

Analysis of carotid wall mechanics based on ultrasound imaging

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Declaration of Originality

I hereby certify that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institute of tertiary education. Information derived from the published and unpublished work of others has been acknowledged in the text and references are given.

London, December 2014

Zhongjie Wang

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Abstract

Stroke is the third biggest killer and the leading cause of severe disability in the UK. The most common type of stroke is known as an ischaemic stroke in which blood vessels in the brain become blocked, most often as a result of rupture of atherosclerotic plaques formed in the carotid arteries, especially at the bifurcation and in the entrance to the internal carotid artery which feeds the cerebral circulation. The carotid arteries can be examined through ultrasound scans, which provide images of the vessel allowing assessment of the severity of carotid disease.

In this project, ultrasound images of carotid arteries acquired from patients with varying degrees of carotid disease are analysed and computational models are built to predict the mechanical stresses within carotid arteries with or without atherosclerosis. Ultrasound imaging was chosen owing to its non-invasive nature and wide availability.

Work presented in this thesis follows a logical progression. First, image analysis tools are developed and presented in Chapter 3. Based on the processed ultrasound images, finite element models of carotid arteries are constructed and biomechanical analyses of varying degrees of complexity are carried out. In Chapter 4, the carotid artery is assumed as an elastic material, and comparisons are made between 2-D and 3-D models based on idealised geometry. In an attempt to improve the predictive ability of the model and achieve better understanding of disease progression, the viscoelastic behaviour of the carotid vessel wall is taken into account, and detailed analyses of the effect of vessel wall viscosity and hysteresis are presented in Chapter 5. Methods used to derive subject-specific viscoelastic material properties from *in vivo* pressure-diameter data are also described. Finally, in order to understand the effect of interaction between the viscoelastic vessel wall and blood flow in carotid arteries, fully coupled fluid-structure interaction (FSI) models are developed, and the FSI model as well as its validation are presented in Chapter 6.

Work reported in this thesis has shown that by combining ultrasound measurement with computational analysis, it is possible to provide additional information that will

aid clinicians in their diagnosis and decision making. Carotid biomechanical analysis can be carried out with subject-specific information, such as viscoelastic wall properties and geometry, derived from *in vivo* data acquired non-invasively. The ultrasound-image based modelling approach developed in this thesis will also help improve our understanding of the role of vessel wall motion in the development and progression of carotid diseases.

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Nomenclature

a	Diameter of the narrowed lumen
b	Diameter of the outer arterial wall
c	Diameter of the normal ICA lumen
d	Fibrous cap thickness
e	logarithmic strain
f	Frequency
h	Intima-media thickness
t_n	n th time step
t_{n+1}	$n+1$ time step
i, j	Tensor indices
u, v, w	Velocity components in Cartesian coordinate system
x, y, z	Cartesian coordinate
D	Diameter
$\mathbf{D}$	stiffness matrix
E	Young' modulus
E_e	equilibrium modulus
E_θ, E_r and E_l	Green's strain components in the circumferential, radial and longitudinal directions
E_i	relaxation strengths
F	force
G	shear modulus
J	the ratio of the deformed volume over the un-deformed volume of material
I_1 and I_2	the first and second invariants of the strain tensor
L	Length of model
P	Pressure
R	Radius
T	Cardiac cycle
$\mathbf{T}$	Cauchy traction vector
W	strain energy per unit mass
ρ	mass density

ρ_i	relaxation time
σ	normal stress
τ	shear stress
τ_w	WSS magnitude
μ	viscosity
ν	Poisson's ratio
ω	angular frequency
ε	strain

Abbreviation

2D	2-Dimensional
3D	3-Dimensional
AHA	American Heart Association
ALE	Arbitrary Lagrangian-Eulerian
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
CEMRA	Contrast-Enhanced MRA
CFD	Computational Fluid Dynamics
CSM	Computational Structural Mechanics
CT	Computer assisted Tomography
CTA	Computed Tomography Angiography
CTS	Circumferential Stress
DOS	Degree of stenosis
ECA	External carotid artery
ECST	European Carotid Surgical Trial
FEA	Finite element analysis
FEM	finite element method
FSI	Fluid-Structure Interaction
ICA	Internal Carotid Artery
IMT	Intima-Media Thickness
IVUS	Intravascular Ultrasound
LDL	Low-Density Lipoprotein
MRA	Magnetic Resonance Angiography
MRI	Magnetic resonance imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NMR	Nuclear Magnetic Resonance
OCT	Optical Coherence Tomography
PET	Positron Emission Tomography
RF	Radio Frequency
ROI	Region Of Interest
US	Ultrasound

VMStress	Von Mises stress
VMStrain	Von Mises strain
WSS	Wall shear stress

Chapter 1 Introduction

1.1. Motivation

Rupture of atherosclerotic plaque in carotid arteries is the main cause of ischemic cerebrovascular events. When this occurs, the embolized thrombus or clot travels to blood vessels in the brain, causing occlusion of a narrow cerebral artery. This can rapidly lead to loss of brain functions due to lack of oxygen supply to the brain. Every five minutes someone in the UK suffers from a stroke, which has become one of the leading causes of mortality and morbidity in the UK, just after heart disease and cancer, and is the largest cause of adult disability. One third of strokes lead to death and most stroke survivors are afflicted by neurological disability which requires long-term care. Moreover, the risk of stroke recurrence increases substantially after its first episode. In the United State, about 795,000 people experience a new or recurrent stroke every year, with approximately 610,000 of these being first attacks. Mortality data from 2008 indicate that stroke led to about 1 in 18 deaths in the United State. The projections showed that an additional 4 million people would have had a stroke by 2030, a 24.9% increase in prevalence from 2010 (Heidenreich et al., 2011, Roger et al., 2012). As an underlying problem of stroke, the development of atherosclerotic plaque in the carotid artery has attracted significant research effort, and understanding the biomechanical behaviour of carotid arteries is an important part of this research.

1.2. The carotid artery

Arteries are blood vessels that carry blood away from the heart. Except the pulmonary and umbilical arteries, most arteries carry oxygenated blood. The blood pressure in large arteries varies between the systolic pressure (the peak pressure during heart contraction) and diastolic pressure (the minimum pressure when the heart expands and refills).

Maintaining the normal function of the circulatory system is very important as it provides oxygen and nutrients to the body, and removes carbon dioxide, waste products from the cells. The carotid arteries are the main oxygenated blood supply to the brain and the neck. There are two carotid arteries, one on each side of the neck. As shown in Figure 1-1, the left common carotid artery arises from the aortic arch, and its average lumen diameter is 7.5-8 mm; while the right CCA arises from the upper branch of the brachiocephalic artery with a lumen diameter varying between 6.0 and 6.8 mm. The brachiocephalic artery is an artery that supplies blood to the right arm, head and neck. The left CCA can be thought as containing two sections: the chest section and the neck section, while the right CCA usually starts from the neck, so it lacks a thoracic portion.

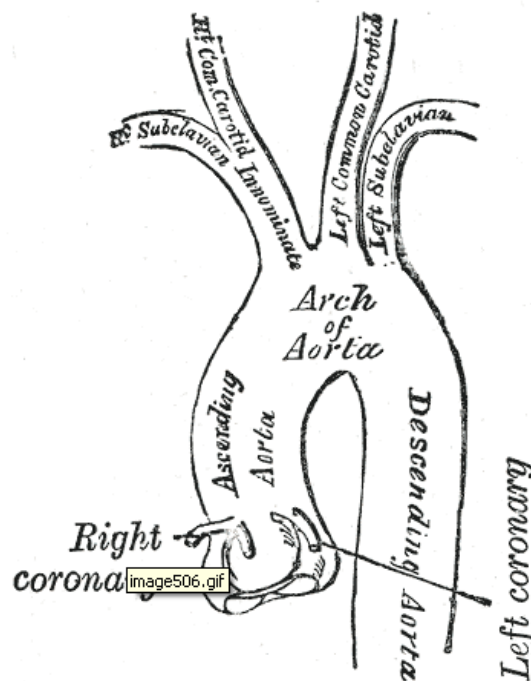


Figure 1- 1 The common carotid arteries and their origins (Gray, 1995).

The common carotid artery bifurcates into the external carotid artery (ECA) and internal carotid arteries (ICA) (Figure 1-2). The ECA provides blood to the facial muscle and external structure of the skull, whereas the ICA supplies blood to the brain, eye and nose. Generally, the lumen diameter of ECA is smaller than that of ICA, and is usually between 3.5 mm and 5 mm. A distinct feature of the ICA is that it contains a sinus, usually called the carotid bulb, at its proximal end.

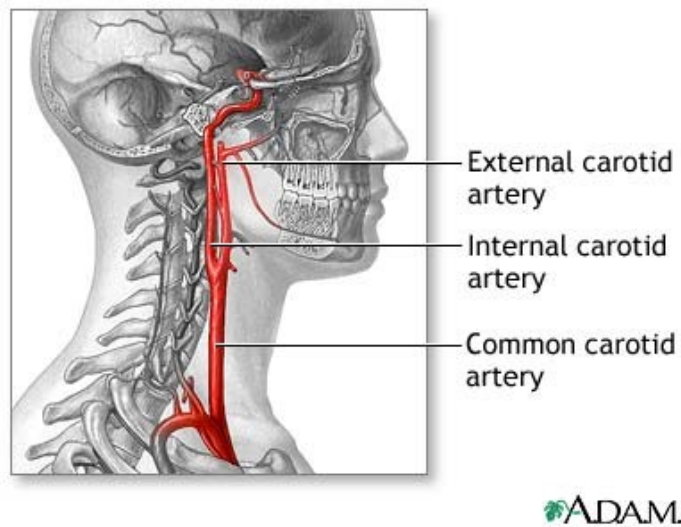


Figure 1- 2 The carotid artery bifurcation.

Atherosclerotic plaques are prone to develop in areas of complex geometries including bifurcations and areas of large curvature, suggesting that the fluid mechanical factors are involved in the process of the disease. The carotid bifurcation is one of the areas where atherosclerotic plaques are frequently found, and about 25% of all ischemic stroke events are caused by the rupture of carotid plaques (Weinberger, 2005). Experimental and Computational studies (Ku et al., 1985) have been carried out to examine detailed flow patterns at the carotid bifurcation and correlations between wall shear stress and intimal thickening.

1.3. Biomechanics factors related to plaque rupture

Over a period of time, it was thought that cardiovascular events were caused by building up of fatty deposits that narrowed or completely blocked the vessel in the heart and brain. However, more recent studies revealed that not all the patients who suffered a heart attack had flow limiting plaques in the coronary artery. In fact, some non-flow limiting plaques could be more dangerous than flow limiting plaques. Atherosclerotic plaques can be generally divided into two categories: vulnerable plaque or stable plaque. Vulnerable plaques were defined by Naghavi et al. (Naghavi et al., 2003), who stated that all types of atherosclerotic plaques which have a high possibility to cause thrombotic complications such as morphology infarction or stroke or a plaque that

tends to progress rapidly should be considered as vulnerable plaques. However the exact mechanism of plaque rupture still remains unclear. Some plaque features, such as large lipid pool which is more than half of the plaque volume, thin fibrous cap and high content of inflammatory cells, have been related to vulnerable plaques (Naghavi et al., 2003).

Carotid endarterectomy is a surgical procedure to remove an atherosclerotic plaque from the carotid artery. For many years, conventional assessment methods, including the degree of stenosis of carotid lumen (Inzitari et al., 2000), intima-media thickness (den Hartog et al., 2013) or the grey-scale median of atherosclerotic plaque (Geroulakos et al., 1993, Grogan et al., 2005), have been used to assess the risk of ipsilateral embolic stroke, which is a major determinant for eligibility for carotid endarterectomy (CEA). However, these conventional assessments do not uniquely correlate with plaque vulnerability, or strongly guide treatment for patients. It has been reported that the risk reduced by CEA in patients with over 60% stenosis is from 2% to 1% per year, while the group who received medical treatment and blood pressure control together with changing life style has reduced the annual risk of stroke by 1%. As a result many researchers are questioning the need for CEA. Therefore, further research for the development of diagnostic methods to reliably predict the risk of carotid artery rupture is needed in order to identify the characteristics which define a vulnerable carotid plaque.

It has been accepted that plaque vulnerability is influenced by both plaque morphology and biomechanical stress of the plaque (Sadat et al., 2010). The association between vascular biomechanical stresses and the formation and rupture of atherosclerotic plaque has been examined by many researchers. The region of simultaneous high tensile stress and low wall shear stress (WSS) tends to overlap with the region where atherosclerotic plaques are commonly found (Lee and Xu, 2002, Zhao et al., 2000). And atherosclerotic plaques tend to form at bends and bifurcations (Taeymans et al., 1992), indicating that there may be a link between flow-related parameters and the development of atheroma. It was believed that atherosclerotic lesions began in the region of low shear stress, and the development of lesions was inhibited or retarded in regions of high shear (Caro et al., 1971). More evidence was given by Ku et al. who showed a positive correlation between plaque location and low and oscillating shear

stress in a carotid artery bifurcation (Ku et al., 1985). Glagov et al. expanded on this finding, and demonstrated that intima-media thickening tended to form at the outer wall of a bend and within the carotid sinus of the ICA (Glagov et al., 1987). Since carotid arteries are easily accessible by ultrasound, ultrasound has become a method of choice for assessing carotid artery disease.

A healthy carotid arterial wall has elastic properties that resemble those of an elastic tube. However, mechanical behaviour of carotid arteries can be altered by several factors, such as ageing, hypertension and diabetes (Sadat et al., 2010). The carotid artery may behave as a hyper-elastic or viscoelastic material, which can influence the biomechanical stress in the arterial wall. It is important to gain qualitative and quantitative understanding of biomechanical stress and strain distributions under physiologically realistic conditions.

1.4. Basic parameters for carotid wall mechanical analysis

To study the mechanical behaviour of carotid arteries, knowledge of the elastic properties of the arterial wall is essential. No solid material is completely rigid. Without displacing a solid body, parts of the body may move relative to one another when forces act on it. After the force is removed, if the body regains its original state, it is said to be perfectly elastic; if the body retains the deformation, it is said to be plastic. Stress (σ) can be defined as the intensity of force (F) which produces the deformation. If it is uniformly distributed over the area (A), the stress is F/A , and the force at a point in a plane can be resolved into two components, one is normal to the plane (tensile or compressive stress), the other is tangential to the plane (shear stress). Strain can be described as the rate of deformation (ε) of the original body. Shear strain is used to describe angular deformation while compressive strain occurs when there is a large volume change. Hooke's law states that for an isotropic linear elastic material, the strain is directly proportional to stress.

$$\sigma = E\varepsilon \quad (1-1)$$

where the proportionality constant, E , is called Young's modulus. The mean and standard deviation of Young's modulus of common carotid arteries were found to be 701 ± 324 kPa, which was determined on 3,321 white male and female subjects (between the age of 45 and 64 years) by using ultrasound and noninvasive measurement of pulse pressure (Riley et al., 1992).

Poisson's ratio is the ratio of transverse to longitudinal strain. It depends on the nature of the material. For a perfectly incompressible material, the Poisson's ratio is 0.5 (Nichols and O'Rourke, 2004). The Poisson's ratio is set to 0.49 (nearly incompressible) for carotid artery in the current study.

Since circumferential stress (CTS) is an important parameter in arterial wall mechanics, it has traditionally been estimated using Laplace's law, which relates CTS to the luminal pressure, lumen diameter and intima media thickness (IMT). This is given by (Nichols and O'Rourke, 2004):

$$CTS = \frac{PD}{2h} \quad (1-2)$$

where P is the luminal pressure, D is the lumen diameter and h is the IMT. In fact, Laplace's law does not apply to complex geometries so numerical models are needed for calculation of mechanical stress in realistic geometries. This will be discussed later in the thesis.

Knowledge of tensile stress distribution and magnitude may help understand the role of biomechanical factors in atherogenesis. CTS acts on smooth muscle cells and intercellular matrix. It is speculated that high CTS induced by pulsating blood pressure may cause thickening of the vessel wall, hence affecting its distensibility, causing hypertrophy and predisposition to plaque formation. It has been shown that in the carotid arteries of hypertensive patients, increased arterial stiffness is due to higher luminal pressure rather than changes in wall composition (Bussy et al., 2000). Cheng et al. calculated the distribution of CTS in 12 ruptured and 12 stable coronary atherosclerotic lesions, and they found that 10 out of the 12 lethal lesions occurred in the region of maximum CTS (Cheng et al., 1993).

Extensive biomechanical studies of the formation of atherosclerosis plaques have also been performed from the hemodynamic point of view, where wall shear stress (WSS) - the frictional force exerted by the flowing blood on endothelium, the inner lining of vessel wall – is the parameter that has received the most attention. For laminar flow of a Newtonian fluid in a straight, circular tube, the magnitude of WSS is given by

$$\tau_w = \left| \mu \frac{du}{dr} \right|_{r=R} \quad (1-3)$$

where τ_w is the WSS magnitude, μ is the fluid viscosity, du/dr is the shear rate, r is the radial position and R is the tube radius. It has been found that WSS can influence the function and phenotype of endothelial cells in arteries. WSS in the range of 1 to 6 Pa may protect the artery from atherosclerotic disease (Malek et al., 1999). A study by Zhao et al suggested that there was an overlap of high wall stress region and low WSS in the human carotid bifurcation, coinciding with the location known to be prone to plaque formation (Zhao et al., 2002). However, biomechanical stresses cannot be measured directly *in vivo*, but can be predicted by image-based modelling – an active research field which combines computational fluid and solid mechanics with medical imaging.

Compared to MRI and CT, 3D ultrasound has several advantages; it is safe, non-invasive and relatively inexpensive. Previous studies performed by Augst et al. have demonstrated the accuracy and reproducibility of computational fluid dynamics (CFD) predicted WSS by using 3D ultrasound images (Augst et al., 2003). Later Glor et al. compared 3D ultrasound with MRI for carotid geometry reconstruction and flow simulation, and concluded that 3D ultrasound was comparable to MRI for carotid geometry reconstruction, but the hand-held 3D ultrasound system adopted in their study was highly operator dependent (Glor et al., 2003). Therefore, a hand-free system would be a great advantage for such an application. A premium performance ultrasound system, iU22 xMATRIX (Philips Co.) is currently used at Ealing Hospital, London. The ultrasound transducer incorporated into this system is VL13-5, which is a 3D broadband, linear array probe (Phillips Co). This transducer provides a wide frequency

range between 13 to 5 MHz and supports high resolution 2-, 3- and 4-D imaging. Unlimited planes in all directions can be viewed and examined by using this system's multi-directional beam steering. Additionally, specially designed software called Q-Lab® (Phillips Co) was installed on the machine (iU22 xMATRIX) for navigation and 3D reconstruction of the underlying structures.

1.5. Research Objectives

Conventional methods for assessing lesion severity of the carotid artery (i.e. by using the degree of stenosis or plaque burden) are not accurate enough to predict plaque vulnerability and to guide surgical decision making. By combining ultrasound measurement with computational analysis, it is possible to provide additional information that will aid clinicians in their diagnosis and decision making. It would be highly desirable to carry out carotid biomechanical analysis with subject-specific information, including viscoelastic wall properties and geometry, derived from *in vivo* data acquired non-invasively. Although a large amount of effort has been spent on understanding carotid artery haemodynamics and wall mechanics, none of the studies reported in the literature has incorporated viscoelastic wall behaviour with blood flow in a realistic carotid artery geometry. It is therefore the goal of this study to develop an ultrasound-image based modelling approach that allows this to be achieved. It is hoped that the model developed in this thesis will help improve our understanding of the role of vessel wall motion in the development and progression of carotid diseases. The specific objectives of this project are stated as follows:

- To create a computational model for biomechanical analysis of the carotid artery by applying an established finite element code, ANSYS, to patient-specific models of carotid arteries reconstructed from ultrasound data.
- To develop robust image processing methods for extraction of the key features of carotid arteries from 3D ultrasound images, and to apply the developed image processing algorithms to 3D ultrasound images of carotid plaques in order to assess their suitability.
- To compare 2D and 3D models for finite element stress analysis based on idealized and realistic geometries. This will allow us to determine whether 2D models would be

sufficient for predictive purpose.

- To evaluate and compare linear elastic and viscoelastic models for biomechanical analysis of the carotid artery. For this purpose, a method will be developed for estimation and representation of patient-specific viscoelastic material properties in the form of Prony series.
- To develop a coupled fluid-structure interaction (FSI) model for predicting the dynamic responses of carotid arteries.

1.6. Outline of thesis

Chapter 1 introduces the project and highlights the importance of biomechanical analysis of carotid arteries to provide evidence for its utility in assessing plaque vulnerability and likelihood of rupture. In **Chapter 2**, essential background information is given on arterial functions and structures that are related to the development of atherosclerosis, and on vascular imaging techniques. A review of the literature on biomechanical analysis of large arteries is also covered.

Since ultrasound imaging was adopted to provide essential input data for subsequent biomechanical analysis, **Chapter 3** is dedicated to image processing techniques, including image segmentation and geometry reconstruction. In addition to geometric data, additional information that is useful for clinical diagnosis is also extracted from ultrasound images. Based on the processed ultrasound images, finite element analyses of carotid arteries are presented in Chapter 4 and Chapter 5. In **Chapter 4**, the carotid artery is assumed as an elastic material, and comparisons are made between 2-D and 3-D models based on idealised geometry. In an attempt to improve the predictive ability of arterial dynamics, the viscoelastic behaviour of carotid vessel wall is taken into account, and detailed analyses of the effect of vessel wall viscosity and hysteresis are presented in **Chapter 5**. Methods used to derive subject-specific viscoelastic material properties from *in vivo* pressure-diameter data are also described. In order to understand the effect of dynamic interaction between the viscoelastic vessel wall and blood flow in carotid arteries, fully coupled fluid-structure interaction (FSI) models are developed, and the FSI model as well as its validation are presented in **Chapter 6**. Although individual results and conclusions are summarized in each chapter, the

overall conclusions and recommendation for future studies are given in **Chapter 7**. By implementing ultrasound measurement and computational analysis, it is possible to carry out patient-specific analysis incorporating detailed information on wall properties and vessel geometry.

Chapter 2 Literature review

2.1. Clinical and biological background

2.1.1. Arterial Function, Structure and Composition

Blood is carried through the body via blood vessels. Arteries are blood vessels that carry blood away from the heart. Since most of the oxygen delivered by arteries is consumed by cells, the blood that returns to the heart through the veins has less oxygen. Except the pulmonary and umbilical arteries, most arteries carry oxygenated blood as shown in Figure 2-1. Blood pressure in arteries varies between the systolic pressure (the peak pressure during heart contraction) and diastolic pressure (the minimum pressure when the heart expands and refills).

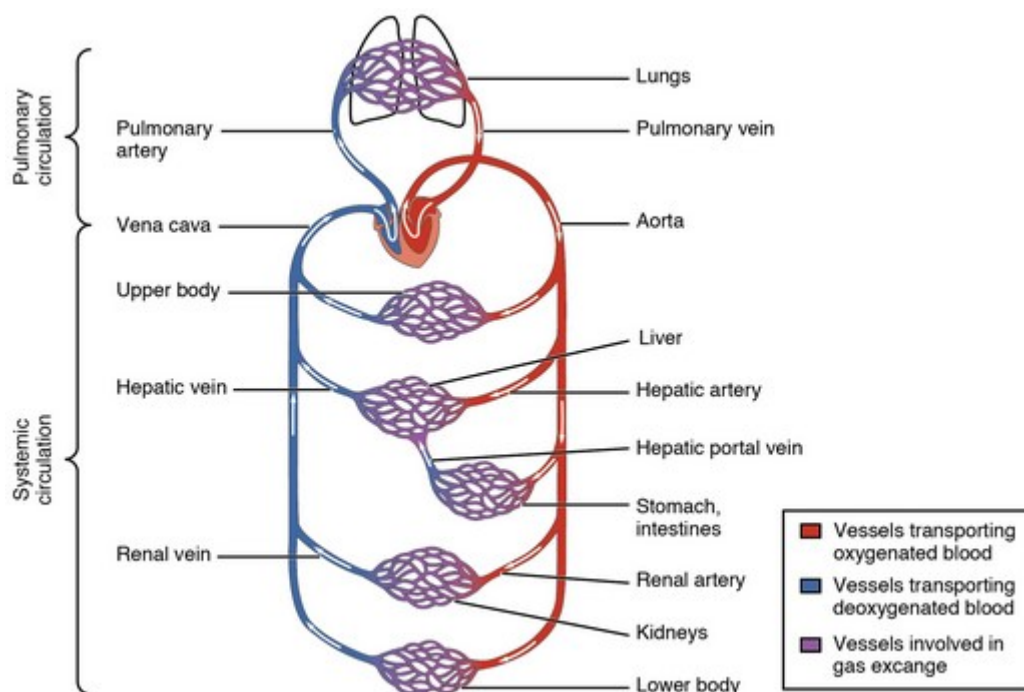


Figure 2- 1 Two distinct circuits in cardiovascular circulation (courtesy of OpenStax)

Although arteries and veins vary in their functions and structures, they share certain common features. Blood vessels have a complex structure which consists of three layers as shown in Figure 2-2: tunica adventitia, tunica media and tunica intima. These

constituents are the major contributors to the biomechanical properties of arterial walls. The strong outer covering of artery is tunica adventitia, composed of connective tissue, elastic fibres and collagen. These fibrous components allow the artery to stretch to prevent overexpansion resulting from the pressure of blood flow. The middle layer is called tunica media, which is composed of elastic fibres and smooth muscle cells arranged in bundles. This layer is the thickest layer in a carotid artery. In normal conditions, media and adventitia are the major constituents influencing the mechanical properties of large arteries. Finally the innermost layer is tunica intima, which is very thin in a healthy artery. It is lined with endothelium cells, and the endothelium layer is supported by an internal elastic lamina, which separates media from intima. Although intima is normally very thin and plays an insignificant role in providing vessel wall strength, its thickness increases with age and in the circumstance of arterial diseases, such as atherosclerosis, which is generally recognized as the consequence of a pathological process involving smooth muscle cell proliferation and migration from media to intima. The width of the layer between tunica intima and external elastic membrane is called intima-media thickness (IMT), which is taken as an indicator of atherosclerosis.

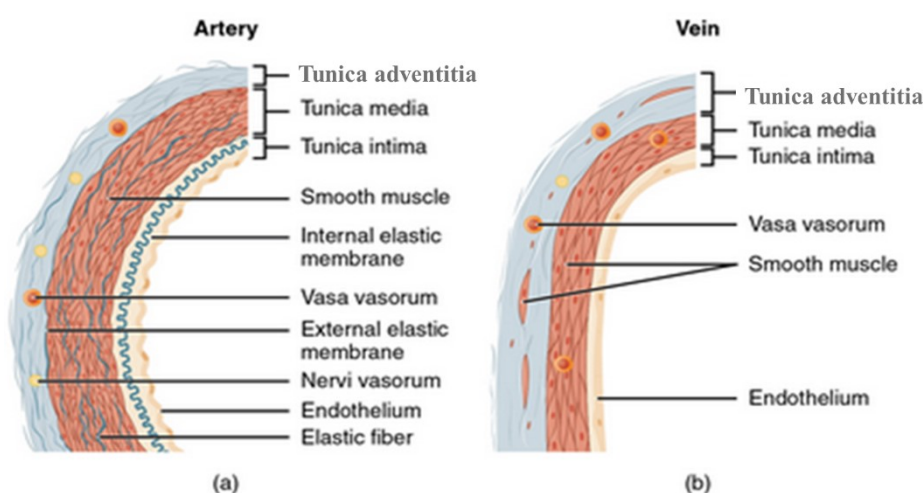


Figure 2- 2 Structure of a healthy large artery (a) and vein (b) with three morphologically distinct layers (courtesy of OpenStax).

According to the relative proportion of elastic and muscular tissues in the tunica media layer and the size and makeup of the internal and external elastic lamina, arteries can be divided into three types: arterioles, elastic arteries and muscular arteries. Due to their different functions in the body, elastic arteries have the largest cross-sectional area,

containing a high percentage of elastic fibers in all three of their tunics, for transporting large volumes of blood from the heart. The large amount of elastin in the wall of elastic arteries helps to dissipate the large fluctuation between systolic and diastolic pressure. Arteries larger than 10 mm in diameter are typically elastic. During a cardiac cycle, arterial walls expand as the local pressure increases to hold the additional blood volume, and decrease as the pressure drops to release the additional blood.

2.1.2. Atherosclerosis

Atherosclerosis is an arterial wall disease, which is characterized by hardening and thickening of the vessel wall. It is the primary cause of heart disease and stroke, and accounts for about 50% death in developed countries (Lusis, 2000). The word of “atherosclerosis” is from Greek and can be separated in to “athera” and “sclerosis”. “Athera” means paste or gruel in Greek, while “Sclerosis” means hardening. Atherosclerotic lesions start at the tunica intima layer, and progressively affect the whole artery (Insull, 2009). Atherosclerosis can cause the formation of thrombus or stenosis, and in advanced stages can reduce or totally block blood flow in the lumen. This process, which is also known as stenosis, can cause further problem due to rupture or damage to tissue in the downstream regions. As a consequence of the risk factors and alterations of the biomechanical environment including low wall shear stress and increased disturbance at the specific arterial site such as branches , bifurcations and curvatures (Traub and Berk, 1998), low-density lipoprotein (LDL) starts to accumulate in the vessel wall. This very early step of atherogenesis can take place in childhood. It precedes the formation of atherosclerotic lesion that takes place in the endothelium, changing the permeability to lipoproteins and other plasma constituents, as shown in Figure 2-3 (a).

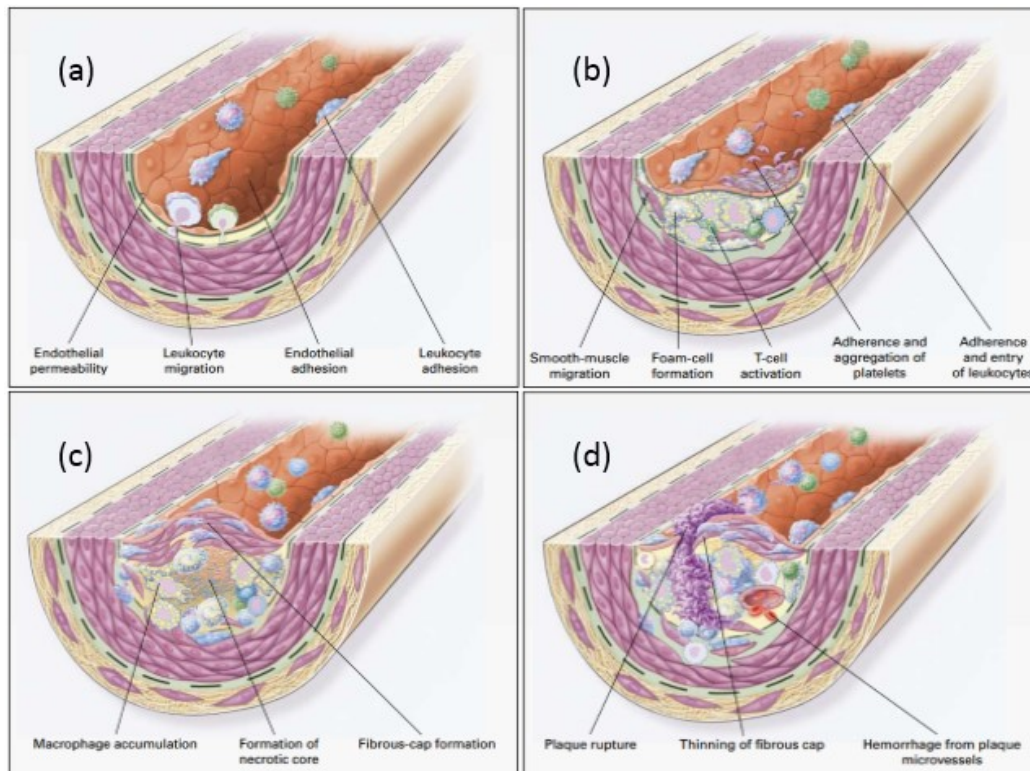


Figure 2- 3 (a) Endothelial dysfunction in atherosclerosis (b) Fatty streaks formation in atherosclerosis (c) Advanced, complicated lesion of atherosclerosis (d) Unstable fibrous plaque in atherosclerosis (Ross, 1999)

This stage is followed by accumulation of high-lipid macrophages and T-lymphocytes, as well as formation of fatty streaks in the intima. The fatty streaks initially consist of macrophages (foam cell) and lipid-laden monocytes together with T lymphocytes as shown in the Figure 2-3 (b). During this step, accumulation of various numbers of migratory smooth muscle cells takes place, contributing to the damage of all arterial layers.

Later, as the fatty streak progresses to an intermediate stage or even an advanced level, a fibrous cap is formed on the luminal surface of the lesion, as illustrated in Figure 2-3 (c). This represents a type of healing or fibrous response to injury. The fibrous cap covers a mixture consisting of leukocytes, lipid, and debris, which may cause the formation of necrotic core. With continued leukocyte adhesion and entry, these lesions expand at their shoulders. The necrotic core forms as a result of apoptosis and necrosis, increased photolytic activity, and lipid accumulation. A number of factors are involved in the formation of fibrous cap, including osteopontin, decreased connective-tissue degradation, as well as increased activity of platelet-derived growth factor,

transforming growth factor β , interleukin-1, and tumour necrosis factor α .

Ultimately, rupture or ulceration of the fibrous cap may occur at the site with thinning fibrous cap that covers the advanced lesion (Figure 2-3 (d)). Thinning of the fibrous cap is a consequence of continuing influx and activation of macrophages which releases metalloproteinase and other proteolytic enzymes. Degradation of the matrix caused by these enzymes can ultimately lead to haemorrhage from the lumen of the artery or from the vasa vasorum and cause thromboembolism and occlusion of a downstream artery, e.g. the mid-cerebral artery.

2.1.3. Risk factors

Atherosclerosis is a chronic arterial disease that can start in childhood and remain asymptomatic for many years. Epidemiological studies have revealed a large number of risk factors that are related to the formation of atherosclerotic plaque. These can be classified into two categories: environmental and genetic. Environmental factors include urbanization and globalization and their negative impacts on physical activity, consumption of a healthy diet and cigarette smoking. . Raised cholesterol and glucose levels in blood, raised blood pressure and body mass index are as a result of these unhealthy behaviours (Mendis et al., 2007).

The importance of environment and genetics in human has been examined in many family and twin studies (Goldbourt and Neufeld, 1986, Lusa, 2000). Certain disorders are related to genetic risk factors: Obesity and diabetes (Assmann et al., 1999, Mayer-Davis et al., 1998); systemic inflammation; familial history (Goldbourt and Neufeld, 1986); hypertension; reduced level of high-density lipoproteins (HDL) (Gordon and Rifkind, 1989); elevated level of low-density lipoproteins (LDL) (Assmann et al., 1999); sex of individual and below the age of 60 (Nathan and Chaudhuri, 1997); depression, increased levels of haemostatic factors (Assmann et al., 1999) and other behavioural traits (Lusa, 2000).

2.1.4. Evaluations of patients with atherosclerotic plaques

There are several methods to grade atherosclerosis. The American Heart Association (AHA) proposed a numerical classification of histological definition of atherosclerotic lesion into 6 types (Stary et al., 1994). Due to the limitations reported (Virmani et al., 2000), it was subsequently expanded into 8 types which ascend in severity from type I to type VIII (Stary, 2000). In the accompanying studies, Virmani et al. defined their own plaque classification without numerical classification (Virmani et al., 2000). These classifications are predominately based on studies of coronary lesions, but they can also be extrapolated to the studies of carotid arteries. As outlined in Figure 2-4, types I to III characterise the early stages, when endothelial lesion exposes intima to deposition of a small amount of lipid, inciting a local inflammatory reaction by macrophages. Although endothelial cells in the early stage remain intact and stable, there are increase in stress fibre contents and decrease in the alignment of blood flow. In the later stages, types IV to VIII are distinguished by accumulations of lipid, cells, and matrix components, deformation of the arterial wall or intimal disorganization and thickening.

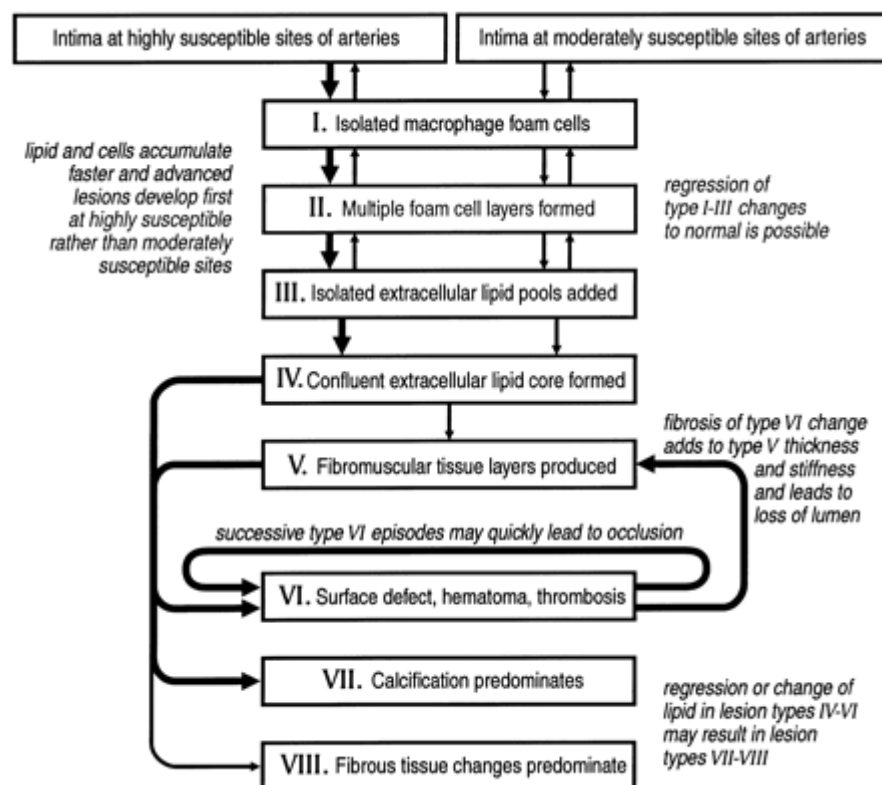


Figure 2- 4 Outline of sequence in the evolution of atherosclerotic lesion from type I to type IV and of the possible subsequent bypath beyond type IV (Stary, 2000)

On the other hand, the severity of atherosclerosis can be graded by the degree of stenosis (DOS) which can be measured by using many imaging techniques, including duplex ultrasound (US), computerized tomographic angiography (CTA), magnetic resonance imaging (MRI) or intravascular ultrasound (IVUS). These imaging techniques are described later. There are two methods for grading of carotid stenosis. One is based on the European Carotid Surgical Trial (ECST); the other is from the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Their definitions are given in Figure 2-5, where a stands for the diameter of the narrowed lumen, b is the diameter of the outer wall, and c is the diameter of the normal ICA lumen.

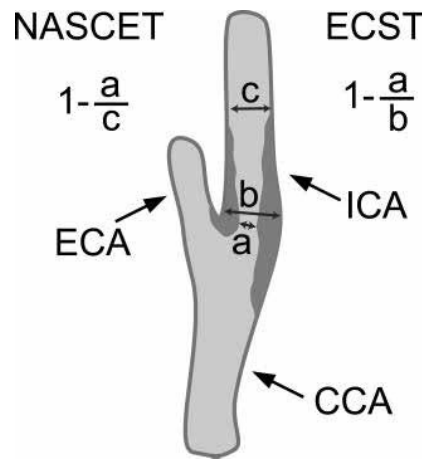


Figure 2- 5 Definitions of degree of stenosis in an ICA based on the NASCET and ECST criterion (Ota et al., 2005).

The relationship between ECST and NASCET is given by:

$$\text{ECST}\% = 0.6\text{NASCET}\% + 40\% \quad (2-1)$$

The NASCET method underestimates the DOS compared to the other method (Staikov et al., 2000). In cases where images are acquired for the section of narrowed artery only and there is no information about the normal diameter of the carotid artery, the ECST definition has to be adopted to describe the DOS.

Plaque burden, which is also referred to as plaque index, is the percentage of wall

volume relative to the whole vessel volume (i.e. lumen and wall volume inclusive). Using a wall tracking system, Stork et al. found that plaque burden was a reliable predictor of all-cause in elderly human cases. Although this restricted age group narrowed the range of carotid artery stiffness, it proved the important role of plaque burden in cardiovascular mortality risk analysis (Stork et al., 2004).

Takase et al. compared three coronary artery disease prognosis indicators: endothelial dysfunction, coronary artery plaque burden and conventional exercise-induced myocardial ischemia. Their results showed that all three indicators could reflect prognosis in patients with suspected coronary artery disease, but coronary artery plaque burden, which was obtained by carotid artery IMT measurement using high-resolution ultrasound, seemed to have less power than the other two measures for predicting future cardiac events. This could be due to the small number of severe stenosis cases in the population of patients studied (Takase et al., 2008). Stein et al. reviewed previous works on coronary artery atherosclerosis, with over 38,000 subjects combined, showed that there were significant correlations between carotid plaque burden and coronary artery disease (Stein et al., 2006). The same observations were found in an early autopsy study (Mitchell and Schwartz, 1962).

During arterial remodelling, the thickness of intima and media increase, so that intima-media thickness (IMT) has been of particular interest in cardiovascular research. Studies by the AXA study show that there are significant relations between IMT of carotid arteries and most of the risk factors, for example body mass index, systolic and diastolic blood pressure, cholesterol and smoking. It is commonly found that there is an increase of IMT in patients with peripheral vascular diseases. IMT has been used in early diagnosis of atherosclerosis (Garipey et al., 1998).

2.1.5. Clinical Management

Although atherosclerosis cannot be cured completely, it can be hindered or prevented. This can be achieved by minimizing the risk factors mentioned above. Vulnerable patients should reduce intake of fat and high cholesterol food, adopt a well-balanced healthy diet, stop smoking and take more exercises which will help to lower blood

pressure levels. These non-pharmaceutical methods are commonly used as the first choice of treatment. If the degree of lesion increases, medication would be needed to control blood pressure, such as ACE inhibitor, or reduce cholesterol and glucose levels to near-normoglycemic levels for patient with diabetes (Hobson II et al., 2008).

For more risky atherosclerotic plaques, surgery is usually required to remove the blockage from the affected artery to prevent heart attack or stroke. Surgical removal of the carotid artery plaque is called endarterectomy which is not without risk, because this procedure may cause blood clots to escape from the artery, resulting in arterial embolism in crucial areas. An alternative procedure, which is called angioplasty, involves inserting a balloon catheter in the affected artery and flattening the plaque to enlarge the diameter of artery to its normal size. Although angioplasty is less risky and more affordable than endarterectomy, this procedure may need to be repeated as restenosis of the treated artery often occurs, and this may result in further hardening or damage of the vessel. Stenting is an alternative surgical therapy, which involves insertion of a self-expandable tubular metal wire mesh into the affected artery. This often follows angioplasty. The most radical surgical procedure is bypass graft, which diverts blood from narrowed or occluded part of the artery to improve blood flow and oxygen supply by using a piece of normal vein or artificial conduit.

