while details are kept for the later section. Gadolinium (Gd)-based contrast agent was injected intravenously into the patient and acquisition began at the peak contrast intensity. Following an elliptical-centric encoding approach, the central k-space data was captured during the peak arterial phase to attain higher image contrast while the outer data was collected after the Gd peak to enhance image resolution. Even though these CEMRA were segmented using a semi-automated level set approach that seeks the edges of the image, widely accepted as an objective definition of the lumen boundary, the reconstructed surfaces have reduced areas.

We hypothesize that these area-underestimations are caused by relatively long scan times used in our studies. In conventional elliptical-centric CEMRA acquisitions of carotid arteries, contrast agent is injected for ~7sec with nominal scan times of 30-45seconds to obtain sufficient image resolution. Although, the contrast agent was injected for ~7sec in our studies, the scan time was increased to 90sec to enhance the image resolution. We believe that owing to these relatively long scan times, the edges may be blurred. This means that the data around the middle of k-space, containing the bulk of the image contrast, would have higher intensities, while data at the outer reaches of k-space, containing the information about the high spatial frequencies in the image (e.g., lumen-wall boundaries), would have lower intensities. This non-uniform distribution of intensities within k-space could cause the lumen walls to shift inwards and thus underestimate the true area. Previous studies have also reported a dependence of FWHM on scan duration [15] [16]. More specifically, simulations of Fain et al. have reported that significant increase in scan times causes the FWHM to decrease, but did not seem to think it was a practical issue clinically.
Figure 20 illustrates our hypothesis of this area reducing artifact in more detail.

In order to confirm our hypothesis, we performed a simulation of the CEMRA artifact and later used a novel approach to correct our CFD models. In the following section, we describe the patient information, imaging parameters, segmentation protocols, and CFD specifications before discussing our artifact simulation and CFD model correction techniques.

**Figure 20:** Contrast dilution in longer scans blur the edges, and as a result, underestimate the lumen boundary. A) The scan begins at peak intensity, corresponding to t=30sec on the contrast bolus curve, and acquires the k-space for 45sec. Due to elliptical-centric encoding approach, the central k-space, defining image contrast, has high intensity but drops to ~25% when the scan reaches the outer regions of k-space, corresponding to high-spatial frequencies (e.g., lumen boundary). The lumen boundaries are well formed. B) All acquisition parameters remain constant except the scan time is increased to 90sec, causing the peripheral k-space intensity to drop to 5%. This results in a steep intensity gradient from central to the outer k-space, resulting in high contrast images with relatively blurred boundaries.
2.4 Methods

From the previous section, we understand that dilution of contrast agent due to longer scan times cause a steep intensity gradient in k-space leading to a blurred edges in our CEMRA images, and thus, area underestimations. The aim of this section is to describe the methods used in our studies to investigate this artifact. In particular, we describe the patient information, CEMRA acquisition parameters, segmentation protocols, and CFD specification. Later we describe the technique used to confirm the presence of this artifact, and a novel approach to correct our CFD models.

2.4.1 Patient Information

The data used in our studies was acquired from the NIH-sponsored VALIDATE initiative. This seminal research initiative aims to answer the critical question of why and how aging is associated with increase prevalence of atherosclerosis. Specifically, the carotid geometries used in our study were derived from the normal vascular aging group recruited from Baltimore Longitudinal Study for Aging (BLSA) participants. All the participants provided written consents and approval was received by the institutional review board [17].

2.4.2 CEMRA Acquisition Parameters

A part of this initiative was to perform a comprehensive MRI survey of the carotid bifurcations. In this survey, 3D CEMRA were acquired coronally using elliptical-centric k-space encoding technique, with a field-of-view reaching from the aortic arch to the circle of Willis. Since surface radiofrequency coils were used due to the focus on carotid bifurcations, the resulting images had reduced signal at the thoracic origins of the CCA. For that reason, we preferred the cases acquired using 3.0 Tesla scanner (Achievia; Philips Health Care; Best; Netherlands) as opposed to the 1.5 Tesla scanner since the thoracic origins of the CCA were more discernable. The CEMRA acquisition parameters, an important part of our study, include 6cm thick coronal slab portioned into 1mm slices overlapping by 0.5mm, 33 cm field-of-view acquired with 408x405 acquisition matrix zero-padded to 512x512, and Magnevist (Bayer Schering Pharma AG, Berlin, Germany) contrast injection of 0.1 mmol kg\(^{-1}\) at 2mLs\(^{-1}\) [17].
2.4.3 Segmentation Protocols

The patient-specific carotid geometries for our CFD simulations were extracted from the CEMRA. The level set method implemented in Vascular Modeling Toolkit (VMTK), an open-source image and surface analysis library, was used to reconstruct the 3D surface models from the CEMRA data. The detailed physics behind this method is not relevant to our work, but what must be noted is that the final reconstructed surface is located on the regions corresponding to the steepest change of image intensity [18].

2.4.4 CFD Specifications

The first step in performing the CFD simulations of the segmented surfaces is to mesh them into small elements. ICEM-CFD (ANSYS Inc., Canonsburg, PA) was used to generate quadratic tetrahedral-element meshes with a node spacing of 0.1-0.2 mm for N=20 cases. In order to apply the pulsatile boundary conditions in each of the patient-specific CFD models, we first determined the lumen boundaries of the 32 PCMRI images corresponding to the 32 time points per cardiac cycle using a semi-automated, in-house software package employing a gradient-based segmentation approach [19]. For each of the lumen boundaries, we extracted the flow rates for CCA, ECA and ICA by integrating over the velocity profile. The effects of wall compliances, loss of flow into small branches, and uncertainties in PCMRI measurements can result in CCA inflow rates to not exactly match the ECA+ICA outflow rates [20] [21]. In order to maintain mass conservation in our rigid CFD models, the CCA, ICA, and ECA waveforms were first temporally aligned and then the instantaneous ICA and ECA flow rates were reset by scaling the instantaneous CCA flow rates by instantaneous ICA: ECA flow division. Based on these flow rates, fully-developed pulsatile (i.e. Womersley) boundary conditions were imposed at the CCA inlet and ICA outlet while traction-free boundary conditions were imposed on the ECA outlet. Constant blood viscosity of 0.035 cm$^2$/s and rigid walls were assumed for all of the CFD models. Lastly, the cardiac cycle was simulated using 4800 time-steps and at least three cycles to damp the initial transients [22].

2.4.5 Simulation of CE-MRA Artifact

Before confirming the presence of the area-reducing artifact caused by longer scan times, we must ensure that this underestimation in area is not due to insufficient image resolution, and only caused by longer scan times. We conducted two CEMRA simulations to show that: i)
Artifact is not due to insufficient image resolution; ii) Artifact is caused by longer scan times. Firstly, we validate our MRA simulation tool, and quantitatively demonstrate that it is in good agreement with data published in literature. After validating the MRA simulation tool, we conduct previously mentioned CEMRA artifact simulations to relate area underestimations to longer scan times.

To understand the effects of longer scan times on area-underestimation, we employed an analytical solution for Fourier transform of a solid cylinder of radius $R$, as outlined by Antiga et al. [23]. The analytical $k$-space of a uniformly magnetized circular cylinder, taken to represent an artery in our context, is defined by Jinc function, also known as Sombrero function due to the shape of the resulting $k$-space. The following expression was used to compute $k$-space of the uniformly magnetized “artery”:

$$F(k_x, k_y) = \frac{2J_1 \left( \pi \sqrt{k_x^2 + k_y^2} \right)}{\pi \sqrt{k_x^2 + k_y^2}}$$

where, $k_x$ and $k_y$ are spatial frequencies in x and y directions

$J_1$ is first order Bessel function

Figure 21 A shows a cylindrical section, representing a constant diameter CCA having a uniform intensity throughout its cross-section. Using the above equation, we can compute the $k$-space of this cylindrical section. One of the ways to solve this equation is to make use of the Bessel Function provided in one of the mathematical libraries of any high-level programming language.

