COMPUTATIONAL ANALYSIS OF ARTERIAL MASS TRANSPORT: FLUID AND WALL-SIDE EFFECTS

by

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A thesis submitted in conformity with the requirements for the Degree of Doctor of Philosophy, Department of Mechanical and Industrial Engineering, University of Toronto

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The transport of macromolecules, such as low density lipoproteins (LDLs), across the artery wall and their accumulation in the wall is a key factor in the development and progression of atherosclerosis. Previous computational studies of arterial mass transport have been limited by models that only include one region of the artery - the lumen or the wall. In this thesis, the limitations associated with single-region approaches were addressed through the development of a method that more tightly couples the mass transfer effects in the wall to those in the lumen than has previously been the case. This approach was used to model LDL mass transport in both the lumen and wall regions of a constricted, axi-symmetric tube simulating a stenosed artery. Coupled analysis of lumenal and transmural flow was achieved using Brinkman's model, which is an extension of the Navier-Stokes equations for porous media. Numerical complications due to the convection dominated mass transport process (low LDL diffusivity) were handled by the streamline upwind/Petrov-Galerkin (SUPG) finite element method.

Several factors that influence LDL transport were studied including a state of elevated transmural pressure (hypertension), the presence of a flow-disturbing stenosis, changes in wall Darcian permeability, and changes in endothelial LDL permeability. The results indicated that LDL infiltration and mean LDL wall concentration increased at the downstream side of the stenosis. This effect was markedly exaggerated by hypertension and/or the higher Darcian permeability thought to occur in regions containing atheromatous lesions. Increased transmural filtration in such regions, when coupled with a concentration-dependent endothelial permeability to LDL, could significantly increase LDL transport into the wall and possibly contribute to a more rapid progression of atherosclerosis. The results also indicated that concentration polarization is unlikely to be the root cause of hypertension as a risk factor for atherosclerosis. Instead, a pressure-linked increase in endothelial LDL permeability is more likely to be responsible.
Two roads diverged in a wood, and I -
I took the one less traveled by,
And that has made all the difference.

*Robert Frost, The Road Not Taken*

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This journey could not have been completed without the support of some long-suffering folk. I am, as always, at the mercy of my diabolically structured nature and shall therefore go in chronological order.

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Finally, to keep everything in perspective I have drawn from the words of the incomparable Albert Einstein: "As far as the laws of mathematics refer to reality, they are not certain, and as far as they are certain, they do not refer to reality."
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LIST OF SYMBOLS

Alphanumeric

$B = \text{hindered transport coefficient}$

$c_p = \text{plasma concentration}$

$c = \text{concentration}$

$C_0 = \text{inlet concentration}$

$D = \text{diffusivity}$

$D_{\text{eff}} = \text{effective diffusivity in the wall}$

$D = \text{pressure mass matrix}$

$D_a = \text{Darcy number}$

$G_f = \text{Guretzki factor}$

$h = \text{wall thickness}$

$H = \text{reaction rate constant}$

$K = \text{Darcian permeability}$

$L = \text{continuity matrix}$

$M = \text{endothelial permeability}$

$M_{\text{eff}} = \text{effective membrane permeability}$

$M = \text{mass matrix}$

$M_c = \text{concentration mass matrix}$

$n = \text{normal coordinate}$

$N = \text{convection matrix}$

$N_c = \text{concentration convection matrix}$
\[ p = \text{pressure} \]
\[ q = \text{species flux} \]
\[ \text{Pe} = \text{Peclet number} \]
\[ r = \text{radial coordinate} \]
\[ R = \text{inlet radius} \]
\[ \text{Re} = \text{Reynolds number} \]
\[ \text{Re}_{\text{eff}} = \text{effective Reynolds number} \]
\[ \text{Re}_1 = \text{pressure scaling term} \]
\[ S = \text{diffusion matrix} \]
\[ S_c = \text{concentration diffusion matrix} \]
\[ \text{Sc} = \text{Schmidt number} \]
\[ \text{Sc}_{\text{eff}} = \text{effective Schmidt number} \]
\[ t = \text{time} \]
\[ u = \text{axial velocity component} \]
\[ U = \text{mean inlet velocity} \]
\[ v = \text{radial velocity component} \]
\[ v_w = \text{lumen/wall interface filtration velocity} \]
\[ w = \text{Gauss point weights} \]
\[ x = \text{axial coordinate} \]
Greek Symbols

$\alpha =$ Womersley parameter

$\delta =$ boundary layer thickness

$\Gamma =$ boundary of numerical domain

$\Delta t =$ time step

$\varepsilon =$ penalty parameter

$\varepsilon_s =$ species partition coefficient

$\eta, \xi =$ isoparametric coordinates

$\mu =$ fluid viscosity

$\nu =$ kinematic viscosity

$\rho =$ fluid density

$\tau =$ upwind parameter

$\tau_w =$ wall shear stress

$\phi =$ velocity shape function

$\varphi =$ concentration shape function

$\psi =$ pressure shape function

$\omega =$ circular frequency

$\Omega =$ area of numerical domain
CHAPTER 1

1 Introduction

1.1 Motivation

Cardiovascular disease is the leading cause of death in Western society. Atherosclerosis is the most common form of cardiovascular disease and primarily affects large and medium sized arteries. Atherosclerotic plaques develop in these arteries, which can eventually result in haemorrhage, ulceration, and thrombosis, and cause catastrophic arterial occlusion leading to the oxygen deprivation and cell death of vital organs [59]. The clinical manifestations of atherosclerosis include myocardial infarction, stroke, sudden cardiac death, or peripheral vascular disease.

Although atherosclerosis is a highly complex disease, cholesterol has been implicated as a key contributor to the development and progression of the disease. As early as 1847, it was observed that relatively large quantities of cholesterol were found in atherosclerotic plaques in the artery wall. Then, in 1913 [2], it was discovered that atherosclerotic lesions could be produced in rabbit aortic walls when the rabbits were fed a diet rich in egg yolks (a high-cholesterol containing substance). These findings stimulated a great deal of interest in the role of cholesterol in atherosclerosis, and a critical question emerged: how is cholesterol transported into the artery wall?
correlation between atherosclerosis and elevated cholesterol levels in blood plasma would seem to imply that the cholesterol found in the artery wall most likely originates from the blood plasma. This hypothesis has been confirmed by several experimental studies [19], which showed that atherosclerotic plaques contained plasma low-density lipoproteins (LDLs), which are the chief vehicles for cholesterol transport in the artery [84, 105]. Hence, it appears that the cholesterol that is found in atherosclerotic plaques is transported into the wall by plasma LDLs. This conclusion sparked interest in the study of arterial LDL transport, and the question posed above changed to: what factors influence the transport of LDL into the wall?

The endothelium, a cellular monolayer forming the boundary between the arterial plasma and the artery wall, is a key player in the process of transporting LDL into the wall. In order for LDL to penetrate into the artery wall from the plasma, it must cross the endothelium. The rate at which this occurs is strongly dependent on the concentration of LDL in the plasma at the endothelium, which is in turn dependent on the bulk concentration of LDL in the plasma. However, the LDL concentration at the endothelium is also affected by arterial fluid dynamics. In the artery, molecules such as LDL are transported axially by flowing blood, as well as radially by a slow flow arising from a filtration of blood plasma across the artery wall. As a result of the semi-permeable nature of the endothelium to large particles, very few LDL molecules can actually pass across the endothelium boundary. Consequently, a concentration polarization of LDL molecules occurs at the boundary, thereby increasing the LDL concentration to which the endothelium is exposed [14]. The occurrence and extent of
concentration polarization is dependent on local fluid dynamics, and hence hemodynamics may play an important role in the transport of LDL into the wall.

There is another interesting aspect of fluid dynamics in the atherosclerosis puzzle. Atherosclerosis is localized in nature, i.e. it tends to occur at specific sites in the arterial tree, such as bends, branches, and constricted regions [11, 65, 80]. This latter site is brought about by the development of atherosclerotic plaque in the wall of the artery, which encroaches on the arterial diameter and can eventually lead to full occlusion of the artery. Although in this situation atherosclerosis is already present, the ensuing constriction could adversely influence the progress of the disease. The arterial geometric features listed above lead to disturbed blood flow patterns, which include the formation of recirculating flows and low wall shear stresses [4, 46, 77]. Experimental studies have also revealed that when normal animals are fed a cholesterol-rich diet, sites in the animals that are prone to atherosclerotic lesion development show high concentrations of LDL in the wall [81]. Taken together, these observations suggest that fluid dynamics exert an important effect on the transport of LDL into the wall, particularly in regions of disturbed flow. As a result, there has been substantial interest in studying the factors that influence arterial fluid dynamics and their subsequent impact on the mass transport of atherogenic molecules, such as LDLs, in the artery and its wall.

In studying the mass transport of species in the arterial lumen and wall, various experimental and/or computational methods can be employed. Experimental approaches are powerful, but also suffer important drawbacks. These include the suitability of
animal models for the human disease condition [1, 82], the challenge of properly controlling all relevant experimental conditions in animal models, and the difficulty of obtaining measurements with adequate spatial resolution. From a computational perspective, relatively few studies have been conducted to date due to significant difficulties in the numerical solution of the governing mass transport equation. These complications arise due to the convection-dominated nature of arterial mass transport and have required the development of specialized computational techniques (see Section 2.2.2).

If a computational approach is taken to study arterial mass transport, the basic geometry of the artery can be simplified by considering the artery to be subdivided into two distinct regions - the lumen, which is the main channel through which blood flows, and the arterial wall (Figure 1.1). Existing computational studies (see Section 1.3) have either focussed on mass transfer effects in the lumen or in the wall. In considering only one part of the geometry, simplifying assumptions are made, which can significantly limit the computational model. These include:

**Lumenal Transport**

- The interface between the lumen and wall is treated as a “hard” boundary, and coarse assumptions are made regarding the behaviour of the fluid and the transported species at that boundary. Such an approach is suitable for many species, since the transmural fluid filtration across the lumen/wall boundary can be neglected. However, in situations where the rate of convective transport towards the wall due to transmural
filtration is comparable to other transport processes, a more sophisticated boundary treatment at the wall is indicated (see Section 1.4). This latter scenario is typical of the transport of large macromolecules such as LDL.

**Wall Transport**

- One-dimensional models are commonly implemented, which assume a constant transmural velocity across the wall. These models cannot incorporate more interesting two-dimensional geometries, such as a thickening of the artery wall induced by atherosclerosis and an atherosclerotic plaque (Figure 1.1).

- Existing wall models do not account for the variations in *lumenal* LDL concentration at the lumen/wall interface, which can be caused by the disturbed flow patterns associated with geometry changes such as those seen in Figure 1.1. As discussed above, this lumenal concentration at the endothelium boundary is critical in determining the transport of LDL into the wall.

In summary, there is evidence of a link between arterial LDL transport and atherosclerosis, and existing computational studies of LDL transport have been limited because of their independent treatment of lumenal and wall mass transport. This points to the need for a model that can *couple* the mass transfer effects in the lumen to those in the wall. This would improve the picture of arterial LDL transport and would assist in understanding some of the features that can affect the development and progression of atherosclerosis.
Figure 1.1: Artery shown with constriction (stenosis) due to atherosclerosis. The unshaded area is the arterial lumen and the gray-shaded area is the arterial wall. Stenosis region shows thickening of the wall and reflects the presence of atherosclerotic plaque.

1.2 Atherosclerosis and the Artery Wall

The development and progression of atherosclerosis can be broken into fairly distinct stages. Before detailing these stages, it is useful to describe some of the cellular and structural characteristics of the arterial wall. The total thickness of the wall varies from vessel to vessel; however, the ratio of wall thickness \( h \) to vessel diameter \( 2R \) is fairly consistent \( h/2R \approx 0.04 \) amongst vessels [66]. For example, a carotid artery with a diameter of 7mm would have a wall thickness of approximately 300 microns, and a thoracic aorta with a diameter of 25mm would have a wall thickness of about 1000 microns.

The primary structure of the wall can be separated into three layers: the intima, media and adventitia. (Figure 1.2). The intima is very thin (only a few microns), and the bulk of the artery wall consists of the media and the adventitia. The inner layer of the
intima consists of the endothelium in direct contact with the flowing blood in the lumen. It is through this layer that the various species in the blood must pass in order to progress further into the wall. A thin connective tissue layer separates the endothelium from a fenestrated elastic membrane, the internal elastic lamina (IEL). The IEL forms the inner boundary of the next primary layer, the media. The media mainly consists of smooth muscle cells (SMCs) that are arranged in multiple layers, with small amounts of collagen, connective tissue, and elastic tissue between them. Although the number of these layers decreases with decreasing vessel diameter, the media is always the predominant element in the wall. In many vessels, the boundary between the media and the adventitia is marked by a very thin band of elastic tissue called the external elastic lamina (EEL). The final layer of the artery wall is the adventitia, which is relatively thin. It is composed of loose connective tissue containing few elastin and collagen fibers. It is within this layer that the vasa vasorum are typically found, although in larger vessels the vasa vasorum can reach into the medial layer. The vasa vasorum are blood vessels that supply the adventitia with nutrients, while the intima and media are supplied from the lumen. The adventitia gradually merges with the surrounding tissue such that there is no clear anatomical marker that defines the adventitial limits [12, 101].

The different layers and components of the artery wall serve various purposes. The focus of this work, however, is on atherosclerosis, and hence the discussion will be restricted to the features that affect this disease. The intimal layer of the artery wall is of primary interest in the study of atherosclerosis. Clearly the endothelium is of vital importance as it acts as a barrier to the infiltration of atherogens (e.g. LDLs) into the
The endothelium is permeable, and hence important nutrients, such as oxygen, can easily pass through it. However, it is substantially less permeable to larger macromolecules, which include LDLs with a mean diameter of approximately 22nm and a molecular weight of $3 \times 10^6 \text{Da}$ [94].

The progression of atherosclerosis within the intima and, in some advanced cases, the media, can be followed through eight stages (I-VIII) of lesion development [90]. Type I-III lesions consist of small lipid deposits that do not disorganize the normal intimal structure or deform the artery. Type I lesions involve minimal histologic changes in the intima, and consist of small, isolated groups of macrophages and macrophages containing lipid droplets. Type II lesions (fatty streaks) represent a further development from type I, in that lipid particles are visible in the extracellular matrix. Progression to type III involves the formation of multiple separate pools of extracellular lipid that disrupt the coherence of some structural intimal smooth muscle cells (SMCs).

Type IV-VIII lesions display accumulations of lipids, cells and matrix components, including minerals, which cause structural disorganization, intimal thickening and deformity of the artery wall. Type IV lesions show an increase in extracellular lipid, which forms a lipid core occupying a well-defined region of the intima. The progression to type IV also involves the formation of new connective tissue matrix. This new matrix, which includes collagen, is synthesized by intimal SMCs in response to the disorganization of the intimal structure by the extracellular lipid. A type V lesion results when substantial collagen has been generated. At this stage significant
intimal thickening occurs, which stems from the proliferation of SMCs. The SMCs appear to produce increased levels of collagen in response to tissue disruption and some cell-death (necrosis). It is the process of intimal thickening that encroaches on the lumenal diameter and can eventually lead to full occlusion of the artery. Type V lesions can also have a multilayered structure that involves two or more lipid cores that are stacked irregularly with layers of fibrous tissue and cells between them. This is thought to be the result of the development of a stenosis (arterial constriction), which causes alterations in the fluid dynamics and hence modifies the site of lipid accumulation.

Type VI lesions consist of a surface disruption, hematoma or thrombus. It is this class of lesion that is responsible for the majority of atherosclerotic morbidity and mortality. Type VII (calcific) lesions occur when 50% or more of the cross-sectional area of the lesion consists of mineral. Mineralization occurs in the organelles of some intimal SMCs that are embedded in the lipid core and have been injured in some way. When these injured cells die, they disintegrate and the mineralized organelles accumulate in the core. Type VIII lesions are composed primarily of collagenous fibrous tissue with no lipid core. This type of lesion can occur as a result of the extension of the fibrous component of an adjacent type V lesion, or the regression of a lipid core. Type VIII lesions can also exhibit some quantity of mineralization.
Figure 1.2: Transverse section of an arterial wall. Not to scale.
Figure 1.3: Microscopic images of coronary artery wall. (a) Normal artery with no signs of atherosclerosis. (b) Artery with advanced atherosclerosis. Light section on right-hand side is area of calcification. Lumenal diameter has been reduced by 50%. From: http://www-medlib.med.utah.edu/WebPath/ATHHTML/ATHIDX.html#1
1.3 Previous Studies

The factors that contribute to the progression of atherosclerosis are varied and complex. As described in Section 1.1, one process that has been linked to the disease is that of arterial mass transport [29, 30, 34, 50, 62, 102]. Two species that are of interest in this area of study are oxygen and LDL. The transport of LDL is relevant due to the abnormally high levels of LDL that are found in atherosclerotic plaques and lesion-prone zones in the artery wall. The transport of oxygen is of interest as it is an important blood-borne cellular metabolite, and abnormalities in oxygen tension in the arterial wall have been linked to atherosclerotic lesion formation [15, 39, 57].

Because of oxygen’s small size, simplifying assumptions can be made in analyzing its mass transport [6, 61]. These assumptions cannot be made for larger species such as LDL, however, and as a result more complex computational tools must be developed. Since LDL is so closely linked to atherosclerosis there has been substantial interest in developing these tools to better elucidate LDL transport in the artery and its wall. Due to the complexity of this task, studies have either focussed on mass transport in the lumen or in the wall. The following is a brief review of the relevant literature.

1.3.1 Lumenal Mass Transport

Computational studies of mass transport in the arterial lumen have examined species such as oxygen, albumin and LDL. Researchers have investigated the link between disturbed flow patterns and irregular levels of species concentration at the
lumen/wall interface. Although the focus of the present work is on LDL, some of the methods of and the findings from the study of oxygen and albumin are relevant and have been included here. One of the limitations in all of the cases cited below is that the fluid boundary condition treatment at the lumen/wall interface is either no-slip or a constant filtration velocity. This limitation is discussed further in Section 1.4.

1995 Deng et al. [21] used a second upwind finite difference method to numerically analyze the LDL concentration at the lumen/wall interface of a straight tube model. A mass balance of LDL and a constant fluid filtration velocity were applied at the interface. It was shown that the LDL concentration at the interface increased with increasing filtration velocities. These results were confirmed experimentally in canine carotid arteries. The experimental results showed an increase in wall uptake rate of tritium-cholesterol (carried by LDL) with increasing transmural pressure (filtration velocity). It was concluded that the rate of lipid infiltration into the wall is affected by the lumenal interface concentration.

1995 Deng et al. [20] used a finite difference model to numerically analyze the effect of blood flow on the transfer of LDL from flowing blood to the lumen/wall interface in a two-dimensional T-junction model. A mass balance of LDL and a constant fluid filtration velocity were applied at the interface. It was shown that the highest concentration of LDL at the interface occurred in the areas of the reattachment points. It was concluded that locally disturbed flows provide
favourable conditions for the accumulation of LDL at the lumen/wall interface, 
thus increasing the potential for LDL infiltration into the artery wall.

1996 Rappitsch et al. [74] used the Streamline Upwind/Petrov-Galerkin (SUPG) finite 
 element technique to numerically analyze oxygen transport in a stenosed artery. 
 Two models for the solute flux at the lumen/wall interface were implemented: 
 constant wall permeability and shear-dependent permeability. A no-slip fluid 
 boundary condition was used. It was shown that the oxygen concentration profile 
 at the lumen/wall interface was highly dependent on the solute flux model. This 
 indicates the need for sound boundary condition treatment.

1996 Rappitsch et al. [75] used SUPG to numerically analyze albumin transport in a 
 stenosed artery. The solute flux at the lumen/wall interface was based on a shear- 
 dependent wall permeability model, and a no-slip fluid boundary condition was 
 used. It was shown that the albumin concentration at the lumen/wall interface 
 varied along the arterial section and was strongly dependent on the different flow 
 regimes. This provides evidence of the link between fluid dynamics and 
 macromolecular concentration distribution.

1997 Ma et al. [56] used a finite volume approach to numerically analyze oxygen mass 
 transfer in the human carotid bifurcation. A constant concentration was assumed 
 at the lumen/wall interface, and a no-slip fluid boundary condition was used. It 
 was shown that regions of low oxygen mass transport were similar to regions of
low wall shear stress. The distribution of regions of low mass transfer correlated well with experimental measurements of wall thickening in human specimens. It was suggested that the mass transfer rates of macromolecules may also be flow-dependent.

1999 Wada et al. [93] used SUPG to numerically analyze LDL transport in an artery with multiple bends. A mass balance of LDL and a constant fluid filtration velocity were applied at the lumen/wall interface. It was shown that regions of low wall shear stress corresponded to locally elevated concentrations of LDL at the interface. These regions corresponded well to sites of wall thickening observed in the human right coronary artery after which Wada et al.'s geometry of multiple bends was modelled. It was concluded that flow-dependent concentration polarization of LDL plays an important role in atherosclerosis.

1999 Fatouraee et al. [27] used a second upwind finite difference model to analyze LDL transport in an artery with varying degrees of stenosis. A mass balance of LDL and a constant fluid filtration velocity were applied at the lumen/wall interface. It was shown that the highest concentration of LDL at the interface occurred at the flow separation point.

1.3.2 Wall Mass Transport

Computational mass transport studies in the artery wall have either been based on fiber matrix theories, which model the porous media of the wall as a matrix of randomly
packed fibers of uniform radius, or on simplified one-dimensional models that assume a constant linear transmural fluid velocity through the wall. In neither case do the modelers link the species lumenal concentration at the lumen/wall interface to the concentration in the wall. This is a significant limitation in studying two-dimensional geometries such as an arterial stenosis, since local variations in LDL concentration at the interface may exert an important effect on the LDL profiles in the wall.