2.2. Medical imaging techniques

A variety of imaging techniques, either invasive or non-invasive, can be used to obtain detailed anatomical information of blood vessels; these include computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), optical coherence tomography (OCT), and intravascular ultrasound (IVUS). All of these have been employed by various researchers to provide anatomical information suitable for computational fluid dynamics simulations. These methods are described below from their basic principles to applications in vascular scanning. In 1959, Sones performed the first coronary angiography to assess the degree of narrowing in a coronary artery, based on x-ray lumenographic technique. However this method cannot provide details of the arterial wall (Sones, 1962). For this reason, more advanced imaging techniques would be required, and there has been a significant advancement in vascular imaging techniques

since then.

2.2.1. Computed tomography

Computed tomography (CT) is based on modified X-ray technology which has been used for a long time for non-invasive medical diagnostics. Usually it is used to assess bone fractures. A patient is placed in front of an X-ray source which emits radiation through the body. Each X-ray incident on the body would be attenuated by tissue when it passes through its linear flight path. The principle of CT scan is that different tissue types in the body exhibit different levels of attenuation of X-ray radiation. Therefore a specific type of tissue can be assigned a value which corresponds to the density of the tissue in Cartesian coordinates. So the density of the tissue can be described by a line integral equation. A 2D projection of the region of interest is acquired by measuring the X-ray on the other side of the patient body. Conventional radiography is a 2D projection of a 3D object, which cannot provide information on internal anatomical structure. To form a 3D representation, a series of 2D axial slices is required and this can be obtained by using a multi-slice CT scanner. Each 2D slice is a matrix of voxel elements containing the calculated tissue density at each point within the region of interest. After image acquisition, the filtered back projection algorithm is performed and 2D individual images are stacked to form a final 3D representation. Although images acquired by a CT scanner are along the axial direction, it is possible to obtain planar view at other orientations by employing mathematical shuffling.

CT can be used to examine the degree of stenosis and the location and size of plaque. However contrast agent is often needed to increase the attenuation of X-ray in order to visualize blood in the vessel. Computed tomography angiography (CTA) is a CT technique which is used to grade the severity of stenosis and visualize arterial and venous vessels throughout the body with the help of administration of iodine contrast. A high pooled sensitivity and specificity for detection in grading carotid stenosis by CTA is shown by Koelemay et al in 2004. In this meta-analysis study, sensitivity of 85% and specificity of 93% were achieved for 70%-99% stenosis; while for detection of a complete carotid occlusion, the sensitivity and specificity were nearly 100% (97% and 99% respectively) (Koelemay et al., 2004). It is also worth mentioning that CTA has the highest specificity (95%) among all non-invasive imaging modalities for plaques with

70% to 90% stenosis (Wardlaw et al., 2006). Even though a good correlation was also found between CTA and carotid plaque specimen histological analysis (Wintermark et al., 2008) and the first image-based CFD of anatomically realistic arterial geometries were derived from it (Steinman, 2002), CTA has rarely been used to provide anatomical data for CFD studies of the carotid artery, which is usually assessed by ultrasound. For this method involves an intravenous injection of an iodinated contrast agent, which enhances the contrast between lumen and the vessel wall. It is associated with patient discomfort and such risks as bleeding, arterial emboli, and development of an atherosclerosis fistula or cholesterol emboli, which limits its application in the patients (Lufft et al., 2002).

2.2.2. Magnetic resonance imaging

Similar to CT imaging, magnetic resonance imaging (MRI) generates 3D data set for the volume of interest. The working principles of MRI are different from those of CT. MRI utilizes radiofrequency (RF) waves and magnetic fields to obtain 3D data to reconstruct internal structures, based on the principle of Nuclear Magnetic Resonance (NMR). In the diagnosis of carotid artery stenosis MRI and contrast-enhanced MRA (CEMRA) are increasingly used to provide supplementary information for Doppler ultrasound. Resonance is the tendency of a system to oscillate with larger amplitude at some frequencies than others. In quantum mechanics and quantum field theory, resonances are also referred as unstable particles. In the case of MRI or NMR, the source is radiofrequency (RF) energy, and the object resonating is the nuclei of atoms. When induced by an external magnetic field, nuclei are promoted to a higher energy state via the absorption of RF energy. Once the RF is switched off, the higher energy state or excited state cannot be indefinitely maintained, releasing a characteristic RF energy when the promoted nuclei return to their lower state. This RF energy can be picked up. A map of distribution of hydrogen atoms can be created using spatial and temporal encoding techniques, yielding information about the material composition.

A nucleus' sensitivity to its MR signal largely depends on the gyromagnetic ratio γ which is defined as a nucleus' RF in one Tesla squared external field and is constant for every isotope. Sensitivity increases linearly with signal frequency. Therefore hydrogen has the largest MR signal sensitivity. When subjected to an external magnetic field B_0 ,

protons align with this field and simultaneously experience a torque due to B_0 . As a result, they spin around the B_0 axis at a rate given by the Larmor relationship.

$$f_{Larmor} = \gamma B_0 \quad (2-2)$$

An illustration of precession in an external magnetic field B_0 is shown in Figure 2-6. A population of protons in a given volume in the B_0 field will always be aligned in the low energy state, as opposed to the higher energy state.

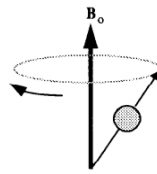


Figure 2- 6 Nuclei precession in external magnetic field. (Acharya et al., 1995)

This excess parallel state population is represented by the net magnetization vector, $\overline{M}$, which is ultimately responsible for the emitted MR signal, and increases proportionally to the external field strength B_0 . For MR image processing, pulse sequences are employed to extract different information about the tissue. $\overline{M}$ can be divided into two components, M_z (in the same direction with B_0) and M_{xy} (in the plane orthogonal to B_0). The MR receiver coils are oriented such that only the component M_{xy} induces a measurable signal. As shown in Figure 2-7, a second external magnetic field B_1 which is created by RF field is induced in the system. If the RF is oscillating at the Larmor frequency, $\overline{M}$ will redirect to become perpendicular to B_0 . This transition can be visualised using either a stationary or rotating frame .

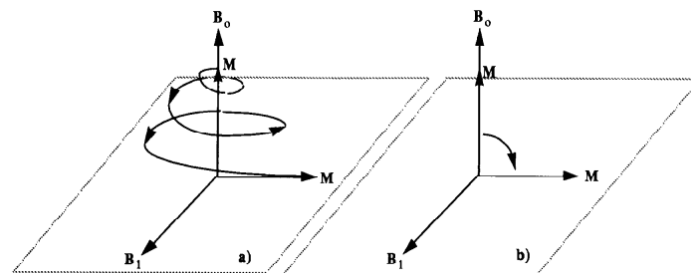


Figure 2- 7 Frames of reference in MR imaging: (a) stationary frame, (b) rotating frame, (Acharya et al., 1995)

Because hydrogen is present in nearly all human tissues, it can be assumed that MRI signal can be obtained from all the tissues by imaging the concentration of tissue hydrogen. The most important tissue-related factors that influence the emitted MR signal are the relaxation times. Relaxation is referred to as the process by which the spins respond to the loss energy effects by both their environment and external RF pulses. There are two types of relaxation, namely T1 and T2 (Acharya et al., 1995). MRI is non-invasive and can provide quantitative information about the arterial wall geometry, but it remains expensive and time consuming when compared with ultrasound and is often limited in availability and patient tolerability. The limitations of MRI include the inability to perform on patients with implantable pacemakers and defibrillators and overestimation of carotid stenosis due to movement artefacts (Bates et al., 2007).

A sample MR image acquired from a carotid artery plaque is shown in Figure 2-8, where yellow and red arrows point at the fibrous cap and lipid core in the plaque, respectively.

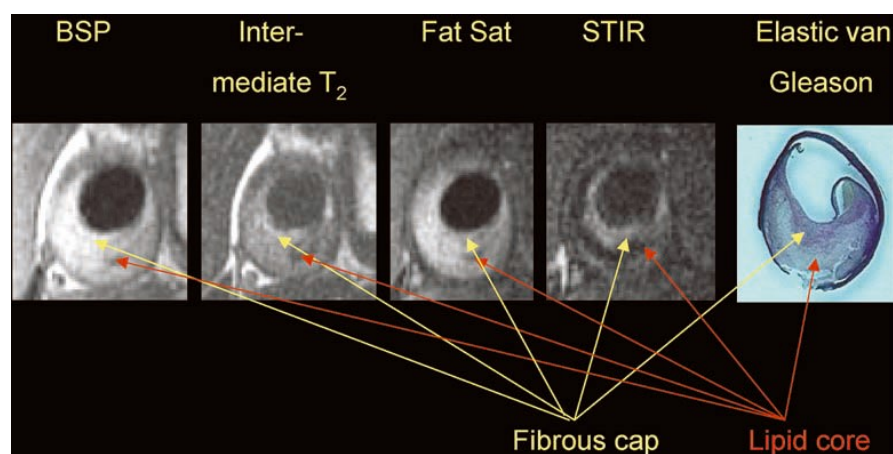


Figure 2- 8 High-resolution MRI of plaque using multispectral imaging to demonstrate fibrous cap (yellow arrows) and lipid core (red arrows) (Gillard, 2004)

2.2.3. Positron emission tomography

Although CT images can be used to assess the severity of arterial stenosis, they do not offer any information about the degree of plaque inflammation. Positron emission

tomography (PET) is a radionuclide imaging technique and relatively new in carotid artery research. Qualitative and quantitative information about atherosclerotic plaques can be provided by using radiolabeled ligands targeted at particular tissues. [^{18}F]-fluorodeoxyglucose (FDG) is a kind of glucose analogue which is highly sensitive to metabolically active processes and was originally developed to identify malignancy in neuroimaging (Figure 2-9). It has also been used for identification and quantification of carotid atherosclerotic plaque inflammation (Rudd et al., 2010). Because of a high correlation between FDG uptake and the degree of macrophage infiltration of carotid plaques, arterial FDG-PET has been suggested as a biomarker for assessment of the metabolic activity of atherosclerosis (Rudd et al., 2002). The limitation of PET is that its spatial resolution is very low, about 3 to 4 mm, requiring a combination of CT or MRI to guide localization of the FDG signal. More recently, a new hybrid PET/CT, which combines functional and structural whole body imaging modalities, has been developed (Kai, 2010).

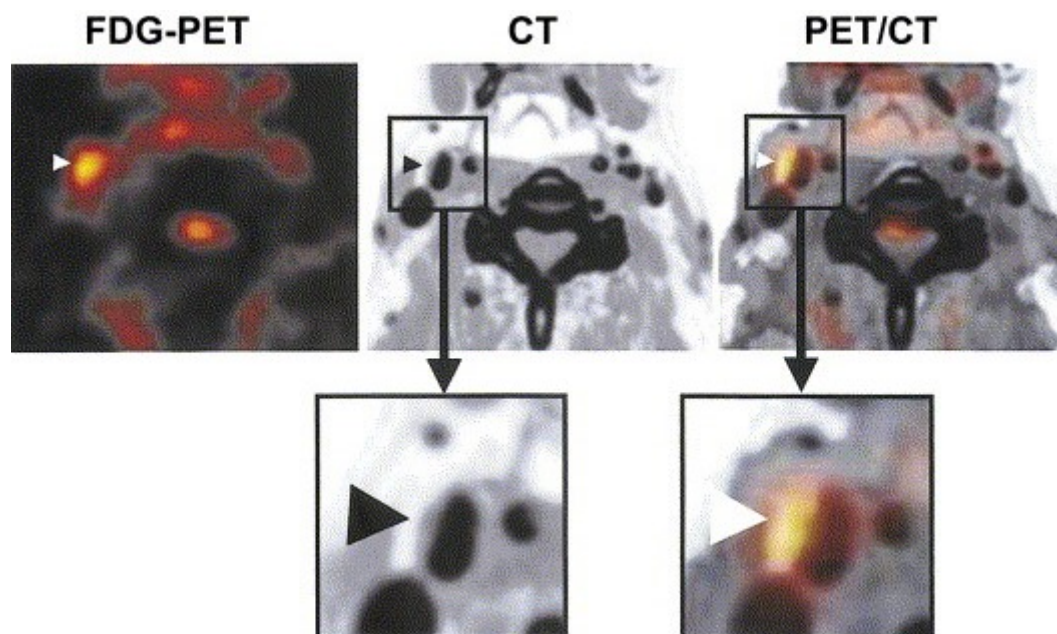


Figure 2- 9 ^{18}F FDG uptakes in the carotid arterial plaques (Tahara et al., 2006)

2.2.4. Ultrasound imaging

Although CT and MRI can provide 3D volumetric vascular information at multiple sections, they have their own limitations. Due to the lack of harmful radiation,

non-invasive nature, wide availability and low cost, ultrasound has been the most widely used tool to provide information for carotid artery diagnosis (Gillard, 2004). Regarding vascular ultrasound imaging, ultrasound is not only able to provide geometry but also flow information, such as velocity and volumetric flow rate, in the same section of the vessel. Ultrasound can also be used to examine the composition of atherosclerotic plaque, which is very important for diagnosis and clinical decision making. As mentioned previously, lipid rich ulcerated plaque with a thin fibrous cap is more prone to rupture and haemorrhage than calcified fibrous plaques. However, the disadvantage of ultrasound technique is scanning depth, as it is not able to penetrate bones, limiting its accessibility to superficial vessels, such as the carotid artery. Even for the carotid artery, ultrasound imaging is limited by the presence of jaw bone, meaning that only a short section of the carotid bifurcation can be captured. As a result, the overall vessel length covered by ultrasound imaging is usually much shorter than that by other imaging modalities (Allott et al., 1999).

The principle of ultrasound is based on the reflection and transmission of ultrahigh frequency sound waves. These waves are generated by a transducer and can be reflected or absorbed as they are transmitted through tissues. Depending on the composition of the tissue, high frequency sound waves, which are sent into the tissue, are attenuated and returned at separate intervals as an echo. The speed of sound varies as it travels through different materials. However the sonography assumes that the velocity of sound in soft tissues is constant at 1540 m/s. Based on this assumption, the depth of tissue boundary causing the echo can be determined from these intervals (Dhawan, 2003).

When ultrasound waves propagate through a tissue, they become weaker, which is known as attenuation. Human body is not an ideal media, which is viscous and always causes thermal consumption when ultrasound propagates in it. Apart from viscosity in the body, a part of the signal is reflected or scattered by the boundary of tissues with different densities. Acoustic scattering is another main reason for the removal of acoustic energy. The greater the difference between the acoustic impedance, the larger the echo is. If the acoustic impedance difference is so great that most of the acoustic energy is reflected, it becomes impossible to detect deeper. This is called acoustic shadowing.

The main component of an ultrasound scanner is its transducer (probe), which generates high frequency sound waves and evaluates the echo at the same time. Typically a sound wave is produced by a piezoelectric transducer or a capacitive micromachined transducer. The electrical pulses produced by the machine force the transducer ring at the desired frequency, which normally varies between 2 and 18 MHz. Because the velocity of sound in soft tissues is assumed as constant at 1540 m/s, an ultrasound wave with higher frequencies has a corresponding smaller wavelength, which can be used to view more detailed subjects. However attenuation of the sound wave is also increased at higher frequencies, so in order to achieve better penetration of deeper tissues, a lower frequency should be used.

Many modes of ultrasound can be used to form medical images, including A-mode, B-mode, C-mode, M-mode, Doppler mode, Pulse inversion mode and Harmonic mode. To collect topological information, B-mode and M-mode ultrasound are the main modes, while other ultrasound modes are based on them.

A-mode ultrasound

A-mode (amplitude mode) ultrasound is the most basic mode of ultrasound. It is a 1D technique which scans a line through the body and plots the information of depth on the screen.

B-mode ultrasound

B-mode (brightness mode) ultrasound scans the tissue by using a linear array of transducers at the same time. A plane through the body that can be viewed as a 2D image on the screen is scanned simultaneously by a linear array of transducers, so that B-mode ultrasound is also known as 2D ultrasound.

M-mode ultrasound

M-mode (motion mode) ultrasound is a combination of A-mode and B-mode ultrasound. It takes A-mode and B-mode images in quick succession. This is analogous to recording a video in ultrasound. The depth of organ boundaries to the probe can be measured, which allows for determination of the velocity of the specific organ structure.

Doppler ultrasound

Due to the Duplex effect, an ultrasonic wave is scattered by a moving target that has a component of velocity along the beam propagation direction. The shift in frequency of sound emitted or reflected from a moving object can be recorded and used for velocity estimation. It can be used to measure and visualise blood flow. Several studies have demonstrated that Doppler ultrasound also has a high accuracy in evaluating the degree of stenosis of the carotid artery (Jahromi et al., 2005).

A new generation of 3D ultrasound system is used in the present study. Its main features, functions and comparison with conventional ultrasound system are presented in the next chapter.

2.3. Finite element method for structural analysis

The finite element method (FEM) is a powerful technique developed for numerical solution of complex problems in structural mechanics. It uses variational methods to minimize the error function and produce a stable solution. Analogous to the idea that a large circle can be approximated by many short straight lines, FEM encompasses all the methods for connecting many simple element equations over many small subdomains, named finite elements, to approximate a more complex equation over a larger domain.

While the theory of FEM can be presented in different perspectives, its development for structural analysis follows a more traditional approach via the virtual work principle. The principle of virtual work, which is the form of the principle of least action applied to these systems, states that the path actually followed by the particle is the one for which the difference between the work along this path and other nearby paths is zero. The formal procedure for computing the difference of functions evaluated on nearby paths is a generalization of the derivative known from differential calculus, and is termed the calculus of variations. The more general approach is the virtual work principle as it is applicable to both linear and non-linear material behaviours. The principle of virtual displacements for the structural system expresses the mathematical identity of external and internal virtual work. The principle of virtual work for a

deformable body can be expressed as:

$$\text{Total external virtual work} = \int_V \delta \epsilon^{*T} \sigma dV \quad (2-3)$$

To derive the principle of virtual displacements in variational notations for support bodies, the virtual displacements and strains are specified as δu and $\delta \epsilon$. The virtual work equation then becomes the principle of virtual displacement:

$$\int_{S_t} \delta u^T T dS + \int_V \delta u^T f dV = \int_V \delta \epsilon^{*T} \sigma dV \quad (2-4)$$

where T is the external force, f is body force and σ is internal stress in the free body diagram of a deformable body which is composed of an infinite number of differential cubes. This relation is equivalent to the set of equilibrium equations written for a differential element in the deformable body as well as of the stress boundary condition on the part of the surface.

2.3.1. Basic concepts of structural analysis

Stress and Strain

The basic concepts of structural analysis provide the foundation for the rest of the chapter, including coordinate transformation and constitutive equations. Continuum mechanics is used to describe deformation and stress in an orthotropic material, where stress is defined as the average force per unit area of a surface within a deformable body on which internal forces act. It can be expressed by the Cauchy traction vector T which is defined as the traction force F between adjacent parts of the material across an imaginary separating surface A . The stress vector T can be expressed as:

$$T = \frac{F}{A} \quad (2-5)$$

According to Cauchy, the stress tensor can be represented in any chosen Cartesian coordinate system. For a coordinate system in x , y , and z direction, the matrix of nine components of stress can be written as:

$$\sigma = \begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix} \quad (2-6)$$

The stress vector T acts in the same direction as the force vector F . Because the stress vector T may be regarded as the sum of two components: the normal stress which is perpendicular to the surface and the shear stress which is parallel to the surface. If n and t are the unit vectors in the normal and tangential direction of the area, respectively, the stress vector can be expressed as:

$$T = \sigma_n n + \tau t \quad (2-7)$$

where σ_n is the result of normal stress while τ is the result of shear stress. Usually, mechanical bodies experience more than one types of stress at the same time. In this case, it is called combined stress which cannot be described using a single vector, even if the material is stressed in the same way throughout the whole volume. Based on the principle of conservation of angular momentum which dictates that the stress tensor is symmetric, the stress tensor may be written by six independent parameters, rather than nine.

$$\sigma = \begin{bmatrix} \sigma_x & \tau_{xy} & \tau_{xz} \\ \tau_{xy} & \sigma_y & \tau_{yz} \\ \tau_{xz} & \tau_{yz} & \sigma_z \end{bmatrix} \quad (2-8)$$

where σ_x , σ_y , σ_z are known as orthogonal normal stresses, and τ_{xy} , τ_{xz} , τ_{yz} are the orthogonal shear stresses; σ is known as the Cauchy stress tensor. Note that the index-switched shear stress does not change its value in magnitude. However these shear stresses point in different directions, as shown in Figure 2-10.

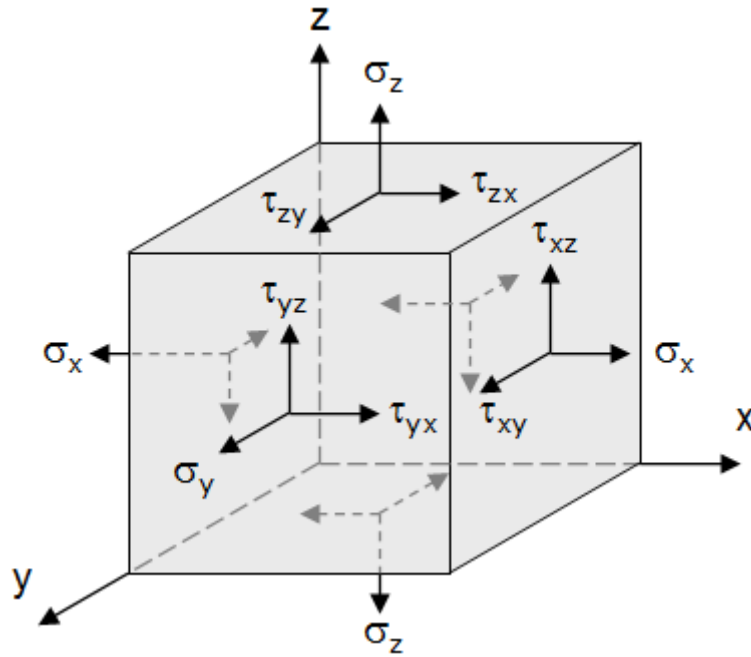


Figure 2- 10 Sign conventions and notations for stresses on a cube

For certain structural configurations, such as a thin plate, only stresses in the x and y directions would be considered. So all the stress components with a z subscript may be neglected, and considered as zero. The stress tensor becomes

$$\sigma = \begin{bmatrix} \sigma_x & \tau_{xy} & 0 \\ \tau_{yx} & \sigma_y & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad (2-9)$$

This two-dimensional simplification is called a plane stress state. Owing to the symmetry of the stress matrix, the plane stress can be characterized by three independent stress components.

A strain is a normalized measure of deformation representing the displacement between particles in the body relative to a reference length. A general deformation is a measurement of changes in the shape or size of the body. A strain is in general a tensor quantity. As with stresses, it can also be decomposed into normal and shear components. Within a deforming body, the amount of stretch or compression along the material line elements is the normal strain, and the amount of distortion associated with the sliding of plane layer over each other is called the shear strain. If the normal strain increases the length of material line, it is called tensile strain; otherwise, if the length of material line

is reduced or compressed, this normal strain is called compressive strain.

According to different deformation theories, the strain can be defined in different ways. The Cauchy strain or engineering strain is expressed as the ratio of total deformation to the initial dimension of the material body in which the forces are being applied. If the original length of the line element is L , and the change in length is ΔL , the Cauchy strain ε can be expressed as

$$\varepsilon = \frac{\Delta L}{L} = \frac{l-L}{L} \quad (2-10)$$

where l is the final length of the element and L is the original length. The tensile strain is positive, while the compressive strain is negative. Considering an incremental strain, true strain or logarithmic strain e is obtained by integrating the incremental strain δe :

$$\int \delta e = \int_L^l \frac{\delta l}{l} \quad (2-11)$$

$$e = \ln\left(\frac{l}{L}\right) = \ln(\lambda) = \ln(1 + \varepsilon) \quad (2-12)$$

Here stretch ratio λ is a measurement of the extensional strain of a differential line element. It is defined as the ratio between the final length and the initial length.

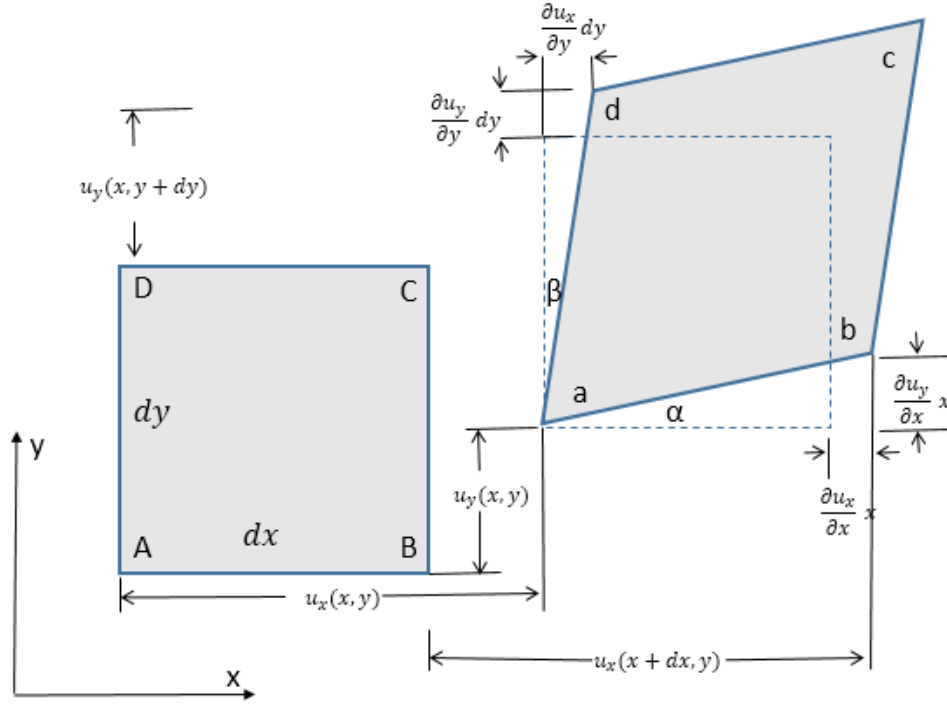


Figure 2- 11 Geometric deformation of an infinitesimal material element

Considering a two-dimensional infinitesimal rectangular material element with dimensions $dx \times dy$ deforming into a rhombus shape, as shown in Figure 2-11, the length of the edges can be expressed as:

$$AB = dx \quad (2-13)$$

$$ab = \sqrt{\left(dx + \frac{\partial u_x}{\partial x} dx\right)^2 + \left(\frac{\partial u_y}{\partial x} dx\right)^2} = dx \sqrt{1 + 2 \frac{\partial u_x}{\partial x} + \left(\frac{\partial u_x}{\partial x}\right)^2 + \left(\frac{\partial u_y}{\partial x}\right)^2} \quad (2-14)$$

For infinitesimal displacement the squares of the derivatives with respect to y is very small and can be neglected:

$$\text{length}(ab) \approx dx + \frac{\partial u_x}{\partial x} dx \quad (2-15)$$

The engineering strains in the x and y direction of the rectangular element are defined by:

$$\varepsilon_x = \frac{ab - AB}{AB} = \frac{\partial u_x}{\partial x} \quad (2-16)$$

$$\varepsilon_y = \frac{ac-AC}{AC} = \frac{\partial u_y}{\partial y} \quad (2-17)$$

The engineering shear strain is defined as the change in angle between the lines of initial shape. As shown in Figure 2-11, the engineering shear strain (γ_{xy}) between the lines $\overline{AC}$ and $\overline{AB}$ can be expressed as

$$\gamma_{xy} = \alpha + \beta \quad (2-18)$$

For small rotations, $\alpha \approx \tan\alpha$ and $\beta \approx \tan\beta$, therefore,

$$\gamma_{xy} = \tan\alpha + \tan\beta = \frac{\frac{\partial u_y}{\partial x}}{1 + \frac{\partial u_x}{\partial x}} + \frac{\frac{\partial u_x}{\partial y}}{1 + \frac{\partial u_y}{\partial y}} \quad (2-19)$$

And again for small displacement,

$$\frac{\partial u_x}{\partial x} \ll 1 \quad (2-20)$$

$$\frac{\partial u_y}{\partial y} \ll 1 \quad (2-21)$$

Thus, we have

$$\gamma_{xy} = \tan\alpha + \tan\beta = \frac{\frac{\partial u_y}{\partial x}}{1 + \frac{\partial u_x}{\partial x}} + \frac{\frac{\partial u_x}{\partial y}}{1 + \frac{\partial u_y}{\partial y}} = \frac{\partial u_y}{\partial x} + \frac{\partial u_x}{\partial y} \quad (2-22)$$

Stress-Strain Relationship

The material relationship discussed in this section is limited to linear materials. The stress is related to the strain by:

$$\{\sigma\} = [D]\{\varepsilon\} \quad (2-23)$$

where $\{\sigma\}$ is the stress vector and $\{\sigma\} = [\sigma_x \ \sigma_y \ \sigma_z \ \tau_{xy} \ \tau_{yz} \ \tau_{xz}]^T$, $[D]$ is stiffness

matrix, and $\{\varepsilon\}$ is the strain vector, which is defined as $[\varepsilon_x \ \varepsilon_y \ \varepsilon_z \ \gamma_{xy} \ \gamma_{yz} \ \gamma_{xz}]^T$.

Equation (2-24) may also be inverted to

$$\{\varepsilon\} = [D]^{-1}\{\sigma\} \quad (2-24)$$

where the flexibility or compliance matrix, $[D]^{-1}$ can be expressed as:

$$[D]^{-1} = \begin{bmatrix} 1/E_x & -v_{xy}/E_x & -v_{xz}/E_x & 0 & 0 & 0 \\ -v_{yx}/E_y & 1/E_y & -v_{yz}/E_y & 0 & 0 & 0 \\ -v_{zx}/E_z & -v_{zy}/E_z & 1/E_z & 0 & 0 & 0 \\ 0 & 0 & 0 & 1/G_{xy} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1/G_{yz} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1/G_{xz} \end{bmatrix} \quad (2-25)$$

where typical terms of E_x is Young's modulus in the x direction, v_{xy} is major Poisson's ratio, v_{yx} is minor Poisson's ratio, and G_{xy} is shear modulus in xy plane. Also, the $[D]^{-1}$ matrix is presumed to be symmetric, so that:

$$\frac{v_{xy}}{E_x} = \frac{v_{yx}}{E_y} \quad (2-26)$$

$$\frac{v_{xz}}{E_x} = \frac{v_{zx}}{E_z} \quad (2-27)$$

$$\frac{v_{zy}}{E_z} = \frac{v_{yz}}{E_y} \quad (2-28)$$

The shear moduli can be computed as:

$$G_{xy} = \frac{E_x}{2(1+v_{xy})} \quad (2-29)$$

$$G_{yz} = \frac{E_y}{2(1+v_{yz})} \quad (2-30)$$

$$G_{xz} = \frac{E_z}{2(1+v_{xz})} \quad (2-31)$$

For isotropic materials ($E_x=E_y=E_z$ and $v_{xy}=v_{yz}=v_{xz}$), a material constitutive relation can be completely defined by only two constants among shear modulus G , Young's

modulus K and Poisson's ratio ν . If the shear moduli G_{xy} , G_{yz} , and G_{xz} are not specified, they can be computed as $G_{xy} = G_{yz} = G_{xz} = \frac{E_x}{2(1+\nu_{xy})}$.

This brief description of structural mechanics fundamentals provides the essential information of the underlying theory. More details of the continuum mechanics theory relevant to the FEA performed in this study can be found in ANSYS theory reference (ANSYS, 2012).

2.3.2. Mechanical properties of the carotid artery

Researchers have long sought to understand the mechanical behaviour of carotid arteries. Owing to the importance of its location and its involvement in arterial diseases, it is necessary to determine the mechanical properties of carotid arteries and how they may be affected by ageing and disease.

Many studies have focused on quantifying the mechanical property of arteries, which is associated with its complex multi-layered structure. As described, an artery is composed of three layers with varying proportions of endothelial cells, smooth muscle cells, collagen and elastin. Although these components are not distributed uniformly in an artery, arterial wall is generally assumed as a homogenous, isotropic, single-layered structure, because the media accounts for approximately 90% of the vessel wall thickness in elastic arteries and is responsible for most of its mechanical strength (Holzapfel et al., 2000). Most studies of the carotid artery employ a single-layer model assuming homogeneity and isotropy throughout the vessel wall. More detailed layer-specific models have also been developed to investigate the effect of different layers within the carotid artery (Holzapfel et al., 2002).

Heterogeneity

Arteries are histologically heterogeneous, due to their multi-layered structure and varying volume fractions of individual constituents within each layer. Histological studies of arterial walls show clearly that they are not homogeneous. Since most of the *ex vivo* mechanical tests were performed on a whole vessel, it would be reasonable to treat the

arterial wall as a homogenous material (Patel et al., 1969). This assumption was supported by Dobrin, who demonstrated the almost identical extensibility through the thickness of the media (Dobrin, 1999). In their experiment, local deformations of four elastic lamellae were measured at four equidistant locations across the media. Under pressure loads between 0 and 200 mmHg, the lamellae would undergo varying degrees of deformation. Because of incompressibility, the innermost layer of the artery specimen must undergo larger deformation than the outer layer, which is manifested through thinning of the arterial wall. Taking incompressibility into account, each experiment was performed twice, in both normal cylindrical configuration and an inverted cylinder with inside-out (Dobrin, 1999). Averaged deformation of individual lamellae obtained in both normal and inverted vessel segments were obtained and their results showed that the distensibility of the elastic lamellae across the thickness of the media was uniform, demonstrating that the elastic lamellae behave uniformly in both circumferential and longitudinal directions at different locations across the wall thickness. Although arteries are histological heterogeneous, these experimental results suggested that arterial media act mechanically as a homogenous material. Therefore, from a macroscopic perspective, this assumption is reasonable and justifiable.

Anisotropy

In material science, anisotropy characterizes the dependence of mechanical response of an arbitrary point on the direction of the principle strain at that point. Most materials exhibit anisotropic behaviour. Even though arteries are treated as an isotropic material for simplicity in many numerical studies (Tang et al., 2004a, Lee et al., 2004), the mechanical response of arteries is anisotropic due to its texture patterns (Patel and Fry, 1969). In the experiments carried out by Patel and Fry, specimens of the common carotid arteries were isolated, hung vertically, and pressurized under physiological ranges of loading, as shown in Figure 2-12. The shear strains and elongating strains associated with different levels of pressure were measured, and their results showed that the shear strains were much smaller than the corresponding elongating strains, suggesting that the vessel can be treated as a cylindrically orthotropic tube.

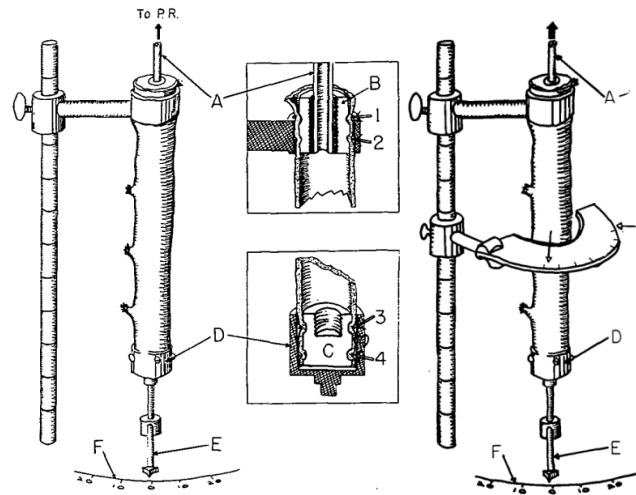


Figure 2- 12 Diagrams of experimental setup of the pressurized artery (left) and the experimental setup for determination of the shear strain (right) (Holzapfel et al., 2000)

The tunica media of an elastic artery consists of a number of fibre-reinforced layers which are separated by a network of elastic and collagen fibrils and elastic lamina. The helical pitch of the fibrils which are almost circumferentially oriented, gives the media resilience, high strength and the ability to resist loads in both longitudinal and circumferential directions (Holzapfel et al., 2000). When the vascular specimen was stretched circumferentially and longitudinally at the same strain, anisotropy was observed and the stresses obtained were different (Holzapfel et al., 2000).

Incompressibility

If there is no or only a slight change in volume during the deformation of a material, the material is regarded as ‘incompressible’. Artery has been treated as an incompressible material in almost all finite element simulations (Holzapfel et al., 2000). The validity of this assumption was tested, and results from an *in vivo* study showed that change in arterial wall volume was less than 0.165% when it was inflated by a pressure as large as 181 mmHg (Carew et al., 1968). Later, Chuong and Fung examined the compressive properties of arterial wall by applying uniaxial compressive force directly on rabbit thoracic aorta, and found that the volumetric strain was between 0.5% and 1.26% by radial compressive stress of 10 kPa. If the applied compressive stress was higher than 30 kPa, the percentage of fluid extrusion per unit compression pressure decreased (Chuong and Fung, 1984). These experimental results suggest that the arterial wall is slightly compressible, and for most practical purposes arteries may be considered incompressible.

Residual stress

When modelling stress and strain in arteries, another complexity is the presence of residual stress. Residual stress is the stress that exists when externally applied loads are removed. It was first alluded to by Bergel (Bergel, 1960), which drew considerable research effort. The presence of residual stress in arteries has been proved and generally accepted since then (Nichols et al., 2011, Holzapfel and Ogden, 2010).

Residual stresses can be measured and characterized by the opening angle of a sector-like cross-section which arises when an unloaded ring segment is radially cut (Chuong and Fung, 1986), as shown in Figure 2-13 (Rachev and Greenwald, 2003). Based on their experiments on the rabbit thoracic aorta, Chuong and Fung showed that the ratio of maximum circumferential stress to its mean value was about 1.4 when residual stress was taken into account, whereas the ratio rose to 6.5 in the absence of residual stress. The residual stress in the arteries reduced the stress gradient across the wall thickness. They also suggested that a single radial cut in an arterial cross-section would be sufficient to remove all externally acting loads, and to yield the zero-stress state. The opening angle α is frequently used as a measure for the quantification of residual circumferential deformation of a vessel (Chuong and Fung, 1986). It varies along the artery tree. For the human carotid artery, it was reported to be ranging from 5° to 10° . By correlating stresses with changes in residual strain, Fung found a fundamental biological law relating the rate of growth or resorption of tissue with the stress in the tissue, indicating that residual stresses are related to vessel wall remodelling (Fung, 1993). It provides a biomechanical foundation for tissue engineering that when stress changes the blood vessel remodels itself (Fung, 1991). Li and Hayashi also employed edge angle γ as an alternative measure for this purpose (Li and Hayashi, 1996). However, residual stresses of arteries cannot be measured *in vivo*, thus they are generally neglected in computational modelling of realistic arteries.

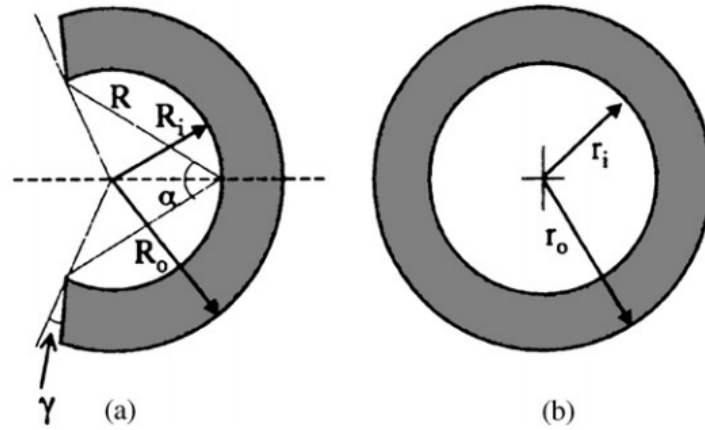


Figure 2- 13 Diagrams for configuration of the residual stress of artery (Rachev and Greenwald, 2003).

Strain rate effects

Strain rate is used to measure the rate of change in strain of a material with respect to time during an elongation or compression test. The carotid arteries from seven ferrets were stretched longitudinally *ex vivo* at either a low strain rate (0.2-2 Hz) or a high strain rate (200 Hz). The specimens were tested in physiological saline at 37 °C (Lee and Haut, 1992, Park and Ateshian, 2006). An ultimate stretch ratio and load were found, supporting their previous finding of insensitivity of tensile failure properties of human cerebral bridging veins (Lee and Haut, 1989). It is generally accepted that biological soft tissues should be tested in biological buffer media that mimic the *in vivo* environment as closely as possible. It has been demonstrated by Yang et al. that although strain is a major factor influencing stress relaxation of arterial wall, stress is independent of strain rate at low loading rate (1 Hz in their study) (Yang et al., 2011). Again, because of the lack of experimental data on human specimen, most studies of the human carotid artery assume its stress to be independent of strain rate.

2.3.3. Constitutive models of arteries

When choosing a constitutive equation for computational modelling of arterial vessels, all the properties described above should be considered. Several constitutive models have been developed for the mechanical properties of arteries. Before deciding on the form of constitutive equation to be employed, an important initial decision is whether

the material is considered as homogeneous or heterogeneous. The heterogeneity of arterial tissue has been experimentally studied, where a homogenous assumption is generally acceptable (Dobrin, 1999). The homogeneous approach assumes the length scale of microstructure being much smaller than that of the arterial tissue, so that mechanical responses on the micro-scale can be represented by volume-averaged properties on the macro-scale. After the vascular tissue is treated as a mechanically homogenous material, the development of constitutive model can rely upon the fundamentals of continuum mechanics.

Directly deriving a constitutive model based on microstructure that contributes to the mechanical behaviour is very difficult, due to the need for identifying all the distributions, orientations and interactions of the constituents of vessel wall. However several studies of vascular tissue are based on this approach (Wuyts et al., 1995, Holzapfel et al., 2002, Sokolis et al., 2002, Gasser et al., 2006). In practice, the most common method to obtain a constitutive model for arterial tissue is from experiments such as mechanical tests. Generally arteries have been treated as an elastic, hyperelastic or viscoelastic material in finite element structural modelling.

2.3.3.1. Elastic constitutive models

If a material is perfectly elastic, its mechanical behaviour can be described by a strain energy function which could be justified on the basis of thermodynamics. Biological soft tissues such as arteries are not perfectly elastic. Perfect elasticity is an approximation of the real world and few materials remain purely elastic even under very small deformation. Under physiological loading, arteries undergo large deformation in both longitudinal and circumferential directions, with strains up to 50% and 20%-40%, respectively. This is normally caused by the axial force from surrounding tissues and arterial pressure. However, the deformation caused by pulse pressure (the difference between systolic and diastolic pressure) is not that large, with a strain less than 10% (Hayashi and Imai, 1997). Most biomechanical studies of the carotid artery have assumed that the vessel wall is a non-linear, incompressible and hyperelastic material. Based on experimental stress/strain data, hyperelastic constitutive models have been derived and adopted by many researchers (Gasser et al.,

2006, Tang et al., 2009, Tang et al., 2008, Tang et al., 2004b).