Now that we have defined the basics of our MRI simulation tool, we need to ensure it validates against data presented in the literature. Previous studies have shown that MRI process imposes fundamental limits on the accuracy with which vessel diameters and areas are extracted. Hoogeveen et al. conducted in-vitro experiments and simulations to show that accurate determination of lumen diameter or cross-sectional area can be severely affected solely due to
the MR image acquisition process, even when flow-related artifacts are not present [24]. In order to confirm whether our CEMRA acquisitions had sufficient resolution, we first repeated the simulations of Hoogeveen et al. to validate our tool, and later performed our simulations of CEMRA artifact.

Figure 22 shows numerical errors in diameter measurements of a circular artery as a function of image resolutions. We compare our results to those of Hoogeveen et al. According to Hoogeveen et al., the large underestimation in diameter measurements occurring between 1.3 and 3 pixels/diameter is the mere consequence of the MR reconstruction. For resolutions above 3 pixels/diameter, the error drops to less than 5%. As seen from the plot, our dataset is in good agreement with that of Hoogeveen et al. for resolution greater than 2.5 pixels/diameter. For resolutions below 2.5 pixels/diameter, our dataset deviates downwards while the trend of a steep trough is still evident. The exact cause of this deviation is not fully understood, and, as we find out soon, is not strictly important for our studies. However, we must note that when truncating our k-space matrix to even samples to obtain the desired resolution, an extra set of negative frequencies appear, which can also be treated as positive frequencies. The differences that arise from this treatment of even samples, especially at lower resolutions and sample sizes, may be the cause of the deviation in our plots.
This may not be an issue since our CEMRA were acquired at resolutions well above the point of deviation (i.e. 2.5 pixels/diameter). Based on the CEMRA parameters mentioned previously, the resolution in frequency- and phase-encoding directions are 0.8mm, and 1mm respectively. For a carotid artery diameter of 5.5mm, this results in 6.9 pixels/diameter in frequency-encoding direction and 5.5 pixels/diameter in the phase-encoding direction, well above the threshold of 2.5 pixels/diameter for which our simulations are valid. In addition, this plot also reveals that our CEMRA resolutions are sufficient to keep the errors within 5%, and thus, area-underestimations in our models cannot be due to resolution effects.

**Figure 22:** Validation of our simulations (red line) against those of Hoogeveen et al. (blue line). The simulations show errors in numerical diameter measurements of a circular artery as a function of resolution in frequency- and phase-encoding directions using the FWHM. Error was calculated using the average vertical and horizontal diameter measurements. Logarithmic scale is used on the x-axis.
Now that we have validated our MRA simulation tool and understood its limitations, we can perform necessary simulations of the CEMRA artifact. To confirm the origin of the area underestimation, we simulated a CEMRA acquisition of a circular artery with a representative CCA diameter of 5.5 mm. The analytic solution for the Fourier transform (i.e., k-space) of a uniformly magnetized circle was computed using our CEMRA acquisition parameters. The first simulation was conducted using uniform intensity distribution through k-space to ensure our CEMRA acquisition parameters were sufficient to accurately estimate the lumen diameters. The k-space was then modulated by a normalized time-intensity curve, representing the decay of the signal as the ~7sec contrast agent bolus disperses:

\[
\text{Intensity} = A + (1 - A)e^{-kt^2}
\]

The asymptotic intensity, A, and the decay rate, k, were set to 0.35 and 0.0005 respectively, to match signal intensity curves from literature [25]. Specially, Riedy et al. published three time-intensity curves for contrast bolus in the right carotid artery of a pig to investigate CEMRA optimization technique. The curves show contrast signal-intensities for injection rates of 0.5mL/sec, 1mL/sec and 3mL/sec. Since injection rate used in our studies was 2mL/sec, we first digitized the 1mL/sec and 3mL/sec curves to obtain an interpolated curve at 2mL/sec. Based on this interpolated curve, the steady-state intensity was noted to be approximately 0.35. This value was used as the asymptotic intensity, A, in the above equation. The steepness of the curve was approximated by plotting a range of decay rates, k, and value that best matched the interpolated curve was used. It should be noted that Riedy et al. used 8cc of volume on average at 2mL/sec, resulting in injection time of ~4sec compared to ~7sec in our studies. This is reasonable since human body weight is higher than pig, and thus, more contrast is required. In order to avoid the effects of ringing artifacts or venous enhancements, we began acquiring our simulations at the peak contrast intensity. The modulation assumed that t=0 corresponded to the center of k-space, and spiraled outward elliptically at a constant rate per k-space point until the end of the acquisition at t=90sec. This modulated k-space was then inverse Fourier transformed to produce the simulated CEMRA image, from which the diameters along the cardinal axes were calculated using FWHM criterion, comparable to the maximum gradient criterion of the 3D level set segmentations used as the basis for image based CFD.
Our CEMRA acquisitions were acquired in 3D whereas we conducted our simulations in
2D, raising the question of whether conclusions drawn from such 2D simulations can be
extrapolated to 3D. Here we discuss our 2D approach in more detail, and compare it to the
conventional 3D elliptical-centric approach, and later address this issue. After determining the
inverse FT of a circular artery to obtain the k-space, we needed to convolve this k-space with the
time-intensity curve. The time-intensity curve was interpolated for MxN points where M
represents the number of rows and N represents the number of columns of the 2D k-space matrix.
Beginning at the center of k-space, we followed an elliptical-centric approach to move outwards
while multiplying each grid value with corresponding time, $t_i$, where $i=1,2,3,\ldots,N\times M$. In this
approach, the next point from the origin is determined by calculating the point closest to origin
not already acquired, and thus, creating an elliptical shape. Figure 24 shows elliptical-centric

**Figure 23:** Normalized time-intensity curve representing the decay of the MRI signal as the 7-second contrast agent bolus disperses. Shown is the curve with $A=0.35$ and $k=0.0005$, values chosen to approximately match the shape of a time-intensity curve taken from the literature [25].

![Normalized time-intensity curve](image)

$$
\text{Intensity} = A + (1 - A) e^{-kt^2}
$$

$$
\text{Time [s]}
$$
encoding method for 3D acquisitions. In 3D acquisitions, we follow the same approach used in 2D to determine the next point, but fill the array in frequency-encoding direction before moving further outwards in phase-encoding directions. The time intensity curve is interpolated over NxMxZ points. Comparing the 3D with the 2D elliptic-centric approach, this essentially means that each of the time-step in the 2D simulation will be further divided in Z points to fill the array in the frequency-encoding direction. Since 2D and 3D elliptical-centric encoding techniques follow the same principle, the outcome should remain indifferent.

**Figure 24:** In 3D elliptical-centric k-space encoding, acquisition begins at the center of k-space and move outwards, adding layers in a pattern of concentric elliptical cylinders of increasing size. If the lengths in both phase encoding directions are equal (i.e. M=N), concentric circular cylinders will form. The elliptical shape forms if one of the phase-encoding lengths is different from the other (M≠N). Image adapted from Biglands et al. [26].
2.4.6 Estimation of CFD velocity errors

As noted in the introduction to this chapter, since CFD model flow rates are derived directly from the 2D cine PCMRI images, overestimation of velocity levels by CFD can be attributed to differences in the CFD model vs. true lumen area. The following equations describe this mathematically:

\[ Q_{CFD} = Q_{PCMRI} \]
\[ (V_{CFD})(Area_{CFD}) = (V_{PCMRI})(Area_{PCMRI}) \]

If \( V_{CFD} > V_{PCMRI} \), then \( Area_{CFD} < Area_{PCMRI} \)

An estimate of the true lumen area can be obtained by averaging the segmented PCMRI lumens; however owing to the uncertainties in the segmentation of the PCMRI lumen boundaries, we sought a more direct comparison of velocities. For each corresponding CFD and PCMRI slice, velocities were divided into 10 isovelocity contour levels, shown in Figure 25, equally distributed from the respective maximum velocity down to 0. Assuming CFD and PCMRI velocity profile shapes are identical, the area enclosed by each CFD velocity counter should be smaller by some constant factor, \( K \), i.e., the fraction area underestimation. In light of the difference in velocity profile shape, as well as noise in the PCMRI images, an optimal value for

![Figure 25: PCMRI and CFD velocity profile (not to scale) in CCA of one of the patients. PCMRI velocity profile was segmented to determine the lumen boundary (not shown in the diagram), and both CFD and PCMRI were divided into 10 isovelocity contours. Only levels 1 to 7 were used in our correction techniques due to noise encountered around the lumen boundaries in PCMRI.](image-url)
Figure 26: A simple representation of velocity-based correction method used to correct the areas in our CFD models. A) If CFD and PCMRI velocity profiles were identical, the areas enclosed by each of the 10 isovelocity contour levels will be equal. B) Since CFD lumen area is underestimated by a constant factor, $K$, areas enclosed by each of the 10 isovelocity contour levels will be underestimated by the same constant, $K$, as well. C) We can estimate the true lumen areas by minimizing the root-mean-square-difference between CFD and PCMRI contour areas, and readjusting the velocities in our CFD model. The diagram shows all 10 contour levels, but only 7 were used in our studies.

