Mathematical Modelling of Mass Transport in Large Arteries

by

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Abstract

Atherosclerosis is a major cause of morbidity and mortality in the western world. The focal depletion of oxygen and accumulation of macromolecules are believed to initiate, accelerate and complicate the development of atherosclerosis. However, species concentrations in vessel walls are difficult to measure in vivo non-invasively. Therefore, it is essential to obtain detailed concentration profiles of atherogenic molecules to gain further understanding of the mass transfer mechanisms within arterial walls.

In the present study, comprehensive mathematical models describing species transport in large arteries are developed and presented. Existing mathematical models are reviewed and reconciled. A fluid phase model, a single-layered and a multi-layered fluid-wall models are employed to simulate the mass transfer processes in pro-atherosclerotic arteries. Since trans-endothelial transport is considered to be an important sub-process in the system and is dependent on wall shear stress (WSS) imposed on the endothelial surface, shear-dependent transport properties are derived from relevant experimental data in the literature. A novel approach, which exploits the optimisation theory, is proposed and used to determine model parameters based on the experimental data. Furthermore, numerical schemes to accommodate the effects of pulsatile flow on lipid transport in the arterial wall are presented in the thesis. Mathematical models and numerical schemes are tested and compared using idealised computational geometries. Then the models are applied to realistic geometries to investigate: 1) oxygen transport in a normal human abdominal aorta and an abdominal aortic aneurysm (AAA) with intraluminal thrombus (ILT); 2) macromolecular transport in a mildly stenosed human right coronary artery (RCA). Based on the model predictions, mechanisms inducing hypoxia and macromolecular accumulation are discussed in depth.
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Introduction

Atherosclerosis is a major cause of mortality and morbidity in the developed and developing world. The development of atherosclerosis begins in childhood and characteristically shows a focal distribution, with a particular predisposition to occur at sites of branching and curvature. Macromolecular accumulation and hypoxia (depletion of oxygen) each plays a role in atherogenesis and focal distribution of atherosclerosis suggests that mechanical factors, especially wall shear stress (WSS) are implicated in its development. Therefore, in this thesis, mass transport of oxygen and macromolecules in large arteries as well as its relationships with fluid mechanics and localisation of atherosclerosis are to be studied. In this chapter, background and preliminaries of the research are introduced. Then the objectives and strategies of the project are given followed by a plan of the thesis.
1.1 Preliminaries

Atherosclerosis is a disease of the arterial wall initiated by the accumulation of macro-
molecules. To understand the progression of atherosclerosis and the arterial mass trans-
port processes, it is important to have a basic knowledge about the arterial wall struc-
ture. Therefore, in this section, arterial wall structure, atherosclerosis, and arterial
mass transport are introduced in sequence.

1.1.1 Structure of the arterial wall

Arteries are muscular blood vessels that carry oxygenated blood away from the heart∗. They are contrasted with veins, which carry blood toward the heart. Arteries can be generally classified into three categories: elastic arteries, muscular arteries, and arterioles. Elastic arteries are the largest arteries such as aorta and carotid. Muscular arteries are the medium size vessels such as coronary and femoral arteries that conduct the blood to specific organs. Arterioles are smaller vessels and represent the ultimate branches of the arterial system.

The arterial wall is made up of different layers which are clearly shown in Figure 1.1. The endothelium is the innermost layer of an artery, which is an interface between circulating blood in the lumen and the vessel wall. It is a thin membrane, comprising a layer of well aligned endothelial cells. The endothelium maintains homeosta-
sis through effects on elements of blood, within the intima, and on vascular smooth
cells in the media (Vane et al., 1990). In particular, it serves as a continuous selective molecular sieve on blood contacting surfaces, inhibiting platelet adherence to the vessel wall and regulating the solute passage. The rest of the arterial wall is conventionally divided into three concentric zones [Nichols and O’Rourke, 2005]: the tunica intima, media and adventitia. The intima consists of a thin subendothelial layer of elastin and collagen fibres†. Its thickness varies with arterial geometry, age and disease. The ex-
tremely thin intima that can be found in a young adult could thicken and stiffen due to

∗Pulmonary arteries are the only arteries that carry deoxygenated blood from the heart to the lungs.
†The intima can also refer to both the endothelium and the subendothelial layer.
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2.2. HISTOLOGY AND TYPICAL MECHANICAL BEHAVIOR

and the carotid and iliac arteries), while muscular arteries are located at the periphery (for example, femoral, celiac, cerebral arteries). However, some arteries exhibit morphological structures of both types. Here we focus attention on the microscopic structure of arterial walls composed of three distinct layers, the intima (tunica intima), the media (tunica media), and the adventitia (tunica externa). We discuss the constituents of arterial walls from the mechanical perspective and emphasize those aspects which are important to researchers interested in constitutive issues.

Figure 2.1 shows a model of a healthy elastic artery.

Figure 1.1: Diagrammatic illustration of the major components of a healthy artery composed of the intima, media, and adventitia. Adapted from Gasser (2001).

aging and progression of atherosclerosis. Partition between the intima and the media is provided by the internal elastic lamina (IEL). It is a complex structure mainly consists of a fenestrated membrane. The tunica media forms the major part of the wall, comprising of orderly arranged fibres and smooth muscle cells. The external elastic lamina (EEL) partitions the media and the adventitia. The adventitia consists of collagen and elastic tissues. It merges with the surrounding connective tissue and is penetrated by the vasa vasorum which is a network of smaller vessels that supply cells in the outer arterial wall.

1.1.2 Atherosclerosis

Atherosclerosis is the predominant cause of various cardiovascular diseases (CVDs) such as coronary heart disease (CHD) and stroke. Cardiovascular diseases are the leading cause of death in the world. The World Health Organization estimated that CVDs
1.1 PRELIMINARIES

corresponded to a third of global deaths in 1999. In the UK, 36% of total death is attributed to CVDs which killed 208,000 people each year and costed the health care system £14,750 million in 2003. An increase in the prevalence of CVD was also observed in the Health Survey for England, increasing from 7.1% to 9.1% in men and from 5.2% to 6.3% in women between 1994 and 2003. Cardiovascular diseases or atherosclerosis therefore have major medical and economic implications.

Atherosclerosis is a disease of large- and medium-size arteries which also have thick walls and are exposed to systemic blood pressure. It is commonly referred to as a “hardening” or “furring” of the arteries and caused by the formation of plaques within the arterial wall. Its progression mainly involves physical phenomena occurring in the inner layers of the arterial wall, such as the endothelium, the intima and the inner media. Atherosclerosis is commonly characterised by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the arterial wall. Figure 1.2 shows a transverse section of a coronary artery with atherosclerosis, where buildups of fatty plaques in the arterial wall can be seen.

![Figure 1.2](image-url)
Atherosclerosis is a slow, progressive disease that may start in childhood. The events leading to formation of an advanced lesion are shown in Figure 1.3. The progression starts with the infiltration and entrapment of low-density lipoprotein (LDL) in the arterial wall. Once entrapped in the vessel wall, LDL particles are modified through oxidation. Endothelial cells react to lipid modifications by attracting monocytes to the area (Ross, 1999). After migrating through the endothelium, monocytes transform into macrophages which digest oxidised lipids. However, macrophages lack the ability to regulate the uptake of modified LDL and the cytoplasm of the cells will be packed with lipid eventually. The collection of lipid-packed macrophage cells generally has a foamy-like appearance and is called fatty streaks. This represents the initial phase of atherosclerosis. As the fatty streak progresses, smooth muscle cells migrate from the media to the subendothelial space where they proliferate and produce connective tissue to form a fibrous cap. This fibrous plaque represents the second phase of atherosclerosis. The final stage leads to the development of a complicated lesion which can manifest calcification, hemorrhage, ulceration and thrombosis.

Figure 1.3: Schematic of events leading to formation of an advanced lesion.

The risk factors of atherosclerosis include hypertension (high blood pressure),

*The oxidation pathway is a hypothesis which is not supported by any strong evidence.
hypercholesterolemia (high blood cholesterol level), cigarette smoking, diabetes, obesity, physical inactivity, advancing age and male sex. Having a close relative who developed atherosclerosis at an early age also increases the risk.

Non-pharmaceutical means such as cessation of smoking and regular exercise are usually used as the first method of treatment. If the situation does not improve, medicines are usually the next step in treating atherosclerosis.

1.1.3 Mass transport in large arteries

Arterial mass transport refers to the movement of atherogenic molecules from flowing blood to and through the arterial wall. It is related to the localisation of vascular diseases, especially atherosclerosis. Mass transport of solutes encounters resistances in both the arterial lumen and the arterial wall. These resistances not only are influenced by various factors such as fluid mechanics and endothelial cell metabolism but also interact with each other, leading to a complicatedly coupled mass transport system.

Considering the arterial wall structure, this complex mass transport system can be divided into three parts: 1) mass transport from the bulk blood flow to the endothelium or trans-lumenal transport, 2) mass transport across the endothelium or trans-endothelial transport, and 3) mass transport through the arterial wall or trans-mural transport. Therefore, in different phases of transport, the solute molecules are subject to various resistances to their movements. Figure 1.4 is a schematic view of the resistances involved in the arterial mass transport system.

It should be noted that since lipid deposition normally takes place in the intima and the media, the adventitia is not considered in the present study and the term “arterial wall” refers to the intima and the media in this thesis, if not stated otherwise.

1.1.3.1 Trans-lumenal transport

The trans-lumenal transport process is the mass transport process of solutes in the fluid (blood) phase, which is coupled with fluid dynamics of the bulk blood flow. Due to the nature of the bulk blood flow and the low plasma diffusivities of the solutes of interest,
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**Figure 1.4:** Schematic diagram of resistance involved in mass transport in large arteries. Adapted from [Ethier](2002).

i.e. oxygen, albumin and LDL, mass transport is dominated by convection in the fluid phase. Therefore, a thin boundary layer can be usually found near the lumenal surface. The resistance to solute transport is mainly provided by this boundary layer.

1.1.3.2 Trans-endothelial transport

When the solute molecules are transported to the lumenal surface, they can possibly move further into the arterial wall. For example, oxygen may be transported across the entire endothelial surface because it is soluble in the plasma membrane. Other pathways for trans-endothelial transport have been identified as intercellular junctions, leaky junctions and vesicles. *Intercellular junctions* between endothelial cells are the pathway for transport of water and hydrophilic solutes below the size of albumin ([Pappenheimer et al.](1951)). *Leaky junction* which only associates with less than 0.001% of the endothelial cells is a pathway for macromolecular transport ([Weibaum et al.](1985)). In spite of its small fraction, the leaky junction is able to elevate the endothelial permeability to macromolecules by 50-100% due to the local variations in cell turnover in arteries. [Chen et al.](1995) presented detailed data of leaky junctions in the rat aorta. They reported that about one cell in 3000 had a leaky junction and this leakage would last on average about one hour before a well-formed new junction was established. The leaky junctions which allowed macromolecules permeating through the endothelium were located around mitotic and dying cells. *Vesicle* is another pathway for macromolecules transport besides the leaky junction ([Lodish et al.](2003)).
It should be pointed out that the solute molecules on the luminal surface have the possibility of being retarded and not being transported across the endothelium due to the insufficient capacity of transport pathways. For instance, macromolecules which are mainly transported via leaky junctions and vesicles have very high possibility of being retarded at the luminal surface while oxygen can easily pass the endothelial barrier. In other words, the endothelium, which acts as a molecular sieve, provides a significant resistance to macromolecules.

### 1.1.3.3 Transmural transport

Transmural transport refers to transport of solute molecules inside the tissue phase (arterial wall). It is coupled with the transmural flow. The order of magnitude of the transmural flow is at $10^{-8} \, m \, s^{-1}$. Therefore, for more diffusive species such as oxygen, transport in the wall is dominated by diffusion whereas for macromolecules such as albumin and LDL, transport is still dominated by convection. Mass balancing of solutes in the arterial wall also involves chemical reactions since solutes are continuously consumed by various cells in the wall.

### 1.1.3.4 Identification of rate limiting process

The trans-lumenal, trans-endothelial and transmural transport processes not only are coupled with fluid dynamics in the lumen and the wall, but also interact with each other. Among these three sub-processes, trans-endothelial transport plays a role as an intermediary. Therefore, whether the transport process is limited by lumen-side transport or by wall-side transport is somehow determined by the efficiency of trans-endothelial transport.

If trans-lumenal transport is more efficient than trans-endothelial transport, that is, many solute molecules are convected to the luminal surface but few being transport across the endothelium, an accumulation of solute molecules would be found on the luminal surface. This phenomenon is called concentration polarisation. Figure 1.5 shows a schematic drawing of LDL concentration polarisation phenomenon. Specifically, concentration polarisation is usually observed in macromolecular trans-
port: macromolecules are forced to the lumenal surface by a strong convection driven by the transmural flow, but most of them are retarded to remain on the lumenal surface because of the limited capacity of transport pathways. In this case, the transport

![Figure 1.5: A schematic drawing showing LDL in blood flowing in an artery. Transmural fluid flux produces a concentration polarization layer on the lumenal surface. Adapted from Wada and Karino (1999).](image)

is described as limited by the endothelium or limited by the wall. On the other hand, if trans-luminal transport is less efficient than trans-endothelial transport, a depletion of solute molecules would be found on the lumenal surface. Oxygen transport often shows this characteristic depletion because it is spontaneously uptaken by the endothelium and consumed by the arterial wall. In this case, the transport is said to be limited by the fluid phase.

### 1.1.3.5 Time-scales of arterial mass transport

It has been mentioned that trans-luminal transport is coupled with the bulk blood flow whereas transmural transport is coupled with the transmural flow. The magnitude of the transmural flow ($10^{-8} \, \text{m} \cdot \text{s}^{-1}$) is several orders of magnitude smaller than that of the bulk blood flow ($10^{-1} \, \text{m} \cdot \text{s}^{-1}$). Therefore, the time-scales characterising these two sub-processes are dramatically different. The time-scale for trans-luminal transport is the same as the period of a cardiac cycle or around one second, whereas the time-scale for transmural transport is measured using the time needed by plasma to flow across
1.2 Objectives and Strategies

As pointed out previously, both low WSS and abnormal arterial mass transport which leads to accumulation of macromolecules and depletion of oxygen are implicated in the development of atherosclerosis. There are a large number of studies in the literature focusing on the localisation of atherosclerosis and low WSS. However, it should be pointed out that low WSS, as an external force acting on the endothelium should influence atherogenesis via certain mechanisms. One of the favourable hypotheses is that low WSS (or flow patterns that give rise to low WSS) causes abnormal arterial mass transport, such as lipid accumulation \cite{Caro} \cite{1971}. Therefore, the main aims of this thesis include:

- Developing a computational model for the simulations of mass transport of oxygen, albumin and LDL in arteries that are prone to arterial diseases.
- Determining the mechanisms underlying the shear-dependent macromolecular accumulation in the arterial wall.
- Identifying the relationship between localisations of atherosclerosis, low WSS, and abnormal mass transport.
- Evaluating the low WSS hypothesis in the context of mass transport.

To achieve these objectives, the research involves the following steps:

1. Formulate the mathematical models for momentum and mass transport processes. These models should include: fluid dynamics models to account for the

\[ \text{wall or } 300 \, \mu m / 0.03 \, \mu m s^{-1} = 10^4 \, s^{*}. \text{ The influence of this remarkable difference is discussed later in the thesis.} \]
bulk blood flow in the lumen and the transmural flow in the wall; *solute dynamics models* to account for mass balances of transport species in the lumen and the wall.

2. Determine the model parameters using a systematic approach. Many of the model parameters are very difficult to measure directly in the experiments and need to be estimated carefully from limited data in the literature.

3. Test the mathematical models and model parameters in simple idealised computational geometries.

4. Apply the tested mathematical models to realistic image-based computational geometries.

1.3 Plan of the thesis

The thesis is organised in a logical sequence. In Chapter 2, a literature survey is given for the research containing relevant basic knowledge and recent developments in modelling of arterial mass transport process. In Chapter 3, different classes of mathematical models are formulated and numerical procedures used to carry out transient transport simulations are described. In Chapter 4, systematic approaches are used to estimate model parameters that are poorly documented in the literature. Mathematical models, numerical procedures and parameter values are tested in Chapter 5 using idealised computational geometries. In Chapters 6 and 7, mathematical models are applied to anatomically realistic human arterial geometries to investigate oxygen, albumin and LDL transport. Finally, conclusions and suggestions for future study are given in Chapter 8.
Literature Review

In this chapter, a brief literature survey is carried out. First of all, the roles haemodynamics, lipid accumulation, and hypoxia play in atherosclerosis are introduced. Then one of the important characteristics of arterial mass transport, the shear-dependence, is discussed. Finally, a complete review is given on computational modelling of arterial mass transport.

2.1 Role of haemodynamics in atherosclerosis

Haemodynamics describes the dynamic behaviours of the blood flow. Blood is periodically pumped by the heart throughout the cardiovascular system. Many factors influence haemodynamics, including blood density, blood viscosity, and most importantly the geometry (size and shape) of the vessels. On the other hand, atherosclerosis is a localised disease and it is suspected that haemodynamic factors may play important roles in atherogenesis.
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2.1.1 Localisation of atherosclerosis

Atherosclerosis is a focal disease. It was found that atherosclerosis normally occurs in carotid bifurcations, aortas and coronary arteries, where blood flow separates or is disturbed (Glagov et al., 1988). More specifically, atherosclerotic plaques develop preferentially in arterial walls exposed to low wall shear stress. Figure 2.1 compares localisation of plaques and distribution of WSS in human carotid bifurcations. The

Figure 2.1: Localisation of plaques at human carotid bifurcation. In the left and middle panels, single arrow indicates flow divider side, whereas double arrows indicate lateral wall opposite flow divider. It was obvious that proximal sinus (level B) and middle sinus (level C) of internal carotid artery were markedly affected. Adapted from Glagov et al. (1988).

The figure revealed well-developed atherosclerotic plaques at lateral wall opposite flow divider of the carotid bifurcation where the wall was exposed to low WSS due to the flow separation. On the other hand, little or no plaque formation was found at the
flow divider side of the wall which was exposed to high WSS. The co-localisation of atherosclerosis and disturbed blood flow patterns indicates that the “abnormal” flow characteristics may initiate and facilitate the arterial wall remodelling and finally lead to atherosclerosis.

2.1.2 Role of wall shear stress

The dynamic behaviours of the blood flow are described by haemodynamics. Among many haemodynamic factors, WSS is the main suspect of contributing to progression of the disease. WSS is a tangential drag force of the blood flow along the surface of the endothelium. Fully developed flow under steady, laminar, incompressible Newtonian conditions in a rigid, smooth and cylindrical tube is described by Poiseuille’s law and the velocity profile is parabolic:

$$u(r) = 2U_0 \left(1 - \left(\frac{r}{R}\right)^2\right)$$  \hfill (2.1)

where $r$ is the radial position, $R$ is the radius of the tube, and $U_0$ is the mean velocity.

The wall shear stress is defined as follows

$$\tau_w = \mu \frac{\partial u}{\partial y} \bigg|_{y=0}$$  \hfill (2.2)

where $\mu$ is the dynamic viscosity of blood, $u$ is the velocity component parallel to the endothelium, and $y$ is the distance from the endothelium. For Poiseuille flow, the WSS can be calculated as Equation (2.3).

$$\tau_w = \mu \frac{\partial u}{\partial y} \bigg|_{y=0} = \frac{4\mu U_0}{R}$$  \hfill (2.3)

The endothelium in vivo could be exposed to various flow patterns and flow-induced WSS patterns: steady flow, which generates a steady WSS; undisturbed pulsatile flow which generates substantial temporal gradients but small spatial gradients in WSS; and disturbed pulsatile flows in regions of flow separation, recirculation and reattachment that generate considerable temporal and spatial shear gradients. However, atherosclerotic plaques are normally identified in regions subject to low WSS or oscillatory WSS with low mean values. These regions include curved arteries, such as
the aortic arch and the right coronary artery (RCA), and bifurcating arteries, such as the carotid and the left coronary artery (LCA) bifurcation.

Many studies attempted to explain the correlation between “abnormal” WSS and atherogenesis. Among these studies, Caro et al. (1971) found that the distribution of early atheroma is coincident with low WSS and dismissed an earlier hypothesis that atheroma is associated with wall damage caused by the blood flow. They firstly suggested that atherogenesis is associated with shear-dependent mass transport phenomena based on their theoretical analysis on mass transport across flow boundary layer and experimental observations on the distribution of cholesterol in arteries. This hypothesis stated that trans-lumenal arterial mass transport is dependent on the bulk flow pattern which can be characterised by WSS. It stimulated a bulk of studies on shear-dependent arterial mass transport. Ando et al. (1987) and Cho et al. (1997) showed that low WSS not only caused enhanced migration and proliferation of endothelial cells but also increased endothelial cell death due to apoptosis.

A popular hypothesis states that the mass transport of lipids across the endothelium is shear-dependent while abnormal mass transport may be related to atherogenesis (Caro et al., 1971). Davies et al. (1984) and Sprague et al. (1987) reported shear-dependent fluid-phase endocytosis and internalisation of LDL in bovine aortic endothelial cells (BAECs). More recently, Sill et al. (1995); Kudo et al. (1998), among others, reported that the trans-endothelial transport of plasma and albumin are both shear-dependent in BAECs. Specifically, plasma transport was found to be enhanced under high shear conditions (Sill et al., 1995), whereas albumin permeability increased with increasing WSS under low shear conditions and decreased with increasing WSS under high shear conditions (Kudo et al., 1998). In the present study, these measurements are used to derive shear-dependent transport parameters. Their limitations are discussed later in this chapter (see page 45).

Although diverse explanations have been proposed to explain the correlation between WSS and atherogenesis, it is widely believed that remodelling of vascular wall and modulation of vascular wall behaviour in regions of “abnormal” WSS in conjunction with the impact of risk factors such as smoking, hyperlipidemia and hypertension
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promote a chronic fibroinflammatory response to the resultant arterial injury.

2.1.3 CFD in haemodynamics

Given that haemodynamic factors, especially WSS, are implicated in atherogenesis, computational fluid dynamics (CFD) has been used in cardiovascular research. This is because the computational approaches give researchers full control of geometry and flow data while producing detailed distributions of parameter of interests. In early studies, idealised geometries were constructed using mathematical descriptions and flow conditions were also approximated with simple waveforms. Due to the advances in medical imaging technology and computer sciences in the recent years, subject specific geometries were reconstructed from medical images and flow conditions were also more realistic. In this subsection, the development of CFD application in vascular research will be briefly reviewed with an emphasis on early works which set up and validated the methodologies.

2.1.3.1 CFD with idealised geometries

For many years, vascular CFD models were based on idealised geometries, which were derived from averaged geometries in vivo. Normally, features of a number of arterial samples were compiled to extract key parameters such as diameters and bifurcation angles. These parameters were then used in the mathematical descriptions of the arterial geometries.

The early models further simplified the geometries to two spatial dimensions. **Friedman and Ehrlich (1984)** used a two-dimensional model to calculate WSS in human aortic bifurcations which agreed well with experimental measurements in casts of the same vessels. Three-dimensional models gave a better description of the arterial geometries and were used by researchers in more recent studies. In the 1990s, a number of researchers studied the effects of three-dimensional geometrical features on flow patterns. For instance, **Perktold and Resch (1990)** investigated a number of geometric factors and their effects on blood flow patterns. It was found that flow separation and the duration of separated flow were influenced by the geometry. **Perktold et al.**
focused the investigation on effects of bifurcation angle on flow and found that it was an important factor in determining the extent of recirculation regions. These findings casted doubts on the usage of idealised and averaged geometries and called for subject-specific investigations.

However, it should be noted that idealised arterial geometries are still used in recent years. They are commonly employed to 1) test new mathematical models and numerical techniques, or 2) study fundamental physical phenomena.

2.1.3.2 Image-based CFD

In the recent ten years, researchers realised that averaged geometries were unable to account for much more complicated geometrical features in vivo, which were proven to be significantly influential to flow patterns. Therefore, a huge progress was made towards the use of anatomically realistic CFD models derived from in vivo medical images.

Krams et al. (1997) developed an angiography and ultrasound (ANGUS) approach to quantify wall thickness and WSS in a human coronary segment. Maximum and minimum values of WSS were found to occur at the outer and inner walls along the curvature, respectively. Furthermore, an inverse relationship between wall thickness and WSS was identified. A number of follow-up studies (Langenhove et al., 2000; Wentzel et al., 2001a,b) also used the ANGUS method to investigate the role of WSS in cardiac interventional procedures. It should be pointed out that the ANGUS method is highly invasive and only applicable to animal models or patients referred for cardiac catheterisation.

Steinman et al. (1996, 1997) investigated steady flows in an end-to-side anastomosis model using the a combined MRI and CDF approach to validate the blood flow velocity measurements. Good agreement was found between measured velocity and computational results. Steinman and Rutt (1998) used the developed method to study the nature and reduction of plaque-mimicking flow artifacts in black blood MR images of human carotid bifurcations. Milner et al. (1998) reconstructed three-dimensional models of the carotid bifurcations. Flow boundary conditions were specified based
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Figure 2.2: Calculated WSS distribution in two anatomically realistic carotid bifurcations. Adapted from Milner et al., (1998).

on artery flow rate waveform determined using MRI phase-contrast velocity imaging. As seen in Figure 2.2, a strong inter-subject variations in WSS patterns were observed, which suggested that the averaged arterial geometries was insufficient. It was also found that helical flow patterns were induced by the asymmetric nature and curvatures of the subject-specific geometries. However, the use of realistic flow waveform was found to play a relatively minor role. Steinman et al., (2002) used the same protocol to investigate blood flow in a carotid bifurcation reconstructed from MR images. The study demonstrated a correlation between wall thickening and low and oscillating WSS at the carotid bulb.

Long et al., (1998) developed a protocol to combine MRI data and CFD to investigate arterial haemodynamics. The protocol was then used to investigate blood flow patterns in a human carotid bifurcation (Long et al., 2000b). Similar to Milner et al., (1998), it was found that the geometry of the carotid bifurcation was highly complex with helical curvatures and non-planar branching. Therefore, the flow patterns were found to be significantly different from those found in simplified carotid models. Long et al., (2000a) also investigated blood flow in a human aorto-iliac bifurcation using the same method. The calculated flow patterns were in a good quantitative agreement
with measured MRI velocity data. Major differences in WSS distributions between iliac arteries were also observed. [Zhao et al. (2000)] extended the method to incorporate the movement of compliant arterial wall by carrying out fluid-structure interaction (FSI) simulations. In this work, branch flow rates, local wall thickness and wall elastic modulus were acquired using ultrasound imaging techniques in a subject-specific manner. It was found that the movement of the arterial wall induced a reduction in the magnitude of WSS and the regions of high mechanical stress were found to co-localise with regions of low WSS (see Figure 2.3). The reproducibility of the MRI-based CFD model was investigated by [Glor et al. (2003)]. The subjects were scanned twice; three-dimensional geometries were reconstructed from each scans and CFD predictions were obtained. Generally speaking, the results were proved to be highly reproducible, although variations near the bifurcation apex existed.

Flow in coronary arteries has also been investigated using image-based CFD since early 2000s. [Myers et al. (2001)] investigated blood flow in a right coronary artery recontracted from computer tomographic (CT) scans of an anatomically realis-
tic acrylic flow mode. The study focused on the effect of waveform variations on RCA haemodynamics and found that changes in the inlet velocity profiles did not produce significant changes in the velocity field and WSS distribution. Furthermore, geometric effects were found to dominate the flow patterns, which highlighted the importance of subject-specific image-based investigations. In a more recent study, Zeng et al. (2003) attempted to investigate the effects of cardiac motion on haemodynamics in human RCAs. Arterial motion was specified based on biplane cineangiograms, and incorporated with realistic bending and torsion. Significant variations in WSS distributions were observed between moving and static geometries. However, time-averaged WSS was found to be similar. Currently, a more sophisticated study using navigator-gated interleaved spiral sequence MRI to track the movement of RCAs is being carried out by Torii et al. (2007b). Preliminary results suggest that time-averaged WSS calculated in a time-averaged geometry can somehow represent the time-averaged WSS calculated using the moving geometry.

In the recent years, image-based CFD was adopted as a conventional tool in investigations of haemodynamics. Furthermore, the method has been extended to include FSI and mass transport simulations. For instance, image-based FSI simulations and stress analysis are now widely used to evaluate the risk of rupture of aneurysms and plaques. On the other hand, the application of image-based CFD to mass transport simulations is still in an early stage. A detailed review on simulation of mass transport (including image-based studies) is given in §2.4.

## 2.2 Lipid accumulation and hypoxia in atherosclerosis

Lipid accumulation and hypoxia in the arterial wall are important characteristics of atherosclerosis. In this section, their roles in atherogenesis are briefly discussed.

### 2.2.1 Macromolecular transport and atherosclerosis

The development of atherosclerosis usually starts from childhood in humans with initial atherosclerotic lesions. The accumulation of atherogenic, plasma-derived lipopro-
teins in the arterial intima initiates specific cell reactions that lead to formation of the initial lesions [Getz, 1990; Stary et al., 1995]. The size and complexity of lesions are associated with the accumulation of lipoproteins in the intima. However, in normal subjects with no pathogenic complications, lipoproteins do exist in the intima with lower concentration. This indicates that a threshold lipoprotein intimal concentration exists. However, such a threshold is still not known.

Epidemiological analyses indicated that high blood cholesterol level plays a positive role in atherogenesis. Newman et al. (1986) assessed the relation of risk factors for cardiovascular diseases to early atherosclerotic lesions in aortas and coronary arteries in 35 persons. They found that aortic and coronary fatty streaks were strongly correlated with LDL and very low density lipoprotein (VLDL) plasma concentrations, independently of race, sex and age. Keys et al. (1986) also found that high blood cholesterol levels were strongly correlated with the presence and severity of coronary heart disease by studying 11,579 humans aged 40-59 years in seven countries.

Clinical and animal data showed positive links between high lipoprotein concentration and atherosclerosis. Hoff et al. (1983) and Spring and Hoff (1989) found elevated levels of apoprotein B in swine aortic segments and in human distal abdominal aorta with thick intima. Increased levels of LDL in lesion-prone regions of the aortic intima were also found in rabbits fed a high-cholesterol diet (Schwenke and Carew, 1989a,b).

2.2.2 Hypoxia and atherosclerosis

Hypoxia in the arterial wall has been implicated in atherogenesis (Crawford and Blankenhorn, 1991). Especially, hypoxia are thought to affect the uptake of LDL and other macromolecules by the arterial wall. First of all, local hypoxia affects endothelial cell metabolism and increases endothelial permeability. For instance, hypoxia induces the formation of inter-endothelial gaps leading to enhanced macromolecular transport (Al-Haboubi and Ward, 1996; Fischer et al., 1996; Kondo et al., 1996). Furthermore, hypoxia enhances macromolecular transport through leaky junctions by inducing en-
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dothelial cell apoptosis [Aoki et al., 2001; Matsushita et al., 2002]. Secondly, hypoxia up-regulates VEGF released by vascular smooth muscle cells; and VEGF may permeabilise the endothelium, which increases transport of lipid into the wall [Tarbell, 2003]. This is supported by a number of recent studies [Couffinhal et al., 1997; Ramos et al., 1998; Blann et al., 2002] which found the enrichment of VEGF in human atherosclerotic lesions.

2.3 Shear-dependence of trans-endothelial transport

Fluid dynamics influences macromolecular transport in two parallel ways. First, transport of macromolecules from the lumen to the wall is dominated by convection and hence the complex flow patterns in arteries affect the concentration gradient near the wall. Second, endothelial transport properties are altered by blood flow patterns because WSS regulates endothelial structure and function [Langille and Adamson, 1981]. The first effect was briefly discussed in §1.1.3 and §2.1 whereas this section will focus on the second effect.

2.3.1 Permeabilities of the endothelium

Both plasma and solutes are transported across the endothelium. The plasma flux is determined by the permeability of the endothelium to water, which is formally called endothelial hydraulic conductivity \(L_{p,\text{end}}\). It is the ratio of the plasma flux to the pressure drop across the endothelium

\[
L_{p,\text{end}} = \frac{J_{v,\text{end}}}{\Delta p_{\text{end}} - \sigma_{d,\text{end}} \Delta \pi_{\text{end}}} \quad (2.4)
\]

where \(J_{v,\text{end}}\) is the plasma flux, \(\Delta p_{\text{end}}\) is the hydrostatic pressure drop across the endothelium, \(\Delta \pi_{\text{end}}\) is the corresponding osmotic pressure difference, and \(\sigma_{d,\text{end}}\) is the reflection coefficient.

In the case of solute transport, the situation is complicated by the fact that the flux is contributed by both the convective component and the non-convective compo-
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Figure 2.4: *In vitro* response of albumin permeability of the bovine aortic endothelial cells (BAEC) monolayer to step changes in WSS. $P_e$ is the non-convective permeability of albumin. Adapted from Jo et al. (1991).

In this thesis, the permeability ($P_{end}$) is defined using the non-convective flux

$$P_{end} = \frac{N}{c_{end,l} - c_{end,w}}$$

(2.5)

where $N$ is the non-convective flux of the solute across the endothelium, $c_{end,l}$ and $c_{end,w}$ are endothelial solute concentrations on the lumenal side and the wall side, respectively. The non-convective flux consists of diffusive flux and flux contributed by vesicles. It is important to point out that, by using such a notation, it is implicitly assumed that vesicular transport is concentration-dependent.

There are a considerable amount of studies on the shear-dependence of these parameters in the literature. The most relevant ones are reviewed and discussed below.