1977 Bratzler et al. [9] used a simple one-dimensional model to theoretically analyze the in vivo transport of labeled LDL through the artery wall. A constant transmural fluid velocity was assumed and concentration boundary conditions were dependent on the bulk plasma (lumenal) concentration. The model was fit to experimental data and it was concluded that the endothelium is the limiting resistance to LDL transport in the arterial wall.

1987 Saidel et al. [78] developed a mathematical model to describe the in vivo transmural accumulation of an injected tracer (e.g. labeled LDL) in the aortic wall. A constant transmural fluid velocity was assumed and concentration boundary conditions were dependent on the bulk plasma concentration. The concentration of the tracer in the plasma varied as a function of time and an analytic solution of the concentration distribution of the tracer across the wall was presented.
Morris et al. [63] developed a dynamic mass transfer model that describes labeled LDL concentration profiles in the artery wall. A constant transmural fluid velocity was assumed and concentration boundary conditions were dependent on the bulk plasma concentration. The model included the effects of the LDL lumenal permeability, convection, diffusion and degradation (LDL is degraded by cells within the artery wall). These parameters were obtained by fitting the model to experimental data. In order to obtain the best set of parameter values, a sensitivity analysis was performed and an optimal design of experiments was recommended.

Penn et al. [68] used a one-dimensional model to numerically analyze the in vivo transport of labeled horseradish peroxidase (a macromolecule) across the artery wall. Convection was neglected and concentration boundary conditions were dependent on the bulk plasma concentration. The model was fit to experimental data in order to obtain the permeability coefficient of the endothelium to horseradish peroxidase.

Kim et al. [49] used Darcy’s law and a fiber matrix theory to model the transport of albumin in the media of an artery wall. The results were compared to experimental profiles of albumin in the artery wall at various transmural pressures. It was concluded that albumin transport through the aortic media is dominated by convection rather than diffusion.
1996 Huang et al. [41] modelled the media of a blood vessel wall as a heterogeneous medium consisting of a continuous interstitial fluid phase of proteoglycan and collagen fibers and a periodic array of cylindrical SMCs. An analytical solution of the transmural fluid flow was determined by applying Brinkman's model. The reaction of the transported species at the surface of SMC membranes was treated as a boundary condition and the mass transfer in the media was solved using a finite volume technique. It was shown that the mass transfer to the surface of smooth muscle cells is "reaction limited" for small molecules, whereas, for larger molecules such as LDL, the mass transfer may not be reaction limited.

1.3.3 Coupled Lumen and Wall Studies

Only one study to date has been found that combines lumen and wall-side mass transfer effects for macromolecular transport. This published work was very short, and it was therefore difficult to fully evaluate the details of the methodology.

1999 Karner et al. [47] used the finite element method and an upwind stabilization procedure to numerically analyze macromolecular transport across the different layers of the wall. The mass transport in the lumen and the wall were coupled by the mass flux across the endothelium. This flux was modelled mathematically using a dual set of equations for the fluid and solute fluxes. A constant filtration velocity was assumed in each layer of the wall based on Darcy's law. It was concluded that the endothelium provides the primary resistance to
macromolecular transport from the lumen into the wall. It was also found that the macromolecular concentration in the media is very low.

1.4 Transport Resistance Analysis

In examining the work described in the preceding sections, it is apparent that various simplifying assumptions have been made in order to model the transport of different species in the artery and its wall. If arterial mass transport is to be modelled accurately it is important to establish the most important factors influencing mass transport through the blood and artery wall. To this end it is useful to conduct an order-of-magnitude analysis of transport resistances in these regions. To do so, it is helpful to consider blood-to-wall mass transport (or vice versa) in terms of an equivalent electrical circuit [28] containing the following resistances: the resistance through the mass transport boundary layer (from the flowing blood to the endothelium), the trans-endothelial resistance, and the mass-transfer resistance of the wall itself. It is convenient to evaluate the conductance (=1/resistance) of each pathway in terms of transport velocities per unit concentration difference, and this approach is adopted in the following analysis. Two physiologically important species are considered, oxygen and LDL, for which the diffusivities in blood are $1\times10^{-5}\text{cm}^2/\text{s}$ [5] and $5\times10^{-8}\text{cm}^2/\text{s}$ (Appendix C), respectively.

**Blood-to-endothelium:** There are two parallel pathways for transport from the blood to the endothelial surface: (i) a convective one due to the presence of a normal velocity component near the vessel wall, and (ii) a diffusive one across the mass transport
boundary layer. The near-wall normal velocity component equals the transmural filtration velocity, which is reasonably consistent between animal species and artery types, and is of order $4 \times 10^6$ cm/s (Appendix C). The diffusional velocity through the mass transport boundary layer is approximated by the ratio $D/\delta$, where $D$ is the species diffusivity and $\delta$ is a typical boundary layer thickness. The boundary layer thickness clearly depends on local hemodynamic features in a complex way; here, as a first approximation, $\delta$ is estimated using the Graetz-Nusselt solution for a developing mass transfer boundary layer in a straight tube, which for high Schmidt numbers yields [73]:

$$\frac{\delta}{R} = \left( \frac{x}{R} \right)^{\frac{1}{3}} \text{Pe}^{-\frac{1}{3}} \quad (1.1)$$

where $R$ is the arterial radius, $x$ is the axial position from the origin of the mass transfer boundary layer, and Pe is the Peclet number. It is clear that the assumptions underlying the Graetz-Nusselt solution do not strictly hold within the arterial tree. However, at bifurcations or bends there is substantial secondary flow that promotes cross-sectional mixing, after which point the concentration profile can be approximated as being fairly uniform and thus similar to that at the origin of the Graetz-Nusselt problem. Arbitrarily, boundary layer thicknesses 10 diameters downstream of such a mixing site are studied here.

A range of arterial sizes and flow rates are also considered. At the upper end of the range of large arteries prone to atherosclerosis a human abdominal aorta
(diameter=1.4 cm, time-average Re=700 [66]) is considered, while at the lower end of the size range a human carotid artery (diameter=0.7 cm, time-average Re=400 [26]) is considered. These vessels yield average diffusional velocities across the mass transfer boundary layer for oxygen of 7 to 12 x 10^{-4} cm/s and for LDL of 2.1 to 3.4 x 10^{-5} cm/s (Table 1.1).

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Transport Velocities (x10^{-6} cm/s)</th>
<th>For Oxygen'</th>
<th>For LDL''</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood-to-endothelium</td>
<td>Due to convection normal to wall</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Due to passive diffusion</td>
<td>700 to 1200</td>
<td>21 to 34</td>
</tr>
<tr>
<td>Trans-endothelial</td>
<td></td>
<td>2000</td>
<td>0.02</td>
</tr>
<tr>
<td>Trans-mural</td>
<td>Due to transmural convection</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Due to passive diffusion</td>
<td>360 to 710</td>
<td>0.018 to 0.036</td>
</tr>
</tbody>
</table>

'Oxygen has a molecular weight of 32 Da and a molecular diameter of 370 pm
''LDL has a molecular weight of 3 x 10^6 Da and a molecular diameter of 22 nm

Table 1.1: Comparison of transport velocities from blood in arterial lumen to wall tissue (per unit concentration difference). Ranges represent different-sized arteries, as discussed in text. See text for detailed description of how all quantities are computed.

*Trans-endothelial:* The net rate of transport across the endothelium is the permeability of the endothelium to the transported species, which equals 2 x 10^{-3} cm/s for oxygen [31] and 2 x 10^{-8} cm/s for LDL (Appendix C).
**Transmural**: Transport within the wall occurs by two parallel mechanisms: passive diffusion and convection driven by the transmural fluid flux. Passive diffusion is considered first. Assuming transport in the wall occurs from both the lumenal blood and from the vasa vasorum, a relevant characteristic distance in the wall is half the distance from endothelium to the vasa vasorum. Arterial wall thicknesses have been reported in the literature as approximately 4% of the vessel diameter [66], a value that is quite consistent among human arteries ranging from the femoral artery to the thoracic aorta. The effective diffusivity in the wall, $D_{eff}$, is $1\times10^{-5}\text{cm}^2/\text{s}$ for oxygen [79] and $5\times10^{-10}\text{cm}^2/\text{s}$ for LDL (Appendix C), which yield transmural diffusional velocities of 3.6 to $7.1\times10^{-4}\text{cm/s}$ and 1.8 to $3.6\times10^{-8}\text{cm/s}$, respectively (Table 1.1).

To estimate convective transport rates in the wall it is necessary to know the extent to which convective motion of the transported species is hindered by interaction with wall components. For oxygen there is essentially no hindrance (note that the ratio between free diffusivity and effective diffusivity in the wall is one for oxygen), and thus oxygen's transmural convection velocity is $4\times10^{-6}\text{cm/s}$. For LDL there is appreciable hindrance (note that the ratio of hindered to free diffusivity is 0.01). To quantify the hindrance, the extracellular matrix of the arterial wall is approximated as a fixed matrix of hyaluronic acid [48], since glycosaminoglycans moieties within the wall are expected to be primarily responsible for transport restriction. The studies by Laurent are used [51, 52] in which the sedimentation rates of various substances in solutions of hyaluronic acid were determined, as summarized by the following relationship:
where $V_m$ is the macromolecular velocity, $V_f$ is the unhindered velocity, A and B are molecule-dependent constants and $\phi$ is the volume fraction of hyaluronic acid. For a molecule with the diameter of LDL (22nm), A and B are equal to 1.94 and 33.2 [51], assuming the density of hyaluronic acid to be 1.85g/ml. Using the semi-empirical approach of Levick [54], the solid volume fraction of the arterial wall tissue matrix ($\phi$) can be approximated as $1.74 \times 10^{-2}$. This volume fraction accounts for the presence of glycosaminoglycans, proteoglycan protein, collagen, and elastin. These values yield a hindered convective velocity for LDL in the wall of approximately $1 \times 10^{-7}$cm/s, which is reasonably close to the value that would be obtained by assuming that the relative hindrance of LDL convective transport in the wall is equal to relative hindrance of LDL diffusive transport.

Several conclusions can be drawn from the values in Table 1.1. First, in the case of oxygen, transmural convective velocities can be neglected. Second, the greatest overall resistance to oxygen transport is exerted in the wall, consistent with previous findings [61], and the endothelial resistance to oxygen does not play an important role.

For LDL, the situation is somewhat different, and the major conclusions from this theoretical analysis are:
• The endothelium offers the majority of the resistance to LDL transport, which is consistent with previous numerical model findings [9, 47]. As a result, factors that influence endothelial LDL permeability are critical. One such factor appears to be the LDL concentration itself. For example, Guretzki et al. [38] performed an experiment in which aortic endothelial cells were cultured on microporous membranes and then exposed to varying concentrations of LDL. The rate of transfer of LDL across the endothelial monolayer was determined using transwell chambers so as to assess the endothelial LDL permeability. Exposure of the endothelial cells to LDL-cholesterol concentrations greater than 1mg/mL induced a concentration-dependent, exponential increase in endothelial permeability. The magnitude of this effect is not small: assuming that Guretzki et al.'s cell culture data can be extrapolated to the in vivo situation, a 50% increase in LDL concentration (from 1.2mg/ml to 1.8mg/ml) would result in a 420% increase in endothelial LDL permeability.

• Convective effects dominate LDL transport in the artery wall. This is consistent with Kim et al.'s [49] numerical model findings for albumin transport.

• LDL transport in the lumenal mass transfer boundary layer is usually dominated by diffusion, with a small effect due to convection. However, in regions where the boundary layer is thicker than that predicted by the simple Graetz-Nusselt analysis, convective transport becomes important. This will occur in regions of flow stagnation, and incipient or actual flow separation, which are of course precisely the areas of primary interest in studying LDL transport. In such regions, a significant
amount of LDL concentration polarization occurs at the arterial wall [14, 20, 21]. In general, therefore, when studying lumenal LDL mass transport it is critical to accurately model convective transport at the wall, which in turn requires an accurate treatment of fluid convection within the wall.

1.5 Objectives

From the above review it is evident that improvements in arterial mass transport modelling are required. The specific issues that need to be addressed are the following:

- The analysis of lumenal LDL transport requires a more sophisticated treatment of the convective velocity at the lumen/wall interface.

- The analysis of wall LDL transport requires the inclusion of properly modelled convective terms.

- The solution of LDL mass transport in the wall needs to be linked to the lumenal LDL concentration at the lumen/wall interface.

- The existing LDL mass transport models in the wall need to be extended to two-dimensions to permit the modelling of more complex two-dimensional geometries, such as an arterial stenosis.
Accordingly, the overall objective of this work is to provide an improved model that addresses these issues and more tightly couples the mass transfer effects in the wall to those in the lumen than has previously been the case. To achieve this objective, the first step will be to develop and improve the LDL transport computational methodology. Specifically, this will consist of:

- Modifying an existing two-dimensional finite element based Navier-Stokes solver to solve the mass transport equation in the presence of transmural filtration.

- Incorporating the Streamline Upwind/Petrov Galerkin method to deal with the computational complexities associated with the convection-dominated transport of low diffusivity species such as LDL.

- Developing a more physiologically realistic pressure boundary condition treatment for the fluid that removes the need for simplifying assumptions at the lumen/wall interface.

- Constructing a two-dimensional model of a stenosed (constricted) artery with both lumen and wall regions. This model will include a region representing the atherosclerotic plaque and the different components of the plaque, such as a necrotic core.

With this methodology in place, the following questions will be answered:
1. What are the effects of elevated arterial pressure (hypertension) on:
   
   (a) the infiltration of LDL into the artery wall?
   
   (b) the level and distribution of LDL in the artery wall?

2. What is the mechanism by which hypertension facilitates LDL transport into the wall?

3. What are the effects of altering the Darcian permeability of the wall (secondary to plaque development) on:
   
   (a) the infiltration of LDL into the wall at an arterial stenosis?
   
   (b) the level and distribution of LDL in the wall at an arterial stenosis?

4. What are the effects of altering endothelial LDL permeability on:
   
   (a) the infiltration of LDL into the artery wall?
   
   (b) the level and distribution of LDL in the artery wall?

5. What are the implications of the above effects on the progression, or regression, of atherosclerosis?
CHAPTER 2

2 Methods

2.1 Fluid Flow Modelling

2.1.1 Governing Equations

A standard assumption made in arterial flow modelling is that blood is a homogeneous, isothermal, incompressible fluid. The incompressibility assumption breaks down if the fluid velocity approaches the speed of sound in the fluid, but since arterial blood velocities are significantly below 1% of the sound speed the incompressibility assumption is valid [12]. Despite the fact that blood is a suspension of particles, it is also valid to treat it as a homogeneous fluid. This is because the diameter of the suspended particles, such as red blood cells, is much smaller than the internal diameter of the artery [12, 66]. In the smaller vessels, such as capillaries, the homogeneity assumption cannot be applied; however, the focus of this work is on medium to large sized arteries, hence blood is assumed to be homogeneous. Assuming that blood acts as a Newtonian fluid is also an established approach, due to the predominantly high shear rates in medium to large arteries. Under this assumption the fluid viscosity is taken to be equal to the high shear rate limit of the viscosity of blood [66]. In order to validate this assumption, Perktold et al. [70] conducted a study in which
pulsatile Newtonian and non-Newtonian results were compared in a three-dimensional human carotid bifurcation model. It was found that the flow phenomena were essentially unchanged and that there were only minor differences in the basic flow characteristics when non-Newtonian effects were included.

Under the above assumptions, the laminar flow of blood is governed by the Navier-Stokes and continuity equations. To reduce computational complexities these equations are non-dimensionalized using the following characteristic parameters: velocity $U$, length $R$, and time $\omega^1$ (inverse of circular frequency):

$$
\begin{align*}
\tilde{x} &= \frac{x}{R} & \tilde{r} &= \frac{r}{R} \\
\tilde{u} &= \frac{u}{U} & \tilde{v} &= \frac{v}{U} \\
\tilde{p} &= \frac{p}{\max(\mu U / R, \rho U^2)} & \tilde{t} &= \omega t
\end{align*}
$$

where $u$ and $v$ are the axial ($x$) and radial ($r$) velocity components respectively, $p$ is pressure, $t$ is time, $\mu$ is the fluid viscosity, and $\rho$ is the fluid density. The primitive-variable form of the non-dimensionalized equations in an axisymmetric domain is:
where \( \nu \) is the kinematic viscosity, \( \alpha = R(\omega / \nu)^{1/2} \) is the Womersley parameter, \( Re=UR/\nu \) is the Reynolds number, and \( Re_1=\max(1,Re) \) is a pressure scaling term. In the subsequent sections, the \( \sim \) has been dropped from the dimensionless variables. Unless dimensional units are explicitly presented, variables are therefore taken to be dimensionless.

In this work, fluid flow is modelled in both the lumen and the wall of an artery simultaneously. Essentially there are two regions, porous (wall) and non-porous (lumen), which is an example of fluid in an open region flowing over the surface of a porous material. A convenient method used to treat this type of problem is Brinkman’s model [64], in which a body force term (Darcy term) is added to the governing momentum equations (Eq. 2.1). The Darcy term is of the form \( \mu u / K \), where \( \mu \) is the fluid viscosity, \( u \) is the velocity vector and \( K \) is the Darcian permeability of the medium. This method is desirable as it is computationally simple and allows matching of normal stresses at the interface. Brinkman’s model involves approximations, however it does give the correct behaviour in the limits as \( K \) approaches zero and infinity, reducing to Darcy’s law or the Navier-Stokes equations. Other studies [23, 25, 41, 95] have successfully implemented Brinkman’s model and it is the method used in the present work. It can be written, in non-dimensionalized form, as:
Brinkman's model is applied to both the lumen and wall regions of the artery by assuming that the dimensionless inverse Darcy number, $R'IK$, is zero within the lumen and some prescribed value in the wall.

\[ \alpha^2 \frac{\partial u}{\partial t} + \text{Re} \left( u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial r} \right) + \text{Re}_1 \frac{\partial p}{\partial x} = \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial r^2} + \frac{1}{r} \frac{\partial u}{\partial r} \right) + \frac{R^2}{K} u = 0 \]

\[ \alpha^2 \frac{\partial v}{\partial t} + \text{Re} \left( u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial r} \right) + \text{Re}_1 \frac{\partial p}{\partial r} = \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial r^2} + \frac{1}{r} \frac{\partial v}{\partial r} - \frac{v}{r^2} \right) + \frac{R^2}{K} v = 0 \quad (2.2) \]

\[ \frac{\partial u}{\partial x} + \frac{\partial v}{\partial r} + \frac{v}{r} = 0 \]

Brinkman's model is applied to both the lumen and wall regions of the artery by assuming that the dimensionless inverse Darcy number, $R'/K$, is zero within the lumen and some prescribed value in the wall.

### 2.1.2 Implementation of Finite Element Method

There are many numerical methods that can be used to solve partial differential equations such as Brinkman's model. One such technique is the Finite Element Method (FEM). The primary advantages of the FEM are that it has a good theoretical foundation, it works well with quite simple basis functions, the linear systems that arise are usually well conditioned, boundary conditions are easily handled, and the elements can be fit together to cover almost any region. In this work an existing well-tested, in-house Finite Element Method code [85, 86] is modified to include the Darcy term and is used to solve Equation 2.2. The FEM used in the code is based on the following algorithm:

1. The domain is discretized into simple, geometric shapes called "finite elements". Each element consists of a selected number of discrete nodes such that, across the domain, there are a total of $N_u$ nodes upon which velocity is described and $N_p$ nodes
upon which pressure is described. Shape functions are defined on each of these elements. The element type used in the existing Navier-Stokes solver is the nine-noded modified $Q^+_2$-$P_1$ Crouzeix-Raviart element (Appendix D).

2. The independent variables ($u$, $v$, and $p$) in the governing equations are expanded in terms of shape functions and nodal unknowns ($u_i$, $v_i$, and $p_i$) by the following relations:

$$u = \sum_{i=1}^{N_u} \phi_i u_i, \quad v = \sum_{i=1}^{N_v} \phi_i v_i, \quad p = \sum_{i=1}^{N_p} \psi_i p_i$$ (2.3)

where $\phi_i$ are the velocity shape functions and $\psi_i$ are the pressure shape functions.

3. The governing equations are spatially discretized. In the existing Navier-Stokes solver, Galerkin's technique is used to perform the discretization. This consists of multiplying the equations by the shape functions, $\phi_i$ and $\psi_i$, integrating over the domain, $\Omega$, with boundary $\Gamma$, and setting the resulting weighted residual to zero to obtain:
where \( \mathbf{n} = \mathbf{n}_e + n_e \mathbf{e}_r \) is the unit vector normal to \( \Gamma \).