$K$ was obtained iteratively by minimizing the root-mean-square (RMS) difference between CFD vs. PCMRI contour areas, excluding the three lowest velocity levels owing to noise in the PCMRI velocities. The CFD velocity profile was then simply “corrected” by multiplying the lumen area, and dividing the lumen velocities, by $K$. Figure 26 illustrates our velocity correction based technique for an idealistic case and “realistic case”. In reality, since CFD velocity profile is not identical to PCMRI, the shape differences between the two can lead to high RMS values.
2.5 Results and Discussion

In the previous section, we described methods to simulate MRA acquisition with CEMRA parameters used in our studies, and to correct our CFD models using velocity-levels based approach. Through the use of this MRA simulation tool, we show that our CEMRA studies have sufficient resolution to accurately segment the lumen boundaries, and the area-underestimation in our geometries is attributed to longer scan times. By varying the diameter in our MRA simulation, we investigate this artifact further, and show how error varies with diameter. Secondly, through the use of the velocity-based correction technique, we present area-underestimations in 20 patient-specific CFD models at the CCA, and using these estimated values, present the corrected CFD velocity profiles. Lastly, we compare our estimated errors with those predicted by the MR simulation.

2.5.1 MRA simulation of CEMRA artifact

To better understand the reasons for the area reduction, Figure 27, also shown previously in introduction to this chapter, compares TOF and elliptical-centric CEMRA intensities along the horizontal axis, with corresponding FWHM diameter measurements.

![Figure 27: CEMRA vs. TOF images from a VALIDATE participant, also showing image intensity profiles along the horizontal axis, with corresponding FWHM diameter measurements.](image)

![Figure 28: Simulated CEMRA images of a 5.5 mm diameter artery, with and without accounting for the effect of a finite contrast injection during the elliptic centric acquisition. Note the good agreement with the features and trends shown in Figure 27](image)
center of the CCA for a representative VALIDATE participant. Using the FWHM criterion, CEMRA diameter was 14% smaller compared to TOF diameter. Figure 28 compares FWHM of a 90-second CEMRA acquisition simulated with and without the effect of contrast intensity variations, the latter crudely simulating TOF acquisition. An 7% horizontal diameter underestimation was observed in the CEMRA simulation, which, when combined with the slightly greater vertical diameter underestimation due to coarser resolution in the phase-encoding direction, results in 17% area reduction and hence 17% velocity increase. Our results echo the finding of Fain et al., where they varied the scan times from 10 to 230 seconds to show that, indeed, FWHM decreases with increased scan times. Further discussion of FWHM dependence on scan time is provided in Chapter 4.

In order to further investigate the effect of longer scan times on area-underestimation, we incrementally increased the scan times from 10sec to 200sec, while keeping the circular artery diameter constant to 5.5mm. Figure 29 shows a plot of scan time versus area underestimation, and corresponding simulated artery at four intermediate scan times. Based on the plot, the dilution effects are negligible for scan times < 50secs. This means that both central and outer regions of

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<td>D</td>
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![Figure 29](image)

**Figure 29:** The effect of scan time on area underestimation is shown for a circular artery of 5.5mm diameter. For scan times < 50secs, the area-underestimation is within 5%. As scan time increases to 100sec, the area-underestimation rapidly increases to 17%, and afterwards, falls linearly. In the right panel, we see the lumen boundaries getting blurred with increasing scan times due to low signal in high-spatial-frequency dominated peripheral regions of k-space.
k-space have sufficient resolution to estimate the areas within 5%. As scan time is increased, the dilution of contrast agent causes the high-spatial frequency regions to have a loss in intensity due to elliptical-centric encoding approach used to fill k-space, where as low spatial frequencies will have increased intensities. This non-uniform distribution of intensities will result in lumen boundaries to move inwards, leading to area underestimations. If we further increase the scan times, both low and high spatial frequencies will be affected by contrast dilution resulting in a largely uniform, steady-state, intensity distribution in k-space. We must note that, in reality, increasing the scan-times allows us to acquire higher-spatial frequencies, and thus, larger k-space and comparatively higher resolution images, an aspect not considered in our simulations.

Since CCA has varying radii from its thoracic root to the bifurcation, we investigated the effect of change in radius on lumen underestimation. Figure 30 shows the effect of varying radius on lumen underestimations for contrast, and non-contrast virtual MRA simulations. The y-axis is plotted in absolute radius errors, rather than in percent area underestimations, since the latter can be misleading. In case the absolute errors were to remain largely constant regardless of the diameter variation, the percent errors would be magnified for smaller arteries and deflated for

![Figure 30](image)

**Figure 30**: The effect of varying circular artery diameter on lumen underestimation for a 90sec long virtual CEMRA simulation. In the left panel, the open circles represent the non-contrast MRA simulation (i.e., without the time-intensity curve) and open squares represent a CEMRA simulation with idealized time-intensity bolus. On the right panel, A, B and C, correspond to FWHM for arteries with radii of 2, 2.5 and 4 mm respectively, where blue curve represents non-contrast simulation and red curve corresponds to contrast-injected simulation.
larger arteries, thus, resulting in misleading trends. As seen from the plot, the radius errors for contrast-injected MRA simulations are significantly larger than for non-contrast MRA simulation. However, as arteries increase in size, the errors in contrast-injected MRA simulations approached to a constant value.

2.5.2 Estimation of Velocity Errors

Figure 31 uses the N=20 cases presented in the introduction to this chapter to show that CFD-computed velocity profiles had higher velocities than PCMRI velocity profiles in vivo at the same location in the CCA. The mean velocity overestimation based on the iso-velocity comparison approach was 26% while the average error based on PCMRI segmented lumen area approach was 23%. In most cases, errors predicted by the two independent methods were consistent. Simply rescaling the CFD lumen areas and velocities according to the iso-velocity percent error improved the agreement between CFD and PCMRI; however, a perfect match was not possible due to differences in shapes of CFD and PCMRI velocity profiles (e.g. Cases 2, 6, 7, 8, 14, 20)

In order to compare the area-underestimations calculated from iso-velocity method for patient-specific CFD models against those estimated by our idealized virtual MRA simulations, we overlapped the iso-velocity errors onto Figure 30. We calculated the mean radius of each of the 20 patient-specific CFD slices proximal to CCA bifurcation, shown earlier in Figure 31, and inferred the true radii from the measured mean radius and iso-velocity based error estimate. The patient-specific cases were plotted against the simulated cases, and a linear regression is shown in Figure 32. For the CEMRA simulations, the absolute radius errors decrease as the CCA becomes larger and approaches to a constant value. An inverse relationship between radius and radius error is also apparent from the in-vivo data, although a precise relationship cannot be deduced due to spread of data points. One possible reason for this spread is that there was likely variation in time-intensity curves due to spread of timing from one patient to another. Another possibility is that the iso-velocity correction method is dependent on there being a similarity between CFD and PCMRI velocity profile shapes, whereas this was often not the case, and so means that, to correct the CEMRA artefact, rescaling an entire patient specific carotid bifurcation model by a constant correction factor is not feasible because area underestimations vary with radius. That means that the area underestimation errors would be lower at the carotid bulb, and higher near the thoracic CCA.
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**Figure 31:** Cycle-averaged PCMRI and CFD axial velocity profiles upstream of the carotid bifurcation for 20 cases. a) PCMRI velocity profile, b) CFD velocity profile, c) corrected CFD velocity profile after rescaling by the estimated error, d) error based on PCMRI velocity iso-contours, e) error based on PCMRI segmented lumen area.
Validation of CFD models of carotid bifurcations against PCMRI revealed an overestimation in CFD velocity levels. Since flow rates used in our CFD models were derived from PCMRI, we deduced that area underestimation in CEMRA-based geometries used in our CFD models could be the cause. Independent analysis of TOF and CEMRA geometries at a comparable location in the same subject revealed that CEMRA-based areas were underestimated. We attributed this area underestimation to comparatively longer scan times of 90sec used in.