### 2.3.2 Examinations of shear-dependent permeabilities

Jo et al. (1991) were among the first ones to investigate shear-dependence of endothelial permeability systematically. The authors found that after an exposure of bovine aortic endothelial cells (BAEC) to 1 Pa of shear stress, endothelial permeability to albumin increased rapidly, peaked at 30 min and maintained at a value that is more than 10-fold of the value in the absence of flow. When the flow was ceased, the permeability to albumin rapidly returned to preshear levels (see Figure 2.4). Lever et al. (1992)
examined the transmural flux across the wall of an isolated rabbit common carotid artery, where they found a relatively slow lumenal flow caused a reversible increase in the transmural flux by 20%–30% relative to the value in the absence of flow. It should be noted that this increase was rather small. This was so because the whole arterial wall rather than the endothelial monolayer was examined in this case and the media still provided significant resistance (estimated to be about 50% by Tedgui and Lever (1984)) when the endothelial resistance was down-regulated by WSS.

In a more recent study, Sill et al. (1995) found that hydraulic conductivity was very sensitive to shear stress, although the mechanism might be different from the case of albumin. Hydraulic conductivity increased by 2.2-fold after the exposure of 1 Pa of WSS for 1 h. Hydraulic conductivity under other shear conditions was also measured and showed a similar trend except that under shear stress of 0.01 Pa, where there was no increase (see Figure 2.5). Based on microscopic examination which suggested that the endothelium was not damaged by shear stress, it was indicated that the increase in

Figure 2.5: *In vitro* response of hydraulic conductivity of the BAEC monolayer to step changes in WSS. Adapted from Sill et al. (1995).
hydraulic conductivity was not due to endothelial injury. Furthermore, it was found that this shear-dependence of hydraulic conductivity could be reversed with dibutyryl adenosine 3',5'-cyclic monophosphate (DBcAMP) and completely blocked by preincubation with a general phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine. Therefore, it was suggested that the shear-dependence was mediated, at least partially, by signal transduction. Chang et al. (2000) showed that it was actually mediated by nitric oxide (NO) production in response to steady WSS, whereas the albumin permeability response to steady shear stress is independent of NO production. This implied that albumin was transported across the endothelium via different physical pathway than water.

Hillsley and Tarbell (2002) showed that when BAEC was exposed for 3 h to steady stress of 2 Pa or oscillatory shear stress of 1±1 Pa, a 3-fold increase in hydraulic conductivity could be observed. However, when BAEC was exposed to oscillatory shear stress of 1±1.5 Pa, no increase was observed, suggesting that oscillatory shear stress with negative values could not up-regulate hydraulic conductivity. Again, the shear-dependence was found to be mediated by NO production. Because NO production was dramatically increased under reversing oscillatory shear conditions, it was argued that there was a dual response of hydraulic conductivity to NO: at low levels, increase in NO production increases hydraulic conductivity, while at high levels, increase in NO production decreases hydraulic conductivity.

Kudo et al. (1998) and Ueda et al. (2004) reported a dual response of albumin uptake by BAEC to shear stress. As shown in Figure 2.6, it was found that albumin uptake increased with increasing WSS at lower shear stress (< 1 Pa) and decreased with increasing WSS at higher shear stress (> 2 Pa). The authors also examined the microstructure of glycocalyx using electron microscopy and found that at shear stress of 3 Pa, the thickness of the glycocalyx layer increased by 70% and the glycocalyx charge increased by 80%. Furthermore, albumin uptake at a shear stress of 3.0 Pa for cells with a neutralized glycocalyx layer was almost doubled compared with that of cells with charged layer. Consequently, the authors suggested that glycocalyx influenced albumin uptake at higher shear stress and its properties (thickness and charge level) were
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Figure 2.6: *In vitro* effects of different WSS on albumin permeability of endothelial cells. A characteristic dual response pattern can be observed. Adapted from Kudo et al. (1998).

involved in the shear-dependent albumin uptake process.

An *in vivo* experimental-numerical investigation on the correlation between WSS and endothelial albumin permeability was presented by Himburg et al. (2004). Calculated WSS distribution in the external iliac branches of a porcine was compared on a point-by-point basis with *in vivo* uptake of albumin in the same arteries. As seen in Figure 2.7, it was found that *in vivo* endothelial permeability to albumin decreased with increasing time-averaged shear stress in the normal range. Therefore, combining with the findings of Jo et al. (1991), this suggested that endothelial albumin permeability indeed follows a dual response mechanism to WSS: increases with increasing WSS under low shear conditions (observed by Jo et al. (1991) *in vitro*) and decreases with increasing WSS under high shear conditions (observed by Himburg et al. (2004) *in vivo*). This is consistent with the observations made by Kudo et al. (1998) and Ueda et al. (2004).

It is important to point out that, most of the *in vitro* measurements (Jo et al., 1991; Sill et al., 1995; Kudo et al., 1998; Chang et al., 2000; Ueda et al., 2004) were made with endothelial cells grown under static conditions which were then exposed to shear stress for a short period of time. Consequently, the observed response may
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Figure 2.7: Correlation between WSS and albumin uptake by the arterial wall observed in a porcine in vivo, where WSS was calculated using CFD and concentration of marked albumin was measured indirectly using optical density. Adapted from Himburg et al. (2004).

be the adaptation to a changing shear stress environment rather than a direct effect of fluid shear stress on transport pathways (Ogunrinade et al., 2002). Therefore, the effect of variations in shear stress once endothelial cells have adapted to one shear stress still needs to be investigated to gain an insight on the in vivo response.

2.3.3 Remarks on reflection coefficients

Besides hydraulic conductivity and permeability, there are two other basic endothelial transport properties, water reflection coefficient $\sigma_{d,\text{end}}$ and solute reflection coefficient $\sigma_{f,\text{end}}$. These two parameters are dimensionless and vary between 0 and 1. For small molecules, these two values are close to 0, while as the molecular size of solute increases, they approach 1. It would be intuitive to argue that the reflection coefficient should be shear-dependent too. However, there is no supporting experimental data in the literature. Therefore, it is assumed that they hold constant values under all shear conditions in the present study.
2.3.4 Remarks on endothelial permeability to oxygen

Although macromolecular trans-endothelial transport was found to be shear-dependent, there is no evidence showing that oxygen permeability is influenced by WSS. Unpublished data provided by Kudo and Tanishita (1993) showed that there was no shear-dependence for oxygen transport across the endothelium (see Figure 2.8). Therefore, in the present study, it is assumed that endothelial oxygen permeability remains constant under all shear conditions.

![Figure 2.8: Permeable resistance of cell layer subject to fluid shear stress. Provided by Kudo and Tanishita (1993).](image)

2.4 Modelling of arterial mass transport

A powerful way to investigate arterial mass transport is computational modelling, which provides detailed descriptions of local transport features (Ethier, 2002). In this section, early studies as well as recent developments on computational modelling of arterial mass transport are reviewed.

Before presenting the review, it is appropriate to define a number of dimensionless measures of mass transport. The balance between convection and diffusion
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can be measured by the Peclet number which is defined as
\[ Pe = \frac{U_0 L_0}{D_l} = Re Sc \]  (2.6)

where \( U_0 \) is the mean inlet velocity, \( L_0 \) is the reference length, \( Re = \frac{\rho U_0 L_0}{\mu} \) is the Reynolds number, and \( Sc = \frac{\mu}{\rho D_l} \) is the Schmidt number. When the Peclet number is much greater than one \( (Pe \gg 1) \), the system is convection-dominated. The Peclet number is determined by solute diffusivity \( D_l \) and the flow velocity for a given fluid. The fluid phase mass transfer efficiency can be measured by the Sherwood number defined as
\[ Sh = \frac{k_l D}{D_l} \]  (2.7)

where \( k_l \) is the fluid-phase mass transfer coefficient and \( D \) is the diameter of the artery. To identify the rate limiting process, it is conventional to compare the Sherwood number with the Damkholer number. The Damkholer number measures the uptake efficiency of the wall and can be defined in a number of ways depending on the uptake mechanism of the wall. If the Sherwood number is greater than the Damkholer number, the transport is limited by the wall side transport; otherwise, the transport is limited by the fluid phase transport.

2.4.1 The early works

Computational modelling of arterial mass transport started from 1970s. In early studies, researchers focused on trans-lumenal transport and did not include wall-side transport. Furthermore, finite difference method (FDM) was predominantly popular and thus the studies were limited to two-dimensional simple geometries.

Back (1975a,b) studied steady lipoprotein and oxygen transport in various blood flow regions that occur in arteries. For lipoprotein transport, through parametric study, the authors found that higher filtration velocities and lower diffusivities increased the accumulation of lipoproteins on the luminal surface. For oxygen, increased transport was predicted in accelerated flow regions, but significantly reduced transport was indicated in decelerated flow regions and at separation locations. The
authors concluded that oxygen deprivation and lipoprotein accumulation somehow had the same nature. Furthermore, it was suggested that \textit{in vivo} measurements were needed to test the computational findings and help to understand the contribution of abnormal mass transport to atherogenesis.\cite{Back1977} extended the work to pulsatile flow conditions and study oxygen transport in the lumen. The results showed similar trend indicated in their steady flow studies.\cite{Friedman1975, Friedman1977}

were also among the first to investigate convective diffusion processes in the arterial lumen. Due to the complicated nature of the high Peclet number convection-diffusion equation and a lack of computing power, semi-analytical solution was sought by applying boundary layer theory and Laplace transforms. The authors employed a two-dimensional symmetric bifurcation and set the Peclet number $Pe = 250,000$. It was found that the concentration on the lumenal surface was strongly correlated with WSS. However, concentration field in the bulk flow which was surely disturbed in the bifurcation was not fully presented.\cite{Fry1985a}

\cite{Fry1985a} developed both a numerical model and an analytical model to study one-dimensional convective diffusion transport of macromolecules across the arterial wall. The parameters in the analytical model were estimated by fitting measured albumin transmural concentrations with the model. It was found that parameter estimation was sensitive to wall inhomogeneity. Therefore, in a follow up study,\cite{Fry1985b} use a multi-layered wall model. It was found that the transport properties of the endothelium and the IEL of the arterial wall played important interactive roles in the accumulation of macromolecules in the intimal layer. It should be noted that in these two studies, vascular scale models were employed, whereas subcellular scale models were predominantly used in more recent studies when transmural transport was the only concern. For subcellular scale models, which are beyond the scope of this thesis, studies by\cite{Huang1997, Tada2004} (among others) can be referred to for details.
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2.4.2 Modelling of mass transfer in the arterial lumen

Following the pioneering investigations, Ma et al. (1994) studied mass transfer in a separated flow region under pulsatile flow conditions using heat transfer analogue. A two-dimensional axisymmetric sudden expansion was used as the computational geometry. It was found that heat transfer in the recirculation region was maximum near the area where WSS was minimum. An important finding in this study was that the mass transport efficiency did not change significantly during one flow cycle and the time-averaged transport pattern was similar to that of steady flow simulation using the mean Reynolds number. In a follow-up study, Ma et al. (1997) studied mass transport in a generalised two-dimensional carotid bifurcation. The flow was assumed to be steady. It was found that convection of oxygen was impaired in the carotid bulb, creating a thickened concentration boundary layer, which resulted in a lower mass transfer rate (see Figure 2.9). Results given by different Schmidt numbers were examined and it was observed that the location of minimum transfer rate was irrelevant to Schmidt number. The authors tried to correlate mass transfer coefficient with intimal thickness and argued that oxygen convection might be low in regions of early intimal thickening. In both of these two studies, constant concentration was prescribed at the wall, in which case the mass transport efficiency can only be evaluated using mass transfer coefficient rather than the more straightforward concentration values.

![Cross Sections of Concentration Boundary Layer](image)

**Figure 2.9:** Correlation between concentration boundary layer and flow recirculation. A thickened concentration boundary layer can be observed in the flow recirculation region. Adapted from Ma et al. (1997).
Deng et al. (1993) study LDL concentration polarisation on the luminal surface under steady flow conditions in a two-dimensional T-junction model. Counter-diffusion from the luminal surface to the bulk flow was found to be suppressed in the two regions of disturbed flow, one in the main vessel, the other in the subsidiary vessel. The lowest concentration gradients (diffusion rates) were at the points of flow separation and were much lower than those in the undisturbed flow regions. Lower counter-diffusion rates led to greater degree of concentration polarisation on the luminal surface and increased the driving potential of LDL movement into the arterial wall. In a follow-up investigation, Deng et al. (1994) carried out a parametric study on filtration velocity and examined its sensitivity on LDL concentration polarisation. The filtration velocity was varied among $1 \times 10^{-8} \text{ m s}^{-1}$, $5 \times 10^{-8} \text{ m s}^{-1}$ and $1 \times 10^{-7} \text{ m s}^{-1}$. Although a fairly low Reynolds number was employed, the results showed that the degree of concentration polarisation was very sensitive to the filtration velocity: a higher filtration velocity led to a higher degree of concentration polarisation due to a stronger convection of LDL towards the wall. In Deng et al. (1995a), the authors furthered their earlier study in the T-junction by varying the Reynolds number from 50 to 150. It was found that maximum LDL concentration migrated downstream in the daughter vessel due to the expansion of recirculation region when Reynolds number was increased. However, the maximum LDL concentration decreased while Reynolds number was increased because of a stronger LDL removal from the luminal surface at higher Reynolds numbers. Fatouraee et al. (1998) carried out pulsatile flow simulations based on earlier steady flow studies in the same research group. First of all, relatively moderate degrees of concentration polarisation were observed for three different Schmidt numbers 660,000 ($< 14\%$ of elevation of LDL concentration), 330,000 ($< 9\%$), and 160,000 ($< 6\%$) even though a fairly high filtration velocity $4 \times 10^{-8} \text{ m s}^{-1}$ was employed. It was also found that pulsatile flow did not induce significant temporal variations in the degree of concentration polarisation (only 0.01% in one cardiac cycle), and the time-averaged LDL concentration on the luminal surface was very similar to that under steady flow conditions (with only around 0.002% underestimation in the steady flow simulation).
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Figure 2.10: Contours of normalised wall oxygen flux (upper picture) and normalised wall oxygen concentration (lower picture) for pulse phase angle of maximum flow. Low oxygen flux and concentration can be seen at the inner wall of the curvature. Adapted from Rappitsch et al. (1997).

Rappitsch and Perktold (1996a) investigated fluid phase oxygen transport in an axisymmetric stenosis. An interesting feature of this study was the usage of a shear-dependent oxygen permeability of the endothelium and its comparison with a constant permeability. Their analysis illustrated an essential influence of the flow patterns on mass transport: in the flow recirculation region downstream of the stenosis, oxygen concentration was decreased to only 75% of the inlet concentration value. Specifically, results given by both shear-dependent and constant permeability showed a reduction of wall flux just downstream the location of maximum constriction at the incipient flow separation point, agreeing with the results found by Back et al. (1977). The shear-dependent permeability led to an even stronger spatial variation in the wall flux and a second minimum flux occurred at the reattachment point. In a follow-up study, Rappitsch et al. (1997) presented an investigation of oxygen transport in a three-dimensional curved tube under pulsatile flow conditions. Again, the shear-dependent oxygen permeability was employed. Their main observation was a substantial reduction in wall flux through the inner wall of the curvature where the fluid boundary layer resistance was high and the wall permeability was low (see Figure 2.10). Given these interesting results, it is still important to point out that, oxygen trans-endothelial transport may not be dependent on WSS due to its diffusive pathway. The authors also admitted this by stating “this simple model may not be valid for oxygen trans-
fer through the wall in this strong form”. However, the shear-dependent permeability did demonstrate its potential importance in macromolecular transport modelling. Rappitsch and Perktold (1996b) attempted to investigate albumin transport in an axisymmetric stenosis under pulsatile flow conditions. A shear-dependent endothelial albumin permeability was assumed using the experimental data published by Jo et al. (1991). The shear-dependent model was set to be monotonously increasing with increased WSS. The results showed differences up to 30% between time-averaged flux and steady flux in the flow recirculation region downstream of the stenosis. However, since only two data points in the low WSS range (at 0.1 Pa and 1 Pa) and no data point in high WSS range were available in the curve fitting process where shear-dependent permeability from 0 Pa to 25 Pa was calculated, the accuracy of this model and its numerical results was questionable. Furthermore, concentration polarisation of albumin was not observed because plasma filtration was not taken into account. Therefore, this study was essentially an investigation of oxygen transport with reduced diffusivity rather than of macromolecular transport.

Wada and Karino (1999) were the first to carry out a systematic and comprehensive study on LDL concentration polarisation. The authors studied the influences of various physical and fluid mechanical factors such as WSS, diffusivity of LDL, and filtration velocity of plasma through the arterial wall, on the degree of LDL concentration polarisation. Due to the simplicity of the computational geometry (a straight tube), the observations led to some fundamental conclusions. Specifically, it was found that the degree of concentration polarisation increased with increasing filtration velocity, decreasing flow rate, and decreasing LDL plasma diffusivity. Under physiological conditions where the flow rate and LDL diffusivity are within certain narrow ranges, the most influencing factor is therefore the filtration velocity controlled by the transmural pressure. This may explain how hypertension contributes to greater LDL accumulation in the arterial wall. Using the model developed in this study, the authors carried out pioneering investigations on LDL trans-lumenal transport in two anatomically realistic geometries. Wada and Karino (2002) studied LDL concentration polarisation in a segment of a human right coronary artery with multiple bends. Flow-
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Dependent concentration polarisation of LDL was found at the luminal surface of the vessel. The authors mapped WSS with LDL concentration on the luminal surface and observed that LDL concentration was elevated at locations where WSS was low and increased sharply as WSS decreased from 1 \( \text{Pa} \) to 0 \( \text{Pa} \) (see Figure 2.11). On the other hand, the scattering data points indicated that WSS was not the only factor influencing concentration polarisation even when the filtration velocity and diffusivity were fixed. Furthermore, it should be noted that both filtration velocity and LDL permeability were assumed to be constant, implying that when the shear-dependent transport pathways were discounted, the concentration polarisation phenomenon was still dependent on WSS. But this dependence was in effect not via a specific shear-dependent mechanism but through the flow driven convection and removal of LDL particles, which were somehow characterised by WSS distribution. Wada et al. (2002) investigated LDL concentration polarisation in two dog femoral arteries: one had a stenosis and the other was “healthy”. Up to 20% of LDL concentration polarisation was found downstream of the stenosis (see Figure 2.12) and no significant concentration polarisation was found in the other geometry. Furthermore, the maximum LDL concentration co-localised with intimal thickening observed in the animal model. In this series of studies, Wada and Karino carried out comprehensive investigations on
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Figure 2.12: Simulated flow characteristics and LDL concentration on the lumenal surface in a dog femoral artery. A co-localisation between wall thickening and LDL accumulation can be identified. Adapted from Wada et al. (2002).

LDL concentration polarisation in idealised as well as realistic three-dimensional models and gave fundamental and conclusive arguments on the topic. The most significant limitation of these studies was that the arterial wall was omitted and therefore the filtration velocity had to be specified rather than calculated. As their conclusion suggested, the filtration velocity was an important factor and needed to be determined carefully. Furthermore, since the ultimate objective of modelling LDL transport is to estimate concentration in the intima, a fluid-wall model would be preferable.

Qiu and Tarbell (2000) investigated oxygen transport in a two-dimensional idealised compliant model of a curved coronary artery. They carried out preliminary analysis on oxygen transport and remarked that the balance of oxygen transport can be studied by comparing the Sherwood number in the lumen and the Damkholer number in the wall. More specifically, if the Sherwood number is greater than the Damkholer number, the transport process is limited by arterial wall, and when the Damkholer number is greater than the Sherwood number, the process is limited by the fluid phase. The authors prescribed coronary artery movement and diameter variation to simulate blood flow and oxygen transport in the idealised model. It was found that the Sher-
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The Damkohler number on the outer wall of the artery (around 55) was much greater than that of inner wall (around 2). Since the Damkohler number was estimated to be $10.9 - 49.0$, it was concluded that, at the inner wall, the transport was limited by fluid phase; whereas at the outer wall, fluid phase transport did not limit the wall consumption of oxygen. Kaazempur-Mofrad and Ethier (2001) extended the study and simulated oxygen transport in an anatomically realistic human right coronary artery (RCA). Focusing on the effects of local geometric features on mass transfer from blood to artery walls, they found that the oxygen concentration field within the RCA closely followed primary and secondary flow features. Furthermore, it was observed that oxygen transfer patterns were more sensitive to local geometric features than were WSS patterns (see Figure 2.13). Therefore, it was argued that complex secondary flows in a realistic arterial model can produce substantial local variations in blood-wall mass transfer rates and precise geometries should be acquired to ensure the accuracy of flow and hence concentration predictions. To further evaluate the effects of local geometrical variations

Figure 2.13: Calculated Sherwood number distribution, which is a measure of mass transport efficiency, on walls of the right coronary artery. Labels A and B point to areas of low Sherwood number. Adapted from Kaazempur-Mofrad and Ethier (2001).
on mass transport, Kaazempur-Mofrad et al. (2005) compared oxygen transport in an axisymmetric and an asymmetric arterial models with mild stenoses. It was found that although similarities existed between the two models, such as a thickened concentration boundary layer downstream of the stenosis, the two models differed in the mass transport patterns in the vicinity of the stenoses and distal to the stenoses. In the asymmetric model, circumferentially non-uniform concentration distributions were found due to the development of downstream secondary flows. Again the authors argued that accurate representation of arterial geometries was crucial for arterial mass transport investigations.

Lutostansky et al. (2003) investigated mass transport in the recirculation region downstream of an axisymmetric sudden expansion. The computational results were validated by carrying out experimental investigations on transient mass transfer applying zero flux at the wall. After good agreements were obtained, the authors simulated ADP concentration polarisation on the lumenal surface and found that endothelial ADP concentration was increased by six to twelve percent of the bulk flow concentration. This study was among the first to carry out experimental validation, although the experiment did not provide any physiological information.

Most of the computational models reviewed previously assumed rigid arterial wall (excepted for Qiu and Tarbell (2000)). In the recent years, due to the enhanced computing power, a number of studies included the movement of the arterial wall in their mass transport models. Tada and Tarbell (2006) investigated oxygen mass transport in a generalised human carotid bifurcation, focusing on the effects of the wall compliance on the temporal variation and spatial distribution of oxygen wall flux. It was found that flow separation on the outer wall of the sinus provided a very strong barrier to oxygen transport; whereas at the inner wall of the sinus, the mechanism of transport was controlled by the wall consumption rate. Furthermore, the authors observed that oxygen transport in the fluid phase was more efficient under pulsatile flow conditions than that under steady flow conditions because the convective mechanism was enhanced by the secondary flow generated in the geometry. However, the wall compliance seemed to reduce the mass transport efficiency when WSS was hardly af-
fected. It should be noted that although the fluid-structure interaction (FSI) simulation was carried out, oxygen transport in the wall was not included. This was probably because the time-scales of transmural transport is much greater than that of trans-lumenal transport, making it infeasible to carry out fully coupled simulation. Therefore, it is difficult to estimate the effect of wall compliance on the fluid-wall oxygen transport process. Valencia and Villanueva (2006) also carried out FSI simulations in modelling of LDL transport in various stenotic arteries. Unfortunately, the filtration velocity at the wall was not included and zero LDL concentration was prescribed at the wall. Due to these unrealistic boundary treatments, the authors failed to model the physiological transfer patterns and did not observed the concentration polarisation phenomenon. Furthermore, a rather thick concentration boundary layer was found although a much thinner one was expected. Therefore, the authors were simulating oxygen transport with reduced diffusivity rather than simulating LDL transport. Kolandavel et al. (2006) simulated LDL and oxygen transport in an idealised moving coronary artery model under both steady and pulsatile flow conditions. A sinusoidal curvature waveform was specified for the wall motion boundary conditions. As expected, elevated LDL flux, reduced oxygen flux and low WSS were found along the inner wall of the coronary. Furthermore, it was observed that, although pulsatile flow and wall movement did not induce significant concentration variations during one cardiac cycle, it did change the time-averaged flux with moderate degrees (26% for oxygen and 12% for LDL). Therefore, the wall motion may play an important role in coronary mass transport processes.

The studies including movement of the wall either by FSI simulations or directly prescribing the motion reviewed above did not model transmural transport. As mentioned previously, this might be attributed to the difference in time-scales in the transport processes, as transmural transport is not synchronised with flow pulsations. By discounting transmural transport, it is doubted that the role played by wall movement can be fully identified.
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2.4.3 Modelling of fluid-wall mass transfer

Moore and Ethier (1997) were among the first to couple blood side transport with wall side transport. Oxygen transport was simulated in an idealised axisymmetric stenosis model for several wall thicknesses using a fluid-wall coupled model. Since oxygen transport in the arterial wall is diffusion-dominated, the transmural flow and convection-diffusion model in the wall were not included. It is worth mentioning that the authors also considered the important roles played by hemoglobin, which had long been ignored. They found that the neglect of oxygen binding by hemoglobin led to large an underestimation (by 67%) of the transport efficiency. This result provided a general reference for studies in which the transport by hemoglobin is absent.

Stangeby and Ethier (2002a) refined the model proposed by Moore and Ethier (1997) by extending it to macromolecular transport. Their fluid-plus-porous-wall method (FPPWM) coupled the transmural flow to the bulk blood flow and LDL transport. A concentration and WSS dependent endothelial permeability was also assumed based on experimental data. In a severely stenosed artery, elevated LDL concentration downstream of the stenosis was found. It was suggested that increased transmural flow and concentration-dependent endothelial LDL permeability could be important contributors to the LDL accumulation. Stangeby and Ethier (2002b) investigated unsteady transport of LDL using three different sets of model parameters: transmural pressure of 120 mmHg with low permeability, transmural pressure of 160 mmHg with low permeability, and transmural pressure of 160 mmHg with high permeability. The results showed that when the transmural pressure was elevated without a change in the permeability, the concentration field predicted in the arterial wall was very similar to the situation under low transmural pressure, which was contradictory to experimental observations. However, using the third set of parameters produced largely elevated concentration profile in the wall. This indicated that the non-convective component in the trans-endothelial transport played an important role.

Karner and Perktold (2000) investigated the influences of endothelial damage and blood pressure on albumin transport using a fluid-wall model with a multi-layered
description of the wall. The transmural flow was modelled using Darcy’s Law and albumin transmural transport was modelled using the volume-averaged convection-diffusion-reaction equation. Separate physical descriptions were given to different wall layers: the intima and the media were treated as transport domains while the endothelium and the IEL were assumed to be membranes where matching conditions were prescribed. To estimate transport parameters of the macromolecules in different wall layers which are almost impossible to measure in experiments, the authors employed pore theory. The results demonstrated a high resistance of the healthy endothelium to albumin transport; whereas endothelial injury caused higher concentration levels due to the reduced resistance provided by the endothelium (see Figure 2.14). Furthermore,

![Figure 2.14: Simulated albumin concentration distribution for different degrees of endothelial injury (1% leaky cells, 5% leaky cells, 10% leaky cells and 50% leaky cells). Increasing percentage of leaky endothelial cells corresponded to increasing albumin concentration within the wall. Adapted from Karner and Perktold (2000).](image)

high blood pressure was found to increase albumin concentration in the media. Although this study only employed a straight tube as the computational geometry, it was the first one to consider the arterial wall as a multi-layered structure and give detailed
concentration fields in both the intima and the media separately. As an extension of this work, Karner et al. (2001) simulated both LDL and albumin transport using the same approach. Significant efforts were made on determination of LDL and albumin transport properties in different wall layers and a full set of parameter values was provided. This was the first study to employ a systematic approach to carry out parameter estimations.

Using a similar mathematical model to Karner and Perktold (2000), Zunino (2002) carried out investigations of oxygen and LDL transport in various two-dimensional idealised geometries. To simplify the model, the author lumped the intima and the media as one layer. It was shown that oxygen transmural transport was dominated by diffusion and therefore transmural flow may not be included in the model. Prosi et al. (2005) used the same model employed by Karner et al. (2001) to investigate LDL transport. A novel electric analogy approach was used to derive the values of transport parameters because a mismatch in LDL trans-endothelial flux was found by using the parameter values determined by Karner et al. (2001). This zero-dimensional method used experimental data as inputs to seek the transport resistances provided by different layers of the wall. Resulting LDL concentration distribution in the wall generally agreed with experimental data reported by Meyer et al. (1996), although considerable local discrepancies existed. In the simulation of LDL transport in an axisymmetric stenosis, consistent results given by a model with single-layered wall formulation and a model with multi-layered wall formulation were observed: both showed about 5% – 10% variations in LDL wall concentration in the expansion part of the stenosis. It should be noted that LDL permeability was assumed to be constant and authors remarked that a shear-dependent permeability may be included to acquire more realistic results. Prosi (2003), applied a single-layered model to simulate LDL transport in an anatomically realistic human carotid bifurcation. A rather constant transmural velocity and less than 3% of concentration polarisation (see Figure 2.15) were found in the “healthy” geometry. It was also found that LDL concentration in the wall was at the same level everywhere. The question raised was if there was no geometrical preference of LDL accumulation in a “healthy” vessel, how would atherosclerosis be initiated.
Figure 2.15: LDL concentration on the lumenal surface calculated in a carotid bifurcation. Concentration polarisation less than 3% was observed. Adapted from Prosi (2003).

The possible explanation would be, constant transport parameters were assumed and shear-dependent trans-endothelial transport was not included.

Koshiba et al. (2007) carried out an FSI simulation to study LDL transport in a geometry with multiple bends. The arterial wall was approximated using a poro-hyperelastic model such that both the transmural flow and the viscoelastic behaviours can be accounted for. As seen in Figure 2.16, it was found that there existed a reverse flow pattern in the transmural flow which was presumably attributed to the “squeezing” effect of wall deformations. Furthermore, in the FSI model, the maximum LDL concentration in the wall was observed at the position of 3% wall thickness from the lumen-wall interface; while in the rigid wall model, it should be observed at the lumen-wall interface. These striking findings suggested that wall deformation may play a role...
Figure 2.16: Temporal and spatial distribution of transmural flow velocity calculated using a porohyperelastic model. Adapted from Koshiba et al. (2007).

in macromolecular transport in the arterial wall. However, it is important to point out that it was implicitly assumed that the endothelial hydraulic conductivity and the convective pathway of LDL were non-selective in direction: the endothelial resistances to water and convective LDL transport entering the wall and leaving the wall were the same.

In two successive studies, Ai and Vafai (2006) and Yang and Vafai (2006) used a four-layered model, where the endothelium, the intima, the IEL, and the media were all treated separately as layers of porous medium, to study LDL transport in various of stenoses. The authors used the porous media theory to model the transport in each layer, hoping to determine the transport properties. However, due to the lack of fundamental data such as porosities and the limitation of the theoretical model, their computation resulted in considerable mismatches with experimental data they referred to Meyer et al. (1996). As a matter of fact, the endothelium and the IEL are usually regarded as thin membranes and can be effectively treated as “thicknessless” layers in the model. For instance, it would not be plausible to model the endothelium as a layer
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of porous medium but do not take into account the endothelial cell structure given that the endothelium consists of a monolayer of endothelial cells.

2.4.4 Remarks on the determination of parameters

Due to the complex and coupled dynamics in the mass transport process, slight variations of model parameters may bring about substantial changes in mass transfer patterns. The transport parameters can be classified into two groups, momentum transport properties and mass transport properties. The momentum transport properties, including blood density, viscosity and hydraulic conductivity, determine the characteristics of the bulk flow and the transmural flow. The mass transport properties, including permeability and solute diffusivity, determine the convection-diffusion transport of solute molecules.

The complexity of model inputs, i.e. transport properties, of mathematical models depends on the description of the arterial wall. If the model only account for fluid phase transport, the model parameters which are mainly transport properties of solute molecules in the blood plasma, are relatively easy to measure in experiments and apply to computations. In models that include wall-side transport, the effective transport properties of solute molecules in the porous wall are far more difficult to measure. Furthermore, it is almost impossible to obtain directly the heterogeneous transport properties corresponding to different layers of the wall using current experimental techniques. The existing methods of parameter determination include theoretical modelling, especially using the fibre-matrix theory and analysing experimental data.

A number of researchers assumed that the wall layers were porous structures whose physical properties could be identified by pore theory (Shyy et al., 1997). For instance, Wang and Tarbell (1995) exploited pore theory and applied a fibrous matrix model to determine the hydraulic permeability of the media and calculate the transmural flow therein. Similarly, Huang and Tarbell (1997) used pore theory to correlate Darcian permeability with intimal thickness and calculated water filtration. Further-
more, Karner and Perktold (2000) and Karner et al. (2001) applied the fibre-matrix theory to determine a series of transport properties of different layers in the arterial wall and employed the resulting parameters in LDL and albumin transport simulations. Ai and Vafai (2006) also employed porous media model to determine the transport properties. However, using the determined parameters, the simulation results did not agree well with experimental observations (as seen in Figure 2.17).

Figure 2.17: Comparison between simulation results and experimental data in medial LDL concentration. Adapted from Ai and Vafai (2006).

As pointed out by Prosi et al. (2005), unrecognised biological phenomena might be omitted in the theoretical models when using pore theory which only account for the physical transport phenomena. For instance, the endothelial LDL permeability was underestimated by pore theory in Karner et al. (2001). Realising the need of analysing experimental data in determination of transport parameters, Prosi et al. (2005) reinterpreted the basic equations governing the mass transport through the arterial wall (convection-diffusion-reaction equation) by means of electric analogy to derive algebraic equations and determine the unknown physical parameters using available experimental data. The specific experimental data considered were LDL con-
centration profiles reported by [Meyer et al. (1996)]. However, model parameters estimated by [Prosi et al. (2005)] still could not yield fully satisfactory predictions. This was because the mass transport problem was degraded into a zero-dimensional problem when using an electrical analogy and only the boundary values were considered.