4. Boundary conditions are applied. There are four boundary types in the problems considered in this work: inlet, wall, outlet and symmetry. Inlet conditions are Dirichlet-type and hence Equation 2.4 is replaced by a simple boundary equation at each inlet boundary node:

\[
\frac{\partial u}{\partial x} + \frac{\partial v}{\partial r} = 0
\]

At this point it will be assumed that boundary nodes on the wall receive the same treatment. More complex boundary treatments of the wall will be discussed in Section 2.1.3. At a line of symmetry, streamlines are parallel to the symmetry boundary and hence there is no flow across the symmetry line. Consequently, the normal velocity and the transverse gradient of the tangential velocity both vanish.
For example, if the symmetry boundary is the x-axis then the boundary conditions are:

\[ \frac{\partial u}{\partial r} = 0 \]

\[ v = 0 \]

Since the symmetry line coincides with the x-axis the pressure term in the line integral for the \( u \) component of the velocity vanishes \( (n=0) \) and the corresponding right-hand side of Equation 2.4 is zero. Finally, at the outlet the integrands of the line integrals of Equation 2.4 are also set to zero by assuming a traction-free boundary condition of the form:

\[ -Re_p n + \frac{\partial u}{\partial n} = 0 \]  \hspace{1cm} (2.5)

5. The discrete approximations of \( u, v, \) and \( p \) are substituted into the discretized equations generated in Step 3 and a system of \( 2N_u + N_p \) equations is obtained, which can be written in matrix form as follows:

\[ M \frac{du}{dt} + [S + N(u)]u + L^T p + \frac{R^2}{K} Mu = 0 \]  \hspace{1cm} (2.6)

\[ Lu = 0 \]
where \( \mathbf{u} \) is the vector of velocity unknowns, \( \mathbf{N}(\mathbf{u}) \) is the convection matrix, \( \mathbf{M} \) is the mass (inertial) matrix, \( \mathbf{p} \) is the vector of pressure unknowns, \( \mathbf{L} \) is the continuity matrix and \( \mathbf{S} \) is the diffusion matrix. These vectors and matrices are defined as follows:

\[
\mathbf{u} = [u_1, \ldots, u_{N_u}, v_1, \ldots, v_{N_u}]^T \\
\mathbf{p} = [p_1, \ldots, p_{N_p}]^T \\
\mathbf{M} = \alpha^2 \begin{bmatrix}
\int_\Omega \phi_i \phi_j d\Omega & 0 \\
0 & \int_\Omega \phi_i \phi_j d\Omega
\end{bmatrix}_{i,j=1 \ldots N_u} \\
\mathbf{S} = \begin{bmatrix}
0 & \int_\Omega \phi_i \phi_j d\Omega \\
0 & \int_\Omega \frac{\partial \phi_i}{\partial x} \frac{\partial \phi_j}{\partial x} + \frac{\partial \phi_i}{\partial r} \frac{\partial \phi_j}{\partial r} + \frac{\phi_i \phi_j}{r^2} d\Omega
\end{bmatrix}_{i,j=1 \ldots N_u} \\
\mathbf{N} = \text{Re} \begin{bmatrix}
u_k \int_\Omega \phi_i \phi_j \frac{\partial \phi_k}{\partial x} d\Omega & u_k \int_\Omega \phi_i \phi_j \frac{\partial \phi_k}{\partial r} d\Omega \\
v_k \int_\Omega \phi_i \phi_j \frac{\partial \phi_k}{\partial x} d\Omega & v_k \int_\Omega \phi_i \phi_j \frac{\partial \phi_k}{\partial r} d\Omega
\end{bmatrix}_{i,j,k=1 \ldots N_u} \\
\mathbf{L} = \text{Re} \begin{bmatrix}
\int_\Omega \psi_i \frac{\partial \phi_j}{\partial x} d\Omega & \int_\Omega \psi_i \frac{\partial \phi_j}{\partial r} + \frac{\psi_i \phi_j}{r} d\Omega \\
\int_\Omega \psi_i \frac{\partial \phi_j}{\partial x} d\Omega & \int_\Omega \psi_i \frac{\partial \phi_j}{\partial r} + \frac{\psi_i \phi_j}{r} d\Omega
\end{bmatrix}_{i=1 \ldots N_p, j=1 \ldots N_u}
\]

The above system could be solved for velocity and pressure. There is a problem, however, with the existing formulation. Since pressure does not appear in "its equation" (continuity), there is a zero block on the diagonal of the system matrix. One way of avoiding this problem is to arbitrarily introduce pressure into the continuity equation by modifying it to read: \( \nabla \cdot \mathbf{v} + \epsilon = 0 \). The error that is introduced by the addition of this pressure term is minimized through the selection of a very small value for \( \epsilon \), the penalty
parameter. This above equation can be used to eliminate the pressure term from the momentum equations. The necessary modifications to the formulation are made and the resulting matrix form of the system of penalized equations is:

\[
\alpha^2 M \frac{du}{dt} + \left[ S + \text{Re} N(u) - \frac{\text{Re}_L \mathbf{L}^T \mathbf{D}^{-1} \mathbf{L}}{\varepsilon} \right] u + \frac{R}{K} \mathbf{M} u = 0 \tag{2.7}
\]

where \( \mathbf{D} \) is the "pressure mass matrix". Entries in \( \mathbf{D} \) are given by:

\[
\mathbf{D} = \text{Re}_L \left[ \int_{\Omega} \psi_i \psi_j d\Omega \right]_{i,j=1...N_p}
\]

Before the system described in Equation 2.7 can be solved the convective terms must be linearized and the temporal derivative must be discretized. In the existing code, Newton's method is used to linearize the convective terms, and the second order Gear closed multistep formula is used for temporal discretization. Note that when steady flow problems are considered the Gear coefficients of the discretized time terms are set to zero.

There is an important detail to note in the implementation of the penalty method in this work. Care must be taken in using the penalty method to solve Brinkman's equation since the inverse Darcy number \( K/R^2 \) is typically very small in the porous region. If \( \varepsilon \) is too large then the order \( \varepsilon^{1/2} \) error in the velocity field due to the penalty
formulation [76] will overwhelm the impact of the permeability term, and the wall velocity field will not be properly resolved. On the other hand, if $\varepsilon$ is too small then the system of equations can become ill-conditioned and Newton's method will not converge to an accurate solution of the lumenal velocity field. The ideal value of $\varepsilon$ is a trade-off that requires validation of both the lumenal and wall velocity fields to ensure proper convergence. This value is case specific and dependent on $K/R^2$. For example, in the arterial model used in this work, $K/R^2$ is $2 \times 10^{-13}$ and it was found that $\varepsilon = 1 \times 10^{-10}$ yielded adequate resolution in both the lumen and wall regions. Adequate resolution was defined to have been reached when the velocity field in the wall region yielded an $L_2$ norm error of less than 0.1% compared to a smaller value of $\varepsilon$ and the velocity field in the lumen region yielded an $L_2$ norm error of less than 0.1% compared to a larger value of $\varepsilon$. In addition to selecting $\varepsilon$, a convergence tolerance must be chosen for the Newton iterations. In this work an error tolerance of $10^{-3}$ is used, which was shown previously to give converged solutions [85].

The final linear algebraic system can be solved for $u$ and $v$ either via direct or iterative methods. Direct solvers use a straightforward Gaussian elimination method to solve the equations, which tends to be very memory-intensive. On the other hand, iterative solvers do not explicitly form and factorize the matrix equations, and thus they are very useful for problems in which a direct solver would require excessive storage. The problems examined in this work are 2D problems that can be solved directly using an efficient storage technique such as a band or skyline solver. The existing Navier-Stokes solver makes use of a direct skyline solver.
2.1.3 Pressure Boundary Treatment

As described in Section 1.3.1, traditional boundary treatments of the lumen/wall interface include the application of a no-slip condition or a constant filtration velocity (Figure 2.1a). Solving the momentum equations in both the lumen and the wall simultaneously removes the need for a boundary condition at the interface. Instead, the boundary treatment can be moved to the outer boundary of the computational domain, which for the arterial model considered in this work, is the location of the adventitial vasa vasorum. Using the adventitial vasa vasorum as a boundary allows for the use of a pressure boundary treatment, which enables the velocity at the lumen/wall interface to develop continuously and appropriately (Figure 2.1b). From a computational perspective this means that there is no longer a simple boundary equation that can be applied to the nodes along the outer boundary. Instead, a constant value for the pressure is applied at each boundary node thus requiring the pressure terms in the line integrals of Equation 2.4 to be evaluated explicitly. For example, if a non-dimensionalized pressure of $p$ is to be applied at the vasa vasorum, then the right hand side of Equation 2.4 for the $u$ component of the velocity becomes:

\[ \int_{\Gamma} [- \text{Re} \, p n_x \, \mathbf{v} \cdot d\Gamma] \]

The normal velocity derivatives that appear on the right hand side of Equation 2.4 are unknown and must consequently be expanded in terms of the velocity shape functions and transferred to the left hand side of the equation, yielding (for the $u$ component):
\[ \int_{\Omega} \left[ \alpha^2 \frac{\partial u}{\partial t} \phi_i + \text{Re} \left( u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial r} \right) \phi_i - \text{Re}_1 \left( \frac{\partial p}{\partial x} + \nabla u \cdot \nabla \phi_i + \frac{R^2}{K} u \phi_i \right) \right] d\Omega - \int_{\Gamma} \left[ \frac{\partial u}{\partial n} \right] \phi_i d\Gamma \]

\[ = \int_{\Gamma} \left[ - \text{Re}_1 p n_x \right] \phi_i d\Gamma \]

Figure 2.1: Boundary treatment methods for arterial modelling. (a) traditional, where \( v_w \) is the filtration velocity; (b) new pressure treatment, where \( p \) is the pressure.
2.1.4 Numerical Integration

2.1.4.1 Area Integrals

Each of the area integrals required to form the matrices appearing in Equation 2.6 involve a product of shape functions, or shape function derivatives. Consequently, the integrands can be expressed as a polynomial. The method used in the existing code to evaluate these integrals is Gaussian quadrature, in which the integrand is evaluated at some number of pre-selected locations (Gauss points) in the integration interval. However, this integration is non-trivial due to the complex shape of the finite elements, which results from the complexities of the domain geometry. To overcome this difficulty a map is defined between the physical shape and a simpler reference shape. An example of this mapping for the 9-noded Crouzeix-Raviart is shown in Figure 2.2.

![Diagram of physical and reference elements](image)

**Figure 2.2:** Mapping of physical element to isoparametric reference element. (a) physical element, where \((x,y)\) is the coordinate of a point in physical space. (b) reference element, where \((r,s)\) is the coordinate of a point in the reference system.
The shape functions introduced in Step 2 of Section 2.1.2 are used to create the mapping from physical to reference elements. This is done by isoparametric mapping and, for a 9-noded element, takes the form:

\[
x(r,s) = x_1 \phi_1(r,s) + x_2 \phi_2(r,s) + \ldots + x_9 \phi_9(r,s) = \sum_{i=1}^{9} x_i \phi_i(r,s)
\]

\[
y(r,s) = y_1 \phi_1(r,s) + y_2 \phi_2(r,s) + \ldots + y_9 \phi_9(r,s) = \sum_{i=1}^{9} y_i \phi_i(r,s)
\]

With the mapping defined, integrals can be computed in physical space by the transformation:

\[
\int_{\Omega} f(x,y) \, dx \, dy = \int_{-1}^{1} \int_{-1}^{1} f(x(r,s), y(r,s)) |J| \, dr \, ds
\]

where \( \Omega \) is the physical element, \( \Omega_{\text{ref}} \) is the reference element, and \( |J| \) is the determinant of the Jacobian of the transformation that is defined:

\[
|J| = \left| \begin{array}{c}
\frac{\partial(x,y)}{\partial(r,s)} \\
\frac{\partial(x,y)}{\partial(r,s)}
\end{array} \right| = \begin{vmatrix}
\frac{\partial x}{\partial r} & \frac{\partial x}{\partial s} \\
\frac{\partial y}{\partial r} & \frac{\partial y}{\partial s}
\end{vmatrix}
\]

Gaussian integration can now be performed on the reference elements:
\[ \int_{-1}^{1} \int_{-1}^{1} \int_{r} f(r,s)J \, dr \, ds = \sum_{i=1}^{n} \sum_{j=1}^{n} w_i w_j f(r_i, s_j) J(r_i, s_j) \]

where \( n \) is the number of Gauss points per co-ordinate direction, \((r_i, s_j)\) is the coordinate of the Gauss point, and \(w_i\) and \(w_j\) are the Gauss point weights. This formula exactly integrates a polynomial of order \(2n-1\). In the existing Navier-Stokes solver it was found that a total of 16 Gauss points (4 in each co-ordinate direction) were sufficient to integrate the integrals associated with Equation 2.6 [85].

2.1.4.2 Line Integrals

In Section 2.1.3 a pressure boundary treatment was considered that required the evaluation of the line integrals of Equation 2.6. This integration is performed using a modification to the method outlined in Section 2.1.4.1. Since the integral only extends over the boundary edge of the elements, one of the reference coordinates will be held constant. For example, if the element is positioned such that the top edge of Figure 2.2b is aligned with the boundary, then \(s=+1\) across the line integral. Gaussian integration is then performed along the top edges of the boundary elements and can be written [69]:

\[ \int_{-1}^{1} f(r,1) \, d\Gamma^{\text{ref}} = \sum_{i=1}^{n} w_i f(r_i, 1) \, d\Gamma^{\text{ref}} (r_i, 1) \]

where \(\Gamma^{\text{ref}}\) is the reference element and is evaluated by the expression:
\[ s = \text{constant} : \quad d\Gamma^\text{ref} = \left[ \left( \frac{dx}{dr} \right)^2 + \left( \frac{dy}{dr} \right)^2 \right]^{\frac{1}{2}} \] 

\[ r = \text{constant} : \quad d\Gamma^\text{ref} = \left[ \left( \frac{dx}{ds} \right)^2 + \left( \frac{dy}{ds} \right)^2 \right]^{\frac{1}{2}} \]

Due to the reduction in order of the integrand polynomials (either \( r \) or \( s \) is constant), 4 Gauss points are used to integrate the line integrals.

### 2.2 Mass Transport Modelling

#### 2.2.1 Governing Equations

The concentration field in the lumen is computed via the solution of the mass transport equation, which can be written in non-dimensionalized form as:

\[
\alpha^2 \frac{\partial c}{\partial t} + \text{Re} \left( u \frac{\partial c}{\partial x} + v \frac{\partial c}{\partial r} \right) - \frac{1}{\text{Sc}} \left( \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial r^2} + \frac{1}{r} \frac{\partial c}{\partial r} \right) = 0
\]

where \( c \) is the concentration of the transported species, non-dimensionalized by a reference concentration \( C_0 \), \( \text{Sc} = \nu D \) is the Schmidt number, and \( D \) is the diffusivity of the species in the lumen. In this work the normalizing concentration \( C_0 \) is always taken as the bulk plasma concentration.
The concentration field in the wall is computed via the solution of a modified version of Equation 2.8. It is written in non-dimensionalized form as:

\[
\alpha^2 \frac{\partial c}{\partial t} + \text{Re}_{\text{eff}} \left( \frac{\partial c}{\partial x} + \frac{\partial c}{\partial r} \right) + \text{Re}_{\text{eff}} \frac{H c}{\text{Sc}_{\text{eff}}} \left( \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial r^2} + \frac{1}{r} \frac{\partial c}{\partial r} \right) = 0 \quad (2.9)
\]

where \( \text{Sc}_{\text{eff}} = \nu / D_{\text{eff}} \) is the effective Schmidt number based on the effective diffusivity \( (D_{\text{eff}}) \) of the species in the wall, \( \text{Re}_{\text{eff}} = B^* \text{Re} \) is the effective Reynolds number based on the hindered transport coefficient \( (B) \) of the species in the wall, and \( H \) is a normalized apparent first order reaction rate constant that represents the binding and degradation of the transported species by the cells of the media [78]. The parameter \( B \) is a measure of the hindering effect caused by the interactions between the transported species and the wall components. For example, the analysis of the hindered transport of LDL in the artery wall in Section 1.4 yielded a value of \( B = 0.02 \).

2.2.2 Streamline Upwind/Petrov-Galerkin Method

2.2.2.1 Background

In Chapter 1 it was stated that there are numerical complications associated with the computational analysis of arterial mass transport. These complications arise from large values of the Peclet number, defined as:

\[
\text{Pe} = \frac{|\mu| R}{D}
\]
where \( l \) is the magnitude of the velocity, \( R \) is a characteristic length, and \( D \) is the diffusivity. In the case of numerical modelling, the appropriate characteristic length is the grid size. This yields a grid Peclet number, which is a measure of the relative strength of convective and diffusive mass transfer over a single grid cell.

From the mass transport equation (Eq. 2.8) it can be noted that the transport of species with high Schmidt numbers, and therefore high grid Peclet numbers, will be convection dominated. Unfortunately the standard Galerkin method described in Section 2.1.2 fails when applied to convection-dominated problems. Spurious oscillations in the solution, which can "pollute" the entire computational domain, appear in regions where high gradients are expected. Traditionally, the only method that was available for removing the oscillations was to severely refine the mesh, thus reducing the grid Peclet number to an acceptable level. Clearly this approach would be prohibitively memory-intensive for large two- or three-dimensional problems. As a result, there was interest in developing alternate methods to remove the oscillations.

In efforts to eliminate oscillations, several "upwind" techniques were developed which are based on the principle of artificial diffusivity. This approach is best understood by considering a central-difference scheme, which is appropriate since the Galerkin FEM yields central-difference type approximations of differential operators. These approximations can be best illustrated through the use of a 1-D example. Imagine a set of points spaced equally between \( x=0 \) and \( x=R \). If \( x_j \) is an arbitrary point between 0
and $R$, then $x_{j-1}$ is its left neighbour and $x_{j+1}$ is its right neighbour. Using the central-difference scheme the approximations to the differential operators are:

\[
\frac{\partial \theta}{\partial x}(x_j) = \frac{-\theta_{j-1} + \theta_{j+1}}{2\Delta x}
\]

\[
\frac{\partial^2 \theta}{\partial x^2}(x_j) = \frac{\theta_{j-1} - 2\theta_j + \theta_{j+1}}{\Delta x^2}
\]

where $\Delta x$ is the spacing between the points. The corresponding finite difference molecules or stencils are:

The upwind technique was established when it was found that if the convective derivatives were approximated with solution values at the upstream and central nodes of a three-node stencil, the oscillations were eliminated. This upwind difference stencil is:
This approach can be interpreted as simply adding artificial diffusivity to the central difference treatment, which triggered criticism of upwind techniques [53]. Next, it was found that the ideal quantity of artificial diffusivity could be added to the central formulation by considering the Peclet number. This was called "smart" or "ideal" upwinding.

The upwinding technique when applied to FEM originally consisted of weighting the element upstream of a node more heavily than the downstream element [13]. Other methods followed that also gave exact solutions for one-dimensional problems [42, 43]. However, when applied to multi-dimensional problems, many of these methods suffered from overdiffusion in the cross-stream direction. To address this, the streamline upwind/Petrov-Galerkin (SUPG) technique was developed, which employs an upwind weighting in the weighted residual formulation that acts only in the streamline direction [10]. The SUPG method has been used effectively in previous arterial mass transport studies [74, 75], and as a result of its previous success, SUPG was selected for implementation in this work.
2.2.2.2 Formulation

The SUPG method consists of modifying the weighting functions used in the FEM weighted residual formulation. In the standard Galerkin formulation the shape functions used to describe the independent variables are also used as the weighting functions in the weak statement of the problem. In the SUPG method an upwind term is added to the shape functions:

$$\varphi^* = \varphi + \boldsymbol{u} \cdot \nabla \varphi$$ \hspace{1cm} (2.10)

where $\varphi^*$ is the SUPG weighting function, $\varphi$ is the Galerkin weighting function (shape function), and $\tau$ is the upwind parameter. Here $\tau$ determines the amount of upwind weighting on an elemental basis. For bilinear elements $\tau$ is defined as [10]:

$$\tau = \frac{\alpha_\xi h_\xi u_\xi + \alpha_\eta h_\eta u_\eta}{|\boldsymbol{u}|} \cdot \frac{1}{2|\boldsymbol{u}|}$$ \hspace{1cm} (2.11)

where the subscripts $\xi$ and $\eta$ refer to locally defined isoparametric reference element directions such that $h_\xi$ and $h_\eta$ are the characteristic element dimensions and:

$$\alpha_\xi = \coth\left(Pe_\xi^h\right) - \frac{1}{Pe_\xi^h} \hspace{1cm} \alpha_\eta = \coth\left(Pe_\eta^h\right) - \frac{1}{Pe_\eta^h}$$

$$Pe_\xi^h = \frac{u_\xi h_\xi}{2D} \hspace{1cm} Pe_\eta^h = \frac{u_\eta h_\eta}{2D}$$

$$u_\xi = e_\xi \cdot \boldsymbol{u} \hspace{1cm} u_\eta = e_\eta \cdot \boldsymbol{u}$$
where \( \mathbf{e}_\xi \) and \( \mathbf{e}_\eta \) are unit vectors directed positively along the local isoparametric axes.

Since we are dealing with discretized equations all calculations are conducted at integration points. In isoparametric elements the local co-ordinate directions may vary from point to point. As a result, Petera et al. [71] calculate integration point values in place of the above element-wise definition of unit vectors, which is the approach used in the current work:

\[
\mathbf{e}_\xi = \left( \sum x_i \frac{\partial \phi_i}{\partial \xi}, \sum r_i \frac{\partial \phi_i}{\partial \xi} \right) \quad \sqrt{D_\xi} \qquad \mathbf{e}_\eta = \left( \sum x_i \frac{\partial \phi_i}{\partial \eta}, \sum r_i \frac{\partial \phi_i}{\partial \eta} \right) \quad \sqrt{D_\eta}
\]

\[
D_\xi = \left( \sum x_i \frac{\partial \phi_i}{\partial \xi} \right)^2 + \left( \sum r_i \frac{\partial \phi_i}{\partial \xi} \right)^2 \\
D_\eta = \left( \sum x_i \frac{\partial \phi_i}{\partial \eta} \right)^2 + \left( \sum r_i \frac{\partial \phi_i}{\partial \eta} \right)^2
\]

where \((x_i, r_i)\) are the cylindrical nodal coordinates. Petera et al. also use point-wise definitions of the element characteristic dimensions in the \( x \) and \( r \) directions:

\[
h_x = 2 \left| \sum x_i \frac{\partial \phi_i}{\partial \xi} + \sum x_i \frac{\partial \phi_i}{\partial \eta} \right| \\
h_r = 2 \left| \sum r_i \frac{\partial \phi_i}{\partial \xi} + \sum r_i \frac{\partial \phi_i}{\partial \eta} \right| \\
h_\xi = \mathbf{e}_\xi \cdot (h_x, h_r) \\
h_\eta = \mathbf{e}_\eta \cdot (h_x, h_r)
\]
2.2.3 Subelement Technique

As a result of the very high Peclet number flow associated with LDL transport (Pe\(\equiv2\times10^8\)), a very thin concentration boundary layer forms at the lumen/wall interface. Extremely high grid resolution must be applied in this region to correctly capture the concentration gradients. A subelement technique [75] was implemented such that each velocity-pressure element was divided into 16 concentration elements (Figure 2.3). Not only does the subelement technique provide high resolution in the concentration boundary layer, but it also has the added benefit of reducing the grid Peclet number. In addition, to ensure that the concentration field was adequately resolved a mesh was developed with very fine resolution near the wall. A mesh refinement study was also performed (see Section 4.2.4).