**Figure 32:** Plot showing true radius vs. radius errors (i.e., \( R_{\text{true}} - R_{\text{simulated}} \)) for a 90sec long virtual CEMRA simulation. The open circles represent the non-contrast MRA simulation (i.e., without the time intensity curve) and open squares represent a CEMRA simulation with idealized time-intensity bolus. The filled scatter symbols represent patient specific errors obtained from CFD results shown in Figure 31.

### 2.6 Summary

Validation of CFD models of carotid bifurcations against PCMRI revealed an overestimation in CFD velocity levels. Since flow rates used in our CFD models were derived from PCMRI, we deduced that area underestimation in CEMRA-based geometries used in our CFD models could be the cause. Independent analysis of TOF and CEMRA geometries at a comparable location in the same subject revealed that CEMRA-based areas were underestimated. We attributed this area underestimation to comparatively longer scan times of 90sec used in.
VALIDATE CEMRA studies. Since CEMRA was acquired using elliptical-centric encoding approach, we hypothesized that the central k-space would have higher intensities, and due to the dilution of contrast agent, the outer k-space would have lower intensities, causing the edges in the resulting images to blur. To confirm this hypothesis, MRA simulations were performed to show that resulting area-reductions from these blurred images were due to longer scan time and not caused by insufficient resolutions. Lastly, we developed a novel technique to correct the area-underestimations in our CFD models, and showed the inverse trends with increasing artery radii, also visible from our MRA simulations.
Chapter 3
Effects of Common Assumptions in CFD modeling of Carotid Arteries

3.0 Introduction

CFD analysis of carotid bifurcations, a common site for the development of atherosclerosis, can provide us with insight into the hemodynamic quantities relevant for clinical diagnosis of the disease. Such CFD studies of carotid bifurcations are widely available in the literature, but a thorough validation is still lacking. In the previous chapter, we compared CFD velocity profiles against PCMRI in the CCA of 20 patients to show the presence of an area-reducing artifact in our CEMRA-derived CFD models, and corrected this area-underestimation using a novel approach. In this chapter, we focus on the differences in the shapes of the velocity profiles, rather than the velocity levels. Referring back to Figure 31, we notice that CFD velocity profiles are skewed compared to PCMRI. Figure 33 takes a closer look at the velocity profiles of

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**Figure 33:** CFD models of two patients are compared against PCMRI proximal to the carotid bifurcation. The relatively higher velocities in the Original CFD slice reveal the presence of area-reduction. Correct CFD profile shows rescaled velocities using a novel approach described in Chapter 2. A) The PCMRI velocity profile shape is in good agreement with the CFD velocity profile shape. B) The PCMRI velocity profile appears to be axisymmetric whereas CFD velocity profile is highly skewed, a common trend seen in most of the cases presented in Figure 31.
two of the 20 cases presented in Figure 31. The PCMRI and CFD velocity profiles match closely for the first case, which is an exception rather than the norm. The more likely occurrence is the second case, where PCMRI shows a largely axisymmetric velocity profile while CFD predicts a comparatively skewed velocity profile, irrespective of the velocity scale.

The aim of this chapter is to better understand the cause of such discrepancies in velocity profile shapes, particularly in the CCA. Firstly, we examine the effect of area-underestimations, causing higher Reynolds number in our CFD models. Afterwards, we investigate the effect of common assumptions implied in our CFD models, such as Newtonian rheology and fully-developed inlet conditions, which may affect the flow dynamics in the CCA more than the ECA and ICA due to the absence of strong geometric feature (i.e. carotid bifurcation). Consideration of these aspects can provide us with better insight into the cause of velocity profile skewing observed in our CFD models.

3.1 Effect of area-underestimations on flow dynamics

In the previous chapter, we observed that longer scan times in our CEMRA acquisitions caused area-underestimations in our segmented patient-specific carotid geometries, and as a result, higher velocities in our CFD models. Large area-underestimations can cause the Reynolds number to increase, and thus, potentially affect the flow dynamics in our CFD models. An average area-underestimation of 27%, obtained from the iso-velocity contour approach in the previous chapter, can cause the diameters to decrease by 13%, and as a result, increase the Reynolds number by 13%. Experience shows that such modest changes in Reynolds number have a relatively minor effect on gross flow patterns.

To ensure that area-underestimations had negligible effects on flow dynamics, we repeated the CFD simulation for Case#2 (Refer to Figure 31) with a 13% decrease in Reynolds number, essentially having the same effect as a 13% increase in diameter. Based on Figure 32, we know that area-underestimations is a function of diameter, which means that diameter underestimation may not be constant throughout the length of the CCA, varying from thoracic root to carotid bifurcation. Since patient-specific time-intensity curves are unavailable, it is not possible to accurately rescale the diameters. However, as a first approximation, we can rescale the geometry by a constant factor to determine whether such changes significantly affect the flow patterns. Figure 34 shows that decreasing the Reynolds number by 13% has negligible effect on
the shape of the velocity profile, and the shape differences between PCMRI and re-simulated
CFD model remain even when areas have been corrected. This study reveals that there are other
sources of errors that cause the velocity profile in our CFD models to over-predict the skewness
when compared to PCMRI of the same patient.

3.2 Effect of CFD modeling assumption on flow dynamics

We understand from the previous section that area-underestimation in our CFD models
caused higher Reynolds number, which was shown to have negligible effect on the flow patterns.
Moreover, CFD velocity profiles were still skewed in comparison to PCMRI. We hypothesize
that these differences are caused by CFD modeling assumptions in inlet conditions, rheology,
and wall compliance. In this section, we introduce the assumptions associated with inlet
conditions, and rheology, and how they might affect velocity profile skewing, while wall
compliance will be discussed in the last chapter.
3.2.1 Assumptions about the inlet conditions in our CFD models

Due to limitations in current computational resources, we need to perform CFD simulations of carotid bifurcations in isolation from the vascular network. Consequently, inlets in the CCA, and the two outlets in the ECA and ICA must be truncated. However, these inlets and outlets must have sufficient length to accurately capture the flow dynamics in the carotid bifurcation, but not so long as to waste limited computational resources. As a result, we must make assumptions about the nature of the velocity profile in the CCA inlet, and ICA and ECA outlets. As noted in Chapter 1, the most common assumption, especially for the CCA inlet, is that of fully-developed velocity profile (Womersley), which implicitly assumes that vasculature upstream of the truncated section is straight enough that the flow will be fully-developed, or alternatively, the CCA has been truncated far enough from the carotid bifurcation that the effect of fully-developed velocity profile assumption is negligible.

Previous study from our group has revealed that assumptions about the CCA inlet conditions may have an effect on the flow patterns downstream. Manbachi et al. segmented and performed geometric analysis on 32 patient-specific carotid arteries to reconstruct three idealized CCA models, shown in Figure 35, representative of the patient dataset. The three representative CCA models had thoracic curvature of 1:10, 1:15, and 1:45 respectively. In all three models, fully-developed velocity profile was applied at the thoracic CCA inlet and it was noted that velocity profile downstream in the cervical segment remained largely independent of the thoracic curvature. Lastly, it was noted that velocity profile skewing was strongest for the isolated cervical segment [17]. This work by Manbachi et al. has some important implications relevant to our work. As described previously, we hypothesize that our truncated patient-specific carotid models (i.e. fully-developed velocity profile at the inlet) have non-negligible effects downstream, resulting in our CFD models to predict over-skewed velocity profile when compared against PCMRI of the same patient. This hypothesis is supported by the cervical-only simulation of Manbachi et al., revealing that fully-developed inlet conditions can cause strong velocity profile skewing downstream in comparison to full CCA models.