### 2.4.5 Remarks on the effect of WSS

The effect of WSS on arterial mass transport is one of the important issues in computational studies. Besides the shear-dependence of trans-endothelial transport mentioned previously, it has been conventionally argued that WSS influences transport of solutes from the lumen to the wall. In fact, trans-lumenal transport is affected by the bulk flow patterns, for which WSS is an indicator. In other words, the transport of solutes from the lumen to the wall is determined by the flow patterns, whereas WSS characterises these patterns. Most computational investigations reviewed above observed the dependence of arterial mass transport on bulk blood flow: oxygen tends to deplete while macromolecules tend to accumulate in the low WSS regions, both due to a poor transport efficiency associated with slow and recirculating flow patterns. Back to shear-dependent trans-endothelial transport, it is probably more important because the endothelium contributes significantly to the overall transport resistance. It has been modelled using analytical models which were usually constructed from available experimental data. In the following paragraph, such analytical models are summarised.

[Rappitsch and Perktold (1996a) and Rappitsch et al. (1997)] used a linear shear-dependent model for oxygen endothelial permeability. However, the model was purely imaginary without the support of experimental data. As mentioned previously, oxygen trans-endothelial transport is unlikely to be shear-dependent. However, the model did illustrate the importance of the shear-dependence since the calculated concentration field was considerably altered when the model was adopted. [Rappitsch and Perktold (1996b)] used a logarithm model for albumin endothelial permeability based on the experimental data reported by [Jo et al. (1991)]. However, the data points were too sparse to cover the whole physiological WSS range. Therefore, the accuracy of the model was doubted. [Stangeby and Ethier (2002a)] used a combined concentration-
and shear-dependent model for LDL endothelial permeability based on the experimental data reported by Guretzki et al. (1994) on concentration-dependence and by Caro (1974) on shear-dependence.

In these few previously studies, the shear-dependent models were mostly either experimentally baseless or based on sparse experimental data. This indicates one of the main problems in the research area where the computational studies suffer from a lack of experimental data. Furthermore, shear-dependent plasma transport across the endothelium was not taken into account although such a shear-dependence was observed and suggested to be important.

2.4.6 Remarks on the effect of pulsatile flow conditions

Most of the existing models assumed steady flow conditions, although pulsatile flow conditions may play a major role in the process that mediates arterial mass transport. This is because trans-endothelial transport is determined by WSS and pulsatile flow conditions produce high frequency fluctuations in WSS. However, fluid-wall coupled pulsatile flow simulations are difficult to implement, especially when shear-dependent trans-endothelial transport is considered. Arterial mass transport is characterised by two dramatically different time-scales: one is counted in seconds (in the lumen and the endothelium) and the other in hours (in the wall). Nevertheless, there exists a couple of studies where pulsatile flow but shear-dependent trans-endothelial transport was considered within the fluid-wall model framework.

Stangeby and Ethier (2002b) investigated the effects of pulsatile flow in a straight tube. The authors assumed unsteady but zero axial flow in their model. It was shown that after 30 minutes, LDL still could not penetrate into the outer most layer of the wall and this provided a guideline to experimentalist on the duration of the experiments. Yang and Valai (2006) investigated LDL transport in a straight tube and found that “impact of pulsation on the LDL transport across the arterial tissue is negligible for a simple straight axi-symmetric geometry”. These studies were limited to simple computational geometries and overlooked the shear-dependence of trans-endothelial
Despite of its unpopularity in the literature, the consideration of pulsatile flow is important; Ethier (2002) pointed out that steady flow simulations may only give a reasonable first approximation to time-averaged unsteady results but pulsatile flow simulation should be carried out when endothelial transport is coupled to WSS. In fact, Rappitsch and Perktold (1996b) already proved this statement in terms of transluminal transport. In this thesis, the investigation will be furthered by including the wall-side transport while considering shear-dependent trans-endothelial transport. Special numerical procedures are also to be developed to adapt physical phenomena characterised by different time scales into the fluid-wall model framework.
Mathematical Models and Numerical Procedures

In this chapter, mathematical models for arterial mass transport problems, including a fluid phase model, a single-layered and a multi-layered fluid-wall models are formulated using systems of partial differential equations (PDEs) and corresponding boundary conditions (BCs). Special numerical procedures for implementation of transient mass transport simulations are also proposed and discussed.

3.1 Mathematical models

Arterial mass transport has been extensively investigated using computational approaches. The domains of interests include the arterial lumen and the arterial wall. It is worth noting that, in the context of arterial mass transport, the arterial wall refers to the intima and the media, with the adventitia as the outer boundary (not included in the models). Depending on the treatment of the arterial wall, mathematical models can
be classified into two groups: the fluid phase model and the fluid-wall models. The fluid-wall models include the single-layered model and the multi-layered model. These models deal with different aspects of the arterial mass transport problems: the fluid phase model solely addresses the influences of haemodynamics on trans-lumenal transport by treating the arterial wall as a boundary condition with user-prescribed concentrations or outward flux; the single-layered model considers the interactions between transport processes in the arterial lumen and the wall by assuming the arterial wall as a single layer of porous medium; the multi-layered model emphasises on a more accurate prediction of transmural transport by treating the intima and the media separately as two layers of porous medium.

Arterial mass transport is coupled with both the bulk blood flow in the lumen and the transmural flow in the wall. Therefore, fluid dynamics models and solute dynamics models should be included. In this section, each of the three mathematical models discussed above will be formulated together with appropriate boundary conditions.

3.1.1 Fluid phase model

The fluid phase model, or wall-free model, is the simplest and has been used to model the trans-lumenal transport of oxygen \cite{Rappitsch1996a, Rappitsch1997, Ma1997, Qiu2000, Kaazempur2001, Kaazempur2005}, albumin \cite{Rappitsch1996b}, and LDL \cite{Deng1993, Deng1995, Wada1999, Wada2002, Wada2002}. In these cases, the arterial wall was treated as a boundary condition, thus the transport process therein was not included.

The computational domain and boundaries for the fluid phase model are shown in Figure 3.1. The bulk blood flow is assumed to be incompressible, laminar, Newtonian and hence governed by the Navier-Stokes equations, while mass transport is governed by the convection-diffusion equation. Therefore, a general form of the fluid phase model can be formulated as follows:
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Figure 3.1: Computational domain and boundaries of the fluid phase model. $\Omega_l$ is the lumen domain; $\Gamma_{l,\text{in}}$ and $\Gamma_{l,\text{out}}$ are the inlet and outlet boundaries of the lumen domain, respectively; $\Gamma_{\text{end}}$ is the endothelial boundary.

**fluid dynamics** in the arterial lumen ($\Omega_l$) is governed by

$$\rho \partial_t u_l - \mu \nabla^2 u_l + \rho (u_l \cdot \nabla) u_l + \nabla p_l = 0 \quad \text{in } \Omega_l, \ t > 0 \quad (3.1a)$$

$$\nabla u_l = 0 \quad \text{in } \Omega_l, \ t > 0 \quad (3.1b)$$

with BCs

$$u_l = u_{l,\text{in}} \quad \text{on } \Gamma_{l,\text{in}}, \ t > 0 \quad (3.2a)$$

$$t_l \cdot u_l = 0, \ n_l \cdot T = -p_{l,\text{out}} \quad \text{on } \Gamma_{l,\text{out}}, \ t > 0 \quad (3.2b)$$

$$t_l \cdot u_l = 0, \ n_l \cdot u_l = v_{f,l} \quad \text{on } \Gamma_{\text{end}}, \ t > 0 \quad (3.2c)$$

and **solute dynamics** in the arterial lumen ($\Omega_l$) is governed by

$$\partial_t c_l + \nabla \cdot (-D_l \nabla c_l + u_l c_l) = 0 \quad \text{in } \Omega_l, \ t > 0 \quad (3.3)$$

with BCs

$$c_l = c_{l,\text{in}} \quad \text{on } \Gamma_{l,\text{in}}, \ t > 0 \quad (3.4a)$$

$$D_l \nabla c_l n_l = 0 \quad \text{on } \Gamma_{l,\text{out}}, \ t > 0 \quad (3.4b)$$

$$-D_l \nabla c_l n_l + v_{f,l} c_l = P_{\text{end}} (c_l - c_w) \quad \text{on } \Gamma_{\text{end}}, \ t > 0 \quad (3.4c)$$

where $u_l$ is blood velocity in the lumen, $p_l$ is pressure, $\mu$ is dynamic viscosity of blood, $\rho$ is density of blood, $c_l$ is the solute concentration in the arterial lumen, and $D_l$ is solute diffusivity in the arterial lumen.
For fluid dynamics, the Navier-Stokes equations (Equation (3.1)) are employed to model the bulk blood flow in the arterial lumen. BC (3.2a) prescribes a given velocity profile at the inlet, $\Gamma_{l,in}$; BC (3.2b) assigns an outer pressure $p_{l,\text{out}}$ at the outlet, $\Gamma_{l,\text{out}}$, assuming that the total stress tensor $T = (-p_I I + \mu (\nabla u_l + (\nabla u_l)^T))n_l$ is equilibrated by the outer pressure; BC (3.2c) assumes a zero velocity at the tangent direction and a given filtration (transmural) velocity at the normal direction (outward) of the endothelial boundary, $\Gamma_{\text{end}}$, respectively.

Solute dynamics of the transport species in the arterial lumen is governed by the convection-diffusion equation (Equation (3.3)). BC (3.4a) prescribes a flat concentration profile at the inlet, $\Gamma_{l,in}$; BC (3.4b) defines a null diffusive flux at the outlet, $\Gamma_{l,\text{out}}$; BC (3.4c) assigns a total outward flux at the endothelial boundary, $\Gamma_{\text{end}}$, which is determined by the permeability of the endothelium and a wall concentration.

The governing Equations (3.1, 3.3) together with BCs (3.2, 3.4) give a general form of the fluid phase model which is applicable to oxygen and macromolecular transport. In the case of oxygen transport where passive diffusion contributes far more greatly than convection normal to the wall (Stangeby and Ethier, 2002a), the convective component can be eliminated in BCs (3.2c, 3.4c).

### 3.1.2 Single-layered model

The single-layered fluid-wall model considers the interactions among trans-lumenal, trans-endothelial and transmural transport processes. The microscopically heterogeneous arterial wall is usually modelled by a macroscopically homogeneous porous medium. Specifically, in the single-layered model, the arterial wall is lumped into a layer of porous medium with homogeneous transport properties. The single-layered model has been employed to model oxygen and LDL transport by Stangeby and Ethier (2002a,b) and Prosi (2003).

The computational domains and dividing boundaries for the single-layered model are shown in Figure 3.2. Same as the fluid phase model, the bulk blood flow is governed by the Navier-Stokes equations. The transmural flow is modelled by Darcy’s
Figure 3.2: Computational domains and boundaries of the single-layered model. $\Omega_l$ and $\Omega_w$ are the lumen domain and the wall domain, respectively; $\Gamma_{l,\text{in}}$ and $\Gamma_{l,\text{out}}$ are the inlet and outlet boundaries of the lumen domain, respectively; $\Gamma_{w,\text{in}}$ and $\Gamma_{w,\text{out}}$ are the side boundaries of the wall domain; $\Gamma_{\text{end}}$ is the endothelial boundary; $\Gamma_{\text{adv}}$ is the outer wall boundary (the external elastic lamina and the adventitia).

Law. The mass balance of the solutes is governed by the convection-diffusion mechanism. Therefore, a general form of the single-layered model can be formulated as follows:

**fluid dynamics in the arterial lumen** ($\Omega_l$) is governed by

$$\rho \partial_t u_l - \mu \nabla^2 u_l + \rho (u_l \cdot \nabla) u_l + \nabla p_l = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \quad (3.5a)$$

$$\nabla u_l = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \quad (3.5b)$$

with BCs

$$u_l = u_{l,\text{in}} \quad \text{on} \quad \Gamma_{l,\text{in}}, \ t > 0 \quad (3.6a)$$

$$t_l \cdot u_l = 0, \ n_l \cdot T = -p_{l,\text{out}} \quad \text{on} \quad \Gamma_{l,\text{out}}, \ t > 0 \quad (3.6b)$$

$$t_l \cdot u_l = 0, \ n_l \cdot u_l = J_{v,\text{end}} \quad \text{on} \quad \Gamma_{\text{end}}, \ t > 0 \quad (3.6c)$$

while **fluid dynamics in the arterial wall** ($\Omega_w$) is governed by

$$u_w - \nabla \cdot \left( \frac{\chi_w}{\mu_p} p_w \right) = 0 \quad \text{in} \quad \Omega_w, \ t > 0 \quad (3.7a)$$

$$\nabla u_w = 0 \quad \text{in} \quad \Omega_w, \ t > 0 \quad (3.7b)$$
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with BCs

\[ \mathbf{u}_w \cdot \mathbf{n}_w = 0 \quad \text{on} \quad \Gamma_{w,\text{in}} \cup \Gamma_{w,\text{out}}, \ t > 0 \] (3.8a)
\[ \mathbf{u}_w \cdot \mathbf{n}_w = -J_{v,\text{end}} \quad \text{on} \quad \Gamma_{v,\text{end}}, \ t > 0 \] (3.8b)
\[ p_w = p_{\text{adv}} \quad \text{on} \quad \Gamma_{\text{adv}}, \ t > 0 \] (3.8c)

and solute dynamics in the arterial lumen \( (\Omega_l) \) is governed by

\[ \partial_t c_l + \nabla \cdot (-D_l \nabla c_l + \mathbf{u}_l c_l) = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \] (3.9)

with BCs

\[ c_l = c_{l,\text{in}} \quad \text{on} \quad \Gamma_{l,\text{in}}, \ t > 0 \] (3.10a)
\[ D_l \nabla c_l \mathbf{n}_l = 0 \quad \text{on} \quad \Gamma_{l,\text{out}}, \ t > 0 \] (3.10b)
\[ -D_l \nabla c_l \mathbf{n}_l + \mathbf{u}_l c_l \mathbf{n}_l = J_{s,\text{end}} \quad \text{on} \quad \Gamma_{s,\text{end}}, \ t > 0 \] (3.10c)

while solute dynamics in the arterial wall \( (\Omega_w) \) is governed by

\[ \partial_t c_w + \nabla \cdot (-D_w \nabla c_w + K_{\text{lag},w} \mathbf{u}_w c_w) = r_w c_w \quad \text{in} \quad \Omega_w, \ t > 0 \] (3.11)

with BCs

\[ c_w \mathbf{n}_w = 0 \quad \text{on} \quad \Gamma_{w,\text{in}} \cup \Gamma_{w,\text{out}}, \ t > 0 \] (3.12a)
\[ -D_w \nabla c_w \mathbf{n}_w + K_{\text{lag},w} \mathbf{u}_w c_w \mathbf{n}_w = -J_{s,\text{end}} \quad \text{on} \quad \Gamma_{s,\text{end}}, \ t > 0 \] (3.12b)
\[ c_w = c_{\text{adv}} \quad \text{on} \quad \Gamma_{\text{adv}}, \ t > 0 \] (3.12c)

where \( \mathbf{u}_w \) is the velocity of the transmural flow in the arterial wall, \( p_w \) is pressure in the arterial wall, \( \mu_p \) is viscosity of blood plasma, \( \kappa_w \) is Darcian permeability coefficient of the arterial wall, \( c_w \) is solute concentration in the arterial wall, \( D_w \) is effective solute diffusivity in the arterial wall, \( K_{\text{lag},w} \) is solute lag coefficient in the arterial wall\(^*\), and \( r_w \) is consumption rate constant in the arterial wall.

\(^*\)The solute lag coefficient determines how easily the solute can be transported by convection. A higher value generally indicates that the solute of interest is smaller in size and can move more easily in the wall due to convection.
For fluid dynamics, the Navier-Stokes equations (Equation (3.5)) and Darcy’s Law (Equation (3.7)) are employed to model the bulk blood flow in the lumen and the transmural flow in the wall, respectively. Boundary conditions for the Navier-Stokes equations are similar to those imposed in the fluid phase model. However, in BC (3.6c), the filtration velocity assigned in the normal direction (outward) is a variable \( \langle J_{v,\text{end}} \rangle \) which needs to be calculated, instead of a constant \( \langle v_{f,i} \rangle \). For Darcy’s Law which governs the transmural flow, BC (3.8a) dictates a zero velocity normal to the side boundaries of the arterial wall, \( \Gamma_{w,\text{in}} \) and \( \Gamma_{w,\text{out}} \); BC (3.8b) prescribes a transmural velocity \( \langle J_{v,\text{end}} \rangle \) normal (inward) to the endothelial boundary, \( \Gamma_{\text{end}} \); BC (3.23c) assigns a constant pressure \( \langle p_{\text{adv}} \rangle \) at the outer wall boundary, \( \Gamma_{\text{adv}} \).

For solute dynamics, the convection-diffusion equation (Equation (3.9)) and the convection-diffusion-reaction equation (Equation (3.11)) are employed to model the mass balance of solutes in the lumen and the wall, respectively. For the convection-diffusion equation in the arterial lumen, boundary conditions are similar to those imposed in the fluid phase model. However, at the endothelial boundary, \( \Gamma_{\text{end}} \), the assigned total flux (outward) is a more complex variable \( \langle J_{s,\text{end}} \rangle \), which needs to be calculated taking into account the interactions between fluid side and wall side transport, instead of a term determined only by the fluid side concentration \( \langle P_{\text{end}}(c_l - c_w) \rangle \). For the convection-diffusion-reaction equation in the arterial wall, BC (3.12a) imposes an insulated condition at the side boundaries of the arterial wall, \( \Gamma_{w,\text{in}} \) and \( \Gamma_{w,\text{out}} \); BC (3.12b) assigns a total flux \( \langle J_{s,\text{end}} \rangle \) across (inward) the endothelial boundary, \( \Gamma_{\text{end}} \); BC (3.12c) prescribes a constant concentration \( \langle c_{\text{adv}} \rangle \) at the outer wall boundary, \( \Gamma_{\text{adv}} \).

In order to calculate the volume flux (transmural velocity, \( J_{v,\text{end}} \)) in BCs (3.6c, 3.8b) and the solute flux (\( J_{s,\text{end}} \)) in BCs (3.10c, 3.12b), matching conditions (MCs) at the endothelial boundary (\( \Gamma_{\text{end}} \)) given by Kedem-Katchalsky equations [Kedem and Katchalsky, 1958] are prescribed. For fluid dynamics, the matching condition is

\[
J_{v,\text{end}} = L_{p,\text{end}} (\Delta p_{\text{end}} - \sigma_{d,\text{end}} \Delta \tau_{\text{end}}) \quad \text{on} \quad \Gamma_{\text{end}} \tag{3.13}
\]

whereas the matching conditions for solute dynamics is given by

\[
J_{s,\text{end}} = P_{\text{end}} \Delta c_{\text{end}} + (1 - \sigma_{f,\text{end}}) J_{v,\text{end}} \xi_{\text{end}} \quad \text{on} \quad \Gamma_{\text{end}} \tag{3.14}
\]
In these equations, $L_{p,\text{end}}$ is hydraulic conductivity of the endothelium; $\Delta c_{\text{end}}$ is the solute concentration difference across the endothelium; $\Delta p_{\text{end}}$ is the pressure drop across the endothelium; $\Delta \pi_{\text{end}}$ is the osmotic pressure difference across the endothelium; $\sigma_{d,\text{end}}$ and $\sigma_{f,\text{end}}$ are osmotic reflection coefficient and solvent reflection coefficient of the endothelium, respectively; $P_{\text{end}}$ is solute permeability of the endothelium; $\bar{c}_{\text{end}}$ is the mean concentration across the endothelium. In the present study, the osmotic pressure difference $\Delta \pi_{\text{end}}$ is neglected to de-couple fluid dynamics from solute dynamics. Furthermore, the mean concentration in the endothelium $c_{\text{end}}$ is represented by the logarithmic average for thin selective permeable membranes and given by

$$
\bar{c}_{\text{end}} = \frac{c_{\text{end,l}} - c_{\text{end,w}}}{\ln(c_{\text{end,l}}/c_{\text{end,w}})}
$$

(3.15)

Thus the matching conditions can be rewritten as

$$
J_{v,\text{end}} = L_{p,\text{end}} (p_{\text{end,l}} - p_{\text{end,w}}) \quad \text{on} \quad \Gamma_{\text{end}}
$$

(3.16)

for fluid dynamics and

$$
J_{s,\text{end}} = P_{\text{end}} (c_{\text{end,l}} - c_{\text{end,w}}) + (1 - \sigma_{f,\text{end}})J_{v,\text{end}} \frac{c_{\text{end,l}} - c_{\text{end,w}}}{\ln(c_{\text{end,l}}/c_{\text{end,w}})} \quad \text{on} \quad \Gamma_{\text{end}}
$$

(3.17)

for solute dynamics. As pointed out previously, the values of endothelial hydraulic conductivity and macromolecular permeability are dependent on WSS acting on the endothelial surface. These shear-dependent behaviours will be discussed in Chapter 4.

\[\text{Figure 3.3: A schematic diagram of the single-layered model.}\]
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Diagram of the model is shown in Figure 3.3. This general form of the single-layered model is applicable to oxygen and macromolecular transport. However, in the case of oxygen transport where contribution from passive diffusion is much greater than convection in the wall [Stangeby and Ethier, 2002a], the convective component can be neglected (assuming zero transmural velocity) in the governing Equation (3.11), BCs (3.6c, 3.8b, 3.10c, 3.12b), and MCs (3.16, 3.17).

3.1.3 Multi-layered model

The single-layered model does not account for the heterogeneous transport properties through different layers of the wall, thereby compromising the model complexity as well as accuracy. The multi-layered fluid-wall model is so far the most comprehensive; it treats the arterial wall as a number of layers of porous medium with different transport properties. However, the application of the multi-layered model was usually limited to two-dimensional idealised geometries due to its high computational cost [Karner and Perktold, 2000; Karner et al., 2001; Prosi et al., 2005].

Figure 3.4: Computational domains and boundaries of the multi-layered model. Ωl, Ωi, and Ωm are the lumen domain, the intima domain and the media domain, respectively; Γl,in and Γl,out are the inlet and outlet boundaries of the lumen domain, respectively; Γi,in and Γi,out are the side boundaries of the intima domain; Γm,in and Γm,out are the side boundaries of the media domain; Γend is the endothelial boundary; Γiel is the IEL boundary; Γadv is the outer wall boundary (the external elastic lamina and the adventitia).
The computational domains and dividing boundaries for the multi-layered model are shown in Figure 3.4. By dividing the wall domain of the single-layered model into the intima and the media domains, a general form of the multi-layered model can be formulated as follows:

**fluid dynamics in the arterial lumen** \((\Omega_l)\) is governed by

\[
\begin{align*}
\rho \frac{\partial u_l}{\partial t} & - \mu \nabla^2 u_l + \rho (u_l \cdot \nabla) u_l + \nabla p_l = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \\
\nabla u_l &= 0 \quad \text{in} \quad \Omega_l, \ t > 0
\end{align*}
\]

(3.18a) with BCs

\[
\begin{align*}
u_l &= u_{l,in} \quad \text{on} \quad \Gamma_{l,in}, \ t > 0 \\
t_l \cdot u_l &= 0, \ n_l \cdot T = -p_{l,out} \quad \text{on} \quad \Gamma_{l,out}, \ t > 0 \\
t_l \cdot u_l &= 0, \ n_l \cdot u_l = j_{v,end} \quad \text{on} \quad \Gamma_{end}, \ t > 0
\end{align*}
\]

(3.19a)

while **fluid dynamics in the intima** \((\Omega_i)\) is governed by

\[
\begin{align*}
u_i - \nabla \cdot \left( \frac{x_i}{\mu_p} p_i \right) &= 0 \quad \text{in} \quad \Omega_i, \ t > 0 \\
\nabla u_i &= 0 \quad \text{in} \quad \Omega_i, \ t > 0
\end{align*}
\]

(3.20a) with BCs

\[
\begin{align*}
u_i \cdot n_i &= 0 \quad \text{on} \quad \Gamma_{i,in} \cup \Gamma_{i,out}, \ t > 0 \\
u_i \cdot n_i &= -j_{v,end} \quad \text{on} \quad \Gamma_{end}, \ t > 0 \\
u_i \cdot n_i &= j_{v,iel} \quad \text{on} \quad \Gamma_{iel}, \ t > 0
\end{align*}
\]

(3.21a)

and **fluid dynamics in the media** \((\Omega_m)\) is governed by

\[
\begin{align*}
u_m - \nabla \cdot \left( \frac{x_m}{\mu_p} p_m \right) &= 0 \quad \text{in} \quad \Omega_m, \ t > 0 \\
\nabla u_m &= 0 \quad \text{in} \quad \Omega_m, \ t > 0
\end{align*}
\]

(3.22a) with BCs

\[
\begin{align*}
u_m \cdot n_m &= 0 \quad \text{on} \quad \Gamma_{m,in} \cup \Gamma_{m,out}, \ t > 0 \\
u_m \cdot n_m &= -j_{v,iel} \quad \text{on} \quad \Gamma_{iel}, \ t > 0 \\
p_m &= p_{adv} \quad \text{on} \quad \Gamma_{adv}, \ t > 0
\end{align*}
\]

(3.23a)
and solute dynamics in the arterial lumen ($\Omega_l$) is governed by

$$\partial_t c_l + \nabla \cdot (-D_l \nabla c_l + u_l c_l) = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \quad (3.24)$$

with BCs

$$c_l = c_{l,in} \quad \text{on} \quad \Gamma_{l,in}, \ t > 0 \quad (3.25a)$$

$$D_l \nabla c_l n_l = 0 \quad \text{on} \quad \Gamma_{l,ont}, \ t > 0 \quad (3.25b)$$

$$-D_l \nabla c_l n_l + u_l c_l n_l = J_{s,end} \quad \text{on} \quad \Gamma_{end}, \ t > 0 \quad (3.25c)$$

while solute dynamics in the intima ($\Omega_i$) is governed by

$$\partial_t c_i + \nabla \cdot (-D_i \nabla c_i + K_{lag,i} u_i c_i) = r_i c_i \quad \text{in} \quad \Omega_i, \ t > 0 \quad (3.26)$$

with BCs

$$c_i n_i = 0 \quad \text{on} \quad \Gamma_{i,in} \cup \Gamma_{i,ont}, \ t > 0 \quad (3.27a)$$

$$-D_i \nabla c_i n_i + K_{lag,i} u_i c_i n_i = -J_{i,end} \quad \text{on} \quad \Gamma_{end}, \ t > 0 \quad (3.27b)$$

$$-D_i \nabla c_i n_i + K_{lag,i} u_i c_i n_i = J_{i,iel} \quad \text{on} \quad \Gamma_{iel}, \ t > 0 \quad (3.27c)$$

and solute dynamics in the media ($\Omega_m$) is governed by

$$\partial_t c_m + \nabla \cdot (-D_m \nabla c_m + K_{lag,m} u_m c_m) = r_m c_m \quad \text{in} \quad \Omega_m, \ t > 0 \quad (3.28)$$

with BCs

$$c_m n_m = 0 \quad \text{on} \quad \Gamma_{m,in} \cup \Gamma_{m,ont}, \ t > 0 \quad (3.29a)$$

$$-D_m \nabla c_m n_m + K_{lag,m} u_m c_m n_m = -J_{m,iel} \quad \text{on} \quad \Gamma_{iel}, \ t > 0 \quad (3.29b)$$

$$c_m = c_{adv} \quad \text{on} \quad \Gamma_{adv}, \ t > 0 \quad (3.29c)$$

with subscripts $i$ and $m$ stand for intima and media, respectively; $u$ is the velocity of the transmural flow, $p$ is pressure, $\kappa$ is the Darcian permeability coefficient, $c$ is the solute concentration in the arterial wall, $D$ is the effective solute diffusivity in the arterial wall, $K_{lag}$ is the solute lag coefficient, $r$ is the consumption rate constant.

For fluid dynamics, the Navier-Stokes equations (Equation (3.18)) and Darcy’s Law (Equations (3.20, 3.22)) are employed to model the bulk blood flow in the arterial
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lumen and the transmural flow in the intima and the media, respectively. The boundary conditions for the Navier-Stokes equations are the same as those in the single-layered model. For Darcy’s Law in the intima, BC \((3.21a)\) dictates zero velocity normal to the side boundaries of the intima, \(\Gamma_{i,\text{in}}\) and \(\Gamma_{i,\text{out}}\); BC \((3.21b)\) assigns a transmural velocity \((J_{v,\text{end}})\) normal (inward) to the endothelial boundary, \(\Gamma_{\text{end}}\); BC \((3.21c)\) prescribes a transmural velocity \((J_{v,iel})\) normal (outward) to the IEL boundary, \(\Gamma_{iel}\). For Darcy’s Law in the media, BC \((3.23a)\) dictates zero velocity normal to the side boundaries of the media, \(\Gamma_{m,\text{in}}\) and \(\Gamma_{m,\text{out}}\); BC \((3.23b)\) prescribes a transmural velocity \((J_{v,iel})\) normal (inward) to the IEL boundary, \(\Gamma_{iel}\); BC \((3.23c)\) assumes a constant pressure \((p_{adv})\) at the outer wall boundary, \(\Gamma_{adv}\).

For solute dynamics, the convection-diffusion equation (Equation \((3.24)\)) is employed to model the mass balance of solutes in the arterial lumen, while the convection-diffusion-reaction equations (Equations \((3.26, 3.28)\)) are used to model the mass balances of solutes in the intima and the media. The boundary conditions for the convection-diffusion equation in the arterial lumen are the same as those in the single-layered model. For the convection-diffusion-reaction equation in the intima, BC \((3.27a)\) imposes an insulated condition at the side boundaries of the intima, \(\Gamma_{i,\text{in}}\) and \(\Gamma_{i,\text{out}}\); BC \((3.27b)\) assigns a total flux \((J_{s,\text{end}})\) across (inward) the endothelial boundary, \(\Gamma_{\text{end}}\); BC \((3.27c)\) prescribes a total flux \((J_{s,iel})\) across (outward) the IEL boundary, \(\Gamma_{iel}\). For the convection-diffusion-reaction in the media, BC \((3.29a)\) imposes an insulated condition at the side boundaries of the media, \(\Gamma_{m,\text{in}}\) and \(\Gamma_{m,\text{out}}\); BC \((3.29b)\) assigns a total flux \((J_{s,iel})\) across (inward) the IEL boundary, \(\Gamma_{iel}\); BC \((3.29c)\) prescribes a constant concentration \((c_{adv})\) at the outer wall boundary, \(\Gamma_{adv}\).

To calculate the volume flux \(J_{v,\text{end}}\) in BCs \((3.19c, 3.21b)\) and \(J_{v,iel}\) in BCs \((3.21c, 3.23b)\) as well as the solute flux \(J_{s,\text{end}}\) in BCs \((3.25c, 3.27b)\) and \(J_{s,iel}\) in BCs \((3.27c, 3.29b)\), the Kedem-Katchalsky equations are used as matching conditions (MCs) at the endothelial boundary \((\Gamma_{\text{end}})\) and the IEL boundary \((\Gamma_{iel})\). The matching conditions for fluid dynamics are given by

\[
J_{v,\text{end}} = L_{p,\text{end}} (p_{\text{end},i} - p_{\text{end},o}) \quad \text{on} \quad \Gamma_{\text{end}} \quad (3.30a)
\]

\[
J_{v,iel} = L_{p,iel} (p_{iel,i} - p_{iel,m}) \quad \text{on} \quad \Gamma_{iel} \quad (3.30b)
\]
whereas the matching conditions for solute dynamics are given by

\[
J_{s,\text{end}} = P_{\text{end}} \left( c_{\text{end},i} - c_{\text{end},i} \right) + \left( 1 - \sigma_{f,\text{end}} \right) \frac{c_{\text{end},i} - c_{\text{end},i}}{\ln(c_{\text{end},i}/c_{\text{end},i})} \quad \text{on} \quad \Gamma_{\text{end}} \quad (3.31a)
\]

\[
J_{s,\text{iel}} = P_{\text{iel}} \left( c_{\text{iel},i} - c_{\text{iel},m} \right) + \left( 1 - \sigma_{f,\text{iel}} \right) \frac{c_{\text{iel},i} - c_{\text{iel},m}}{\ln(c_{\text{iel},i}/c_{\text{iel},m})} \quad \text{on} \quad \Gamma_{\text{iel}} \quad (3.31b)
\]

Figure 3.5: A schematic diagram of the multi-layered model.

The governing Equations \([3.18, 3.20, 3.22, 3.24, 3.26, 3.28]\) together with BCs \([3.19, 3.21, 3.23, 3.25, 3.27, 3.29]\) and MCs \([3.30, 3.31]\) give a general form of the multi-layered model. A schematic diagram of the model is shown in Figure 3.5. This general form of the multi-layered model is applicable to oxygen and macromolecular transport. However, since oxygen diffuses freely in the arterial wall, the heterogeneous nature of the arterial wall does not influence its transport significantly. Therefore, an expensive multi-layered model is generally not recommended for oxygen transport simulations (Zunino, 2002).

### 3.2 Implementations of transient simulation

It is straightforward to carry out steady state simulations once the mathematical models and boundary conditions are fully formulated: with all the time dependent terms eliminated in the governing equations. Since the Kedem-Katchalsky equations are simplified by removing the osmotic pressure terms in the present study, the system becomes one way coupled from fluid dynamics to solute dynamics. Consequently, the fluid dynamics simulations can be carried out first, and the resulting flow fields are
3.2 IMPLEMENTATIONS OF TRANSIENT SIMULATION

used to simulate solute dynamics.