There are two very important studies based on the strain energy density function. One is the exponential model proposed by Chuong and Fung (Chuong and Fung, 1983). The strain energy function is described in the form:

$$\rho_0 W = \frac{c}{2} e^Q \quad (2-32)$$

where

$$Q = b_1 E_\theta^2 + b_2 E_z^2 + b_3 E_r^2 + 2b_4 E_\theta E_z + 2b_5 E_z E_r + 2b_6 E_r E_\theta \quad (2-33)$$

W represents the strain energy per unit mass, ρ_0 is the mass density of the vessel wall so that the left hand side of Equation (2-32) is the strain energy per unit volume, b_i ($i = 1 \dots 6$) are material constants. E_θ , E_r and E_z are Green's strain components in the circumferential, radial and longitudinal directions, respectively. The other form is a logarithmic type of strain energy density function which is used to describe the arterial wall properties under physiological loading conditions (Takamizawa and Hayashi, 1987). It was proposed by Takamizawa and Hayashi, and expressed as:

$$W = -C \ln(1 - \psi) \quad (2-34)$$

Delfino et al. characterized the material property of carotid artery by a strain energy function W (Delfino et al., 1997) as shown by Equation (2-35). A nonlinear modified Mooney-Rivlin model was used by Tang et al. to describe the material properties of vessel wall as well as the plaque components for steady flow in both thin-walled and thick-walled distensible vessels (Tang et al., 2008, Tang et al., 2005).

$$W = \frac{a}{b} [\exp(\frac{b}{2} (I_1 - 3))] \quad (2-35)$$

or

$$W = c_1(I_1 - 3) + c_2(I_2 - 3) + D_1\{\exp[D_2(I_1 - 3)] - 1\} \quad (2-36)$$

where W is the strain energy function, I_1 and I_2 are the first and second invariants of the strain tensor and a , b , c_i and D_i are constants chosen to match experimental measurements. D is the material incompressible parameter. J stands for the ratio of the

deformed volume over the un-deformed volume of material. This model was extended to a five-parameter, second order polynomial function by matching the corresponding values in the literature using curve fitting method (Gao and Long, 2008).

$$W = c_{10}(I_1 - 3) + c_{01}(I_2 - 3) + c_{20}(I_1 - 3)^2 + c_{11}(I_1 - 3)(I_2 - 3) + c_{02}(I_2 - 3)^2 + \frac{1}{d}(J - 1)^2 \quad (2-37)$$

2.3.4. Finite element structural analysis of carotid arteries with elastic material properties

There is a large body of literature on computational studies of arterial wall mechanics where the walls were treated as an elastic material, using either 2D or 3D models (Loree et al., 1992, Lee et al., 2004, Zhao et al., 2002). Loree and his colleges investigated the risk factors other than the stenosis severity that predispose atherosclerotic plaque to rupture by using idealized 2D cross sections of diseased vessels based on intravascular ultrasound images. They found that the maximum circumferential stress increased as the lipid pool expanded. With a constant degree of stenosis of 70%, the peak stress in the plaque increased by four-fold when the size of lipid pool increased from 38% to 54%. In the absence of lipid pool, increasing stenosis severity actually decreased peak stress in the plaque (Loree et al., 1992).

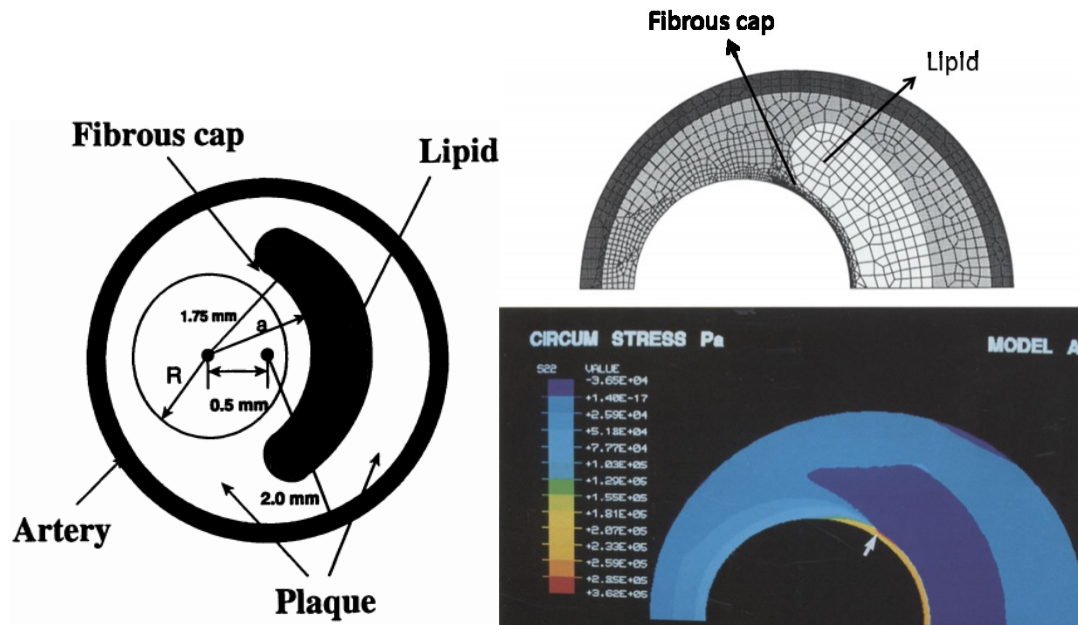


Figure 2- 14 Diagram showing the geometry with fibrous cap and lipid pool (upper), and contour map of circumferential stress (Loree et al., 1992).

Salzar et al. assumed a uniform and constant pressure load throughout the carotid artery. Later, Zhao et al. used patient-specific Young's modulus of the carotid arteries in their FSI model (Zhao et al., 2002). Although the elastic modulus was lower than that reported in the study by Salzar et al. (Salzar et al., 1995), the maximum principal stresses in both studies were located at the bifurcation point of the carotid artery. To obtain arterial geometry *in vivo* for patient-specific computational modelling, Lee et al. acquired ultrasound images of the common carotid artery in a patient with an early atherosclerotic plaque forming a mild asymmetrical stenosis. They compared the predictions obtained with different wall compliance to investigate the effects of wall distensibility (Lee et al., 2004).

2.3.5. Linear viscoelastic theory

Viscoelastic materials exhibit both elastic and viscous characteristics when undergoing deformation. Most biomaterials exhibit linear or nonlinear viscoelastic behaviour under small stress levels. Since linear viscoelastic theory is relevant to the present study, this will be described in detail below.

The mechanical responses of viscoelastic materials to an applied load are described for a one-dimension problem first, which will then be expanded into a 3D formulation. As the viscoelastic response is time-dependent, the linear elastic constitutive relation of stress and strain can be described by Hooke's law:

$$\sigma_{(t)} = E_{(t)}\varepsilon_{(t)} \quad (2-38)$$

where $\sigma_{(t)}$, $E_{(t)}$ and $\varepsilon_{(t)}$ are the stress, Young's modulus and strain respectively. Materials can deviate from Hooke's law in various ways. For a viscoelastic material, which exhibits viscous-like as well as elastic characteristics, the modulus is known to be a function of time at a given temperature.

The fundamental assumption of linear viscoelastic theory is that the response of a material at a given time is equal to the sum of all the responses to excitations imposed at previous times. The linearity assumption is expressed mathematically by the following equation:

$$\sigma(a\varepsilon_1 + b\varepsilon_2) = a\sigma\varepsilon_1 + b\sigma\varepsilon_2 \quad (2-39)$$

i.e. the stress response (σ) of a material due to the sum of a given number of applied strains (ε) is the superposition of the individual stress responses due to each individual applied strain. Here ε_1 and ε_2 are two strain histories, and a and b are multiplicative scalars that can be factored as shown. The stress applied to the material at time τ_1 and τ_2 can be expressed as.

$$\sigma_{1(t)} = E(t - \tau_1)\Delta\varepsilon_1 \quad (2-40)$$

$$\sigma_{2(t)} = E(t - \tau_2)\Delta\varepsilon_2 \quad (2-41)$$

The total stress of individual stresses can be described as

$$\sigma_{(t)} = \sigma_{1(t)} + \sigma_{2(t)} \quad (2-42)$$

If the stress responds to a finite number of applied strains, then it can be given in series form by:

$$\sigma_{(t)} = \sum_{i=1}^n E(t - \tau_i)\Delta\varepsilon_i \quad (2-43)$$

For an infinite number of applied strains, the stress applied can be given by integrating all the stress at each infinitesimal time, $d\tau$.

$$\sigma_{(t)} = \int_{-\infty}^t E(t - \tau_i) \frac{d\varepsilon}{d\tau} d\tau \quad (2-44)$$

This is the fundamental mathematical statement of linear viscoelastic model, which is also known as Boltzmann Superposition Integral. It is based on the mathematical properties governing all linear systems. Similarly by integrating the strain increments from time $-\infty$ to time t over all the increment $d\tau$, the strain response can be written as.

$$\varepsilon_{(t)} = \int_{-\infty}^t D(t - \tau_i) \frac{d\sigma}{d\tau} d\tau \quad (2-45)$$

Time-dependence of mechanical properties: Creep and stress relaxation

Relaxation and creep behaviour are two fundamental attributes of viscoelastic materials. The generalized relaxation and creep responses of a viscoelastic material are shown in Figure 2-15. In relaxation, a constant strain is applied to the specimen in a quasi-static manner at time 0. The relaxation modulus function is always a decreasing function constrained on the y-axis by instantaneous modulus, E_i , and the equilibrium modulus, E_e . The compliance function is approximately the glassy compliance, D_g , and the rubbery compliance, D_r , respectively. These parameters are directly derived from the generalized models for linear viscoelastic behaviour and it is hypothesized that with certain specified test parameters, including loading rate, loading amplitude and loading

duration, these parameters may be determined experimentally.

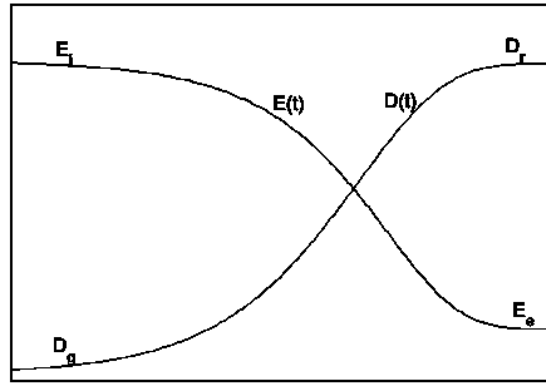


Figure 2- 15 Generalized relaxation and creep responses of a viscoelastic material

For the relaxation behaviour, a constant strain of ε_0 is applied with a unit step function $u(t)$.

$$\varepsilon(t) = \varepsilon_0 u(t) \quad (2-46)$$

where $u(t)$ equals to 1 when t is positive, otherwise it is 0. After applying Laplace transform, it yields

$$\bar{\varepsilon} = \frac{\varepsilon_0}{s} \quad (2-47)$$

Then the Laplace stress can be written as,

$$\bar{\sigma} = E^* \bar{\varepsilon} = E^* \frac{\varepsilon_0}{s} \quad (2-48)$$

and the Laplacian relaxation modulus can be written as,

$$\bar{E}(s) = \frac{\bar{\sigma}}{\varepsilon_0} = \frac{E^*(s)}{s} \quad (2-49)$$

From which E^* is given by:

$$E^*(s) = s \bar{E}(s) \quad (2-50)$$

The Laplacian stress is rewritten as,

$$\bar{\sigma} = E^*(s)\bar{\varepsilon} = s\bar{E}(s)\bar{\varepsilon} = \bar{\dot{E}}\bar{\varepsilon} = \bar{E}\dot{\bar{\varepsilon}} \quad (2-51)$$

The integral of the stress in the time domain is:

$$\begin{aligned} \bar{\sigma}(t) &= \int_0^t E(t-\tau)\dot{\varepsilon}(\tau)d\tau \\ &= \int_0^t \bar{E}(\tau)\dot{\varepsilon}(t-\tau)d\tau \\ &= \int_0^t \dot{E}(t-\tau)\varepsilon(\tau)d\tau \\ &= \int_0^t \dot{E}(\tau)\varepsilon(t-\tau)d\tau \end{aligned} \quad (2-52)$$

For the creep behaviour, a constant stress of σ_0 is applied with a unit step function $u(t)$.

$$\sigma(t) = \sigma_0 u(t) \quad (2-53)$$

Applying Laplace transform yields an expression for Laplacian stress.

$$\bar{\sigma} = \frac{\sigma_0}{s} \quad (2-54)$$

Using Laplacian compliance, D^* , the Laplacian strain can be written as.

$$\bar{\varepsilon} = D^*\bar{\sigma} = \frac{D^*\sigma_0}{s} \quad (2-55)$$

and the Laplacian compliance and Laplacian strain are

$$\bar{D}(s) = \frac{D^*(s)}{s} \quad (2-56)$$

$$\bar{\varepsilon} = D^*\bar{\sigma} = s\bar{D}(s)\bar{\sigma} = \bar{\dot{D}}\bar{\sigma} = \bar{D}\dot{\bar{\sigma}} \quad (2-57)$$

Integration in the time domain for strain yields,

$$\begin{aligned}
\varepsilon(t) &= \int_0^t D(t-\tau) \dot{\sigma}(\tau) d\tau \\
&= \int_0^t \bar{D}(\tau) \dot{\sigma}(t-\tau) d\tau \\
&= \int_0^t \dot{D}(t-\tau) \sigma(\tau) d\tau \\
&= \int_0^t \dot{D}(\tau) \sigma(t-\tau) d\tau
\end{aligned} \tag{2-58}$$

Based on the equations described above, the relationship between relaxation modulus and creep compliance can be obtained.

$$\bar{\sigma} = s\bar{E}\bar{\varepsilon} \text{ and } \bar{\varepsilon} = s\bar{D}\bar{\sigma} \tag{2-59}$$

By applying the convolution integral theorem and converting to the transient domain, the two most common forms of relaxation modulus and creep compliance convolution integrals are obtained.

$$\int_0^t E(t-\tau)D(\tau)d\tau = t \tag{2-60}$$

$$\int_0^t E(\tau)D(t-\tau)d\tau = t \tag{2-61}$$

The Boltzmann superposition principle states that creep is a function of the entire past loading history, and each loading step makes an independent contribution to the final deformation. Based on this, the total deformation can be obtained by the addition of all the contributions.

2.3.6. Viscoelastic models

Viscoelastic behaviour can be represented by mechanical models consisting of varying combinations of ideal elastic springs and linear viscosity dashpots. Ideal elastic (spring) deformation is proportional to the applied stress, and the deformation is instantaneous

and completely recoverable. Conversely, viscous (dashpot) deformation occurs slowly depending on the viscosity and is not recoverable; the extension rate is proportional to the applied stress. The Maxwell model, Kelvin-Voigt model and their general forms are basic viscoelastic models. These mechanical models are accurately represented mathematically by a finite series of exponential decay elements. It can also be shown that this series representation comes directly from fundamental linear viscoelastic theory. The Maxwell model is a spring in series with a dashpot, whilst the Kelvin model is a spring and dashpot in parallel, as shown in Figure 2-16.

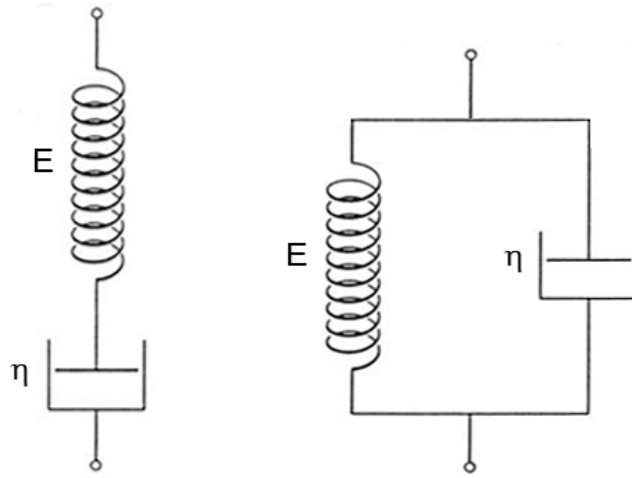


Figure 2- 16 Schematic representation of the Maxwell model (left) and Kelvin-Voigt model

The Maxwell model can be expressed either in the differential form (Equation 2-62) or the time integral form (Equation 2-63).

$$\dot{\epsilon}(t) = \dot{\epsilon}_d(t) + \dot{\epsilon}_s(t) = \frac{\dot{\sigma}(t)}{E} + \frac{\sigma(t)}{\eta} \quad (2-62)$$

$$\epsilon(t) = \frac{\sigma(t)}{E} + \frac{1}{\eta} \int_0^t \sigma(\tau) d\tau \quad (2-63)$$

and the Kelvin-Voigt model can be written as.

$$\sigma = E\epsilon + \eta\dot{\epsilon} \quad (2-64)$$

The basic models of Maxwell and Kelvin-Voigt can be used to build more complex models. The generalized Maxwell model and generalized Kelvin-Voigt model are the two more complex models built from the Maxwell and Kelvin-Voigt models in blocks.

The generalized Maxwell model consists of a spring in parallel with n Maxwell units, whereas the generalized Kelvin-Voigt model consists of a spring in series of n Kelvin-Voigt units. Since in each branch of the generalized Maxwell model the strain applied is equal, it is primarily used in the modelling of relaxation behaviour. In the generalized Kelvin-Voigt model, the stress is equivalent in each branch, allowing for the total strain to be solved by simply summing all the strains, so the generalized Kelvin-Voigt model is used primarily in the modelling of creep behaviour.

The relaxation modulus derived from generalized Maxwell model is given by:

$$E(t) = E_e + \sum_{i=1}^n E_i e^{-\left(\frac{t}{\rho_i}\right)} \quad (2-65)$$

where E_e (the equilibrium modulus), E_i (relaxation strengths), and ρ_i (relaxation time) are all positive constants. The series expression of E_i and ρ_i are often referred to as Prony series. The generalized Kelvin-Voigt model can characterize the creep compliance more easily as shown (Park and Schapery, 1999)

$$D(t) = D_g + 1/\eta_0 + \sum_{j=1}^n E_j (1 - e^{-\left(\frac{t}{\tau_j}\right)}) \quad (2-66)$$

where D_g (the glassy compliance), η_0 (the long-time viscosity), D_j (retardation strengths) and τ_j (retardation times) are all positive constants. Biot showed that the generalized Maxwell model and generalized Kelvin-Voigt model are mathematically equivalent (Biot, 1954). These two models are the most general representations possible for isothermal cases (Schapery, 1964).

The Zener model (Figure 2-17) is a special case of the generalized Maxwell model. There are 3 parameters: E_1 and E_2 are the moduli of elasticity of the first and second Hookean spring respectively. The second spring is in series with a dashpot whose viscosity is η .

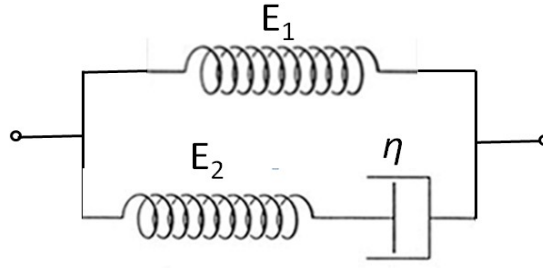


Figure 2- 17 Schematic representation of the Zener model

The stress (σ) and strain (ϵ) relation in the Zener model is given by

$$\sigma + \lambda_{\epsilon} \dot{\sigma} = E_0 (\epsilon + \lambda_{\sigma} \dot{\epsilon}), \quad \lambda_{\epsilon} \sigma(0) = E_0 \lambda_{\sigma} \epsilon(0) \quad (2-67)$$

where $\lambda_{\epsilon} = \frac{\eta}{E_1}$ and $\lambda_{\sigma} = \frac{\eta}{E_0} (1 + \frac{E_0}{E_1})$ are the relaxation time of constant strain and constant stress respectively.

2.3.7. Dynamic-mechanical properties of viscoelastic material

The dynamical methods usually involve study of the viscoelastic material undergoing oscillatory stress. A viscoelastic material will respond with sinusoidal strain under an applied stress varying sinusoidally with time. These sinusoidal variations, for example blood pressure, are usually described as a rate specified by the frequency f (Hz) or angular speed ω (rad/sec). The strain of a viscoelastic material is out of phase with the stress applied, by a phase angle, δ . Dynamic stress, σ , and strain ϵ , can be described as:

$$\sigma = \sigma_0 \sin(\omega t + \delta) \quad (2-68)$$

$$\epsilon = \epsilon_0 \cos(\omega t) \quad (2-69)$$

where ω is the angular frequency. Thus, stress can be divided into two parts, an in-phase component ($\sigma_0 \sin \delta$) and an out of phase component ($\sigma_0 \cos \delta$), so that it can be rewritten as:

$$\sigma = \sigma_0 \sin(\omega t) \cos \delta + \sigma_0 \cos(\omega t) \sin \delta \quad (2-70)$$

Dividing stress by strain yields in a Young's modulus, expressed as E' (in-phase or 'real' part) and E'' (out of phase or 'imaginary' part).

$$E' = \frac{\sigma_0}{\varepsilon_0} \cos \delta \quad (2-71)$$

$$E'' = \frac{\sigma_0}{\varepsilon_0} \sin \delta \quad (2-72)$$

$$\sigma = \varepsilon_0 E' \sin(\omega t) + \varepsilon_0 E'' \cos(\omega t) \quad (2-73)$$

$$\sigma = \sigma_0 \exp(i\omega t + \delta) \quad (2-74)$$

$$\varepsilon = \varepsilon_0 \exp(i\omega t) \quad (2-75)$$

$$E = \frac{\sigma_0}{\varepsilon_0} \exp i\delta = \frac{\sigma_0}{\varepsilon_0} (\cos \delta + i \sin \delta) = E' + iE'' \quad (2-76)$$

The real part of modulus describes the ability of the material to store potential energy and release it upon deformation. The imaginary part is associated with energy dissipation in the form of heat upon deformation. Based on the above equation, shear modulus can be rewritten as,

$$G = G' + iG'' \quad (2-77)$$

where the single and double primes designate the real and imaginary parts of shear modulus. The phase angle, which is a dimensionless measure of viscoelastic damping of the material, can be defined by

$$\tan \delta = \frac{G''}{G'} \quad (2-78)$$

The tangent of the phase angle δ is called loss tangent. The storage modulus is often regarded as the stiffness of a material, and is related to Young's modulus. The dynamic loss modulus is often associated with internal friction and is sensitive to different kinds of molecular motions, relaxation processes, transitions, morphology and other structural heterogeneities. The dynamic properties provide information at the molecular level which may help improve the understanding of disease progression.

2.4. Summary

Atherosclerotic diseases of the carotid artery are responsible for more than 25% of all strokes (Levy et al., 2008). The morphology and composition of carotid arteries measured by medical imaging techniques provide complementary information to luminal stenosis in predicting clinical presentation in both symptomatic and asymptomatic patients. Because of its wide availability and relatively low cost, ultrasound was chosen as the image modality for the present study. The methodology of extraction of clinically relevant measures from 3D ultrasound images will be given in Chapter 3. However, information obtained from medical images alone may not be sufficient for accurate prediction of the risk of stroke for a patient, and detailed knowledge of local haemodynamic and biomechanical forces is also required. Although carotid plaques biomechanics has been studied by many researchers, computational models that incorporate the effect of viscoelastic properties of the carotid wall are lacking. The effect of viscoelastic behaviour and its interaction with blood flow will be investigated in this thesis.

Chapter 3 Ultrasound image analysis

Medical image processing is an essential step in constructing a patient-specific model for accurate simulation of vascular biomechanics. Three-dimensional (3D) ultrasound is a hand-free operator-independent system, which would make an ideal medical diagnosis tool for carotid artery atherosclerosis. In order to extract key features and generate a 3D geometry for subsequent flow and wall mechanics analysis, it is necessary to develop image processing tools that are applicable to 3D ultrasound images.

In this chapter, an image segmentation and analysis tool for 3D ultrasound images is presented. Detailed procedures are described, including image acquisition, segmentation and 3D reconstruction. Outlines of the carotid wall and lumen are obtained based on manual segmentation and region growing algorithm, respectively. The reconstructed patient-specific geometries from 3D ultrasound images are used in the computational wall mechanics analysis presented in the following chapters. Moreover, methods for deriving clinically relevant measures, such as the degree of stenosis (DOS) and grey scale median (GSM), are described. Reproducibility of these methods is also assessed.

3.1. 3D ultrasound

To further improve the accuracy and applicability of ultrasound imaging, new modalities and techniques have been developed, and promising results have been obtained. 3D ultrasound has been tested for calculation of plaque volume and evaluation of therapeutic responses of carotid plaque (Coleman et al., 2005). As 3D ultrasound is the main source of images in this study, more details of 3D ultrasound are given below.

Conventional 2D (B-mode) ultrasound has been widely used for diagnosis of carotid artery disease for decades, owing to its low cost and non-invasive nature. Even today

2D ultrasound imaging is still highly competitive among more advanced 3D imaging techniques, such as CT and MRI, and it is the primary choice for examining patients with peripheral artery diseases. The easy accessibility of 2D ultrasound equipment together with its good reproducibility and high specificity makes it ideally suited for patients with carotid artery diseases. However, 2D ultrasound imaging is unable to capture details of plaque structure, and it has limited dimensional views. This may affect the accuracy of plaque characterization because the information obtained does not cover the entire volume of the plaque. Moreover, vascular geometries reconstructed from 2D ultrasound images are highly operator dependent. Although MR and CT angiography can provide vascular structure at different planes and different view angles, these techniques have their own limitations such as high cost, limited accessibility, more invasive nature and radiation. Combining the advantages of CT and MRI with the nature of ultrasound, 3D ultrasound has been developed with automatic tracking of the position of the probe and beam. It can offer multiple, consecutive and equidistant slice images which can be further processed using dedicated software such as VOCAL® or Q-Lab®.

The basic concept of 3D ultrasound imaging is that a 3D volume of the targeted structure is obtained by combining a series of 2D ultrasound cross-sectional slices. The first step is the acquisition of a series of 2D ultrasound images through manual or mechanical scanning. Early generation scanners involved obtaining serial 2D transverse images using a hand-held 2D ultrasound probe in conjunction with a tracking device for 3D information. However it is very difficult to guide a probe into the right place using conventional 2D ultrasound. An important limitation of this method is the uncontrolled scanning speed which is highly operator-dependent, affecting the accuracy and reproducibility of the volume measurement. This is the reason why a new generation of 3D probe has been developed to perform mechanical scanning with a constant speed, either by freehand motion or by a motor (Lindseth et al., 2013, Fenster et al., 2011). In practice, three types of 3D probes have been developed; these are motorized, freehand and real-time 3D ultrasound probes.

Motorized (mechanical) 3D ultrasound: A motor is used to control the motion of a conventional ultrasound probe by tilting (Figure 3-1 A), translating (Figure 3-1 B) and rotating (Figure 3-1 C) in the region of interest. The motor can either be mounted inside

the probe or be applied externally.

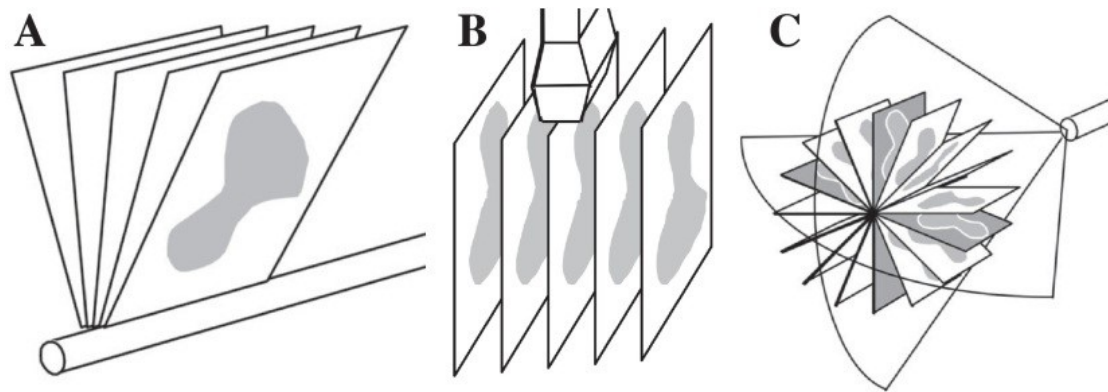


Figure 3- 1 Tilting (A), translating (B) and rotating (C) probes (Fenster et al., 2011)

Freehand 3D ultrasound: Due to its flexibility, freehand 3D ultrasound is the most popular method. This involves scanning the area of interest using a conventional 1D array that is tracked, and reconstructing the position-tagged ultrasound frames into a regular 3D volume that can be used in the same way as preoperative MR or CT. As shown in Figure 3-2, several methods are available for reconstruction of 2D frames into a 3D volume (Lindseth et al., 2013).

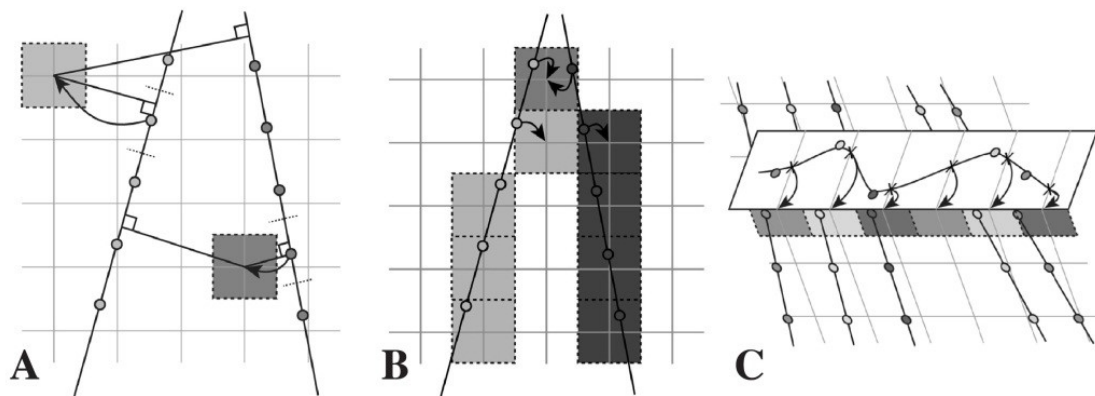


Figure 3- 2 3D ultrasound image reconstruction methods: Voxel nearest neighbour (A), Pixel nearest neighbour (B), Functional based methods (C) (Lindseth et al., 2013)

The first one is a voxel-based method which gathers information from the input 2D images and traverses each voxel into the target. Voxel nearest neighbour is the simplest method in this category which traverses each voxel into the target volume and assigns the value of the nearest image pixel, as shown in Figure 3-2 (A). Pixel-based method (Figure 3-2 B) consists of two steps: a distribution step where the input pixels are

traversed and applied to voxels, and a hole-filling step where the voxels are traversed and empty voxels are filled. Pixel nearest neighbour belongs to this category, which runs through the entire 2D input images and assigns the pixel value to the nearest voxel in the target 3D volume. The third type, known as functional based method, involves choosing a particular function and determining the coefficients to make the function pass through the input pixels (Figure 3-2 C). Functional based method produces the highest quality reconstructed volumes, but it is very computational intensive, which limits its use. These reconstruction methods can also be applied to motorized 3D ultrasound images. As the movement is known, tracking of the probe is not needed.

Instead of using a conventional 1D array transducer which is moved by freehand or a motor to cover the anatomy of interest, a real-time 3D ultrasound transducer with 2D phased array has been developed to generate 3D images in real time, as shown in Figure 3-3 A. The ultrasound beam (Figure 3-3 B) is controlled by an electronic device, sweeping a volume with the shape like a truncated pyramid (Figure 3-2 C).

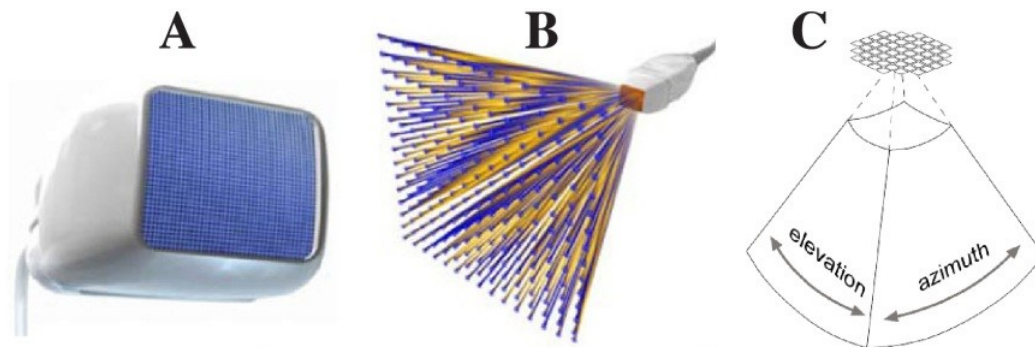


Figure 3- 3 (A) The VL13-5, 3D ultrasound probe using 2D array of elements by Philips co. (B) xMATRIX transducer provides unlimited planes in all directions with degradation in image quality. (C) Truncated pyramid of data is acquired (Lindseth et al., 2013).

3.2. Image acquisition

Motorized 3D ultrasound imaging involves manual scanning with a 2D ultrasound probe, an electromagnetic position and orientation measurement (EPOM) device and a PC containing the acquisition software, as shown in Figure 3-4. In order to avoid corrugation of the images due to vessel motion, electrocardiogram (ECG) synchronization is required. During a scan, the probe is swept slowly over the patient's

neck. The transducer is translated along the arteries while 2D ultrasound images are acquired by a computer and reconstructed into a 3D image. The most important limitation of conventional 3D ultrasound imaging is that not all the 2D slices are taken at the same time which could affect the accuracy and reproducibility of the volume measurement.



Figure 3- 4 A mechanical linear scanner mechanism used to acquire 3D ultrasound images of the carotid artery (Fenster et al., 2004).

Unlike motorized 3D ultrasound probe, a new generation of 3D freehand probes is able to perform mechanical scanning at a constant speed. A premium performance ultrasound system, iU22 xMATRIX (Philips Co.), available in Ealing Hospital, London, was used in this project. It is equipped with a 3D broadband, linear array probe (VL13-5, Phillips Co), as shown in Figure 3-5. This transducer provides a wide frequency range between 13 to 5 MHz and supports high resolution 2D, 3D and 4D imaging. Unlimited planes in all directions can be viewed and examined precisely without any degradation in image quality by using this system's multi-directional beam steering. Additionally, the system has preinstalled software, Q-Lab® (Phillips Co), for navigation and 3D reconstruction of the underlying structure. The Philips iU22 ultrasound scanner offers a spatial resolution in the range of 0.029 to 0.067 mm/pixel (Bastida-Jumilla et al., 2013). Images acquired in this study have a spatial resolution of 0.058 mm/pixel which was specified by the radiologist at Ealing hospital.



Figure 3- 5 VL13-5 broadband linear array probe

During image acquisition, the patient was placed in a semi-recumbent position on the couch with the chin slightly extended. Both 2D and 3D images were acquired at this stage using ultrasound. Starting from the left side of the neck, the ultrasound transducer was placed at the base of the neck to obtain trans-axial images from the proximal section of the common carotid artery to the angle of the jaw where the carotid bifurcation is normally located. In the 2D examination, colour flow was used to help identify cholesterol rich deposits inside the carotid artery. To acquire 3D ultrasound images, a dedicated 3D volume ultrasound probe was used in both transverse and longitudinal sections. The collection of images obtained by the 3D examination included B-mode, colour flow and power Doppler images.

The acquired B-mode images were processed by Q-Lab® (installed within the 3D ultrasound probe) to generate a series of cross-sectional RGB images. An RGB image, also referred to as a true colour image, is stored as an $m \times n \times 3$ data array that defines red, green, and blue colour components for each individual pixel. The colour of each pixel is determined by the combination of the red, green, and blue intensities stored in each colour plane at the pixel's location which yields a potential of 16 million colours. The ultrasound images were obtained with the following parameters: matrix size of $644 \times 1024 \times 3$, and 1 mm interslice thickness which was predetermined when the image data were processed. The pixel size was 17 pixels/ mm. These colour images were then transferred from the scanner to PC for off-line processing. They were read into a MATLAB programme by using the 'imread' function. This was followed by conversion

of colour images to grayscale images by using 'rgb2gray' in MATLAB, in order to eliminate the hue and saturation information while retaining the luminance (as shown in Figure 3-6). The greyscale images were then cropped to reduce the size of the data for further processing. As can be seen from the original image shown in Figure 3-6 (upper), the region of interest (ROI), i.e. the carotid artery in this application, occupies less than a tenth of the total image area. The cropped image, shown in Figure 3-6 (lower) was used in image segmentation and geometry reconstruction.

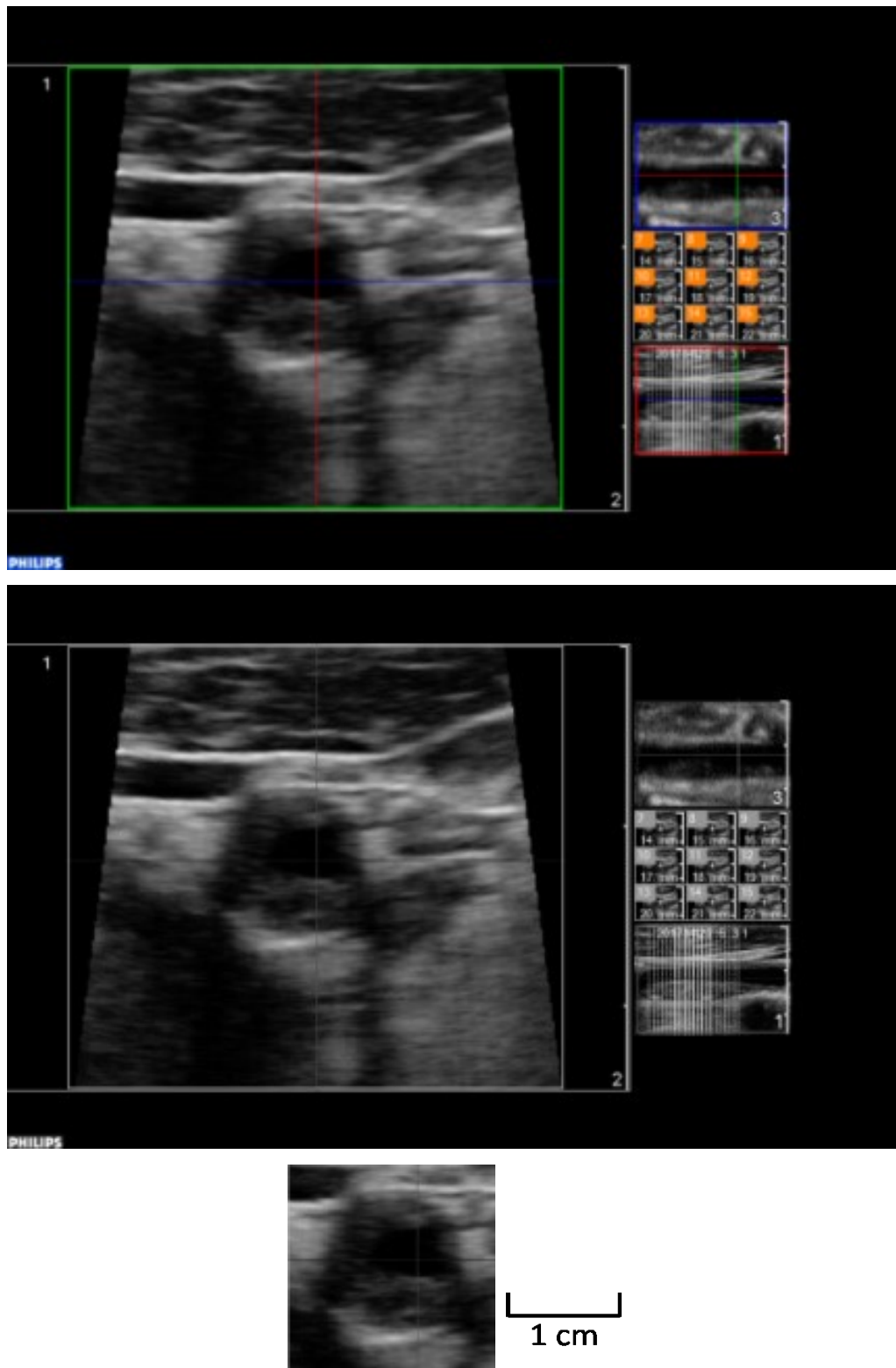


Figure 3- 6 3D ultrasound image: original (upper), after conversion to greyscale (middle), after cropping (lower)

Image noise can be partially removed by applying a filter which is available in MATLAB in order to enhance the image quality. This function was required in both

automatic and manual segmentation of the vessel contours. A median filter, medfilt2, was adopted for the present application. It allows a nonlinear smoothing operation by blurring the odd points in an image, which is known as “salt and pepper” noise. It is more effective than convolution when the goal is to simultaneously reduce noise without blurring the boundary at the edge. Each output pixel contains the median value of $m \times n$ neighbourhood around the corresponding pixel in the input image (Equation 3-1). The odd points are replaced by the average intensity of the neighbourhood:

$$\bar{f}(x, y) = \text{median}_{(s,t) \in (x,y)} \{g(s, t)\} \quad (3-1)$$

where $g(s, t)$ is the neighbour of pixel (x, y) and $\bar{f}(x, y)$ is the median value of the image intensity in $g(s, t)$. Figure 3-7 shows an example of the cropped greyscale image before (left) and after filtering (right). The median filter showed excellent noise removal ability. The two crossing lines on the pre-filtered image were removed after image filtering.

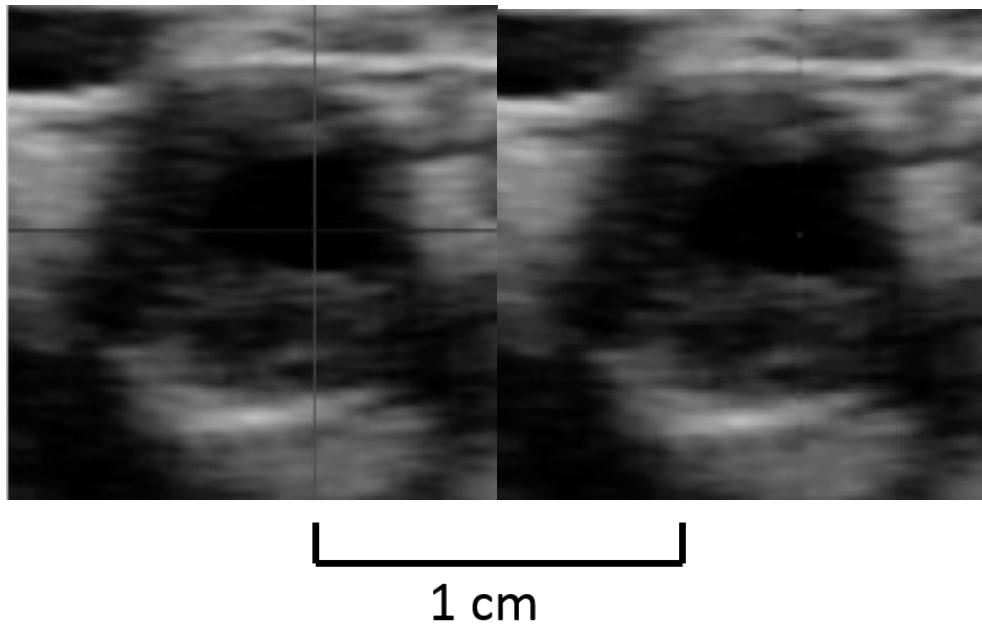


Figure 3- 7 The cropped image (left) and after 3×3 median filtering (right)

3.3. Image segmentation

After pre-processing, which involved cropping and filtering as described above, image

segmentation was preformed. Image segmentation is a process by which images are partitioned into multiple segments and labels are assigned to each segment. There are various ways to perform image segmentation, either manually or automatically.