We believe that since neglecting the thoracic segment of the CCA causes strong velocity profile skewing in comparison to the full CCA model, it is possible that neglecting the aortic arch in our studies may have caused strong velocity profile skewing in comparison to the Aorta+CCA model. In the light of our discussion, we attach an aorta to the CCA model to observe differences
at the outlet. Such a study could reveal whether fully-developed inlet conditions in our CCA models have non-negligible effects downstream.

### 3.2.2 Assumptions about the rheology in our CFD models

A general assumption made in computational modeling of carotid arteries is about the blood rheology. Even though blood is a complex fluid, comprised of fluid-filled vesicles suspended in a water-like carrier, making it highly non-Newtonian, it is generally modeled as Newtonian fluid in CFD of carotid bifurcations. In this section, we provide a brief introduction about blood properties, its Newtonian treatment in carotid bifurcations and why such an
assumption may cause noticeable velocity profile skewing in CCA, and not necessarily the bifurcation region.

Blood is comprised of water like carrier, with some dissolved protein, and is widely accepted to behave as a Newtonian fluid having a constant viscosity. The fluid filled vesicles that are suspended in this water-like carrier, known as erythrocytes, or more commonly as red blood cells (RBC), comprise 40-45% of blood by volume. Depending on the prevailing flow conditions, RBC can adopt a variety of shapes. However, they are generally found to be shaped like bi-concave disks having an 8-µm diameter and 2-µm height. It is due to the concentrated suspension of these microscopic, flexible cells in the largely Newtonian plasma that gives blood its most famous non-Newtonian property: Shear-thinning. Shear-thinning non-Newtonian property causes the blood viscosity to decrease with increasing shear rates. Depending on the vasculature, blood can exhibit a variety of non-Newtonian properties. However, in literature of large artery hemodynamics, such as the carotid bifurcations, the term “non-Newtonian” often explicitly or implicitly corresponds to shear-thinning properties alone.

Neglecting the shear-thinning property of blood can potentially cause significant errors in computational hemodynamics. As seen in Figure 36, for shear rates at or above 100s⁻¹, the viscosity asymptotes to a constant value, and is widely reported to be between 3-4 cPoise. On the other hand, for shear rates below 100s⁻¹, blood viscosity increase exponentially, causing blood to form stacks, also known as rouleaux. Previous work has shown that the effects of simplifying assumptions of Newtonian rheology are negligible for vessels where geometric features dominate, such as the carotid bifurcation [27]. However, this may not be the case for more subtly curved vessels like the CCA. Gijsen et al., for example, have shown that small shear-rate variation even around shear rates of 100s⁻¹, at which shear-thinning non-Newtonian effects of erythrocytes are assumed to be insignificant, can cause non-negligible changes in velocity profile [28]. We investigate the effect of shear-thinning property of blood in the idealized CCA model of Manbachi et al. to see whether non-negligible differences are observed at the outlet in comparison to the Newtonian model. Such a study could reveal the cause of velocity profile skewing observed in our CFD models compared to the PCMRI of the same subject.
3.3 Methods

From the above sections we understand that the decrease in Reynolds number, caused by area-underestimation, in our CEMRA-derived carotid geometries has negligible effect on velocity profile shape in the CCA, and the differences in CFD and PCMRI velocity profiles still remain. We also found that assumptions of fully-developed inlet conditions and Newtonian blood rheology in our CFD model of mildly curved CCA geometries might have non-negligible effects downstream. In this section, we describe the methods used to investigate the effects of fully-developed inlet conditions and Newtonian rheology on the shape of velocity profiles in the CCA.

3.3.1 Idealized CCA model

We reconstructed the CCA model of Manbachi et al. to perform our studies. We briefly describe the methods used by Manbachi et al. to construct the CCA model, and the interested reader is referred to the [17]. The idealized model of CCA was constructed based on statically determined geometric parameters. Briefly, the geometric parameters were characterized by segmenting the CCA of 32 patients from a field-of-view encompassing the aortic arch to carotid

![Figure 36: Blood shows shear-thinning non-Newtonian property, where viscosity can vary depending on the shear-rate in the fluid. These are modeled by Carreau and generalized power low (Ballyk) curve fits. Image Source: [29]](image-url)
bifurcation. A plane was fitted to cervical and thoracic segment of the CCA using least-squares approach, and each segment was projected onto its respective plane. A best fit arch was used to characterize the segment’s mean radius of curvature (RC). The mean segmented lumen radius, and the straight line distances (SLD) from the arc end points to the pivot points were also noted. The relative orientation of the two best fit planes were characterized by tilt angle, calculated from the dot product of two tangent vectors of the best fit planes, and twist angle, calculated from the dot product of the normal vectors of the best fit planes. The parameters used to reconstruct an idealized CCA were based on the mean quantities [17]: \( RC_{\text{Cervical}} = 15\text{cm} \); \( RC_{\text{Thoracic}} = 3.75\text{cm} \); \( SLD_{\text{Cervical}} = 6\text{cm} \); \( SLD_{\text{Thoracic}} = 4\text{cm} \); Twist=90° and Tilt=25°. Manbachi et al. also reported a mean cervical CCA diameter of 5mm; however, they acknowledge that this value was underestimated compared to other measurements reported in the literature. In light of the 20-30% area-reductions that we observed in the previous chapter, we increased this diameter by 10%, to 5.5mm. The reconstructed model of CCA is shown in Figure 37.

**Figure 37:** CCA models reconstructed from the parameters defined by Manbachi et al. [17]. The CCA geometry was constructed by spline fitting through 7 points shown in red circles.
3.3.2 Idealized Aorta Model combined with CCA model

An idealized model of an aorta was constructed using the parameters described by Mori et al. [30] and Nakamura et al. [31]. The model neglects the major branches and minor vessels leaving the aorta. The main trunk of the aorta was divided into five sections: the ascending aorta, ascending arch, descending arch, upper descending aorta, and lower descending aorta. Six consecutive points were used to describe the boundary of each section from the inlet to the outlet of the aorta, and these points were defined in terms of three parameters: $\alpha$, $\beta$, and $l$. Based on

![Figure 38: The idealized Aorta model with 3cm diameter constructed by splining fitting through six points as described by Mori et al. [30]. The CCA model described previously has been attached to aortic arch at the point of maximum curvature.](image)
clinical data of Yoshi et al. [32], $\alpha=40^\circ$, $\beta=144^\circ$, and $l=4\text{cm}$ to mimic a healthy aorta. The aorta model was created by fitting a B-spline through the six points to define the centerline, and \textit{vmtk}'s pollyball modeler was used to extrude a constant diameter of $3\text{cm}$ along the centerline to generate a surface. The CCA was attached on top of the aortic arch, at the point of maximum curvature, and aligned along the anteroposterior axis. Figure 38 shows this model in the same coordinate system as the CCA model previously shown in Figure 37.

3.3.3 Blood Rheology

A Carreau-Yasuda model was used to account for the shear thinning behavior of blood by relating the shear rate to dynamic viscosity:

$$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = \left[1 + (\dot{\gamma})^a\right]^{\frac{n-1}{a}}$$

where, $\mu_0$ and $\mu_\infty$ are asymptotic viscosities at zero and infinite shear rates, and $n$ and $a$ are empirically determined parameters. The commonly accepted values in literature [33] for blood viscosities at zero and infinity shear rates are: $\mu_0 = 0.056\text{Pa.s}$, and $\mu_\infty = 0.00345\text{Pa.s}$. In order to be consistent with the kinematic viscosity of Newtonian simulations (i.e. $\nu=0.035\text{cm}^2/\text{s}$), a density of $\rho=986\text{kg/m}^3$ was chosen. The parameters relevant to Carreau-Yasuda models are: $\lambda=1.902\text{s}$, $n=0.22$, and $a=1.25$.