So far, most of the computational studies on arterial mass transport have assumed steady flow conditions. Because development of atherosclerosis is a long term process, the steady flow assumption seems reasonable. However, mass transport from the arterial lumen to and through the arterial wall is coupled with pulsatile blood flow whose cycle periods are normally less than a second, indicating that the mass transport process is influenced by two dramatically different time-scales. The time-scales of blood flow and mass transport are illustrated and compared in Figure 3.6. It is clearly shown that the dynamics of the bulk blood flow ($U_l$) and the transmural flow ($U_w$) are periodic with a cycle period $t_p$. However, macromolecular transport in the arterial wall ($c_w$) is a long term process which finally reaches equilibrium many cardiac cycles after the perturbation is imposed. The perturbation in vivo includes, for instance, local geometrical changes (e.g. thickening of arterial wall and narrowing of the lumen) to dietary changes and medication that leads to elevated or reduced circulating concentrations of macromolecules. Other short term physiological responses to physical activities and diurnal variations could also perturb the transport process. Although concentration fluctuations are negligible within one cardiac cycle, the accumulated effect of haemodynamic factors over a longer time span could be significant.

$$t = t_0$$

$$U_l$$

$$U_w$$

$$c_w$$

$$t = t_e$$

**Figure 3.6:** Time-scales of the arterial mass transport system. $U_l$ denotes dynamics of bulk blood flow, $U_w$ denotes dynamics of transmural flow, and $c_w$ denotes dynamics of LDL transport in arterial wall. $t_p$ is the period of a cardiac cycle.

Therefore in the multi-time-scale transport system, the effects of blood flow
pulsatility on long term transport of macromolecules needs to be investigated and the
validity of the assumption of steady flow needs to be examined. However, it is dif-
ficult to carry out transient simulation of fluid-wall macromolecular transport over
a long time span using the single-layered and multi-layered models. First of all, to
model transient mass transport while considering pulsatile blood flow, an extremely
high temporal resolution has to be employed, which is not computationally feasible
over a prolonged time period. Secondly, a transient numerical procedure requires dy-
namic coupling between concentration fields in the lumen and wall, further increasing
the computational demand. To circumvent these difficulties in transient simulations
of transmural macromolecular transport, a lumen-free cyclic (LFC) and a lumen-free
time-averaged (LFTA) computational procedures are proposed to incorporate with the
fluid-wall models. It is worth noting that although the proposed procedures are termed
“lumen-free”, detailed haemodynamics in the fluid domain is included.

3.2.1 Assumptions in the lumen-free methods

There are two assumptions specially made for the development of the lumen-free meth-
ods. Firstly, a constant fluid side macromolecular concentration is assumed. Secondly,
the endothelial transport properties are assumed to respond instantaneously to the
change in WSS.

3.2.1.1 Constant fluid side solute concentration

The computational schemes are termed “lumen-free” because the highly convection-
dominated mass transport in the lumen is omitted and a constant macromolecular
concentration is assumed in the arterial lumen. It is important to point out that the
convection of macromolecules to and within the endothelium could induce concen-
tration polarisation. The level of concentration polarisation can be influenced by the
haemodynamics through two mechanisms with opposing effects: 1) a decrease in WSS
would result in less convection at the luminal surface due to a reduction in hydraulic
conductivity of the endothelium*, leading to a reduced concentration on the luminal

*This will be discussed in the next chapter.
3.2 IMPLEMENTATIONS OF TRANSIENT SIMULATION

A decrease in WSS could also lessen the removal of accumulated macromolecules from the lumenal surface, causing an elevation in concentration. Based on these two mechanisms, it can be speculated that the degree of concentration polarisation varies only within a small range \textit{in vivo} and that the influence of fluid phase macromolecular transport on transmural macromolecular transport is minor because the rate limiting process is wall-side transport \citep{Caro1973, Caro1974, Tarbell2003}. Therefore, unlike trans-endothelial transport of oxygen which is considerably affected by transport efficiency in the fluid phase, passage of lipid molecules through the endothelium is determined by permeability of the membrane rather than the concentration on the lumen side. For instance, \citep{Prosi2003} reported that LDL concentration in the arterial wall was not sensitive to polarisation of lumenal concentration when constant transport parameters were employed.

3.2.1.2 Instantaneous endothelial response to WSS

As mentioned previously, the fluid-wall models involve two shear-dependent transport parameters, namely endothelial hydraulic conductivity \(L_{p,\text{end}}\) and permeability to macromolecules \(P_{\text{end}}\). Since WSS changes instantaneously under pulsatile flow conditions, it is important to model the dynamical response of these two parameters to change in WSS. However, in the present study, it is assumed that endothelial transport properties respond instantaneously to WSS and that hydraulic conductivity and macromolecular permeability of the endothelium changes simultaneously with WSS. Although this may not be true \textit{in vivo}, there are a number of difficulties that limit the development of a mathematical model accounting for the dynamics of transport property variations.

First of all, our current understanding of the dynamic process is limited. \citep{Fry1968} speculated that endothelial transport properties alter as a consequence of endothelial structural and functional changes mediated by WSS. Furthermore, \citep{Friedman1993} assumed that transport properties respond linearly to the rate of structural or functional changes and the time constant of endothelial transport variation is determined by the dynamics of structural and functional changes. Thus further stud-
ies are required to enrich the knowledge of these structural and functional changes, which will facilitate our understanding of the dynamic change in hydraulic conductivity and macromolecular permeability. Secondly, the instantaneous variation of WSS provides a complicated and cyclical perturbation. Thus even if these effects are fully understood, a very high time resolution would have to be employed to capture the dynamic response of the endothelial transport properties, which would certainly require excessive computational resources.

Therefore, currently, the assumption of instantaneous response of endothelial transport properties to WSS is justifiable and has been employed in a number of studies (Rappitsch and Perktold, 1996b; Rappitsch et al., 1997).

3.2.2 Lumen-free cyclic method

A lumen-free cyclic (LFC) procedure is proposed to investigate the accumulated effect of haemodynamics and the influence of flow pulsatility on long term macromolecular transport. Figure 3.7 shows the schematic view of the LFC procedure.

In the LFC procedure, the periodic bulk blood flow is simulated over three cardiac cycles using a time step ($\Delta t$) to determine instantaneous values of WSS. Based on these WSS values, shear-dependent transport properties, i.e. hydraulic conductivity and solute permeability of the endothelium, are calculated. The calculated instantaneous hydraulic conductivity is then employed to simulate the transmural flow over 3 cardiac cycles using the same time steps as in the pulsatile flow simulation. The resulting transmural flow field of the last cycle is then repeatedly applied to the simulation of macromolecular transport in the arterial wall employing the calculated instantaneous solute permeability. Thus, in the simulation of macromolecular transport over a long time span, the transmural flow field is used as a cyclic condition. An appropriately selected time step, $\Delta t'$, is used to preserve the characteristics of transmural flow within each cardiac cycle and save computational time.

For instance, if the LFC procedure is applied to macromolecular transport simulation using the single-layered model, governing Equation (3.5) is solved first with
3.2 IMPLEMENTATIONS OF TRANSIENT SIMULATION

Solve $U_l$ over three cardiac cycles under pulsatile flow conditions with time-step $\Delta t$.

Calculate instantaneous shear-dependent endothelial hydraulic conductivity, $L_{p,\text{end}}$.

Solve $U_w$ over three cardiac cycles under pulsatile flow conditions with time-step $\Delta t$.

Calculate instantaneous shear-dependent endothelial solute permeability, $P_{\text{end}}$.

Solve $c_w$ using $U_w$ as a cyclic condition with time-step $\Delta t'$.

Instantaneous WSS

Instantaneous $L_{p,\text{end}}$

Convective force

Instantaneous $P_{\text{end}}$

Figure 3.7: A schematic view of the proposed lumen-free cyclic (LFC) procedure. $U_l$ represents the dynamics of the bulk blood flow, $U_w$ the dynamics of the transmural flow, and $c_w$ the dynamics of macromolecular transport in the arterial wall. $\Delta t$ is the time-step for pulsatile flow simulations. $\Delta t'$ is the time-step for transient macromolecular transport simulations.
pulsatile inlet velocity and modified boundary conditions (instead of BC \(3.6c\), non-slip condition is applied at the endothelium); instantaneous endothelial transport properties are then calculated using the resulting WSS; governing Equation \(3.7\) is solved to obtain transient transmural velocity field in the arterial wall; based on the transmural velocity, governing Equation \(3.11\) is solved assuming constant lumenal concentration to acquire the evolution of concentration field in the wall.

### 3.2.3 Lumen-free time-averaged method

- Solve \(U_l\) over three cardiac cycles under pulsatile flow conditions with time-step \(\Delta t\).
  - Instantaneous WSS
  - Calculate instantaneous shear-dependent endothelial hydraulic conductivity, \(L_{p,\text{end}}\).
  - Instantaneous \(L_{p,\text{end}}\)
  - Convective force
  - Solve \(c_w\) using \(U_w\) as a cyclic condition with time-step \(\Delta t'\).

- Solve \(U_w\) over three cardiac cycles under pulsatile flow conditions with time-step \(\Delta t\).
  - Instantaneous \(P_{\text{end}}\)

- Solve \(U_l\) over three cardiac cycles under pulsatile flow conditions

**Figure 3.8:** A schematic view of the proposed lumen-free time-averaged (LFTA) procedure. \(U_l\) represents the dynamics of the bulk blood flow, \(U_w\) the dynamics of the transmural flow, and \(c_w\) the dynamics of macromolecular transport in the arterial wall. \(\Delta t\) is the time-step for pulsatile flow simulations.

In addition to the LFC procedure, a lumen-free time-averaged (LFTA) proce-
3.2 IMPLEMENTATIONS OF TRANSIENT SIMULATION

dure is also proposed to simulate the wall-side transport of macromolecules under a steady-state framework with time-averaged endothelial transport properties calculated from pulsatile blood flow simulation using instantaneous WSS. As shown in Figure 3.8, periodic bulk blood flow is simulated over 3 cardiac cycles to determine the instantaneous WSS. On this basis, time-averaged shear-dependent model parameters are obtained and used in transmural momentum and LDL transport simulations.

For instance, if the LFTA procedure is applied to macromolecular transport simulation using the single-layered model, governing Equation (3.5) is solved first with pulsatile inlet velocity and modified boundary conditions (same as the LFC procedure, non-slip condition is applied at the endothelial boundary); time-averaged endothelial transport properties are then calculated using the resulting instantaneous WSS, after which governing Equation (3.7) is solved to obtain steady transmural velocity field in the arterial wall; based on the transmural velocity, governing Equation (3.11) is solved assuming constant lumenal concentration to acquire “time-averaged” concentration field in the wall.
Determination of Model Parameters

In this chapter, the momentum transport properties are validated against experimental data reported by Meyer et al. (1996). An oxygen mass transport property is determined by solving a reverse problem analytically. The macromolecular mass transport properties are determined using an optimisation approach based on one-dimensional simulations and data published by Meyer et al. (1996). Furthermore, shear-dependent models of endothelial hydraulic conductivity and albumin permeability are derived from experimental data reported by Sill et al. (1995) and Kudo et al. (1998), respectively.

4.1 Momentum transport parameters

Momentum transport parameters in the current setup of mathematical models include fluid phase parameters and tissue phase parameters. The values of fluid phase parameters, i.e. blood density ($\rho$) and viscosity ($\mu$) are well defined in the literature. In the present study, blood density is assumed to be $1.05 \times 10^3 \text{ kg m}^{-3}$, and blood is assumed
4.1 Momentum Transport Parameters

to be a Newtonian fluid with a constant viscosity $3.5 \times 10^{-3}$ Pa s. However, the tissue phase parameters need to be validated against experimental data to ensure that an accurate transmural velocity can be predicted in the simulations.

4.1.1 Validation of tissue phase momentum transport parameters

The values of tissue phase momentum transport parameters used in this study are validated against transmural velocities measured by Meyer et al. (1996). These parameters include blood plasma viscosity ($\mu_p = 7.2 \times 10^{-4}$ Pa s), endothelial hydraulic conductivity ($L_{p,\text{end}} = 3 \times 10^{-12}$ m s$^{-1}$ Pa$^{-1}$), IEL hydraulic conductivity ($L_{p,\text{iel}} = 3.05 \times 10^{-10}$ m s$^{-1}$ Pa$^{-1}$), and Darcian permeabilities ($\chi_w = 1 \times 10^{-18}$ m$^2$ in the single-layered models; $\chi_i = 9.5 \times 10^{-17}$ m$^2$ and $\chi_m = 1 \times 10^{-18}$ m$^2$ in the multi-layered models). These parameter values are mainly taken from Karner et al. (2001) and Prosi et al. (2005).

The one-dimensional form of Equation (3.7) coupled with MC (3.16) are solved for validation of the momentum transport parameters ($L_{p,\text{end}}$ and $\chi_w$) in the single-layered model; the one-dimensional form of Equations (3.20, 3.22) coupled with MC (3.30) are solved for validation of the momentum transport parameters ($L_{p,\text{end}}$, $L_{p,\text{iel}}$, $\chi_i$, and $\chi_m$) in the multi-layered model. In both cases, different values of transmural pressure ($\Delta p$), i.e. 70 mmHg, 120 mmHg and 160 mmHg, are assumed.

The transmural velocities given by the one-dimensional single-layered and multi-layered models are compared with experimental data under transmural pressures of 70, 120 and 160 mmHg in Figure 4.1. It is shown that both the single-layered and the multi-layered models are able to predict transmural velocities in a reasonable range with constant momentum transport parameters under different transmural pressures. Thus it could be assumed that the elevation of transmural velocity, corresponding to increases in transmural pressure, is primarily due to the increased driving force, rather than change in resistance within the arterial wall and this assumption is adopted in the computations.
4.1 MOMENTUM TRANSPORT PARAMETERS

### Figure 4.1: Comparison between the 1-D simulation results and the experimental data of transmural velocity to test the hypothesis of WSS-independence of momentum transport properties. Solid line and dashed line are results given by the single-layered model and the multi-layered model, respectively.

#### Table 4.1: Summary of momentum transport parameters used in the present study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \rho ), ([kg\ m^{-3}])</td>
<td>(1.05 \times 10^3)</td>
</tr>
<tr>
<td>( \mu_p ), ([Pa\ s])</td>
<td>(7.2 \times 10^{-4})</td>
</tr>
<tr>
<td>( \kappa)</td>
<td>(9.5 \times 10^{-17})</td>
</tr>
<tr>
<td>( L_{p,\text{end}} ), ([m\ s^{-1}\ Pa^{-1}])</td>
<td>(3 \times 10^{-12})</td>
</tr>
<tr>
<td>( L_{p,iel} ), ([m\ s^{-1}\ Pa^{-1}])</td>
<td>(3.05 \times 10^{-10})</td>
</tr>
</tbody>
</table>

#### 4.1.2 Summary of momentum transport parameters

The momentum transport parameters used in the present study are summarised in Table 4.1. It should be noted that endothelial hydraulic conductivity \( (L_{p,\text{end}}) \) is assumed to be shear-dependent and the listed value is employed as a base value when scaling the shear-dependent endothelial hydraulic conductivity in §4.3.3. Furthermore, all momentum transport parameters are assumed to be independent of transmural pressure.
4.2 Mass transport parameters

Mass transport parameters refer to the model parameters which characterise the transport properties of solutes in different subdomains of the system, including the arterial lumen and the wall (the intima and the media in the case of the multi-layered model). The solute transport properties in the arterial lumen are well defined in the literature, whereas the determination of solute transport properties in the arterial wall is usually difficult and needs specially designed methods to exploit the limited experimental observations. In this section, mass transport parameters of oxygen, albumin and LDL are determined and discussed.

4.2.1 Oxygen transport parameters

Oxygen diffuses freely in the arterial wall, in which case convection can be omitted in the arterial wall and the multi-layered model is not necessary. Therefore, the mass transport parameters to be determined include oxygen diffusivities in the arterial lumen ($D_{l,oxy}$) and wall ($D_{w,oxy}$), endothelial oxygen permeability ($P_{end,oxy}$), and the first-order consumption rate constant ($r_{w,oxy}$) in the arterial wall. The values of oxygen diffusivities and permeability are well documented in the literature. Oxygen diffusivity in the arterial lumen, $D_{l,oxy} = 1.6 \times 10^{-9} \text{ m}^2 \text{s}^{-1}$ [Rappitsch and Perktold, 1996a]; oxygen diffusivity in the arterial wall, $D_{w,oxy} = 1.08 \times 10^{-9} \text{ m}^2 \text{s}^{-1}$ [Buerk and Goldstick, 1982]; and endothelial oxygen permeability, $P_{end,oxy} = 1.96 \times 10^{-4} \text{ m s}^{-1}$ [Qiu and Tarbell, 2000]. The only parameter remains undetermined is the first-order consumption rate constant of oxygen in the arterial wall ($r_{w,oxy}$). To determine its value, it is possible to solve a reverse problem involving a one-dimensional steady-state diffusion-reaction equation, which is modified from Equation (3.11) by dropping the convection term:

\[-D_{w,oxy} \frac{d^2c_w}{dx^2} = r_{w,oxy}c_w \quad (4.1)\]

where $x$ is the coordinate of the one-dimensional domain and $r_{w,oxy}$ is the consumption rate constant to determine. Equation (4.1) has a general form of solution as follows

\[c_w(x) = C_1 \cdot e^{\sqrt{A}x} + C_2 \cdot e^{-\sqrt{A}x} \quad (4.2)\]
where $A = -r_{w,oxy}/D_{w,oxy}$, $C_1$ and $C_2$ are constants to be determined by boundary conditions applied to the differential equation.

Given a domain length $l$, an endothelial oxygen concentration $c_w(0)$, and an oxygen concentration in the adventitia $c_{adv} = c_w(l)$, $C_1$ and $C_2$ can be calculated as

$$C_1 = \frac{c_w(l) - c_w(0) \cdot e^{-\sqrt{A}l}}{e^{\sqrt{A}l} - e^{-\sqrt{A}l}} \quad (4.3)$$

$$C_2 = \frac{c_w(0) \cdot e^{\sqrt{A}l} - c_w(l)}{e^{\sqrt{A}l} - e^{-\sqrt{A}l}} \quad (4.4)$$

By finding the stationary point of the solution given in Equation (4.2), the minimum concentration in the domain can be determined. Specifically, the coordinate of the stationary point is given by

$$x_{C_{min}} = -\frac{\ln(C_1/C_2)}{2\sqrt{A}} \quad (4.5)$$

and the minimal concentration can be then calculated by substituting $x$ in Equation (4.2) with Equation (4.5) as follows

$$c_{min} = C_1 \cdot e^{\frac{\ln(C_1/C_2)}{2}} + C_2 \cdot e^{\ln(C_1/C_2)/2} \quad (4.6)$$

with which $r_{w,oxy}$ can be calculated when the domain length $l$, oxygen concentration at the endothelium $c_w(0)$, oxygen concentration in the adventitia $c_w(l)$, and minimal concentration in the arterial wall $c_{min}$ are given. Buerk and Goldstick (1982) provided all these necessary data: $l = 5 \times 10^{-4} m$, $c_w(0) = 1$, $c_{adv} = 0.7333$, and $c_{min} = 0.301$. Thus, the first-order consumption rate constant of oxygen in the arterial wall is calculated as $r_{w,oxy} = -4.89 \times 10^{-2} s^{-1}$.

*The second order derivative of the right hand side of Equation (4.2) is $AC_1 e^{\sqrt{A}l} + AC_2 e^{-\sqrt{A}l}$. It can be shown that this is always positive for $0 \leq x \leq l$. Therefore, a local minimum can be found at the stationary point.

Buerk and Goldstick (1982) reported the oxygen tensions as $p_w(0) = 75 mmHg$, $p_{adv} = 55 mmHg$, and $p_{min} = 23 mmHg$ and these values are normalised with $75 mmHg$ for the ease of calculation.
4.2 MASS TRANSPORT PARAMETERS

4.2.2 Albumin and LDL transport parameters

Similar to the case of oxygen, the mass transport properties of albumin and LDL in the arterial lumen can be easily found in the literature. It should be noted that macromolecular diffusivity has different values in plasma and blood. This is because the plasma does not contain red blood cells which may decrease the diffusivity. In the near wall region, the concentration of red blood cells is much lower than that in the centre of the lumen. Thus the fluid near the wall behaves like blood plasma rather than blood. In order to reduce the computational complexity, a constant value is used in the whole lumen domain for each solute. This constant value is assumed to be the plasma diffusivity to obtain an accurate observation of concentration polarisation near the wall. Therefore, albumin diffusivity and LDL diffusivity in the arterial lumen are chosen to be $D_{alb} = 9.01 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ (Karner and Perktold, 2000) and $D_{ldl} = 2.867 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ (Karner et al., 2001), respectively. Macromolecular transport properties in the arterial wall are poorly documented in the literature. Therefore, many attempts have been made to determine these parameters (see §2.4.4 for details). In the present study, a simulation-based optimisation approach is proposed to accurately estimate these model parameters.

4.2.2.1 A simulation-based optimisation approach

To analyse the experimental data in a sophisticated way and derive reliable parameter values, an optimisation approach which minimises the difference between one-dimensional simulation results and experimental data is developed.

In the formulation of the optimisation problem, the mass transport parameters are denoted by a vector $\mathbf{x}$ as the model inputs; the simulated concentration distribution samples at predefined locations according to experimental data are denoted by a vector $\mathbf{c}$; the relationship between $\mathbf{x}$ and $\mathbf{c}$ is described by a one-dimensional convection-diffusion-reaction transport model $\mathbf{c} = f(\mathbf{x})$ with appropriate boundary conditions. Therefore, the optimisation problem can be formulated using the least
squares method as follows

\[
\min \sum_{j=1}^{n} W_j \left( C_j - c_j \right)^2
\]

\[
\text{s.t.} \quad c_j = f(x_1, x_2, \ldots, x_m), \quad j = 1, 2, \ldots, n
\]

\[
lb_k \leq x_k \leq ub_k, \quad k = 1, 2, \ldots, m
\]  \tag{4.7}

where \( C_j \) is the experimental value of LDL concentration at the \( j \)th sampling point, \( c_j \) is the simulation result of LDL concentration at the \( j \)th sampling point, \( W_j \) is the weighting coefficient of the \( j \)th sampling point, \( lb \) is the vector of lower bounds of \( x \), and \( ub \) is the vector of upper bounds of \( x \). In the present study, higher weights (\( W_j \)) are given to the first two points (those are closest to the lumen). This is to ensure that concentration profiles in the intima and inner media where atherogenesis initiates can be predicted accurately with the optimal parameters. To determine transport parameters in the single-layered model, the one-dimensional model \( c = f(x) \) refers to the governing Equation (3.11) in combination with corresponding boundary conditions and matching conditions. To determine transport parameters in the multi-layered model, the one-dimensional model refers to governing Equations (3.26, 3.28) in combination with corresponding boundary conditions and matching conditions. In this formulation, all the sampling points in the experimental data are taken into account and hence the algorithm preserves the concentration distribution in the arterial wall, whereas zero-dimensional methods such as an electrical analogy only retain boundary values but not the entire distribution.

In order to solve the optimisation problem, the weighted accumulated-error (sum of the differences between the simulation result and the experimental data at each data point) is minimised by finding the optimal vector \( x \) subject to physiological bounds \( lb \) and \( ub \). In the present study, the constrained optimisation problem is solved by a compass search routine. The compass search method is the simplest procedure among direct search optimisation techniques. Direct search techniques only use the objective function value to carry out minimisation without considering the first and second derivatives. It is suitable to solve the problem formulated above because it is very difficult to calculate the derivatives in this simulation-based optimisation prob-
4.2 MASS TRANSPORT PARAMETERS

The compass search method is very easy to interpret and implement. For an unconstrained minimisation problem with only two manipulating variables, the algorithm can be summarised as follows: try steps to the East, West, North, and South in the 2D coordinate; if one of these steps yields a reduction in the function, the improved point becomes the new iterate; if none of these steps yields improvement, try again with steps half as long; the procedure will be terminated when the step size falls below a threshold. Therefore, for a problem with $m$ manipulating variables, $2^m$ directions will be searched in each iteration. In other words, to solve the optimisation problem given by Equation (4.7), if $m$ model parameters need to be determined, the one-dimensional simulation will be carried out $2^m$ times in each iteration.

The compass search routine is written using MATLAB® (the Mathworks Inc., USA) which calls a subroutine to simulate one-dimensional transmural mass transport in each iteration. Figure 4.2 shows a schematic diagram of the compass search routine used in the present study. Moreover, since the optimisation problem is bounded within physiological ranges of the parameters, it is ensured that these constraints are not violated in each iteration.

The experimental data chosen to derive parameter values using the optimisation approach were reported by Meyer et al. (1996), who provided albumin and LDL concentration distributions in rabbit aortas with respect to the distance from the lumen in the arterial wall under different transmural pressures. It should be mentioned that the experiments were only 30 minutes in duration, which was too short for transmural transport to reach equilibrium. However, these experimental data were used to obtain optimal transport parameters under a steady-state model framework because they were the most comprehensive and accessible. Six sets of data were measured in the experiments, including albumin and LDL concentration profiles under transmural pressures of 70 mmHg, 120 mmHg, and 160 mmHg, which are digitised from the original paper and shown in Figure 4.3. For the sake of convenience, these data sets are named ALB70, ALB120, ALB160, LDL70, LDL120 and LDL160 corresponding to albumin concentration profiles under transmural pressures of 70 mmHg,
Simulate concentration distribution with given initial guess of transport parameters.

Calculate the difference between simulation results and experimental data.

Obtain stepsize based on current values of transport parameters.

Calculate new guesses of transport parameters using the stepsize in each searching direction.

Does stepsize fall below tolerance?

Simulate concentration distribution with new guesses of transport parameters in all searching directions.

Calculate the difference between simulation results in each searching direction and experimental data.

Is the best searching direction giving improvement compared with current best function value?

Half the stepsize.

Update current best function value and current parameter values. Iteration=Iteration+1.

Is Iteration greater than maximum number of iterations?

Suboptimal found.

Figure 4.2: A schematic diagram of the compass search optimisation routine.
120 mmHg and 160 mmHg and LDL concentration profiles under transmural pressures of 70 mmHg, 120 mmHg and 160 mmHg, respectively.

![Experimental data on transmural distributions of albumin and LDL under different transmural pressures in rabbit aortic walls.](image)

**Figure 4.3:** Experimental data (Meyer et al., 1996) on transmural distributions of albumin (a) and LDL (b) under different transmural pressures in rabbit aortic walls.

It can be seen that given a certain species of transport, higher transmural pressures led to higher concentrations in the arterial wall. This can be attributed to a stronger convection driven by the transmural flow and a pressure-induce increase in endothelial permeability. Furthermore, profiles ALB70, LDL70, LDL120 and LDL160 show a characteristic “U” shape which is a typical observation made in experiments (Bratzler et al., 1977). However, the same distribution pattern can not be identified in profiles ALB120 and ALB160 which show higher concentration in the middle of the wall than in the inner wall. Therefore, there might be some unknown factors giving rise to these unusual ALB120 and ALB160 profiles in the experiments. To ensure the reliability of parameter estimation, only profiles ALB70, LDL70, LDL120 and LDL160 are used to derive parameter values.

The mass transport parameters to be determined include solute diffusivities in the arterial wall ($D_w$ in the single-layered model; $D_i$ and $D_m$ in the multi-layered model), solute permeabilities of the endothelium ($P_{end}$) and the IEL ($P_{iel}$), solute consumption rate constants in the arterial wall ($r_w$ in the single-layered model; $r_i$ and $r_m$...
in the multi-layered model), solute lag coefficients in the arterial wall \( (K_{\text{lag},w} \) in the single-layered model; \( K_{\text{lag},i} \) and \( K_{\text{lag},m} \) in the multi-layered model). Solute reflection coefficients of the endothelium \( (\sigma_{f,\text{endo}}) \) and the IEL \( (\sigma_{f,\text{iel}}) \) are not included in the parameter estimation because, first of all, the concentration field is not significantly sensitive to these parameters within their small physiological ranges; secondly, both the pore theory [Karner et al., 2001] and the electrical analogy [Prosi, 2003] worked out similar values of these parameters, which are used in the present study.

The parameters \( (D_w, P_{\text{endo}}, r_w \) and \( K_{\text{lag},w}) \) for the single-layered model are firstly determined by implementing the simulation-based optimisation approach. In the current estimation procedure, it is assumed that the consumption rate constant does not change under different transmural pressures. Because the media occupies more than 95% of the total thickness of the arterial wall (from the endothelium to the media-adventitia interface), it is assumed that the mass transport properties of the media in the multi-layered model are the same as the mass transport properties of the arterial wall in the single-layered model. It is also assumed that the endothelial permeability \( (P_{\text{endo}}) \) is the same in the single-layered and the multi-layered models to ensure the consistence in trans-endothelial flux. Furthermore, solute consumption rate constants and solute lag coefficients are assumed to have the same values in the intima and the media \( (r_i = r_w \) and \( K_{\text{lag},i} = K_{\text{lag},m}) \) because the intima is very thin and the concentration distribution therein could not be recorded in experimental data reported in [Meyer et al., 1996]. For the same reason, solute diffusivity in the intima cannot be estimated, and parameter values are taken from the literature. Based on these assumptions, the only parameter need to be determined in the multi-layered model is the solute permeability of the IEL \( (P_{\text{iel}}) \) whose optimal value is found by solving the optimisation problem corresponding to the multi-layered model. The determined parameter values are given in Table 4.2 and compared with values used in other studies. The comparisons show that although the derived optimal values differ from data in the literature, they are generally within the ranges of literature values.

Using these determined mass transport parameters, one-dimensional simulation results are obtained and compared with experimental data for profiles ALB70,
4.2 MASS TRANSPORT PARAMETERS

Table 4.2: Parameters determined by the simulation-based optimisation approach for data sets ALB70, LDL70, LDL120 and LDL160. Those listed in the footnotes are the literature values of the parameters.

<table>
<thead>
<tr>
<th>Data set</th>
<th>( D_w, [m^2 s^{-1}] )(^a)</th>
<th>( P_{end}, [m s^{-1}] )(^b)</th>
<th>( P_{iel}, [m s^{-1}] )(^c)</th>
<th>( r_w, [s^{-1}] )(^d)</th>
<th>( K_{lag,w} )(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB70</td>
<td>( 8.16 \times 10^{-11} )</td>
<td>( 1.20 \times 10^{-9} )</td>
<td>( 4.71 \times 10^{-8} )</td>
<td>( -1.04 \times 10^{-3} )</td>
<td>1.58</td>
</tr>
<tr>
<td>LDL70</td>
<td>( 1.42 \times 10^{-12} )</td>
<td>( 5.21 \times 10^{-10} )</td>
<td>( 1.60 \times 10^{-8} )</td>
<td>( -6.05 \times 10^{-4} )</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL120</td>
<td>( 3.50 \times 10^{-12} )</td>
<td>( 4.84 \times 10^{-9} )</td>
<td>( 1.55 \times 10^{-7} )</td>
<td>( -6.05 \times 10^{-4} )</td>
<td>1.05</td>
</tr>
<tr>
<td>LDL160</td>
<td>( 1.56 \times 10^{-12} )</td>
<td>( 9.38 \times 10^{-9} )</td>
<td>( 1.95 \times 10^{-7} )</td>
<td>( -6.05 \times 10^{-4} )</td>
<td>0.90</td>
</tr>
</tbody>
</table>

\(^a\) 8.14 \times 10^{-13} \text{ (Zunino, 2002)} for LDL.
\(^b\) 2 \times 10^{-10} at 70 mmHg, 1.76 \times 10^{-9} at 120 mmHg and 8.61 \times 10^{-9} at 160 mmHg \text{ (Prosi, 2003)} for LDL.
\(^c\) 1.59 \times 10^{-9} \text{ (Zunino, 2002)} and 3.18 \times 10^{-6} \text{ (Prosi, 2003)} for LDL.
\(^d\) \(-1.4 \times 10^{-4} \text{ (Zunino, 2002)} and (-2.7646 \times 10^{-4} \text{ (Prosi, 2003)} for LDL.
\(^e\) 0.682 \text{ (Prosi, 2003)} for LDL.

LDL70, LDL120 and LDL160 in Figure 4.4. Both the single-layered and the multi-layered models adequately predict the medial distributions seen in the experimental data using the estimated mass transport parameters.

4.2.2.2 Remarks on the estimated macromolecular transport parameters

It is believed that hypertension, especially when associated with hypercholesterolemia, accelerates the complications of atherosclerosis \text{ (Chobanian et al., 1989)}. Changes in macromolecular transport across the arterial wall under high transmural pressures might be one of the mechanisms through which hypertension contributes to atherogenesis \text{ (Fry, 1987)}. The estimated macromolecular transport parameters in the present study support this hypothesis. First of all, under a higher transmural pressure, convection that is driven by the transmural flow is stronger. Furthermore, convection is not the only transport pathway which is pressure-dependent. As seen in the estimated LDL endothelial permeabilities \( P_{end,ldl} \), IEL permeabilities \( P_{iel,ldl} \), and diffusivities in the arterial wall \( D_{w,ldl} \) under different transmural pressures (see Figure
4.2 MASS TRANSPORT PARAMETERS

Figure 4.4: Comparison between optimal 1-D simulation results and the experimental data on transmural albumin concentration under transmural pressure of 70 mmHg (a) and LDL concentration under three different transmural pressures of 70 mmHg (b), 120 mmHg (c) and 160 mmHg (d). Solid lines and dashed lines are optimal results given by the single-layered model and the multi-layered model, respectively.
4.2 MASS TRANSPORT PARAMETERS

Figure 4.5: Optimal parameter values of $D_{w,ldl}$, $P_{end,ldl}$ and $P_{iel,ldl}$ under transmural pressures of 70 mmHg, 120 mmHg and 160 mmHg.