![Diagram: Original quadratic velocity element (9 nodes/element) is subdivided into 16 bilinear concentration elements (4 nodes/element)](image)

Figure 2.3: Original quadratic velocity element (9 nodes/element) is subdivided into 16 bilinear concentration elements (4 nodes/element)
2.2.4 Implementation of Finite Element Method with SUPG

The steps outlined in Section 2.1.2 are repeated with certain modifications as follows:

1. The computational domain is divided into finite elements such that there are a total of \( N_c \) concentration nodes in the domain. As a result of the subelement technique the element type used for the solution of the mass transport equation is a 4-noded bilinear element.

2. The independent variable \((c)\) in the governing equation is expanded in terms of shape functions and nodal unknowns \((c_i)\) by the following relation:

\[
c = \sum_{i=1}^{N_c} \phi_i c_i \quad (2.15)
\]

where \(\phi_i\) are the concentration shape functions.

3. The governing equation is spatially discretized using the SUPG method. This consists of multiplying the equations by the SUPG weighting functions, \(\varphi^*\), integrating over the domain, \(\Omega\), with boundary \(\Gamma\), and setting the resulting weighted residual to zero to obtain:

\[
\int_{\Omega} \left[ \alpha^2 \frac{\partial c}{\partial t} \varphi^*_i + \text{Re} \left( u \frac{\partial c}{\partial x} + v \frac{\partial c}{\partial y} \right) \varphi^*_i + \frac{1}{Sc} \nabla c \cdot \nabla \varphi^*_i \right] d\Omega = \int_{\Gamma} \left[ \frac{1}{Sc} \frac{\partial c}{\partial n} \right] \varphi^*_i d\Gamma \quad (2.16)
\]
Note that Equation 2.16 represents the discretization of the lumenal mass transport equation (Eq. 2.8). For brevity, this section will show the technique for Equation 2.8. This technique can be developed in an analogous manner for the wall mass transport equation (Eq. 2.9).

4. Boundary conditions are applied. The treatments follow the same format listed in Step 4 of Section 2.1.2. The inlet and wall boundary nodes are Dirichlet-type, there is a zero normal concentration gradient applied at the axis of symmetry, and zero axial concentration gradient at the outlet. Again, the right-hand side of Equation 2.16 is zero for the outlet and symmetry boundary conditions. More complex mixed wall boundary conditions are considered in Section 2.2.6.

5. The discrete approximation of \( c \) is substituted into the discretized equation generated in Step 3 and a system of \( N_c \) equations is obtained, which can be written in matrix form as follows:

\[
M_c \frac{dc}{dt} + [S_c + N_c(u)]c = 0
\]  

(2.17)

where \( c \) is the vector of concentration unknowns, \( N_c(u) \) is the convection matrix, \( M_c \) is the mass matrix and \( S_c \) is the diffusion matrix. These vectors and matrices are defined as follows:
This system of equations is solved using the same solver described for the momentum equations. Note too that the velocity field calculated in Section 2.1.2 is used directly in the solution of the mass transport equation and that Equation 2.17 is linear.

\[ c = [c_1, ..., c_{N_c}]^T \]
\[ M_c = \alpha^2 \left[ \int_\Omega \phi_i^* \phi_j d\Omega \right]_{i,j=1,...,N_c} \]
\[ S_c = \frac{1}{Sc} \left[ \int_\Omega \frac{\partial \phi_i^*}{\partial x} \frac{\partial \phi_j}{\partial x} + \frac{\partial \phi_i^*}{\partial r} \frac{\partial \phi_j}{\partial r} d\Omega \right]_{i,j=1,...,N_c} \]
\[ N_c = \text{Re} \left[ u_j \int_\Omega \phi_i^* \phi_j \frac{\partial \phi_k}{\partial x} d\Omega + v_j \int_\Omega \phi_i^* \phi_j \frac{\partial \phi_k}{\partial r} d\Omega \right]_{i,j,k=1,...,N_c} \]

2.2.5 Semi-Coupled Approach

There is another difference in the solution of the concentration field in the two-region arterial model considered in this work. Unlike the velocity field, which is solved simultaneously in both the lumen and the wall, the concentration field is first solved in the lumen and then in the artery wall. This is due to the nature of the endothelial layer separating the lumen from the wall, which acts as a very restrictive barrier to the passage of macromolecules such as LDL. Consequently, the LDL concentration on the wall-side of the endothelium is approximately two orders of magnitude less than the concentration on the lumenal side. In and of itself this does not present a problem; however, the endothelium is extremely thin (~2x10\(^{-3}\)mm compared to an arterial diameter of 7mm), which creates computational issues. Attempting to model the rapid change in concentration over such a small distance would be very challenging. As a result, the
concentration fields in the lumen and the wall are solved in a segregated manner, as follows. First the concentration is solved in the lumenal region, without taking account of the wall region. Then the concentration is computed in the wall. The two regions are coupled by accounting for the lumenal concentration in the solution of the wall concentration. This is done in the wall through the boundary condition at the lumen/wall interface, which includes a term for the *lumenal* concentration at the interface. In this way the wall concentration field is coupled to the concentration field in the lumen. This is discussed in more detail in the Section 2.2.6.

The approach discussed in the preceding paragraph was considered to be acceptable for the following reason. As described above, the LDL concentration on the wall-side of the endothelium is approximately two orders of magnitude less than the concentration on the lumenal side. Consequently, the amount of lumenal LDL that is lost to the wall is so small, compared to the bulk plasma concentration, that the lumenal concentration field is only very weakly affected by the uptake into the wall. Thus it is assumed that the lumenal concentration field can be solved first, independently from the wall, and then used as a key input to the wall concentration computations. This assumption is revisited in Section 2.2.6.1.

### 2.2.6 Concentration Boundary Conditions

The discussions presented in the previous section and Chapter 1 have indicated the importance of a sound treatment of the concentration boundary conditions, which is crucial to obtaining a meaningful analysis of the arterial mass transport of LDL. In
Section 2.2.4 the boundary conditions at the inlet, outlet and axis of symmetry were established. The treatment of the "wall" boundary conditions is more complex. Because the mass transport is solved separately in the two regions, the discussion of the "wall" boundaries will also be undertaken in two parts.

Consider first lumenal mass transport. In this region the "wall" boundary is the interface between the lumen and the wall, which can be seen in Figure 2.4a.

Figure 2.4: Depiction of "wall" boundaries in the arterial (a) lumen, and (b) wall.

An appropriate treatment of this lumenal "wall" boundary is to apply a mass balance at the interface. Here, the amount of the species passing into the wall is determined as a
difference between the amount carried to the vessel wall by transmural filtration and the amount that diffuses back to the mainstream [93]. This results in a mixed boundary condition that is written:

\[
\frac{u_n c}{ReSc} \frac{1}{\partial n} \frac{\partial c}{\partial n} - \frac{M}{U} c = 0
\]

where \(u_n\) and \(c\) are the normalized velocity and concentration at the lumen/wall interface, \(n\) is the dimensionless coordinate normal to the wall (directed away from the lumen), and \(M\) is the overall mass transfer coefficient (permeability) of the species at the arterial wall. More generally, this type of boundary condition can be written in the form:

\[
\frac{\partial c}{\partial n} = a_0 (u_n c) + a_1 (c) + a_2
\]

where, in the case of Equation 2.18, \(a_0 = ReSc\), \(a_1 = -MReSc/U\), and \(a_2 = 0\).

The treatment of the wall mass transport involves two "wall" boundaries, which can be seen in Figure 2.4b. The outer boundary is located at the adventitial vasa vasorum (boundary #1), and the inner boundary is located at the lumen/wall interface (boundary #2). At boundary #2 the influx of LDL from the lumen must equal the convective-diffusive flux on the medial side of the interface [63]. This is written
where $M$ is the species permeability of the endothelium. $\varepsilon_s$ is the species equilibrium distribution coefficient representing the fraction of tissue space into which the LDL can enter and distribute, and the activity, and therefore partition coefficient, of the species. This coefficient accounts for the difference in LDL affinity between the two media (lumen and wall). $c_p$ is the concentration of the species in the plasma and is taken to be the local lumenal LDL concentration at the lumen/wall interface.

A less distinct physical barrier separates the media from the adventitial blood supply than from the lumenal blood supply (boundary #1). However, the concentration boundary condition at the adventitial vasa vasorum is implemented in an analogous manner with the boundary acting as an "effective membrane" [63]

$$- \text{Re}_{\text{eff}} \frac{M}{BU} \left( \frac{1}{\varepsilon_s} c - c_p \right) = \text{Re}_{\text{eff}} u_n c - \frac{1}{S_{\text{c}_{\text{eff}}} \frac{\partial c}{\partial n}}$$  \hspace{1cm} (2.20)

where $M_{vv}$ is the normalized species permeability of the effective membrane separating the adventitial blood supply from the media, and $c_p$ is the bulk plasma concentration.

Examining Equation 2.20 and Equation 2.21, it can be noted that the values of $\varepsilon_s$ and $D_{\text{eff}}$ were kept constant. This is due to the approach used for the lumenal boundary represented by Equation 2.20, in which the endothelium, intima and IEL are taken
together and treated as a single boundary. In this way only the media is modelled and it is assumed that the transport properties of the media are constant throughout the wall. As a result, $\varepsilon$, and $D_{\text{eff}}$ do not change.

Equation 2.20 and Equation 2.21 can also be written in the form of Equation 2.19. The values for $a_0$, $a_1$, and $a_2$ are $Re_{\text{eff}}Sc_{\text{eff}}$, $MRe_{\text{eff}}Sc_{\text{eff}}/(BU\varepsilon)$, and $-Mc_pRe_{\text{eff}}Sc_{\text{eff}}/(BU)$, respectively, for Equation 2.20, and $Re_{\text{eff}}Sc_{\text{eff}}$, $-MvRe_{\text{eff}}Sc_{\text{eff}}/(BU\varepsilon)$, and $Mv^c_pRe_{\text{eff}}Sc_{\text{eff}}/(BU)$, respectively, for Equation 2.21.

Akin to the pressure boundary treatment described in Section 2.1.3, the mixed boundary condition treatments for concentration shown above result in non-zero integrands for the right-hand side of Equation 2.16. As a result, substituting Equation 2.19 into Equation 2.16 yields:

$$
\int_{\Omega} \left[ \alpha \frac{\partial c}{\partial t} \varphi^* + Re \left( \frac{\partial c}{\partial x} + \nu \frac{\partial c}{\partial r} \right) \varphi^* + \frac{1}{Sc} \nabla c \cdot \nabla \varphi^* \right] d\Omega = \int_{\Gamma} \left[ \frac{1}{Sc} \left( a_0 \nu + a_1 \right) \varphi^* \right] d\Gamma
$$

Equation 2.22

The integrals shown in Equation 2.22 are evaluated using the same method described in Section 2.1.4.
2.2.6.1 Semi-Coupled Assumption

Recall from 2.2.5 that it was assumed that the lumenal LDL concentration field is only very weakly affected by the uptake of LDL into the wall. This assumption can be checked by conducting an order of magnitude analysis on the terms in Equation 2.18. If the assumption is correct, then the wall flux term in Equation 2.18 should be negligible compared to the convective and diffusive terms. The convective and diffusive terms can be approximated by the corresponding transport rates in the boundary layer. These were determined in Section 1.4 to be approximately $4 \times 10^{-6}$ cm/s and 21 to $34 \times 10^{-6}$ cm/s for convection and diffusion, respectively. The flux into the wall is governed by the permeability of the endothelium to LDL, which is $0.02 \times 10^{-6}$ cm/s. Thus it can be seen that the convective and diffusive terms are much larger than the wall flux term, and it can be concluded that the uptake of LDL into the wall only very weakly affects the lumenal concentration field.

2.3 Steady State Assumption

Although blood flow is pulsatile in nature, as a simplifying assumption only steady flow is investigated in this work. This was considered to be reasonable due to previous studies by Ma et al. [55] and Rappitsch et al. [75] that indicate pulsatility does not exert a significant effect on macromolecular mass transport. Ma et al. studied high Schmidt number mass transfer in the separated flow region of a sudden expansion model under pulsatile conditions. It was found that there was very little difference in the wall mass transfer coefficient distribution at various time points throughout the flow cycle.
Rappitsch et al. studied albumin mass transport in a constricted artery under pulsatile conditions. It was found that the pulsatile time-averaged wall flux and steady wall flux profiles were almost identical. Based on these findings, unsteady effects are not included in the mass transport studies in this work.
CHAPTER 3

3 Validation Tests

3.1 Introduction

As detailed in Chapter 1, the goal of this work is to study convection-dominated mass transport in the two regions of the artery, lumen and wall, simultaneously. Considerable modifications to the original Navier-Stokes code by Steinman had to be made before this goal could be achieved. The primary additions to the code included the addition of a porous wall module to solve Brinkman’s equation (Eq. 2.2), a mass transport module to solve the mass transport equation (Eq. 2.8 and 2.9), and the SUPG method to treat high Peclet number mass transport. Before these modules could be used together to solve arterial LDL transport problems, each formulation was tested individually to ensure its accuracy. The respective validation tests are presented in the subsequent sections.

3.2 Porous Wall Module

In order to test the implementation of Brinkman’s model, two different geometries were constructed. The first was a straight channel, in which the flow has a known analytical solution, and the second was an axisymmetric tube with a constriction. This
second model was built to examine the performance of the module on a more complicated geometry that better reflects the arterial models used in later studies (Chapters 4-6).

3.2.1 Straight Channel

A theoretical study by Poulikakos et al. [72] determined an analytical solution for fully developed flow in a channel partially filled with a porous matrix (see Figure 3.1). This study was relevant for the work presented here as Poulikakos et al. used Brinkman's model to model the flow inside the porous region.

![Figure 3.1: Straight channel geometry. x is the horizontal directional, y is the vertical direction, u is the x component of velocity and h is the height of the channel. The location y=s is the interface between the porous regions (shaded gray) and the non-porous region (unshaded).](image-url)
The boundary conditions at \( y=0 \) and \( y=h(=1) \) were taken to be \( u=0 \) and \( \partial u/\partial y=0 \), respectively. Based on these boundary conditions, the theoretical solution for the velocity distribution in the channel was determined to be:

\[ u = \begin{cases} 
\frac{1}{2}(y^2 - s^2) - Da^2 s \tanh \left( (1-s)Da \frac{1}{2} \right) + Da \left[ \frac{1}{\cosh \left( (1-s)Da \frac{1}{2} \right)} - 1 \right], \\
Da \cosh \left( (s-y)Da \frac{1}{2} \right) - Da^2 s \sinh \left( (1-y)Da \frac{1}{2} \right) \end{cases} \]

\[(3.1)\]

where \( y \) is the vertical position, \( u \) is the velocity, \( s \) is the vertical location of the interface, \( Da=K/h^2 \) is the Darcy number, and \( K \) is the Darcian permeability.

For testing purposes, a 2D straight channel mesh, modelled after Figure 3.1, was created with \( s=0.8 \). The mesh contained 1400 elements and extended from \( x=0 \) to \( x=6 \). The velocity field was computed for 3 different values of inverse Darcy number (\( Da^{-1} \)): \( 1 \times 10^1 \), \( 1 \times 10^3 \) and, \( 1 \times 10^5 \). The results were compared to the corresponding analytical solution (Eq. 3.1) and were all found to be accurate within an \( L_2 \) norm error of order \( 1 \times 10^{-6} \). The outlet profiles (at \( x=6 \)) from these runs can be seen in Figure 3.2.
In addition to comparing the computational solutions to the analytical solutions, it was verified that the continuity equation was satisfied on an elemental basis in each run. Recall from Section 2.1.2 that the penalty method was used to solve Brinkman's model in this work. As a result, mass can only be conserved within the value selected for the penalty parameter, $\varepsilon$. For the straight channel solutions discussed here, $\varepsilon$ was set at
For each run the error in mass conservation was computed element-wise. Each element was found to have an error that was less than the penalty parameter, and the average error per element was found to be $1 \times 10^{-8}$, which was well within the error bound expected from the value of the penalty parameter.

### 3.2.2 Constricted Tube

The ultimate goal of this research is to model LDL transport in an arterial geometry. In the study of haemodynamics one type of geometry that is of interest is that of a constricted (stenosed) artery, as discussed in Chapter 1. In order to test the porous wall module on a model more akin to a stenosed artery, a geometry comprising of a tube with a constriction was created. The mesh for this geometry consisted of a curved constriction that provided a height reduction of 50% at its center with a porous region located just above the constriction. This can best be understood by examining the mesh in Figure 3.3.

![Figure 3.3: Tube with constriction. Porous region is shaded gray.](image)
The velocity field in the tube model was computed under the boundary conditions: Poiseuille inlet profile, no-slip at the wall and traction-free flow at the outlet. The Reynolds number was set at 13 and three different inverse Darcy numbers were tested: 0, $1 \times 10^5$ and $1 \times 10^{12}$. The last value was selected as it was close to the inverse Darcy number of an actual artery wall, and would therefore test the module under conditions similar to the ones imposed in the arterial studies. The results for the three inverse Darcy numbers can be seen in Figure 3.4.
Figure 3.4: Velocity plots for constricted tube. Right side: magnified section from left side. (a) (b) inverse Darcy number=0; (c) (d) inverse Darcy number=1x10^5; (e) (f) inverse Darcy number=1x10^{12}. Ref vector=mean inlet velocity (left) and 0.1 times mean inlet velocity (right).
In Figure 3.4a and Figure 3.4b the inverse Darcy number is so low \((0)\) that there is no barrier to flow in the porous media and the fluid moves through unimpeded. In Figure 3.4c and Figure 3.4d the inverse Darcy number is higher \((10^5)\) and the flow is more restricted through the porous region. Finally, in Figure 3.4e and Figure 3.4f the inverse Darcy number is so high \((10^{12})\) that although there is flow within the porous media the velocity is several orders of magnitude smaller than that of the bulk flow and thus the porous velocity vectors cannot be seen when plotted on the same scale.

Although they cannot be compared against an analytical solution, the velocity fields displayed in Figure 3.4 appear to be credible. Combined with the validation results from the channel/analytical test, it was concluded that the implementation of Brinkman’s model was working accurately.

### 3.3 Mass Transport Module

A key addition to the existing Navier-Stokes code was the implementation of a mass transport module to solve the mass transport equation (Eq. 2.8 and Eq. 2.9). At this stage, the standard Galerkin Finite Element Method was used to test the operation of the mass transport module, thus excluding the additional complexities associated with the implementation of the SUPG method. Due to the similarities between the Navier-Stokes equations and the mass transport equation, much of the formulation outlined in Section 2.1.2 was applicable. However, owing to particulars of the original code, the nine-noded Crouzeix-Raviart element could not be used for mass transport. Instead, an eight-noded
(no centroid) 'serendipity' element was employed [104]. Ultimately, bilinear elements were used for the implementation of SUPG, such that the serendipity elements were only used for the following test of the mass transport module.

Due to the inability of Galerkin's technique to handle convection-dominated problems, the testing of the mass transport module was restricted to low Peclet number flow. A suitable test problem with a known analytical solution was sought. Kaazempur [45] developed a 2-dimensional solution to the mass transport equation for the case of a Gaussian-shaped concentration profile convected in a uniform flow field. At time \( t=0 \) and position \((x, y)\), the solution can be written in non-dimensionalized form as:

\[
c(x, y,0) = \exp\left\{-\frac{R^2}{2\sigma_0^2} [r - r_0]^2 \right\}
\]

(3.2)

where \( c \) is the concentration, \( r=(x, y) \) is the position vector, \( r_0=(x_0, y_0) \) is the position of the center of the Gaussian hill at \( t=0 \), \( R \) is the characteristic length, and \( \sigma_0 \) is the standard deviation of the Gaussian profile at \( t=0 \). The concentration distribution at time \( t \) is given by:

\[
c(x, y, t) = \left(\frac{\sigma_0}{\sigma(t)}\right)^2 \exp\left\{-\frac{R^2}{2\sigma(t)^2} \left[r - \left(r_0 + \frac{Re}{\alpha^2} ut\right)\right]^2\right\}
\]

(3.3)
where \( u \) is the velocity vector, \( \alpha \) is the Womersley parameter, \( Re \) is the Reynolds number, and

\[
\sigma(t) = \sigma_0 \left( 1 + \frac{R^2}{\alpha^2 Sc \sigma_0^2} \right)^{1/2}
\]  

(3.4)

where \( Sc \) is the Schmidt number.

This problem was solved computationally on the domain \(-1<x<1\) and \(-1<y<1\) using a mesh containing 625 elements. The velocity field was constant and uniform with components \( u_x = u_y = 1/\sqrt{2} \), and the time step was chosen to be \( \Delta t = 0.001 \) for all runs. Boundary conditions were obtained by calculating the analytical solution at each of the four boundaries at every time step. At \( t=0 \), the initial concentration distribution was centered at \((x_0, y_0) = (0,0)\) and can be seen in Figure 3.5.
Figure 3.5: Original concentration distribution for mass transport module test problem. Arrow shows direction of flow.