In this study, manual segmentation was needed to detect the edges of the outer wall, due to the lack of contrast between the wall and its surrounding tissues. The screen selection function was activated to select points manually along the edge of the object of interest, i.e. the carotid artery wall. Wall contours were then outlined from the ROI using cubic spline fitting to the selected points. This process was repeated for all slices covering the entire volume of interest. Figure 3-8 shows examples of outlined wall contours.

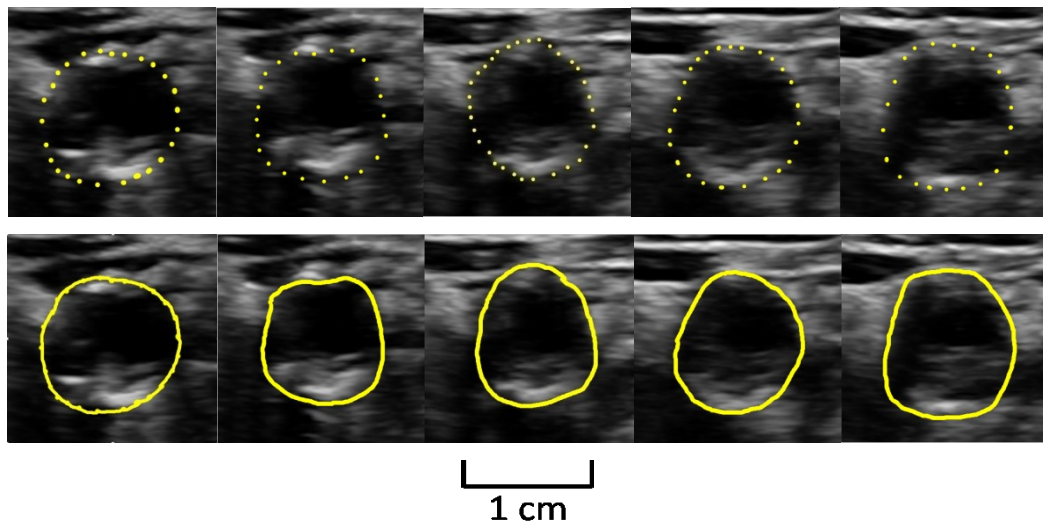


Figure 3- 8 Examples of outlining wall (yellow) contour of the CCA

The obtained contours were stored as pixel positions of discrete points in the imaging frame. Since there were 17 pixels per 1 mm distance in the 3D ultrasound images utilised, this information was used to convert pixel positions to physical coordinates. Smoothing of the obtained contour was necessary to remove artificial irregularities. This was achieved by the *csaps* function, which is available in MATLAB Spline Toolbox. A smoothing factor of 0.8 was chosen based on previous experience (Tang et al., 2004a, Bathe, 1996) to reduce physical artefacts, such as sharp corner or kink on the cross-sectional contour.

Due to the limitations of ultrasound as described in Chapter 2, some regions of the

vessel may be absent, making it impossible to extract the lumen boundary from B-mode images. Therefore, power Doppler images were used to delineate the outline of carotid lumen which is the boundary between blood and the vessel wall. A semi-automatic method based on the region growing algorithm, was employed for segmentation of lumen contours. Figure 3-9 shows an example of power Doppler image acquired with the 3D ultrasound system, where blood flow through the lumen is displayed in colour.

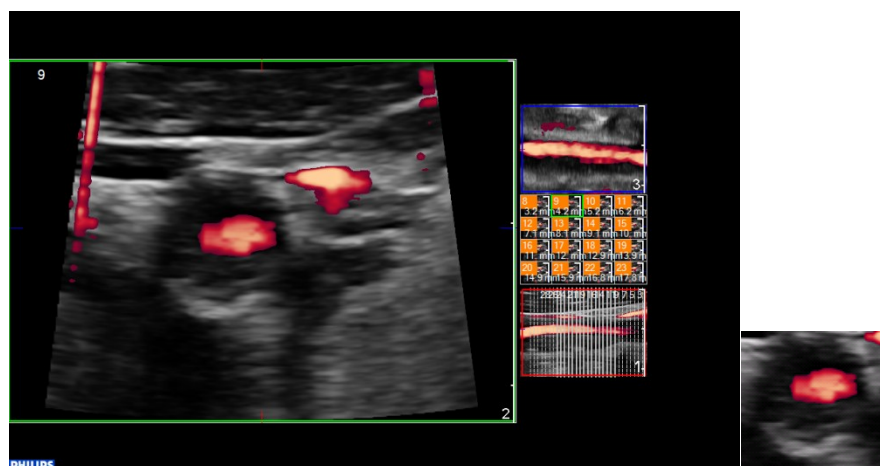


Figure 3- 9 Power Doppler image acquired with the 3D ultrasound system (left) and after cropping (right)

After the ROI was cropped and image noises were filtered, region growing segmentation was performed. Region growing algorithm is a region-based image segmentation method, which involves a selection of initial seed points as input for the images to be processed. The principle of region growing method is based on the assumption that the neighboring pixels within one region have similar image intensity. The first step in region growing method is to select initial seed points based on user specified criteria. Since the lumen area of the carotid artery was the ROI, an initial seed point was selected manually in the lumen. The region was iteratively grown by comparing neighboring pixels with this initial seed point, in order to determine whether these unallocated neighboring pixels should be included in the region or not. The advantage of region growing method is that it can deal with image noises relatively easily by applying masks to filter holes or outliers; it is a technique for determining a region directly and can provide a good segmentation result for the original images with clear edges. The iterative procedure was stopped until changes in two successive iterative stages were sufficiently small, and examples of the extracted carotid lumen are

shown in Figure 3-10. Now both the lumen and outer wall at each cross-section were outlined and saved in the data file for 3D reconstruction.

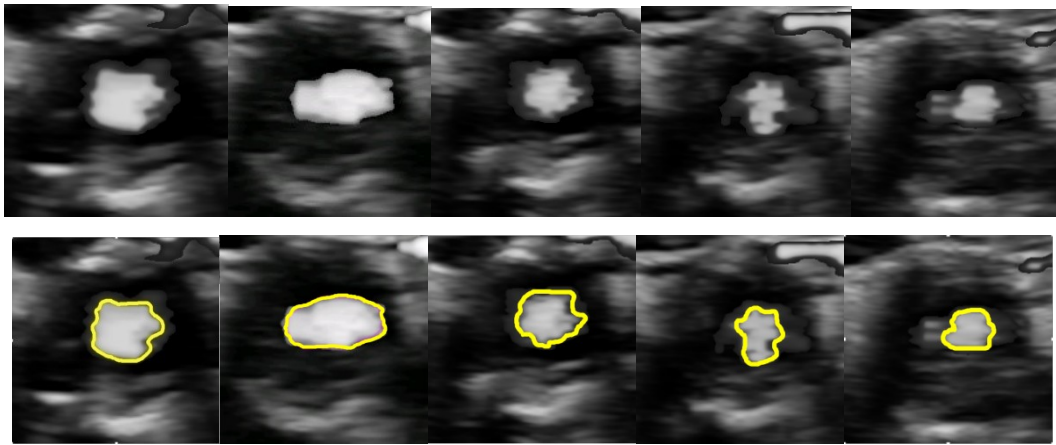


Figure 3- 10 Filtered power Doppler images (upper) and the extracted lumen contours (lower)

3.4. 3D geometry reconstruction

The transaxial 2D contours obtained from image segmentation were stacked in a 3D space as shown in Figure 3-11.

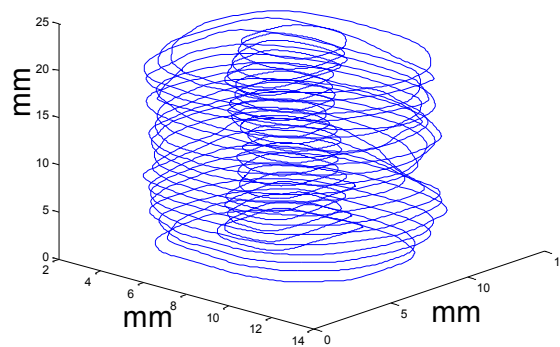


Figure 3- 11 Stacked cross-sectional inner and outer wall contours

In order to eliminate errors due to artefacts and subject movement during a scan, smoothing was necessary before a 3D patient-specific geometry model could be used for further biomechanics analysis. This was achieved through centroid registration and smoothing, followed by surface smoothing. The vessel centreline is defined as the loci of the centre points of lumen contours. Centreline smoothing was performed by using

polynomial regression (*polyfit* in MATLAB), while surface smoothing was carried out by using B-spline approximation (*spap2* in MATLAB). In order to correct longitudinal misalignment due to possible neck motion during ultrasound image acquisition, a smoothing factor of 0.7 was employed for centreline smoothing, which has been justified by researchers in our group (Augst et al., 2003). The degree of smoothing should be carefully controlled so as to retain essential features in the original geometry and avoid over-smoothing. To eliminate errors from the image segmentation procedure, an additional smoothing step called surface smoothing was performed. This process should ideally produce a 3D surface that represents faithfully the real carotid artery geometry without excessive modification of authentic geometric features (Augst et al., 2003). The smoothed lumen and wall contours were calculated and saved as a geometry file in STL format using 'surf2stl' function in MATLAB. The STL technique was developed for rapid prototyping that creates a solid physical model directly from digitalised data. Based on medical images acquired from MRI, CT or ultrasound, this technique has shown a good accuracy in human anatomy representation (Bouyssie et al., 1997). STL files contain point cloud as shown in Figure 3-12, and the surface information is ready to be used as 3D boundary surface coordinates for computational mesh generation.

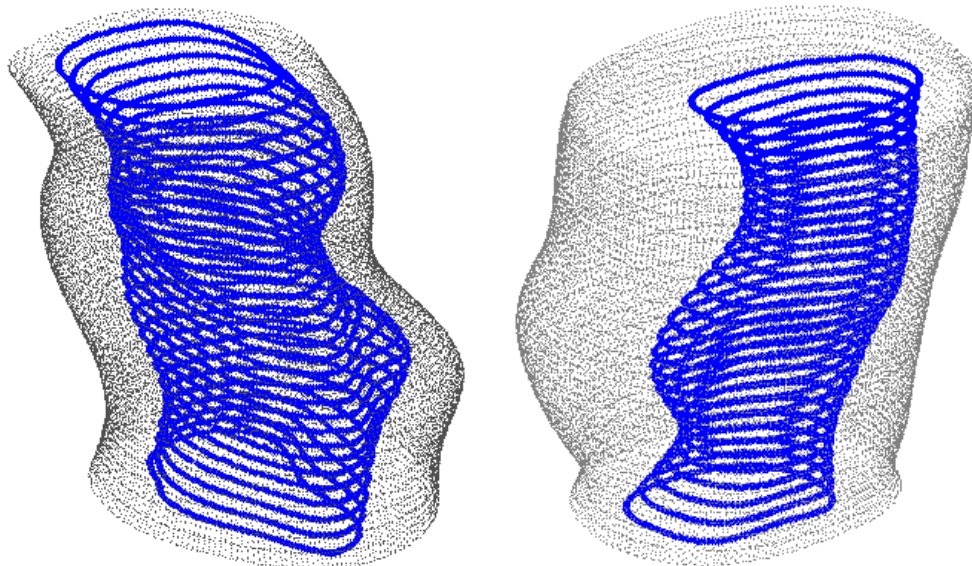


Figure 3- 12 The reconstructed lumen and vessel wall surface from Patient 1 (left) and Patient 2 (right)

The effect of interslice distance (ISD) on the measurement of plaque volume by using

3D ultrasound has been investigated (Landry et al., 2004, Ludwig et al., 2008). Both of these studies showed that variations of plaque volume were smaller for larger plaque size. Ludwig et al. found that the reliability of volume measurement of small plaque could be improved by using a smaller ISD. Landry et al. investigated the effect of ISD on volume measurement and found that ISD in the range of 1.0 mm and 3.0 mm offered a good accuracy, but the measurement variability increased significantly with ISD above this range. In this study, the inter slice distance was 1.0 mm.

3.5. Clinical criteria derived from ultrasound images

By utilising texture measures extracted from ultrasound images, computer aided plaque morphology analysis can assist in risk assessment of stroke (Kyriacou et al., 2012). In this section, methods to derive some of the clinically relevant parameters introduced in Chapter 2 are described.

Degree of stenosis

Owing to arterial remodelling, the lumen of carotid artery gradually narrows with the accumulation of lipid, protein and cholesterol esters in the vessel wall (Zarins et al., 2001). As described in Chapter 2, until now, the degree of stenosis (DOS) is still the main criterion used by surgeons to decide whether surgical intervention would be needed or not (1998, Rothwell et al., 2003). In this study, DOS was defined and evaluated based on the ECST standard which requires information about the narrowed lumen and outer wall diameters only.

$$\text{DOS} = 1 - \frac{a}{b} \quad (3-2)$$

where a stands for the diameter of the narrowed lumen, b is the diameter of the outer wall. Values for a and b were taken as the equivalent diameter calculated from the lumen and the outer wall area, respectively. For a given carotid artery, DOS was calculated for all the cross-sections obtained from 3D ultrasound, and the peak DOS was used to represent the severity of carotid narrowing.

Plaque burden

Another useful criterion adopted by clinicians is plaque burden, which is the percentage of wall volume relative to the whole vessel volume. It is also referred to as plaque index. It has been demonstrated that plaque burden is a reliable predictor of all-cause cardiovascular mortality in the elderly patients group (Stork et al., 2004). Even though this restricted age group corresponded to a narrow range of carotid artery stiffness, this study proved the importance of plaque burden in predicting the risk of cardiovascular mortality. Because a constant ISD of 1 mm was used in this study, plaque burden of the carotid artery was evaluated as the ratio of the total area of the wall to the area of the whole vessel. In order to evaluate plaque burden from the acquired ultrasound images, the number of pixels in the wall and that in the whole vessel were counted for each slice. Figure 3-13 shows the outlines of the lumen and outer wall delineated from 3D ultrasound images of the carotid artery in patient 1.

Texture analysis of carotid plaque

Echoluency refers to the ability of some areas of the body to let ultrasound waves go through without being blocked. On a sonogram, the dark (black) areas are echolucent. It has been shown that echoluency of the ultrasound images of carotid plaques can be used to predict the risk for plaque rupture in symptomatic and asymptomatic patients (Gronholdt et al., 2001).

Mean grey value (MGV) is the averaged value of normalized grey-scale values in an ultrasound image. It was found that MGV was lower in the symptomatic group of carotid plaques with moderate stenosis (<70%) compared to plaques with high-grade stenosis, and that MGV for symptomatic plaques with moderate stenosis was significantly lower than for asymptomatic plaques (Heliopoulos et al., 2008). Another parameter is grey-scale median (GSM), which is the median value of the global grey scale value of an image. It has been claimed that GSM evaluates carotid plaque echogenicity more objectively and accurately than MGV (Mayor et al., 2003). Plaques with lower GSM in 2D ultrasound images were found to have higher absolute risk in symptomatic patients, suggesting that measurement of GSM together with DOS may improve selection of patients for carotid endarterectomy (Gronholdt et al., 2001). The association between plaque vulnerability and plaque echoluency is due to the fact that soft tissue components, such as lipid and haemorrhage, are echolucent, while fibrous content in a plaque is associated with rich-echo (ElBarghouty et al., 1996). This was

further proved by other investigators (Grogan et al., 2005).

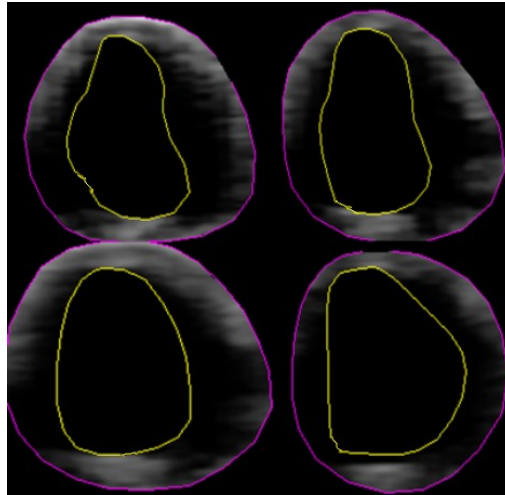


Figure 3- 13 Outlines of lumen and outer wall extracted from 3D ultrasound images for DOS calculation for Patient 1.

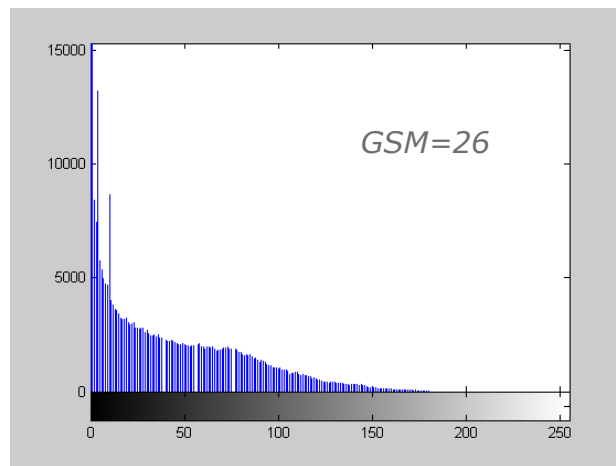


Figure 3- 14 Global grey scale histogram for Patient 1

Plaque GSM values were calculated using MATLAB. First, images were normalized based on the criteria developed for GSM analysis of the carotid plaque (Elatrozy et al., 1998): inside the lumen a grey scale value of 0 was assigned, while the adventitia, being the brightest, was assigned a grey scale value of 255. After normalization, the histogram of grey scale was plotted and GSM was evaluated. As shown in Figure 3-14, the global GSM of the entire plaque volume for Patient 1 is 26. The corresponding histogram for Patient 2 is shown in Figure 3-15, with a GSM of 17.

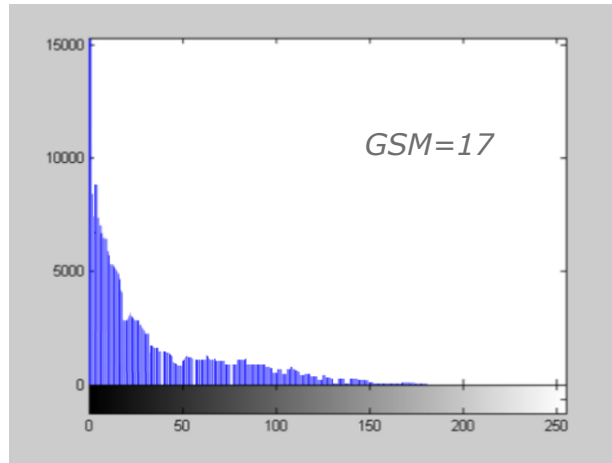


Figure 3- 15 Global grey scale histogram for Patient 2

Table 3-1 gives a summary of selected clinically relevant measures extracted from ultrasound images for Patient 1 and Patient 2.

Table 3- 1 Selected clinically relevant measures extracted from ultrasound images for Patient 1 and Patient 2

Patients	1	2
DOS (ECST)	68.14%	71%
Plaque burden	0.166	0.311
GSM	26	17
Lumen Volume	1500 mm ³	1169.9 mm ³
Wall volume	1797 mm ³	1698 mm ³

3.6. Discussion

3D ultrasound has been employed in this project to provide geometric information for reconstruction of carotid artery model and measurement of clinically relevant data. Patients with atherosclerotic plaques in the carotid arteries were recruited to Ealing Hospital, where they underwent ultrasound examination using the Philips iU22 3D scanner. This new generation of scanner offers far superior spatial resolution (17 pixel/mm) compared to the widely used conventional 2D scanner. However, the quality of the images provided by the clinical researcher varied considerably; as a result, only

two sets of images were deemed usable.

Because an accurate luminal measurement and characterization of plaque surface can be provided by Power Doppler images (Steinke et al., 1996), which have been shown to be superior to images acquired with colour-flow Doppler and angiography (Griewing et al., 1996) with regard to differentiation of plaque surface morphology, the lumen surface of the carotid artery was reconstructed from Power Doppler images using automatic image segmentation based on region growing algorithm. The segmented lumen contours were verified by comparing with manually traced lumen surface by a trained clinical researcher at Ealing hospital.

Prior studies have shown that compared to 2D ultrasound, 3D ultrasound technique offers better visualisation and quantification of carotid plaque (Fenster et al., 2006, Schminke et al., 2000), with good accuracy and reproducibility (Landry et al., 2004). Because of the lower contrast at boundaries parallel to the ultrasound beam than at boundaries orthogonal to the beam, most existing automatic segmentation methods for carotid plaques were developed for longitudinal images (Destrempes et al., 2011, Loizou et al., 2007, Delsanto et al., 2007), which cannot be applied to cross-sectional images. Only a limited number of studies on segmentation of carotid plaque based on transverse ultrasound images can be found in the literature (Buchanan et al., 2012, Seabra et al., 2009, Cheng et al., 2013), and all of these require extensive operator interactions. In this project, a combination of manual and automatic segmentation was needed as the contrast between the outer wall and its surrounding on transverse ultrasound images was insufficient for automatic segmentation. A manual segmentation tool has been developed to extract the outline of carotid outer wall by using MATLAB. However, only the common carotid artery images were acquired and used in segmentation and 3D reconstruction. Although the same image analysis tool can be extended to the internal and external carotid arteries, in practice, only a limited segment of the carotid branches can be acquired due to the presence to jaw bone, which is a serious limitation of all ultrasound-based techniques (except intravascular ultrasound).

With regard to clinically relevant carotid plaque measures, Biasi et al. measured the carotid plaque echolucency and found that GSM of less than 25 was associated with increased risk of stroke in carotid artery stenting (Biasi et al., 2004). Based on their

finding (Mayor et al., 2003, Biasi et al., 2004), the carotid plaque of Patient 2 is more vulnerable than that of Patient 1 as it has higher DOS and lower GSM. However, this assessment is based on the images alone, and as it will be shown later in Chapter 5 that the plaque biomechanics analysis may predict a different outlook.

3.7 Summary

The aim of this chapter was to develop an image processing tool to extract the key features of atherosclerotic carotid arteries from ultrasound images. This should not only allow evaluation of clinically relevant measures, but also provide a 3D volumetric geometry for patient-specific biomechanics analysis. Manual image segmentation was employed to extract the outer wall, while automatic image segmentation based on region grow algorithm was used to aid the identification of carotid lumen boundary. The reconstructed 3D carotid wall volume can be used in subsequent finite element analysis to be presented in Chapters 4, 5 and 6. Using the method developed for the evaluation of DOS, GSM and plaque burden, 3D ultrasound images acquired from patients with carotid artery diseases can be analysed rapidly, providing clinicians with important data to aid their diagnosis and decision making.

Chapter 4 Finite Element analysis of

stenosed carotid arteries

Finite element analysis (FEA) has been widely used to predict the deformation and stress in large vessels (Lee et al., 2004, Gao et al., 2011, Leach et al., 2010). The biomechanical environment of atherosclerotic plaques plays an important role in patient risk stratification, because under physiological conditions atherosclerotic plaques are at high risk of rupture when the stresses they experience exceed their material strength. A number of studies suggested that mechanical stresses within atherosclerotic plaques could be of clinical use to help assess the rupture potential of a plaque (Augst et al., 2003, Gao and Long, 2008, Tang et al., 2009). Although mechanical stresses within a plaque depend on plaque morphology and pulsatile blood pressure, their predicted values are also affected by the different computational strategies employed, such as two-dimensional (2D) or three-dimensional (3D) finite element analysis (FEA).

This chapter focuses on the application of FEA in carotid arteries for the investigation of stress and strain distribution under pulsatile pressure. Numerical simulations were performed on patient-specific models of the carotid artery created using the method described in Chapter 3 and with elastic material properties. An additional purpose of this chapter was to quantify the differences between 2D and 3D carotid artery finite element analysis, and an idealized model of carotid artery stenosis was used for this purpose. Maximum and average Von Mises stress and displacement obtained from 2D and 3D finite element models were assessed under physiological realistic pulse pressures.

4.1. Introduction

There have been a large number of studies focusing on the biomechanics of atherosclerotic arteries using FEA. The decision of using 2D or 3D FEA modelling

depends on a number of factors. 2D finite element analyses have been used to investigate the crucial factors that influence the stress level and stress distribution within arterial walls (Kaazempur-Mofrad et al., 2003, Zhu et al., 2010). 3D FEA may achieve a higher degree of fidelity of physical reality than 2D and provide a more realistic representation of the mechanical behaviour of human arteries, whereas 2D modelling can only provide limited dimensional results with insufficient information on the entire volume of a plaque. However 3D FEA is time consuming and demands more computational resources. Therefore, 2D FE models have been frequently used for deformation and stress analysis of carotid plaques (Loree et al., 1992, Hayashi and Imai, 1997, Imoto et al., 2005).

Tang et al. compared the predicted stress/strain results between 2D and 3D models based on patient-specific geometry by using ADINA (Tang et al., 2004b). Due to the complexity of carotid plaques, the shape, size and components of plaques can vary significantly among individuals (Kaazempur-Mofrad et al., 2004). In order to quantify the difference between 2D and 3D FE models and to understand the influence of individual geometric factors, it was considered necessary to employ a hypothetical model where the geometry could be varied in a controlled manner. For this purpose, idealized 2D and 3D multi-component human carotid plaque models were built and detailed comparison of computational results was made in terms of the maximum and mean stress/strain values. The effects of degree of stenosis (60% and 80%) and pressure loads (40 mmHg and 60 mmHg) on the difference between 2D and 3D models were also investigated.

4.2. Material and Methods

4.2.1. 3D reconstruction of carotid plaque geometry

An idealized 3D model of the human common carotid artery plaque was developed based on data extracted from the literature (Li et al., 2006). The model consisted of a straight tube with an asymmetric plaque in the middle; a sinusoidal function was used to describe the shape of the plaque which also contained a soft lipid core. Basic geometric

parameters of the model are listed in Table 4-1, which are representative of a lipid-rich plaque in the common carotid artery. The degree of stenosis is defined as the percentage of stenosis based on the definition used in NASCET.

Table 4- 1 Geometric parameters of the 3D model

Geometry	length
Vessel diameter (D)	10 mm
Length of plaque (L)	20 mm
Inlet length (IL)	30 mm
Outlet length (OL)	30 mm
Degree of stenosis ($\frac{D-A}{D}$)	60%, 80%
Plaque cap thickness (d)	0.5 mm
Vessel wall thickness (w)	1 mm

As shown in Figure 4-1, the shape of plaque (y_1) and that of the lipid pool (y_2) are described by sinusoidal functions given by:

$$y_1 = \frac{D-A}{2}(1 + \cos x) \quad (4-1)$$

$$y_2 = \frac{D-A}{2}(1 + \cos x) - d \quad (4-2)$$

where D and A are the outer and inner carotid artery diameter, respectively, and d is the cap thickness, which is the distance between the inner wall and lipid pool. Based on data reported by Li et al. (Li et al., 2006), where the cap thickness of human carotid plaques varied between 0.5 and 2 mm, a thin cap was chosen ($d = 0.5$ mm), which was kept constant along the lipid pool surface. Figure 4-1 shows the longitudinal (upper) and cross-sectional views (lower) at the throat of the stenosis. The cross-sectional shape of the lipid pool was assumed to be elliptical, with its long axis (in the horizontal plane) being twice as long as its short axis (in the vertical plane).

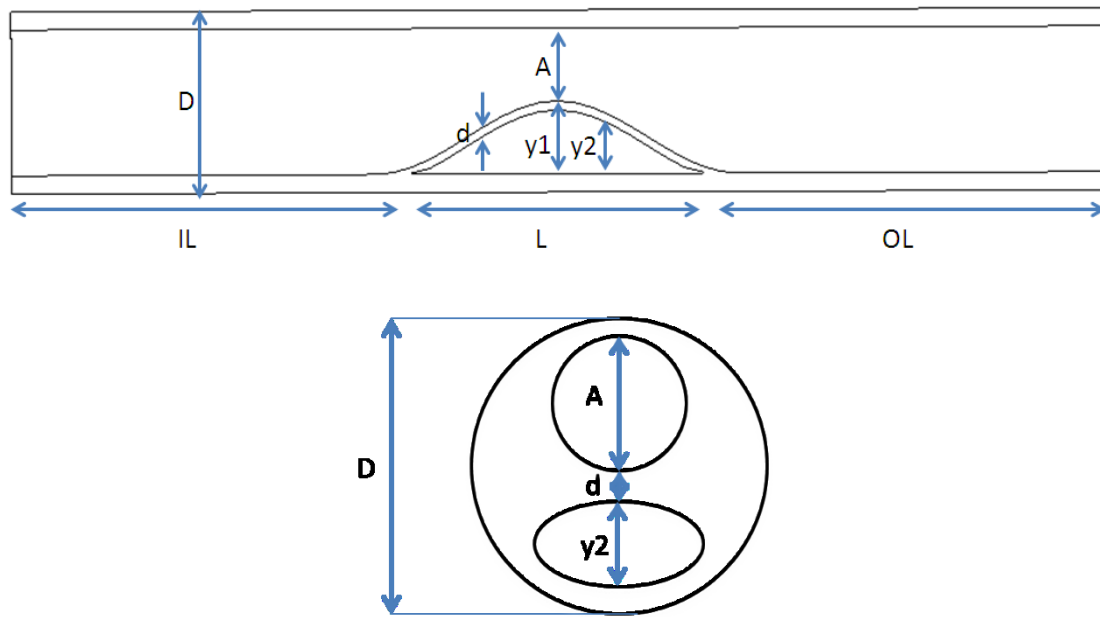


Figure 4- 1 Geometry of the idealized model

The 2D models were created by taking the transverse sections of the 3D model at equal distance along the plaque as shown in Figure 4-2. With an inter-section distance of 1 mm, fifteen 2D models were built covering the whole plaque length.

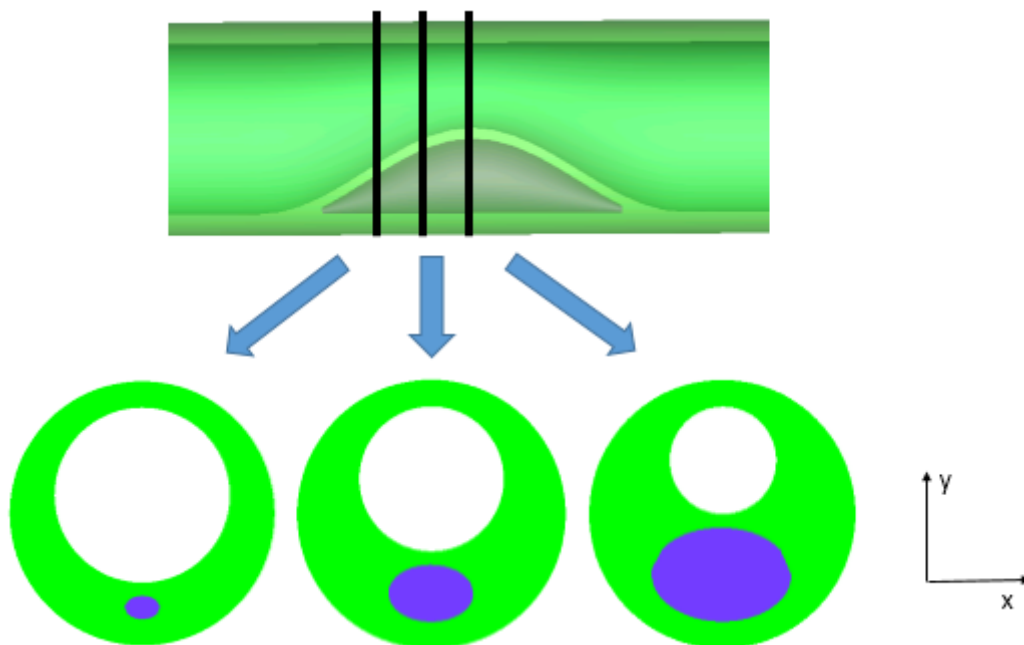


Figure 4- 2 2D models corresponding to the 3D model

4.2.2. FE modelling strategy

Computational meshes for the 2D and 3D models were generated using “SOLID187” element (ANSYS, 2012), which is a high order 10-node element consisting of three degrees of freedom at each node along x, y and z directions. Considering the changing geometry of the lipid component, a free mesh algorithm was adopted for mesh generation. Mesh sensitivity tests were performed for the 2D model, and the predicted stress values obtained from a fine and coarse mesh were compared. Comparisons showed that increasing the number of nodes from 9347 to 44276, only resulted in a change of less than 1% in nodal average maximum stress. Therefore, a mesh consisting of 9347 nodes (shown in Figure 4-3) was considered sufficient for 2D FE analysis. The 3D computational mesh was generated based on the same mesh size as for the 2D model, where the maximum edge length of the elements was 0.2 mm in the artery and 0.1 mm in the lipid pool. As the lipid pool is much softer than its surrounding tissue, larger deformations are expected to occur in this region. Hence, the maximum edge length of the element in the lipid pool was 0.1 mm.

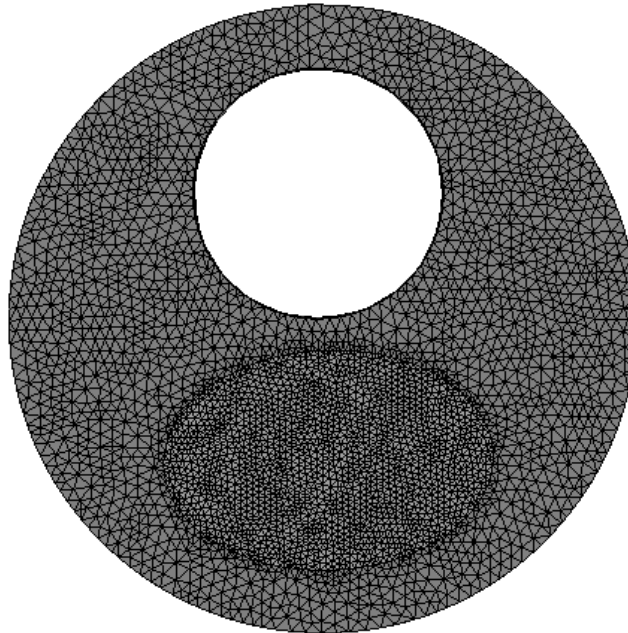


Figure 4- 3 Finite element mesh of a 2D model

Knowledge of arterial wall and plaque mechanical properties is required for accurate

prediction of stress in atherosclerotic arteries. Because these vary among individuals and can only be approximated, data from the literature were used. Sensitivity studies carried out by Williamson *et al.* demonstrated insignificant differences in predicted wall stress between isotropic nonlinear and linear models (Williamson et al., 2003). Using a 2D FE model, they also conducted tests on the sensitivity of plaque material properties, and found that doubling the elastic modulus led to no more than 10% difference in the predicted position of the rupture site. A subsequent study carried out by Tang et al. using a 3D FE model showed that the maximum stress values and stress/strain distributions differed by less than 2%, even when the Young's modulus of vessel was doubled (Tang et al., 2004a).

Since a hypothetical model was used in the comparative study, the carotid arterial wall and lipid pool in both 2D and 3D models were simplified as a linear, isotropic and incompressible material, with a Young's modulus of 350 kPa and Poisson's ratio of 0.49 which is close to 0.5 for a perfect incompressible material (Lee et al., 2004), while the lipid core was much softer than the arterial wall with a Young's modulus of 2 kPa and Poisson's ratio of 0.49 (Finet et al., 2004).

The load acting on the lumen surface was the pulse pressure, which is the difference between peak systolic and diastolic pressure, at 40 mmHg (5333 Pa) for normal subjects, and 60 mmHg (8000 Pa) for hypertensive subjects. Different boundary conditions were imposed for the 2D and 3D models. In the former, nodes with the smallest y coordinate were fixed, while nodes with the largest x coordinate were also fixed to prevent displacement in the circumferential direction. In the 3D model, both ends of the vessel were fixed in all directions. The equations governing the stress and strain behaviour of the carotid plaque model were solved by a FE structural solver Ansys (Ansys Inc., USA).

4.3. Results

4.3.1. Comparison of predicted stress and strain between the 2D and 3D models

Simulation results, such as stress and strain distributions, were analysed and the corresponding cross-sectional average and maximum values were derived. For 2D and 3D FE model comparison, we should be aware that the boundary conditions of these two models were different. For a 3D model, both ends were tethered, while 2D models were only fixed at a point at the bottom of each 2D slice. The first principal stresses (σ_1), also referred to as the maximum principal stresses, and von Mises stresses were chosen for comparison between the two models. Because of its importance in predicting plaque rupture, more attention was focused on the maximum value of Von Mises stress, which together with von Mises strain is defined as:

$$VMStress = \sqrt{\frac{(\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2}{2}} \quad (4-3)$$

$$VMStrain = \frac{1}{(1 + \nu)} \sqrt{\frac{(\varepsilon_1 - \varepsilon_2)^2 + (\varepsilon_2 - \varepsilon_3)^2 + (\varepsilon_3 - \varepsilon_1)^2}{2}} \quad (4-4)$$

where VMStress is von Mises stress, VMStrain is von Mises strain, σ is the principal stress and ε is the principal strain. Subscripts 1, 2 and 3 refer to the first, second and third principal stress in a 3D coordinate system.

The simulated VMStress and VMStrain for the 3D model are shown in Figure 4-4, while comparisons of VMStress and VMstrain between the 2D and 3D models are given in Figure 4-5 and Figure 4-6, respectively. These results show that the maximum stress occurred within the thin plaque cap, and the minimum stress occurred inside the lipid pool and outer wall. Although the stress level was low in the lipid pool, the displacement there was large as the lipid component was very soft. For this reason, the lipid pool under the fibrous cap experienced a larger deformation compared to other parts of the carotid wall, and the maximum strain was observed under the thin fibrous cap as shown in Figure 4-4.

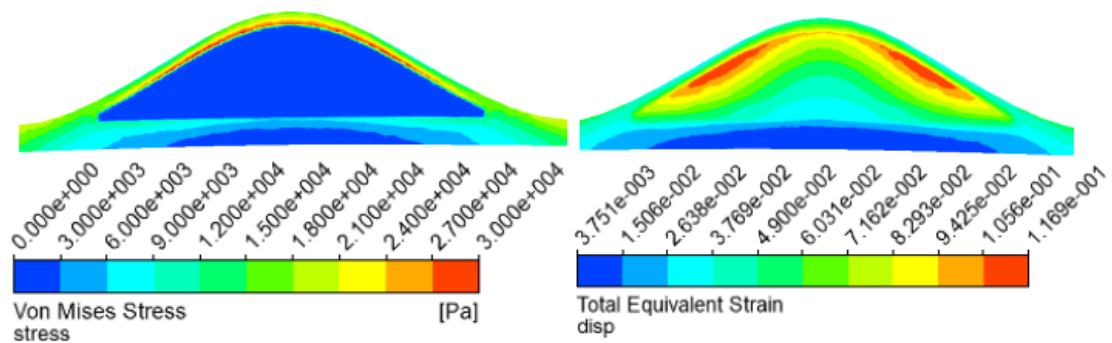


Figure 4- 4 VMStress (left) and VMStrain (right) maps in a longitudinal plane of the idealized 3D model with 60% stenosis for a pulse pressure of 40 mmHg

In order to quantify the difference between 2D and 3D FE models, predicted stresses and strains were compared at 15 selected cross-sections which are evenly spaced along the length of the carotid plaque, as shown in Figure 4-5 and Figure 4-6.

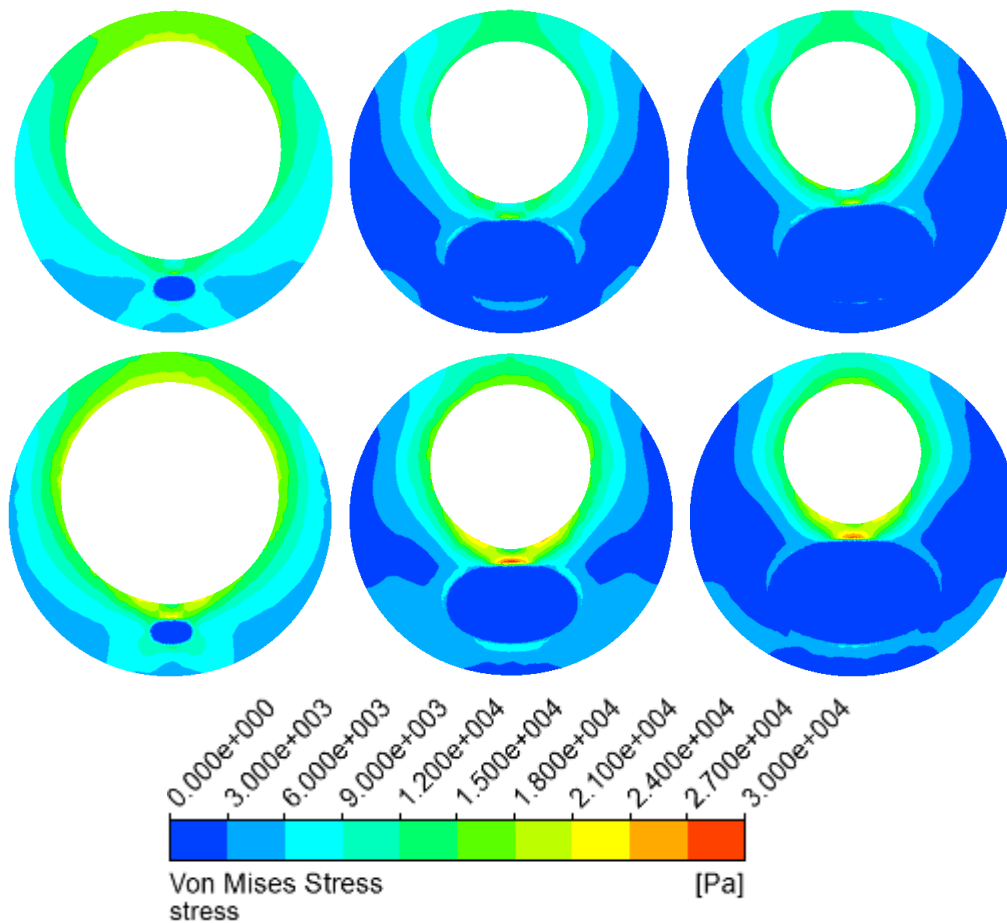


Figure 4- 5 Comparison of VMStress from 2D models (upper) and 3D model (lower) with 60% stenosis for a pulse pressure of 40 mmHg at various cross-sections.