In Figure 4.5, it can also be noticed that these three transport parameters are raised substantially when transmural pressure is increased from 70 mmHg to 120 mmHg. However, surprisingly, when the transmural pressure is increased from 120 mmHg to 160 mmHg, $P_{end,ldl}$ and $P_{iel,ldl}$ are only raised slightly with $D_{w,ldl}$ being decreased (although it is still higher than the value at 70 mmHg). Complex deformation patterns of the fibre-matrix structures in the arterial wall may be responsible
for this observation.

Because the mass transport parameters are determined based on the experimental data reported by Meyer et al. (1996), it is worth pointing out the possible uncertainties involved in the estimation brought by experiments. First of all, the experiments were only 30 minutes in duration, which was too short for albumin and LDL transport to reach equilibrium (Bratzler et al., 1977). Secondly, the rabbit aorta could distend freely without being limited by surrounding tissue in the experiments. Particularly, when transmural pressure was raised from 70 mmHg to 120 mmHg, the diameter of the aortic segments displayed a 22.4% increase from 5.22±0.08 mm to 6.39±0.14 mm, which was much greater than the distension that occurs in vivo. Consequently, the in vivo effect of transmural pressure on arterial wall transport properties is likely to be somewhat less than the difference estimated here.

4.2.3 Summary of mass transport parameters

The mass transport parameters used in the present study for oxygen (OXY), albumin at transmural pressure of 70 mmHg (ALB70), LDL at transmural pressures of 70 mmHg (LDL70), 120 mmHg (LDL120) and 160 mmHg (LDL160) are summarised in Table 4.3.

4.3 Shear-dependent parameters

Trans-endothelial momentum and mass transport is believed to be influenced by biomechanical forces, especially WSS (Caro et al., 1971). A conventional approach to examine the influence of WSS on trans-endothelial transport and the whole arterial mass transport system is to employ analytical models for shear-dependent transport parameters, such as hydraulic conductivity and endothelial solute permeability. Therefore, in this section, analytical models of a shear-dependent endothelial hydraulic conductivity ($L_{p, end}$) and a shear-dependent endothelial albumin permeability ($P_{end, alb}$) are constructed from available experimental data in the literature. A model for a shear-dependent endothelial LDL permeability ($P_{end, ldl}$) is not formulated and $P_{end, ldl}$ is as-
4.3 SHEAR-DEPENDENT PARAMETERS

Table 4.3: Summary of mass transport parameters for oxygen (OXY), albumin at transmural pressure of 70 \textit{mmHg} (ALB70), LDL at transmural pressures of 70 \textit{mmHg} (LDL70), 120 \textit{mmHg} (LDL120) and 160 \textit{mmHg} (LDL160).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OXY</th>
<th>ALB70</th>
<th>LDL70</th>
<th>LDL120</th>
<th>LDL160</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_l$, $[m^2 s^{-1}]$</td>
<td>$1.60 \times 10^{-9}$</td>
<td>$9.01 \times 10^{-11}$</td>
<td>$2.867 \times 10^{-11}$</td>
<td>$2.867 \times 10^{-11}$</td>
<td>$2.867 \times 10^{-11}$</td>
</tr>
<tr>
<td>$D_w$, $[m^2 s^{-1}]$</td>
<td>$1.08 \times 10^{-9}$</td>
<td>$6.05 \times 10^{-12}$</td>
<td>$1.42 \times 10^{-12}$</td>
<td>$3.50 \times 10^{-12}$</td>
<td>$1.56 \times 10^{-12}$</td>
</tr>
<tr>
<td>$D_i$, $[m^2 s^{-1}]$</td>
<td>$5.99 \times 10^{-11}$</td>
<td>$1.20 \times 10^{-11}$</td>
<td>$1.20 \times 10^{-11}$</td>
<td>$1.20 \times 10^{-11}$</td>
<td>$1.20 \times 10^{-11}$</td>
</tr>
<tr>
<td>$D_m$, $[m^2 s^{-1}]$</td>
<td>$6.05 \times 10^{-12}$</td>
<td>$1.42 \times 10^{-12}$</td>
<td>$3.50 \times 10^{-12}$</td>
<td>$1.56 \times 10^{-12}$</td>
<td>$1.56 \times 10^{-12}$</td>
</tr>
<tr>
<td>$P_{end}$, $[m s^{-1}]$</td>
<td>$1.96 \times 10^{-4}$</td>
<td>$1.20 \times 10^{-9}$</td>
<td>$5.21 \times 10^{-10}$</td>
<td>$4.84 \times 10^{-9}$</td>
<td>$9.38 \times 10^{-9}$</td>
</tr>
<tr>
<td>$P_{iel}$, $[m s^{-1}]$</td>
<td>$4.71 \times 10^{-8}$</td>
<td>$1.60 \times 10^{-8}$</td>
<td>$1.55 \times 10^{-7}$</td>
<td>$1.95 \times 10^{-7}$</td>
<td>$1.95 \times 10^{-7}$</td>
</tr>
<tr>
<td>$r_w$, $[s^{-1}]$</td>
<td>$-4.89 \times 10^{-2}$</td>
<td>$-1.04 \times 10^{-3}$</td>
<td>$-6.05 \times 10^{-4}$</td>
<td>$-6.05 \times 10^{-4}$</td>
<td>$-6.05 \times 10^{-4}$</td>
</tr>
<tr>
<td>$\sigma_{f,end}$</td>
<td>$0.82$</td>
<td>$0.997$</td>
<td>$0.997$</td>
<td>$0.997$</td>
<td>$0.997$</td>
</tr>
<tr>
<td>$\sigma_{f,iel}$</td>
<td>$1.94 \times 10^{-3}$</td>
<td>$1.93 \times 10^{-2}$</td>
<td>$1.93 \times 10^{-2}$</td>
<td>$1.93 \times 10^{-2}$</td>
<td>$1.93 \times 10^{-2}$</td>
</tr>
<tr>
<td>$K_{lag,w}$</td>
<td>$1.58$</td>
<td>$0.15$</td>
<td>$1.05$</td>
<td>$0.90$</td>
<td>$0.90$</td>
</tr>
</tbody>
</table>


Assumed to be constant due to a lack of suitable data. Moreover, oxygen trans-endothelial transport is mainly dominated by diffusion and is unlikely to be dependent on shear stress \cite{Kudo1993}, hence a constant $P_{end, oxy}$ is also assumed.

4.3.1 Shear-dependent endothelial hydraulic conductivity

The effect of shear stress on hydraulic conductivity ($L_{p, end}$) of bovine aortic endothelium was examined \textit{in vitro} by \cite{Sill1995} and \cite{Chang2000} under constant shear stress conditions. It was found that when exposed to higher shear stresses, the endothelial monolayer presented higher hydraulic conductivity. The experimental data reported by \cite{Sill1995} are summarised in Table 4.4.

Since the experiments were conducted over a period of 240 minutes, the measured hydraulic conductivity varied with time. Here the maximum values under each shear stress condition are used to derive the relationship between shear stress and hydraulic conductivity. These experimental data are fitted with a logarithmic function to obtain a mathematical model of the shear-dependent hydraulic conductivity. The
4.3 SHEAR-DEPENDENT PARAMETERS

Table 4.4: Experimental data on shear-dependent endothelial hydraulic conductivity reported by Sill et al. (1995).

<table>
<thead>
<tr>
<th>WSS [Pa]</th>
<th>0.01</th>
<th>0.05</th>
<th>0.1</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalised $L_{p,\text{end}}$</td>
<td>1</td>
<td>2.39</td>
<td>2.95</td>
<td>2.86</td>
<td>3.76</td>
</tr>
</tbody>
</table>

Figure 4.6: Comparison between experimental data reported by Sill et al. (1995) and the fitted analytical model on shear-dependent endothelial hydraulic conductivity ($L_{p,\text{end}}$). All the values of $L_{p,\text{end}}$ are normalised in both the experiments and the analytical model.

The resulting logarithmic function is given by

$$g(|\tau_w|) = 0.4669 \ln(|\tau_w| + 0.015) + 3.327$$  \hspace{1cm} (4.8)

where $\tau_w$ is WSS, and $g$ is the normalised hydraulic conductivity. This fitted curve is compared with experimental data in Figure 4.6.

4.3.2 Shear-dependent endothelial albumin permeability

Jo et al. (1991) were among the first to report shear-dependent endothelial albumin permeability. It was found that the endothelial albumin permeability increased monotonously when shear stress was elevated from 0 Pa to 0.1 Pa and 1 Pa. However, in their inves-
tigation, only two shear conditions were examined, leading to difficulties in formulating an analytical model. In Kudo et al. (1998) and Ueda et al. (2004), Tanishita and coworkers reported a dual response of albumin uptake by cultured endothelial cells to shear stress. It was found that the albumin uptake increased with increasing WSS at lower shear stresses (\(< 1 \text{ Pa}\)) and decreased with increasing WSS at higher shear stresses (\(> 2 \text{ Pa}\)). The experimental data reported by Kudo et al. (1998) are summarised in Table 4.5. Since a relatively wide range of shear conditions was examined, these data are used in the present study to construct an analytical model for a shear-dependent endothelial albumin permeability.

**Table 4.5:** Experimental data on shear-dependent endothelial albumin permeability reported by Kudo et al. (1998).

<table>
<thead>
<tr>
<th>WSS [Pa]</th>
<th>0.1</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalised (P_{\text{end,alb}})</td>
<td>1</td>
<td>1.2</td>
<td>1.3</td>
<td>0.74</td>
<td>0.31</td>
<td>0.24</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Figure 4.7:** Comparison between experimental data reported by Kudo et al. (1998) and the fitted analytical model on shear-dependent endothelial albumin permeability \((P_{\text{end,alb}})\). All the values of \(P_{\text{end,alb}}\) are normalised in both the experiments and the analytical model.

The data are fitted with a Gaussian function to obtain an analytical model.
which is given by

\[ h(\tau_w) = 1.0175 \exp \left( -\frac{(|\tau_w| - 0.804)^2}{1.887} \right) + 0.2778 \]  \hspace{1cm} (4.9)

where \( \tau_w \) is WSS, and \( h \) is the normalised endothelial albumin permeability. This fitted curve is compared with experimental data in Figure 4.7.

### 4.3.3 Scaling of shear-dependent parameters

Equation (4.6) and Equation (4.7) give analytical models for normalised endothelial hydraulic conductivity \( (L_{p,\text{end}}) \) and albumin permeability \( (P_{\text{end,alb}}) \). However, absolute values of these two parameters need to be used in the simulations. Therefore, the two analytical models are scaled. The base values of \( L_{p,\text{end}} = 3.0 \times 10^{-12} \text{ m s}^{-1} \text{ Pa}^{-1} \) and \( P_{\text{end,alb}} = 1.2 \times 10^{-9} \text{ m s}^{-1} \) are validated or determined in previous sections and used to scale the normalised analytical models.

#### 4.3.3.1 Scaling of endothelial hydraulic conductivity

In the case of endothelial hydraulic conductivity, the base value is considered to be an appropriate value under physiological conditions (Karner and Perktold, 2000; Karner et al., 2001; Zunino, 2002). Therefore, it is assumed that under a certain physiological shear condition, the value of endothelial hydraulic conductivity should be the base value \( 3.0 \times 10^{-12} \text{ m s}^{-1} \text{ Pa}^{-1} \). For a human coronary artery, assuming vessel diameter \( d = 0.004 \text{ m} \) and mean velocity \( U_0 = 0.24 \text{ m s}^{-1} \), WSS can be calculated using Equation (2.3) for Poiseuille flow as \( 1.68 \text{ Pa} \). Assuming \( L_{p,\text{end}}(\tau_w)|_{\tau_w=1.68} = 3.0 \times 10^{-12} \text{ m s}^{-1} \text{ Pa}^{-1} \), the analytical model for the shear-dependent endothelial hydraulic conductivity can be obtained by scaling Equation (4.8).

\[
L_{p,\text{end}}(|\tau_w|) = 3.92 \times 10^{-13} \ln(|\tau_w| + 0.015) + 2.7931 \times 10^{-12}. \hspace{1cm} (4.10)
\]

The scaled model for \( L_{p,\text{end}} \) is given by Equation (4.10) and plotted in Figure 4.8.

#### 4.3.3.2 Scaling of endothelial albumin permeability

In the case of endothelial albumin permeability, the base value is determined from experimental data reported by Meyer et al. (1996) using the simulation-based optimi-
4.3 SHEAR-DEPENDENT PARAMETERS

Figure 4.8: An analytical model for the shear-dependent endothelial hydraulic conductivity.

sation approach. In the original experiments, the vessels were “filled” with labelled albumin and LDL solutions without flowing fluid. Hence, no WSS was applied at the endothelium and the base value is the value under a zero shear condition, i.e. $P_{\text{end, alb}}(\tau_w)\big|_{\tau_w=0} = 1.2 \times 10^{-9}$. Using this relation, the analytical model for the shear-dependent endothelial albumin permeability can be obtained by scaling Equation (4.9).

$$P_{\text{end, alb}}(\tau_w) = 1.221 \times 10^{-9} \exp \left( -\frac{(\tau_w - 0.804)^2}{1.887} \right) + 3.334 \times 10^{-10} \quad (4.11)$$

The scaled model for $P_{\text{end, alb}}$ is given by Equation (4.11) and plotted in Figure 4.9.
Figure 4.9: An analytical model for the shear-dependent endothelial albumin permeability.
Model Tests

In this chapter, commercial softwares used in the present study are briefly described, after which the mathematical models and numerical schemes are tested in idealised arterial geometries. For steady flow simulations, six test cases are investigated including LDL transport in a straight tube (case F1), oxygen transport in an idealised abdominal aortic aneurysm (case S1), albumin transport in an idealised stenosed coronary artery (cases S2a and S2b), and LDL transport in an idealised stenosed coronary artery (cases M1 and M2). While for pulsatile flow simulations, both LFC and LFTA procedures are applied to model LDL transmural transport in an idealised stenosed coronary artery (cases T1 and T2).

5.1 CFD codes description

The mathematical models formulated in Chapter 3 are implemented in two commercial softwares, i.e. Comsol Multiphysics® (COMSOL AB, Sweden) and ANSYS.* Case named with prefix “F” employs the fluid phase model; cases named with prefix “S” employ the single-layered model; cases named with prefix “M” employ the multi-layered model.
5.1 CFD CODES DESCRIPTION

CFX® (ANSYS Inc, USA). Comsol Multiphysics is a finite element package for solving various forms of PDEs, whereas ANSYS CFX is a finite volume package mainly for solving fluid flow and heat transfer models.

Cross-code comparisons of flow simulations between Comsol Multiphysics and CFX were carried out by Cheong (2004) and a good agreement was observed. However, it was found that Comsol Multiphysics required 30-time more computational time to finish the same flow simulation than ANSYS CFX, indicating that CFX solvers are much more efficient than Comsol Multiphysics in solving fluid flow problems. Especially, the adaptive time-stepping scheme employed in transient simulations by Comsol is very inefficient and sometimes fails in reaching convergence. However, Comsol Multiphysics provides better implementation of mass transport models, especially those with complex boundary conditions and matching conditions. Through cross-code comparisons of mass transfer simulations between Comsol Multiphysics and CFX, it is found that excessive numerical diffusion is employed in CFX to stabilise the solution and inaccurate concentration distributions are obtained in the boundary layer.

Therefore, in the present study, to capitalise on the efficient flow solvers of CFX, the Navier-Stokes equations are solved using ANSYS CFX for anatomically realistic geometries (in Chapters 6 and 7). Furthermore, the time-dependent Navier-Stokes equations in idealised geometries are also solved using ANSYS CFX. On the other hand, to ensure the accuracy of the obtained concentration field, all other equations are solved using Comsol Multiphysics. Because it is assumed that the velocity field is independent of concentration field, the information exchange between the two softwares can be easily carried out off-line.

5.1.1 Comsol Multiphysics

Various PDEs can be solved using Comsol Multiphysics, including the Navier-Stokes equations, Darcy’s Law, and the convection-diffusion equations. The discretisation scheme employed in Comsol Multiphysics is the finite element method (FEM). The
PDEs are approximated with a problem that has a finite number of unknown parameters based on a mesh, a partition of the geometry into small units of a simple shape. This simple shape can be, for instance, line sections in one-dimension, triangles or quadrilaterals in two-dimension, and tetrahedra or hexahedra in three-dimension. Over each element, a simple variation of the dependent variables is assumed and this piecewise description is used to approximate how the variables vary over the whole domain. The discretisation yields a system of linear or nonlinear algebraic equations depending on the nature of the original PDEs. These algebraic equations are then passed to the linear or nonlinear solver to calculate the values of the finite number of unknown parameters which can approximate the solution of the original PDEs.

In the present study, solutions to linear systems, such as Darcy’s Law and the convection-diffusion equations with linear boundary conditions, as well as nonlinear systems, such as the Navier-Stokes equations and the convection-diffusion equations with nonlinear boundary conditions (especially when Kedem-Katchalsky equations come in as matching conditions), need to be sought. A build-in highly efficient direct solver called unsymmetric multifrontal sparse LU factorization package (UMFPACK) is chosen to solve the linear systems in two-dimensional problems while a more memory efficient iterative solver called generalized minimal residual method (GMRES) is chosen to solve the linear systems with the incomplete LU preconditioner (ILU) in three-dimensional problems. The nonlinear solver in Comsol Multiphysics uses an affine invariant form of the damped Newton method. The time-dependent solver in Comsol Multiphysics uses large scale differential algebraic equation solver (DASPK), which is an implicit time-stepping scheme. Detailed information on the implementation of the models can be found in User’s Guide of Comsol Multiphysics 3.3 (Comsol AB, 2007).

5.1.2 ANSYS CFX

ANSYS CFX is a widely used CFD package based on the finite volume method (FVM). As in the finite element method, the first step in the finite volume method is to divide the domain into a number of control volumes (elements) where the variable of interest is located at the centroid of the control volume. Then the differential forms of the
governing equations are integrated over each control volume. Interpolation profiles are then assumed in order to described the variation of the variables between cell centroids. The resulting discretised equation expresses the conservation principle for the variables inside the control volume.

The basic solution algorithm used in ANSYS CFX is the SIMPLEC pressure correction scheme which uses a variety of linear solvers. In the present study, the advection term is discretised using a build-in high resolution scheme, which guarantees that the discretisation is as close as possible to second order accuracy while ensures that robust solutions can be obtained. For transient problems, the time stepping procedure used in the present study is a fully implicit second order backward Euler scheme, which is robust and imposes no limit on the time step. After the discretisation step, the governing equations are all transformed into linearised algebraic equations. Since these equations are derived for each control volumes, they can be regarded as describing a particular variable in a particular control volume. Specifically, the algebraic equations characterise the influences of 1) other variable in the same control volume, 2) the same variable in neighbouring control volumes, and 3) other variables in neighbouring control volumes. During each time-step, the system of algebraic equations is solved at two iteration levels: an inner iteration to solve for the spatial coupling for each variable and an outer iteration to solve for the coupling between variables. Therefore, a subsystem of algebraic equations for a variable is solved in each inner iteration, regarding all other variables as fixed. The implementation details of ANSYS CFX can be found in Users’ Manual of ANSYS CFX 10.0 [ANSYS Inc, 2005].

5.2 Mesh density test

Due to the strong convection caused by the bulk blood flow, mass transport process in the arterial lumen is highly convection-dominated. Due to the extremely low diffusivity of solutes in blood, the magnitudes of Peclet numbers are approximately $10^6$ for oxygen, $10^6 \sim 10^7$ for albumin, and $10^7 \sim 10^8$ for LDL under physiological conditions, indicating that trans-lumenal transport is highly dominated by convection. Numeri-
5.2 MESH DENSITY TEST

cal solutions to this highly convection-dominated problems are usually unstable and call for stabilisation techniques. The streamline upwind Petrov-Galerkin (SUPG) technique developed by Brooks and Hughes (1982) is a well accepted stabilising technique and has been used in a number of computational studies on arterial mass transport (Rappitsch and Perktold, 1996a,b; Rappitsch et al., 1997; Prosi et al., 2005). In the present study, the SUPG technique is also adopted and implemented in Comsol Multiphysics.

Furthermore, in highly convection-dominated transport problems, the concentration boundary layer is very thin. The mass transfer boundary layer thickness can be estimated using the Graetz-Nusselt theory in a straight tube (Zunino, 2002). At a given axial coordinate, it can be calculated as

\[
\delta = \left( \frac{x}{D} \right)^\frac{1}{3} Pe^{-\frac{1}{3}}
\]

(5.1)

where \(\delta\) is the boundary layer thickness, \(D\) is the diameter of the tube, \(x\) is the axial coordinate, and \(Pe\) is the Peclet number. Assuming \(Re = 300\) and \(Sc = 1,160,000\) or \(Pe = 3.5 \times 10^7\), corresponding to LDL transport in a right coronary artery (RCA), the thinnest boundary layer thickness encountered in the present study can be calculated. Choosing \(x = 25D\), the boundary layer thickness \(\delta\) is around 0.009\(D\). To resolve such a thin boundary layer, a very fine mesh is necessary near the endothelium. However, due to the limitation of computational resources, the mesh density needs to be constrained within a practical range, especially in three-dimensional simulations. Therefore, mesh density tests are carried out to ensure that a satisfactory computational accuracy can be obtained with a non-excessive mesh density.

It is impractical to test mesh sensitivity in each investigated geometry with the available computational resources, especially in three-dimensional subject-specific geometries. Therefore, an axisymmetric straight tube shown in Figure 5.1 is used in a general mesh sensitivity test. The diameter of the tube is chosen to be 0.004\(m\), length of tube 0.08\(m\), mean inlet velocity 0.24\(m\ s^{-1}\), LDL diffusivity \(2.867 \times 10^{-11} m^2 s^{-1}\), the resulting Peclet number is around \(3.5 \times 10^7\). The fluid-phase model formulated in Chapter 3 is used to model LDL transport. At the inlet, a fully developed parabolic
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Figure 5.1: An axisymmetric geometry of a straight tube for mesh density tests. $D = 0.004 \, m$ is the diameter of the tube, while $20D$ or $0.08 \, m$ is the length of the tube. $\Gamma_{l,\text{in}}$ and $\Gamma_{l,\text{out}}$ denote inlet and outlet of the tube, respectively. $\Gamma_{\text{end}}$ is the wall boundary. The dashed line is the axis of symmetry.

velocity profile is prescribed, and the filtration velocity $v_{f,i}$ in BC (3.4c) is assumed to be $1.78 \times 10^{-8} \, m \, s^{-1}$ corresponding to the transmural velocity when $\Delta p = 70 \, mmHg$.

Different nodal spacings ($h_0$) near the wall boundary $\Gamma_{\text{end}}$, i.e. $h_0 = 0.003D$, $h_0 = 0.004D$, $h_0 = 0.0055D$ and $h_0 = 0.01D$ are tested. Figure 5.2 compares the LDL concentration on the lumenal surface calculated using these four different meshes. It is shown that when $h_0 = 0.01D$ (only one node in the boundary layer), the simulation results fail to capture the boundary layer development; when $h_0 = 0.0055D$ (two

Figure 5.2: Comparison of computational results of LDL concentration on the lumenal surface given by different mesh spacings from the wall in the radial direction, i.e. $0.003D$, $0.004D$, $0.0055D$ and $0.01D$. 
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nodes in the boundary layer), the boundary layer development can only be predicted to some extent. On the other hand, when \( h_0 = 0.004D \) (three nodes in the boundary layer) or \( h_0 = 0.003D \) (four nodes in the boundary layer), the concentration gradient along the luminal surface can be satisfactorily resolved. Therefore, it is ensured that all computational meshes used in the present study satisfy \( h_0 \leq 0.004D \) to give sufficient resolution for mass transfer simulations.

5.3 Steady flow simulations

5.3.1 Case F1: LDL transport in a straight tube

Using the same geometry and computational mesh as those in the mesh sensitivity test, concentration polarisation of LDL on the luminal surface is investigated. Different filtration velocities ranging between \( 2.5 \times 10^{-8} \text{ m s}^{-1} \) and \( 10 \times 10^{-8} \text{ m s}^{-1} \) are employed to study the effects of filtration on LDL concentration polarisation. The model parameter set LDL120 given in Table 4.3 is used.

![Figure 5.3: Comparison of LDL concentration polarisation on the luminal surface when filtration velocity is set to 2.5 \times 10^{-8} \text{ m s}^{-1} \) (solid line), 5 \times 10^{-8} \text{ m s}^{-1} \) (dashed line), 7.5 \times 10^{-8} \text{ m s}^{-1} \) (dashed dotted line), and 10 \times 10^{-8} \text{ m s}^{-1} \) (dotted line).]

As shown in Figure 5.3, the degree of LDL concentration polarisation strongly
depends on the filtration velocity: a higher filtration velocity leads to a higher degree of concentration polarisation. This is because concentration polarisation phenomenon is induced by plasma filtration across the endothelium: the macromolecules brought by convection to the endothelium cannot pass the membrane due to a low permeability and hence accumulate on the luminal surface. Therefore, a greater convection driven by a higher filtration velocity results in a more significant macromolecular accumulation. This observation indicates that an accurate prediction of transmural velocity in a fluid-wall model is important to calculate the fluid phase transport correctly.

It should be noted that the degree of concentration polarisation can also be affected by other factors, including the flow velocity (stronger flow clears the accumulation on the luminal surface), the endothelial macromolecular permeability (higher permeability allows more macromolecule enter the wall hence less accumulation), and the macromolecular plasma diffusivity (higher diffusivity causes greater counter diffusion hence less accumulation). Wada and Karino (1999) investigated all the factors mentioned above in a straight tube and can be referred to for details.

5.3.2 Case S1: oxygen transport in an idealised abdominal aortic aneurysm

The abdominal aortic aneurysm (AAA) is a degenerative, asymptomatic disease where the afflicted person suffers from a localised dilatation of the abdominal aorta. An average aorta is 150 mm long and has a diameter of between 15 mm and 20 mm. An aneurysm is generally accepted as being when the diameter of the aorta exceeds 35 mm. It is reported that 90% of the AAA cases are caused by atherosclerosis (Drake et al., 2004). The abnormal geometrical and flow characteristics of AAAs cause insufficient supply of oxygen to the aortic wall by the bulk blood flow, leading to wall tissue hypoxia. This will further degenerate the arterial wall and accelerate the progression of the disease. Therefore, a preliminary study of oxygen transport in an idealised AAA geometry is carried out as a test of the single-layered model.
5.3.2.1 Computational geometry

An hypothetical axisymmetric geometry of an AAA is adopted. As shown in Figure 5.4, the total length (z-axis) of the geometry is $17.5D$, where $D = 0.02 \text{ m}$ is the diameter of the non-dilated region of the aorta. The length of the aneurysm is $7.5D$, leaving $5D$ upstream and $5D$ downstream of the dilatation to minimise the effects of boundary conditions.

Figure 5.4: An axisymmetric geometry of an idealised abdominal aortic aneurysm. $D = 0.02 \text{ m}$ is the diameter of the normal aorta, while $D' = 0.06 \text{ m}$ is the maximum diameter of the aneurysm. $\Omega_l$ and $\Omega_w$ are the lumen and the wall domains, respectively. $\Gamma_{l,in}$ and $\Gamma_{l,out}$ denote inlet and outlet of the arterial lumen, respectively. $\Gamma_{end}$ is the endothelial boundary. $\Gamma_{w,in}$ and $\Gamma_{w,out}$ denote sides of the arterial wall. $\Gamma_{adv}$ is the outer wall boundary. The dashed line is the axis of symmetry.

The lumen shape of the idealised AAA is described by a Gaussian function [Raghavan, 1998] given by

$$r_{end}(z) = \frac{(D' - D)}{2} \exp \left( -\frac{1}{2} \left( \frac{(z - z_1) - \frac{z_2 - z_1}{2}}{\rho_g} \right)^2 \right) + \frac{D}{2} \quad (5.2)$$

where $r_{end}(z)$ is the radial position of the endothelium given as a function of the axial position of the aneurysm, $D'$ is the maximum diameter of aneurysm, $D$ is the diameter of a healthy aorta, $z$ is the axial position, $z_1 = 5D$ is the starting point of the aneurysm, $z_2 = 12.5D$ is the end point of the aneurysm, and $\rho_g = 0.027$ [Raghavan, 1998] is the shape factor defining the curvature of the bulge. To model the arterial wall, a constant intima-media thickness of $500 \mu\text{m}$ [Järvisalo et al., 2001] is added to the Gaussian function used to generate the luminal geometry.
5.3.2.2 Computational details

The single-layered model, where the convection terms are dropped in the arterial wall, is applied to simulate the oxygen transport process. The mass transport parameter set OXY given in Table 4.3 is employed. A fully developed parabolic steady velocity profile is prescribed at the lumen inlet boundary $\Gamma_{\text{in}}$

$$u(r) = 2U_0 \left(1 - \left(\frac{2r}{D}\right)^2\right)$$  \hspace{1cm} (5.3)

where $u(r)$ is the velocity in the axial direction at radial position $r$, and $U_0 = 0.12 \text{ m s}^{-1}$ is the mean inlet velocity. The resulting Reynolds number $Re = 720$ and Peclet number $Pe = 1,512,000$. The inlet oxygen concentration ($c_0$) is assumed to be a normalised value 1, while oxygen concentration at the outer wall boundary $\Gamma_{\text{adv}}$ is assumed to be 0.61$^\circ$.

The fluid domain ($\Omega_l$) is divided into 25,000 quadrilateral elements with 25,551 nodes for solution of the Navier-stokes equations (Equation 3.5 on page 73) and 150,000 quadrilateral elements with 151,151 nodes for the convection-diffusion equation (Equation 3.9 on page 74). While the wall domain ($\Omega_w$) is divided into 20,000 quadrilateral elements with 21,021 nodes for solution of the diffusion-reaction equation (Equation 3.11 on page 74 without the convection term).

5.3.2.3 Computational results

Cross-sectional profiles of velocity in the axial direction ($v$) at four different locations in the AAA are compared in Figure 5.5. At the entrance of the AAA, the velocity profile is a perfect parabola indicating that the flow is not disturbed. While at $z = 7.5D$ and $z = 10D$ where flow recirculates, negative axial velocities exist. At the exit of the AAA, no reverse flow is found but flow has not fully redeveloped, showing some differences from the profile at the entrance of the AAA.

Variations of WSS magnitude, trans-endothelial oxygen flux, and endothelial

---

*The inlet oxygen tension is assumed to be the arterial oxygen tension 90 mmHg and the oxygen tension in the adventitia is assumed to be 55 mmHg according to Buerk and Goldstick (1982). These values are converted into oxygen concentration using Henry’s Law and normalised with the inlet value.
Figure 5.5: Cross-sectional profiles of axial velocity ($v$) in the AAA at the entrance or $z = 5D$ (solid line), in the flow recirculation region upstream of the maximum dilatation or $z = 7.5D$ (dashed line), in the flow recirculation region downstream of the maximum dilatation or $z = 10D$ (dashed dotted line), and exit of the AAA or $z = 12.5D$ (dotted line). $r/R$ is the radial position normalised by local radius of the AAA.

Oxygen concentration in the axial direction of the AAA are given in Figure 5.6. The two points where WSS values are zero correspond to the separation point and the reattachment point, respectively. The area between these two points with low magnitudes of WSS is the flow recirculation region. As shown in Figure 5.6b, the trans-endothelial oxygen flux decreases when the flow enters the dilated region of the aorta, remains at low levels in the recirculation region and recovers to a higher level at the distal side of the AAA. This can be explained by the flow-induced boundary layer disturbance and redevelopment. Normalised endothelial oxygen concentrations on the lumen and wall sides are compared in Figure 5.6c. It is found that the difference between the two profiles is very small because the endothelium is highly permeable to oxygen. Such an observation supports the hypothesis that endothelial oxygen concentrations on the lumen and wall sides have the same value in the fluid phase oxygen transport model developed by [Qiu and Tarbell (2000)]. Furthermore, oxygen concentration on the luminal surface in the recirculation region is generally low due to the weakened oxygen
convection by the blood flow.

Cross-sectional oxygen concentration profiles in the lumen and the wall upstream of the AAA ($z = 1D$) and in the flow recirculation region ($z = 10D$) are compared in Figure 5.7. It is seen that at the upstream of the AAA where the flow is not disturbed, a very thin concentration boundary layer is formed in the fluid phase. However, due to the flow recirculation, a characteristic step-like profile can be identified at $z = 10D$. Wall concentrations at both locations show similar shape. Oxygen concentration in the inner wall is lower at $z = 10D$ than at $z = 1D$; but oxygen concentrations in the outer wall are similar at the two locations; indicating that 1) the
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Figure 5.7: Cross-sectional profiles of oxygen concentration in the lumen and the wall upstream of the AAA or $z = 1D$ (solid line) and in the flow recirculation region (downstream of the maximum dilatation) or $z = 10D$ (dashed line). The radial position in the lumen are normalised by local radius of the aorta while the radial position in the wall ($\delta_w$) is normalised by the total thickness of the aortic wall ($\Delta_w$).

inner wall in the recirculation region is subject to a certain degree of hypoxia, and 2) the oxygen supply to the outer wall is primarily provided by the vasa vasorum in the adventitia.