Several computational runs were conducted using various values for $\alpha$ and $Pe$. In each instance the $L_2$ norm of the error was calculated, where the error is defined to be the difference between the analytical solution and the computational solution. In simulations such as these, where there is no imposed time scale, $\omega^1$, the natural scaling for the time variable is the convective time scale, $R/U$. Under such circumstances, it is convenient to define a dimensionless time, $t^*$, obtained by scaling real time by $R/U$. The dimensionless
time used in the numerical algorithm ($t$) is then related to $t'$ by the relationship $t = t' \alpha^2 / \text{Re}$. Therefore, to ensure that the results from runs with different values of $\alpha$ and $\text{Re}$ were comparable, all simulations were run out to a value of $t' = 0.1$, in which case the displacement of the center of the Gaussian profile was the same for all runs.

The results in Figure 3.6 illustrate the impact of $\alpha$ and the grid Peclet number ($\text{Pe}_\Delta = \text{ReSc}\Delta x$) on the $L_2$ norm error, and Figure 3.7 shows the results at $t = t_{\text{final}}$ for the case of $\alpha = 10$ and $\text{Pe}_\Delta = 1.6$. In all of the results shown in Figure 3.6, the grid Peclet number was varied by changing the value of the Schmidt number while keeping the Reynolds number ($= 200$) and grid spacing ($= 0.04$) constant.
Figure 3.6: $L_2$ norm of error vs. grid Peclet number ($Pe_{\Delta x}$) for a range of $\alpha$ values.
Figure 3.7: Computed concentration distribution for mass transport module test problem. (a) at time $t=0$; (b) at time $t=t_{\text{final}}$. 
Examining the results in Figure 3.6, it can be seen that the error increased for increasing grid Peclet number. Recall that the grid Peclet number increases as the problem becomes more dominated by convection. Since the standard Galerkin method, used to study this problem, is not well suited to convection-dominated problems, it was expected that the error would increase as the grid Peclet number increased. It can also be noted from Figure 3.6 that the error increased with decreasing Womersley parameters, which can be explained as follow. The mass transport equation (Eq. 2.8) can be written as:

$$\frac{\alpha^2}{\text{Re}} \frac{\partial c}{\partial t} = f(c)$$

which is equivalent to

$$\frac{\partial c}{\partial t^*} = f(c)$$

for $t^*$ as defined above. When discretized by using a second order accurate scheme, such as the Gear method used in the code, this gives the equivalent differential equation

$$\frac{dc}{dt^*} + \text{const}(\Delta t^*)^2 \frac{d^3 c}{dt^{*3}} + \cdots = f(c)$$
which shows that the truncation error is proportional to $(\Delta t^*)^2 \frac{d^3 c}{dt^*^3}$. Since $c$ depends physically on $t^*$ ($t^*$ is the time scale for convection), the $d^3 c/dt^*^3$ term in the truncation error is the same for all runs, and therefore the truncation error depends on $(\Delta t^*)^2$. Thus the error per time step, $\Delta t$, is proportional to $\Delta t^2 Re^2/\alpha^4$. The number of time steps needed to march out to a fixed $t^*$ scales with $\alpha^2/Re$, such that the total error (per run) scales with $\Delta t^2 Re/\alpha^2$. Consequently, the total error should decrease with increasing Womersley parameter $(\alpha)$, which was observed in Figure 3.6. As further confirmation of this analysis, each of the curves in Figure 3.6 was multiplied by the square of its respective Womersley parameter $(\alpha^2)$. $\Delta t$ and Re were not included as they were held constant in every run. As predicted by the above analysis, when multiplied by $\alpha^2$, the original curves collapsed into one curve, which can be seen in Figure 3.8.
Figure 3.8: $L_2$ norm of error times $\alpha^2$ vs. grid Peclet number ($P_{e\Delta x}$) for the range of $\alpha$ values shown in Figure 3.6.

The results from this analysis indicated that the mass transport module was performing as expected. This conclusion was drawn based on the following observations:

- The error was found to be acceptably small.
- The error showed the expected dependence on $P_{e\Delta x}$ and $\alpha$. 
3.4 SUPG Module

Validation of the SUPG module was executed in two steps. First, standard benchmark tests for convection-dominated flow problems were carried out. In all cases the results clearly demonstrated SUPG’s ability to handle high Peclet number flow, and were in very good agreement with the original results published by Brooks et al. [10]. As a next step it was desired to validate the implementation of SUPG on more relevant arterial models. Two existing arterial mass transport studies in a constricted axisymmetric tube were chosen [74, 75]. The results from these studies were reproduced and were also found to be in very good agreement with the original published results.

3.4.1 Benchmark Tests

Two benchmark tests were selected from the original paper on SUPG [10]. They are entitled: “Advection Skew to a Mesh” and “Cone Impinging on a Mesh Boundary”.

3.4.1.1 Advection Skew to a Mesh

In this problem the flow was unidirectional, constant (||v||=1) and at an angle of 45° to the mesh. The Peclet number was taken to be $10^6$ and a ten-by-ten mesh of equal sized square elements was used. The inflow boundary conditions can be seen in Figure 3.9, and the two different outflow conditions that were considered are:

1. Homogeneous Natural Boundary Condition (Neumann type): Due to the high Peclet number the solution of this case is basically the advection of the inflow boundary
condition in the direction of flow. The results can be seen in Figure 3.10 and demonstrate the improvement of the SUPG method over the standard Galerkin method.

2. Homogeneous Essential Boundary Condition (Dirichlet type): This solution is identical to the previous one except where a very thin 'boundary layer' forms at the downwind boundary. The results can be viewed in Figure 3.10, but due to the coarseness of the mesh the essential features of the exact solution could not be captured by SUPG. The Galerkin solution was wildly oscillatory which further illustrates the superiority of SUPG over Galerkin for high Peclet flow.

![Figure 3.9: Mesh and inlet boundary conditions for "advection skew to a mesh" problem](image)
Figure 3.10: Concentration profiles for "advection skew to a mesh" problem. Concentration is represented along the z-axis.
3.4.1.2 Cone Impinging on a Mesh Boundary

In this problem a Gaussian concentration distribution, illustrated as a cone in Figure 3.11, was placed in a 30-by-30 element square mesh filling the computational domain \(-1<x<1\) and \(-1<y<1\). The center of the cone was initially located at \((-0.5, 0.0)\). A time step of 0.015 was used with a unidirectional velocity field of: \(u_x=-1, u_y=0\), and a natural boundary condition was applied to the mesh boundary that the cone impinged on. The results of this test can be seen in Figure 3.12. After 100 time steps with the Galerkin method, oscillations of about 3% of the original cone height still remained in the mesh long after the cone had left. By contrast the largest oscillations remaining in the case of SUPG were only about 0.0001% of the original height. These errors were found to match with those published by Brooks at al. (3% for Galerkin and \(-10^{-4}\)% for SUPG).

Figure 3.11: Original cone placement for "Cone Impinging on a Mesh Boundary".
3.4.2 Arterial Model Testing

Having confirmed the implementation of the SUPG method with benchmark testing the next step was to seek agreement with arterial models in the literature. The two models that were used for validation testing were the fluid-side studies conducted by
Rappitsch et al. [74, 75]. Both of these studies consisted of the numerical analysis of momentum and mass transport in an axisymmetric tube with a local constriction simulating a stenosed artery. The two papers differ in the species that were studied, oxygen and albumin, and in the treatment of the boundary condition at the lumen/wall interface. In both cases the results were reproduced using the current SUPG module and matched very well with Rappitsch et al.'s published work.

3.4.2.1 Oxygen Transport

In this study oxygen transport was modelled in a stenotic artery with 75 percent area reduction, which represents a moderate stage of atherosclerotic disease. The geometry of the model can be seen in Figure 3.13. An upstream length of 6 inlet radii was chosen to ensure fully developed flow. The constriction length was taken to be 2 inlet radii and the downstream length was set at 90 inlet radii in order to minimize the influence of the outlet boundary conditions. The diffusivity of oxygen in plasma combined with the flow features in the artery ($Re_0=500$) resulted in a Peclet number of approximately $9 \times 10^5$. This is clearly a convection dominated flow problem and its solution requires the use of a method such as SUPG.
Figure 3.13: Stenotic artery geometry used in Rappitsch studies. Bottom edge is line of symmetry, top edge is lumen/wall interface, and geometry dimensions are shown as a function of the radius length $R$.

The fluid boundary conditions for this problem were: a fully developed parabolic inlet profile, no-slip at the lumen/wall interface, zero normal velocity gradient and zero cross flow at the axis of symmetry, and a traction free condition at the outlet. The concentration boundary conditions were: constant inlet concentration ($c_0$), zero normal concentration gradient at the axis of symmetry, and zero axial concentration gradient at the outlet. At the lumen/wall interface two different flux boundary conditions were compared. The first boundary condition imposed a constant value for the wall permeability, $a$:

$$q_w = -D \frac{\partial c}{\partial n} \bigg|_w = ac_w$$

where $D$ is the diffusivity of the species, $q$ is the flux, and the subscript $w$ denotes the wall. The second treatment included a permeability model that was dependent on the wall shear stress magnitude:
\[ q_w = -D \frac{\partial c}{\partial n}\bigg|_w = g(|\tau_w|)k_w \]

where \( g(|\tau_w|) \) is the shear dependent wall permeability function and \( \tau_w \) is the wall shear stress calculated from

\[ \tau_w = \mu \frac{\partial u_t}{\partial n}\bigg|_w \]

where \( u_t \) is the velocity component tangential to the wall. In this study the wall permeability was taken to be linear with a constant proportionality factor \( b \):

\[ g(|\tau_w|) = b|\tau_w| \]

In order to allow direct comparison of results from these two permeability models, the wall permeability at the flow entrance was set to be the same in both models. Rappitsch et al. obtained this permeability from physiological data, and determined \( a \) and \( b \) to be \( 1.87 \times 10^{-3} \) cm/s and \( 9 \times 10^{-4} \) cm²/s/g, respectively.

The models described above were solved using the SUPG module and the results can be seen in Figure 3.14.
Figure 3.14: Results from oxygen transport study: (a) oxygen isoconcentration contours for shear dependent permeability model (b) normalized oxygen wall concentration profiles ($c_w/c_o$) for shear dependent and constant permeability models (c) normalized oxygen wall flux profiles ($q_w/q_o$) for shear dependent and constant permeability models. The normalizing factor for wall flux, $q_o$ is defined as $q_o=2Dc_o/R$.

The analysis of these results is not included here since this model only serves as a validation test. The only relevant conclusion is that the results displayed in Figure 3.14 are very close to those from Rappitsch et al.'s original publication (Figure 3.15). This provides the necessary support for the correct operation of the SUPG module.
3.4.2.2 Albumin Transport

This study differed from the oxygen transport of Section 3.4.2.1 in two ways:

1. Albumin has a much lower diffusity in plasma than does oxygen, which resulted in a higher Peclet number of approximately $2 \times 10^7$. 

Figure 3.15: Results from Rappitsch et al.'s study [74]. (a) normalized oxygen wall concentration profiles ($c_w/c_0$) for shear dependent (solid line) and constant permeability (dashed line) models (b) normalized oxygen wall flux profiles ($q_w/q_0$) for shear dependent (solid line) and constant permeability (dashed line) models. The normalizing factor for wall flux, $q_0$, is defined as $q_0 = 2Dc_0/(L_0/2)$, where $L_0$ is the vessel diameter. $z$ is the coordinate in the axial direction.
2. The model used was identical to that of the oxygen transport study; however, a more complex shear dependent wall permeability function, \( g(\tau_w) \), was implemented:

\[
g(\tau_w) = a_0 + a_1 \ln(\tau_w + a_2)
\]

Using experimental data, Rappitsch et al. numerically fit the curve described by \( g(\tau_w) \) to yield appropriate values for the parameters \( a_0 \), \( a_1 \) and \( a_2 \), which were found to be \(-12.3 \times 10^{-6} \text{cm/s} \) \((\pm 2.3 \times 10^{-6} \text{cm/s})\), \(22.6 \times 10^{-6} \text{cm/s} \) \((\pm 4.1 \times 10^{-6} \text{cm/s})\), and \(5.1 \text{g/cm·s}^2 \) \((\pm 0.5 \times 10^{-6} \text{g/cm·s}^2)\), respectively.

This numerical problem was also analyzed using the SUPG module and the results can be seen in Figure 3.16. Again, the profiles displayed in Figure 3.16 were in good agreement with Rappitsch et al.'s results (Figure 3.17), providing further validation of the SUPG module.
Figure 3.16: Results from albumin transport study: (a) albumin isoconcentration contours (b) normalized albumin wall concentration profiles (c) normalized albumin wall flux profiles ($q_w/q_o$). The normalizing factor for wall flux, $q_o$ is defined as $q_o = Dc_o/R$. 


Figure 3.17: Results from Rappitsch et al.'s study [75]. (a) normalized albumin wall flux profile \( q_w/q_o \) (b) normalized albumin wall concentration profiles \( c_w/c_o \). The normalizing factor for wall flux, \( q_o \) is defined as \( q_o = Dc_o/(L_o/2) \), where \( L_o \) is the vessel diameter. \( z \) is the coordinate in the axial direction.

3.5 Conclusion

Based on all of results from the validation testing, it was concluded that the porous wall, mass transport and SUPG modules were all operating correctly.
CHAPTER 4

4 Arterial Test Model

4.1 Introduction

In Chapter 3, the various modifications and additions to the original Navier-Stokes solver were tested and validated. Having extensively tested each module separately, the next step was to combine them. The primary consideration in running the two modules together was the selection of a meaningful test case. To this end, an arterial geometry was constructed with two regions: lumen and wall (Appendix E). The test then consisted of comparing the LDL transport (in the lumen only) using a traditional method, which neglected the wall region, and the new method, which included the wall region. Using the traditional method a constant velocity boundary condition at the lumen/wall interface was applied (Figure 4.1a). The new method involved moving the velocity boundary condition out to the adventitial vasa vasorum, thus enabling the velocity field along the lumen/wall interface to develop without constraint through the solution of Brinkman's equation in the wall (Figure 4.1b). Although the results from the two methods could not be compared directly, it was anticipated that there should not be a significant difference in the wall velocity fields for suitably chosen velocity boundary conditions. As long as the two methods yielded results that were reasonably close, it could be assumed that the new boundary treatment method was valid. The details and results of this test are presented in the following sections.
4.2 Computational Details

4.2.1 Geometry

The geometry developed for the test case was based on the 75% stenotic artery model used by Rappitsch et al. (Figure 3.13) with the addition of a permeable region that would simulate the artery wall. The details of the artery wall region were from the model by Moore et al. [61] in which the artery wall extended from the blood-wall interface to the vasa vasorum (outer wall layer). Away from the stenosis the distance from the
interface to the vasa vasorum was 4% of the unstenosed lumen (channel) diameter, which is consistent with data for healthy arteries. Within the stenosis region the distance increased to 12.5% of the unstenosed lumenal diameter, which is typical of the state of a specimen with arterial disease. This latter distance creates an effect within the stenosis region wherein the outer boundary of the geometry, the location of the vasa vasorum, moves closer to the lumen (Figure 4.2). This effect reflects the observed response of the vasa vasorum to a thickening of the artery wall, in which the vasa vasorum penetrate further into the wall so as to supply the middle layers of the wall with the necessary nutrients [103]. The complete geometry can be seen in Figure 4.2.

Figure 4.2: Geometry of a stenotic artery with the addition of a wall region extending from the lumen/wall interface to the vasa vasorum.

4.2.2 Permeability

One of the most critical aspects of solving the velocity field in the wall region is the selection of an appropriate Darcian permeability. Whale et al. [98] have measured the specific hydraulic conductivity of the human aortic wall and found it to be approximately
2x10^{14}\text{cm}^2. For an artery with a diameter of 0.62cm this yields a value of 5x10^{12} for the inverse Darcy number.

### 4.2.3 Boundary Conditions

For both the traditional and new treatments the velocity boundary conditions were: fully developed parabolic inlet velocity, zero normal velocity gradient and zero cross flow at the axis of symmetry, and a traction-free condition at the outlet. In the case of the traditional treatment a constant filtration velocity of 4x10^{-6}\text{cm/s} (Appendix C) was applied at the lumen/wall interface. This same velocity was used in the new treatment, but was applied at the vasa vasorum. The new treatment also included a constant inlet velocity in the wall region of 4x10^{-6}\text{cm/s} and a traction-free condition at the outlet of the wall.

The conditions used for mass transport in both treatments were: constant LDL inlet concentration \(c=C_0\), zero normal concentration gradient at the axis of symmetry, and zero axial concentration gradient at the outlet. The treatment of the concentration at the lumen/wall interface was applied using Equation 2.18, which, for convenience, is rewritten here:

\[
\nu_w c_w - \frac{1}{\text{ReSc}} \frac{\partial c}{\partial n} \bigg|_w = \frac{M}{U} c_w
\]  

(4.1)

where \(\nu_w\) (written \(u_n\) in Eq. 2.18) and \(c_w\) are the normalized transmural filtration velocity and normalized concentration at the blood-wall interface and \(n\) is the normalized
coordinate normal to the wall. Note that the value used for $v_w$ in Eq. 4.1 is different for the two treatment methods. In the traditional method $v_w$ is simply the normalized constant filtration velocity. When using the new treatment the value for $v_w$ is taken from the computed solution of Brinkman's equation.

The remaining parameters used in this study were: an inlet radius of $R=0.31$cm, a mean inlet velocity of $U=17$cm/s, a kinematic viscosity of $\nu=0.031$cm$^2$/s, a diffusivity for LDL of $D=5\times10^{-8}$cm$^2$/s (Appendix C), and a permeability of LDL of $M=2\times10^{-8}$cm/s (Appendix C) for physiologic conditions. These values yield a Reynolds number of $Re=330$, a Schmidt number of $Sc=6.3\times10^5$, and hence a Peclet number of $Pe=2.1\times10^8$.

4.2.4 Mesh

Due to the high concentration gradients anticipated near the lumen/wall interface, a mesh was created with very fine resolution near the wall. A mesh refinement study was conducted to ensure that the resolution was sufficient. Mesh density was increased from 8000 to 27000 velocity-pressure elements in 50% increments and the resulting concentration and velocity profiles at the lumen/wall interface were examined. Mesh independence was judged to have been achieved when there was no visible mesh dependence in the normalized concentration profile when plotted on a scale of $c/C_0=1.0$ to $c/C_0=1.2$, and in the normalized velocity profile when plotted on a scale of $v/U=0$ to $v/U=3\times10^7$. The number of required elements was 235200 concentration elements and 21560 velocity-pressure elements. As a result there were a total of 88245 velocity nodes
and 239181 concentration nodes. A section of the mesh in the vicinity of the stenosis can be seen in Figure 4.3.

![Figure 4.3: Section of mass transport mesh taken near the stenosis. Mesh is orthogonal and shown to scale.](image)

**4.3 Results**

The new treatment method involved solving the velocity in the lumen and the wall simultaneously. The resulting velocity fields are displayed in Figure 4.4. In Figure 4.4a it can be seen that the fluid moves in an essentially normal direction in the wall from the lumen/wall interface to the vasa vasorum. In Figure 4.4b the streamtraces in the fluid region illustrate the impact of the stenosis on the flow field. At a position just downstream of the stenosis throat the flow separates and a recirculation zone develops. The flow then reattaches further downstream at about $x/R = 23$. With the exception of the lumen/wall interface, the lumen velocity field for the traditional treatment follows the same behaviour seen in Figure 4.4b.
Figure 4.4: Velocity results for the new treatment. (a) velocity field in wall region of stenosis section. Reference vector corresponds to $2.5 \times 10^{-7}$ times the mean inlet velocity. Shown to scale. (b) streamtraces in the lumen (note different scales for horizontal and vertical axes in panel b).

The purpose of this test study was to compare the lumenal LDL concentration using the traditional and new treatment methods. Figure 4.5 shows the normalized concentration profiles at the lumen/wall interface for the two different methods. The slight difference between the profiles for the two methods can be explained as follows. Recall that in Eq. 4.1 the value of $v_w$ is not the same for the two boundary treatments. As it turns out, the solution of the velocity field at the blood-wall interface using the new treatment yielded a slightly higher value for $v_w$ than the normalized constant filtration
velocity used in the traditional method. The result was a slightly elevated concentration and concentration flux profile from the new treatment. The higher value of \( v_w \) is simply due to the axisymmetric nature of the geometry and is not a result of the new formulation. This was verified through a comparison of the volumetric flow rates at the two surfaces - the lumen/wall interface and the adventitial vasa vasorum. If the formulation is accurate then the volumetric flow rates at these surfaces should be the same. The flow rate can be expressed as:

\[
Q(r) = v_w \cdot 2\pi l
\]

where \( Q \) is the volumetric flow rate, and \( l \) is the section length. Removing the parameters common to the two surfaces (2\( \pi l \)) it can be shown that the ratio of the velocities should be equal to the inverse ratio of the radial locations of the surfaces. This can be expressed:

\[
\frac{v_w(r_i)}{v_w(r_{vv})} = \frac{r_{vv}}{r_i}
\]

where the subscripts \( i \) and \( v \) denote the lumen/wall interface and vasa vasorum, respectively. The velocity at the vasa vasorum was \( 4 \times 10^{-6} \) cm/s (applied) and the resulting velocity at the lumen/wall interface was computed to be \( 4.3 \times 10^{-6} \) cm/s, which yielded a ratio of \( v_w(r_i)/v_w(r_{vv}) \) of 1.075. This was considered to be acceptably close to the radial position ratio: \( r_{vv}/r_i=1.08 \).
In addition to the test of the new treatment method, one of the important assumptions made in this work was further validated (Section 2.2.5). Recall that it was assumed that the lumenal concentration field would be only very weakly affected by the uptake into the wall. This assumption was validated in Section 2.2.6.1 using an order of magnitude analysis. In order to provide further validation a computational test was
conducted, which consisted of repeating the study discussed above with a zero value of $M$ in Equation 4.1. If this assumption was correct, then setting $M$ to zero would have a negligible impact on the solution of the lumenal concentration field. When the resulting normalized LDL concentration profiles at the lumen/wall interface were plotted on the same plot as Figure 4.5 it was found that there was no visible difference between the profiles generated with $M=0$ versus those generated with $M=2 \times 10^{-8}$ cm/s.