3.3.4 Mesh Generation

Linear tetrahedral element meshes were generated using \textit{vmtk} with 589K elements for the CCA and 450K elements for the aorta, corresponding to approximately 11 elements/diameter in each case. The mesh density distribution can be seen in Figure 39. A finer CCA mesh was chosen because we were more interested in the hemodynamics of the CCA rather than the aorta. Moreover, since we only needed the gross velocity patterns entering the thoracic inlet of the CCA to understand the effects of fully developed inlet conditions, finer aorta mesh would have been unnecessary.
3.3.5 Boundary Conditions

The average adult CCA flow waveform with 65bpm, characterized by Hoi et al. [34], was used to compute the pulsatile velocity profile (Womersley) for the inlet of isolated CCA simulation. For the aorta-attached CCA simulation, a patient-specific ascending-aorta flow waveform, provided by Gallo et al. [35] with 54bpm, was modified and applied to inlet of the aorta. Specifically, the diastolic phase of the aortic flow waveform was truncated and smoothed.
to have the same heart rates as the CCA flow waveform, reflecting the fact that differences in heart rate are accommodated by the changes in the duration of diastole. In order to maintain mass conservation, the peaks of ascending aorta and CCA flow waveforms were aligned, and latter subtracted from the former to deduce the descending aorta flow waveform. The ascending and descending aorta flow waveforms were used to calculate a pulsatile velocity profile and applied at the aorta inlet and outlet, respectively. A traction-free boundary condition was applied at the CCA outlet for both isolated CCA and aorta-attached CCA simulations. The resulting waveforms, normalized by respective peak flow rates, are shown in Figure 40. Cycle-averaged flow rates were 6.5 mL/s for the CCA, 97 mL/s for the original ascending aorta, and 112 mL/s for the modified ascending aorta.

**Figure 40:** Patient-averaged CCA and patient specific ascending aorta flow waveforms normalized by their respective peak flow rates. The original ascending aorta waveform was modified by truncating its diastolic phase to match the 65 bpm heart rate of CCA waveform, and then time-shifting to approximately align the respective peaks and troughs.
3.3.6 CFD simulations

The in-house CFD solver, described in the previous chapter, was used to perform the CFD simulations of patient-specific carotid geometries. This solver has been used in our studies for over a decade, and has been particularly molded to handle carotid geometries. The necessary pre-processing and post-processing scripts developed during this period made it extremely easy to run the simulations. However, for our application, the disadvantages of this solver were the lack of parallel implementation, necessary for our large CCA+Aorta mesh, and unavailability of non-Newtonian models. To overcome this difficulty, we resorted to FENICS (http://fenicsproject.org/), a collection of libraries for automated and efficient solution of differential equations. The details of the solver are available in [36], and interested readers are encouraged to read further. The simulation was carried out using 5000 time steps per cardiac cycle and three cycles were simulated to damp initial transients. Mesh refinement study of the CCA was performed to ensure convergence. A constant kinematic viscosity of 0.035cm\(^2\)/s was assumed for the Newtonian simulations and Carrea-Yashuda relation was used to model shear-thinning non-Newtonain property of blood. Rigid walls were assumed in all the simulations.

3.3.7 CFD validation Study

We now understand the methods used to construct our geometries, mesh these geometries, apply the boundary conditions and perform the CFD simulations. Now we need to perform a mesh refinement study with sufficient temporal resolution to ensure our solutions are converged. Although, the study of Manbachi et al. used 2500 time steps per cardiac cycle, we implemented 5000 time steps to minimize the effects of temporal resolution. Since one of our goal is to understand the effects of fully-developed inlet conditions downstream in the cervical outlet of the CCA, capturing all the flow scales in the Aorta model would be unnecessary, and thus, temporal resolution of 5000 time steps is sufficient. In order to ensure our solutions were converged, we repeated the simulations with element size varying from 0.35mm to 1mm with boundary layer elements added to resolve the flow near the lumen wall. Figure 41 shows the results of the convergence study for three different mesh sizes. As seen from the diagram, all three mesh sizes result in similar velocity profiles downstream at the CCA outlet. However, mesh resolution of 1mm results in sharp edges at the lumen boundary, and thus, mesh corresponding to resolution of 0.5mm was used in our studies.
<table>
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**Figure 41:** Grid refinement study for the idealized CCA model. **A)** Mesh resolution is incrementally increased resulting in mesh size of 100k, 600k, and 20000k corresponding to three meshes shown in the diagram. The boundary layer elements are added to resolve the flow near the boundary. **B)** The magnitude of velocity at cervical outlet of the CCA for three mesh sizes.
3.4 Results and Discussion

In the previous section, we described methods to perform CFD simulations of idealized CCA to understand the effects of full-developed inlet conditions and Newtonian rheology in our models and relate that to overly skewed velocity profiles observed in our patient-specific carotid geometries. Such a study could reveal the effects of common CFD assumptions and their impact on the flow dynamics. In this section, we first discuss our results due to higher Reynolds number, and then look at the effects of fully-developed inlet conditions and Newtonian rheology.

3.4.1 Effect of Higher Reynolds number

In the introduction to this chapter, we investigated the effect of higher Reynolds number, caused by area-underestimations, in a patient specific carotid geometry. We had re-simulated one patient-specific case with 13% lower Reynolds number and observed that such a change does not

![Figure 42: The effect of higher Reynolds number in idealized CCA model. A) Reference simulation with nominal CCA diameter. B) Simulation with 10% higher Reynolds number to approximate the effect of area-underestimation in our patient-specific carotid geometries.](image)
affect the shape of the velocity profile. We test the same hypothesis, but now in an idealized CCA model to confirm that velocity profile skewness is not caused by area-underestimations.

In order to show the negligible effect of area-underestimation on velocity profile shapes, we simulated the idealized CCA model, first, with a literature based diameter of 5.5mm, and then to show the effect of area-underestimation, re-simulated the same idealized CCA model with 10% higher Reynolds number, equivalent to making the CCA diameter 5mm. Fully-developed inlet conditions and Newtonian viscosity of 0.035cm$^2$/s were used in both cases. In order to increase the Reynolds number by 10%, we decreased the viscosity by 10%. Figure 42 shows axial velocities for the two simulations at five locations along the length of the CCA. As seen from the diagram, increasing the Reynolds number by 10% has negligible effect on the shape of the velocity profile, which confirms our previous observations in patient-specific geometries. Based on the findings from this idealized CCA model, we can conclude that area-reductions in our carotid geometries are not the cause of overly skewed velocity profiles in our patient-specific carotid geometries.

3.4.2 Effect of fully-developed inlet conditions

We understand from previous simulations of idealized CCA model that velocity profiles remain unchanged regardless of small variations in Reynolds number, and based on this observation, we deduced that area-underestimations are not the cause of velocity profile skewing in our patient-specific carotid models. As mentioned in the introduction, we also hypothesized that fully-developed inlet conditions might have non-negligible effects downstream in the cervical CCA, causing velocity profiles in patient-specific models to skew compared to PCMRI of same subject. We test this hypothesis by comparing a reference CCA-only simulation against Aorta+CCA simulation to observe whether velocity profiles, particularly at the CCA outlet, change due to the non-fully developed flow entering into the thoracic CCA from the aortic arch. Figure 43 shows velocity profiles for the two models along the length of the CCA. Comparing the two models, we see that adding the aorta served to introduce stronger velocity profile skewing and secondary flows into the thoracic CCA (slice E), but these were largely damped out upon entry into the cervical CCA (slice C), resulting in a negligible effect on the CCA velocity profile proximal to the bifurcation (slice A). Based on CFD simulations of idealized models, we deduce that fully-developed inlet conditions have negligible effect on velocity profile skewing.
3.4.3 Effect of Newtonian rheology

From above discussion, we understand that fully-developed inlet conditions have negligible effect downstream in the CCA near the bifurcation, and as a result, we imply that velocity profile skewing observed in our patient-specific carotid models are not caused by assumption of fully-developed inlet flow at the thoracic CCA inlet. Now we present our results, shown in Figure 44, regarding the assumption of Newtonian rheology in our CFD models. Comparison of the two cases reveals that introduction of non-Newtonian (shear-thinning) rheology appeared to have a negligible effect on velocity profile shape throughout the CCA. This was confirmed by a CFD simulation using a characteristic Newtonian viscosity, which has previously been shown to approximate the effects of non-Newtonian rheology on flow [28] [29]. In this case, the characteristic viscosity was found to be $v=0.0402\text{cm}^2/\text{s}$ (i.e., 15% higher than the

![Figure 43: The effect of fully-developed inlet conditions in the idealized CCA models. A) Velocity profiles for CCA-only simulation with fully developed inlet conditions. B) Velocity profiles for Aorta+CCA simulation with non-fully developed flow entering the thoracic CCA.](image)

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nominal viscosity), based on Carreau-Yasuda curve with characteristic shear rate of $\dot{\gamma} = \frac{2V}{R}$ [29] where $V=27$ cm/s is the characteristic velocity and $R=0.275$ cm is the CCA radius.