5.3.3 Cases S2a and S2b: albumin transport in an idealised model of a stenosed coronary artery

Coronary artery disease is the most common type of heart disease in human beings. It happens when the arteries that supply blood to the heart muscles become hardened and narrowed due to the formations of multiple plaques. As the plaques grow and intrude into the lumen, less blood can flow through the arteries. Eventually, this can lead to a heart attack. Therefore, it is important to investigate macromolecular transport in coronary arteries. Again a preliminary analysis is carried out in an idealised geometry.
5.3.3.1 Computational geometry

An axisymmetric stenosis with 51% area reduction is adopted. As shown in Figure 5.8, the total length (z-axis) of the geometry is $25D$, where $D = 0.004\ m$ is the diameter of the non-stenosed region of the artery. The length of the stenosis is $1D$, leaving $4D$ upstream and $20D$ downstream of the stenosis to minimise the effects of boundary conditions.

![Diagram of axisymmetric stenosed geometry]

Figure 5.8: An axisymmetric geometry of a mild stenosed (51% constriction by area) coronary artery for the single-layered model. $D = 0.004\ m$ is the diameter of the normal coronary artery, while $D' = 0.7D$ is the diameter of the artery at the throat of the stenosis. $\Omega_l$ and $\Omega_w$ are the lumen and the wall domains, respectively. $\Gamma_{l,in}$ and $\Gamma_{l,out}$ denote inlet and outlet of the arterial lumen, respectively. $\Gamma_{end}$ is the endothelial boundary. $\Gamma_{w,in}$ and $\Gamma_{w,out}$ denote sides of the arterial wall. $\Gamma_{adv}$ is the outer wall boundary. The dashed line is the axis of symmetry.

The axisymmetric stenosed lumen geometry is modelled by the following cosine expression:

$$\frac{r_{end}(z)}{R} = \frac{\alpha_{end}}{D} \cos \left( \frac{2\pi(z - z_1 - z_2)}{z_2 - z_1} \right) + \frac{\beta_{end}}{D} \tag{5.4}$$

for $4D < z < 5D$, where $r_{end}(z)$ is the position of the endothelium (radius of the lumen) at location $z$ in the arterial segment, $R$ is the radius of the non-stenosed region of the artery, $\alpha_{end} = \frac{D - D'}{2}$ and $\beta_{end} = \frac{D + D'}{2}$ are the parameters for lumen constriction, $D' = 0.7D$ is diameter of the artery at the throat of the stenosis, $z_1 = 4D$ is the start point of the stenosed region, and $z_2 = 5D$ is the end point of the stenosed
region. The wall geometry is defined as $r = 0.575D$ with a wall thickness of $0.075D$ at the non-stenosed region and $0.225D$ at the throat of the stenosis.

### 5.3.3.2 Computational details

The single-layered model is applied to simulate albumin transport. The transmural pressure is assumed to be 70 mmHg and the mass transport parameter set ALB70 given in Table 4.3 is employed. To investigate the effects of shear dependent transport parameters, both constant and shear-dependent endothelial hydraulic conductivities ($L_{p,\text{end}}$) and albumin permeabilities ($P_{\text{end,alb}}$) given in Chapter 4 (page 103) are used in the simulations. The simulations using constant and shear-dependent transport parameters will be referred to as cases S2a and S2b, respectively. A fully developed parabolic steady velocity profile with mean velocity $U_0 = 0.24 \text{ m s}^{-1}$ is prescribed at the lumen inlet boundary $\Gamma_{\text{l, in}}$. The resulting Reynolds number $Re = 288$ and Peclet number $Pe = 10,655,000$. The inlet albumin concentration ($c_0$) is assumed to be a normalised value 1. The normalised albumin concentration at the outer wall boundary $\Gamma_{\text{adv}}$ is assumed to be 0.00785 according to Meyer et al. [1996].

The fluid domain ($\Omega_l$) is divided into 19,950 quadrilateral elements with 20,774 nodes and 291,213 quadrilateral elements with 293,820 nodes for solutions of the Navier-stokes equations (Equation 3.5 on page 73) and the convection-diffusion equation (Equation 3.9 on page 74), respectively. While the wall domain ($\Omega_w$) is divided into 7,890 quadrilateral elements with 8,789 nodes and 49,780 quadrilateral elements with 52,290 nodes for solution of Darcy’s Law (Equation 3.7 on page 73) and the convection-diffusion-reaction equation (Equation 3.11 on page 74), respectively.

### 5.3.3.3 Computational results

Cross-sectional profiles of velocity in the axial direction ($v$) upstream of the stenosis ($z = 3D$), in the flow recirculation region ($z = 5.5D$), and downstream of the stenosis ($z = 20D$) are compared in Figure 5.9. It can be seen that at the upstream of the stenosis, flow velocity profile is fully developed and parabolic as prescribed at the inlet. While in the flow recirculation region, reverse flow is present near the arterial wall. At
far downstream of the stenosis, the flow pattern is redeveloped and almost parabolic when compared with the profile at upstream.

![Graph showing cross-sectional profiles of axial velocity](image)

**Figure 5.9:** Cross-sectional profiles of axial velocity in the geometry upstream of the stenosis or $z = 3D$ (solid line), in the flow recirculation region or $z = 5.5D$ (dashed line), and downstream of the stenosis or $z = 20D$ (dotted line). $r/R$ is radial position normalised by the radius of the artery.

Variations of WSS magnitude in the axisymmetric geometry is shown in Figure 5.10. Imposing shear-dependent endothelial hydraulic conductivity has little effect on the near-wall flow field and WSS, due to the fact that the transmural flow is several orders of magnitude smaller than the bulk flow. The two points where WSS values are zero correspond to the separation point ($z = 4.673D$) and reattachment point ($z = 5.865D$) respectively. The area between these two points is the flow recirculation region.

The transmural velocity ($J_{z,\text{end}}$) and trans-endothelial albumin flux ($J_{s,\text{end}}$) profiles in the immediate vicinity of the stenosis in cases S2a and S2b are compared in Figure 5.11. The reduction in transmural velocity at the stenosis in both cases is due to the higher resistance provided by the thickened wall. In case S2b where shear-dependent parameters are employed, the transmural velocity has two minima which correspond to the separation point and the reattachment point, respectively. This is
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Figure 5.10: Magnitude of WSS distribution in the whole axisymmetric geometry (a) and in the vicinity of the stenosis (b).

because, the endothelium, when subject to low WSS, provides a higher resistance to the trans-endothelial plasma transport. Moreover, the transmural velocity is much lower in the post-stenotic region when the shear-dependent hydraulic conductivity is taken into account. This suggests that the transmural flow is extremely sensitive to endothelial resistance, although the endothelium represents only a thin layer of the arterial wall. Similarly, due to a higher resistance (because of an increased thickness) provided by the arterial wall, reduction in the trans-endothelial albumin flux can be observed at the stenosis in both cases. Especially, the dip near the throat of the stenosis in case S2b is far more prominent due to the fact that, the endothelium, when subject to a relatively high WSS, provides a higher resistance to the trans-endothelial albumin transport. In the flow recirculation region, where the magnitude of WSS is low, an increase in \( J_{s,\text{end}} \) can be found, which is induced by a higher endothelial albumin permeability. However, a reduction in trans-endothelial albumin flux can be observed at the separation and reattachment points where the magnitude of WSS is as low as zero. This is mainly attributed to the decrease in the convective flux driven by the transmural flow. Also, because the shear-dependent endothelial albumin permeability is characterised by a dual response (see Figure 4.9 on page 109), it decreases with
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Figure 5.11: Comparison of transmural velocity (a) and trans-endothelial albumin flux (b) in the vicinity of the stenosis given by simulations employing constant (solid line) and shear-dependent (dashed line) endothelial hydraulic conductivity and albumin permeability. $J_{s,end}$ is normalised by a reference flux $N_0 = 1 \times 10^{-9} \text{ m s}^{-1}$.

The endothelial albumin concentration profiles on the lumen and the wall sides for both cases are compared in Figure 5.12. It is shown that the effect of shear-dependent transport parameters on albumin concentration polarisation is minor. However, endothelial albumin concentration on the wall side is significantly different when shear-dependent transport parameters are employed. The distribution pattern of wall side concentration mainly follows that of trans-endothelial albumin flux, showing a lower concentration at the separation point, the reattachment point and the throat of the stenosis but a higher concentration in the recirculation region.

Cross-sectional albumin concentration profiles in the lumen and the wall upstream of the stenosis ($z = 3D$), flow recirculation region ($z = 5.5D$) and far down-
Figure 5.12: Comparison of endothelial albumin concentration on the luminal side (a) and on the wall side (b) in the vicinity of the stenosis given by simulations employing constant (solid line) and shear-dependent (dashed line) endothelial hydraulic conductivity and albumin permeability.

stream of the stenosis ($z = 20D$) for both cases are compared in Figure 5.13. Again, it can be seen that the effects of shear-dependent transport parameters are insignificant to fluid phase transport because the luminal concentration profiles in both cases look identical. Albumin concentration polarisation of different degrees can be observed at all three locations. Especially, in the flow recirculation region, a thicker concentration boundary layer can be identified due to the flow stagnation. Albumin concentration in the wall is very sensitive to shear-dependent transport parameters. In case S2a (see Figure 5.13b), there is no noticeable difference in albumin concentration profiles at the three different locations, which is in agreement with Prosi (2003) who found a nearly homogeneous LDL concentration distribution at the endothelium on the wall side. However, in case S2b, although albumin concentration profiles in the wall are still identical upstream and far downstream of the stenosis, a noticeable elevation in
**Figure 5.13:** Cross-sectional profiles of albumin concentration in the arterial lumen and the wall upstream of the stenosis or $z = 3D$ (solid line), in the flow recirculation region or $z = 5.5D$ (dashed line), and downstream of the stenosis or $z = 20D$ (dotted line) given by simulations employing constant (a) and shear-dependent (b) endothelial hydraulic conductivity and albumin permeability. The radial position in the lumen are normalised by radius of the artery and the radial position in the wall ($\delta_w$) is normalised by the total thickness of the arterial wall ($\Delta_w$).
albumin concentration in the inner layer of the wall can be found in the recirculation region.

### 5.3.4 Cases M1 and M2: LDL transport in an idealised model of a stenosed coronary artery

Besides albumin transport, LDL transport is also investigated in the idealised stenosis model. Both the single-layered and the multi-layered models are employed for the sake of comparison. Two different transmural pressures, i.e. 70 mmHg and 120 mmHg with corresponding parameter sets are used to investigate the effect of hypertension on LDL transport.

#### 5.3.4.1 Computational geometry

The computational geometry is the same axisymmetric stenosis described previously. However, as shown in Figure 5.14, the wall domain is now divided into the intimal and medial layers in the multi-layered formulation.

In this computational geometry, the endothelium is again modelled by Equation (5.4). On the other hand, the IEL which divides the intima and the media is modelled by another cosine expression as follows:

$$
\frac{r_{iel}(z)}{R} = \frac{\alpha_{iel}}{D} \cos \left( \frac{2\pi(z - z_1 - z_2)}{z_2 - z_1} \right) + \frac{\beta_{iel}}{D}
$$

for $4D < z < 5D$, where $r_{iel}(z)$ is the radial positions of IEL at location $z$ in the arterial segment, $R$ is the radius of the lumen in the non-stenosed region, $\alpha_{iel} = 0.14D$ and $\beta_{iel} = 0.865D$ are arbitrarily assigned parameters for intima thickening. The intima-media thickness in non-stenosed and stenosed sections are assumed to be $0.0025D$ and $0.0725D$, respectively.

#### 5.3.4.2 Computational details

Both the single-layered and the multi-layered models are used to simulate LDL transport in the idealised stenosis model, and results are compared to assess the difference between the two models. The transmural pressure is assumed to be 70 mmHg (case
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Figure 5.14: An axisymmetric geometry of a mild stenosed (51\% constriction by area) coronary artery for the multi-layered model. $D = 0.004\ m$ is the diameter of the normal coronary artery, while $D' = 0.7D$ is the diameter of the artery at the throat of the stenosis. $\Omega_l$, $\Omega_i$, and $\Omega_m$ are the lumen, the intima and the media domains, respectively. $\Gamma_{l,\text{in}}$ and $\Gamma_{l,\text{out}}$ denote inlet and outlet of the arterial lumen, respectively. $\Gamma_{\text{end}}$ is the endothelial boundary. $\Gamma_{i,\text{in}}$ and $\Gamma_{i,\text{out}}$ denote sides of the intima. $\Gamma_{\text{iel}}$ is the IEL boundary. $\Gamma_{m,\text{in}}$ and $\Gamma_{m,\text{out}}$ denote sides of the media. $\Gamma_{\text{adv}}$ is the outer wall boundary. The dashed line is the axis of symmetry.

M1) and 120 $mmHg$ (case M2) to investigate the effects of hypertension. Corresponding parameter sets LDL70 and LDL120 given in Table 4.3 are employed. The shear-dependent endothelial hydraulic conductivity ($L_{p,\text{end}}$) given in Chapter 4 (page 103) is also used in the simulations. A fully developed parabolic steady velocity profile with mean velocity $U_0 = 0.24\ ms^{-1}$ is prescribed at the lumen inlet boundary $\Gamma_{l,\text{in}}$. The resulting Reynolds number $Re = 288$ and Peclet number $Pe = 33,484,000$. The inlet LDL concentration ($c_0$) is assumed to be a normalised value 1. The normalised LDL concentration at the outer wall boundary $\Gamma_{\text{adv}}$ is assumed to be 0.00514 and 0.016 for transmural pressures of 70 $mmHg$ and 120 $mmHg$, respectively, according to Meyer et al. (1996).

The fluid domain ($\Omega_i$) is divided into 19,950 quadrilateral elements with 20,774 nodes and 291,213 quadrilateral elements with 293,820 nodes for solutions of the Navier-stokes equations (Equation 3.18 on page 78) and the convection-diffusion
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The intima domain ($\Omega_i$) is divided into 7,890 quadrilateral elements with 8,789 nodes and 49,780 quadrilateral elements with 52,290 nodes for solution of Darcy’s Law (Equation (3.20) on page 78) and the convection-diffusion-reaction equation (Equation (3.26) on page 79), respectively. The media domain ($\Omega_m$) is divided into 7,890 quadrilateral elements with 8,789 nodes and 49,780 quadrilateral elements with 52,290 nodes for solution of Darcy’s Law (Equation (3.22) on page 78) and the convection-diffusion-reaction equation (Equation (3.28) on page 79), respectively.

5.3.4.3 Computational results for case M1

The fluid dynamics in the arterial lumen is simulated under the same conditions as in cases S2a and S2b. Therefore, the velocity and WSS distributions are found to be the same as those shown in Figures 5.9 and 5.10.

Figure 5.15: Comparison of transmural velocity (a), and trans-endothelial LDL flux (b) variations in the stenosis region between the single-layered model (solid line) and the multi-layered model (dashed line) under transmural pressure of 70 mmHg. $J_{s,\text{end}}$ is normalised by a reference flux $N_0 = 1 \times 10^{-9} \text{ m s}^{-1}$. 

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The transmural velocity and trans-endothelial LDL flux profiles in the immediate vicinity of the stenosis predicted by the single-layered and the multi-layered models are compared in Figure 5.15. Besides two minima of transmural velocity corresponding to the separation point and the reattachment point, a lower transmural velocity in the post-stenotic region can be found in both cases. However, local discrepancies exist between the two sets of computational results. This is because the multi-layered model is very sensitive to local geometry, especially in the very thin intimal layer whose thickness varies dramatically near the stenosis. It is also shown that although the trans-endothelial LDL flux given by the single-layered and the multi-layered model are dissimilar locally, the magnitudes of the flux agree well (both between 0.51 and 0.54), suggesting that the consistence of the trans-endothelial flux is ensured. The local differences are caused by the different patterns of transmural flow mentioned above, which drive the convective component of the LDL flux across the endothelium.

![Figure 5.16](image)

**Figure 5.16:** Comparison of LDL concentration in the intima (a) and at medial side of IEL (b) between the single-layered model (solid lines) and the multi-layered model (dashed lines) under transmural pressure of 70 mmHg.
5.3 STEADY FLOW SIMULATIONS

Figure 5.16 shows the averaged LDL concentration in the intima and LDL concentration at the IEL on the medial side. It is shown that the multi-layered model, compared with the single-layered model, generally predicts a higher LDL concentration in the intima but a lower LDL concentration on the medial side of the IEL. The multi-layered model also predicts more marked local accumulation of LDL in the intima at the reattachment point where WSS is zero. In the multi-layered model, the IEL, which is a complex structure consisting of a fenestrated membrane of elastin lined on the intimal side by a fibrous network, is modelled as a membrane which acts as a molecular sieve, across which the convective flux plays an important role. Thus in the post-stenotic region where WSS is low, there are fewer LDL particles passing through the IEL due to a weaker convective driving force, resulting in a higher LDL concentration in the intima and lower LDL concentration in the media. This finding supports the hypothesis that local LDL accumulation in the arterial wall is caused by weaker convective clearance (Tarbell, 2003).

LDL concentration profiles within the wall at different axial locations are shown in Figure 5.17. A similar concentration distribution of LDL in the media can be found by using the single-layered and the multi-layered models, although the multi-layered model predicts much higher intimal LDL concentration. In fact, the intima, which is more porous than the media in structure (Huang and Tarbell, 1997; Huang et al., 1997; Karner et al., 2001), is lumped with the media by assuming constant transport parameters in the single-layered model. In the multi-layered model, the more porous intima is treated individually, resulting in a higher intimal LDL concentration. Furthermore, it can be found that the intimal LDL concentration at the reattachment point is considerably higher than that upstream and downstream of the stenosis, demonstrating the local accumulation of LDL in the low WSS region.

5.3.4.4 Computational results for case M2

A transmural pressure of 120 mmHg, which is relatively high in vivo, is chosen to investigate the effect of hypertension on arterial LDL transport. Given that the transmural flow is several orders of magnitude smaller than the bulk flow, transmural pres-
Figure 5.17: Comparison between LDL concentration profiles given by the single-layered model (solid lines) and the multi-layered model (dashed lines) upstream of the stenosis (a), at the reattachment point (b), and downstream of the stenosis (c) under transmural pressure of 70 mmHg.
sure has very little effect on fluid dynamics in the blood lumen. Thus the velocity and WSS distribution is almost the same as in the case of low transmural pressure.

Figure 5.18: Comparison of LDL concentration in the intima (a) and at medial side of IEL (b) between the single-layered model (solid lines) and the multi-layered model (dashed lines) under transmural pressure of 120 mmHg.

Averaged intimal LDL concentration and LDL concentration at the IEL on the medial side are shown in Figure 5.18 for transmural pressure of 120 mmHg. There are remarkable differences from the results seen with a transmural pressure of 70 mmHg (Fig. 5.16). Firstly, the global concentration of LDL is greatly increased when $\Delta p_w = 120 \text{ mmHg}$ because of the pressure-related variations of transport properties. Secondly, a number of local differences exist. 1) The multi-layered model revealed variations of LDL concentration in the axial direction around the throat of the stenosis. Again, this can be explained by the fact that the multi-layered model is more sensitive to local geometry than the single-layered model in terms of transmural flow. Especially under a higher transmural pressure, where the convective component of the transport process becomes more prominent, the transport process varies with respect
Figure 5.19: Comparison between LDL concentration profiles given by the single-layered model (solid lines) and the multi-layered model (dashed lines) upstream of the stenosis (a), at the reattachment point (b), and downstream of the stenosis (c) under transmural pressure of 120 mmHg.
5.3 STEADY FLOW SIMULATIONS

to the local geometry. 2) Unlike the situation with a transmural pressure of 70 \text{mmHg},
the single-layered model predicts a noticeable peak in intimal concentration of LDL at
the attachment point, because the convective clearance effect becomes more impor-
tant at higher transmural pressure. 3) A local minimum at the reattachment point
in the concentration profiles at the IEL on the medial side can be found with the
multi-layered model when $\Delta p_w = 70 \text{mmHg}$, whereas when $\Delta p_w = 120 \text{mmHg}$,
a local maximum is observed with both the single-layered and the multi-layered mod-
els. The reason for this phenomenon is complicated. That is, in addition to a greater
amount of LDL particles passing through the IEL due to a higher permeability when
$\Delta p_w = 120 \text{mmHg}$, the convective clearance effect in the media is not strong enough
to flush out the accumulation of LDL particles near the IEL, especially at the reattach-
tment point, where transmural flow is minimum.

LDL concentration profiles within the wall at different axial locations are
shown in Figure 5.19. The medial concentration profiles given by the single-layered
and the multi-layered models agree well, and both the single-layered and the multi-
layered models predict a higher intimal concentration at the reattachment point due
to a weaker convective clearance effect there.

5.3.4.5 Concluding remarks on cases M1 and M2

To investigate the effect of hypertension on transmural LDL transport, two different
transmural pressures with corresponding parameter sets are used in the simulations.
A significantly higher intimal LDL concentration (more than 2.5-fold) is found when
$\Delta p_w = 120 \text{mmHg}$ compared with the concentration level at $\Delta p_w = 70 \text{mmHg}$. However, the increase in transmural velocity from the low to the high transmural pres-
sures is relatively small (1.6-fold), which implies that the convection driven by transmu-
ral velocity is not the only prominent pathway for LDL trans-endothelial transport.
In fact, Prosi et al. (2005) pointed out that assuming LDL flux is mainly contributed
by convection leads to a mismatch between numerical prediction and experimental
measurements since the calculated LDL convective flux is two orders of magnitude
lower than the measured trans-endothelial flux. This mismatch indicates that there is
at least one important but unidentified pathway for LDL trans-endothelial transport. To model LDL transport through the unidentified pathway, it is hypothesised that it follows a pseudo-diffusive mechanism whose contribution to trans-endothelial LDL transport is included in the endothelial LDL permeability. This implicitly assumes that the pathway is concentration-dependent. In the present study, a shear-dependent hydraulic conductivity is employed, but the shear-dependence of endothelial LDL permeability is not taken into account. The shear-dependent hydraulic conductivity, which determines the transmural flow, controls the LDL accumulation in the arterial wall through the convective clearance effect of transmural flow, rather than affecting the LDL flux across the endothelium. Therefore, to investigate the shear-dependence of LDL transport across the endothelium and its consequences, one needs to employ a shear-dependent permeability. However, due to a lack of experimental data, this cannot be implemented in the current stage.

To evaluate the single-layered and the multi-layered models and determine their appropriate usage, these two models are compared using two different sets of model parameters. Though the single-layered model is able to predict similar trans-endothelial LDL flux and medial LDL distribution as the multi-layered model, it cannot provide a separate and accurate description of the intima. However, the same tendency of LDL accumulation is found with both models, especially when using the parameter set LDL120. Because the multi-layered model is computationally expensive, it can be suggested that it would be more suitable for theoretical investigation using idealised geometries, whereas the single-layered model is satisfactory for the application to realistic and complicated geometries, when the computational resource is limited.

### 5.4 Pulsatile flow simulations

As mentioned previously, to investigate the effects of pulsatile flow on mass transport of macromolecules is not straightforward since the physical phenomenon characterised by different time-scales need to be considered simultaneously. Therefore, to avoid simulating the bulk blood flow for a prolonged period, the lumen-free cyclic (LFC) and
5.4 PULSATILE FLOW SIMULATIONS

the lumen-free time-averaged (LFTA) computational procedures developed in Chapter 3 are applied to an axisymmetric stenosis modelled within a coronary arterial segment to study the influences of pulsatile flow on LDL transmural transport and examine the validity of a steady flow assumption.

5.4.1 Cases T1 and T2: transmural LDL transport in an idealised model of a stenosed coronary artery

Two test cases are carried out in this section: one employs the LFC procedure (case T1) and the other employs the LFTA procedure (case T2).

5.4.1.1 Computational geometry

The computational geometry used in these two cases are identical to geometry used in cases S2a and S2b. It is an axisymmetric mild stenosis with 51% area constriction shown in Figure 5.20. Two sampling points A and B, at which the temporal concentration profiles are tracked, are marked in the illustration.

Figure 5.20: An axisymmetric geometry of a mild stenosed (51% constriction by area) coronary artery for the single-layered model. $D = 0.004 \text{ m}$ is the diameter of the normal coronary artery, while $D' = 0.7D$ is the diameter of the artery at the throat of the stenosis. $\Omega_l$ and $\Omega_w$ are lumen and wall domains, respectively. $\Gamma_{l,in}$ and $\Gamma_{l,out}$ denote inlet and outlet of the arterial lumen, respectively. $\Gamma_{end}$ is the endothelial boundary. $\Gamma_{w,in}$ and $\Gamma_{w,out}$ denote sides of the arterial wall. $\Gamma_{adv}$ is the outer wall boundary. The dashed line is the axis of symmetry. Sampling points A and B in the arterial wall are marked.
5.4 PULSATILE FLOW SIMULATIONS

5.4.1.2 Computational details

Figure 5.21: Inlet average velocity waveform. $U_0$ is the mean inlet velocity in one cardiac cycle.

The single-layered model is applied to simulate LDL transmural transport. The transmural pressure is assumed to be 120 mmHg and the mass transport parameter set LDL120 given in Table 4.3 is employed. The shear-dependent endothelial hydraulic conductivity ($L_{p,\text{end}}$) given in Chapter 4 (page 103) is used in the simulations. Both the LFC (case T1) and the LFTA (case T2) procedures are used to incorporate the effects of pulsatile blood flow. For transient flow simulations, a sinusoidal waveform shown in Figure 5.21 is used to describe the variation of mean axial velocity at the inlet ($\Gamma_{in,l}$):

$$\bar{u}_{in}(t) = U_0[1 - \cos(\omega t)] \quad (5.6)$$

where $U_0 = 0.24 \text{ m s}^{-1}$ is the time-averaged mean inlet velocity and $\omega = 2\pi$ is the angular frequency with a pulse period of one second. Womersley velocity profiles corresponding to the waveform are calculated and applied at the inlet (Womersley, 1955). The resulting mean Reynolds number $\bar{Re} = 288$. The LDL concentration in the lumen ($c_0$) is assumed to be a normalised value 1. A convective flux condition is assumed at the outer wall boundary $\Gamma_{adv}$. For the initial condition, zero concentration in the arterial wall is assumed.
The fluid domain ($\Omega_l$) is divided into 85,880 quadrilateral elements with 91,027 nodes for solutions of the Navier-stokes equations (Equation (3.5) on page 73). While the wall domain ($\Omega_w$) is divided into 46,320 quadrilateral elements with 46,980 nodes for solution of Darcy’s Law (Equation (3.7) on page 73) and the convection-diffusion-reaction equation (Equation (3.11) on page 74). The time-steps for pulsatile flow simulation and mass transfer transient simulation are set to be $0.01 \, s$ and $0.05 \, s$, respectively.

### 5.4.1.3 Computational results

![Figure 5.22](image)

**Figure 5.22:** Comparisons between (a) steady WSS (solid line) and time-averaged transient WSS (dashed line) and between (b) instantaneous WSS at 25% (solid line), 50% (dashed line), and 75% (dashed dotted line) of the cardiac cycle.

Variations of WSS magnitude in the axial direction of the stenosis model are shown in Figure 5.22. Time-averaged WSS (TAWSS) calculated using transient results in one cycle is compared with WSS calculated assuming steady flow. It is found that the location of the minimum time-averaged WSS is further downstream in the post-stenotic region compared with the steady flow result and the magnitude of time-
averaged WSS is higher. This is because the reattachment point, where WSS becomes zero, moves along the arterial wall in the post-stenotic region when pulsatile flow is considered, which can be clearly observed in Figure 5.22b.

![Graph showing WSS variations](image)

**Figure 5.23:** Variation of LDL concentration profiles at sampling points A and B with time. The solid line is the profile at sampling point A (upstream of the stenosis). The dashed line is the profile at sampling point B (throat of the stenosis).

In the LFC simulation, the initial LDL concentration is assumed to be zero over the whole subdomain. The evolution of LDL concentration at sampling points A and B (as marked in Figure 5.20) is shown in Figure 5.23. It can be clearly seen that after 2 hours, LDL concentration profiles at the two sampling points level off, indicating that the transport of LDL in the wall reaches a quasi steady-state. Comparing the profiles at sampling points A (upstream of the stenosis) and B (throat of the stenosis), it is found that mass balance at point A reaches the quasi steady-state faster than that at point B and the concentration at point A is higher than that at point B. This is because at the throat of the stenosis, the arterial wall is thicker and provides higher resistance to transmural LDL transport. Cross-sectional profiles of LDL concentration upstream of the stenosis at different time points are shown in Figure 5.24. It is observed that the concentration profile upstream of the stenosis develops significantly from 5 minutes to 30 minutes, moderately from 30 minutes to 90 minutes, and very little from 90 minutes.
5.4 PULSATILE FLOW SIMULATIONS

to 150 minutes. A similar observation can be made at the throat of the stenosis, as shown in Figure 5.24b. These results suggest that LDL concentration evolves at a higher rate within the first 30 minutes after the perturbation is imposed. The rate of change will then decay before equilibrium is finally reached at approximately 90 minutes.

Figure 5.24: Cross-sectional profiles of LDL concentration upstream of the stenosis or \( z = 3D \) (a) and at the throat of the stenosis or \( z = 4.5D \) (b) at time points 5 minutes (solid lines), 30 minutes (dashed lines), 90 minutes (dashed dotted lines), and 150 minutes (dotted lines).

In Figure 5.25 subendothelial LDL concentrations along the stenosis given by the LFC simulation are compared with those obtained by LFTA and steady flow simulations. It is obvious that using time-averaged hydraulic conductivity as input data for steady-state LDL transport simulation (LFTA procedure) produces very similar LDL concentration distribution to the time-dependent LDL transport simulation (LFC procedure). However, LDL concentration profile obtained under the steady flow assumption is very different. The steady flow simulation predicts a pronounced peak
in the post-stenotic region and the maximum concentration of LDL co-localises with the reattachment point. This finding is explained by weaker local convective clearance effects of the transmural flow as in steady flow test cases M1 and M2. Specifically, in the low WSS region, where hydraulic conductivity of the endothelium is low and hence endothelial resistance to transmural flow is higher, LDL particles cannot be effectively “flushed” away from the subendothelial layer. The same explanation can be applied to the wider and less marked peaks predicted by LFC and LFTA simulations. Under pulsatile flow conditions, the flow separation zone in the post-stenotic region expands and contracts during a cardiac cycle, resulting in oscillation of the reattachment point along the luminal surface. Thus when the calculated instantaneous WSS is used to simulate transmural LDL transport, LDL distribution induced by low WSS is more diffuse than under steady flow conditions. Likewise, using the time-averaged transport properties calculated based on instantaneous WSS also tends to diffuse the LDL distribution in the post-stenotic region as shown by the LFTA simulation. The good agreement between results from the LFC and LFTA simulations implies that transmural LDL transport responds slowly to changes in WSS arising from pulsatile
flow, and the transport of LDL is more likely to be influenced by the time-averaged physiological environment (Tarbell, 2003).

5.4.2 **Concluding remarks on pulsatile flow simulations**

5.4.2.1 **Time scale of LDL transport: guideline for experiments**

LDL transport in large arteries is subject to continuous perturbations in vivo ranging from local geometrical changes to dietary changes and medications. The long term LDL transmural transport process is modelled using the LFC procedure assumes no perturbation. The results show that LDL transport reaches a quasi steady-state after \(2 \ h\) assuming that there is no LDL in the wall initially and a transmural pressure of \(120 \ mmH\ g\). This result can serve as a guideline for future experimental investigations on transmural LDL transport. However, it should be noted that the simulation represents an idealised environment without any perturbation, which may not be achievable in experiments. It is possible that LDL transport could take longer to reach quasi steady-state if minor perturbations are present. Furthermore, a reduced transmural pressure (e.g. \(70 \ mmH\ g\) as has been used in some experiments [Curmi et al., 1990; Meyer et al., 1996]) will result in a considerably longer time for LDL transport to reach a quasi steady-state. This is because convection, driven by the transmural pressure, is the primary means of LDL transport in the arterial wall.

5.4.2.2 **Effect of lumen-side LDL transport**

In the LFC and the LFTA procedures, luminal LDL transport is not taken into account and a constant LDL concentration is assumed in the arterial lumen. However, elevated macromolecular concentration on the luminal surface has been observed both experimentally [Colton et al., 1972] and computationally [Wada and Karino, 1999]. As seen in test case F1, the degree of concentration polarisation on the luminal surface is maintained at a relatively low level and it can be assumed that omitting such a low level of concentration polarisation would not induce a considerable error in the LFC and LFTA simulations.
5.4 PULSATILE FLOW SIMULATIONS

Figure 5.26: Comparison between LDL concentration distributions at the endothelium on the wall side given by steady flow simulations without (solid line) and with (dashed line) lumenal side transport.

To examine this assumption, endothelial LDL concentration distributions on the wall side given by steady flow simulations with and without lumenal transport taken into account are compared in Figure 5.26. The two simulations are qualitatively very similar in terms of distribution patterns, although LDL concentration is slightly higher when lumenal transport is considered. It should be pointed out that under certain circumstances, for instance, higher transmural velocity and weaker flow-induced clearance, the concentration polarisation may be much severer. Nevertheless, if a high level of concentration polarisation (> 10%) is present in low WSS regions, 1) it would result in a more pronounced elevated LDL concentration in the arterial wall in accord with the present findings qualitatively; 2) a model setup that takes into account the fluid phase transport would improve the quantitative accuracy of the predictions.

5.4.2.3 The average effect of WSS

Long term LDL transport is coupled with fluid dynamics which is characterised by a much smaller time scale. However, most existing mathematical models assumed steady flow which excludes the effect of the pulsatile nature of blood flow. This steady flow
assumption is examined in this section. It is clearly seen that results given by the steady flow model differ considerably from those obtained from the proposed LFC procedure (see Figure 5.25), and cast doubt on the validity of the steady flow assumption.