4.4 Conclusions

In this chapter Brinkman’s model and SUPG were tested together to ensure they operated correctly in unison. Using an arterial model it was shown that the new method of solving the velocity fields in the lumen and wall simultaneously is a viable alternative to more traditional, and limiting, boundary treatment techniques. It was also confirmed that the LDL uptake into the wall exerted an indiscernible effect on the lumenal LDL concentration profile at the lumen/wall interface. This important result validated the approach used in this work, in which the lumenal LDL concentration field is computed separately from the wall concentration field. These findings provide the groundwork for the more complex physiological studies presented in Chapter 5 and Chapter 6.
CHAPTER 5

5 Lumenal LDL Transport

5.1 Introduction

In Chapter 1, the role of LDL in the development and progression of atherosclerosis was described. In order for LDL to participate in the disease process it must penetrate into the artery wall from the lumen, and therefore pass through the endothelium. The focus of this chapter is to investigate some of the factors that can influence the passage of LDL through the endothelium and thus the infiltration of LDL into the wall. Two of the primary determinants of this LDL passage are the lumenal concentration of LDL at the endothelium, and the permeability of the endothelium to LDL. These two factors are in turn affected by other arterial conditions. The resulting series of effects that can influence the LDL passage can best be illustrated in a block diagram, as seen in Figure 5.1. Each factor is described in more detail below.
Figure 5.1: Block diagram of factors influencing the passage of LDL into the artery wall.

Block 1: The concentration of LDL at the endothelium depends on a number of factors.

In Chapter 1, concentration polarization (Block 3) was discussed as a potentially important influence on LDL concentration at the lumen wall interface. One of the factors that determines the level of concentration polarization is the filtration velocity across the wall (Block 4). The higher the filtration velocity, the higher the level of concentration polarization. The magnitude of the filtration velocity is affected by the pressure driving
force across the wall (the transmural pressure - Block 5) and the Darcian permeability of the wall (Block 6). Not surprisingly, it has been found experimentally that increases in transmural pressure lead to increased filtration velocities \([21, 87, 99]\). It is also clear that increases in the Darcian permeability of the wall would lead to increased filtration velocities. One factor that can influence the Darcian permeability of the wall is the presence of atherosclerotic plaque. A study by Baldwin et al. \([7]\) has revealed that the walls of vessels with atherosclerosis have a Darcian permeability that is 3 times higher than that for healthy vessels. If it is assumed that diseased specimens have regions with plaque as well as healthy regions, this implies that the plaque itself has a permeability that is at least 3 times higher than that of a healthy wall. Thus plaques sites would likely experience an increase in filtration velocity due to the increased Darcian permeability.

**Block 2:** Recall from Section 1.4 that Guretzki et al. \([38]\) observed an exponential relationship between the level of LDL to which endothelial cells were exposed, and the endothelial LDL permeability. This suggests that any changes in LDL concentration at the endothelium boundary could serve to increase the endothelial LDL permeability, thus increasing the LDL infiltration into the wall. This relationship between LDL concentration at the endothelium and endothelial LDL permeability is depicted by the dashed arrow connecting Block 1 to Block 2 in Figure 5.1.

In summary, it appears that concentration polarization and endothelial LDL permeability likely play an important role in the passage of LDL through the endothelium and thus the infiltration of LDL into the wall. The study of concentration polarization is
of particular interest due to several studies that have implicated concentration polarization as a cause of the localized nature of atherosclerosis and as the root cause of hypertension (increased transmural pressure) as an increased risk factor for atherosclerosis [17, 21, 27]. The arterial model developed in Chapter 4 (see also Appendix E) offers the opportunity to investigate the factors that influence the level of concentration polarization. These factors include the presence of a flow-disturbing stenosis, changes in filtration velocity induced by elevations in pressure (hypertension), and changes in wall Darcian permeability due to the presence of a plaque in the stenosis region of the wall (see Figure 5.2). These factors will also be coupled with Guretzki et al.'s observed link between LDL concentration and endothelial LDL permeability to investigate the impact on the overall infiltration of LDL into the wall. Thus, Questions 1a, 3a and 4a, from Section 1.5 will be addressed.

**Figure 5.2:** Arterial stenosis. The unshaded area is the arterial lumen, the gray-shaded area is the arterial wall, and the black-shaded area is the plaque region.
CHAPTER 5: LUMENAL LDL TRANSPORT

5.2 Computational Details

The geometry, flow conditions and boundary conditions were unchanged from the two-region model presented in Chapter 4 with one exception. The momentum boundary treatment applied at the adventitial vasa vasorum was changed from a constant velocity condition to a constant pressure condition (Section 2.1.3). This permits the direct comparison of mass transport results at different arterial pressures (see also Appendix E).

5.3 Results

5.3.1 Pressure Boundary Treatment

The first step in this study was to ensure that the pressure boundary treatment yielded a reasonable velocity field in the wall. A constant transmural pressure of 120mmHg was achieved by applying a pressure of -120mmHg at the vasa vasorum with a pressure of 0mmHg at the outlet. This value was selected because it is in the range used by experimentalists to represent normal arterial transmural pressure [17, 21, 87]. The resulting velocity field and pressure contours are displayed in Figure 5.3 and Figure 5.4. Similar to the results from the test problem in Chapter 4, in Figure 5.3a it can be seen that the fluid in the wall moves essentially normal to the wall from the lumen/wall interface to the vasa vasorum. In Figure 5.3b the streamtraces in the fluid region illustrate the impact of the stenosis on the flow field.

Quantitatively there was a difference in transmural velocity magnitude between the constant velocity treatment ("new treatment method" in Chapter 4) and constant
pressure treatment cases. In the former case the velocity was $4 \times 10^{-6}$ cm/s and in the latter it was $3.5 \times 10^{-6}$ cm/s. This latter value was well within the range of experimental values seen in the literature (Appendix C). These results indicated that the pressure boundary treatment was operating correctly.

Figure 5.3: Velocity results for transmural pressure of 120 mmHg. (a) velocity field in wall region of stenosis section. Reference vector corresponds to $2 \times 10^{-7}$ times the mean inlet velocity. Shown to scale. (b) streamtraces in the lumen.
5.3.2 Pressure Study

Having confirmed the correct operation of the pressure boundary treatment method, the next step was to examine the effect of increasing transmural pressure on the lumenal LDL concentration. Two transmural pressures were selected for analysis based on experimental studies [17, 21, 87]: 120mmHg (normal state) and 160mmHg (elevated state). Figure 5.5 shows the normalized concentration profiles at the lumen/wall interface for the two pressures. The magnitude of the transmural velocity was found to be $3.5 \times 10^{-6}$ cm/s at a pressure of 120mmHg and $4.7 \times 10^{-6}$ cm/s at a pressure of 160mmHg. These values were found to be within the range of experimental values at normal and elevated pressures. In examining the concentration profiles, a number of observations can be made that are consistent with other authors’ findings. It can be seen that in the
regions away from the stenosis the LDL concentration at the lumen/wall interface is about 10-15% higher than that in the bulk flow. This is consistent with the findings by Deng et al. [21], which indicated, through the theoretical analysis of flow and mass transport in a straight tube model, that the presence of filtration flow across the artery wall leads to LDL concentration polarization. Deng et al. also concluded that the interface LDL concentration increases with decreasing wall shear stress. Along the upstream side of the stenosis the flow accelerates around the maximum point of constriction. In this section the flow rate and wall shear stress increase and the effect is a decrease in the LDL wall concentration. By contrast, just after the throat of the stenosis, the flow separates and a recirculation zone develops. Here the flow rate and wall shear stress decrease and the LDL concentration can be seen to increase. A peak in the value of LDL concentration appears as a spike at the separation point, which corresponds to a zero value for the wall shear stress. After the spike, the concentration follows an increasing trend in the recirculation zone up to the point that marks the end of the constriction \((x/R=8)\). These observations are consistent with Fatouraee et al.'s [27] findings for LDL transport in arterial stenoses of varying degrees of constriction. The Peclet number and degree of stenosis constriction in Fatouraee et al.'s study that are closest to the parameters in this work were \(1.7 \times 10^8\) and 60% respectively. Fatouraee et al. used a constant filtration velocity boundary condition treatment at the lumen/wall interface of \(4 \times 10^{-6}\) cm/s. For these conditions Fatouraee et al. observed a normalized concentration peak at the separation point of approximately 1.3. In this work, the normalized concentration peak at the same location was 1.17 at 120 mmHg and 1.25 at 160 mmHg. Recall that these pressures yielded velocities of \(3.5 \times 10^{-6}\) cm/s and \(4.7 \times 10^{-6}\) cm/s.
Fatourae et al.'s velocity of $4 \times 10^{-6} \text{cm/s}$ would fall somewhere between these two pressures and would likely produce a concentration peak of about 1.2. The difference between this value and the one obtained by Fatourae et al. (1.3) could be attributed to the difference in stenosis severity. In Fatourae et al.'s study it was observed that an increase in constriction size led to a decrease in peak concentration. This would support the lower result for the constriction size of 75% used here vs. the 60% used by Fatourae et al.
Figure 5.5: Normalized lumenal LDL concentration profile at lumen/wall interface for normal (120mmHg) and elevated (160mmHg) transmural pressure. Insert at top of plot indicates corresponding axial position along arterial stenosis geometry.

The results in Figure 5.5 also illustrate that the effect of concentration polarization is enhanced at elevated pressures. The difference in peak values between the two pressures was 6%. The higher level of LDL at 160mmHg could result in higher infiltration into the wall. This would be compounded if the endothelial LDL permeability were to increase, as suggested by Guretzki et al.'s cell culture studies.
To investigate this hypothesis further, the net uptake of LDL into the artery wall was calculated. This quantity is simply the product of dimensionless interfacial LDL concentration, \( c_w \), and endothelial LDL permeability, \( M'(c_w) \). The value of \( M'(c_w) \) along the lumen/wall interface was obtained by the following method. First, an exponential relationship was fit to Guretzki et al.'s cell culture data to produce a "Guretzki factor", \( G_f \):

\[
G_f(c_w) = 0.064 \exp(2.75 \times c_w C_0)
\]  

(5.1)

The Guretzki factor represents the amount by which endothelial permeability is increased, compared to "baseline" conditions, when exposed to an LDL concentration of \( c_w C_0 \). The baseline concentration was taken to be 1mg/ml, from Guretzki's data, such that \( G_f \) was equal to 1.0 at that concentration. The graph of this function and Guretzki et al.'s experimental data can be viewed in Figure 5.6. Next, it was assumed that the bulk lumenal LDL concentration was \( C_0=1.2\text{mg/ml} \) [36] and the base endothelial permeability was taken to be \( M=2\times10^{-8}\text{cm/s} \). Finally, the concentration profiles shown in Figure 5.5 were used to calculate \( M'(c_w) (=MG_f) \) along the lumen/wall interface. The resulting plots of the net uptake of LDL into the wall are displayed in Figure 5.7. These results show that although there was only a 6% increase in peak LDL concentration at an elevated pressure of 160mmHg, the exponential effect on the endothelial LDL permeability served to increase the peak LDL transport by 35%. Thus it was demonstrated that an elevation in transmural pressure could result in substantial increases in the LDL infiltration into the wall.
Figure 5.6: Exponential "Guretzki factor" function (see Equation 5.1), and experimental data from Guretzki et al.'s study. Note that the y-coordinate of the experimental data was calculated via a ratio of the original data points. The error bars correspond to that ratio. See Appendix A for further details.
Figure 5.7: Normalized net LDL transport into the wall for normal (120mmHg) and elevated (160mmHg) transmural pressure. Net LDL transport into the wall has been made dimensionless by the product $UC_0$, which in the present case equals 20.3 mg LDL/(cm²·s). Insert at top of plot indicates corresponding axial position along arterial stenosis geometry.

5.3.3 Plaque Study

Here, the impact on LDL transport of variations in Darcian permeability caused by the presence of atherosclerotic plaque in the wall is examined. The geometry from the previous study (Figure 4.2) was used, and the entire wall section of the stenosis (from
x/R=6 to x/R=8) was assigned a permeability that was either 5 or 10 times higher than the value in the rest of the wall. These values were selected based on Baldwin et al.'s findings [7], which revealed that atherosclerotic vessels have a Darcian wall permeability that is 3 times higher than that for healthy vessels. Increases in permeability of 5 and 10 times were selected arbitrarily under the assumption that atherosclerotic specimens would have regions with plaque as well as healthy regions, thus implying that the plaque itself would have a permeability that is at least 3 times higher than that of a healthy wall. Consequently, three values of inverse Darcy number for the plaque region were tested: $5 \times 10^{12}$ (healthy), $1 \times 10^{12}$, and $5 \times 10^{11}$. All other parameters were the same as those implemented in the previous study, and the transmural pressure was taken to be 120mmHg. The resulting LDL concentration profiles at the lumen/wall interface can be seen in Figure 5.8. The increased permeability in the plaque region resulted in an increase in filtration velocity, which in turn increased the LDL interface concentration. The peak concentration just downstream of the stenosis throat was 13% and 32% higher for a plaque permeability value of 5 times and 10 times higher than normal, respectively.
Figure 5.8: Normalized lumenal LDL concentration profile at lumen/wall interface for normal (120mmHg) transmural pressure and plaque inverse Darcy numbers of $5 \times 10^{12}$, $1 \times 10^{12}$ and $5 \times 10^{11}$. Insert at top of plot indicates corresponding axial position along arterial stenosis geometry.

The impact of increased LDL concentration due to elevated plaque permeability was examined by using Guretzki et al.'s relationship (Eq. 5.1) to calculate the net LDL transport into the wall. The resulting plots are displayed in Figure 5.9. From this figure it is clear that an increased Darcian permeability in the plaque region profoundly affects
net LDL transport into the wall: 5- and 10-fold Darcian permeability increases gave peak LDL transport increases of 80% and 340%, respectively.

Figure 5.9: Normalized net LDL transport into the wall for normal (120mmHg) transmural pressure and plaque inverse Darcy numbers of $5 \times 10^{12}$, $1 \times 10^{12}$ and $5 \times 10^{11}$. Net LDL transport into the wall has been made dimensionless by the product $UC_0$, which in the present case equals 20.3 mg LDL/(cm²s). Insert at top of plot indicates corresponding axial position along arterial stenosis geometry.
5.3.4 Plaque Study at Elevated Pressure

In Section 5.3.2 and Section 5.3.3, elevated pressure and the presence of atherosclerotic plaque were investigated as separate effects on the LDL concentration at the lumen/wall interface. In this section the two factors are combined in order to study their potential compounding effect on the transport of LDL into the artery wall.

Again, the plaque was considered to extend from $x/R=6$ to $x/R=8$ and was assigned a Darcian permeability that was either 5 or 10 times higher than the value in the rest of the wall. A pressure of 160mmHg was applied and the resulting LDL concentration profiles at the lumen/wall interface can be seen in Figure 5.10. Similar to the results at 120mmHg the increased permeability in the plaque region resulted in increased LDL interface concentration. However, at the elevated pressure the increase was more substantial due to the non-linear effect of increased filtration velocity on interfacial LDL concentration. The peak concentration just downstream of the stenosis throat was 19% and 46% higher for a plaque permeability value of 5 times and 10 times higher than normal, respectively.
Figure 5.10: Normalized lumenal LDL concentration profile at lumen/wall interface for elevated (160mmHg) transmural pressure and plaque inverse Darcy numbers of $5 \times 10^{12}$, $1 \times 10^{12}$ and $5 \times 10^{11}$. Insert at top of plot indicates corresponding axial position along arterial stenosis geometry.

Similar to the results found at 120mmHg, the effects described above were exaggerated further when Guretzki et al.'s exponential relationship was applied. Guretzki et al.'s enhanced endothelial permeability was implemented in conjunction with elevated Darcian permeabilities in the plaque region and the results can be viewed in
Figure 5.11. Again, the increased Darcian permeability increased the lumenal LDL concentration at the lumen/wall interface, which in turn exponentially increased the endothelial LDL permeability. At 160mmHg the exponential effect of Guretzki et al.’s relationship was even more dramatic: 5- and 10-fold Darcian permeability increases gave peak LDL transport increases of 150% and 850%, respectively.

Figure 5.11: Normalized net LDL transport into the wall for elevated (160mmHg) transmural pressure and plaque inverse Darcy numbers of $5 \times 10^{12}$, $1 \times 10^{12}$ and $5 \times 10^{11}$. Net LDL transport into the wall has been made dimensionless by the product $UC_0$, which in the present case equals 20.3 mg LDL/(cm²s). Insert at top of plot indicates corresponding axial position along arterial stenosis geometry.
5.4 Discussion

The results from the first part of this study imply that regions of low near-wall velocity, and hence low wall shear stress, favour the formation of atherosclerotic plaques due to the increased LDL concentration at the lumen/wall interface. This prediction has been previously made [11, 21, 21] and is consistent with experimental studies, which suggest that atherosclerotic lesions occur preferentially at sites of low wall shear stress [4, 34, 34, 102, 102]. It was also found that a state of elevated pressure further increased the LDL concentration at the lumen/wall interface, thereby exposing the wall to even higher levels of LDL. The second part of this study suggests a new mechanism that could promote plaque growth: an increase in fluid permeability in the plaque region will increase transmural filtration and hence further elevate endothelial LDL concentration. Such an effect would combine synergistically with the dependence of endothelial permeability on LDL concentration [38], as shown in Figure 5.9. Again, it was found that a state of elevated pressure compounded this effect, thus exposing the wall to a dramatically higher infiltration of LDL.

Taken together, the above discussion implies a (strongly non-linear) vicious cycle in which increased LDL infiltration would cause growth of the plaque in the downstream direction, due to increased Darcian wall permeability and increased endothelial LDL permeability in the separation zone distal to the stenosis throat. In fact, such directional growth of plaque has been observed in experimental studies [22, 83]. Smedby found that plaque growth in the downstream direction was significantly more frequent than growth.
in the upstream direction. Dirksen et al. showed that the downstream area of plaques contained significantly more smooth muscle cells than the upstream regions. The proliferation of smooth muscle cells is generally considered to be responsible for a gradual progressive growth of atherosclerotic plaques [37], and thus Dirksen et al.’s observation is consistent with progressive enlargement of plaques from their distal ends.

In this chapter, it was shown that pressure and plaque presence could have a significant impact on the level of LDL transport into the wall. In the next chapter, these factors will be pursued further by expanding the model to include the concentration distribution of LDL in the wall.
CHAPTER 6

6 Wall LDL Transport

6.1 Background

Hypertension has been identified as one of the significant risk factors for atherosclerosis [35]. One of the mechanisms by which hypertension contributes to atherogenesis may be through the increased transport of atherogens, such as LDLs, into the arterial wall [33]. This idea was explored in Chapter 5, but that approach was somewhat limited since the model did not include a calculation of the LDL concentration in the wall (see also Appendix E). Experimentally, in vitro studies have established a relationship between arterial transmural pressure and the concentration of LDLs in the arterial wall [21, 60, 60, 96]. These studies found that increases in pressure led to significant increases in arterial wall LDL concentration; however, the mechanism by which this occurred was uncertain. Computational methods offer an opportunity to further investigate this issue.

To date, numerical analyses of macromolecular concentration profiles in the artery wall have been limited to one-dimensional models that assume a constant value for the transmural convection velocity (see Section 1.3.2). They also assume that the lumenal concentration at the lumen/wall interface is equal to the bulk plasma concentration. These models have two primary limitations:
• They cannot directly determine the effect of pressure on LDL wall concentration. Although one could use trial and error to obtain a filtration velocity boundary treatment that provided the desired pressure distribution, the most convenient method is to apply a transmural pressure directly.

• They cannot study the implications of a complex geometry such as a stenosis. The modelling of LDL transport in a stenosis geometry is of interest since the effect of a region of plaque on LDL concentration in the wall can be examined. A full two-dimensional geometry must be used in this case since the luminal LDL concentration profile at the lumen-wall boundary directly affects the LDL concentration in the wall, and as previously shown in Chapter 5, this luminal profile is sensitive to the presence of a stenosis.

In this chapter the limitations discussed above will be removed and the arterial geometry that was developed in Chapters 4 and 5 (see also Appendix E) will be used to calculate the concentration of LDL in the arterial wall. Specifically, this work will address Questions 1b, 2, 3b, 4b and 5 from Section 1.5:

• Elucidate the mechanism by which elevated arterial pressure increases the LDL concentration in the wall.
• Determine how plaque structure affects the infiltration of LDL into the wall and thereby examine whether plaque structure contributes to the progression, or regression, of atherosclerosis.