### 3.5 Summary

The aim of this chapter was to investigate the cause of relatively skewed velocity profiles observed in our patient-specific CFD models compared to the PCMRI of the same subjects. We hypothesized that this could be the result of: i) underestimated areas in our CEMRA-derived geometries, ii) fully-developed assumption at the thoracic inlet of the CCA, and iii) Newtonian rheology assumed for blood having a shear-thinning non-Newtonian property. Investigation of all three hypotheses revealed negligible effect of each on the shape of the velocity profile downstream in the CCA proximal to the bifurcation.
Chapter 4
Conclusions, Limitations, and Recommendations

4.0 Introduction

In the previous chapters, I have presented my hypotheses, described methods and techniques to test these hypotheses, and discussed the results. In this chapter, I present a summary of my findings and their implications, address the limitations of presented methodologies not previously discussed, and provide recommendations to direct the future work.

4.1 Summary and Implications of Main Findings

4.1.1 Summary

Integration of CFD with medical imaging can provide us with clinically relevant hemodynamic quantities related to the development of atherosclerosis. For that reason, carotid bifurcations, a common site for the development of atherosclerosis, have been the subject of intense computational hemodynamic studies. To perform realistic CFD simulations, we used patient-specific carotid geometries segmented from CEMRA, acquired as part of the NIH-sponsored VALIDATE initiative that aims to study risk factors in vascular aging. In addition to the carotid geometries, patients’ flow rates were also needed. The flow rates in the CCA, ECA and ICA were extracted from 2D cine-PCMRI images, acquired 0.5cm above bifurcation apex for ICA and ECA, and 1.5cm below apex for the CCA. For N=20 cases, the carotid geometries were meshed using ANSYS-ICEM, fully-developed pulsatile boundary condition were applied at the inlet and outlets, and governing equations were solved using in-house CFD solver. Newtonian rheology and rigid walls were assumed in these simulations. In order to validate our CFD simulations against in-vivo data, we plotted the axial velocity onto a 2D slice at the same location and orientation where the 2D cine-PCMRI image was acquired in the CCA of the patient, and noticed two major differences. Comparing the CFD data against PCMRI, we observed that CFD velocity levels were comparatively higher, and CFD velocity profiles were over-skewed.

Since the CFD models were based on the in vivo blood flow rates derived from the PCMRI images themselves, velocity overestimations in the CFD models were attributed to an underestimation of the lumen area from the CEMRA-derived lumen geometries. We noticed the
same trend in comparison of CEMRA and TOFMRA of a patient, and observed that CEMRA areas were underestimated even though the geometries were segmented using an objective gradient-based approach. We therefore hypothesized that the edges were blurred owing to dilution of contrast agent during the relatively long (90-sec) elliptical-centric CEMRA acquisition causing non-uniform intensity distribution in k-space, and as a result, inward shift of lumen walls and thus, area-underestimation. To confirm our hypothesis, we simulated a CEMRA acquisition of a circular CCA artery, and modulated its k-space with normalized time-intensity curve. The results showed 17% smaller areas for CEMRA simulations and confirmed the presence of area-underestimation. Knowing that our CFD models had reduced areas, we estimated the errors based on novel iso-velocity approach, which showed similar trends as those observed from CEMRA simulation. The trends showed that errors were dependent on radius of the artery, where small radii led to large radius errors and asymptote to constant value for larger arteries.

Aside from the higher velocity levels noticed in CFD simulations of patient-specific carotid models, we also observed that CFD velocity profiles were relatively skewed in comparison to the PCMRI of the same subjects. We speculated that increased Reynolds number due to area-reduction in our carotid geometries was the cause of skewed velocity profiles. However, a simulation with a 13% lower Reynolds number, representative of the patient dataset, in one of the patient geometries showed no differences in the shape of the velocity profile. We therefore hypothesized that the velocity profiles in our CFD models were skewed as a result of assumptions of fully-developed inlet conditions, and Newtonian rheology in our simulations. To test our hypothesis of fully-developed inlet conditions, we attached an idealized CCA model atop an idealized aorta model, and compared the velocity profiles along the length of the CCA. Attaching the aorta introduced secondary flows to the thoracic CCA; however, the effects became negligible near the cervical outlet of the CCA, proximal to the carotid bifurcation, where we had compared CFD and PCMRI data. Modeling non-Newtonian shear-thinning property of blood using Carreau-Yasuda in the CCA showed negligible differences in the shape of the velocity profile throughout the length of the CCA model.

We have shown that elliptic-centric CEMRA-derived CFD models can overestimate absolute velocities due to area underestimation, caused by longer scan times in some CEMRA acquisitions. We quantified these velocity errors using PCMRI velocity profiles, and performed
CEMRA simulation to confirm the artifact. Based on idealized CCA, we have shown that these area-underestimations, along with inlet conditions, and non-Newtonian rheology have negligible effects on velocity profile shapes downstream, proximal to the carotid bifurcations, and thus the overly skewed CFD velocities might be due to compliance or other patient-specific effects like secondary curvatures or surface roughness or irregularities.

4.1.2 Implication of Main Findings

Our work has demonstrated that longer scan times can lead to dilution of contrast agent and thus, area-underestimations in CEMRA-segmented geometries. Such area underestimation has major implications in both clinical setting as well as image-based CFD community. In clinical setting, such errors can, for example, affect stenosis measurement. In regards to image-based CFD community, a small diameter error can be magnified by \( \Delta D^2 \) in velocity, and \( \Delta D^3 \) in WSS values, severely affecting the results. Also, As noted from our results in Chapter 2, the errors were dependent on the radius of the artery, and thus, rescaling an entire patient specific carotid bifurcation model by a constant correction factor, as we implicitly did by adjusting the Reynolds number, was not strictly correct, because area underestimations vary with radii. That means that the area underestimation errors would be lower at the carotid bulb, and higher near the thoracic CCA. An important implication of this finding is to exercise caution in gradient-based segmentation methods when dealing with CEMRA having longer than usual scan times. Relying on conventional CEMRA having scan times of 40-45secs would be feasible until the nature of this area-reducing artifact have been fully understood.

We have also investigated the effect fully-developed conditions and Newtonian rheology in idealized carotid models to identify the source of skewed velocity profiles in patient-specific carotid models. Results suggested that neither assumption has a significant impact on the shape of velocity profile at the cervical outlet of the CCA, proximal to the bifurcation. However, we did notice that attaching the aorta to the thoracic inlet of the CCA introduced stronger secondary flows compared to CCA model with fully developed inlet conditions. These differences remained only until the flow entered the tortuous region in the CCA, referred to as “pivot point” by Manbachi et al. Echoing the findings of Manbachi et al. suggesting the negligible effect of thoracic curvature on velocity profile in cervical outlet, our results demonstrate that extending the CCA beyond the thoracic curvature to include the aortic arch may be unnecessary, and CFD simulations of carotid bifurcations must be truncated to include the “pivot point”.

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4.2 Limitations and Recommendations

4.2.1 Idealized Geometries

Limitations:

One of the major assumptions in determining the effect of fully-developed conditions was the use of idealized CCA and aorta models in our CFD simulations. Even though both CCA and aorta models were derived from patient-specific data, the absence of secondary curvature, non-circular lumens, and varying radii along the length of the models could have impacted the shape of the velocity profile downstream. Moreover, the left CCA branches from aortic arch at locations and angles that can vary from patient to patient and our CCA model, aligned along the anteroposterior axis atop the aortic arch, may not be representative of such cases.