However, a complete time dependent simulation of blood flow and transmural LDL transport is computationally very demanding. Therefore, the LFTA procedure is used as an alternative. It is demonstrated that there is very little difference between results given by the LFC and the LFTA procedures (also see Fig. 5.25), suggesting that the influence of transient haemodynamic conditions on LDL transport can be modelled as a time-averaged effect. Furthermore, the LFTA procedure requires significantly shorter computational time (1/30) than the LFC procedure as it avoids prolonged transient transport simulations. As an efficient tool to analyse LDL transport, the LFTA procedure can be applied to physiologically realistic geometries for subject-specific studies.

### 5.5 Summary

In this chapter, several test cases with idealised axisymmetric geometries are analysed. Steady flow simulations are firstly carried out. The fluid phase model is used to model LDL trans-lumenal transport and concentration polarisation on the luminal surface in a straight tube. The single-layered model is used to model oxygen and albumin transport in idealised models of the abdominal aortic aneurysm and stenosed coronary arteries, respectively. The multi-layered model is used to model LDL transport in the stenosis model and the results are compared with those given by the single-layered model. Furthermore, two numerical procedures, LFC and LFTA based on the single-layered model are used to carry out pulsatile flow simulations to study LDL transmural transport. These models and numerical procedures, together with the model parameters determined in Chapter 4, show good ability to simulate the arterial mass transport processes. The observations made in these test cases are summarised as follows:

- The degree of concentration polarisation of macromolecules is strongly correlated with the transmural velocity. Therefore, accurate prediction of transmural
velocity is very important to model trans-lumenal macromolecular transport.

- The delivery efficiency of oxygen from the bulk blood flow to the arterial wall is determined by the patterns, for instance, flow recirculation in the lumen leads to inefficient supply of oxygen to the wall. This is because the oxygen transport is limited by the fluid phase.

- Albumin accumulates in the arterial wall in the low WSS regions mainly because the endothelium presents a higher permeability when subject to low WSS.

- LDL accumulates in the arterial wall in the low WSS regions where the endothelium provides more resistance to the transmural flow and causes weaker convective clearance in the arterial wall. This does not necessarily suggest that LDL accumulation in vivo is not induced by a higher endothelial permeability. But to take into account of shear-dependent trans-endothelial LDL transport, more detailed and complete experimental data are needed.

- The single-layered model, although is less accurate than the multi-layered model in terms of both geometrical and physical descriptions, can provide satisfactory predictions on macromolecular transport while using less computational resources.

- The steady flow assumption in arterial mass transport models may not be adequate, especially when the flow characteristics are complex. To consider the flow pulsatility, which is measured in a much smaller time-scale than transmural transport, LFTA procedure can be adopted due to its computational efficiency by taking advantage of the fact that the influence of transient haemodynamic conditions on macromolecular transport can be modelled as a time-averaged effect.
Model Application One: Oxygen Transport in a Human Abdominal Aortic Aneurysm

The abdominal aorta is the largest artery in the abdominal cavity. As part of the aorta, it is a direct continuation of the descending aorta. The abdominal aorta has a lot of branches and supplies blood to much of the abdominal cavity. The normal diameter of the abdominal aorta is around $15 - 20\, mm$ (Brewster et al., 2003). Abdominal aortic aneurysm (AAA), which is a common disease of the abdominal aorta, is a localised dilatation of the abdominal aorta, that exceeds the normal diameter by more than 50% (Lederle, 2003). AAAs are caused by a degenerative process of the aortic wall and normally involve formation of intraluminal thrombus (ILT) (Curci et al., 2001). It is believed that hypoxia plays an important role in AAA progression and rupture (Vorp et al., 2001). Therefore, oxygen transport efficiency is one of the key parameters in the development of AAAs. In this chapter, oxygen transport in a normal human abdom-
inal aorta and an AAA with ILT are investigated using the single-layered model. The mathematical model described in Chapter 3 is modified to allow for special treatments of the thrombus and the endothelium. Oxygen concentration distributions in the normal and aneurysmal cases are compared to elucidate the influence of the intraluminal thrombus. Parametric studies on oxygen diffusivity in the thrombus and adventitial oxygen concentration are also carried out.

6.1 Computational Geometries

The computational geometries used in this chapter are adapted from a previous study on the stress analysis of AAAs carried out by Leung (2006). In this section, the imaging and geometry reconstruction techniques used by Leung (2006) are briefly described.

6.1.1 Medical imaging techniques

The geometries of large arteries and AAAs can be obtained in vivo from medical imaging modalities. Currently, the three main imaging modalities are magnetic resonance imaging (MRI), computer tomography (CT), and ultrasound. The accuracies of these three modalities were found to be comparable: Wolf et al. (2000) compared ultrasound and CT; Haulon et al. (2001) and Lutz et al. (2003) compared CT and MRI; Glor et al. (2003) and Crowe et al. (2005) compared ultrasound and MRI. Each imaging modality has its advantages and disadvantages. Generally speaking, MRI is superior to the other two modalities because it provides relatively good tissue contrast, velocity profiles to study fluid dynamics, gated images to study wall compliance (Boese et al., 2000), and turbo 50 spin echo to study wall distensibility (Crowe et al., 2003). It can also detect certain types of endoleaks that CT cannot (Haulon et al., 2001). However, inconvenience to the volunteers and costs have limited the study to using CT for geometry data. CT scans of the volunteers were carried out by Dr. Andrew Wright at St. Mary’s Hospital, London.
6.1 COMPUTATIONAL GEOMETRIES

6.1.2 Geometry reconstruction

A 2D segmentation technique [Cheong, 2004], of which the accuracy was verified in a phantom study, was improved and applied to reconstruct the geometries by Leung (2006). First of all, the CT images were cropped and filtered to be segmented. Secondly, the images were segmented to extract lumen and thrombus geometries. Finally, the geometries were smoothed to reduce the noise brought by segmentation and stacking. Detailed description of the reconstruction programme can be found in Leung (2006). It should be noted that although the CT images of abdominal aortic bifurcations were also acquired for both subjects, they were not included in the geometry reconstruction process. This is because stress analysis in the aneurysm was the main task in the original work of Leung (2006) and bifurcations needed not to be included. This argument is also valid in the present investigation of oxygen transport. Nevertheless, the same methodology can be applied to study oxygen transport in bifurcations given that the geometries are available.

![Anterior view](image1.png) ![Right view](image2.png) ![Posterior view](image3.png)

**Figure 6.1:** Anterior (left), right (middle), and posterior (right) views of the reconstructed normal human abdominal aorta. Both proximal and distal sides of the aorta are connected to artificial extensions (not shown) with 5-diameter length.

Figure 6.1 shows the lumen geometry of a normal human abdominal aorta. In this case, the lumen inlet diameter is 17.4 mm or 0.0174 m. The length of the origi-
Mathematical Model Revisited

As discussed previously, arterial oxygen transport can be modelled using the single-layered model as the oxygen diffuses relatively easily in the arterial wall. A general form of the single-layered model has been formulated in §3.1. In the case of oxygen
transport, the model can be simplified in various ways. In this section, a simplified single-layered model tailored for modelling of oxygen transport will be given. Furthermore, a trans-thrombus oxygen transport model is formulated and incorporated into the modified single-layered model for the investigation of oxygen transport in the AAA with ILT.

### 6.2.1 The single-layered model for oxygen transport

A general form of the single-layered model for arterial mass transport is given by governing Equations (3.5, 3.7, 3.9, 3.11) together with BCs (3.6, 3.8, 3.10, 3.12) and MCs (3.16, 3.17). To simplify the model by considering the fact that transmural oxygen transport is dominated by passive diffusion, the convection component can be eliminated (assuming zero transmural velocity) in governing Equation (3.11), BCs (3.6c, 3.8b, 3.10c, 3.12b), and MCs (3.16, 3.17). Therefore, a simplified single-layered model for arterial oxygen transport is given below.

**Fluid dynamics in the arterial lumen** ($\Omega_l$) is governed by

\[
\rho \frac{\partial u_l}{\partial t} - \mu \nabla^2 u_l + \rho (u_l \cdot \nabla) u_l + \nabla p_l = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \tag{6.1a}
\]

\[
\nabla u_l = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \tag{6.1b}
\]

with BCs

\[
u_l = u_{l,in} \quad \text{on} \quad \Gamma_{l,in}, \ t > 0 \tag{6.2a}
\]

\[
t_l \cdot u_l = 0, \ n_l \cdot T = -p_{l,out} \quad \text{on} \quad \Gamma_{l,out}, \ t > 0 \tag{6.2b}
\]

\[
t_l \cdot u_l = 0, \ n_l \cdot u_l = 0 \quad \text{on} \quad \Gamma_{end}, \ t > 0 \tag{6.2c}
\]

while **fluid dynamics in the arterial wall** ($\Omega_w$) is omitted.

**Solute dynamics in the arterial lumen** ($\Omega_l$) is governed by

\[
\frac{\partial c_l}{\partial t} + \nabla \cdot (-D_l \nabla c_l + u_l c_l) = 0 \quad \text{in} \quad \Omega_l, \ t > 0 \tag{6.3}
\]
6.2 MATHEMATICAL MODEL REVISITED

with BCs

\[ c_l = c_{l,\text{in}} \quad \text{on} \quad \Gamma_{l,\text{in}}, \quad t > 0 \]  
\[ D_l \nabla c_l \cdot n_l = 0 \quad \text{on} \quad \Gamma_{l,\text{out}}, \quad t > 0 \]  
\[ -D_l \nabla c_l \cdot n_l = J_{l,\text{end}} \quad \text{on} \quad \Gamma_{\text{end}}, \quad t > 0 \]  

while solute dynamics in the arterial wall (\( \Omega_w \)) is governed by

\[ \partial_t c_w + \nabla \cdot (-D_w \nabla c_w) = r_w c_w \quad \text{in} \quad \Omega_w, \quad t > 0 \]  

with BCs

\[ c_w \cdot n_w = 0 \quad \text{on} \quad \Gamma_{w,\text{in}} \cup \Gamma_{w,\text{out}}, \quad t > 0 \]  
\[ -D_w \nabla c_w \cdot n_w = -J_{w,\text{end}} \quad \text{on} \quad \Gamma_{\text{end}}, \quad t > 0 \]  
\[ c_w = c_{\text{adv}} \quad \text{on} \quad \Gamma_{\text{adv}}, \quad t > 0 \]

The matching condition (MC) for solute dynamics at the endothelial boundary (\( \Gamma_{\text{end}} \)) is simply given by

\[ J_{s,\text{end}} = P_{\text{end}} \Delta c_{\text{end}} \]

whereas a matching condition for fluid dynamics is not needed because the fluid dynamics in the arterial wall is omitted.

Compared with the general form of the single-layered model, this model formulation omits convection in the arterial wall and hence fluid dynamics in the arterial wall is not modelled. Specifically, the convection-diffusion-reaction equation given by Equation 3.11, is replaced by a diffusion-reaction equation, Equation 6.5. Moreover, boundary conditions at the endothelial boundary, which is the interface between the arterial lumen and the wall domains, are modified accordingly: BC 3.6c which dictates a transmural velocity in the normal direction, is changed to BC 6.2c, which imposes a no-slip condition; BCs 3.10c, 3.12b which specify the total flux including diffusion and convection, are changed to BCs 6.4c, 6.6b which prescribe the total flux contributed by diffusion only.
6.2.2 Trans-thrombus transport model

Governing Equations (6.1, 6.3, 6.5) together with BCs (6.2, 6.4, 6.6) and MC (6.7) give a single-layered model formulation for arterial oxygen transport. However, to incorporate oxygen transport in the intralumenal thrombus, a trans-thrombus transport model is needed. In order to model trans-thrombus oxygen transport and estimate oxygen transport property in the thrombus, it is essential to understand what an intraluminal thrombus is and how its presence may change the physiological environment \textit{in vivo}.

A thrombus is a blood clot in a blood vessel. In large arteries, the presence of a thrombus can hinder blood flow through the vessel. Whereas in small vessels, blood flow can be completely blocked by a thrombus causing death of tissues. In the context of AAAs, thrombus is a controversial issue because of its conflicting role in the rupture of aneurysms. On one hand, the presence of thrombus has been identified as a risk factor in aneurysm rupture. Vorp et al. (2001) found that thrombus caused local wall weakening and the underlying mechanism was hypoxia. Vorp and Geest (2005) added that hypoxia caused a decrease in collagen synthesis and further degraded the endothelium by attracting macrophages. Kazi et al. (2003) found that the aortic wall adjacent to thrombus exhibited greater degree of apoptosis and contained fewer smooth muscle cells but more macrophages. On the other hand, thrombus is seen as a cushion which protects aortic wall from high stress. A number of studies (Mower et al., 1997; Wang et al., 2002; Thubrikar et al., 2003) found that thrombus can partially relieve the strain on the wall and reduce the likelihood of rupture.

It is believed that wall stress is a key factor in aneurysm rupture. Therefore, to analyse wall stress, mechanical properties of intralumenal thrombus have been tested \textit{ex vivo} by a large number of researchers (Raghavan and Vorp, 2000; Wang et al., 2002; Di Martino and Vorp, 2003). Compared with the well-documented mechanical properties, the mass transport properties have been seldom studied. Hence, it is difficult to estimate mass transport parameters in the thrombus, i.e. oxygen diffusivity in the present study. However, based on the only published data on water permeability of
thrombus (Adolph et al., 1997), a reasonable range of oxygen diffusivity in the thrombus can be inferred. Adolph et al. (1997) found that water permeability of the thrombus was much higher than that of the wall, which makes sense because the thrombus is more porous than the wall. Therefore, it is assumed that the oxygen diffusivity in the thrombus \( (D_t) \) is no less than that in the wall \( (D_w) \) but no greater than that in the plasma \( (D_l) \). Mathematically, that is \( D_w \leq D_t \leq D_l \). In the present study, an arbitrary value \( D_t = (D_l + D_w)/2 \) is chosen and a sensitivity study is carried out later to justify the choice.

Before formulating the trans-thrombus transport model, a number of assumptions need to be made. First of all, it is assumed that there is no significant plasma movement in the thrombus therefore no oxygen convection. Indeed, a thrombus is essentially a blood clot which has a porous structure and should be filled with blood plasma. But due to a lack of driving force, it is speculated that the plasma stays still rather than flows. Secondly, it is assumed that the presence of a thrombus causes or indicates a degree of endothelium dysfunction and thus the endothelium does not impede oxygen transport. This assumption dictates that the concentration drop across the endothelium is zero and oxygen concentration at the lumen-thrombus and thrombus-wall interfaces satisfies the continuity condition. Given these assumptions, oxygen transport in the thrombus domain \( (\Omega_t) \) can be modelled using a simple diffusion equation as follows:

\[
\frac{\partial}{\partial t} c_t + \nabla \cdot (-D_t \nabla c_t) = 0 \quad \text{in} \quad \Omega_t, \quad t > 0 \quad (6.8)
\]

with BCs

\[
c_t \mathbf{n}_t = 0 \quad \text{on} \quad \Gamma_{t,\text{in}} \cup \Gamma_{t,\text{out}}, \quad t > 0 \quad (6.9a)
\]

\[
c_t = c_l \quad \text{on} \quad \Gamma_{\text{l,t}}, \quad t > 0 \quad (6.9b)
\]

\[
c_t = c_w \quad \text{on} \quad \Gamma_{t,w}, \quad t > 0 \quad (6.9c)
\]

where \( \Omega_t \) is the thrombus domain, \( \Gamma_{t,\text{in}} \) and \( \Gamma_{t,\text{out}} \) are the side boundaries of the thrombus domain, \( \Gamma_{\text{l,t}} \) and \( \Gamma_{t,w} \) are the lumen-thrombus boundary and the thrombus-wall boundary, respectively, \( c_t \) is the oxygen concentration in the thrombus, \( D_t \) is the effective oxygen diffusivity in the thrombus. Equation (6.8) together with Equations
6.3 COMPUTATIONAL DETAILS

(6.1) (6.3) (6.5) give the mathematical model for oxygen transport in AAA with ILT. Furthermore, for mass transport in the lumen and the wall, BCs (6.4c) (6.6b) given previously are modified to match the continuity condition and MC (6.7) is abandoned. A schematic diagram of this model formulation is shown in Figure 6.3.

![Diagram of the model formulation](image)

**Figure 6.3:** A schematic diagram of the model formulation with a modified single-layered model and a trans-thrombus transport model.

6.3 Computational Details

The modified single-layered oxygen transport model is applied to model oxygen transport in the normal abdominal aorta shown in Figure 6.1. While the modified single-layered model integrated with the trans-thrombus transport model is applied to model oxygen transport in the AAA with ILT shown in Figure 6.2. In both cases, mass transport parameter set OXY given in Table 4.3 is employed. As mentioned previously, inlet and outlet extensions are added to minimise the effects of boundary conditions in flow simulations. However, since the mass transport simulations require refined meshes, especially near the lumenal surface, it is unrealistic to include the extensions in the mass transport simulations. Therefore, oxygen transport is only simulated in the original geometry without inlet and outlet extensions to alleviate the computational burden.

The blood flow is assumed to be steady and laminar. Although the steady flow assumption is not physiological realistic, oxygen transport is a much slower process and therefore the flow can be approximated to be steady as an average condition.
6.3 COMPUTATIONAL DETAILS

6.3.1 Input data for both cases

The lumen inlet diameters of the control case and the AAA case are 17.4 mm and 16.0 mm, respectively. Therefore, mean inlet velocities are set to be $U_0 = 0.138 \, m \, s^{-1}$ and $U_0 = 0.15 \, m \, s^{-1}$ for the control case and the AAA case, respectively, to ensure that the Reynolds number, $Re = 720$, is the same in both cases. The resulting Peclet number $Pe = 1,512,000$. The inlet oxygen concentration ($c_0$) is assumed to be a normalised value 1. The oxygen concentration at the outer wall boundary $\Gamma_{adv}$ is assumed to be 0.61 (Buerk and Goldstick, 1982).

6.3.2 Computational mesh for the control case

For the control case, the fluid domain is divided into 76,384 hexahedral elements (including extensions) with 81,627 nodes and 38,192 second order hexahedral elements (excluding extensions) with 314,081 nodes for solutions of the Navier-stokes equations (Equation (6.1) on page 154) and the convection-diffusion equation (Equation (6.3) on page 154), respectively. While the wall domain ($\Omega_w$) is divided into 49,280 hexahedral elements with 52,920 nodes for solution of the diffusion-reaction equation (Equation (6.5) on page 155).

6.3.3 Computational mesh for the AAA case

For the AAA case, the fluid domain is divided into 40,660 hexahedral elements (including extensions) with 43,308 nodes and 20,520 second order hexahedral elements (excluding extensions) with 170,149 nodes for solutions of the Navier-stokes equations (Equation (6.1) on page 154) and the convection-diffusion equation (Equation (6.3) on page 154), respectively. The thrombus domain ($\Omega_t$) is divided into 19,440 hexahedral elements with 22,000 nodes for solution of the diffusion equation (Equation (6.8) on page 157). The wall domain ($\Omega_w$) is divided into 21,600 hexahedral elements with 24,200 nodes for solution of the diffusion-reaction equation (Equation (6.5) on page 155).
6.4 Computational Results

In this section, computational results for the control case and the AAA case are presented and compared to elucidate the effect of ILT on oxygen transport. The results in the first subject (control case) are used as a reference to evaluate the results in the second subject (AAA case).

6.4.1 The control case

6.4.1.1 Flow and WSS patterns

The flow pattern in the first subject (the normal abdominal aorta) is shown in Figure 6.4. From the streamline plot, it can be seen that the flow pattern in the normal abdominal aorta is relatively regular without much disturbance. However, on the distal side of the aorta, near the outlet, an eccentric flow profile can be found. This is because the flow is driven to the left due to the local curvature of the aorta. The distribution of WSS magnitude ($|\tau_w|$) is shown in Figure 6.5. It is observed that WSS is predominantly lower than 1 Pa in the aorta which is consistent with the analysis carried out by Cheong (2004). At the distal part of the aorta, a low WSS region can be found on
6.4 COMPUTATIONAL RESULTS

Figure 6.5: Anterior (left), right (middle), and posterior (right) views of WSS magnitude ($|\tau_w|$) distribution in the normal human abdominal aorta. The right side and a high WSS region can be found on the left side. This is because the flow is driven by the curvature from the right to the left, yielding a higher velocity gradient on the left and a lower velocity gradient on the right. Another hotspot of WSS is found in the posterior view in the middle of the aorta. This is again caused by local geometrical variations.

6.4.1.2 Oxygen concentration distribution

Oxygen concentration distribution at the endothelium on the lumen side is shown in Figure 6.6. It is found that oxygen concentration varies in a wide range on the luminal surface. There are two factors that may cause these variations: 1) the concentration boundary layer development; and 2) the differences in flow patterns.

The influence of the first factor can be clearly identified, in general, oxygen concentration in the proximal part of the aorta is higher than that in the distal part of the aorta because oxygen is continuously uptaken by the aortic wall along the luminal surface. However, this effect on concentration variations is thought to be less prominent when flow is pulsatile. Pulsatile flow enhances the mixing of blood and disturbs (or re-initiate) the concentration boundary layer to minimise the concentration variations due to the boundary layer development (Tada and Tarbell, 2006).
influences of the second factor is not trivial as an obvious correlation between WSS and oxygen concentration on the luminal surface can be seen: regions of low WSS co-localise with low oxygen concentration and vice versa. It should be noted that this strong correlation is not caused by WSS itself since no shear-dependent parameter is employed. As a matter of fact, WSS, to some extent, is a measure of flow patterns, and it is the flow patterns which induce the correlation via convection. It has been pointed out that oxygen transport in the arterial lumen is dominated by convection by many researchers [Rappitsch and Perktold, 1996a; Qiu and Tarbell, 2000; Tarbell, 2003]. The present study further confirms this argument.

Oxygen concentration distribution at the endothelium on the wall side is shown in Figure 6.7. No obvious differences from oxygen concentration distribution at the endothelium on the lumen side can be seen. This is because the endothelium only provides minor or negligible resistance to oxygen transport. Low oxygen concentration at the endothelium on the wall side implies a certain degree of hypoxia. For instance, in the distal part of the aorta where the blood flow is driven to the left, normalised oxygen concentration is lower than 0.2 on the right, indicating a degree of hypoxia. This low concentration is caused by an insufficient supply from the fluid
6.4 COMPUTATIONAL RESULTS

Figure 6.7: Anterior (left), right (middle), and posterior (right) views of normalised oxygen concentration distribution at the endothelium on the wall side ($c_{\text{end.},w}/c_0$) in the normal human abdominal aorta.

phase. As discussed above, this concentration may be underestimated due to the steady flow assumption. Therefore, this region of arterial wall might not be subject to the observed degree of hypoxia in vivo.

6.4.2 The AAA case

6.4.2.1 Flow and WSS patterns

The flow pattern in the second subject (the AAA case) is shown in Figure 6.8. It is observed that the flow is driven to the posterior side of the expansion. This is due to a curvature associated with the constriction at the proximal side of the AAA (refer to Figure 6.2). This geometrical feature also results in a highly disturbed and swirling flow pattern on the anterior side of the expansion, which can be clearly seen in the streamline plot.

The distribution of WSS magnitude ($|\tau_w|$) in the AAA is shown in Figure 6.9. Generally speaking, WSS is higher in this geometry than in the control case. Specifically, at the distal side of the AAA, WSS is predominantly higher than 1 Pa. This is because the intraluminal thrombus occupies a large space and constricts the lumen,
6.4 COMPUTATIONAL RESULTS

Figure 6.8: The flow pattern in the human AAA: velocity contours along the axial direction (left) and streamlines (right).

Figure 6.9: Anterior (left) and posterior (right) views of WSS magnitude (|τ_w|) distribution in the human AAA.
leading to an acceleration of the blood flow and an increase in WSS. There are three main regions of low WSS: 1) anterior-proximal region; 2) anterior recirculation region; and 3) left-distal region. Low WSS in regions 1 and 3 is caused by local curvatures of the geometry. Low WSS in region 2 is mainly due to the expansion of the AAA.

6.4.2.2 Oxygen concentration distribution

Oxygen concentration distribution in the AAA at the lumen-thrombus interface is shown in Figure 6.10. Unlike the control case, normalised oxygen concentration varies in a small range. It has been argued that the significant variations in oxygen concentration on the lumenal surface in the control case are the results of two factors, concentration boundary layer development and varying flow patterns. To explain the minor variations in oxygen concentration on the lumenal surface in the AAA case, these two factors are again analysed. First of all, the first factor behaves differently in these two cases: although the boundary layer thickness should be similar in both cases (because the Schmidt numbers are the same), the rate of change in oxygen concentration along the lumenal surface is much lower in the AAA case because the wall is not in direct contact with the lumen when a thrombus is present. The overall driving force of oxy-
gen transport is roughly the same in both cases because the same lumenal inlet and adventitial concentrations are prescribed. Therefore, much of the driving force in the AAA case contributes to overcome the additional resistance provided by the intraluminal thrombus. Furthermore, by comparing Figures 6.9 and 6.10, a co-localisation between low WSS and low oxygen concentration can be found, indicating that the influence of the second factor is the same in the two cases. To sum up, the observation of a rather homogeneous and high oxygen concentration distribution on the luminal surface can be attributed to the fact that the thrombus provides additional resistances to oxygen transport and causes a lower oxygen efflux from the lumen.

![Figure 6.11: Anterior (left) and posterior (right) views of normalised oxygen concentration distribution at the thrombus-wall interface ($c_{t,w}/c_0$) in the human AAA.](image)

Oxygen concentration distribution in the AAA at the thrombus-wall interface is shown in Figure 6.11. This concentration is equivalent to the concentration at the endothelium on the wall side in the control case. It is seen that normalised oxygen concentration is mostly lower than 0.1 at the thrombus-wall interface compared with higher than 0.9 at the lumen-thrombus interface. This comparison indicates that the oxygen concentration drop across the thrombus is almost 80% of the luminal concentration and supports the earlier speculation that most of the driving force for oxygen transport is “consumed” by the thrombus. The low oxygen concentration also implies that a large area of the aortic wall is subject to a certain degree of hypoxia.
6.4 COMPUTATIONAL RESULTS

Figure 6.12: Anterior (left) and posterior (right) views of thrombus thickness ($\delta_t$) distribution in the human abdominal aortic aneurysm. The thickness is projected at the thrombus-wall interface.

Figure 6.12 shows thrombus thickness distribution (projected on the thrombus-wall interface) in the AAA. The thickness at a point (denoted by A) on the thrombus-wall interface is calculated as the distance from the point A to a point B which is the closest to the point A and on the lumen-thrombus interface. It can be clearly seen that the thrombus is thicker than 5 mm in most parts of the AAA and is the thickest in the anterior-distal part with a thickness above 20 mm. A strong correlation between oxygen concentration at the thrombus-wall interface and thrombus thickness can be identified by comparing Figures 6.11 and 6.12: the thicker the thrombus, the lower the oxygen concentration. To illustrate this correlation clearly, 648 random points are selected from the thrombus-wall interface at which oxygen concentration is plotted against thrombus thickness in Figure 6.13. It is suggested that a thin thrombus ($\delta_t \leq 5 \text{ mm}$) can significantly impede oxygen transport from the arterial lumen to the wall and hence considerably reduces oxygen concentration in the inner layer of the wall. However, further thickening of the thrombus has minor influence on oxygen concentration distribution. As shown in Figure 6.14, cross-sectional oxygen wall concentration profiles at two locations with thrombus thicknesses of 6 mm and 20.6 mm are very similar, with the highest value at the media-adventitia interface and the low-
Figure 6.13: Normalised oxygen concentration against thrombus thickness at 648 randomly selected points at the thrombus-wall interface.

Figure 6.14: Cross-sectional profiles of normalised oxygen concentration at three different locations with thrombus thicknesses of 0.7 mm (solid line), 6 mm (dashed line) and 20.6 mm (dashed dotted line).
est value near the thrombus-wall interface; however, wall concentration at a location with thrombus thickness of 0.7 \( \text{mm} \) is much higher and the lowest value appears in the media, indicating an appreciable inward oxygen flux across the thrombus-wall interface. This phenomenon can be interpreted as follows: if oxygen supply to the inner wall layers is divided into two portions contributed by the arterial lumen and the vasa vasorum, when there is no thrombus or the thrombus thickness is much lower than a critical level, the portion from the arterial lumen is significant; and when the thrombus thickness is greater than a critical level, the portion from the vasa vasorum is dominating and the supply from the arterial lumen is insignificant. Unfortunately, oxygen supplied by the vasa vasorum can hardly “penetrate” the outer wall layers to the inner layer, resulting in a very low oxygen concentration observed in Figure 6.11.

6.4.2.3 Parametric studies on oxygen diffusivity in the thrombus and the adventitial oxygen concentration

As mentioned previously, oxygen diffusivity in the thrombus is hard to determine due to a lack of experimental data. It is assumed that oxygen diffuses more easily in the blood lumen and with greater difficulty in the wall than in the thrombus, or \( D_w \leq D_t \leq D_l \). In the present study, \( D_t = (D_l + D_w) / 2 \) is used as a nominal value. To assess the validity of this arbitrarily chosen value, sensitivity studies are carried out on oxygen diffusivity in the thrombus \( (D_t) \). Furthermore, to investigate the importance of oxygen supplied by the vasa vasorum, sensitivity studies are also carried out on oxygen concentration in the adventitia \( (c_{adv}) \).

The sensitivity studies aim to investigate the influences of parameter variations on certain unknowns. In this case, the parameters are \( D_t \) and \( c_{adv} \), while the unknowns are chosen to be volume-averaged oxygen concentrations in the thrombus and the wall. These volume-averaged concentrations are calculated as follows

\[
\bar{c}_t = \frac{\int_V c_t \, dV}{\int_V dV} \quad (6.10)
\]

\[
\bar{c}_w = \frac{\int_V c_w \, dV}{\int_V dV} \quad (6.11)
\]
Table 6.1: Normalised volume-averaged oxygen concentrations (in percentage) in the intraluminal thrombus ($\overline{c}_t/c_0$) and the aortic wall ($\overline{c}_w/c_0$) calculated using different combinations of oxygen diffusivity in the thrombus ($D_t$) and adventitial oxygen concentration ($c_{adv}/c_0$). The simulated results are compared with experimental data reported by Vorp et al. (2001) shown in the last row.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Parameter sets</th>
<th>$\overline{c}_t/c_0$</th>
<th>$\overline{c}_w/c_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC1</td>
<td>$c_{adv}/c_0 = 0.61$, $D_t = (D_l + D_w)/2$</td>
<td>35.85%</td>
<td>19.33%</td>
</tr>
<tr>
<td>PSC2</td>
<td>$c_{adv}/c_0 = 0.61$, $D_t = D_l$</td>
<td>36.00%</td>
<td>19.58%</td>
</tr>
<tr>
<td>PSC3</td>
<td>$c_{adv}/c_0 = 0.61$, $D_t = D_w$</td>
<td>35.82%</td>
<td>19.16%</td>
</tr>
<tr>
<td>PSC4</td>
<td>$c_{adv}/c_0 = 0.4$, $D_t = (D_l + D_w)/2$</td>
<td>34.82%</td>
<td>19.92%</td>
</tr>
<tr>
<td>PSC5</td>
<td>$c_{adv}/c_0 = 0.2$, $D_t = (D_l + D_w)/2$</td>
<td>33.91%</td>
<td>6.82%</td>
</tr>
<tr>
<td>EXP</td>
<td>Vorp et al. (2001)</td>
<td>39% ± 10%</td>
<td>18% ± 9%</td>
</tr>
</tbody>
</table>

where $c_t$ and $c_w$ are oxygen concentrations in the thrombus and the wall, respectively. Besides the nominal combination (case PSC1), $c_{adv}/c_0 = 0.61$ and $D_t = (D_l + D_w)/2$, another four combinations are tested: the nominal adventitial concentration with a higher oxygen diffusivity in the thrombus (case PSC2), the nominal adventitial concentration with a lower oxygen diffusivity in the thrombus (case PSC3), a lower adventitial concentration with the nominal oxygen diffusivity in the thrombus (case PSC4), and an even lower adventitial concentration with the nominal oxygen diffusivity in the thrombus (case PSC5). The resulting volume-averaged oxygen concentrations in the thrombus and the wall using these five different parameters combinations are summarised in Table 6.1.

By comparing results in cases PCS1, PCS2 and PCS3, it is found that when varying the oxygen diffusivity in the thrombus between $D_w$ and $D_l$, oxygen concentrations in the thrombus and in the wall do not change significantly, indicating that the current selected value of $D_t$ does not induce major errors in the results. The difference between oxygen diffusivities in the blood plasma and the wall is relatively small (around 50% of $D_w$) and $D_t$ is “locked” in a small range based on the assumption that
$D_w \leq D_t \leq D_l$. Therefore, oxygen concentrations in the thrombus and the wall are not sensitive to oxygen diffusivity in the thrombus in its feasible range. On the other hand, by comparing cases PCS1, PCS4 and PCS5, it is found that oxygen concentration in the thrombus is not sensitive to adventitial oxygen concentration but oxygen concentration in the wall is. As discussed previously, oxygen supply to the wall can be divided into two portions, one from the blood lumen, the other from the vasa vasorum. The significant decreases in $\bar{c}_w$ observed under low adventitial oxygen concentration conditions suggest that oxygen supplied by the vasa vasorum to the arterial wall is at least comparable to oxygen supplied by the blood lumen. Therefore, it is reasonable to speculate that the functionalities of outer wall layers are mainly maintained by oxygen supply from the vasa vasorum while that of inner wall layers are mainly maintained by oxygen supply from the blood lumen.