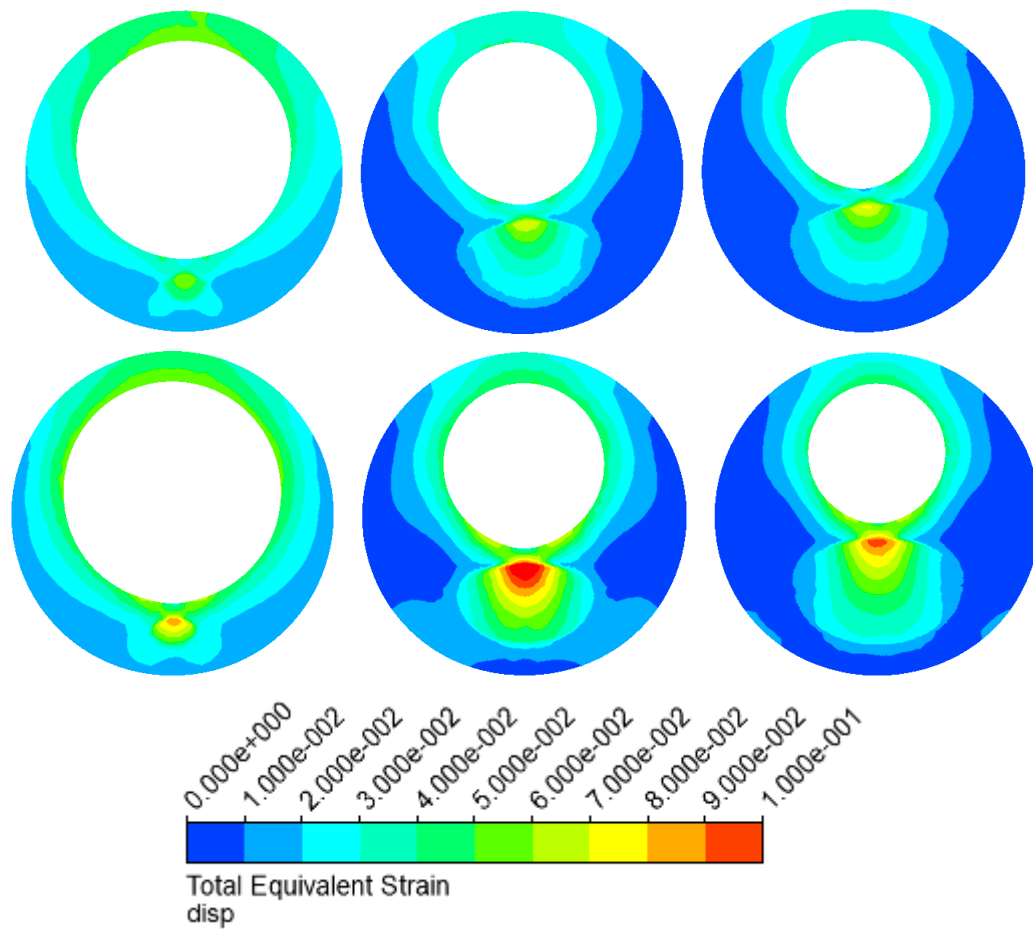


Figure 4- 6 Comparison of VMStrain from 2D models (upper) and 3D model (lower) with 60% stenosis for a pulse pressure of 40 mmHg at various cross-sections.

Similar VMStress and VMStrain patterns were found between the 2D and 3D models, although the predicted VMStress and VMStrain values were lower in 2D models. Because of its importance in predicting plaque rupture, the maximum value of VMstress was compared between the 2D and 3D models, as shown in Figure 4-7. The maximum difference between the 2D and 3D model predictions was 9.6 kPa, observed on the shoulder of the plaque at slice 37. Figure 4-8 shows the linear regression of the maximum VMStress obtained from the two models.

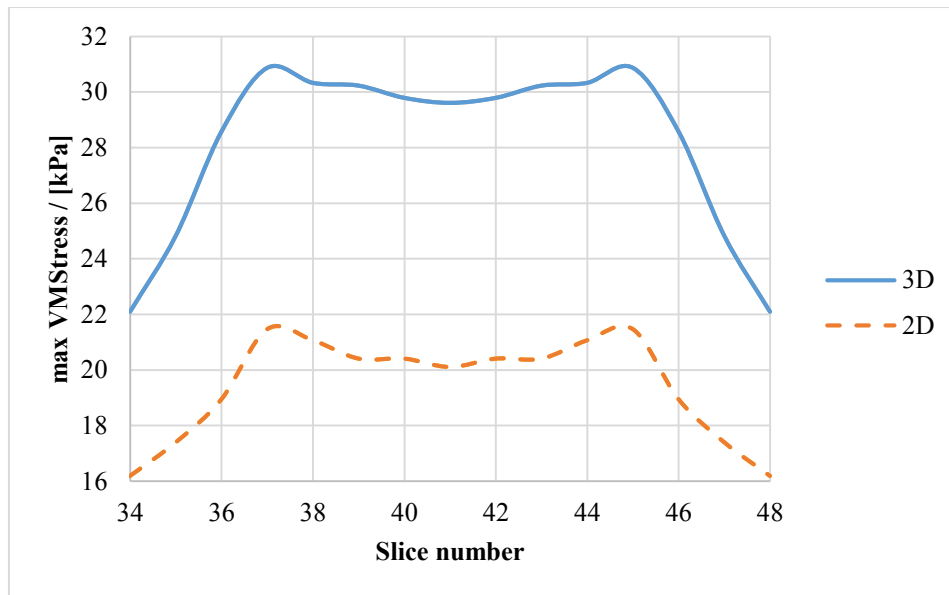


Figure 4- 7 Comparison of the maximum VMStress between the 3D and 2D models with 60% stenosis

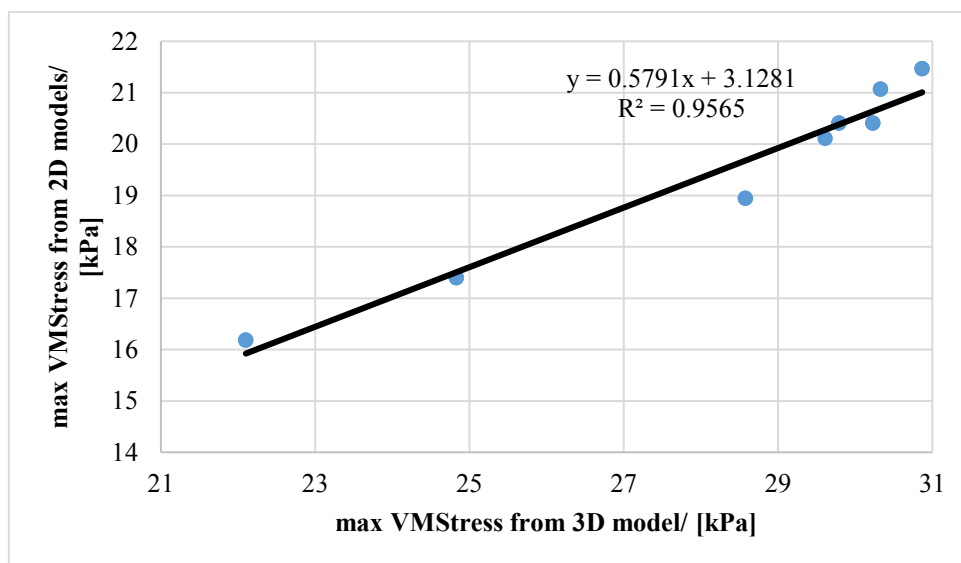


Figure 4- 8 Linear regression of max VMStress between the 3D and 2D models

Cross-sectional average values of VMStress predicted by the 2D and 3D models were also compared. As shown in Figure 4-9, similar trend was found between the two models that with a decrease in lumen area (from slice 34 to 41), the mean VMStress decreased as the lipid pool size increased.

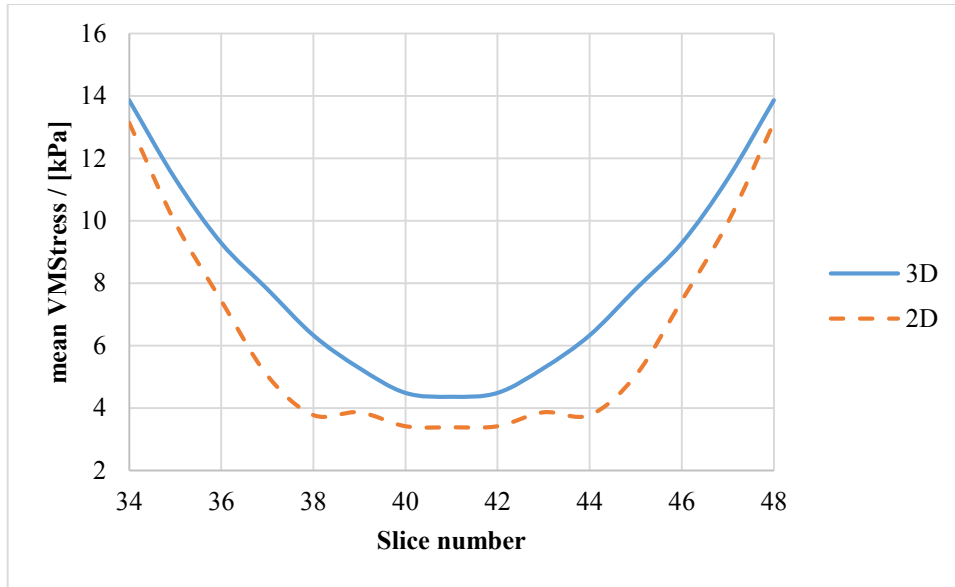


Figure 4- 9 Comparison of cross-sectional average VMStress between the 3D and 2D models

4.3.2. The effect of degree of stenosis on the difference between 2D and 3D models

To examine whether the differences described above would be affected by the degree of stenosis, simulations were repeated for a more severe stenosis (80%), where the narrowest lumen diameter was reduced to 2 mm. VMStress and VMStrain distributions in the longitudinal plane of the 3D model are shown in Figure 4-10. It was interesting to note that due to the increase in the degree of stenosis, the maximum stress and strain were more concentrated on the shoulder of plaque.

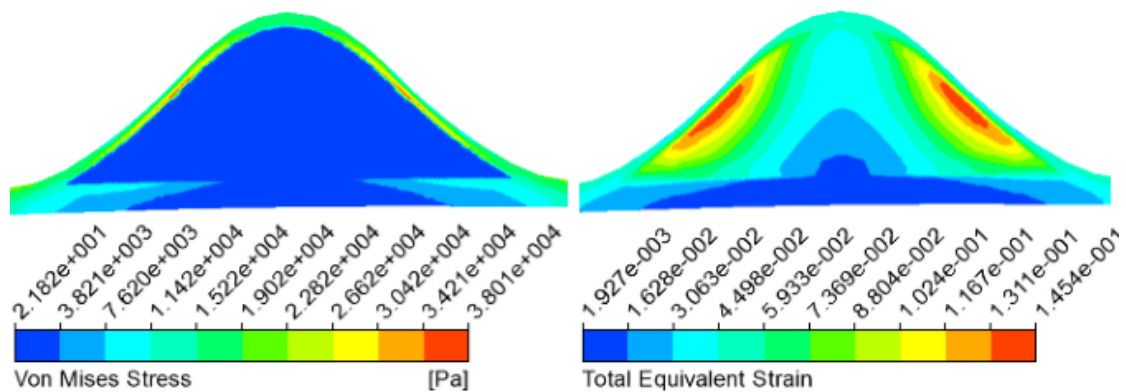


Figure 4- 10 VMStress (left) and VMStrain (right) maps in a longitudinal plane of the idealized 3D model with 80% stenosis for a pulse pressure of 40 mmHg

Results for the maximum VMstress and σ_1 from 2D and 3D models are presented in Figure 4-11 and Figure 4-13, respectively. The comparisons showed that the predicted σ_1 was higher than VMstress and the difference in VMstress between 2D and 3D FE models was larger in the 80% stenosis than 60% stenosis; in the 80% stenosis model, the difference in VMstress between 2D and 3D models (17 kPa) was almost twice as large as in the 60 % stenosis model (9 kPa). Moreover, the degree of stenosis changed the pattern of stress and strain distributions; with 80% stenosis high VMstress occurred on the plaque shoulder as shown in Figure 4-10, while VMstress at the throat was much lower. This was evident from Figure 4-11 where there was a dip in the maximum VMstress at the throat of the 80% stenosis model. Nevertheless, for the same degree of stenosis the mean VMstress patterns were similar between the 2D and 3D models, although there were quantitative differences (Figure 4-11).

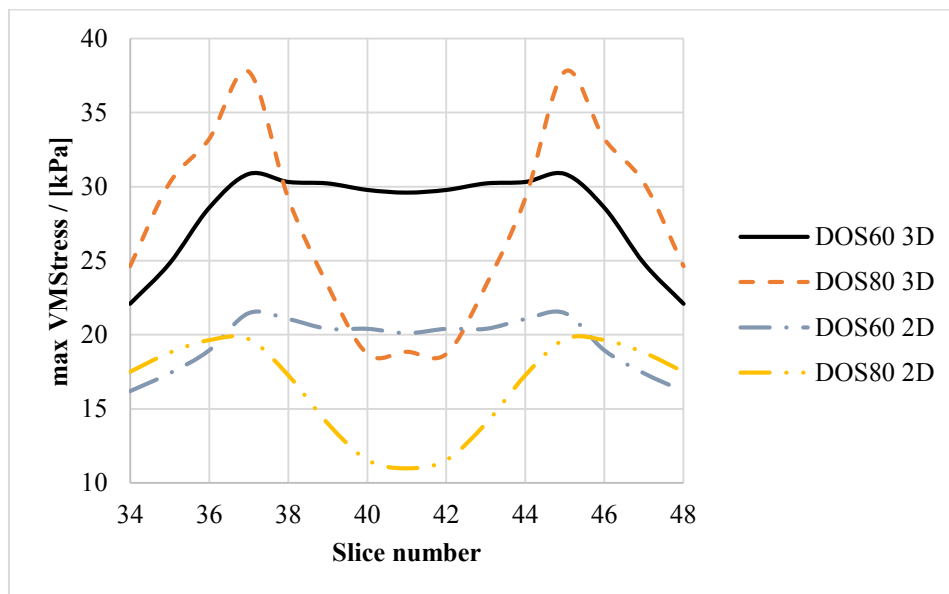


Figure 4- 11 Maximum VMStress in the idealized model with 60% stenosis and 80% stenosis for a pulse pressure of 40 mmHg

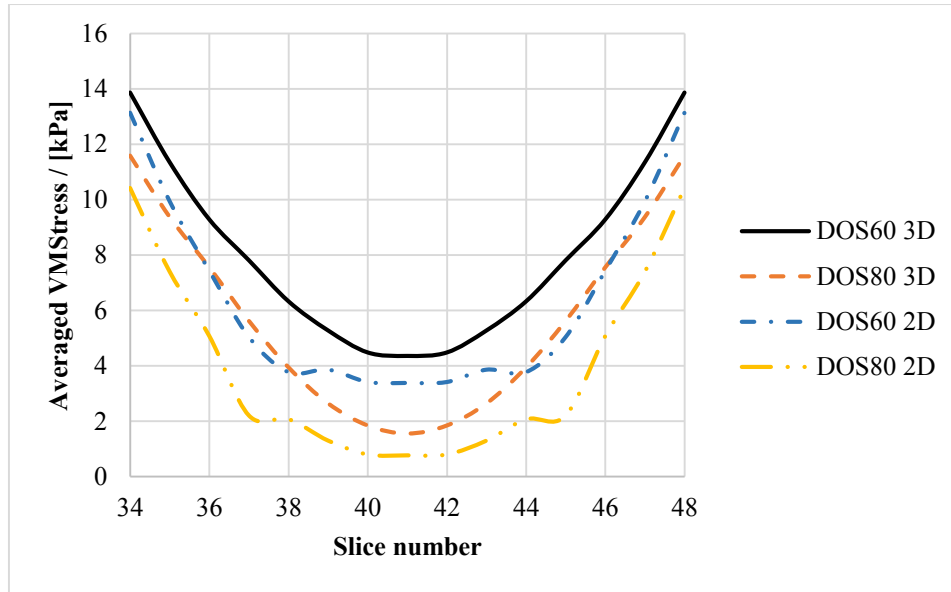


Figure 4- 12 Averaged VMStress in the idealized model with 60% stenosis and 80% stenosis for a pulse pressure of 40 mmHg

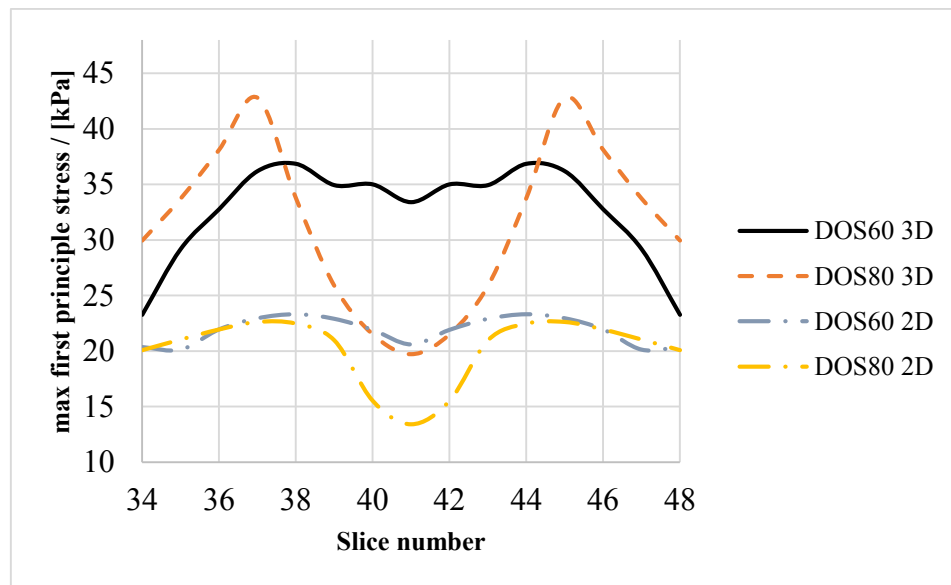


Figure 4- 13 Maximum first principle stress in the idealized model with 60% stenosis and 80% stenosis for a pulse pressure of 40 mmHg

4.3.3. The effect of pulse pressure on the difference between 2D and 3D models

This was investigated by increasing the pressure load on the lumen from 40 mmHg to 60 mmHg in the idealized model with 80% stenosis. Increasing the pulse pressure did

not change the pattern of stress distribution in either 2D or 3D models, but its effect on the magnitude of all stresses was significant. As shown in Figure 4-14, the maximum σ_1 was about 10 kPa higher with a pulse pressure of 60 mmHg compared with a pulse pressure of 40 mmHg. The results suggested that the qualitative trend of σ_1 and VMstress in the 3D model could be predicted by the 2D models (as shown in Figures 4-14 and 4-15).

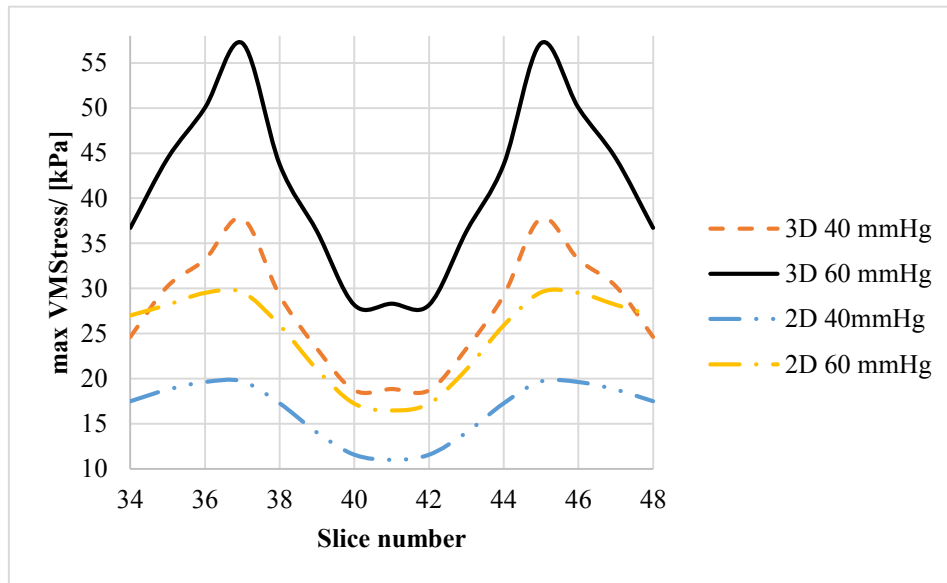


Figure 4- 14 Comparison of maximum VMStress values in the idealized model with 80% stenosis for a pulse pressure of 40 mmHg (left) and 60 mmHg (right)

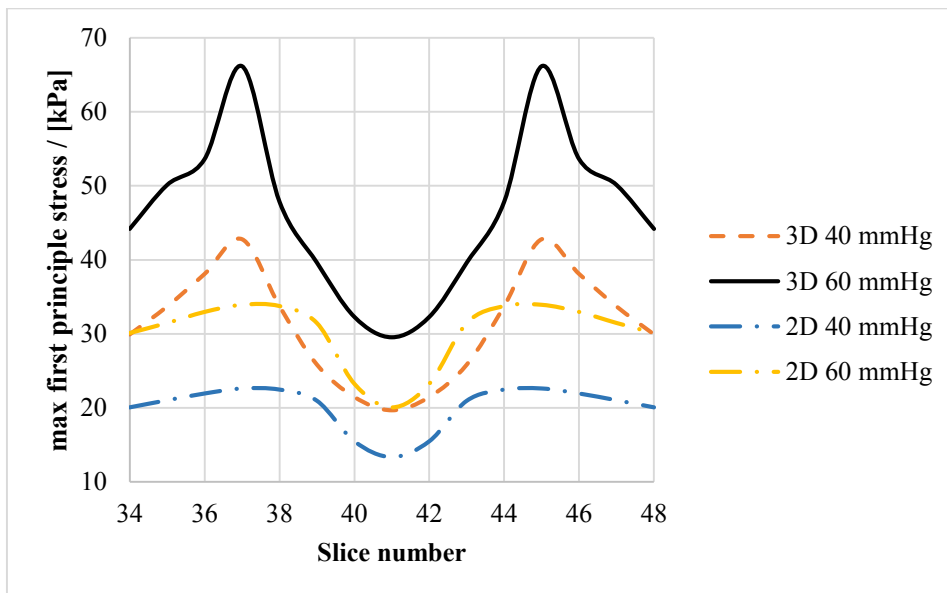


Figure 4- 15 Comparison of maximum first principle stress values in the idealized model with 80% stenosis for a pulse pressure of 40 mmHg (left) and 60 mmHg (right)

4.4. Discussion

Although the 2D and 3D models were subject to different constraints at the boundaries, they provided similar results in terms of stress and strain distributions (Figure 4-5 and Figure 4-6). A large difference in peak stress predicted by 2D and 3D FE models was found. As shown in Figure 4-14, with 80% stenosis for a pulse pressure of 60 mmHg, the maximum VMStress in the 3D FE model was almost doubled compared to that in the 2D FE models. However, the location of peak stress predicted by 2D models was similar to that predicted by the 3D model.

By increasing the degree of stenosis from 60% to 80%, its effect on the difference between 2D and 3D models was determined. As the lumen became narrower, both the 2D and 3D models showed that the location of maximum VMStress and σ_1 moved from the narrowest section to the shoulder of the plaque, forming a dip at the throat of the plaque. The difference in maximum stresses also increased with the degree of stenosis. Therefore, using a 2D model to estimate peak σ_1 and VMStress in a realistic geometry with a severe stenosis ($\geq 80\%$) would incur a larger error compared to smaller degree of stenosis. In order to determine the effect of pulse pressure on the difference between 2D and 3D models, results from 80% stenosis models under pulse pressures of 40 mmHg and 60 mmHg were compared. Both the maximum σ_1 and VMStress were higher in the 3D than in the 2D model, and the difference increased with the pressure load.

Based on *ex vivo* MR and histological images, Tang et al. built a multi-components carotid plaque model to examine the difference between 2D and 3D models of a 78% stenosis (Tang et al., 2004b). Using hyperelastic models for the arterial wall and plaque components, they obtained similar results to this study in that 2D FE model underestimated the maximum VMStress. Maximum σ_1 from their 3D model with 20% axial stretch was 70% higher than that from 2D model. With 20% axial stretch, the σ_1 was 69.6% higher than the result from 2D model. Without axial stretch, there was no marked difference (20%) in σ_1 between their 2D and 3D solid only models (Tang et al., 2004b).

The 2D and 3D FE models have the following limitations: (i) the carotid wall and plaque components were treated as linear materials, (ii) a uniform and constant pressure load was applied, and (iii) the effect of pre-strain and residual stress was neglected. Nevertheless, the results obtained on the 60% stenosis model were similar to those of Tang et al (2004b) for a 78% stenosis with hyperelastic properties. In the 3D model with a higher degree of stenosis (80%), peak VMStress showed a slight increase at the throat compared with the nearby slices (slices 40 and 42) (Figure 4-14), which was not found in the 2D models. This was due to the different boundary conditions applied to the 2D and 3D models and the thickness of fibrous cap. In the 3D model, deformations on the plaque shoulder were restricted by the surrounding tissues, whereas the 2D models were not subject to this constraint. As the carotid artery is a nearly incompressible material, the compressed plaque shoulder would have an effect on the stress and strain distribution in the neighbouring regions.

The peak stress location changed from the narrowest section (in the 60% stenosis case) to the shoulder of plaque (as shown in the 80% stenosis case). This was found in both the 2D and 3D models (Figure 4-11), so the observed change in maximum stress location was not caused by the dimensions of the FE model. The implication of this finding is that for FE analysis of carotid plaques, 2D simulations cannot be performed on the narrowest section only; more slices should be reconstructed from the scanned images and FE analyses carried out in order to capture the maximum stress. In summary, 2D stress analysis can be used as an efficient alternative to 3D analysis of carotid plaques to predict the qualitative pattern of VMstress distribution and critical location prone to rupture. However, 2D models can seriously underestimate the maximum stresses compared to the corresponding 3D models. Moreover, 2D models cannot simulate the non-uniform pressure condition in a carotid artery, and their boundary conditions are different from those in 3D. Therefore, 3D modelling is necessary if the predicted stresses are to be used for clinical assessment of the risk of rupture for an individual plaque.

4.5. Finite element structural analysis of patient-specific models

4.5.1. Patient-specific model based on ultrasound images

The 3D carotid arterial volume was reconstructed from 3D ultrasound images by using the method described in Chapter 3. This was performed for two patients, and the reconstructed geometries are shown in Figures 4-16, where the model for patient 1 had a thinner wall and 68.14 % stenosis, whereas patient 2 had a thicker wall with 71 % stenosis (Figure 4-17). Finite element mesh for the two models was generated using ICEM CFD after centreline, contour and surface smoothing. The wall model was based on the strain-energy function described by the five-parameter Mooney-Rivlin equation, as adopted by other researchers (Gao and Long, 2008). The strain energy function is given by Equation 4-5,

$$W = c_{10}(I_1 - 3) + c_{01}(I_2 - 3) + c_{20}(I_1 - 3)^2 + c_{11}(I_1 - 3)(I_2 - 3) + c_{02}(I_2 - 3)^2 + \frac{1}{d}(J - 1)^2 \quad (4-5)$$

where I_1 and I_2 are the first and second strain invariants, $C = [C_{ij}] = X^T X$ is the right Cauchy-Green deformation tensor, $X = [X_{ij}] = [\frac{\partial x_i}{\partial a_j}]$, with x_i being the current position and a_j being the original position of the deformation tensor. The material parameters were extracted from the literature, with $C_{10}=50,445$ Pa, $C_{01}=30,491$ Pa, $C_{20}=40,000$ Pa, $C_{11}=120,000$ Pa, $C_{02}=10,000$ Pa and $d = 1.44E-7$ Pa⁻¹ (Tang et al., 2004a, Tang et al., 2004b, Gao and Long, 2008). Since no lipid or calcification was found in the cases examined, the carotid artery wall was treated as a single component structure. It was further assumed that the arterial wall was a single-layered homogeneous material with a combined intima and media layer, the thickness of which was extracted from the 3D ultrasound images.

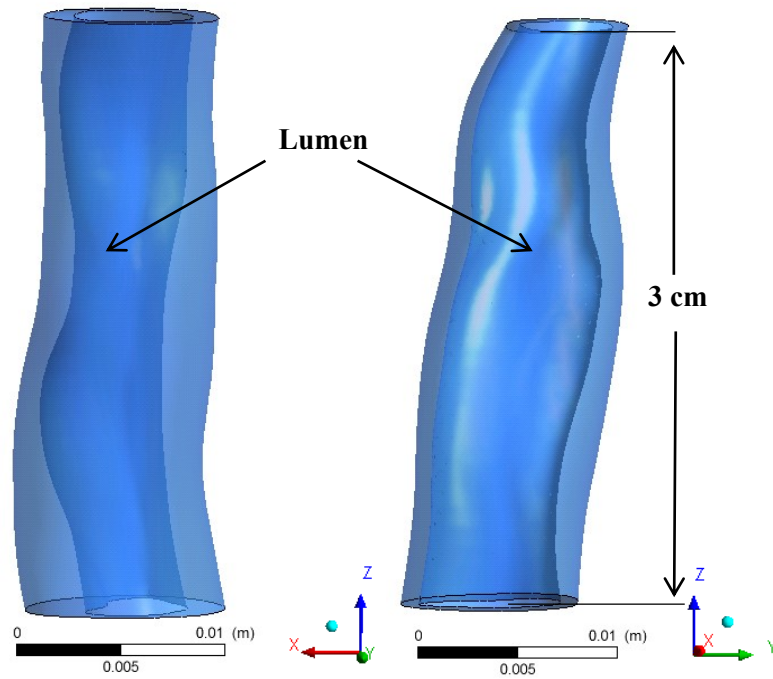


Figure 4- 16 Case 1: 3D reconstructed geometry of the common carotid artery in patient 1

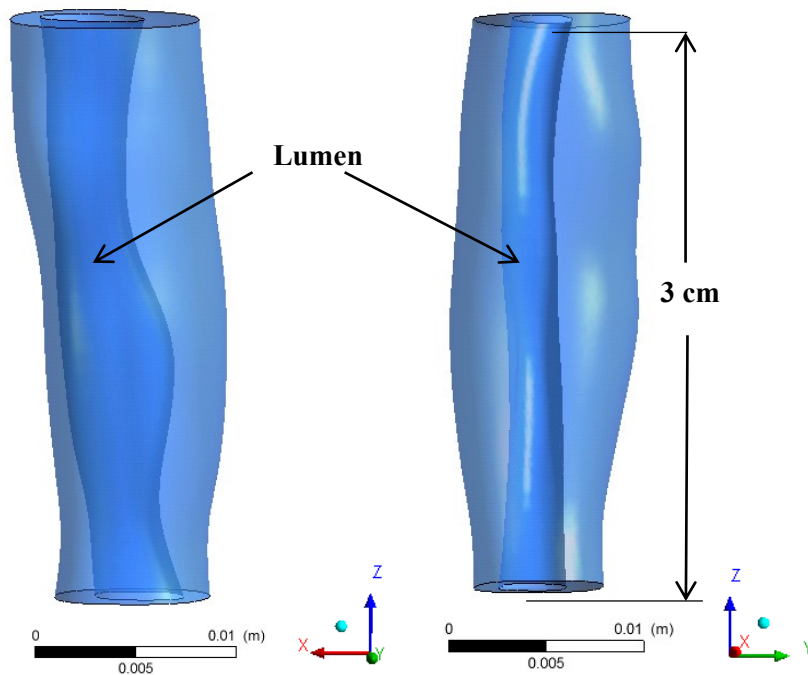


Figure 4- 17 Case 2: 3D reconstructed geometry of the common carotid artery in patient 2

Similar to the idealised model, a second-order 3D 10-node element (SOLID 187) was chosen for structural analysis, as higher order mesh is more suitable for irregular geometries derived from patient-specific data. The geometry was subdivided into tetrahedral elements with a maximum edge size of 0.1 mm and local refinement of 0.05

mm at the lumen surface. Mesh sensitivity tests were performed on both patient-specific models by comparing predicted results of maximum VMStress between a fine and a coarse mesh until differences between solutions from two consecutive meshes are negligible. For the final mesh selected in this study (Table 4-2), differences in the maximum VMStress were less than 3%, and differences in mean VMStress were less than 1%, when compared with a mesh which was 50% finer.

Table 4- 2 Mesh information for the two patient-specific FE models

Patients	Elements	Nodes
1	253179	327993
2	244904	318863

Frontal, lateral and top views of the generated mesh for the carotid artery model of patient 1 are presented in Figure 4-18 as an example.



Figure 4- 18 Spatial discretization of the carotid artery in patient 1: Frontal view (left); Lateral view (middle); Top view (right)

Transient structural analyses were performed with the following boundary conditions: both ends of the wall structure were fixed in all directions and a time-varying pulse

pressure was applied on the inner surface. The pulse pressure waveform was extracted from the literature (Warriner et al., 2008) as shown in Figure 4-19. A fixed time step of 0.01s was specified, and the convergence criteria were 10^{-4} of initial residuals for displacement and 10^{-6} for the force calculation.

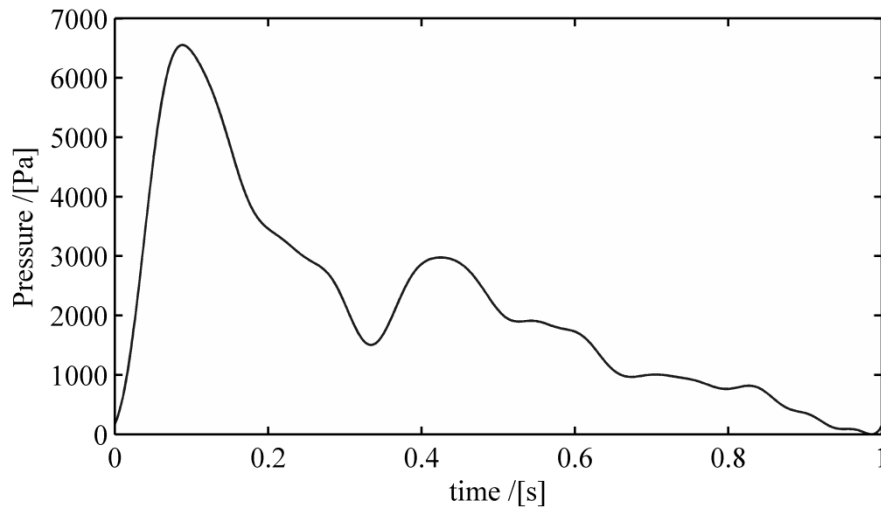


Figure 4- 19 Time-varying pressure applied on the inner wall of the solid only model, extracted from (Warriner et al., 2008). It represents realistic pulse pressure variation in a normal carotid artery with a peak value of 6553 Pa (49 mm Hg).

4.5.2. Results and Discussion

With the time-varying pressure applied on the inner wall, computational simulations were conducted on the patient-specific carotid models shown in Figure 4-16 and Figure 4-17. The effects of hyperelastic material properties were evaluated by examining stress-strain distributions. Figures 4-20 and 4-21 show the predicted VMstress and displacement on the inner surface for patients 1 and 2, respectively. It appears that the maximum VMStresses occurred at the site with the largest curvatures as indicated by the arrows. The locations of maximum displacements were not at the same site as the maximum stresses.

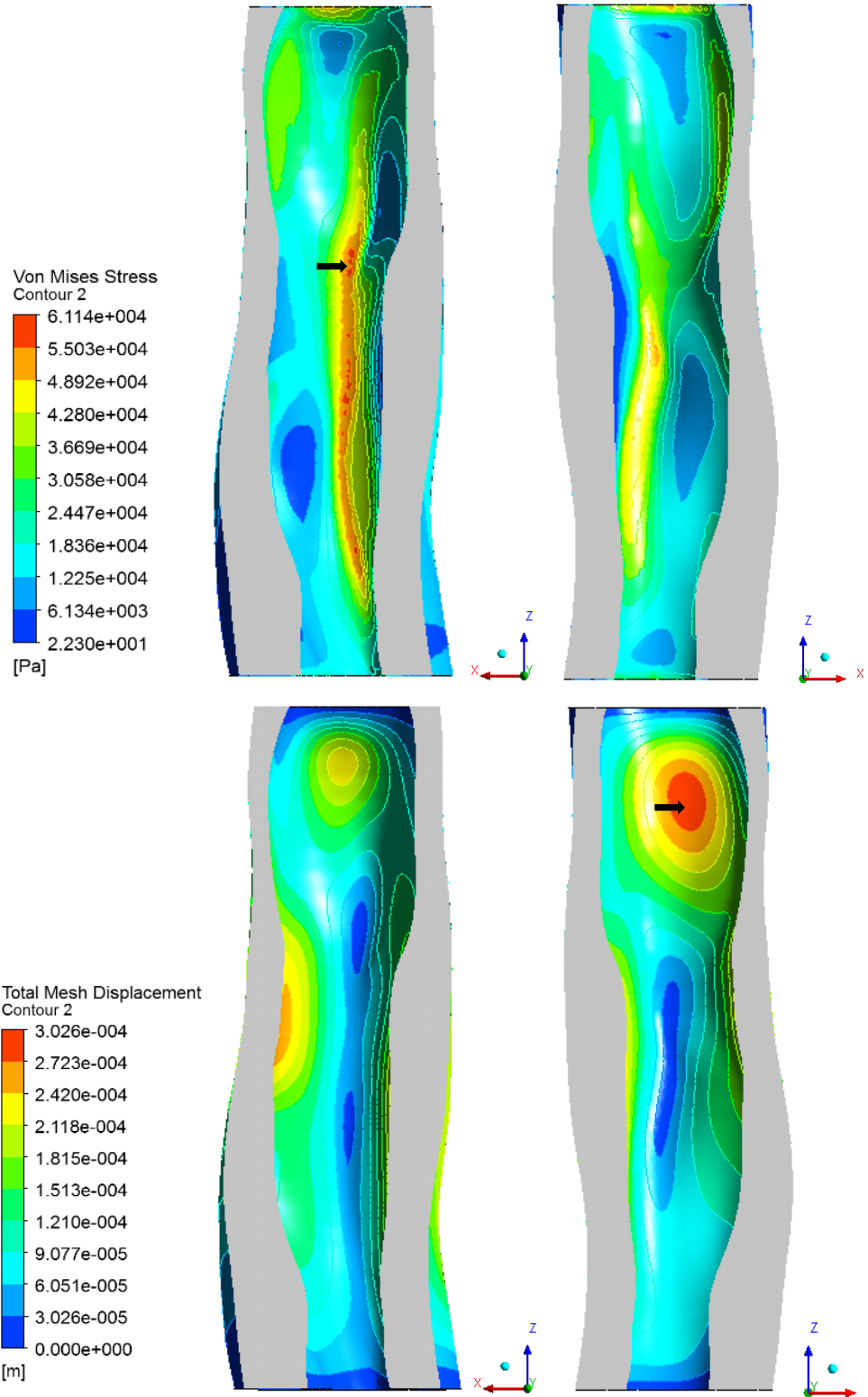


Figure 4- 20 VMStress (upper row) and displacement (lower row) distributions on the inner surface of the carotid artery in patient 1 at 0.1 s (peak systole)

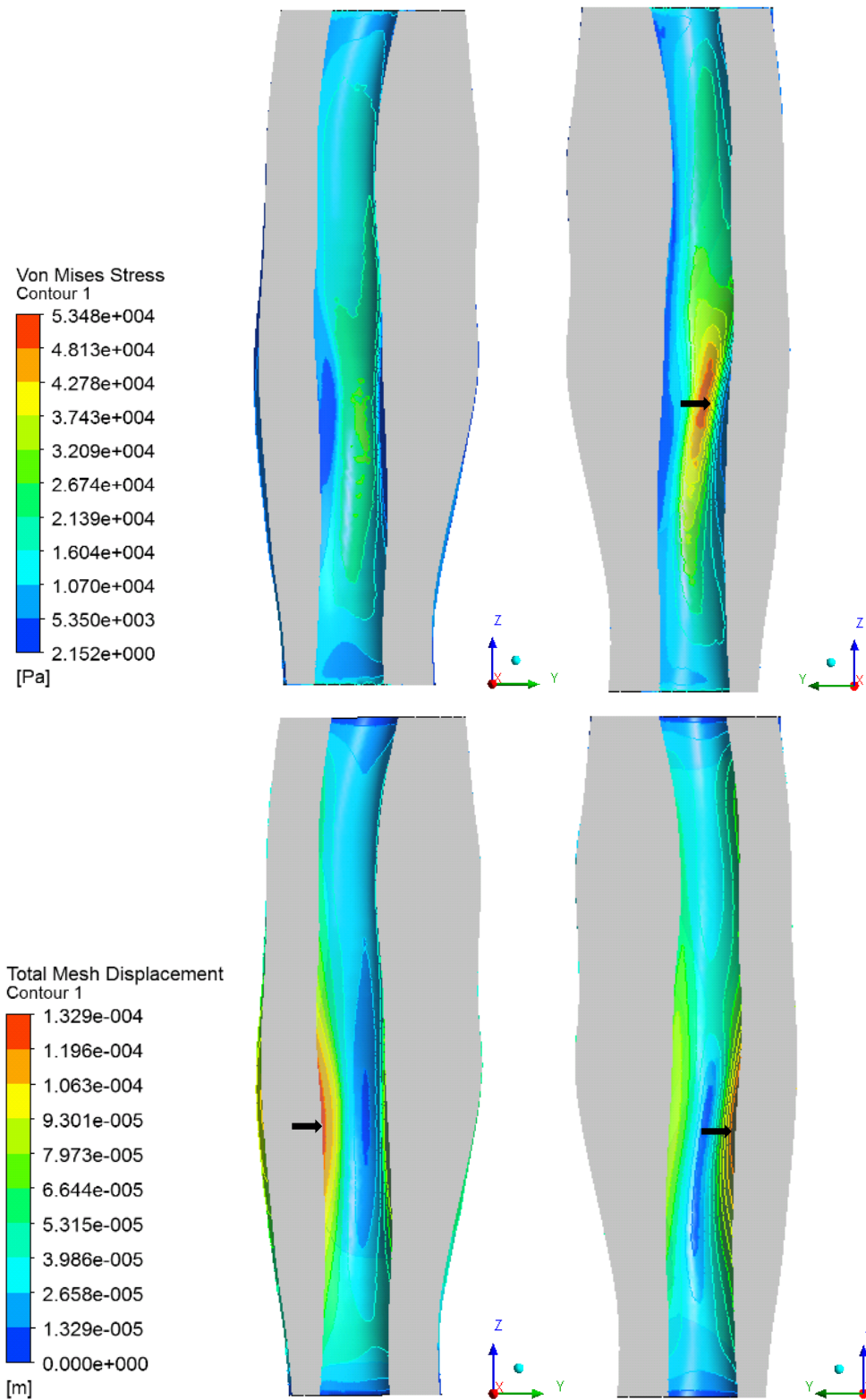


Figure 4- 21 VMStress (upper row) and displacement (lower row) distributions on the inner surface of the carotid artery in patient 2 at 0.1 s (peak systole)

From FE analysis of the two patient-specific models, it can be found that apart from the risk factors listed, such as plaque components and material properties, geometric

features of the arterial wall and plaque were also important in determining the stress/strain distributions in a carotid plaque. Although the carotid artery of patient 2 had a higher degree of stenosis and larger plaque burden, the predicted maximum stress for patient 2 (53.48 kPa) was lower than that for patient 1 (61.14 kPa), indicating that the carotid plaque in patient 2 was less likely to rupture than that in patient 1. Nevertheless, the maximum stresses in both cases were well below the threshold for plaque rupture. By comparing these two patient-specific cases, it showed that increasing stenosis severity actually decreased peak stress in the plaque in the absence of fibrous cap and lipid pool.