6.2 Experimental Studies on Hypertension

Before computationally investigating the effect of hypertension on LDL wall concentration, it is important to establish an understanding of the experimental work that has been conducted in this area. Several in vitro studies have been conducted that measure the change in LDL concentration in the artery wall at normal and elevated arterial pressures [21, 60, 96]. The most significant difference between these studies was that Meyer et al. used a system with no axial flow, whereas Deng et al. and Warty et al. used perfusion apparatus that mimicked physiological flow conditions. Meyer et al. conducted an experiment in which LDL concentration profiles were obtained from the walls of normal rabbit thoracic aortas (Figure 6.1a). Arterial segments were placed in a pressurization chamber and the intralumenal pressure was fixed at either 120mmHg or 160mmHg for 30 minutes. At the end of this period, the artery wall was harvested and assayed to determine LDL concentration profiles. Meyer et al. found that elevated pressure caused the mean normalized concentration of LDL in the wall to increase by a factor of about 1.7, from $2.34 \times 10^{-2} \pm 2.9 \times 10^{-3}$ at 120mmHg to $3.93 \times 10^{-2} \pm 5.6 \times 10^{-3}$ at 160mmHg. Warty et al. performed perfusion experiments on canine carotid arteries at transmural pressures of 100mmHg and 180mmHg. The vessels were perfused at physiological flow rates for 10-20 hours and the LDL wall concentration profiles were obtained (Figure 6.1b). Warty et al. found that the mean normalized concentration of
LDL in the wall increased by a factor of about 2.6, from $1.2 \times 10^{-2} \pm 1.0 \times 10^{-3}$ at 100mmHg to $3.1 \times 10^{-2} \pm 7.0 \times 10^{-3}$ at 180mmHg. Deng et al. also conducted perfusion experiments on canine carotid arteries at transmural pressures of 100mmHg and 200mmHg. The vessels were perfused at physiological flow rates for 1-3 hours and the LDL uptake rate by the wall was measured. Deng et al. found that the LDL wall uptake increased by a factor of about 2.1, from $3.58 \times 10^{-4} \pm 0.95 \times 10^{-4}$ cm/hr at 100mmHg to $7.36 \times 10^{-4} \pm 1.97 \times 10^{-4}$ cm/hr at 200mmHg.
Figure 6.1: Experimental normalized concentration profiles. (a) Meyer et al.'s results for 30 minute no-perfusion study on rabbit thoracic arteries. (b) Warty et al.'s results for 10-20 hour perfusion study on canine carotid arteries. An x-axis position of 0 indicates the lumen/wall interface, and an x-axis position of 1 indicates the media/adventitia interface. Error bars represent SEM.
It would be desirable to reproduce these experimental conditions in a computational model, and thereby explore the mechanism by which elevated pressures lead to increased LDL infiltration into the wall. Unfortunately, there were a number of limitations associated with these experimental studies that preclude a direct comparison with numerical results. They are as follows:

- Although Meyer et al.'s study was only 30 minutes in duration, significant LDL transport into the innermost layers of the media was observed. This was unexpected, since the hindered convective velocity of LDL in the wall is only about $1 \times 10^{-7}$ cm/s (see Section 1.4). Over the course of a 30 minute experiment, LDL would therefore be expected to penetrate only a short distance into the artery wall (normalized infiltration distance into the wall of less than 0.1). This is not what was seen experimentally. Clearly, there was some aspect of their experiment that resulted in more substantial infiltration of LDL at both transmural pressures; however it is not evident from their publication what the cause may have been.

- The length of Warty et al.'s and Deng et al.'s experiments extended over 10-20 hours and 1-3 hours, respectively. Considering the very small convective velocities across the arterial wall ($\sim 10^{-7}$ cm/s), it is unlikely that steady-state would have been reached in either experiment. Consequently, a numerical reproduction of their experiments would need to be conducted under unsteady conditions for a specified duration of
time. Unfortunately, in neither publication did the authors indicate the precise duration of the experiment. To verify that steady-state had not been reached during these experiments, the time required to reach steady-state was estimated and found to be approximately 55 hours (Appendix B). Thus, it was concluded that neither the Warty nor the Deng study had reached steady-state at the time that the LDL wall concentration measurements were made, and consequently there was insufficient information to computationally reproduce their experimental conditions.

- In Warty et al.'s perfusion study, as a result of the developing nature of the mass transfer boundary layer, it is important to know the axial position in the vessel where the wall concentration profiles were measured. This information was not provided.

Despite the obvious differences in Meyer et al.'s, Warty et al.'s and Deng et al.'s experimental set-ups, and the limitations discussed above, two important observations were made that formed the basis of the computational approach used in this chapter:

1. All of the studies revealed an approximate doubling in the infiltration of LDL into the artery wall when pressure was elevated to hypertensive conditions. It was assumed that within an individual study the conditions, other than the transmural pressure, were kept the same at both pressure levels. This meant that regardless of what those conditions were, a relative comparison could be made between LDL concentrations in the wall at different pressure levels in each individual study. In other words, the
effect of pressure on LDL wall infiltration was assumed to be reasonably independent of the experimental procedure.

2. The pressures that were selected to represent normal and hypertensive conditions in each study did not reveal a trend in the factor by which the LDL infiltration increased. Recall that the largest change in pressure was applied in Deng et al.'s study, yet the factor by which LDL infiltration increased (2.1 for a 100mmHg increase) fell between the studies by Meyer et al. (1.7 for a 40mmHg increase) and Warty et al. (2.6 for a 80mmHg increase). In other words, a more significant change in pressure did not result in a more significant increase in LDL infiltration. Based on this observation, it was assumed that a state of normal pressure could be arbitrarily selected from the range 100-120mmHg and a state of hypertensive pressure could be arbitrarily selected from the range 160mmHg-200mmHg. This assumption is discussed further in Section 6.6.1.

With the above assumptions in mind, two computational models were built using the techniques developed in Chapters 2-5 (see also Appendix E). Normal and hypertensive conditions were compared using: a) an unsteady, zero-axial-flow model and, b) a steady flow model. Based on the second assumption, pressures of 120mmHg and 160mmHg were arbitrarily selected to represent normal and hypertensive conditions, respectively. The two models were then used to study the mechanism by which pressure increases LDL infiltration into the wall. In addition, the differences in these two models permitted a test of the first assumption, i.e. that the effect of pressure on LDL infiltration
is independent of factors such as the presence of axial flow and the total duration of the study. The models and their corresponding results are presented in the next sections.

6.3 Computational Details

6.3.1 Unsteady, Zero-Axial-Flow Model

An axisymmetric geometry was created consisting of a straight portion of artery with both lumen and wall regions. This geometry can be seen in Figure 6.2.

![Figure 6.2: Geometry used for unsteady, zero-axial-flow problems. The unshaded area is the arterial lumen and the gray-shaded area is the arterial wall. \( R \) is the arterial radius and \( h \) is the wall thickness. Not shown to scale.]

Since there was no axial flow in this model the geometry was only 4 elements in length. The mesh density in the radial direction was kept the same as for the stenosis mesh in Chapter 5. An assumed constant dimensional filtration velocity, \( v_w \), was applied at the
adventitial vasa vasorum \((r=R+h)\) and the dimensional velocity in the rest of the geometry was calculated using the expression:

\[
\begin{align*}
    u(r) &= 0 \\
    v(r) &= \frac{(R + h)v_w}{r}
\end{align*}
\]

The computational domain only extended to \(r/R=0.1\) since \(v(r)\) approaches infinity as \(r\) approaches 0. The values of \(v(r)\) were normalized using \(v_w\).

The concentration boundary conditions for the lumenal computation consisted of applying zero axial concentration gradient at the inlet and outlet, a constant concentration equal to the bulk concentration \((c=C_0)\) at the location \(r/R=0.1\), and Equation 2.18 at the lumen/wall interface. The concentration boundary conditions for the wall concentration were zero axial concentration gradient at the inlet and outlet, Equation 2.20 at the lumen/wall interface, and Equation 2.21 at the adventitial vasa vasorum. The values of \(M=2 \times 10^{-8}\text{cm/s}, M_{vw}=2 \times 10^{-9}\text{cm/s}, \varepsilon=0.15\), and \(H=2 \times 10^{-5}\text{s}^{-1}\) were taken from experimental and computational studies (Appendix C). The initial conditions were zero concentration in the wall region and \(c=C_0\) in the lumen region.

The mass transport equations (Equation 2.8 and 2.9) were solved for LDL transport in the lumen and wall regions of the geometry described above. The filtration velocity was taken from Meyer et al.'s data \((v_w=2.6 \times 10^{-6}\text{cm/s at 120mmHg})\), which resulted in a lumenal Reynolds number (based on \(v_w\)) of \(2.5 \times 10^{-5}\). The effective
diffusivity of LDL in the wall is 5x10^{-10} \text{cm}^2/\text{s} (Appendix C) yielding an effective Schmidt number in the wall of \( \text{Sc}_{\text{eff}} = 6.3 \times 10^7 \). The hindered transport coefficient of LDL in the wall was taken to be 0.02, which was based on the analysis conducted in Section 1.4. This yielded an effective Reynolds number in the wall of 5x10^{-7}. To model a hypertensive case, a transmural pressure of 160mmHg was selected, and the filtration velocities calculated for the 120mmHg case were multiplied by the ratio 160/120. This yielded a filtration velocity of 3.5x10^{-6} \text{cm/s} at the adventitial vasa vasorum, which was identical to the filtration velocity measured by Meyer et al. at 160mmHg.

6.3.2 Steady Flow Model

The same arterial geometry described in Chapter 5 (Figure 4.2) was used to study steady flow at transmural pressures of 120mmHg and 160mmHg. All flow and geometrical aspects were kept the same (\( \text{Re} = 330 \) and \( \text{Sc} = 6.3 \times 10^5 \)), hence the velocity and lumenal concentration fields were identical to those reported in Chapter 5. The mass transport equation (Equation 2.9) was solved for LDL transport in the wall region using the following boundary conditions: zero inlet axial concentration gradient, zero outlet axial concentration gradient, Equation 2.20 at the lumen/wall interface, and Equation 2.21 at the adventitial vasa vasorum. The values of \( M, M_v, \epsilon_s, H, \text{Sc}_{\text{eff}} \), and the hindered transport coefficient of LDL in the wall were the same as those used in the zero-axial-flow study described in the previous section. The effective Reynolds number in the wall was \( \text{Re}_{\text{eff}} = 3.3 \).
6.4 Results

6.4.1 Hypertension Study

Recall from Section 6.2 that previous experimental studies have revealed an approximate doubling (1.7-2.6) in mean LDL wall concentration when arterial pressure is raised from a normal level to a hypertensive level. Two mechanisms have been proposed that could explain such an increase [17]:

1. An increased LDL influx into the wall resulting from a pressure-dependent increase in endothelial LDL permeability. At 160mmHg Curmi et al. estimated the permeability to be 8x10^{-8} cm/s, which represents a four-fold increase over the permeability measured in vivo at normal arterial pressure [92].

2. An increased transmural velocity resulting from increased transmural pressure. Tedgui et al. [87] reported that an increase in pressure from 70mmHg to 180mmHg resulted in an increase in transmural velocity from 2.8x10^{-6} cm/s to 4.4x10^{-6} cm/s. Such an increase in velocity would have two effects. First, the convective flux of LDL macromolecules through the wall would be increased, which could serve to increase the LDL wall uptake. Second, the concentration polarization of LDL that develops at the lumen/wall interface would be enhanced as a result of the increased ultrafiltration of LDL through the endothelium. This would cause the wall to be exposed to a higher LDL concentration.
These hypotheses were tested using the two models described in the previous section. In order to test the second possibility, the models were run at pressures of 120mmHg and 160mmHg with no change to the endothelial LDL permeability ($M=2\times10^{-8}\text{cm/s}$ at both pressures). To test the first possibility, the models were run at a pressure of 160mmHg with a four-fold increase in endothelial LDL permeability ($M=8\times10^{-8}\text{cm/s}$). These cases are summarized in Table 6.1.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Transmural Pressure (mmHg)</th>
<th>Endothelial Permeability (cm/s)</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>2$\times10^{-8}$</td>
<td></td>
</tr>
<tr>
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<td>160</td>
<td>2$\times10^{-8}$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>160</td>
<td>8$\times10^{-8}$</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.1: Test conditions used for unsteady zero-axial-flow and steady flow models.

The three sets of conditions listed in Table 6.1 were used to calculate the LDL concentration profiles in the wall and the mean LDL wall concentration, for both models. The results are discussed in the next two sections.

6.4.1.1 Unsteady Zero-Axial-Flow Model

The total duration for the unsteady zero-axial flow study was 30 minutes, and the time step size was varied between 0.2 minutes and 15 minutes. It was found that the computed concentration profile in the wall was independent of time step for time steps less than 2 minutes, thus the time step size was set at 2 minutes. The wall concentration profiles can be viewed in Figure 6.3. The mean normalized wall concentration of LDL was calculated for the three cases and was found to be $3.2\times10^{-3}$ (Case 1), $3.3\times10^{-3}$ (Case...
2), and $8.4 \times 10^{-3}$ (Case 3). Clearly, the increased transmural velocity caused by the higher pressure was not sufficient to explain the increase in LDL wall concentration seen in the experimental studies. When the endothelial LDL permeability was not increased at 160mmHg (Case 2), the mean LDL concentration in the wall barely increased ($3.2 \times 10^{-3}$ to $3.3 \times 10^{-3}$). By contrast, when the endothelial LDL permeability was increased four-fold at 160mmHg (Case 3), the mean LDL concentration in the wall increased by a factor of 2.6 ($3.2 \times 10^{-3}$ to $8.4 \times 10^{-3}$). Thus, it appears that the experimental data are most consistent with a pressure-linked alteration of the endothelial LDL permeability that accounts for the increased uptake of LDL by the wall at higher pressures. From the profiles in Figure 6.3, it can also be noted that the distance of penetration of LDL into the wall was closer to the value expected after 30 minutes than was found in the Meyer et al.'s study. Recall from Section 6.2 that the normalized infiltration distance was approximated to be of order 0.1.
Figure 6.3: Normalized computational LDL wall concentration profiles at 120mmHg and 160mmHg for unsteady zero-axial-flow model. Profiles shown for time=30 minutes. An x-axis position of 0 indicates the lumen/wall interface, and an x-axis position of 1 indicates the adventitial vasa vasorum. This notation is used in the remaining figures.

6.4.1.2 Steady Flow Model

The wall concentration profiles for the steady flow model can be viewed in Figure 6.4. The profiles were obtained from a slice arbitrarily taken at an axial position of $x/R=3$. The mean concentration across the wall was calculated in a normal (non-plaque)
section of the geometry, from \(x/R=2\) to \(x/R=4\), for the three cases and was found to be \(2.2 \times 10^{-2}\) (Case 1), \(2.4 \times 10^{-2}\) (Case 2), and \(4.1 \times 10^{-2}\) (Case 3). This region was selected arbitrarily, but was consistent in each of the three cases to ensure that the length from the inlet for concentration boundary layer development was kept constant. Again, the increased transmural velocity caused by the higher pressure was not sufficient to explain the experimentally observed increase in LDL wall concentration. When the endothelial LDL permeability was not increased at 160 mmHg (Case 2), the mean LDL concentration in the wall exhibited a very small increase \((2.2 \times 10^{-2} \text{ to } 2.4 \times 10^{-2})\). By contrast, when the endothelial LDL permeability was increased four-fold at 160 mmHg (Case 3), the mean LDL concentration in the wall increased by a factor of 1.9 \((2.2 \times 10^{-2} \text{ to } 4.1 \times 10^{-2})\). Similar to the results from the unsteady model, it appears that there is a pressure-linked alteration of the endothelial LDL permeability that accounts for the increased uptake of LDL by the wall at elevated pressures.
Figure 6.4: Normalized computational LDL wall concentration profiles at 120mmHg and 160mmHg for steady flow model. Computational results taken from axial position $x/R=3$ (see inset).

The results from the unsteady and steady models have confirmed that the approximate doubling in LDL concentration in the wall observed at higher pressures is reasonably independent of factors such as the presence of axial flow and/or the duration of the computational study. It has also been revealed that there is most likely a substantial pressure-linked increase in endothelial LDL permeability that accounts for the increase in LDL wall infiltration under hypertensive conditions.
For the remaining studies in this chapter the steady flow model described in Section 6.3.2 was used. When a state of normal pressure was modelled, the endothelial LDL permeability was set to $2 \times 10^{-8}$ cm/s. When a state of hypertension was modelled, the endothelial LDL permeability was increased to $8 \times 10^{-8}$ cm/s.

6.4.2 Plaque Study

In Chapter 5, the effects of a plaque region on luminal LDL concentration profiles at the lumen/wall interface were studied. The plaque was considered to extend from $x/R=6$ to $x/R=8$, which is the entire region of the stenosis. In this section the effect of such a plaque on the LDL concentration distribution within the wall itself was examined (see also Appendix E). Using Baldwin at al.'s [7] results, it was assumed that the plaque has a Darcian permeability that is 5 times greater than that in the normal wall. A transmural pressure of 120 mmHg was applied and the resulting LDL concentration in the wall was examined. The mean normalized LDL concentration in the plaque region of the wall (from $x/R=6$ to $x/R=8$) was $1.14 \times 10^{-2}$ when the normal Darcian permeability was used. This value increased by 33% to $1.52 \times 10^{-2}$ when the Darcian permeability was increased by a factor of 5. The LDL wall concentration profiles taken from a slice in the plaque can be compared in Figure 6.5. The LDL wall concentration contours in the plaque can also be examined in Figure 6.6. There were two primary impacts of the higher plaque permeability. The first was an overall elevation of mean LDL concentration in the plaque region that arose from the increase in luminal LDL concentration at the lumen/wall interface. The second was that the LDL penetrated
further into the media as a result of the increased fluid velocity triggered by the increased Darcian permeability.

Figure 6.5: LDL wall concentration profiles for normal (inverse Darcy number=5x10^{12}) and elevated (inverse Darcy number=1x10^{12}) Darcian permeabilities in the plaque region. Profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of x/R=7.5 (see inset). This slice follows the same path as the velocity vectors.
Figure 6.6: Normalized LDL wall concentration contours in plaque region, which extends from $x/R=6$ to $x/R=8$. (a) normal Darcian permeability (inverse Darcy number=$5\times10^{12}$) in plaque region. (b) elevated Darcian permeability (inverse Darcy number=$1\times10^{12}$) in plaque region. Not shown to scale.
In examining the wall concentration profiles in Figure 6.5, another, seemingly paradoxical, observation can be made. Although the higher Darcian permeability in the plaque region prompted an increase in the lumenal LDL concentration at the lumen/wall interface, which in turn caused an overall elevation of mean wall LDL concentration, the LDL concentration at the lumen/wall interface on the wall side decreased. This is related to the terms of the lumen/wall interface boundary condition on the wall side (Eq. 2.20), which will be discussed further in Section 6.4.3.

The effects described above were exaggerated further when Guretzki et al.'s [38] cell culture study results were incorporated into the simulations. Recall from Section 5.3 that Guretzki et al. observed an exponential effect of LDL concentration on endothelial LDL permeability. This enhanced endothelial permeability was implemented in conjunction with an elevated Darcian permeability in the plaque region and the results can be viewed in Figure 6.7 and Figure 6.8. Here, the increased Darcian permeability increased the lumenal LDL concentration at the lumen/wall interface, which in turn exponentially increased the endothelial LDL permeability. The result was that the mean LDL concentration in the plaque region of the wall increased 73% from $1.52 \times 10^{-2}$ to $2.63 \times 10^{-2}$. Comparing Figure 6.8a and Figure 6.8b it can be noted that the effect of Guretzki et al.'s relationship was more prominent in the downstream side of the stenosis. This was due to the significantly higher lumenal LDL concentration on the downstream side (see Chapter 5) and the exponential nature of Guretzki et al.'s relationship. This
effect can also be seen in the LDL wall concentration contours in Figure 6.7 in which the bands of highest concentration are thicker on the downstream side. Further, the mean LDL concentration in the upstream side of the plaque was found to be $2.26 \times 10^{-2}$ compared to $3.01 \times 10^{-2}$ in the downstream side. Note also from Figure 6.7 that there is a small "bump" of elevated wall concentration in the concentration contours at an axial position of about $x/R=7.2$. This was the result of the separation point in the velocity field, which caused a local spike in lumenal LDL concentration at the lumen/wall interface, thereby increasing the wall concentration at that location. This effect is present in the other concentration contour plots in the stenosis region; however, it is more evident in Figure 6.7 due to the additional impact of the enhanced endothelial LDL permeability.
Figure 6.7: Normalized LDL wall concentration contours in plaque region for elevated Darcian permeability (inverse Darcy number=1x10^{12}) and enhanced endothelial permeability (using Guretzki et al.’s relationship). Not shown to scale.
Figure 6.8: Normalized wall LDL concentration profiles for elevated Darcian permeability in plaque region with normal and enhanced (using Guretzki et al.'s relationship) endothelial permeability. (a) Upstream - profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of $x/R=6.5$ (see inset). This slice follows the same path as the velocity vectors. (b) Downstream - profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of $x/R=7.5$ (see inset). This slice follows the same path as the velocity vectors.
6.4.3 Plaque Study at Elevated Pressure

In Section 6.4.1 and Section 6.4.2 elevated pressure and the presence of atherosclerotic plaque were investigated as separate effects on the LDL wall concentration. In this section the two factors were combined in order to study their potential compounding effect on the concentration of LDL in the artery wall.