Vorp et al. (2001) measured oxygen tensions in the aortic wall and the thrombus of AAA patients with ILT of 4 mm or greater thickness during surgery. The authors normalised each measured oxygen tension with lumenal oxygen tension of the same patient. Their data are given in the last row of Table 6.1 for comparison. It is noted that oxygen tensions are measured at the mid-points of the thrombus and arbitrary points in the wall. Although the experimental methodology brings uncertainties in comparison of wall concentrations, the mid-point thrombus measurements should be very close to volume-averaged concentrations in the thrombus. By comparing the nominal case PSC1 and the experimental data EXP, it is found that the present model with the chosen parameters can predict oxygen concentrations in the thrombus and in the wall with a good accuracy.

### 6.5 Summary

In this chapter, oxygen transport in two subject-specific geometries, i.e. a normal human abdominal aorta and a human abdominal aortic aneurysm with an intralumenal thrombus, is simulated. A trans-thrombus oxygen transport model is proposed and incorporated into a modified single-layered model. By analysing the results in these
two cases, it is found that:

- Oxygen concentration distribution in the blood lumen is closely correlated to the flow patterns. A co-localisation between low WSS and low oxygen concentration on the lumenal surface is found.

- The presence of an intraluminal thrombus largely impedes oxygen transport from the aortic lumen to the aortic wall. The oxygen supply from the lumen to the wall is almost cut off when the thickness of the thrombus is greater than a critical value.

- Oxygen concentrations in the thrombus and the wall are not sensitive to the value of oxygen diffusivity in the thrombus within its feasible range. While oxygen concentration in the wall is sensitive to adventitial oxygen concentration, suggesting that the vasa vasorum contributes considerably to total oxygen supply to the aortic wall.
Model Application Two:
Macromolecular Transport in a Human Right Coronary Artery

The right coronary artery (RCA) originates above the right cusp of the aortic valve. It travels down the right atrioventricular groove, towards the crux of the heart. The coronary artery supplies the myocardium with oxygen and nutrients. As a large-medium size artery, the diameter of the RCA is normally around $3 - 4 \text{ mm}$. Coronary artery disease (CAD) is a result of the accumulation of atheromatous plaques in the arterial wall. After decades of progression, some plaques may rupture and start limiting blood flow to the heart muscle. This will eventually cause a heart attack. Since the first step of plaque formation and atherogenic progression is the accumulation of macromolecules, especially lipoproteins, mass transport of LDL and albumin is investigated in a human RCA in this chapter. Specifically, the single-layered model is combined with shear-dependent models for endothelial hydraulic conductivity and albumin permeability.
7.1 Computational Geometry

The LFTA procedure is used to incorporate pulsatile flow simulations to investigate the influence of pulsatility on macromolecular transport in the anatomically realistic geometries.

7.1 Computational Geometry

The computational geometry of the RCA used in this chapter is adapted from a study on coronary haemodynamics carried out by Torii et al. (2007a).

The RCA of a patient was scanned using CT by Dr. Andrew Wright at St. Mary’s Hospital, London. The patient was a 51-year-old male who had a clinically identified stenosis in his RCA. The images were acquired at 75% of the cardiac cycle. The RCA geometry was reconstructed based on CT images employing an image segmentation software, CMRtools (CVIS, London, UK) by Dr. Andrew Dowsey. The images were first loaded into CMRtools and the vascular centreline was extracted. Images were then segmented in cross-sections perpendicular to the centreline. Using the delineated cross-sectional contours, the lumenal surface was constructed with cubic B-splines.

Figure 7.1 shows epicardial side, medial plane and pericardial side of the lumen geometry of the RCA. The lumen inlet diameter of the RCA is 3.8 mm or 0.0038 m. The length of the original RCA segment is about 75 mm or 0.075 m (around 20-diameter). Two local constrictions can be identified in this geometry, one near the proximal end, the other in the middle of the segment. The intima-media thickness cannot be resolved by CT, and is assumed to be 300 µm throughout the whole segment. The wall domain is generated by extruding the lumenal surface in the normal direction by the defined wall thickness. For ease of applying boundary conditions in the flow simulations, straight 5-diameter extensions are added at the inlet and the outlet of the RCA lumen geometry. The end of the inlet extension is designed to be circular so that the corresponding fully-developed velocity profiles could be approximated.

*The study complied with Declaration of Helsinki and was approved by the St. Mary’s Hospital Research Ethics Committee. The patients gave written, informed consent.
Figure 7.1: Epicardial side (top), medial plane (middle), and pericardial side (bottom) of the reconstructed human RCA lumenal geometry. The flow direction is indicated in the middle panel. Both proximal and distal sides of the artery are connected to artificial extensions (not shown) with 5-diameter length.

The single-layered model is applied to simulate LDL and albumin transport in the human RCA shown in Figure 7.1. Similar to the cases in Chapter 6, inlet and outlet extensions are added to minimise the effects of boundary conditions in flow simulations but mass transport simulations are only carried out in the original geometry without extensions to reduce the computational burden. The lumen-free time-averaged (LFTA) procedure proposed in Chapter 3 has been proved to be a good alternative to fully fluid-wall coupled transient mass transfer simulations for a prolonged time span in Chapter 5. Therefore, to investigate the effects of pulsatile flow in the RCA, both steady flow and LFTA simulations are carried out for the sake of comparison.
7.2 COMPUTATIONAL DETAILS

7.2.1 Input data

For pulsatile blood flow simulations in the LFTA procedure, a realistic coronary velocity waveform (see Figure 7.2) obtained by Dr. Nearchos Hadjiloizou using an ECG gated catheter delivered ultrasound Doppler probe (ComboWire, Volcano Co., USA) in a different patient is prescribed and the corresponding Womersley velocity profiles \cite{Womersley1955} are applied at the inlet. Although this was a different patient, he/she also suffered from a coronary stenosis and the waveform should be representative to a certain extent. The temporal mean velocity of the waveform $U_0 = 0.1613 \, \text{m/s}$. Because the lumen inlet diameter is $3.8 \, \text{mm}$, the resulting mean Reynolds number $Re = 184$. In steady flow simulations, fully-developed parabolic profile is applied at the inlet with $U_0 = 0.1613 \, \text{m/s}$, and the resulting Reynolds number $Re = 184$. Therefore, the consistence in flow conditions between steady and pulsatile flow simulations is ensured. Given the Reynolds number, Peclet number in the lumen can be calculated as $Pe = 21,393,000$ for LDL transport and $Pe = 6,807,000$ for albumin transport.

For LDL transport, the transmural pressure is assumed to be $120 \, \text{mmHg}$ and corresponding parameter set LDL120 given in Table 4.3 is used. For albumin trans-
7.3 COMPUTATIONAL RESULTS

In this section, the computational results on fluid dynamics, LDL transport and albumin transport in the human RCA are presented. Steady flow and LFTA results are compared to evaluate the influence of pulsatile flow on macromolecular transport.

7.3.1 Fluid dynamics

Two sets of fluid dynamics simulations, both include a steady flow simulation and a pulsatile flow simulation, are carried out because two different transmural pressures...
are assumed for LDL and albumin transport. However, the transmural pressure does not affect the bulk blood flow to a noticeable level since the transmural velocity is several orders of magnitude smaller than the bulk blood flow.

### 7.3.1.1 Bulk blood flow

Figure 7.3 shows magnitudes of velocity and WSS distributions calculated from steady flow and LFTA simulations in the RCA. In Figure 7.3a, steady velocity contours and WSS distribution on the epicardial side of the RCA are shown. From the velocity contours, it is clearly seen that blood flow is driven towards the pericardial side of the RCA due to the continuous curvature associated with the “C” shape of the geometry. Also, flow separation is observed downstream of the stenosis near the proximal end of the RCA. From the WSS distribution, three main low WSS regions can be found: immediate downstream of the stenosis near the proximal end of the RCA, immediate downstream of the stenosis in the middle of the RCA, and in an expansion near the distal end of the RCA.

In Figure 7.3b-f, velocity contours and WSS distributions on the epicardial side of the RCA at different time steps in the pulsatile flow simulation are shown. Similar to the case of steady flow simulation, the velocity contours for all time steps show that the flow is skewed to the pericardial side of the RCA due to the primary curvature. Furthermore, it is clearly seen that the areas of low WSS are not static during one cardiac cycle, indicating that the flow recirculation regions expand and contract according to the inlet velocity. For instance, at the end of flow acceleration periods, as shown in Figure 7.3b and Figure 7.3f, the low WSS region in the expansion near the distal end splits into two disjoint subregions; while in flow deceleration periods, as shown in Figure 7.3c-e, these two subregions merge. Similar but even more complex distribution patterns at different time steps can be observed in the low WSS region downstream of the stenosis near the proximal end of the RCA.

Contours of WSS magnitude for steady flow and time-averaged WSS (TAWSS) for pulsatile flow are shown on the epicardial and pericardial sides of the RCA in Figure 7.4. Low WSS can be identified in three regions in both sets of results: downstream of
Figure 7.3: Distributions of velocity and WSS magnitude calculated from the steady flow (a) and LFTA simulations at different time steps (b-f) in the RCA. E and P stand for epicardial and pericardial sides, respectively.
7.3 COMPUTATIONAL RESULTS

Figure 7.4: Distribution of WSS magnitude calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA. Three main low WSS regions can be identified and are labelled region 1 (downstream of the main stenosis in the proximal part), region 2 (downstream of a second stenosis in the middle of the RCA), and region 3 (in the expansion at the distal end of the RCA).

the stenosis in the proximal part (region 1 labelled in the figure), downstream of the second stenosis in the middle of the segment (region 2), and in the expansion at the distal end of the RCA (region 3). However, minor differences can be seen between the steady flow results and the pulsatile flow results. First of all, the magnitude of steady WSS is lower than that of TAWSS in low shear stress regions. Secondly, the low WSS regions in the steady flow results are slightly smaller than those in the pulsatile flow results. These differences could be attributed to the fact that the flow recirculation regions are contracting and expanding with the reattachment points oscillating along the luminal surface under the pulsatile flow conditions.
7.3 COMPUTATIONAL RESULTS

Figure 7.5: Distribution of endothelial hydraulic conductivity calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA.

7.3.1.2 Transmural flow

Based on the magnitudes of steady WSS, shear-dependent endothelial hydraulic conductivity ($L_{p,\text{end}}$) is calculated using Equation (4.10) for steady flow simulations and is shown in Figure 7.5a. Similarly, time-averaged shear-dependent hydraulic conductivity is calculated for LFTA simulations and is shown in Figure 7.5b. It is found that $L_{p,\text{end}}$ distribution patterns are very similar to that of WSS. Three main low $L_{p,\text{end}}$ regions can be identified. By comparing the steady and LFTA cases, it can be seen that the distribution in the LFTA results is more diffuse: the magnitude of $L_{p,\text{end}}$ in the low WSS regions is generally lower in the steady flow results than in the LFTA results; the low $L_{p,\text{end}}$ regions are also noticeably smaller in steady flow results than in LFTA results. This is because the nonlinearity of the shear-dependent relation “magnifies” the difference which cannot be easily identified in WSS distributions.

Using the calculated shear-dependent hydraulic conductivities, transmural flows
under two different transmural pressures are simulated. The calculated transmural velocities \( J_{v,\text{end}} \) when \( \Delta p = 120 \text{ mmHg} \) are shown in Figure 7.6 for steady flow and LFTA results. It is found that endothelial hydraulic conductivity has a strong influence on transmural velocity: in the low \( L_{p,\text{end}} \) regions, \( J_{v,\text{end}} \) is considerably lower than that in other regions, indicating that the endothelium contributes significantly to the overall resistance to transmural flow. In addition, highly localised minimum transmural velocity can be observed in the steady flow results but not in the LFTA results. This is due to the fact that the minimum \( L_{p,\text{end}} \) is lower in the steady flow results than in the LFTA results. The predicted value of \( J_{v,\text{end}} \) is generally in the range between \( 2.0 \times 10^{-5} \text{ m s}^{-1} \) and \( 3.5 \times 10^{-5} \text{ m s}^{-1} \), which is consistent with experimental data on filtration velocity under transmural pressure of 120 mmHg reported by Meyer et al. (1996).

Figure 7.6: Distribution of transmural velocity \( (\Delta p = 120 \text{ mmHg}) \) calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA.

Transmural velocities when \( \Delta p = 70 \text{ mmHg} \) are computed and shown in Figure 7.7. Similar to the case when \( \Delta p = 120 \text{ mmHg} \), the transmural velocity is
7.3 COMPUTATIONAL RESULTS

Figure 7.7: Distribution of transmural velocity ($\Delta p = 70 \text{ mmHg}$) calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA.

closely correlated to the shear-dependent endothelial hydraulic conductivity: 1) low transmural velocity can be found in the low $L_{p, end}$ regions; 2) highly localised minimum transmural velocity can be observed in the steady flow results but not in the LFTA results. Due to the reduced driving force, the predicted value of $J_{v, end}$ is in the range between $1.0 \times 10^{-8} \text{ m s}^{-1}$ and $2.0 \times 10^{-8} \text{ m s}^{-1}$, which is also in accordance with data reported by Meyer et al. (1996).

7.3.1.3 Summary

From the computational results on fluid dynamics, co-localisations among low WSS, low endothelial hydraulic conductivity, and low transmural velocity are found in both steady flow and LFTA results. The reasoning of these co-localisations is given as follows: 1) the endothelium subject to low WSS presents a lower hydraulic conductivity; 2) a lower endothelial hydraulic conductivity leads to a higher resistance to the transmural plasma transport; 3) a higher resistance to the transmural flow results in a lower
transmural velocity.

It is also found that minimum WSS in the steady flow results is lower than that in the LFTA results because the flow recirculation regions are expanding and contracting continuously in the pulsatile flow simulation. Therefore, taking the time-averaged value of instantaneous WSS tends to give a diffuse distribution pattern characterised by a higher minimum WSS and a wider low WSS region. The distributions of endothelial hydraulic conductivity and transmural velocity in the LFTA results “inherit” this diffuse feature, which is further “magnified” by the nonlinearity of the shear-dependent $L_{p,\text{end}}$ model.

### 7.3.2 LDL transport

Using the fluid dynamics results obtained at transmural pressure of 120 mmHg, LDL concentration fields are calculated in both steady flow and LFTA simulations. LDL concentration on the lumenal surface calculated from the steady flow simulation is shown in Figure 7.8. Generally speaking, LDL accumulation on the lumenal surface can be found mainly in low WSS regions. In the low WSS regions, 1) convection towards the arterial wall is weaker due to a lower transmural velocity, leading to less LDL being brought to the lumenal surface; 2) the removal of LDL from the lumenal surface is also weakened causing more LDL particles accumulating on the lumenal surface. Based on the observation made in Figure 7.8, it seems that the second consequence of low WSS is dominant, resulting in a higher LDL concentration in the low WSS regions. It should also be noted that, although LDL concentration varied along the RCA, the degree of concentration polarisation is limited and generally not more than 6% above the inlet concentration. Therefore, pulsatile flow simulation employing the LFTA procedure, which assumes a constant LDL concentration on the lumenal side, can be justified.

Endothelial LDL concentration distributions on the wall side calculated from steady flow and LFTA simulations are shown in Figure 7.9. Both sets of results show elevated LDL concentrations in low WSS regions. Such focal accumulations are caused
7.3 COMPUTATIONAL RESULTS

**Figure 7.8:** Distribution of endothelial LDL concentration on the lumen side calculated from the steady flow simulation shown on the epicardial and pericardial sides of the human RCA.

**Figure 7.9:** Distribution of endothelial LDL concentration on the wall side calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA.
by a weaker convective clearance effect of the transmural flow in these locations in the simulations. LDL transport in the arterial wall is dominated by convection driven by the transmural flow. Because the transmural velocity is lower in the low WSS regions, the convection of LDL from the subendothelial layer to the outer wall layers is reduced, leading to significant relative LDL accumulation. The comparison also reveals that the LDL accumulation pattern for steady flow is more distinct than that for pulsatile flow. This is due to the dynamic behaviour of the pulsatile flow as well as the nonlinearity of the shear-dependent model for hydraulic conductivity, which leads to a slightly wider and more diffuse LDL distribution pattern as observed in the pulsatile flow case.

### 7.3.3 Albumin transport

![Figure 7.10: Distribution of endothelial albumin permeability calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA.](image)

In the case of albumin transport, a shear-dependent permeability is employed.
According to the LFTA procedure, the instantaneous values of the shear-dependent permeability are calculated using the instantaneous WSS and the time-averaged shear-dependent permeability is then computed. In Figure 7.10, albumin permeabilities calculated in the steady flow and the LFTA simulations are compared. Several remarkable features are observed: 
1) maximum albumin permeability (in the peripheral areas in regions 1 and 3 labelled in Figure 7.4) and minimum WSS (in the centres of regions 1 and 3) do not co-localise exactly; 
2) the permeability magnitudes in the high permeability regions 1 and 3 calculated from the two simulations are different (the time-averaged values in the LFTA simulation are generally lower); 
3) the area of high permeability of region 2 is different in two simulations, which can be observed on both the epicardial and the pericardial sides. The mismatch in the localisation of maximum permeability and minimum WSS is mainly due to the fact that the shear-dependent relation is not monotonous in the low shear stress range \(0 \text{ Pa} \leq |\tau_w| \leq 2 \text{ Pa}\). In Figure 4.9 on page 109, it can be seen that albumin permeability initially increases with increasing WSS, approaches its maximum value when \(|\tau_w| \approx 0.8 \text{ Pa}\), and then decreases with increasing WSS. The differences in the magnitude of permeability and the area of high permeability regions between the steady flow and LFTA simulations are again attributed to the contraction and expansion of low WSS regions in the pulsatile flow simulations.

Albumin transport is simulated using the fluid dynamics results at transmural pressure of 70 mmHg. Albumin concentration on the lumenal surface calculated by the steady flow simulation is shown in Figure 7.11. It is observed that the degree of concentration polarisation of albumin is substantially lower than that of LDL. The local mass balance of macromolecules at the lumenal surface is primarily determined by the convection normal to the endothelium caused by the transmural flow and the counter diffusion back to the lumen. It should be noted that both of these factors are different in the analyses of LDL and albumin transport. Transmural pressure of 120 mmHg is applied for LDL transport and 70 mmHg for albumin transport, which results in a weaker convection towards the endothelium in albumin transport simulation. Furthermore, the plasma diffusivity of albumin is much higher than that of LDL (according to Table 4.3, \( D_{alb} = 9.01 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}\) and \( D_{ldl} = 2.867 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}\),

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leading to a stronger counter diffusion in the case of albumin transport. Therefore, the observed degree of concentration polarisation of albumin (predominantly < 1%) is much lower than that of LDL and the LFTA procedure which assumes constant concentration on the lumenal surface can be applied.

Trans-endothelial albumin flux calculated in the steady flow and the LFTA simulations are compared in Figure 7.12. Albumin flux across the endothelium comprises a convective component and a non-convective component. The convective flux determined by the transmural flow is lower in the low WSS regions while the non-convective flux determined by the endothelial permeability is higher in the low WSS regions. As seen in Figure 7.12 the non-convective pathway is dominant: the total flux in both the steady flow and the LFTA simulations are higher in the low WSS regions. Furthermore, notable regional variations of albumin flux are observed with the maximum being more than twice that of the minimum. By comparing results from the steady flow and pulsatile flow simulations, obvious differences can be seen especially in the high flux regions which are considerably larger in the pulsatile flow results. This again illustrates the wider and more diffuse distribution pattern discussed previously in the case of LDL transport.

Albumin concentrations at the endothelium on the wall side given by the steady flow and the LFTA simulations are shown in Figure 7.13. It is found that albumin accumulation in the subendothelial layer also co-localises with low WSS. Al-
Figure 7.12: Distribution of trans-endothelial albumin flux calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA. The flux are normalised by a reference $N_0 = 1 \times 10^{-9} \text{ m s}^{-1}$.

though LDL accumulation is found in the same regions, the mechanisms underlying these accumulations are different: LDL accumulation is caused by a weaker convective clearance effect of the transmural flow in the low WSS regions, whereas albumin accumulation is caused by the greater flux across the endothelium in the low WSS regions. In other words, LDL accumulation is due to an insufficient efflux from the subendothelial layer while albumin accumulation is due to an excessive influx to the sub-endothelial layer. Furthermore, discrepancies between steady flow and pulsatile flow results are found: the differences in WSS distribution caused by the expansion and contraction of the recirculation regions in the pulsatile flow simulations, after being “magnified” by the nonlinearity of the shear-dependent models for trans-endothelial transport parameters, lead to a wider and more diffuse distribution pattern in both trans-endothelial albumin flux and sub-endothelial albumin concentration.
7.4 SUMMARY

Figure 7.13: Distribution of endothelial albumin concentration on the wall side calculated from the steady flow simulation (a) and LFTA simulation (b) shown on the epicardial and pericardial sides of the human RCA.

7.4 Summary

In this chapter, LDL and albumin transport in a human RCA are investigated using the single-layered model. In the momentum transport simulations, the shear-dependent endothelial hydraulic conductivity is employed, whereas in the mass transport simulations, the shear-dependent endothelial albumin permeability is used. By analysing the computational results, it is found that:

- Moderate degrees of concentration polarisation of LDL (6%) and albumin (1%) are observed on the lumenal surface. The difference in the degree of concentration polarisation between LDL and albumin is attributed to the fact that transmural pressure is set to be higher in the case of LDL transport and albumin is more diffusive in the lumen.

- LDL and albumin accumulations at the endothelium on the wall side (subendothelial layer) co-localise with low WSS. This indicates that the arterial wall
exposed to low WSS are indeed less protected from atherogenesis due to a greater macromolecular accumulation in the subendothelial layer.

- Two distinct pathways that induce the localised accumulation are identified. The first pathway is an insufficient efflux from the sub-endothelial layer to outer wall layers caused by a weaker transmural flow. More specifically, the endothelium subject to low WSS presents lower hydraulic conductivity and causes a lower transmural velocity. Consequently, the convective clearance effect of the transmural flow is weaker and macromolecules, such as LDL, cannot be effectively "flushed" from the subendothelial layer to outer wall layers. The second pathway is an excessive influx to the subendothelial layer from the lumen caused by a higher permeability of the endothelium. In other words, the endothelium subject to low WSS is more permeable to some macromolecules (albumin in the present study), resulting in a greater flux across the endothelium into the subendothelial layer. Both pathways are influenced by WSS acting on trans-endothelial transport and lead to macromolecular accumulation in the subendothelial layer. This analysis highlights the essential role played by the endothelium in arterial mass transport. Although it is suggested that endothelial uptake of LDL is also dependent on WSS, LDL permeability is assumed to be constant because of a lack of experimental data suitable for constructing an analytical model.

- The degrees of LDL and albumin accumulations in the wall are different. The elevation of LDL concentration at the endothelium on the wall side in the low WSS region is around 10% – 15%, while that of albumin is more than 100%. This discrepancy is caused by the different pathways that induce albumin and LDL accumulations in the present study discussed above. However if LDL permeability were to have similar trends to that albumin, a much more significant LDL concentration elevation in the subendothelial layer would be expected in the low WSS regions. Further experimental studies examining the effect of WSS on LDL permeability would be valuable in future.
It should be pointed out that LDL and albumin transport are simulated under two different transmural pressures that correspond approximately to systolic and diastolic arterial pressures *in vivo*. Cross-solute comparisons under the same transmural pressure are limited by the paucity of experimental data relating blood pressure to transport parameters*. In fact, when comparing between LDL and albumin accumulation patterns, it is interesting to look at the relative amount, i.e. the ratio of maximum concentration to the normal level in each case, rather than the absolute amount. Since a shift in transmural pressure only produces a rather homogeneous global change in solute concentration in the arterial wall, employing different transmural pressures should not substantially affect the earlier analysis.

*Albumin transport parameters under transmural pressure of 120 mmHg are not available whereas the single-layered model used for patient-specific geometries cannot capture LDL accumulation under transmural pressure of 70 mmHg (see Cases M1 and M2 in §5.3.4).
8.1 Main Conclusions

In the present study, mathematical models including a fluid phase model, a single-layered and a multi-layered fluid-wall models are proposed to simulate mass transport of oxygen, albumin and LDL in atherosclerosis-prone arteries. To incorporate time-dependent transport processes in the arterial wall, two lumen-free numerical procedures are developed. Model parameters, especially the transport properties of the arterial wall layers, are estimated using a simulation-based optimisation approach. Furthermore, shear-dependent transport properties, such as hydraulic conductivity and permeability are derived from relevant experimental data in the literature to incorporate the shear-dependence of trans-endothelial transport. The mathematical model and corresponding parameters are tested in idealised arterial geometries as preliminary investigations. The model is then applied to physiologically realistic cases, including oxygen transport in a human abdominal aortic aneurysm and macromolecular transport in a human right coronary artery. The main findings of this thesis are as follows:
8.1 MAIN CONCLUSIONS

- Four sets of model parameters, including albumin transport parameters under transmural pressure of 70 mmHg, LDL transport parameters under transmural pressures of 70 mmHg, 120 mmHg, and 160 mmHg are determined using the simulation-based optimisation approach. The parameters are determined such that the predictions given by the single-layered model and the multi-layered model are consistent. This novel approach leads to much better parameter estimations than existing methods.

- Solute concentration fields simulated in the fluid phase are found to be highly influenced by the flow patterns. Steep concentration gradients are observed near the endothelial boundary due to the fact that the transport is highly convection-dominated. However, thickened boundary layers are found in the flow recirculation regions, implying an impaired transfer efficiency.

- The degree of concentration polarisation of macromolecules is strongly correlated with the transmural velocity. It is predicted to be maintained at a modest level (within 10% of the lumenal inlet concentration) using the estimated model parameters.

- Preliminary model test shows that the conventional steady flow assumption in the arterial mass transport models may not be adequate, especially when the bulk flow is highly disturbed. The LFC and LFTA numerical procedures provide an efficient way to incorporate the effects of flow pulsatility on shear-dependent trans-endothelial transport. Results suggest that the influence of transient haemodynamic conditions on macromolecular transport can be modelled as a time-averaged effect. It is also shown that the LFTA procedure, which relies on time-averaged assumptions and is much computationally cheaper, can capture the mass transport characteristics observed under fully transient conditions.

- Simulation of oxygen transport in a human abdominal aortic aneurysm shows that the presence of an intralumenal thrombus significantly impedes oxygen transport from the arterial lumen to the arterial wall. Even a moderate thrombus (thickness of 5 mm in an aorta with a diameter of 16 mm) would be sufficient to
cut off the oxygen supply from the lumen to the wall. Parametric studies show that averaged oxygen concentration in the aortic wall is sensitive to adventitial oxygen concentration, highlighting the importance of oxygen supply from the vasa vasorum.

- LDL and albumin accumulations in the subendothelial layer are found to be co-localised with low WSS, indicating that the arterial wall exposed to low WSS is atherosclerosis-prone due to a greater lipid accumulation. The underlying mechanisms of the accumulation include 1) LDL accumulation is mainly due to a weaker convective clearance effect of the transmural low in the low WSS region; 2) albumin accumulation is mainly due to a greater influx in the low WSS regions where the endothelium is more permeable.

8.2 Limitations

A number of limitations exist in the present study, including the use of a vascular scale model, parameter-related limitations, limitations in the lumen-free numerical procedures, and other assumption-related limitations.

8.2.1 Drawbacks of vascular scale models

In the present study, mass transport process across the heterogeneous endothelium and arterial wall is approximated using volume-averaged notations, leading to formulation of a vascular scale model which can only simulate the spatially-averaged phenomenon. For instance, although sub-cellular scale variations in LDL concentration polarisation was found (Vincent et al., 2007), the present model predicts a smooth lumenal distribution of LDL because of the vascular scale formulation.

8.2.2 Parameter-related limitations

The present study attempts to utilise available experimental data in the literature to determine the model parameters by a simulation-based optimisation approach.
specific data used were acquired by Meyer et al. (1996). In these experiments, the solution was only circulated for 30 min, which was suggested to be too short to reach the observed levels of concentration in the wall (Stangeby and Ethier, 2002b). The present study also shows that LDL concentration takes more than 2 h to reach a quasi steady-state. Therefore, the experimental data that is used to determine the model parameters are somehow questionable. However, they are the most suitable data and were also used in other studies (Prosi et al., 2005; Ai and Vafai, 2006) to determine model parameters.

Furthermore, a rather high albumin consumption rate (higher than that of LDL) is estimated in the present study. However, it is suggested that albumin is much more inert than LDL in the arterial wall and the characteristic “U” shape profile (with lower concentration in the media) is due to a relatively dense structure of the media and a smaller available space for albumin transport. This problem should be addressed by using a more detailed description of the arterial wall.

In terms of shear-dependent trans-endothelial transport, although models for endothelial hydraulic conductivity and albumin permeability are derived, LDL permeability is assumed to be constant due to a lack of experimental data. It is speculated that if LDL permeability followed the same trend as albumin permeability, the degree of LDL accumulation in the subendothelial layer would be much greater than that observed in the present study.

8.2.3 Limitations in the lumen-free numerical procedures

In the time-averaged numerical procedures, two major assumptions are made: constant lumenal concentration and instantaneous response of the endothelium to changes in WSS.

Lumenal concentration of macromolecules is assumed to be constant to avoid fully transient mass transport simulation for a prolonged period since mass transport in the wall takes much longer time to reach equilibrium. Fortunately, concentration

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*The Tyrode’s solution supplemented with labelled solutes.*
8.2 LIMITATIONS

polarisation on the lumenal surface is found to be modest, suggesting that the assumption is justifiable and would not sacrifice too much accuracy. However, in the long term, a better alternative should be developed, especially when the degree of concentration polarisation is predicted to be high.

The endothelial cells in vitro take hours to reach a new steady state when a simple step change in WSS was imposed (Jo et al., 1991; Sill et al., 1995). However, instantaneous response of the endothelium to WSS is assumed, due to the lack of relevant data and plausible models on how WSS induces changes in endothelial transport properties. This assumption needs to be evaluated further by using a dynamic model for endothelial response to WSS.

8.2.4 Other assumption-related limitations

In the present study, blood is assumed to be Newtonian whereas it is in fact a shear-thinning fluid. Furthermore, the arterial wall is assumed to be rigid. These assumptions are likely to have some influences on the predicted flow patterns and concentration fields.

8.2.4.1 The assumption of blood as a Newtonian fluid

The non-Newtonian behaviour of blood could affect the predictions made for WSS. Augst (2002) compared the Newtonian model with the Quemada model and found that employing the Newtonian assumption could overestimate TAWSS in a carotid bifurcation geometry by 20%. However, the overall distribution patterns predicted by the two models were very similar. Since the trans-endothelial transport properties are modelled as shear-dependent in the present study, the assumption of blood as a Newtonian fluid would certainly affect the predicted concentration field. However, given that the discrepancy in TAWSS was modest and the overall distribution was similar, this assumption is unlikely to have a qualitative effect on the predicted species concentration profiles. The incorporation of non-Newtonian viscosity would be straightforward as long as a suitable model is available.
8.2.4.2 The assumption of rigid wall

The arterial wall is assumed to be rigid in the present study although it is compliant \textit{in vivo}. The preliminary study carried out by Koshiba et al. (2007) illustrated that the concentration profile in the arterial wall was slightly different when the wall compliance was taken into account. It can be explained by the reverse transmural pressure gradient and hence reverse transmural flow observed when the arterial wall is compressed. It should be pointed out that although local (in terms of both time and space) differences were found, the overall distribution exhibited very similar patterns to the results given by a rigid wall model. These findings suggested that wall compliance plays a role in arterial mass transport, but its influence is relatively small. Therefore, carrying out an expensive fluid-structure interaction simulation may not be necessary at the current stage. In the future, when a better understanding of the transport mechanisms under the reverse transmural flow conditions and a higher computing power become available, this assumption can be relaxed.

8.3 Suggestions for Future Work

The long term goal of computational investigations of arterial mass transport is to develop an experiment-assisted computational modelling framework spanning across multiple spatial and time-scales to advance the understanding of arterial hyperlipidemia, hypoxia and their relations to progression and localisation of atherosclerosis. Therefore, the main tasks are to resolve physical and biological phenomena in different spatial and time-scales.

As mentioned earlier, the present study employs vascular scale models with volume-averaged notations which omit focal variations at cellular scale. However, the employment of a sub-cellular scale model has the risk of overlooking the large scale variations. An optimal approach would be the combination of models in different spatial scales. The sub-cellular scale model has a better capacity to accommodate essential microscopic physical phenomena that build up the macroscopic situation. Ideally, the sub-cellular scale model should also take into account the biological phenomena which
cannot be easily included in the vascular scale model. When the sub-cellular scale predictions are made, the vascular scale model should be tuned to adapt to the observation and eventually give a broad picture.

Efforts should also be made to improve the temporal resolution of the model. As discussed in earlier chapters, the arterial mass transport processes are characterised by dramatically different time-scales. Therefore, to gain a complete understanding of the disease progression, it is essential to investigate phenomena that occur at different time-scales. That is to say, when looking at lipid accumulation in the arterial wall, one should not ignore haemodynamics in the fluid phase which determines trans-endothelial transport. The present study attempts to adapt these transport processes into one model framework using time-averaged techniques. However, major improvements (see §8.2.3) are still necessary in the future work.

Furthermore, more subject-specific investigations should be carried out in the future to assess the feasibility of using the model predictions to facilitate disease diagnosis and management.
Appendix: Publications during the Project

Journal papers


Conference Presentations


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Wada, S., M. Koujiya, and T. Karino, 2002: Theoretical study of the effect of local flow
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pages 12, 54, 55, and 70.)