4.6. Summary

In this chapter, finite element simulations of stenosed carotid arteries with idealised and realistic geometries are discussed. In order to quantify the difference between 2D and 3D FE analyses of carotid plaque, a hypothetical model was employed and both 2D and 3D FE simulations were carried out for 60% and 80% degree of stenosis, respectively, under two pressure loads, 40 mmHg and 60 mmHg. This study was the first attempt to use a hypothetical model of the carotid plaque for detailed comparisons of 2D and 3D FE structural analyses. The results showed that the maximum and mean VMStress predicted by the 2D and 3D models were qualitatively consistent for a fixed degree of stenosis, although the 2D model predicted a much lower VMStress than the 3D model for 60% stenosis. For the 80% stenosis model, the predicted stress in the 3D model was higher than the 2D FE model, especially for the first principle stress. Differences in VMStress predicted by the 2D and 3D models were less than 33% (mean 31%) for the maximum VMStress and 40% (mean 20%) for cross-sectional averaged VMStress in the 60% stenosis case. The difference in first principle stresses between 2D and 3D FE models was more sensitive than VMstress to the increase in the degree of stenosis.

The comparative study suggests that 2D finite element analysis is sufficient for predicting the qualitative pattern of stress distribution and the location of peak value for carotid arteries with a moderate degree of stenosis; this would significantly reduce the computational time, allowing more patient data to be processed and analysed in a limited time frame. The level of agreement in stress and strain predicted by 2D and 3D

models is related to the degree of stenosis while the fibrous cap thickness and pressure value on the lumen only affect the peak value of the stress and strain. 2D FE analysis may also be used to evaluate qualitatively the stress distribution as a part of risk assessment when limited medical images are available. However, for more accurate predictions, 3D FE analysis is required. As shown in the 80% stenosis case, peak stress is not necessarily located at the throat of the plaque.

The degree of stenosis and plaque burden of the carotid arteries in patient 1 and patient 2 were calculated in Chapter 3. Although based on ultrasound images alone, patient 2 had a higher risk for plaque rupture than patient 1, the carotid plaque of patient 2 experienced a lower peak stress, suggesting that it would be more stable and less likely to rupture. Plaques characterized by a high degree of stenosis and high plaque burden do not necessarily experience high mechanical stresses as detailed geometric features and plaque components determine the stress distribution. Therefore, it would be desirable to combine ultrasound image analysis with FE stress analysis for a more accurate assessment of a patient's risk for carotid plaque rupture.

Chapter 5 Modelling the viscoelastic behaviour of the carotid artery

This chapter is focused on the viscoelastic characteristics of the carotid artery and their effect on vessel wall displacement in radial and longitudinal directions. Methods to represent carotid wall viscoelastic behaviour based on *in vivo* ultrasound data are also described. Finally, results obtained from finite element analyses of the two patient-specific cases with a viscoelastic material model are discussed.

Researchers have long sought for improved understanding of the mechanical behaviour of the arterial wall, as discussed in Chapter 2. The dynamics of the arterial wall under pulsatile pressure is affected by the development of arterial diseases and ageing. A number of *in vivo* studies have been carried out where measurements of vessel wall displacements were made in both radial and longitudinal directions (Ahlgren et al., 2012, Ahlgren et al., 2009, Cinthio et al., 2006, Cinthio et al., 2005, Persson et al., 2003, Svedlund and Gan, 2011a). However, there is a lack of study on the effects of viscoelasticity as well as the longitudinal displacement of the vessel wall on the stress and strain distribution in carotid arteries, which will be addressed in this chapter.

5.1. Viscoelastic material properties represented by Prony series

Prony series for the characterization of linear viscoelastic behaviour is used widely in polymer industry. The relaxation modulus and creep compliance of the material described by either the generalized Maxwell or the generalized Kelvin-Voigt model can be represented by this particular series (Park and Schapery, 1999). It offers straightforward fitting of experimental data to linear viscoelastic material function by numerical conversion. There are two Prony series representations, one for the generalized Maxwell model (for relaxation behaviour) and one for the generalized

Kelvin model (for creep behaviour). From these two representations, the observed relaxation and creep behaviour can be converted into complex (or dynamic) and Laplacian domains. As shown subsequently, conversion of the material functions into other domains involves solving a linear system of equations. Park and Schapery (1999) reported very high levels of confidence for these methods with errors in converting from a modulus function to a compliance function not exceeding 1%.

When dealing with the time-dependent response of viscoelastic materials, the volumetric and deviatoric behaviours are usually considered separately. The constitutive model is given by (ANSYS, 2012):

$$\sigma(t) = \int_0^t 2G(t-\tau) \frac{d\epsilon_d}{d\tau} d\tau + I \int_0^t 2K(t-\tau) \frac{d\epsilon_v}{d\tau} d\tau \quad (5-1)$$

Both shear modulus G and bulk modulus K can be described by Prony series, which permits the development of efficient numerical solutions for linear viscoelastic boundary value problems, and can be readily implemented in finite element programs. Inter-conversion between linear viscoelastic material functions based on Prony series has been well documented (Park and Schapery, 1999, Schapery and Park, 1999). For simplicity, detailed descriptions are given for the shear modulus G only. The relative shear modulus in the form of Prony series is defined as:

$$\alpha^G(t) = \frac{G(t)}{G_0} \quad (5-2)$$

Here $G(t)$ is the shear stress relaxation modulus at time t , and G_0 is the shear stress relaxation modulus at time 0. This dimensionless modulus can also be expressed by series expansion in exponential form:

$$\alpha^G(t) = 1 - \sum_{i=1}^m \alpha_i^G (1 - e^{-\frac{t}{\rho_i}}) \quad (5-3)$$

where α_i^G is the coefficient of Prony series, and ρ_i is the relaxation time. The real and imaginary parts of shear modulus, $G'_{(f)}$ and $G''_{(f)}$, can be determined based on Equations 5-4 and 5-5.

$$G'_{(\omega)} = G_0(1 - \sum_{i=1}^m \alpha_i^G) + G_0 \sum_{i=1}^m \frac{f^2 \rho_i^2 \alpha_i^G}{f^2 \rho_i^2 + 1} \quad (5-4)$$

$$G''_{(\omega)} = G_0 \sum_{i=1}^m \frac{f \alpha_i^G}{f^2 \rho_i^2 + 1} \quad (5-5)$$

The initial guess of G_0 is determined by the static elastic modulus (Raghu et al., 2011). In the inverse relationships given by (Equation 5-4) and (Equation 5-5), α_i^G and ρ_i of the viscoelastic material can be computed by data fitting using the nonlinear least-squares method in Matlab.

More details about the method of inter-conversion between linear viscoelastic material functions can be found in the literature (Park and Schapery, 1999, Schapery and Park, 1999).

5.2. Viscoelasticity of the carotid artery

Many studies have attempted to correlate biomechanical stresses with the vulnerability of atherosclerotic plaques, using finite element analyses. However, none of the patient-specific studies has considered the viscoelastic behaviour of arterial wall. Given the importance of biomechanical stress in the progression of atherosclerotic disease, it is necessary to examine the effect of viscoelastic behaviour, such as hysteresis, on the stress and deformation of large arteries. Several investigators have studied the viscoelastic behaviour of the carotid artery, by using the Kelvin-Voigt model (Valdez-Jasso et al., 2011, Hasegawa and Kanai, 2004, Bukac and Canic, 2013, Valdez-Jasso et al., 2009), Zener model (Balocco et al., 2010), or a detailed structural version of the general Maxwell model (Svedlund and Gan, 2011a, Hodis and Zamir, 2008, Holzapfel et al., 2002). Although these simplified models have limited numbers of elements, the predicted pressure-area loop agrees well with measured data (Valdez-Jasso et al., 2011). It has also been shown that a healthy carotid artery can be adequately described by a linear viscoelastic model under physiological loading conditions (Valdez-Jasso et al., 2011).

Measuring the viscoelasticity of vessel wall is a complex problem. A wide range of experimental studies of large arteries have been carried out both in animals (Armentano et al., 1995b, Silver et al., 2003b, Garcia et al., 2012, Alastrue et al., 2008, Barber, 2005, Valdez-Jasso et al., 2009) and in human (Antonov et al., 2008, Armentano et al., 2006). Silver et al. carried out incremental tests on porcine aorta, carotid artery and vena cava; they found that elastic and viscous stress-strain curves were approximately linear in each of the low and high strain regions (Silver et al., 2003a). The time-dependent behaviour of viscoelastic properties was examined by Garcia et al. in their relaxation tests on swine carotid arteries, which showed different relaxation behaviour in the distal and proximal regions (Garcia et al., 2012).

Armentano et al. measured the viscoelastic aortic properties in dogs (Armentano et al., 1995b), as well as the carotid and femoral viscoelasticity in human vessels (Armentano et al., 1995a), which have been used in subsequent computational studies (Bukac and Canic, 2013, Canic et al., 2006). The parameters of viscoelastic properties can also be estimated by solving an inverse problem based on iterations between measured wall motion and finite element predictions (Aglyamov et al., 2004) or through fitting to a chosen viscoelastic model (Balocco et al., 2010, Bia et al., 2005, Valdez-Jasso et al., 2011).

Using asymptotic and homogenization theory, Canic et al. developed a ‘one-and-a-half dimensional’ model to investigate the radial viscoelastic behaviour of the vessel wall (Canic et al., 2006). However, due to the fully tethered boundary condition, longitudinal displacement was excluded. Warriner et al. presented an analytically-based computational model by extending the Womersley solution for pulsatile blood flow in viscoelastic arteries (Warriner et al., 2008). This offered a starting point in the study of longitudinal wall movement.

5.3. Structure model with viscoelastic arterial wall behaviour

The results presented here consist of three parts. In the first section the emphasis is on the utility of Prony series for representation of the viscoelastic behaviour of the carotid artery. By converting the corresponding measurements to Prony series, viscoelastic

material properties derived from *in vivo* data can be employed in ANSYS. In the second part, the effect of vessel wall viscosity is investigated based on the Kelvin-Voigt model. Finally, results obtained from the viscoelastic model are compared with those from the hyperelastic model using both single-layered and multi-layered carotid structures.

5.3.1. Representation of complex modulus using Prony series

To describe subject-specific viscoelasticity of the carotid artery, values for the elastic moduli can be determined from blood pressure and diameter waveforms measured *in vivo* (Hasegawa and Kanal, 2004, Zhang et al., 2005), using the expression for the complex material function, E^* .

$$E^* = \sqrt{E_0^2 + (2\pi f \cdot \eta)^2} \cdot \exp(i \cdot \arctan \frac{2\pi f \cdot \eta}{E_0}) \quad (5-6)$$

where E_0 is the static elastic modulus, f is the dynamic frequency, which is the actuation frequency in ultrasound measurement and η is the viscosity constant. Elastic moduli at multiple frequencies can be obtained by generating changes in internal pressure due to remote cyclic actuation. For normal human carotid arteries, E_0 is 260,000 Pa, and η is 3,000 Pa·s (Warriner et al., 2008).

In the absence of *in vivo* pressure and diameter measurement in the present study, the real and imaginary parts of the dynamic shear modulus obtained in the literature (Warriner et al., 2008) were converted and represented in the form of Prony series.

$$G'_{(\omega)} = G_0(1 - \sum_{i=1}^m \alpha_i^G) + G_0 \sum_{i=1}^m \frac{f^2 \rho_i^2 \alpha_i^G}{f^2 \rho_i^2 + 1} \quad (5-7)$$

$$G''_{(\omega)} = G_0 \sum_{i=1}^m \frac{f \alpha_i^G}{f^2 \rho_i^2 + 1} \quad (5-8)$$

where $G(t)$ is the shear stress relaxation modulus at time t , G_0 is the shear stress relaxation modulus at time 0, α_i^G is the coefficient of Prony series, and ρ_i is the

relaxation time.

The conversion was achieved by solving an inverse problem where the Prony series was obtained based on values for the real and imaginary parts of shear modulus G (i.e. G' and G''). First, initial values for G_0 , α_i^G and ρ_i were specified, and the number of terms of the Prony series was set at 5 (i.e. $m=5$). A built-in function in MATLAB called “lsqcurvefit.m” was used to fit the shear modulus into Prony series. This function is based on the least-squares algorithm which aims to optimize a set of parameters by minimising the sum of the squares of the error.

$$\min_x \frac{1}{2} \|F(x, xdata) - ydata\|^2 = \min_x \frac{1}{2} \sum_{i=1}^n (F(x, xdata_i) - ydata_i)^2 \quad (5-9)$$

where coefficient x represents the variable to be solved. For the case of relaxation modulus α_i^G , the given $xdata$ and $ydata$ are the relaxation time τ_i , and shear modulus, respectively. To optimize the solution, x should have a lower and upper bound, lb and ub , respectively. A list of the parameters used in curve-fitting is given in Table 5-1.

Table 5- 1 Parameters for curve-fitting of shear modulus into Prony series

Curve-fitting parameter	Value
Maximum number of iterations	1×10^8
Termination tolerance	1×10^8
Termination tolerance on x	1×10^{-6}
Lower boundary	0
Upper boundary	∞

Although *lsqcurvefit* can be used to solve complex-valued problems directly by using the Levenberg-Marquardt algorithm, this algorithm does not accept bound constraints, and may produce negative values. Hence in this study, the shear modulus was split into real and imaginary parts, as shown in Figures 5-1 and 5-2, which shows good agreements between the fitted Prony series and original data.

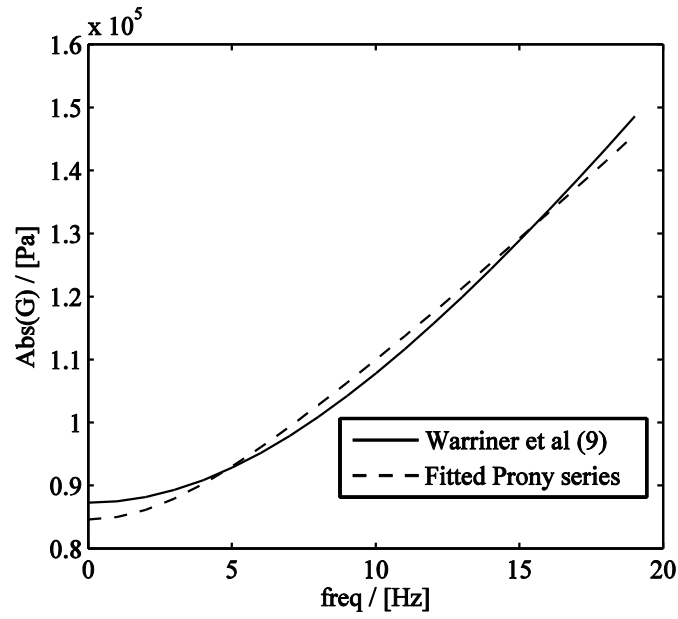


Figure 5- 1 Absolute value of dynamic shear modulus from the literature (Warriner et al., 2008) and the fitted data.

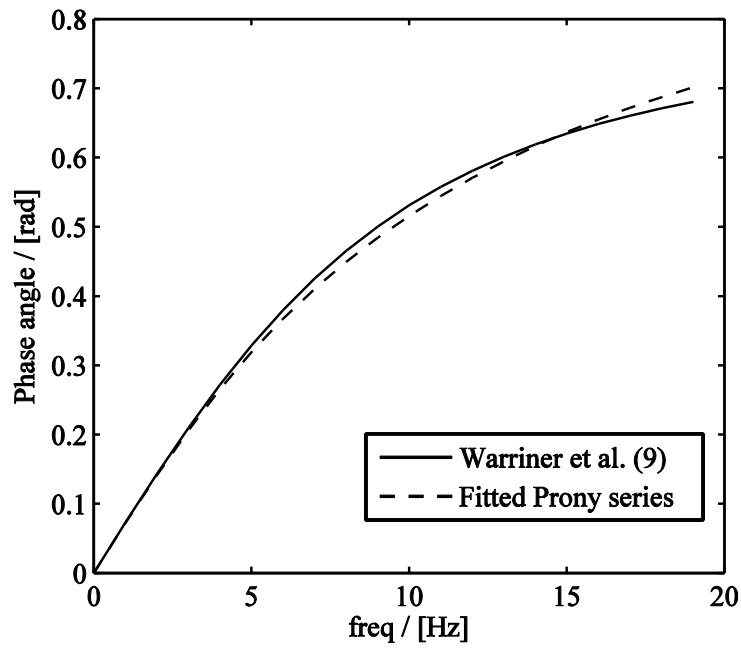


Figure 5- 2 Phase angle of dynamic shear modulus from the literature (Warriner et al., 2008) and fitted data.

5.3.2. Effect of wall viscosity

As a first attempt, an idealized (i.e. a straight tube) three-dimensional model of the

common carotid artery was adopted, so that comparisons between the numerical and analytical solutions (Warriner et al., 2008) could be made. The model is a straight circular cylinder with a diameter of 6 mm (Krejza et al., 2006), a length of 10 diameters, and a uniform wall thickness of 0.6 mm (Bussy et al., 2000). The computational meshes were generated by using ANSYS ICEM CFD, with second order hexahedral mesh for the wall. The computational mesh consisted of 10,000 elements in the vessel wall. Mesh independence tests showed that the differences in peak Von Mises stresses in the wall were less than 1% between the 10,000 and 20,000 elements meshes.

By employing the Kelvin-Voigt model, three wall viscosities were tested: 3,000 Pa·s, 6,000 Pa·s and 9,000 Pa·s, while the elastic moduli were all fixed at 26,000 Pa. After transformation into the form of Prony series, the parameters of viscoelastic materials are listed below.

Table 5- 2 Parameters of viscoelastic materials for hollow, fluid-free models in the form of Prony series to investigate the viscous effect on the vessel wall (see Eqn. 5-4 and Eqn. 5-5 and the relevant text for definitions of symbols)

η / [Pa·s]	G_0 / [Pa]	ρ_1 / [s]	α_1^G	ρ_2 / [s]	α_2^G
3,000	591,470	0.01	0.8401	0.1	0.0134
6,000	894,400	0.01	0.8315	0.1	0.0716
9,000	1189,300	0.01	0.8167	0.1	0.1065

The boundary conditions applied on the hollow, fluid-free models were: both ends of the structure were fixed in all directions, and a time-varying pulse pressure was applied on the inner wall. The pulse pressure waveform was extracted from the literature (Warriner et al., 2008) as shown in Figure 5-3.

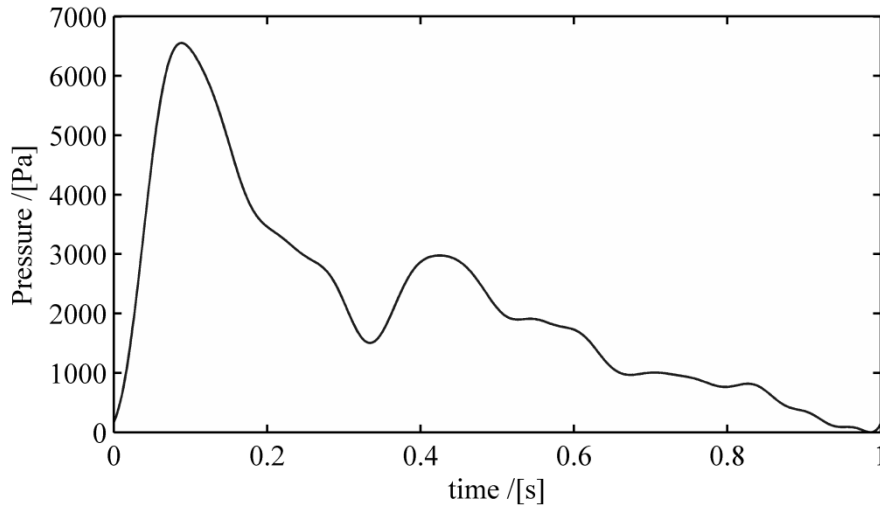


Figure 5- 3 Time-varying pressure applied on the inner wall of the hollow model, extracted from (Warriner et al., 2008). It represents realistic pulse pressure variation in a normal carotid artery with a peak value of 6553 Pa (49 mm Hg) at 0.090s.

Figure 5-4 shows the comparison of calculated radial displacements for different wall viscosities while the elastic moduli in the Kelvin-Voigt models were kept the same. In this case, the static elastic modulus E_0 was 260 kPa. The results show that the radial displacement decreased as the wall viscosity was increased. Increasing the wall viscosity from 3 kPa·s to 9 kPa·s reduced the peak radial displacement, but displacements in diastole were not sensitive to changes in wall viscosity. Comparison with the applied pressure waveform suggested that there was a small phase lag between the pressure and radial displacement as a result of the viscous behaviour of the wall.

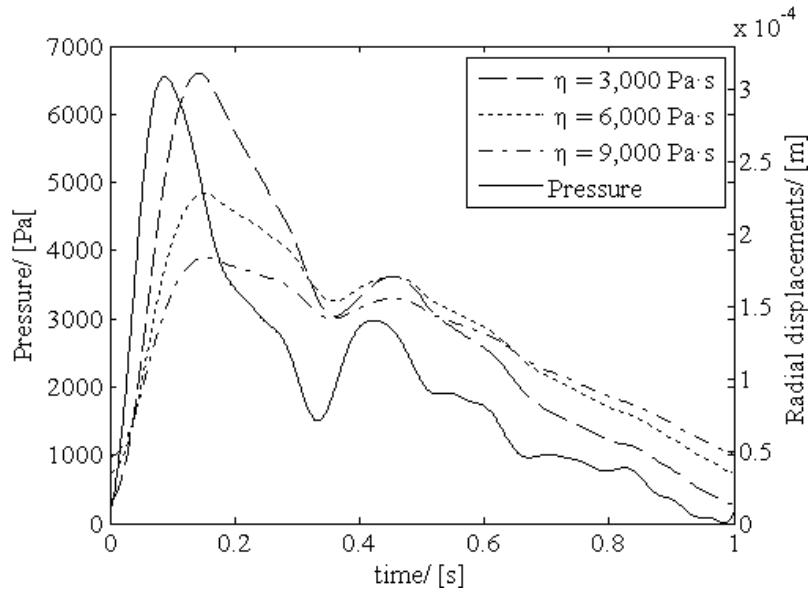


Figure 5- 4 Numerical results of radial displacements for different wall viscosities and the pressure input using the hollow model.

5.3.3. Patient-specific models with viscoelastic wall behaviour

Patient-specific models of the carotid arteries presented in Chapter 4 were employed here, together with the same computational meshes. The viscoelasticity of the carotid arteries was described using the Prony series obtained in the preceding sections. The pulse pressure waveform extracted from the literature (Warriner et al., 2008), as shown in Figure 5-3, was applied at the inner surface, while both ends of the models were fixed in all directions. In order to compare results from the viscoelastic model with the corresponding results from the hyper-elastic model presented in Chapter 4, transient structure analyses were performed under the same conditions as for the hyperelastic model.

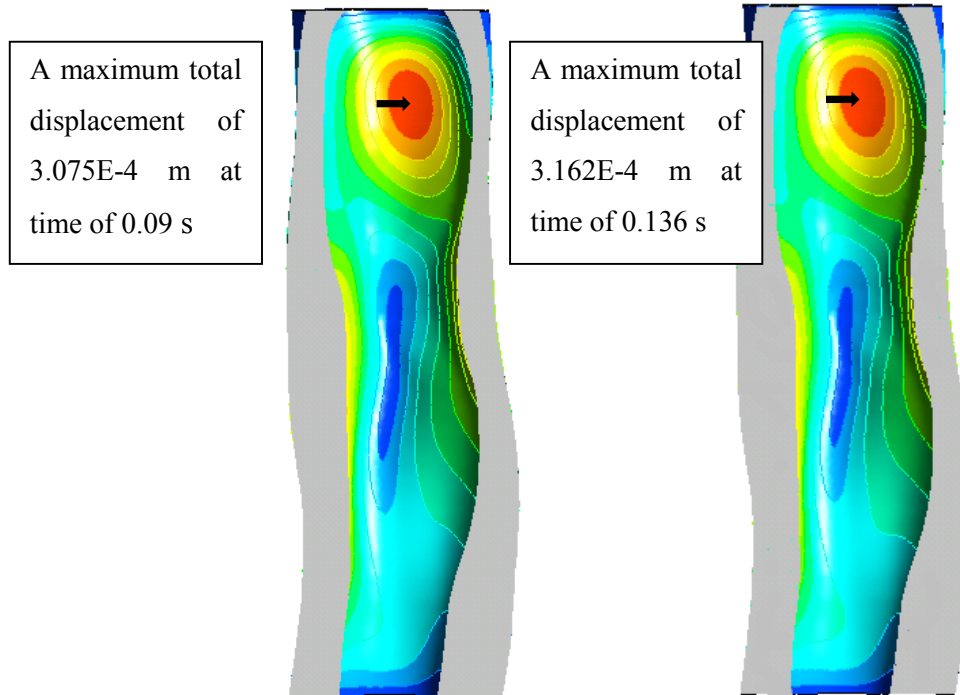


Figure 5- 5 Total displacement of the inner wall of the carotid artery in patient 1: results from the hyper-elastic model showing peak displacement at 0.09 s (left) and results from the viscoelastic model showing peak displacement at 0.136 s (right).

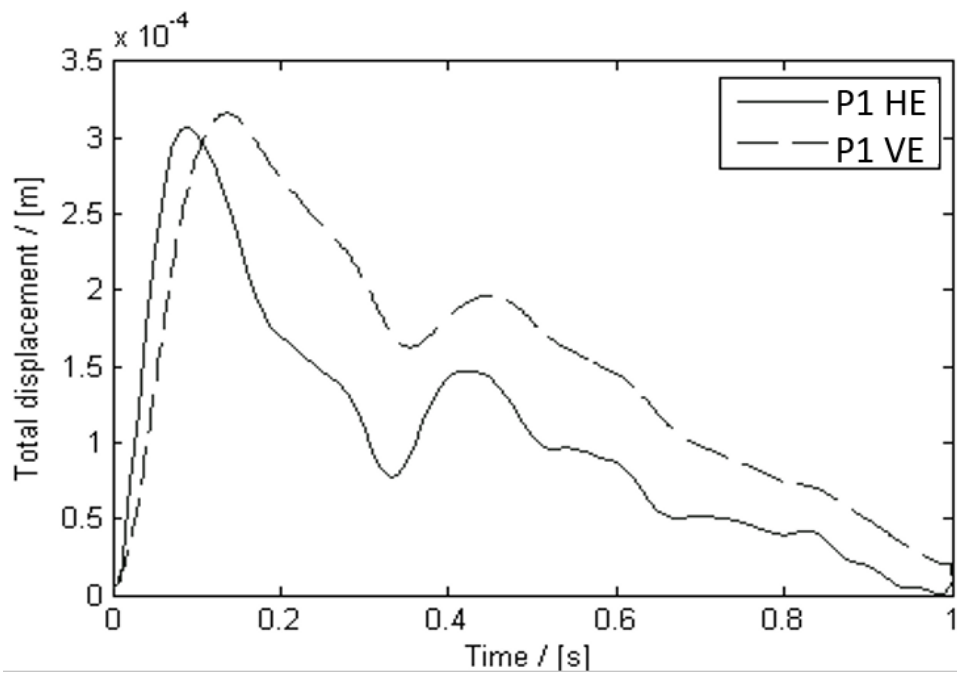


Figure 5- 6 Variations of the maximum total displacement of the carotid artery in patient 1: comparison between the hyper-elastic model (P1 HE) and the viscoelastic model (P1 VE)

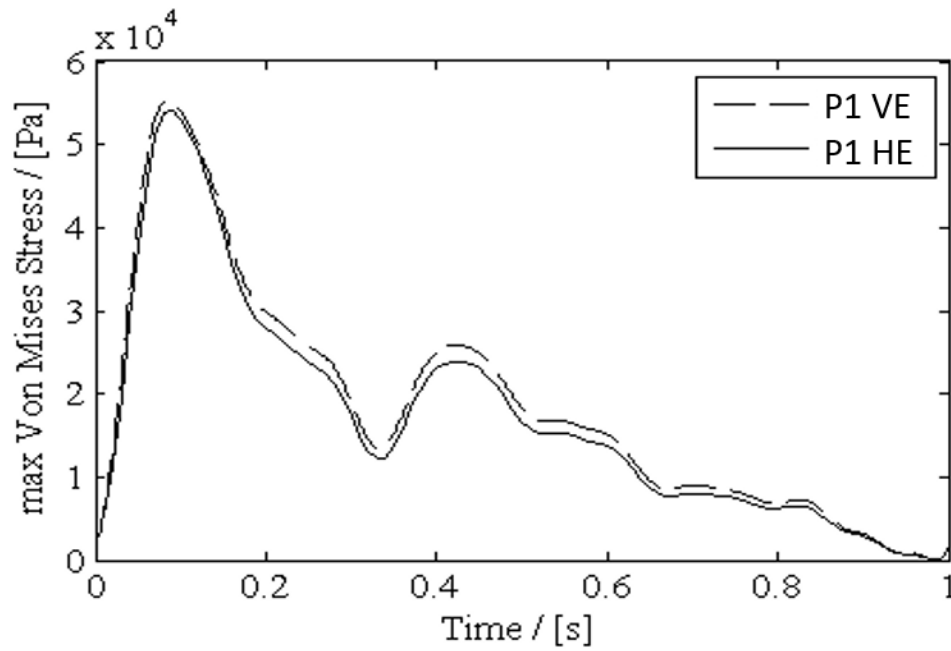


Figure 5- 7 Variation of the maximum Von Mises stress in the carotid artery of patient 2: comparison between the hyper-elastic model ((P2 HE) and the viscoelastic model (P2 VE)

As shown in Figure 5-5, the peak total displacement from the hyper-elastic model occurred simultaneously when the pressure reached its peak at 0.09 s. However, due to the viscosity of the arterial wall, the maximum total displacement occurred 0.046 s after the peak pressure in the viscoelastic model. The hysteresis between the pressure waveform and displacement waveform may change the flow pattern inside the carotid artery. Similar results were also found in the case of patient 2, as shown in Figures 5-8, Figure 5-9 and 5-10.

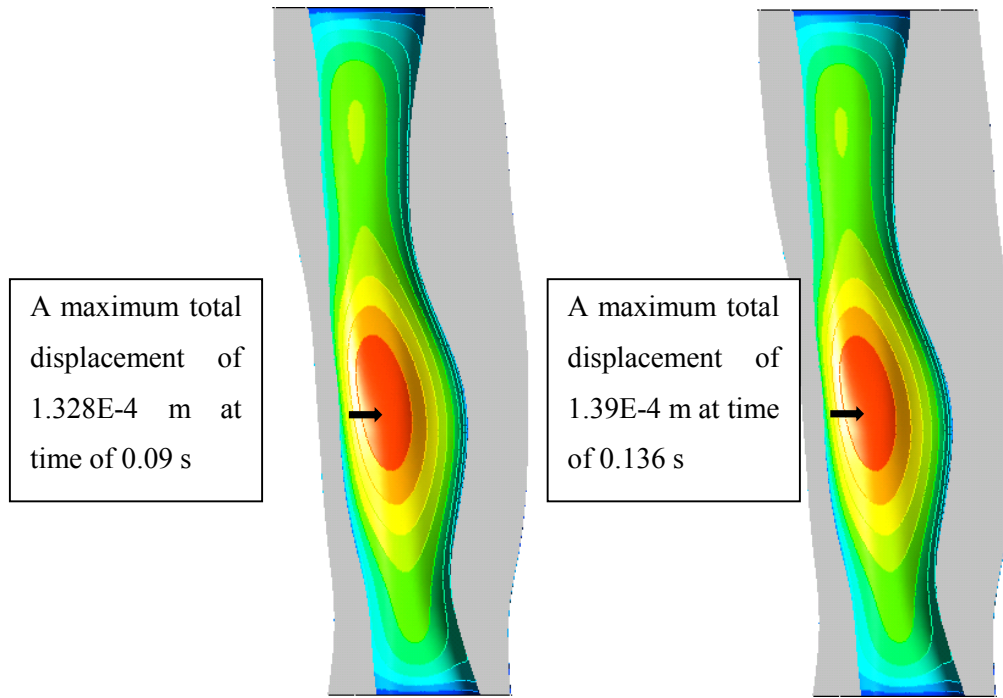


Figure 5- 8 Total displacement of the inner wall of the carotid artery in patient 2: results from the hyper-elastic model showing peak displacement at 0.09 s (left) and results from the viscoelastic model showing peak displacement at 0.136 s (right).

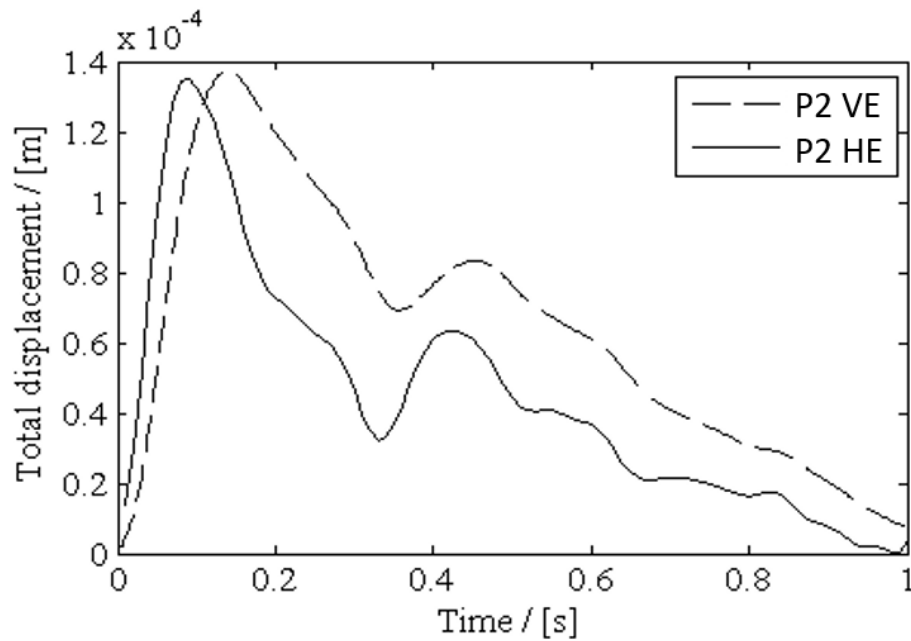


Figure 5- 9 Variation of the maximum total displacement of the carotid artery in patient 2: comparison between the hyper-elastic model (P2 HE) and the viscoelastic model (P2 VE)

Based on the two patient-specific cases, the phase lag due to hysteresis of the viscoelastic wall was 0.046 s. By comparing the hyper-elastic model with the viscoelastic model, the pattern of total displacement distributions changed very little,

but the peak and average values were slightly higher with the viscoelastic model.

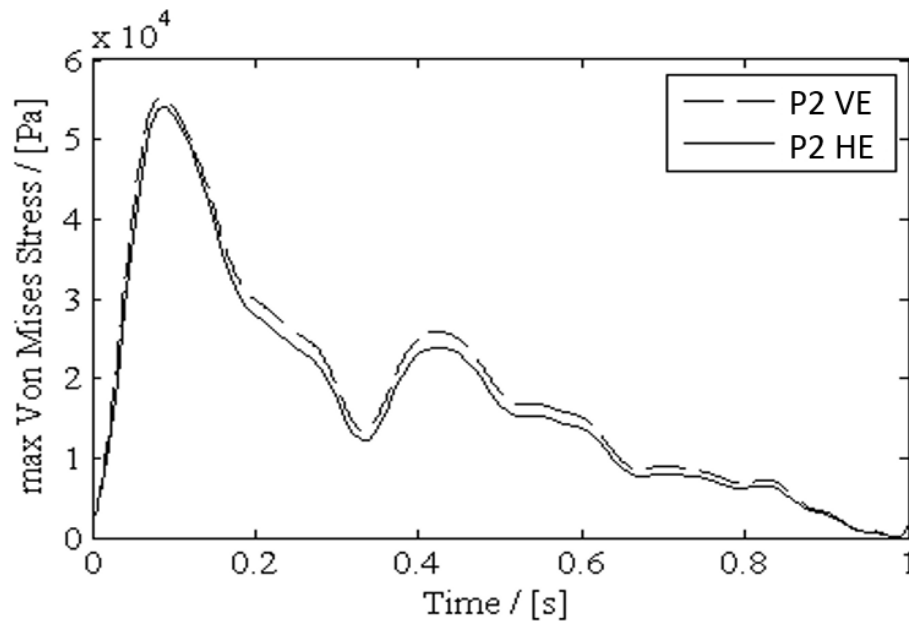


Figure 5- 10 Variation of the maximum Von Mises stress in the carotid artery of patient 2: comparison between the hyper-elastic model ((P2 HE) and the viscoelastic model (P2 VE)

Comparison between the hyper-elastic model and the viscoelastic model showed that both models produced similar stress distributions and the maximum stress level, as shown in Figure 5-7. Although viscoelastic behaviour caused a phase delay between the pressure load and the displacement on the arterial wall, hyper-elastic model could fulfil the requirement for estimation of stress and strain distributions. With regard to the maximum stress in the vessel wall, which is an important parameter in predicting the risk of plaque rupture, both models predicted very similar values with a difference of less than 2% for the viscoelastic properties employed here. However, for different viscoelastic properties the difference between hyper-elastic and viscoelastic models could be higher. Furthermore, when considering the dynamic interaction between the vessel wall and the blood flowing through it, the phase delay owing to hysteresis of the viscoelastic wall may alter the pattern of blood flow and affect the stresses in the vessel wall. Therefore, the interaction between blood flow and the arterial vessel must be considered for its significance, and this will be dealt with through the fluid-structure interaction analysis described in the next chapter.

5.4. Multilayer wall model with viscoelasticity and hyper-elasticity

It is recognized that the mechanical behaviour of human arteries is quite complex. With a multilayer structure model, Gao et al. (2006) found that the stresses were the highest in the media among the three layers, and the stress was higher in vessels with a stiffened media layer (Gao et al., 2006b). The shear (tangential) stress was found to be concentrated in the media layer on the adventitia side, which helped to explain the pathological state which involved a tear splitting across the tunica media to near the tunica adventitia (Gao et al., 2006a). Hodis and Zamir investigated the axial dynamic movement of the arterial wall driven by the oscillatory drag force, by using viscoelastic material properties described by the Maxwell model. For different ratios of viscosity to elasticity of the wall material, they found that displacements and stresses were more confined to the intima layer (Hodis and Zamir, 2008).

In this section, the effects of longitudinal motion on the stress and strain within the vessel wall are investigated, using a single-layered and multi-layered wall models. In order to find out whether a solid only model with multi-layered structure could simulate the longitudinal movement observed in *in vivo* measurements (Cinthio et al., 2006, Persson et al., 2003), results obtained from the viscoelastic and hyper-elastic models are compared.

5.4.1 Material properties and geometries for single-layered and three-layered models

The idealized geometry adopted in Chapter 4 was employed as an initial attempt. The single-layered vessel wall model and three-layered model were generated based on this geometry (see Figure 5-11).

a) Single-layered wall model

Based on the idealized model described in Chapter 4, the thickness of the arterial vessel

is 10% of its lumen diameter (0.6 mm), while the length of the vessel is 10 times its lumen diameter. The wall was assumed to be a hyperelastic material, described by the five-parameter Mooney-Rivlin equation based on the strain energy function (see Chapter 2 for details). The material parameters for the single-layered and three-layered models were extracted from the existing literature (Tang et al., 2009, Tang et al., 2004a, Tang et al., 2004b), as listed in Table 5-3.

b) Three-layered wall model

Since the intimal layer of carotid arteries is remarkably thin and there are no data available in the literature for the different anisotropic behaviours of each carotid wall layer, a mean thickness for each wall layer was assumed. The average thickness ratio of intima/media/adventitia in human iliac arteries was found to be 13:56:31 (Schulze-Bauer et al., 2003), while a thickness ratio of 2:1 for media/adventitia was used in a computational model of the arterial wall (Driessen et al., 2004). In the three-layered model developed here, the thickness ratio of intima/media/adventitia was set to 1:6:3 (Gao et al., 2006a). For a fixed total wall thickness of 0.6 mm, the thickness of each layer in the three-layered model can be calculated.

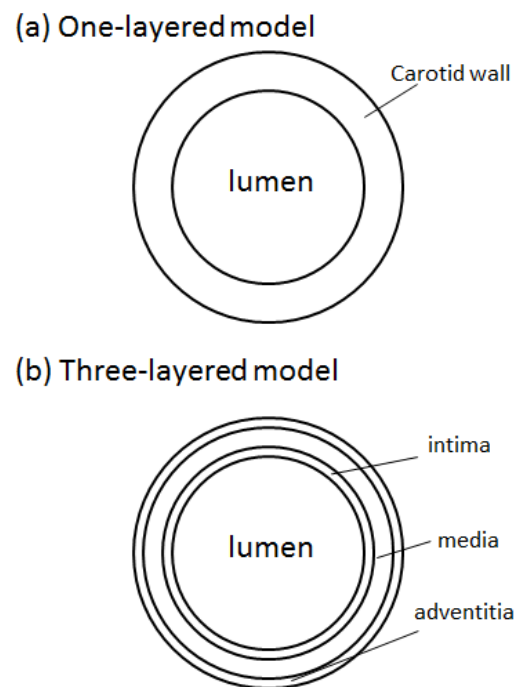


Figure 5- 11 Two models of the carotid wall (re-plotted based on (Gao et al., 2006a))

Based on the experimental results in the literature (Xie et al., 1995), the media was assumed to be three to four times stiffer than the intima and adventitia. According to Gao *et al*, the stiffness of each layer is inversely proportional to the volume of the layer (Gao et al., 2006a). Parameters used in the multi-layered hyperelastic model are listed in Table 5-3.