Recommendations:

A simple and brute force approach is to simulate a patient-specific CCA and aorta model to investigate the effect of fully-developed conditions. However, large computational resources are required to temporally and spatially resolve such meshes, particularly when the dataset is large. Alternatively, we could extract 3D velocity fields along the length of the CCA, and apply

Figure 45: 3D PCMRI images of left carotid artery at five sections along the length of the CCA and above the carotid bifurcation.
them as boundary conditions in patient-specific CCA models. Such an approach allows us to
neglect the aorta, resulting in CFD simulations that require less computational resources.
Towards that goal, our colleagues at Politecnico di Torino, Italy have acquired PCMRI images
along the length of the CCA model as shown in Figure 45. Unlike VALIDATE studies that only
acquired axial velocity fields above and below the carotid bifurcations, our colleagues have
acquired 3D PCMRI images at multiple locations on the CCA, allowing for the possibility to
impose realistic inlet velocity fields in the respective patient-specific carotid model. Imposing
velocity fields obtained from slice A in Figure 45, and comparing the CFD results at downstream
slices B and C against those based on fully-developed inlet conditions in the same patient-
specific model could more directly confirm our results obtained from idealized CCA simulations.

4.2.2 Wall Compliance

Limitations:

All CFD simulations in our studies have being modeled using rigid walls, with the
assumption that radial distention is approximately on the order of +/-5% over a cardiac cycle and
uniform over the CCA length [37], resulting in +/-10% and +/-15% errors in velocities and WSS
respectively from Poiseuille’s law. As shown from our results, a change of 10% in CCA diameter
had negligible effect on overall flow patterns, and thus, distention may be less important in CCA
geometries. However, compliance could have another effect: dispersion or attenuation of flow
pulse as it propagates along the CCA. The consequence is that the flow rate waveform entering
the CCA might not be the same as the flow rate exiting the CCA into the bifurcation. Since the
rigid wall assumption requires instantaneous mass conservation, such inflow:outflow mismatches
cannot be accommodated. When simulating short segments of arteries this is usually not an issue;
however, for longer segments (e.g., ~10-cm-long CCA [17]), these effects may no longer be
negligible.

Recommendations:

Modelling the impact of arterial compliance on blood flow requires the coupling of a
fluids and solids solver, which can be conceptually challenging and computationally intensive for
3D problems. Recently, our lab has begun investigating a newly-proposed approach, which treats
blood as a compressible fluid in a manner that approximates the effects of compliance [38]. In
this way, only a (compressible) fluid solver is required, and differences in inflow and outflow, and along the vessel, can be accommodated via changes to the fluid compressibility. Our lab has only started implementing and testing this approach within the FEniCS framework, but eventually it could be used to test the effect of inflow/outflow mismatch on CCA flow, for example based on inflow/outflow measurements available from our collaborators at Politecnico di Torino as described above.

4.2.3 Iso-velocity contour method

Limitations:

Iso-velocity contour approach used to estimate the area errors in patient-specific carotid models assumed CFD and PCMRI velocity shapes were identical. In reality, this is not the case since some differences were present, in particular the over-skewed CFD velocity profiles. As explained in Chapter 2, our method relied on minimizing the RMS difference between CFD vs. PCMRI contour areas.

In order to better understand the accuracy of our method, we present plots similar to Figure 26, which showed the iso-velocity technique if CFD and PCMRI velocity profile were identical. In Figure 46, we plot the PCMRI contour areas on x-axis and CFD contour areas on y-axis for N=20 patient-specific cases previously presented in Chapter 2. Solid black line in the plots represent if simulated CFD velocity profile were identical to PCMRI, whereas colour lines correspond to our corrected areas for contour levels 5-8 out of 10 for CFD velocity profile (refer to Chapter 2 for detailed methodology). Ideally, all coloured lines should have overlapped the black lines if CFD predicted velocity profiles were identical to PCMRI, but as seen from the plots, the overlap for Case 4, 5, 8, 9, 11, 14, 15, 16 show deviated trends. Since our technique relies on having a perfect match between CFD and PCMRI, these plot raise question about the reliability of our method.

Recommendation:

Until recently, CEMRA images being obtained as part of the VALIDATE study were only acquired for the arterial phase, namely just after the contrast agent is injected. Recently, our collaborators have started acquiring venous phase images just after the ~90 second arterial phase series, after noting that the venous phase images were easier to measure owing to their sharper
boundaries despite their lower signal. We had hypothesized in Chapter 2 that longer scan times caused contrast agent to become diluted leading to loss of signal in the outer regions of k-space, and as a result, area-underestimations in our segmented geometries. Based on this hypothesis, we can deduce that the area-reducing artifact should not be present in the venous phase images when the contrast concentration has asymptoted after 2 minutes of injection time, resulting in constant intensity throughout k-space. In order to ensure our hypothesis regarding the area-underestimation is correct, we carried out a preliminary comparison of the segmented venous and arterial phase CEMRA for eight cases, and based on our hypothesis, we expected to see larger areas for venous compared to arterial phase images.

In order to compare the arterial vs. venous phase acquisition, we first segmented the carotid arteries from both acquisitions using \textit{vmtk}, and included the carotid bulbs as well as ICA and ECA. Owing to slight patient movement between the two acquisitions, a direct comparison of the segmented geometries was not possible. To overcome this, we employed the branch

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure46.png}
\caption{Iso-velocity contour approach minimizes the RMS of CFD vs. PCMRI contour areas. Owing to the noise in the PCMRI images, the last two of the 10 contour areas are not shown. We had used Level 7 in our correction. “Lvl”=Contour Level, “RMS”=Root-mean-Square, “Corr_Fac”=Correction Factor for area-underestimations.}
\end{figure}
splitting technique implemented in vmtk to extract the ICA and ECA branches from the CCA. Since the arterial and venous segmented geometries are the same, vmtk branch splitting technique would identify the point in the center of bifurcation, which would be same for both acquisitions, and thus, eliminating the need to align the geometries. Taking this as the reference point in the extracted CCA model, we computed the centerlines, and using these centerlines with the segmented CCA surfaces, computed the cross-sectional areas along the length of the CCA for arterial and venous phase acquisitions. These cross-sectional areas, along the length of the CCA, were then converted to diameters and plotted in Figure 47.
Even though bifurcation reference point was obtained using an automated technique, loss of signal resulting in rough surfaces in venous segmented geometries may have shifted the reference point in venous images compared to arterial images. For example, it appears from Case 3 and 6 in Figure 47 that arterial plots are shifted slightly. Such a shift can cause a difference in overall axial diameter. Although CEMRA used in Figure 47 were acquired at scan times of 75sec, only 15sec less than cases presented in Chapter 2, the area-underestimations observed in the former are significantly lower than the latter, except for one case that does show the expected behavior (e.g. Case 8). Case 8 has the smallest diameter based on observing its y-axis, while the other cases have smaller errors than the VALIDATE cases despite their diameters (e.g., y-axes) being comparable to the VALIDATE cases. Generally, arterial diameters were on average ~3% smaller than venous phase diameters resulting in only 6% area underestimation, significantly lower than 27% predicted by our iso-velocity approach.

Figure 47: Arterial vs. Venous phase images for 7 cases along the length of the CCA beginning from carotid bifurcation.
The observation that arterial areas and venous areas are comparable seems to contradict our results from CEMRA simulations. This may be due to dependence of FWHM on TR, FOV_y, FOV_z, and scan time \( T_{\text{scan}} \) as derived from equation (7) and (8) presented by Fain et al. [15]:

\[
\text{FWHM} \propto \sqrt{\frac{TR \cdot FOV_y \cdot FOV_z}{T_{\text{scan}}}}
\]

The imaging protocols (e.g. TR, FOV_y, FOV_z, \( T_{\text{scan}} \)) used in VALIDATE studies presented in previous chapters may differ from the arterial vs. venous phase geometries presented in Figure 47. The difference in imaging protocols may have causes the area-reducing artifact to disappear in these arterial and venous phases images. Lastly, another observation evident from the above relation is that FWHM decreases with increasing scan-times, as previously stated in Chapter 2, thus confirming our CEMRA simulations.

The disagreement between our iso-velocity area-underestimations compared to arterial vs. venous comparison maybe resolved by performing CFD simulations of arterial-phase-derived geometries, with 75sec long scan time, to determine whether velocity over-estimations compared to PCMRI remain. If the velocity-overestimation in these CEMRA geometries disappear, than we would suspect that CEMRA protocols, particularly the shorter scan times, may be the cause. More generally, further investigations are required to determine whether modest changes to the clinical vs. VALIDATE CEMRA protocol might explain this apparent discrepancy between expectation and observation.
Bibliography