Table 5- 3 Parameters for the hyper-elastic vessel wall of the single-layered and three-layered models (definitions of symbols can be found in Chapter 2 (Equation 2-37))

	C_{10} (kPa)	C_{01} (kPa)	C_{20} (kPa)	C_{11} (kPa)	C_{02} (kPa)	d (Pa ⁻¹)
Single-layered	50.45	30.49	40.00	120.00	10.00	1.44E-7
Media	69.49	42.00	55.10	165.30	13.78	1.045E-7
Adventitia and Intima	23.16	14.00	18.37	55.10	4.59	3.14E-7

For the three-layered viscoelastic model, the intima and adventitia layers of the carotid wall were described by the same set of Prony series, but with a smaller initial shear modulus. This was because the viscosity of arterial wall is largely attributed to vascular smooth muscle cells (VSM) (Armentano et al., 1995a, Armentano et al., 1995b, Armentano et al., 1998), which are mainly found in the media layer. The relaxation time of the media layer was assumed to be ten times of the normal value used for a single-layered wall.

Table 5- 4 Shear modulus of single-layered and three-layered viscoelastic models

	G_0 [Pa]	ρ_1 [s]	α_1^G	ρ_2 [s]	α_2^G
Single-layered	591,470	0.01	0.8401	0.1	0.0134
Media	814,771	0.1	0.8401	1	0.0134
Adventitia and Intima	271,590	0.01	0.8401	0.1	0.0134

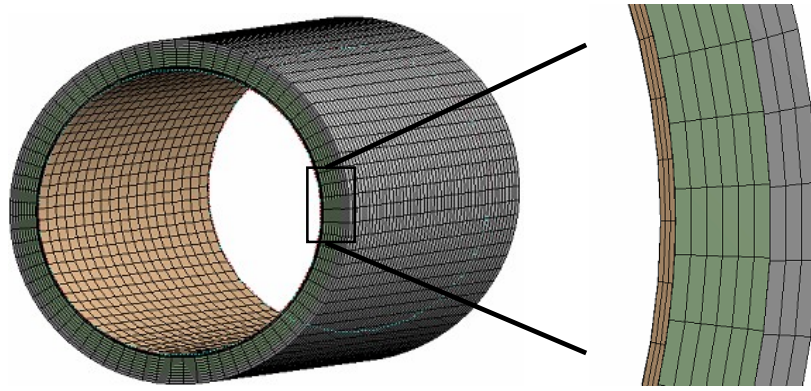


Figure 5- 12 Computational mesh for the three-layered model

The finite element mesh comprised 23712 20-node elements. For the single-layered model all the elements were assigned the same material property. For the three-layered model, different material properties were assigned to different layers separately. The outer wall was tethered in all directions.

5.4.2. Effects of longitudinal displacement

The outer wall of the artery was fixed in all directions, based on the observation that the magnitude of tissue movement was relatively small in the adventitial region (Cinthio et al., 2006). The longitudinal displacement under physiological conditions derived from the literature (Warriner et al., 2008) was applied at the inner surface of the wall model. Figure 5-13 shows a distinct bidirectional longitudinal movement based on ultrasound measurements (Persson et al., 2002, Persson et al., 2003, Cinthio et al., 2006).

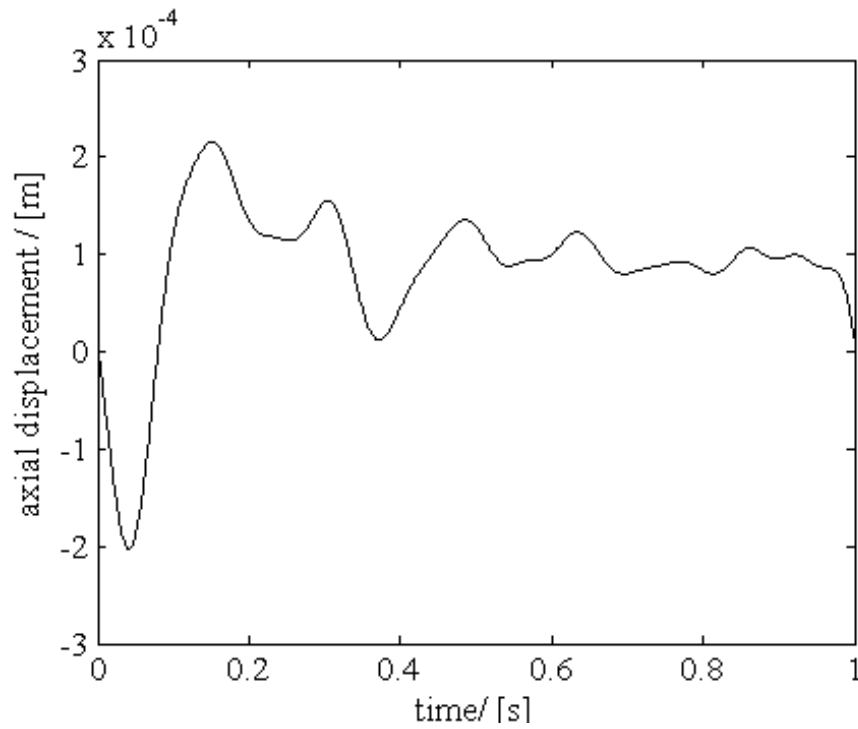


Figure 5- 13 Axial displacement applied on the lumen in the longitudinal direction

And a time-varying pulse pressure was applied on the inner wall. The pulse pressure waveform was extracted from the literature (Warriner et al., 2008) as shown in Figure 5-14.

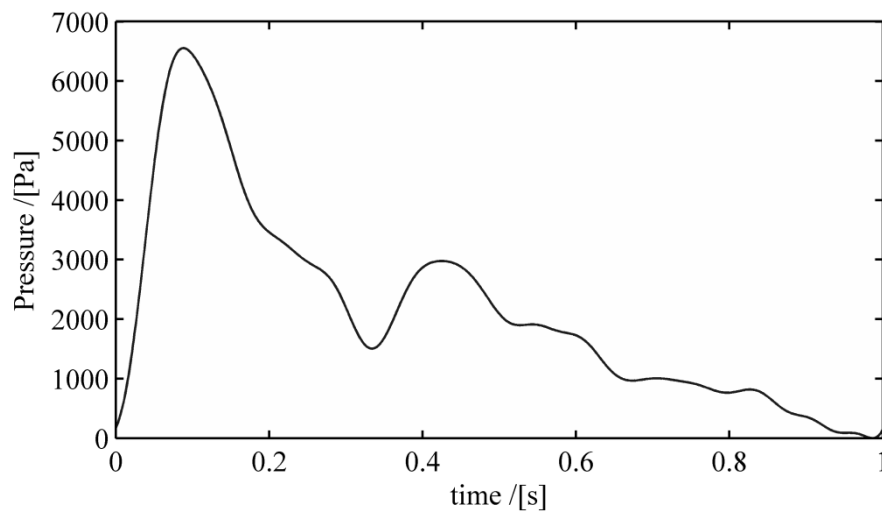


Figure 5- 14 Time-varying pressure applied on the inner wall of the hollow model, extracted from (Warriner et al., 2008). It represents realistic pulse pressure variation in a normal carotid artery with a peak value of 6553 Pa (49 mm Hg) at 0.090s.

Under the applied longitudinal displacement at the inner surface, longitudinal

displacements within the arterial wall were analysed and compared. As shown in Figure 5-15, similar patterns were obtained from the three models. A positive value of longitudinal displacement corresponds to movement in the direction of blood flow.

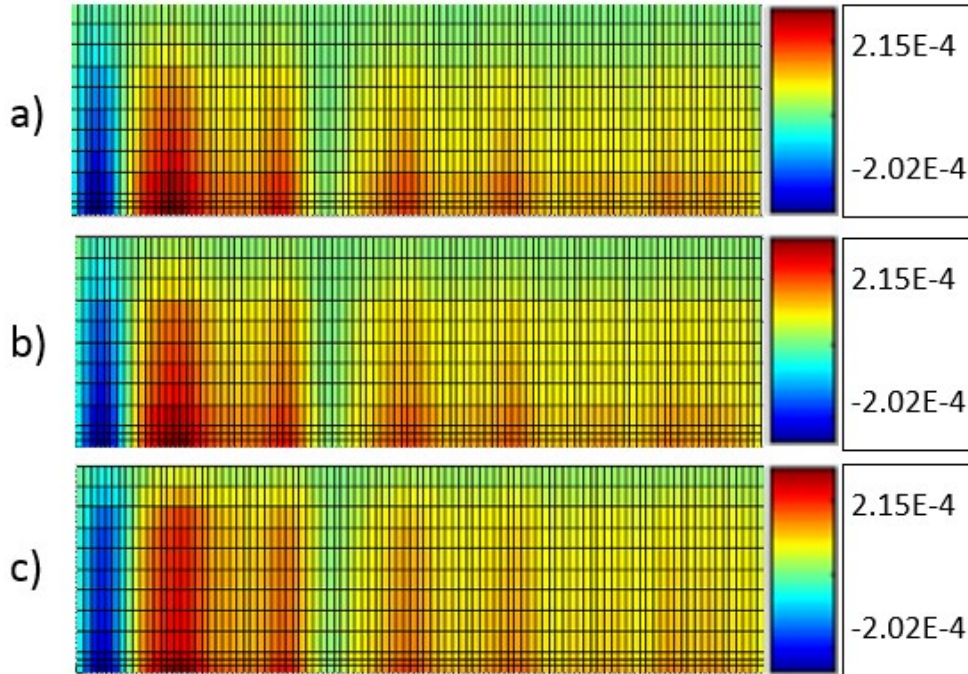


Figure 5- 15 Displacement in the longitudinal direction (m) across the thickness of the vessel wall and within one pulsatile cycle for different models. a) single-layered hyper-elastic model, b) three-layered hyperelastic model, c) three-layered viscoelastic model. Coordinate: Horizontal axis denotes the time (s); vertical axis denotes the distance from the lumen (m).

Because the longitudinal displacement at the lumen surface was applied at a given changing rate as shown in Figure 5-13, the longitudinal stress in the middle section of the artery was plotted across the thickness in order to analyse the differences among the models. In Figure 5-15, the results show that longitudinal displacements predicted by the three-layer viscoelastic model spread the deepest across the thickness of the arterial wall. The multi-layered structure changed the propagating velocity of longitudinal displacement across the thickness of the vessel wall, while displacements in the longitudinal direction were larger near the lumen surface in the single-layered model.

Clear stratification in stress distribution was found in the multi-layered models, as shown in Figure 5-16. Similar patterns of longitudinal stress distribution were obtained between the three-layered models with hyperelastic and viscoelastic material properties, although the ranges of stresses were different. The peak stress in the three-layer

hyperelastic model was nearly 20% higher than that in the single-layered model. It can be found that the peak stresses were concentrated in the intima layer and stresses in the medial layer were lower than those in the other two layers. By comparing the three-layered hyperelastic and viscoelastic models, the peak longitudinal stress occurred earlier in the three-layered viscoelastic model (Figure 5-16 (c)) in order to overcome the high resistance from wall viscosity, and the waveform was smoother than those in the other two models. The peak longitudinal stress in the three-layered viscoelastic model was found in the inner of intima layer. The viscosity of arterial wall in the three-layered model dramatically increased the shear stress in the direction which opposites the flow.

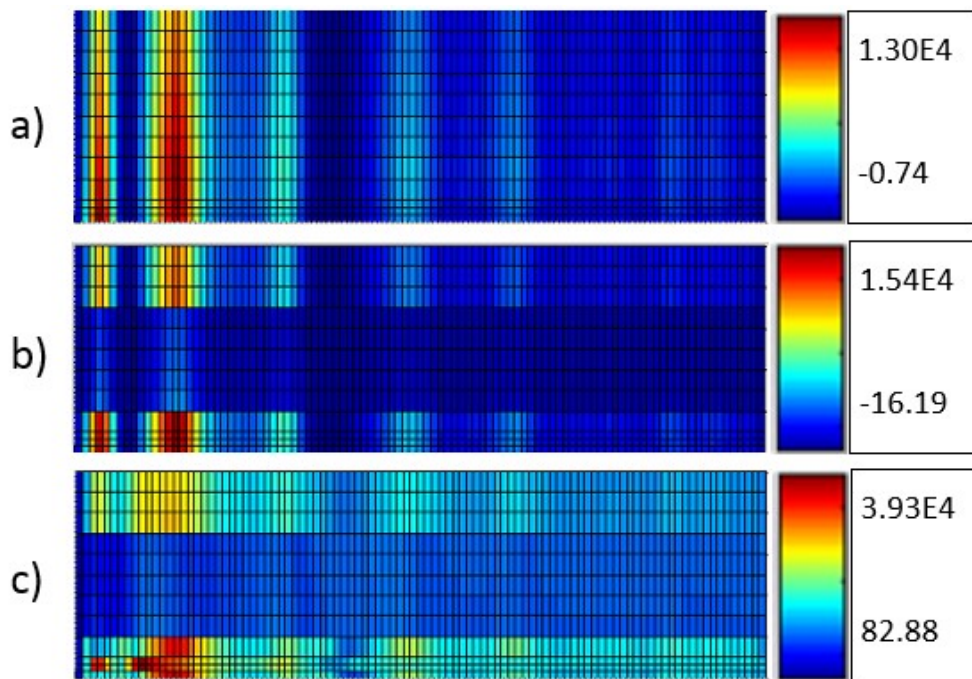


Figure 5-

16 Longitudinal Stress (Pa) across the thickness of the vessel wall within one pulsatile cycle for different models. a) single-layered hyper-elastic model, b) three-layered hyperelastic model, c) three-layer viscoelastic model. Coordinate: horizontal axis denotes the time (s); vertical axis denotes the distance from the lumen (m).

Figure 5-17 shows distributions of circumferential stresses in the single-layered (a) and three-layered models (b and c). In the three-layered models, a more complex circumferential stress pattern was found, in correspondence to the different material properties in different layers. Unlike a continuous stress distribution in the single-layered model, stress distributions in the three-layered models were discontinuous and separated by the interfaces between each layers. The magnitude of

the peak circumferential stress in the three-layered viscoelastic model was the highest among the three models, almost nine times the peak value predicted by the three-layered hyperelastic model.

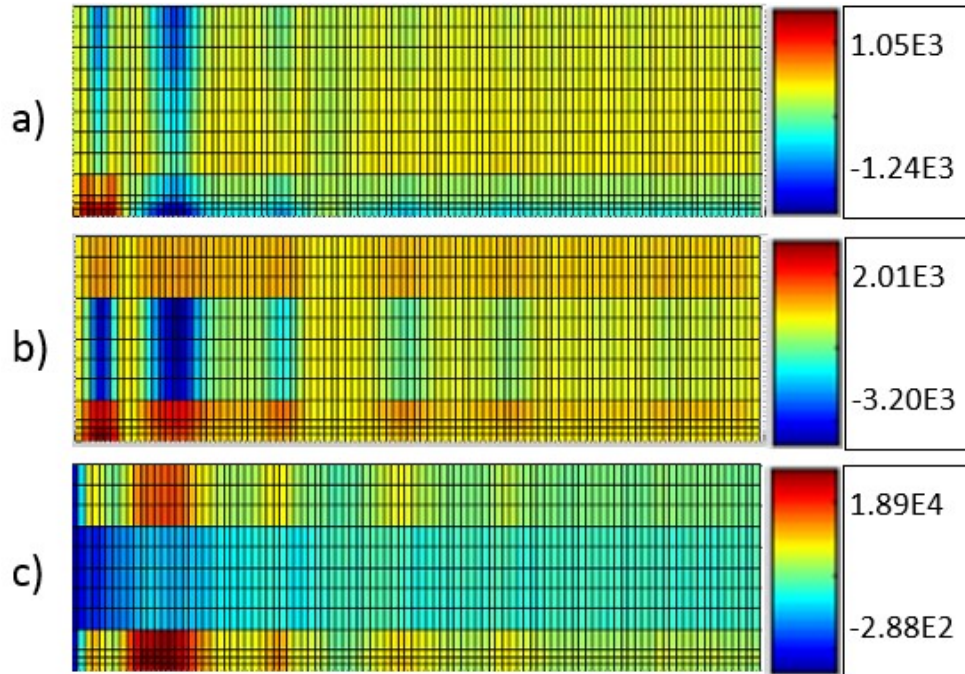


Figure 5- 17 Circumferential stress (Pa) across the thickness of the vessel wall and within one pulsatile cycle for different models. a) single-layered hyper-elastic model, b) three-layered hyperelastic model, c) three-layered viscoelastic model. Coordinate: horizontal axis denotes the time (s); vertical axis denotes the distance from the lumen (m).

5.5. Discussion

In this chapter the interrelationships among the viscoelastic material properties of a carotid artery were examined by using Prony series representation for the dynamic behaviour of the arterial wall. Viscoelastic properties of the human carotid artery are usually presented in complex form in the literature (Warriner et al., 2008). In order to implement these in ANSYS, data for complex elastic and shear moduli were fitted into Prony series (Park and Schapery, 1999). The method presented in this chapter can be used to derive patient-specific viscoelastic properties, represented in the form of Prony series, for finite element stress analysis, based on *in vivo* measurements of pressure and vessel diameter variations over a cycle.

Because of the lack of experimental data on pressure and simultaneously measured vessel diameter, only literature values of viscoelastic material property based on the Kelvin-Voigt model were employed in this study, which were represented using Prony series. The cardiac pulse period was assumed to be 1 s, and the loading modulus was assumed to be unaffected by the loading rate and loading amplitude. The effect of carotid artery viscosity was investigated by varying the wall viscosity while keeping the elastic moduli fixed. The results showed that increasing wall viscosity reduced the radial displacement of the arterial wall. Using viscoelastic properties for the patient-specific models, comparisons could be made with the hyper-elastic model presented in Chapter 4 to determine the effect of wall viscosity. The results showed that the viscosity of the vessel wall caused the peak displacement to occur 0.046 s after the peak pressure, a phase lag which is typically observed in viscoelasticity materials. However the stress and strain distributions and the maximum stress level predicted by viscoelastic and hyper-elastic models were similar, when the vessel wall was treated as a single-layered material.

To further examine the effect of multilayer structure of the vessel wall, single-layered and multi-layered models were built based on an idealised geometry. It was found that the stress and strain distribution in the carotid arterial wall was strongly influenced by the multi-layered wall structure. The results showed clearly boundaries between layers, with the stress and displacement mainly concentrated in the intima layer. Predicted peak stresses were much higher in the multi-layered model than the single-layered model.

Under the applied longitudinal displacement on the lumen surface, the longitudinal stress predicted by the three-layered viscoelastic model was higher than the single-layered model (by 202%) and the three-layered hyperelastic model (by 155%). With regard to peak circumferential stress across the vessel wall, the three-layered viscoelastic model also gave the highest value - 845% higher than that in the three-layered hyper-elastic model, and 18 times higher than that in the single-layered model. For longitudinal displacement across the vessel thickness, the three models produced similar results. This may be due to the same prescribed longitudinal displacement at the lumen surface.

In summary, results presented in this chapter have demonstrated that the hysteresis between radial displacement of the vessel wall and blood pressure can be simulated by using viscoelastic material represented by Prony series. The viscoelastic wall model can provide more insights into the biomechanical behaviour of the vessel wall, which could help improve our understanding of carotid artery diseases. For example, the stress difference between the intima and media layer could be used to explain tear splitting in the media layer of the carotid artery. The multi-layered structure has a strong influence on the stress and displacement distribution across the vessel wall, and gives a clear stratification between layers.

Chapter 6 Fluid-Structure Interaction

analysis of carotid arteries

In this chapter, fluid-structure interaction (FSI) models incorporating viscoelastic wall behaviour are described, together with their applications to idealised and patient-specific carotid arteries under pulsatile flow. Dynamic structural analyses of viscoelastic carotid arteries presented in Chapters 4 and 5 have demonstrated how finite element analysis can be used to predict the hysteresis between blood pressure and radial expansion of the carotid artery, without considering the effect of pulsating blood flow. However, the dynamic interaction between vessel wall motion and blood flow needs to be addressed due to the important role of haemodynamic wall shear stress in the development of atherosclerotic plaque, especially with regard to the effect of wall shear stress on the longitudinal displacement of carotid arteries which was found in recent *in vivo* studies by using ultrasound techniques (Cinthio and Ahlgren, 2010, Svedlund and Gan, 2011b).

Both one-way and two-way FSI simulations were performed on an idealized carotid artery model, and the obtained results were compared in order to examine whether different coupling methods influence FSI simulation results. The geometries and computational meshes employed for the carotid vessel in the FSI models are the same as those used in Chapter 5, and the same viscoelastic material property represented in the form of Prony series as described in Chapter 5 was also employed. The solid domain representing the carotid arteries was discretized using a finite element method, while the Navier-Stokes equations governing the blood flow were solved using a finite volume method. To accommodate a moving fluid domain, an Arbitrary Lagrangian Eulerian (ALE) method was employed.

6.1. Basic theory of FSI analysis

Systems that interact with each other are known as coupled systems. A coupled system consists of two or more distinct systems, which are governed by characteristic sets of

differential equations. There are some variables which are shared by both systems and cannot be solved separately as shown in Figure 6.1.

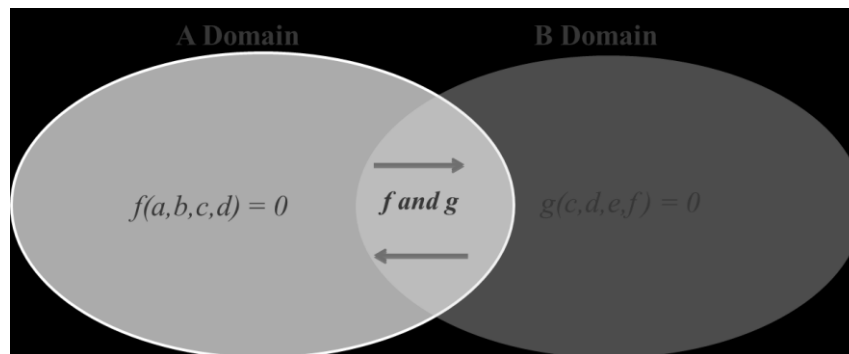


Figure 6- 1 Coupled system: Two domains and a coupling region. Both systems share variables c and d in the coupling region

Fluid-structure interaction (FSI) is a typical example of multi-physics simulations. It consists of two systems: a fluid domain governed by the Navier-Stokes equations, and a structure domain governed by solid mechanics equilibrium. The structure deforms as a result of the forces acting on it by fluid flow, and in turn, the deformation of structure changes the boundary of the fluid flow.

6.1.1. Monolithic and partitioned coupling algorithms

Numerical procedures that can be used to solve an FSI problem are broadly classified into two categories: strong approach and loose approach. In a strong approach (also known as monolithic approach), the CFD equations that describe the behaviour of fluid flow and the computational structural dynamics (CSD) equations that describe the behaviour of the structure are solved as a single coupled system of equations which are solved simultaneously for the entire problem (Hübner et al., 2004, Michler et al., 2004). A strong approach may be suitable for small structural problems, but is often slow and requires large amounts of memory because the fluid and structural dynamics are treated in the same mathematical framework. In addition, the full set of algebraic equations associated with this approach can be too stiff, because the properties and characteristic scales of the CFD, CSD, and computational mesh dynamics (CMD) equations often differ significantly from each other. Although a strong approach is more accurate in

theory, it may require substantially more resources and expertise to develop and maintain such a specialized code.

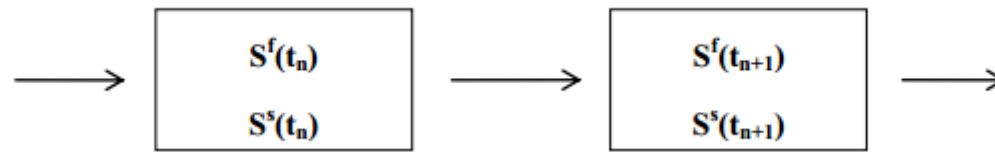


Figure 6- 2 Schematic of monolithic approach for FSI, where S^f and S^s denote the fluid and structure solutions, respectively. (Hou et al., 2012)

On the other hand, in a loose approach (also known as partitioned approach), the CFD and CSD equations are solved independently of each other with their respective mesh discretization and numerical algorithm, which makes the loose approach less computationally demanding. Another advantage of this approach is that solution techniques uniquely tailored to each field can be employed.

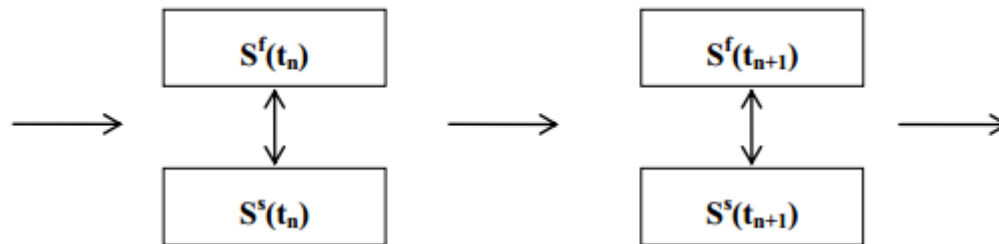


Figure 6- 3 Schematic of partitioned approach for FSI (Hou et al., 2012)

The distinctions between strong and loose approaches are viewed differently by researchers from different fields. From the engineering application point of view, Hou et al. gave a review of numerical methods for FSI (Hou et al., 2012). The advantages of partitioned approach are to allow integration of available discipline-specific algorithms and reduce the code development time to solve FSI problems. However the challenge of this approach is to coordinate the different coordinate systems to achieve accurate FSI solution efficiently. Particularly, the location of the interface which divides the fluid and structure domains is not known a priori and changes with time. This makes partitioned approach cumbersome and error-prone (Hou et al., 2012). However, numerical techniques have been developed to deal with these issues, and in this study, partitioned approach is adopted for its ability to be applied to complex geometries.

Partitioned approach can be divided into one-way and two-way coupling, while the latter can be further divided into strongly and weakly coupling methods. Details of strongly and weakly coupling methods as well as their comparisons can be found in other papers (Jean-Mark et al., 2009, Pozarlik and Kok, 2007).

6.1.2. One-way FSI

One-way FSI typically describes the pure mapping of physical properties resulting from one FE or CFD model to the other CFD or FE model. The two models do not need to have matching meshes and there is no iteration between the two models, which makes it less computationally demanding than two-way FSI. In some cases a one-way coupling is sufficient, which applies to one-way force mapping and one-way pressure mapping. It is suitable for problems where solid deformation is influenced by fluid flow but the effect of solid on fluid is negligible, or the other way round. A schematic diagram of one-way coupling is given in Figure 6-4, where the resulting pressure from the fluid domain which is acting on the structure is transferred to the structure solver.

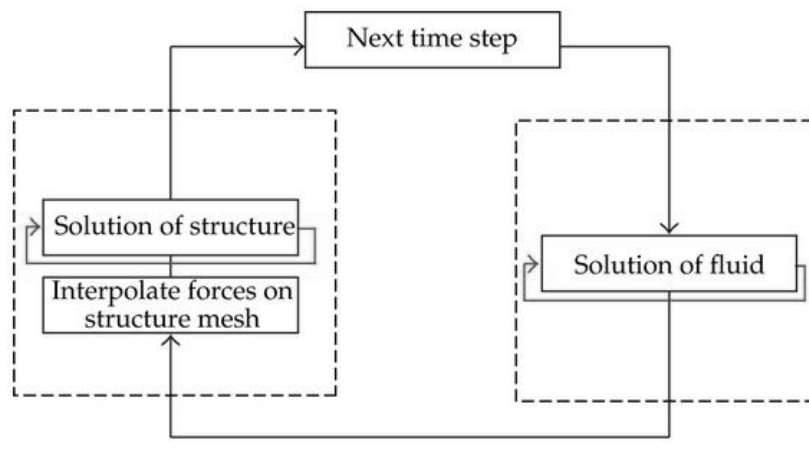


Figure 6- 4 Solution algorithm for one-way coupling (Benra et al., 2011).

Initially, the fluid field is solved until a specified convergence criterion is reached. The calculated forces at the structure boundaries are then interpolated to the structure mesh. Next, the structure domain is calculated until its convergence criterion is met. Then, the

fluid flow is calculated for the next time step. The procedure is repeated until the total calculation time is reached.

By employing a one-way coupled approach, Gao and Long found that the stress level on the fibrous cap was much more sensitive to changes in the fibrous cap thickness than the volume of lipid core (Gao and Long, 2008). Later Gao et al. showed that wall shear stresses were strongly related to the degree of stenosis, but their magnitude was much lower than wall tensile stress on the fibrous cap (Gao et al., 2009).

6.1.3. Two-way FSI

In two-way coupling calculations, dynamic interactions between the fluid motion and solid deformation are considered, i.e. fluid flow can influence the deformation of solid which in turn affects the fluid flow. The pressure acting on the structure, obtained by solving the fluid flow equations, is transferred to the structure part; at the same time the resolved solid displacement is transferred to the fluid solver. After achieving a certain convergence, the FSI simulation moves to the next time step.

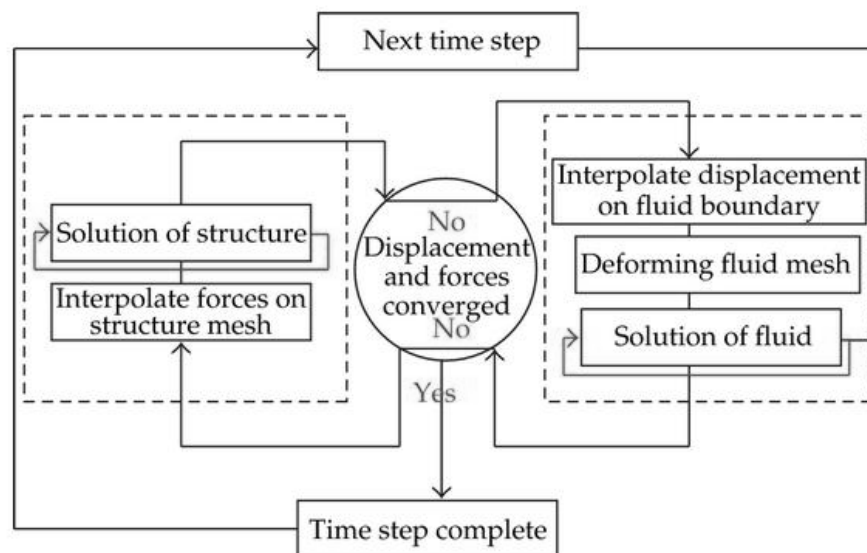


Figure 6- 5 Solution algorithm for two-way coupling (Benra et al., 2011).

The work flow of a two-way FSI coupling algorithm is shown in Figure 6-5. Initially, a converged solution from the fluid domain provides a force acting the solid structure.

Within the same time step of a transient calculation, the interpolated force from the fluid mesh is applied on the solid mesh as a force-load boundary condition like in one-way coupling. Then the response of structural dynamics is obtained. The displacements at the fluid and solid boundary are interpolated which leads to the deformation of the fluid mesh. If a prescribed convergence tolerance is reached, it would close one inner loop of the simulation. For a weakly coupled simulation the convergence at the solid and fluid boundary is not considered, and the next time step is launched directly. For a strong two-way coupling simulation, these steps are repeated until both the force and displacement values are converged within the predetermined limit (Benra et al., 2011).

Because the fluid mesh in a one-way coupling simulation does not require re-meshing, this gives a high constant mesh quality. The advantage of one-way coupling simulation is significantly less computational time, compared to two-way coupling. But unlike two-way coupling, it does not guarantee energy conservation at the interface (Vaassen et al., 2011). The two-way coupling solution is more accurate, especially in cases with large deformation where fluid flow is strongly influenced by the structural deformation.

6.2. Computational Fluid Dynamics in FSI analysis

Computational fluid dynamics (CFD) is a branch of fluid mechanics that uses numerical methods and algorithms to solve and analyse systems involving fluid flows. The numerical approaches involved to solve the necessary fluid equations in the flow are usually in partial differential form. For all the CFD approaches, the same procedure is followed. First is the pre-processing stage, during which the geometry of the problem is defined and the volume occupied is discretised to form a computational mesh. The governing equations and the boundary conditions which specify the fluid behaviour and properties at the boundaries of the physical domain are defined. For transient problems, the initial conditions are also needed. The second stage is iteratively solving the discretized forms of governing equations as a steady-state or transient problem. There are several well established numerical methods for CFD, including finite element method (FEM), finite difference method (FDM) and finite volume method (FVM). Finally post-processing is performed for the analysis and visualization of the resulting

solution.

The equations governing the physical aspects of fluid flow are: conservation of mass, and conservation of momentum. The continuity equation or mass conservation can be expressed as:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{U}) = 0 \quad (6-1)$$

The momentum equations can be described as:

$$\frac{\partial(\rho \mathbf{u})}{\partial t} + \nabla \cdot (\rho \mathbf{u} \mathbf{u}) = -\nabla p + \nabla \cdot (\mu \nabla \mathbf{u}) + S_m \quad (6-2)$$

where ρ is density, $\mathbf{u}$ is the velocity vector, μ is dynamic viscosity, ∇ is the vector differential operator and S_m and S_T source terms. The derivation of this form which is known as the Navier-Stokes equations is under the assumption of Newtonian flow.

6.3. Previous FSI studies on human carotid arteries

The interaction between blood flow and carotid arterial wall has been of great interests over the last two decades, and researchers have carried out CFD and FE structural analysis either separately or in a coupled manner to predict the carotid arterial flow and wall stress. Reuderink et al. were amongst the first who investigated pulsatile flow in elastic arteries (Reuderink et al., 1989). Using an idealised arterial geometry, they compared linear and nonlinear models based on one-dimensional wave propagation. They concluded that despite the rather large nonlinearities in the experimental tube, the linear model was more appropriate, since damping of the wave was strongly underestimated in the nonlinear model (Reuderink et al., 1989). Based on nonlinear shell theory, Perktold and Rappitsch developed a numerical model for a simplified carotid artery bifurcation to investigate the effect of distensible arterial wall on the local flow field and to predict mechanical stress in the carotid arterial wall (Perktold and Rappitsch, 1995). Although the global flow and stress patterns remained unchanged, the magnitude of wall shear stress decreased by 25% in the distensible model. By

comparing with previous numerical results (Reuderink, 1991) and experimental data (Anayiotos, 1990), they also found that the distensible carotid model gave more realistic results (Perktold and Rappitsch, 1995). Similar conclusions were also made by Steinman and Ethier by simulating flow in an idealised distensible end-to-side anastomosis model. Under a physiologic pressure waveform, the heel in the distensible model experienced a 38% more averaged shear stress than the rigid model (Steinman and Ethier, 1994).

The predicted 3D patterns of flow pressure, velocity and stress fields were very different from those calculated by 2D models. With a 78% symmetric stenosis geometry the 3D FSI model gave asymmetric solutions (Tang et al., 1999b). By Comparing results from thin-walled and thick-walled models, Tang et al. found that wall thickness affected wall deformation and stress distributions (Tang et al., 1999b, Tang et al., 1999a). Later they found that large calcification which occupied about 30% of the total plaque volume had considerable effect on the stress and strain distribution in a 3D FSI model (Tang et al., 2004b), while it did not alter stress distribution much in a solid only model (Huang et al., 2001). Five major contributing factors to the stress/strain behaviour in computational FSI models were discussed later, including anisotropic vessel material properties, cyclic bending, accurate plaque structure and axial stretch (Tang et al., 2009).

The large anatomical variation among patients was taken as an important factor by Zhao et al. and Xu et al., while the compliant behaviour of vessel wall and the non-Newtonian behaviour of blood were considered as of secondary importance. An overlap was found between the region of simultaneous high tensile stress and low wall shear stress, and the region where atherosclerotic plaque tends to develop (Lee and Xu, 2002, Zhao et al., 2000). However, none of the FSI models described above incorporated the viscoelastic behaviour of the arterial wall.

Using asymptotic and homogenization theory, Canic et al. developed a one-and-a-half dimensional model to investigate the radial viscoelastic behaviour of the vessel wall (Canic et al., 2006). They adopted a fully tethered boundary condition, which meant that longitudinal displacement was excluded. Warriner et al. presented an analytical model by extending Womersley solution for pulsatile blood flow to viscoelastic arteries

(Warriner et al., 2008), which offered a starting point for the prediction of longitudinal wall movement.

More recently, a loosely coupled FSI model was developed for an incompressible, viscous, Newtonian fluid and a thin-walled linearly viscoelastic structure by using a cylindrical Koiter shell model (Bukac and Canic, 2013). Shell elements were originally developed to efficiently represent thin sheets or plates. A summary of the assumptions made in selected FSI models of the carotid arteries is given in Table 6-1.

Ideally, structures should be discretised using solid elements for finite element stress analysis to avoid the problem of positioning the mid-plane of a shell element, and to exactly represent the sectional properties of components. In the present study a high order 3-D, 10-node solid element was employed, which is particularly suited for irregular geometries. The aim of this study was to develop a fully coupled numerical model for viscoelastic behaviour of carotid arteries under pulsatile flow. It is hoped that the numerical model can be used to predict flow and wall displacements of realistic carotid arteries, in response to changes in wall viscoelastic properties brought about by ageing or arterial diseases. This will help improve our understanding of the role of vessel wall motion in the development and progression of carotid diseases.

Table 6- 1 Assumptions in selected FSI models in the literature

		Solid							Fluid					
		Non linear	Viscoelastic	Compressible	Thick wall	3 Dimensional	Large strain	Method	Non Newtonian	Compressible	Turbulent	Transient	3 Dimensional	Method
Reference	Reuderink et al., 1989	✓	✓	✓	✗	✗	✗	A	✗	✗	✗	✓	✗	A
	Perktold and Rappitsch, 1995	✓	✗	✓	✗	✓	✗	FE	✓	✗	✗	✓	✓	FV
	Steinman and Ethier, 1994	✗	✗	✓	✗	✗	✗	A	✗	✓	✗	✓	✗	A
	Tang et al. 1999b	✓	✗	✗	✗	✓	✓	FE	✗	✗	✗	✓	✓	FV
	Tang et al. 1999a 2004 2009	✓	✗	✗	✓	✓	✓	FE	✗	✗	✗	✓	✓	FV
	Lee and Xu, 2002	✗	✗	✗	✓	✓	✗	FE	✓	✗	✗	✓	✓	FV
	Zhao et al., 2000	✗	✗	✗	✓	✓	✗	FE	✓	✗	✗	✓	✓	FV
	Canic et al., 2006	✗	✓	✗	✗	✗	✗	FE	✗	✗	✗	✓	✗	FE
	Bukac and Canic, 2013	✗	✓	✗	✗	✓	✗	FE	✗	✗	✗	✓	✓	FE

6.4. FSI model generation based on an idealised geometry

6.4.1. Model geometry and computational mesh

As a first attempt, an idealized three-dimensional model of the common carotid artery was adopted, so that comparisons between the numerical and analytical solutions (Warriner et al., 2008) could be made. The model is a straight circular cylinder with a diameter of 6 mm (Krejza et al., 2006), a length of 10 diameters, and a uniform wall thickness of 0.6 mm (Bussy et al., 2000), which is the same as the idealised wall model employed in Chapter 4 and Chapter 5.

The computational mesh was generated by using ANSYS ICEM CFD. It consisted of 10,000 elements in the vessel wall and 340,813 elements in the fluid domain, with second order hexahedral elements for the wall and first order tetrahedrons for the fluid. Although hexahedral cells would be preferred for the fluid domain, a tetrahedral mesh was used owing to the deformation and movement of arterial wall and incompatibility of a hexahedral mesh with the dynamic meshing function used in the current version of ANSYS-Fluent, since re-meshing of the fluid mesh would be needed in the two-way FSI simulation.

Spring-based smoothing, dynamics layering and local remeshing are three mesh motion methods available in ANSYS Fluent to update the volume mesh in the deforming region subject to the motion defined at the boundaries. For re-meshing of the fluid mesh in the two-way FSI model, spring-based smoothing method was used to calculate mesh deformation, where the connections between nodes of the fluid mesh were treated as springs with specific stiffness. The stiffness varies from node to node. Usually the mesh is much stiffer near the interface of the fluid and solid domain, to provide a high quality mesh in the boundary layer. For the structure model, ANSYS Mechanical was used to determine the dynamic response of a carotid artery under pulsatile blood flow. It was coupled with ANSYS Fluent using system coupling in ANSYS Workbench. In order to examine the dynamic behaviour of the carotid wall, Prony series was used to describe the viscoelastic property of the vessel wall. Mesh independence tests showed that differences in peak Von Mises stresses in the wall were less than 1% between the 10,000 and 20,000 elements meshes. Differences in wall shear stress at peak systole between the 340,813 and 680,000 elements meshes were less than 3%.

6.4.2. Computational details and boundary conditions

The FSI model consists of two domains, the fluid (blood) domain and the vessel wall. Fluid flow is governed by the continuity and Navier-Stokes equations, here with the blood being assumed to be Newtonian and incompressible with a dynamics viscosity of 4 mPa·s and a density of 1050 kg/m³.

The flow and wall equations were solved in a coupled manner by one- or two-way coupling of ANSYS Mechanical, which solves the wall mechanics equation, and Fluent which solves the fluid flow equations. FSI was achieved via ANSYS Multi-field solver, which employs a robust iterative coupling where the solid and fluid domains are solved sequentially and convergence is obtained between the individual domains at each time point. The convergence target for structure domain was set to be 10^{-6} , and that for the fluid domain was 10^{-3} . The FSI algorithm facilitates exchange of information (load at fluid/solid interface and wall displacement) between the solid and fluid domains. The simulation started with the fluid domain, and the computed load from the fluid domain was then applied on the inner wall of the solid domain. In the two-way FSI, the calculated wall displacement was passed back to the fluid domain based on Arbitrary Lagrangian-Eulerian (ALE) approach (Donea et al., 1982), while in the one-way FSI the effect of wall displacement on the fluid domain was ignored. Strongly coupled fields were solved sequentially, which ensured that the most recent results from one field solver were applied to the other. Multiple stagger iterations were employed to obtain a fully implicit solution by the end of each multi-field time step, with a convergence of 0.01. To monitor the convergence over time, solutions for pressure, von Mises stress and displacements at the reference point were obtained with time steps of 0.01 s, 0.005 s, 0.002 s and 0.001 s, respectively. The difference between maximum von Mises stresses from simulations with time steps of 0.002s and 0.001 s is less than 1%, hence a multi-field time step of 0.001 s was chosen. The solver iterated between the two physical fields until data transferred across the fluid/solid interface reached the specified convergence.

For the FSI model, boundary conditions specified for the structural domain were similar to those for the solid only model which was fixed at both ends, while a force acting on the carotid lumen was specified as shown in Figure 6-5 instead of a prescribed pressure load. The

following boundary conditions were applied to the fluid domain: at the model inlet, fully-developed time-dependent axial velocity profiles calculated from the volumetric flow waveform were imposed, whereas a pressure waveform corresponding to the inlet flow waveform was imposed at the outlet (see Figure 6-6). The input velocity and pressure waveforms were well fitted to a 20-term Fourier series. In the two-way FSI simulation, the fluid domain was remeshed according to the displacement of the carotid wall, whereas in the one-way FSI simulation only the effect of blood flow on the carotid mechanical response was considered ignoring the influence of wall displacement on blood flow, i.e. the fluid mesh was fixed during a cardiac cycle.

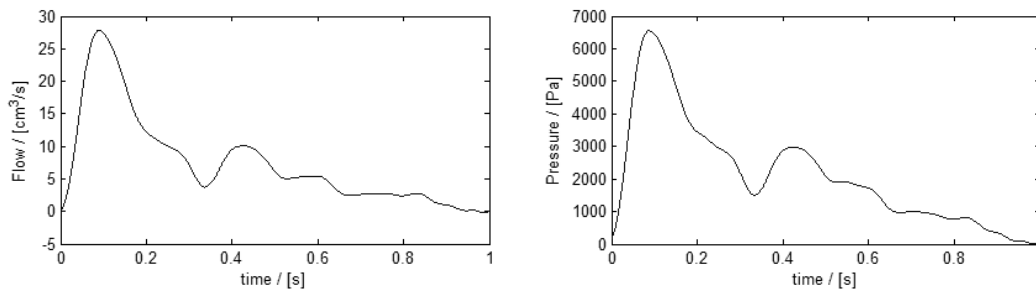


Figure 6- 6 Velocity waveform at the inlet (left) and pressure at the outlet (right) for the FSI model. Data were extracted from (Warriner et al., 2008).

Recent *in vivo* studies have revealed that longitudinal displacements under pulsatile flow are not only of the same magnitude as radial displacements, but also vary along the vessel wall to affect shear stresses within the wall (Cinthio et al., 2006, Persson et al., 2003). For this reason, in the solid domain, both ends were fixed in the radial direction while prescribed longitudinal displacements extracted from the literature (Warriner et al., 2008) were applied in the longitudinal direction (Figure 6-7).

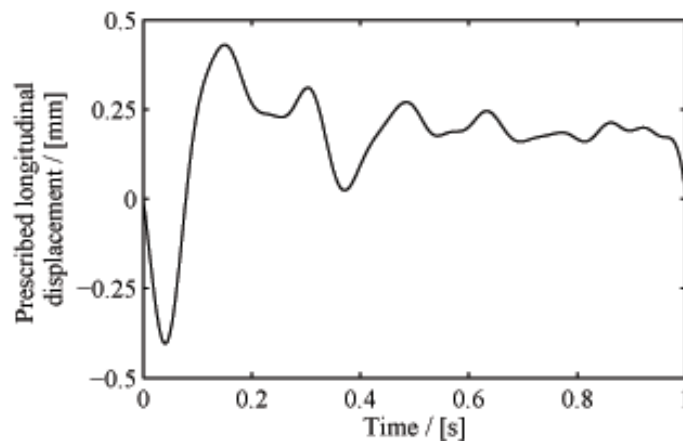


Figure 6- 7 Prescribed longitudinal displacements extracted from (Warriner et al., 2008)

6.4.3. Results

Radial displacement from two-way coupled FSI

Radial displacements obtained from the two-way coupled FSI model are shown in Figure 6-8, together with the corresponding analytical solution and the applied pressure waveform. The analytical model reported by Warriner et al (Warriner et al., 2008) was adopted for comparison with the numerical solutions. It can be observed that there is a 0.044 s phase angle (4.4% of the cardiac cycle) between the predicted radial displacement and the input pulsatile pressure waveform. A smaller phase lag (0.01 s) is obtained with the analytical model. The maximum radial displacement predicted by the FSI model is similar to that of the solid only model, which is higher than the analytical solution (0.29 mm). Predicted radial displacements in late systole and diastole are approximately 20% higher than the corresponding analytical solution.

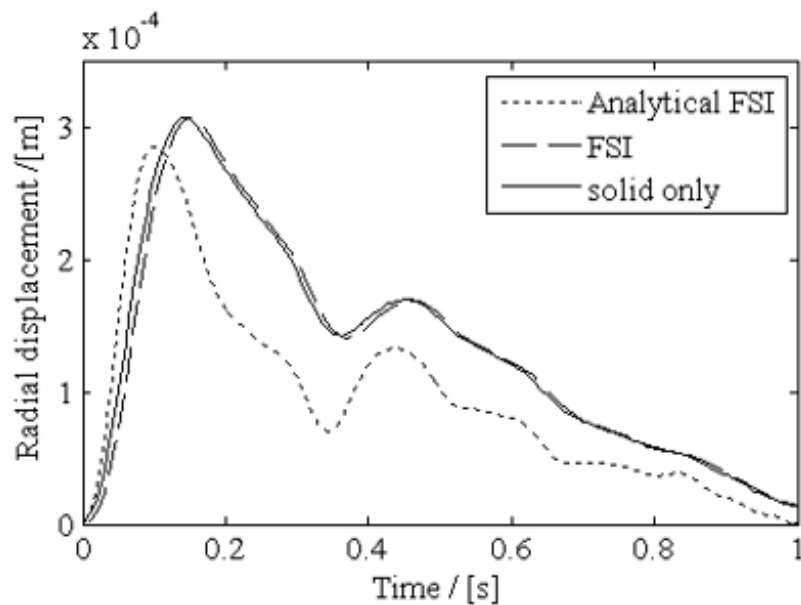


Figure 6- 8 Comparison of normalized pressure and radial displacements from numerical FSI, analytical FSI and solid structure only solutions, the peak value of pressure is 6553 Pa, the peak radial displacements of the numerical model and analytical model are 0.307 mm and 0.29 mm respectively.

Figure 6-9 shows the numerically predicted hysteresis loop compared with that of the analytical solution (Warriner et al., 2008). The area of hysteresis loop predicted by the FSI model is much larger than that from the analytical model.

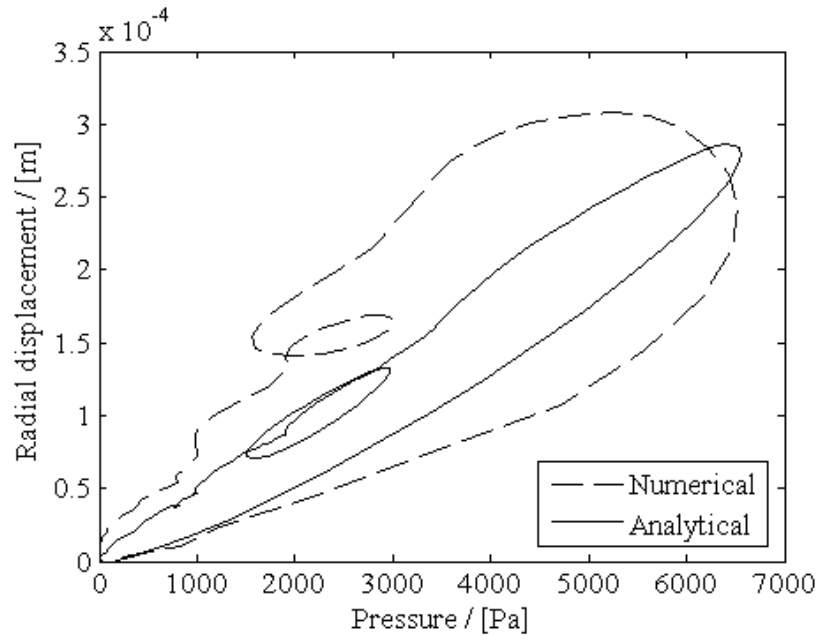


Figure 6- 9 Comparison of hysteresis loops between the numerical FSI model and the analytical solution (Warriner et al., 2008)

Longitudinal displacement for two-way coupled FSI

To investigate the effect of blood flow on longitudinal displacement of the carotid artery with viscoelastic property, a monitoring point was chosen half way along the tube at the fluid/solid interface. Numerically predicted longitudinal displacements at the monitoring point are shown as solid line in Figure 6-10. Although in the analytical model (Warriner et al., 2008), the arterial wall was surrounded by a mass of tissue which tended to dampen longitudinal wall motion, the longitudinal displacement obtained from the FSI model is identical to the corresponding analytical solution (dashed line).

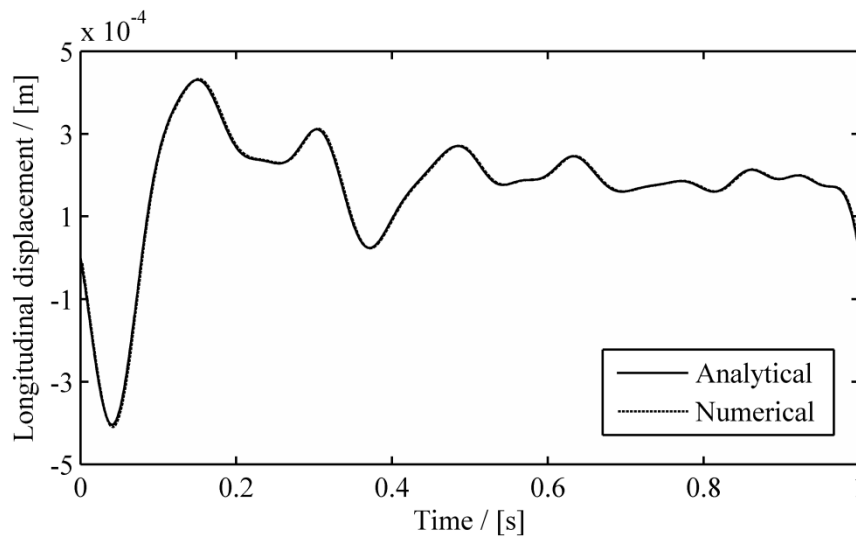


Figure 6- 10 Comparison of longitudinal displacement between the FSI model and analytical solution

Comparison between two-way and one-way coupling

It has already been shown in Figure 6-8 that the difference in arterial wall displacement between the fully coupled FSI model and the solid only model are very small. In order to examine the effect of different coupling methods, one-way coupled simulation was also carried and comparison was made between the two coupling methods. In the one-way coupled FSI simulation, the results of time-dependent pressure load produced by blood flow were applied to the fluid/solid interface at each time step, whereas the effect of wall motion on flow was neglected, hence the predicted wall displacement does not have any effect on blood flow.

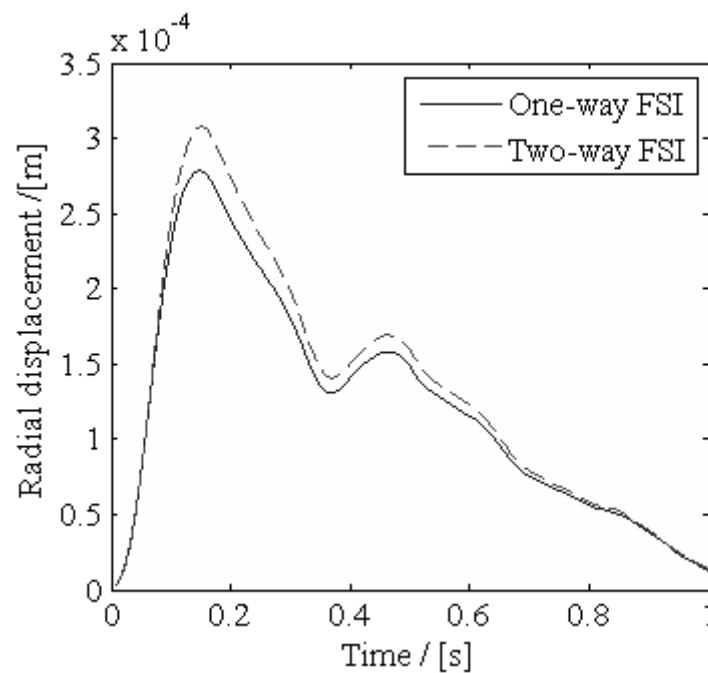


Figure 6- 11 Comparison of radial displacements from one-way and two-way FSI solutions, the peak radial displacements of the one-way and two-way FSI models are 0.28 mm and 0.307 mm respectively.

As shown in Figure 6-11, the peak radial displacement from two-way FSI model is 0.307 mm which is slightly higher than the one-way FSI solution (0.28 mm), while the phase-lags of one-way and two-way FSI models are the same.

6.5. FSI model based on the carotid artery of patient 1

6.5.1. Model geometry and computational mesh

A patient-specific FSI model was developed to predict the vessel wall deformation and blood flow in a human carotid artery based on an anatomically realistic carotid geometry reconstructed from 3D ultrasound images as described in Chapter 3. Flow simulations were carried out with both one-way and two-way FSI, and the results were compared. In order to produce a more accurate result, the inlet and outlet of the fluid domain were extended by 3 cm at each end, allowing the blood flow to become fully developed at the inlet of the carotid artery and the effect of artificial outflow boundary conditions to be minimised (Figure 6-12).

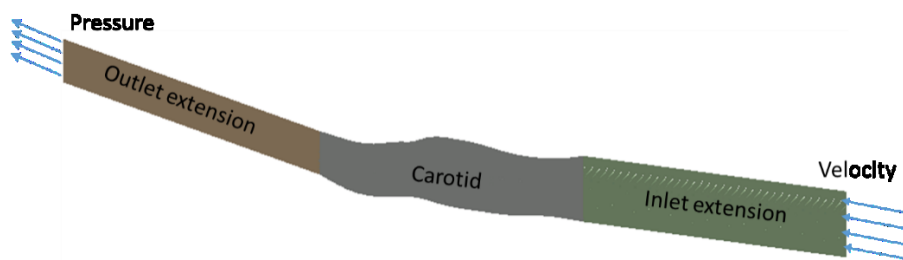


Figure 6- 12 The extended flow domain for patient 1

6.5.2. Computational details and boundary conditions

Due to the absence of the patient-specific pressure waveform and velocity profile for patient 1, the velocity and pressure waveform shown in Figure 6-13 were applied on the extended flow domain respectively, together with a phase shift of 0.02 s corresponding to the relevant physiological value (Olufsen et al., 2000).

The computational mesh for the fluid domain consisted of 227581 cells. The inlet and outlet extensions had the same mesh distribution as in the “carotid” section in order to minimise potential errors due to mesh difference among these sections. Mesh sensitivity test was also carried out which demonstrated that the differences in maximum WSS between the adopted mesh and a finer one were less than 1%.

Numerical simulations were carried out by using one-way and two-way FSI, respectively, and all simulation were run for three cycles with a coupling time step of 0.01s. Stress distributions on the carotid wall and instantaneous WSS on the lumen surface were analysed at selected locations and different time points during the third cycle.

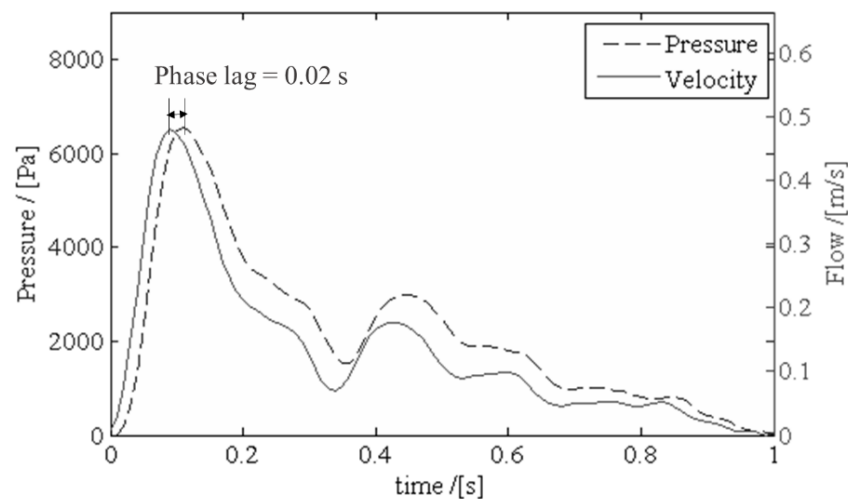


Figure 6- 13 Boundary conditions applied on the inlet and outlet of the FSI model of patient 1

6.5.3. Results

Figure 6-14 shows the comparison of centreline velocity at the outlet of the carotid section between the one-way and two-way FSI simulations. Since the magnitude of carotid deformation is relatively small, it doesn't have an effect on the centreline velocity, as demonstrated through the identical results obtained from the two models.

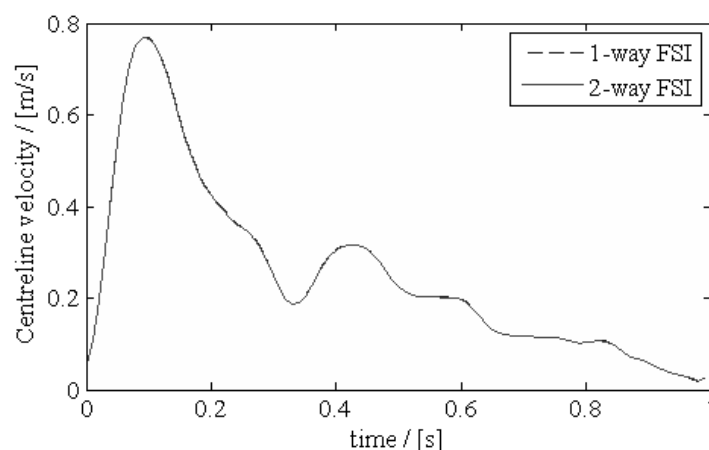


Figure 6-14 Comparison of centreline velocity between 1-way and 2-way FSI models

Figure 6-15 and Figure 6-16 give a comparison of WSS on the lumen surface at peak systole and in systolic deceleration between one-way and two-FSI simulations. It shows that the WSS patterns are similar, but there are differences in the magnitude, with one-way FSI predicting higher WSS values. At peak systole, the peak WSS obtained with one-way FSI (17.16 Pa) is about 18.34% higher than that with two-way FSI (14.50 Pa). This can be explained by the fact that two-way FSI allows the fluid domain to deform and at peak systole, the carotid artery expands in response to increased blood pressure. As a result of radial expansion, WSS is reduced for the same flow rate. On the other hand, on-way FSI does not pass the wall displacement to the fluid domain, so that the flow solutions are obtained under the rigid-wall assumption.

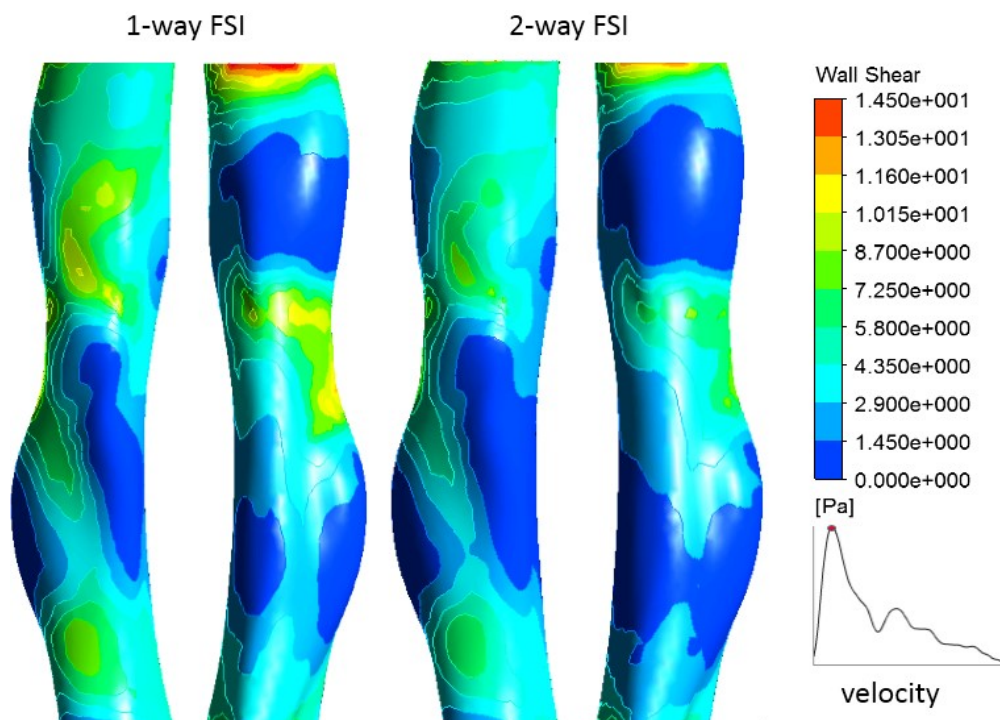


Figure 6- 15 Comparison of WSS contours between one-way and two-way FSI simulations at peak systole

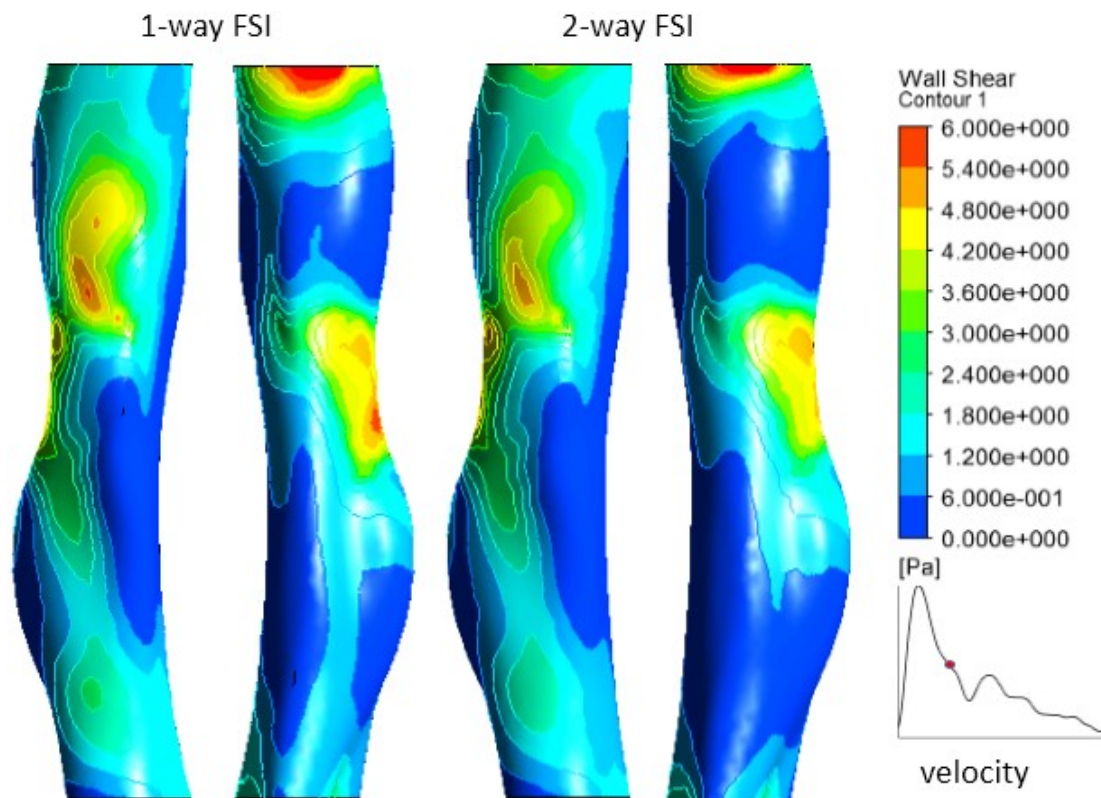


Figure 6- 16 Comparison of WSS contours between one-way and two-way FSI simulations in systolic deceleration

The total displacement contours on the outer wall at peak systole are shown in Figure 6-17. The two models produced very similar results. The maximum total displacement obtained with one-way FSI (0.371 mm) is about 3.34% larger than that with two-way FSI (0.359 mm) at peak systole.

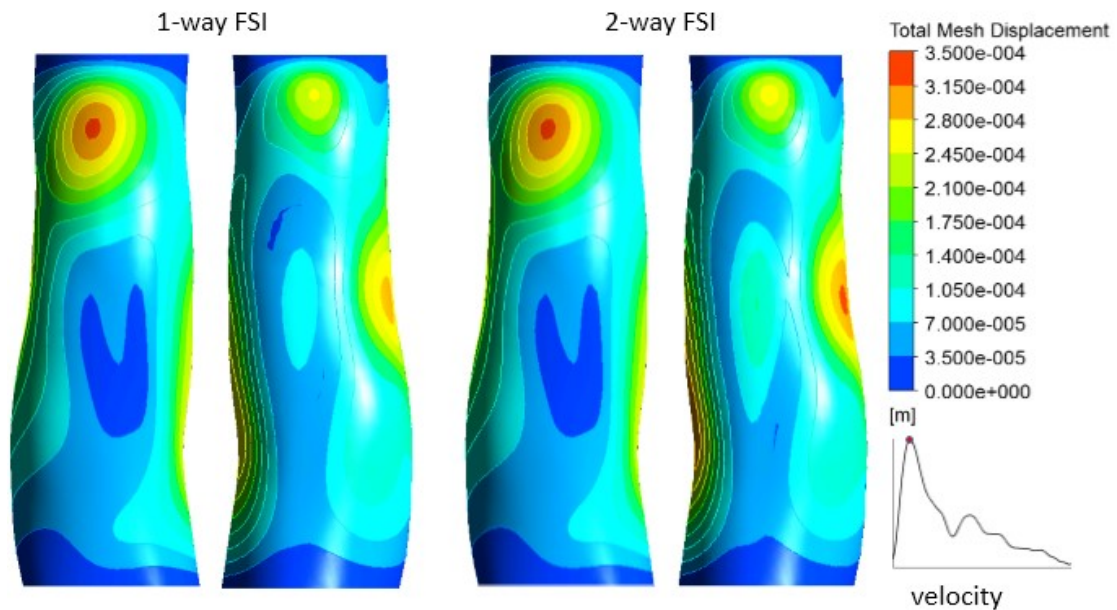


Figure 6- 17 Comparison of total displacements on the carotid artery between one-way and two-way FSI simulations at peak systole

In Figure 6-18, the longitudinal displacement contours are compared between the two models. The interaction between blood flow and carotid wall motion reduces the magnitude of longitudinal displacement on the wall, where the maximum longitudinal displacement is 0.0916 mm from the one-way FSI model and 0.0876 mm from the two-way FSI model (about 4.57% lower).

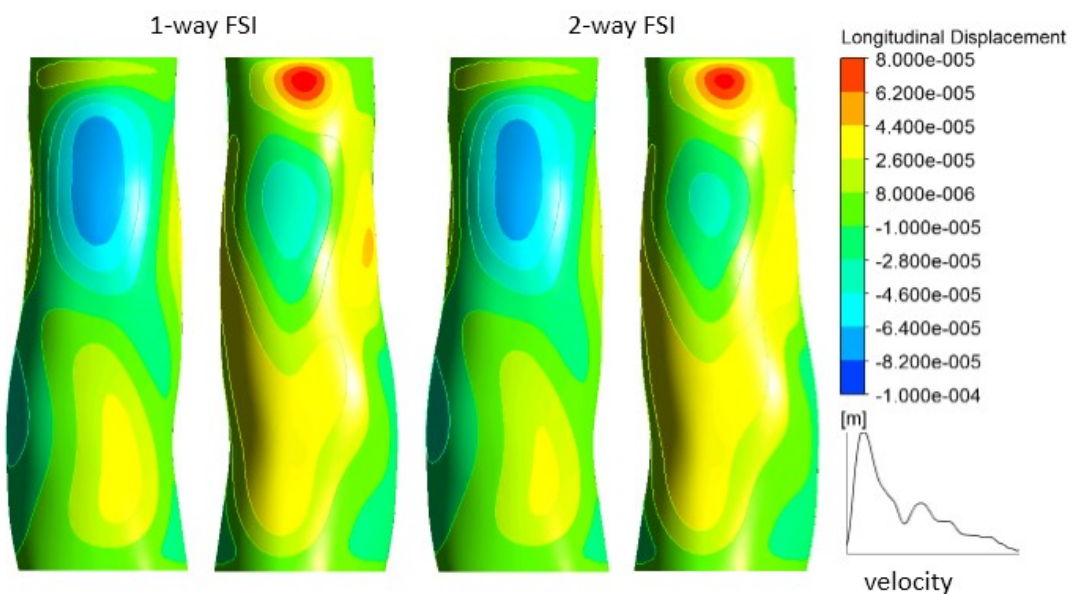


Figure 6- 18 Comparison of longitudinal displacements on the carotid artery between one-way and two-way FSI simulations at peak systole

6.6. Discussion

In the FSI models, Prony series was used to describe the viscoelastic properties of the carotid wall. The results show that the FSI model can be used to predict pressure-diameter hysteresis and the dynamics of radial and longitudinal vessel wall motion under physiological conditions (Figures 6-8 and 6-9). The predicted phase angle between the radial displacement and pressure load was larger than that in the analytical solution (Warriner et al., 2008), and the radial displacements were higher with the numerical model; about 5.5% higher for the peak radial displacement and 20% higher during diastole (Figure 6-8). This was largely due to the different representations of the viscoelastic properties of the wall; the analytical solution was derived for the Kelvin-Voigt model, whereas the numerical FSI model was based on the Kelvin-Voigt model with its viscoelastic modulus being represented by Prony series. As shown in Figures 5-4 and 5-5, minor differences could be observed between the fitted Prony series (used in the numerical model) and the dynamic shear modulus data (used in the analytical model), especially in the low frequency range where the magnitude of dynamic shear modulus was lower with the fitted Prony series. These may have caused the slightly higher radial displacement predicted by the numerical model.

Another difference between the numerical and analytical models was the treatment of boundaries. In the numerical model, the vessel had a finite length (10 diameters) and both ends of the wall were fixed in the radial direction, while prescribed longitudinal displacements were applied in the axial direction. The analytical model assumed that the vessel was of sufficient length so that entrance effects and wave reflections could be ignored, and that the wall was surrounded and tethered by a mass of tissue, which helped to dampen the longitudinal movement (Warriner et al., 2008). The effect of different boundary conditions, including fully tethered and free wall boundary conditions, has been investigated analytically by Hodis & Zamir (Hodis and Zamir, 2011), and they found that for large wavelength (greater than 100 times the vessel wall radius), the radial and longitudinal displacements became de-coupled. From Figures 6-8 and 6-10, it can be observed that time variations of radial and longitudinal displacements did not follow the same pattern. The radial displacement followed closely the pressure waveform with a small phase lag, but the longitudinal displacement was very different. Due to the small magnitude of the prescribed longitudinal displacements relative to the tube length, its effect on the radial displacement and blood flow pattern was insignificant.

It has been reported that unlike radial displacement, longitudinal displacement is highly dependent on the stenosis geometry (Bukac and Canic, 2013). To understand the carotid wall dynamic behaviour and its relation to vessel geometry, a patient-specific common carotid artery geometry was employed to investigate the relation between longitudinal displacements and stenosis geometry. It was found that haemodynamic factors were significantly affected by the carotid morphology. As shown in Figure 6-15, the difference in peak WSS on the lumen surface between one-way and two-way FSI models was as much as 18.34%. However, differences in the simulated displacement in the carotid arterial wall were trivial. This may be due to the small magnitude of WSS compared with the pressure load applied on the vessel wall. As wall shear stress is associated with the growth of atherosclerotic plaque, it would be desirable to predict a more accurate WSS by using two-way FSI based on patient-specific models.

With regard to computational time, all the simulations were conducted on a PC with frequency of 3.40 GHz (Inter ® Core™ i7-3770 CPU) and installed memory of 16 GB. Half of these (4 cores) were assigned to the structural solver and the other cores were assigned to the flow solver. The average time required for a one-way FSI simulation was 12 hours, which was similar to the time required for a solid only model. However, a two-way FSI simulation took about 14 days. For studies that are mainly focused on the dynamic wall behaviour (including wall displacement and stress), one-way FSI can be an efficient option and can also provide an acceptable level of accuracy when compared with results obtained with two-way FSI; the differences in predicted wall displacements between the two models were less than 5% (Figure 6-17 and Figure 6-18). However, if the detailed flow patterns and wall shear stress are also of interest, two-way FSI simulations must be carried out, although they are computationally very intensive.

Chapter 7 Conclusions and Future work

7.1. Main conclusions

This thesis presents the development of finite element models of the human carotid artery for detailed investigation of biomechanical conditions in normal and stenosed carotid arteries. To take full advantage of the non-invasive nature of ultrasound, a new generation of 3D free-hand ultrasound scanner was used for acquiring geometrical information. The carotid artery models were built with an increasing level of complexity, starting with a linear elastic wall model, to hyperelastic, viscoelastic, and finally a fully-coupled viscoelastic model accounting for the dynamic interaction of blood flow and wall motion. With regard to vessel wall geometry, both idealised models and patient-specific carotid artery models were utilised, although the latter were limited to two cases owing to the lack of high quality 3D ultrasound images available to this project.

The methodology for the reconstruction of human carotid arteries from 3D ultrasound images were developed on the basis of previous work within our group (Borghi et al., 2008, Soloperto et al., 2010, Augst et al., 2003). However, the present study differs from previous work in the following aspects: (i) previous researchers used different imaging modalities, including magnetic resonance imaging and a standard hand-held 3D ultrasound system, hence the quality and contrast of images were different; (ii) the region of interest was the lumen and its contours in previous study, whereas the present study is focused on the arterial wall. Clinically relevant parameters that measure the severity of lumen narrowing and components of the plaque were evaluated based on the acquired ultrasound images. A Matlab code was developed to perform all the tasks from image segmentation, smoothing to 3D reconstruction as well as plaque characterisation.

Also addressed in this thesis are factors which need to be considered when developing computational models for arterial biomechanics analysis; these include the dimensions of the model (i.e. 2D or 3D), the viscoelastic behaviour, FSI coupling methods and the effect of multilayer structure. Details of the conclusions are given below.

7.1.1. Comparison between 2D and 3D FE models

For an idealised carotid stenosis with a large lipid pool, the stress and strain distributions predicted by the 2D models were qualitatively similar to those obtained with the 3D model. However, quantitative differences were significant, especially at higher pressure load. Although 2D FE models could be used to qualitatively evaluate the stress distribution when the number of images is limited and time is a constraint, 3D FE analysis is necessary for clinical assessment of the risk of plaque rupture. This is particularly importance for higher degree of stenosis, where the maximum stress may not occur at the section where the lumen is the narrowest. 3D results for the model with 80% stenosis revealed that the peak stress predicted at the shoulder of the plaque would have been missed if 2D analyses were performed on limited transverse sections of the vessel. The general trend that 2D models under-estimated the peak and mean stresses is consistent with findings by other researchers. The unique contribution of the work presented in Chapter 4 was that the difference between 2D and 3D models was strongly dependent on the degree of stenosis. However, the effects of lipid pool shape and size were not investigated here.

7.1.2. Effect of wall viscoelasticity on the deformation of carotid artery

It has been reported in the literature that normal carotid arteries are viscoelastic and their viscoelastic properties vary significantly with age and arterial disease (Meinders and Hoeks, 2004). In young and healthy adults, the carotid artery is soft and less viscous with a viscosity index of 2.73 ± 1.66 mmHg·s/mm and intima-media thickness of 0.58 ± 0.08 mm (Armentano et al., 1998). With ageing and arterial disease, the artery becomes more rigid and more viscous. Armentano et al. found that the viscosity index in hypertensive subjects had more than doubled when compared with normal subjects. They also suggested that such increase in viscosity was positively related to intima-media thickness, as a result of smooth muscle cell alteration in the media layer of arterial wall (Armentano et al., 1998). The idealized solid only model was used to investigate the effect of different levels of wall viscosity on the radial displacement of the wall described by the Kelvin-Voigt model. By keeping the elastic moduli constant and changing the viscosity in the range of 3,000 to 9,000 Pa·s, it was found that increasing wall

viscosity could significantly reduce the peak radial displacement of the vessel wall, but its effect on wall displacement in diastole did not follow the same trend.

With a time-varying pressure applied on the lumen, pulsatile analyses were performed on two patient-specific models which were assumed to behave as a hyperelastic material (Chapter 4) and viscoelastic material (Chapter 5), respectively. A hysteresis of 0.046 s was found in the viscoelastic model, which was not present in the hyper-elastic model. Although the introduction of viscoelastic material property improved the predictability of carotid FE model, differences in the predicted peak Von Mises stress between the hyper-elastic and viscoelastic wall models were minor and could be neglected. Therefore, it can be concluded that while a hyper-elastic model may fulfil the requirement for stress prediction, it may not be sufficient for prediction of vessel wall displacement. Results obtained for the two patient-specific models demonstrated the importance of biomechanical analysis; the patient (Patient 2) with a higher degree of stenosis in the carotid artery and higher plaque burden was found to have lower peak VMstress than the patient (Patient 1) who had a lower degree of stenosis and lower plaque burden. Based on commonly used clinical criteria without resorting to finite element stress analysis, Patient 2 would be considered as having a higher risk for plaque rupture than Patient 1. Moreover, detailed geometric features of the plaque were found to be import in determine the pattern and magnitude of stress, as the maximum stress was found to occur at the site with the largest curvature on the inner wall.

7.1.3. Effect of multilayer structure on wall displacement and stress

Arterial walls are commonly treated as a single-layer structure in most computational studies. A three-layered idealized carotid model was developed and compared with a single-layered model to investigate the effect of multilayer structure on vessel displacements under pulsatile pressure and longitudinal displacement boundary conditions, respectively.

Under the prescribed longitudinal displacement boundary condition, a deeper spread of displacement across the carotid wall was found in the viscoelastic model, while clearly distinctive stress patterns were found in different layers in the multi-layered model, suggesting

that the multilayer structure plays an important role in the mechanical response of carotid arteries. The multi-layered model showed that longitudinal stress were concentrated in the intima layer, and the longitudinal stresses in the media layer were three to four orders of magnitude smaller than the other two layers. This may explain why tears within the arterial wall have been observed clinically (Gao et al., 2006a). The predicted results were in good agreement with *in vivo* ultrasound measurements (Cinthio et al., 2006).

7.1.4. Effect of one-way and two-way FSI coupling

The longitudinal displacement of the common carotid arterial wall is of the same magnitude as the radial displacement (Cinthio et al., 2006). More recently, it has been found that the longitudinal displacement for an individual during rest is highly stable and longitudinal movement patterns are strikingly differently among the healthy subjects of the same age-group and gender (Ahlgren et al., 2012). The mechanisms behind the different longitudinal patterns may be the shear force driven by the blood flow and/or the shear force from the pulse wave and difference in pulse wave reflection (Cinthio et al., 2006). In order to understand the factors that influence the longitudinal displacement, it is necessary to consider the interaction between blood flow and carotid arterial wall by using FSI simulation, and to examine the effect of different coupling methods on FSI simulations of the carotid artery.

Results obtained from the idealized model showed that both one-way and two-way coupling could be used to predict the pressure-diameter hysteresis and the dynamics of radial and longitudinal vessel wall displacements under physiological conditions. The predicted phase angle between the radial displacement and pressure load was larger than that of the analytical solution (Warriner et al., 2008), and the radial displacements were higher with the numerical model; about 5.5% higher for the peak radial displacement and 20% higher during diastole. This was largely due to the different representations of the viscoelastic properties of the wall; the analytical solution was derived for the Kelvin-Voigt model, whereas the numerical FSI model was based on the Kelvin-Voigt model with its viscoelastic modulus being represented by Prony series.

It has been reported that unlike radial displacement, longitudinal displacement is highly dependent on stenosis geometry (Bukac and Canic, 2013). A more realistic geometry based on

3D ultrasound images acquired from patient 1 was employed to investigate the relationship between longitudinal displacement and the degree of stenosis in carotid arteries. Differences in the simulated displacement between the one-way and two-way FSI models were less than 5%. However, deformation of the carotid artery in the two-way FSI model led to changes in haemodynamic WSS in the carotid artery. Due to the expanded lumen cross-sectional area in the two-way FSI model, WSS obtained with the one-way FSI model was up to 18.34% higher than that with the two-way FSI model. Nevertheless, the one-way FSI model provided comparable results for displacement and stress to the two-way FSI model.

7.2. Limitation and future work

7.2.1. Limitations

Due to the limitation of ultrasound technique, the carotid artery reconstructed from 3D ultrasound images did not include the vessels behind the jaw bone. In fact, all the 3D ultrasound images acquired for this project were focused on the common carotid artery, with little coverage of the carotid bifurcation. This limits the application of 3D ultrasound-based biomechanical analysis to plaques in the common carotid artery. The lack of uniformity in acquired 3D ultrasound images also meant that only two sets of images were deemed usable for the present application.

Because of echolucency of the carotid arterial wall, it is difficult to apply automatic image segmentation techniques to cross-sectional ultrasound images. Hence manual segmentation was used to delineate the outer wall of the carotid artery, which is inevitably subject to human errors. Nevertheless, operator-dependent errors involved in the manual segmental of outer wall can be minimised through vigorous training and practice.

Based on the selected clinically relevant measures extracted from ultrasound for Patient 1 and Patient 2 in Chapter 3, it showed the plaque from Patients 2 was more vulnerable than that from Patient 1, for the carotid plaque of Patient 2 has higher DOS, larger plaque burden and smaller GSM. But the peak VMStress of Patient 1 predicted by finite element analysis was higher than Patient 2, as shown in Chapter 4, which gave a conflict prediction of plaque vulnerability. It

mainly because there was no lipid pool or fibrous cap component found in these two sets of images from patients.

With regard to the description of viscoelasticity of the carotid artery, Prony series was used and derived by fitting to data in the literature. It would be desirable to use subject-specific data for this purpose. This would require simultaneous measurement of local blood pressure and vessel diameter as a function of time over a number of cardiac cycles. Unfortunately, our collaborating hospital does not have this facility. The lack of *in vivo* pressure-diameter data has limited the present study to the use of standard viscoelastic properties in the literature, although the method was developed for subject-specific applications.

The dynamic interaction of blood flow and longitudinal wall displacement was investigated by using a prescribed longitudinal displacement as boundary condition on the solid domain. Although this allowed the effect of longitudinal vessel movement on blood flow to be investigated, the effect of wall shear stress on wall motion could not be examined. It is necessary to improve the wall biomechanical model by attaching spring-like elements at either one or both ends of the vessel to allow for longitudinal motion of the vessel to be driven by shear stress acting on the lumen surface.

7.2.2. Future work

The following areas have been identified for future studies.

- 1) The current study demonstrated the potential of using 3D ultrasound images in patient-specific analysis of biomechanical stresses in human carotid arteries. Owing to the lack of good quality 3D ultrasound images, a very limited number of patient-specific studies were performed. In future studies, an optimal imaging protocol should be developed in order to guarantee the quality of 3D ultrasound images, so that the method can be applied to a large cohort of patients with carotid artery diseases.
- 2) *In vivo* pressure-diameter data should be acquired, in order to evaluate viscoelastic properties of the carotid arteries for individual subject. This would allow the method developed in this study to be used to understand the effect of ageing and arterial diseases on changes in viscoelastic behaviour of the carotid artery. In fact, the method is not limited to the carotid artery, and can be readily extended to other large arteries, such as the aorta.

- 3) Ideally, a more detailed patient-specific model with all the measurements based on the same patient should be generated, including pressure and velocity boundary conditions, carotid geometry, and parameters derived for viscoelastic material properties from ultrasound measurement. More morphological features of atherosclerotic carotid plaques should be investigated. In order to overcome the limitations discussed above, cross-sectional 3D ultrasound images should be combined with longitudinal images for a more realistic reconstruction of the carotid artery including its bifurcation.

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