Again, the plaque was considered to extend from $x/R=6$ to $x/R=8$, and it was assumed that the plaque had a Darcian permeability that was 5 times greater than that in the normal wall. A transmural pressure of 160mmHg was applied and the resulting LDL concentration in the wall was examined. The mean normalized LDL concentration in the plaque region of the wall was $1.89 \times 10^{-2}$ when the normal Darcian permeability was used. This average increased by 84% to $3.48 \times 10^{-2}$ when the Darcian permeability was increased by a factor of 5. The LDL wall profiles taken from a slice in the plaque can be compared in Figure 6.9. The LDL wall concentration contours in the plaque can also be examined in Figure 6.10. Consistent with the results at a pressure of 120mmHg, there were two primary impacts of the higher plaque permeability. There was an overall elevation of wall LDL concentration in the plaque and the LDL penetrated further into the media. At 160mmHg, however, these two impacts were significantly greater. The increase in mean LDL concentration in the plaque region of the wall at 120mmHg, as a result of the increased Darcian permeability, was only 33% compared to the 84% found at 160mmHg.
Figure 6.9: Normalized LDL wall concentration profiles at a pressure of 160mmHg for normal (inverse Darcy number=5x10^{12}) and elevated (inverse Darcy number=1x10^{12}) Darcian permeabilities in the plaque region. Profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of x/R=7.5 (see inset). This slice follows the same path as the velocity vectors.
Figure 6.10: Normalized LDL wall concentration contours in plaque region at a pressure of 160mmHg. (a) normal Darcian permeability (inverse Darcy number=5x10^{12}) in plaque region. (b) elevated Darcian permeability (inverse Darcy number=1x10^{12}) in plaque region. Not shown to scale.
Similar to the results found at 120mmHg, the effects described above were exaggerated further when Guretzki et al.’s exponential relationship was incorporated. Guretzki et al.’s enhanced endothelial permeability was implemented in conjunction with an elevated Darcian permeability in the plaque region and the results can be viewed in Figure 6.11 and Figure 6.12. Again, the increased Darcian permeability increased the lumenal LDL concentration at the lumen/wall interface, which in turn exponentially increased the endothelial LDL permeability. The result was that the mean normalized LDL concentration in the plaque region of the wall increased 39% from \(3.48 \times 10^{-2}\) to \(4.85 \times 10^{-2}\). A comparison of Figure 6.12a and Figure 6.12b supports the previous findings (at 120mmHg) that the effect of Guretzki et al.’s relationship was more prominent in the downstream side of the stenosis. This can also be seen in the LDL wall concentration contours in Figure 6.11 in which the bands of highest concentration are thicker on the downstream side. Further, the mean LDL concentration in the upstream side of the plaque was found to be \(4.23 \times 10^{-2}\) compared to \(5.47 \times 10^{-2}\) in the downstream side.
Figure 6.11: Normalized LDL wall concentration contours in plaque region at 160mmHg for elevated Darcian permeability (inverse Darcy number=1x10^{12}) and enhanced endothelial permeability (using Guretzki et al.'s relationship). Not shown to scale.
Figure 6.12: Normalized wall LDL concentration profiles for elevated Darcian permeability in plaque region at 160mmHg with normal and enhanced (using Guretzki et al.'s relationship) endothelial permeability. (a) Upstream - profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of $x/R=6.5$ (see inset). This slice follows the same path as the velocity vectors. (b) Downstream - profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of $x/R=7.5$ (see inset). This slice follows the same path as the velocity vectors.
In examining the impact of Guretzki et al.'s relationship at 120mmHg and 160mmHg it is, at first glance, surprising that the increase in mean LDL wall concentration in the plaque was not more significant at the higher pressure. Recall that when Guretzki et al.'s relationship was applied at 120mmHg the increase in LDL concentration was 73%. The equivalent increase at a pressure of 160mmHg was only 39%. In Section 5.3 it was shown that the luminal LDL concentration at the lumen/wall interface at 160mmHg was higher than at 120mmHg. This was most marked in the plaque region. Since Guretzki et al.'s relationship is exponential it would be anticipated that the higher luminal LDL concentration at 160mmHg would exponentially increase the endothelial permeability and cause even higher levels of LDL infiltration into the wall. However, upon closer examination of the boundary condition outlined in Equation 2.20, it becomes evident that this may not be the case. The influx of LDL into the wall is governed by the product of the endothelial permeability and the effective concentration gradient between the wall and the lumen:

\[
\text{influx} = -P \left( \frac{c}{e_s} - c_p \right)
\]  
(6.1)

where \( P \) is the endothelial LDL permeability and \( c \) is the concentration on the wall side at the luminal/wall interface. It's certainly clear that an increase in endothelial LDL permeability and/or an increase in luminal LDL concentration at the lumen/wall interface will directly increase the LDL influx into the wall. However, increases in endothelial
LDL permeability and/or lumenal LDL concentration also increase the LDL concentration in the wall, $c$. As a result, the concentration gradient between the lumen and the wall can decrease, leading to a less-than-proportional increase in influx for a given increase in $P$ or $c_p$. An example helps illustrate this point. Using the values in Table 6.2 it can be seen that at a pressure of 120mmHg the influx of LDL into the wall increased by 94% when Guretzki et al.’s relationship was applied. The equivalent increase at 160mmHg was only 63%. The endothelial LDL permeability increased dramatically when Guretzki et al.’s relationship was applied at 160mmHg; however, this increase also served to decrease the concentration gradient between the lumen and the wall by increasing the LDL concentration in the wall. The net effect was still an increase in the LDL influx into the wall, but not as substantially as at a pressure of 120mmHg.

<table>
<thead>
<tr>
<th>Pressure (mmHg)</th>
<th>$c_p$</th>
<th>Endothelial LDL permeability (cm/s)</th>
<th>Guretzki Factor</th>
<th>$P$ ($x10^{-8}$cm/s)</th>
<th>$c$</th>
<th>influx ($x10^{-8}$cm/s)</th>
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<tr>
<td>120</td>
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<td>5.17</td>
<td>41</td>
<td>0.176</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Table 6.2: Calculation of LDL influx into the wall based on relation shown in Equation 6.1. All values taken at an axial position of $x/R=7.5$ and for an inverse Darcy number of $1x10^{12}$. $c$ and $c_p$ are the wall-side and lumen-side concentrations of LDL at the lumen/wall interface, respectively. “Guretzki factor” calculated from Equation 5.1. A Guretzki factor equal to 1 indicates that Guretzki et al.’s relationship was not applied.
In this section the effects of increased transmural pressure, increased convective velocities in the plaque (due to increase plaque Darcian permeability), and increased endothelial LDL permeability were examined. The results are summarized in Table 6.3. From these results it was evident that applying Guretzki et al.'s relationship had a substantial impact on the infiltration of LDL from the lumen into the wall. A critical aspect of this finding was that it could potentially undermine the semi-coupled approach taken in this work. Recall from Sections 2.2.6.1 and 4.3 that the semi-coupled approach was validated by showing that the luminal concentration field was only weakly affected by the uptake of LDL into the wall. This was done by demonstrating that an endothelial LDL permeability of 0.02x10^{-6}cm/s could be neglected compared to the convective and diffusive transport rates in the lumen at the lumen/wall interface. However, in the most extreme case studied in this section, the endothelial LDL permeability increased 40-fold to 0.8x10^{-6}cm/s. To confirm that this term could still be neglected, the validation methods from Section 2.2.6.1 and Section 4.3 were employed. First, an order of magnitude analysis was done on the terms in Equation 2.18. Recall from Section 1.4 that the convective and diffusive transport rates in the luminal boundary layer were approximately 4x10^{-6}cm/s and 21 to 34x10^{-6}cm/s, respectively. The most extreme endothelial LDL permeability occurred when the pressure was elevated to 160mmHg and the inverse Darcy number in the plaque was set to 1x10^{12}. In this situation, the convective velocity increased by a factor of approximately 2.5, to 10x10^{-6}cm/s. Thus, it appeared that it was still reasonable to neglect an endothelial LDL permeability of 0.8x10^{-6}cm/s. The second validation method consisted of a computational test, in which the endothelial LDL permeability was set to \( M=0.8x10^{-6} \)cm/s in Equation 2.18. The
resulting luminal LDL concentration profile at the lumen/wall interface was compared to the profile generated at $M=0.02\times10^{-6}$ cm/s. It was found that the two profiles differed by less than 1%. Thus the computational test confirmed that even in the most extreme case the increase in endothelial LDL permeability exerted a negligible effect on the luminal concentration field.

<table>
<thead>
<tr>
<th>Inverse Darcy Number of Plaque Region</th>
<th>Transmural Pressure (mmHg)</th>
<th>Endothelial LDL Permeability</th>
<th>Percentage Increase in Mean LDL Concentration in Plaque Region of Artery Wall$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1\times10^{12}$</td>
<td>120</td>
<td>Normal$^*$</td>
<td>33%</td>
</tr>
<tr>
<td>$1\times10^{12}$</td>
<td>120</td>
<td>Enhanced</td>
<td>131%</td>
</tr>
<tr>
<td>$1\times10^{12}$</td>
<td>160</td>
<td>Normal</td>
<td>205%</td>
</tr>
<tr>
<td>$1\times10^{12}$</td>
<td>160</td>
<td>Enhanced</td>
<td>325%</td>
</tr>
</tbody>
</table>

$^*$Increase over "base case" of normal Darcian permeability (inverse Darcy number=$5\times10^{12}$), normal pressure (=120 mmHg) and normal endothelial permeability (=2x$10^{-8}$ cm/s)

$^*$Normal indicates that Guretzki et al.'s relationship was not applied. Enhanced indicates that Guretzki et al.'s relationship was applied.

Table 6.3: Summary of studies conducted to examine effect of pressure and endothelial LDL permeability on the mean concentration of LDL in the plaque region of an artery wall.

6.5 Necrotic Core Study

Atherosclerotic plaques contain many different zones of cellular and acellular material. For example, the fibrous cap usually consists of a compact layer of smooth muscle cells and connective tissue fibers. The necrotic core is composed of amorphous debris and cholesterol clefts. Bassiouny et al. [8] have conducted a study in which the location and size of these different regions were identified and measured in plaques.
excised from carotid stenoses. Bassiouny et al. found that the distance from the lumen to the necrotic core could range from 0 to 1.4mm. In addition, the percent cross-sectional area that the necrotic core occupied in the plaque was 21%±18%.

Since LDL continues to play an important role in advanced atherosclerotic lesion development (Section 1.2), it is of interest to examine how the presence of a necrotic core could affect LDL transport in the plaque. In order to examine the potential impact, a model was developed in which a region representing a necrotic core was placed in the plaque region of the arterial wall (see also Appendix E). The necrotic core was assumed to be quasi-elliptical in shape, to occupy 18% of the total area of the plaque, and to be located in the downstream side of the stenosis, extending from the lumen/wall interface to the vasa vasorum (see Figure 6.13). This region was created by assuming that the Darcian permeability was lower in the necrotic core. An inverse Darcy number of 2.5x10^{13} was applied, which was 25 times greater than the inverse Darcy number, 1x10^{12}, in the rest of the plaque region. This value was arbitrarily selected to represent a Darcian permeability that was substantially less than normal wall material, which has an inverse Darcy number of 5x10^{12}. The velocity fields for plaques with and without the necrotic core can be compared in Figure 6.14.
Figure 6.13: Location and geometry of necrotic core region. The unshaded area is the arterial lumen, the light gray-shaded area is the normal arterial wall, the dark gray-shaded area is the plaque region, and the black-shaded area is the necrotic core. Not shown to scale.
Figure 6.14: Normalized velocity magnitude contours for elevated Darcian permeability (inverse Darcy number=1x10^{-13}). (a) without necrotic core. (b) with necrotic core (inset shows necrotic core region within which inverse Darcy number=2.5x10^{-13}). Not shown to scale.
It was found that the presence of the necrotic core actually reduced the mean LDL concentration in the plaque region of the wall by 6%, from $1.52 \times 10^{-2}$ to $1.43 \times 10^{-2}$. This was caused by the lower Darcian permeability in the necrotic core, which caused a lower lumenal LDL concentration at the lumen/wall interface. This can be seen in Figure 6.15. Similar to the observations in previous sections, the decreased convective velocity through the core resulted in less LDL infiltration into the middle layers of the wall. This can be observed in Figure 6.16 and Figure 6.17.
Figure 6.15: Normalized luminal LDL concentration profile at lumen/wall interface with elevated plaque Darcian permeability (inverse Darcy number=$1\times10^{12}$) - with and without necrotic core.
Figure 6.16: Normalized wall LDL concentration profiles for plaque region with and without necrotic core. Profiles are taken from a slice that extends from the lumen/wall interface to the vasa vasorum starting at an axial position of $x/R=7.5$ (see inset - necrotic core region shown as shaded section). This slice follows the same path as the velocity vectors.
Figure 6.17: Normalized LDL wall concentration contours in plaque region for elevated Darcian permeability (inverse Darcy number=1x10^{12}) with necrotic core (inverse Darcy number=2.5x10^{13}). Inset shows necrotic core region. Not shown to scale.

6.6 Discussion

6.6.1 Hypertension

In Chapter 5 the occurrence of LDL concentration polarization at the lumen/wall interface was discussed as a possible cause for the localized nature of atherosclerosis, and as a possible explanation of why hypertension is a risk factor for atherosclerosis [21, 27].
In Section 5.3.2, a study of lumenal mass transport showed that increasing transmural pressure from 120mmHg to 160mmHg increased LDL concentration at the lumen/wall interface of a normal (non-stenotic) section of wall by 3%. The corresponding increase in transmural fluid velocity was 36%. In this chapter the distribution of LDL within the wall was computed, taking into account these effects. The findings of Section 6.4.1 suggest that concentration polarization and increased wall convective velocities alone cannot explain the significant increase in LDL wall tissue concentration that is seen acutely in experimental studies using elevated transmural pressures. Instead, it appears that a pressure-linked increase in endothelial permeability at higher pressures most probably accounts for the elevated levels of LDL in the wall.

* A priori, the pressure-linked increase in the level of concentration polarization could be responsible for this increase in endothelial LDL permeability through Guretzki et al.'s relationship. In this sense, concentration polarization would still, in effect, be the culprit. However, this possibility is quantitatively inconsistent with the computed results. Specifically, if the Guretzki factor (Eq. 5.1) is calculated for an LDL concentration increase of 3% at 160mmHg, it only amounts to an increase of 10% in the endothelial permeability. This is far short of the 300% increase in permeability seen at 160mmHg (from 2x10⁻⁸ cm/s to 8x10⁻⁸ cm/s). Therefore, it is unlikely that concentration polarization is responsible for the higher infiltration of LDL into the wall seen at elevated pressures.

A possible explanation for the pressure-linked increase in endothelial LDL permeability has been suggested by Meyer et al. [60]. In Meyer et al.'s study, it was
hypothesized that the suspected increase in endothelial LDL permeability at elevated pressures was caused by a pressure-induced stretching of the artery wall. To test this hypothesis, half of the arterial segments that were pressurized to 120mmHg and 160mmHg were wrapped in external rigid polyester sleeves (to prevent wall stretching) and the other half were left unwrapped. It was found that increases in LDL infiltration at higher pressures occurred in the unwrapped segments, but they did not occur in the wrapped segments. Meyer et al. concluded that a stretching of the artery wall at higher pressures likely increases endothelial LDL permeability, which causes greater LDL infiltration into the wall. This finding could also help explain why the three hypertension studies discussed in Section 6.2 yielded similar results despite their application of different hypertensive pressures (160mmHg, 180mmHg and 200mmHg). It is possible that the arterial wall stretching proposed by Meyer et al. reaches some physical maximum at 160mmHg. This physical maximum could be related to the observation that arteries become stiffer at higher pressure [12]. In other words, an increase in pressure from 160mmHg to 180mmHg or 200mmHg would not produce an increase in the amount of wall distension, and would therefore not further increase the endothelial LDL permeability.

6.6.2 Plaque

In modelling different features of the plaque it is apparent that both the endothelial permeability and the transmural fluid velocity have a significant impact on the level and distribution of LDL concentration in the plaque. The existence of the plaque resulted in an increase in the mean LDL wall concentration of 131%, when a 5-
fold increase in Darcian permeability and Guretzki et al.'s relationship was assumed (Table 6.3). In addition, the increase in LDL concentration in the downstream side of the plaque was larger than on the upstream side. Along with the previous findings in Chapter 5, this is entirely consistent with experimental studies that indicate that plaque grows in a downstream direction [22, 83].

Another effect of the higher Darcian permeability in the plaque was that the higher transmural fluid velocity transported the LDL further into the wall. Interestingly this effect appeared to be reversed in the presence of a necrotic core. The lower Darcian permeability of the necrotic core slowed the transport of the LDL into the inner layers of the wall and reduced the mean concentration of LDL in the plaque region of the wall. This reduction in LDL concentration could have implications for the regression of atherosclerosis. As discussed in Chapter 1, LDL continues to play an important role in the progression of atherosclerotic plaques past the atherogenesis stage. Any reduction in the influx of LDL into the wall could help stem that progression. Several experimental studies have indicated that atherosclerotic plaque growth can be reduced, and even reversed, when experimental specimens are fed a low cholesterol diet [3, 58, 97, 100]. A key finding from regression studies is that the level of lipids in the wall is reduced. The necrotic core, once formed, could exert a similar effect by reducing the influx of LDL into the wall and hence reducing the continued growth of the plaque.
6.6.3 Hypertension and Plaque

In Section 6.4.3 elevated pressure and the presence of atherosclerotic plaque were studied together in order to determine if there would be an additive effect on the increase of LDL concentration in the artery wall. In examining the results summarized in Table 6.3, it is apparent that the dual effects of hypertension and an existing state of atherosclerosis have dire consequences for the infiltration of LDL into the wall. The fluid dynamics at an arterial stenosis caused by atherosclerotic plaque serve to locally increase the luminal LDL concentration at the lumen/wall interface. If Guretzki et al.'s data can be extrapolated to the *in vivo* situation, a state of elevated arterial pressure combined with the pre-existence of an atherosclerotic stenosis could lead to increases of over 300% in the mean LDL concentration in the wall. Again, as a result of LDL's continued role in advanced atherosclerosis this could substantially increase the rate of progression of the disease and potentially lead to a more rapid occlusion of the artery.
CHAPTER 7

7 Summary and Conclusions

7.1 Summary

There is considerable evidence that the mass transport of atherogens, such as low density lipoproteins, is linked to the development and progression of atherosclerosis. Consequently, numerous experimental and computational studies have been undertaken to better elucidate this connection.

Focusing on the computational work in the field of arterial mass transport, previous work has been limited by simplifying assumptions that often arise from treating the problem in one arterial region only - either the lumen or the wall. This has indicated the need for an arterial model that could analyze mass transfer effects in both regions of the artery simultaneously. In the present work, such as approach was taken.

An existing Navier-Stokes solver was modified to solve Brinkman’s model in a dual-region model of an artery. Due to the computational complications that arise from the convection-dominated nature of macromolecular arterial mass transport, the Streamline Upwind/Petrov-Galerkin method was implemented to solve the mass transport equation at high Peclet numbers. The new formulation was validated through a series of
tests, and was found to operate accurately. In addition, a pressure boundary condition treatment of the outermost boundary of the system (the adventitial vasa vasorum) was implemented, which provided a more direct evaluation of the effects of varying arterial pressure on LDL transport.

The new formulation was used to analyze the mass transport of LDL in the lumen and wall of a computational model designed to replicate a stenosed (constricted) artery. More specifically, the dual-region approach was used to determine how key factors that influence LDL transport into the artery wall could effect the progression of atherosclerosis. These factors included hypertension (a state of elevated arterial pressure), the endothelial permeability to LDL, and the presence and morphology of an atherosclerotic plaque. The conclusions from these analyzes are presented in the next section.

7.2 Conclusions and Contributions

Through a transport resistance analysis of the three arterial transport layers (lumenal boundary layer, endothelium, and wall), it was shown that the endothelium offers the majority of resistance to LDL transport, which is consistent with the findings by Karner [47]. It was also concluded that convective effects dominate LDL transport in the wall, and exert an important effect in the boundary layer in regions of flow separation or flow stagnation. This illustrated the need for a proper treatment of convection in LDL transport studies, which would include an accurate treatment in the arterial wall. This led
to the development of the dual-region approach, which has provided key insights into the factors that influence arterial LDL transport and thereby affect the progression and regression of atherosclerosis. Specifically, the questions posed in Section 1.5 were answered as follows (note that the numbers below correspond to the original question numbers):

1. Elevated arterial pressure was shown to increase the lumenal LDL concentration at the lumen/wall interface. This served to increase the LDL transport into the wall, thereby approximately doubling the mean LDL wall concentration. These findings support hypertension as a risk factor for atherosclerosis.

2. It was concluded that concentration polarization was likely not responsible for the higher infiltration of LDL into the wall seen at elevated arterial pressures. A pressure-linked increase in endothelial LDL permeability was considered to be a more probable cause.

3. It was shown that the higher Darcian permeability predicted to occur in atherosclerotic plaque increased the transmural filtration across the wall, which increased the lumenal LDL concentration at the lumen/wall interface. This led to an increase in LDL transport into the wall, which ultimately resulted in an increase in the mean LDL wall concentration of 33% and 84% at transmural pressures of 120mmHg and 160mmHg, respectively.
4. The experimentally predicted dependence of endothelial LDL permeability on LDL concentration, when combined with elevated arterial pressures and/or elevated Darcian permeability in the plaque, resulted in a dramatic increase in LDL transport into the wall. The pressure- and/or plaque-induced increases in LDL concentration at the lumen/wall interface resulted in increases in mean LDL concentration in the wall of as much as 325%.

5. The combined effects of elevated pressure, high plaque Darcian permeability, and enhanced endothelial LDL permeability suggested a strongly non-linear vicious cycle in which LDL infiltration would cause plaque growth in the downstream direction. This is consistent with clinical studies that have revealed such a directional growth of plaque. It was also found that the presence of a necrotic core in the plaque decreased the mean LDL concentration in the wall. This could imply a reduction in plaque growth once a necrotic core, or other region of depressed Darcian permeability, has formed within the plaque.

7.3 Recommendations

The conclusions and contributions presented in the previous sections have provided important insights into the relationship between LDL transport in the artery, and the development and progression of atherosclerosis. However, as with all studies, there is more work that can be done. The dual-region approach developed in this work is a significant step forward in modelling arterial mass transport. The various features of the
approach should be exploited to further our understanding of this critical field of study. With this in mind, the following is a list of recommendations for future work.

- The final point in Section 7.2 indicates that plaque morphology could have ramifications for the growth of atherosclerotic plaque. An interesting extension of this work would be to study the impact of different plaque morphological features, such as the position and extent of the necrotic core region, on the transport of LDL in the arterial lumen and wall.

- The results of this work have been for an axisymmetric geometry; real arterial stenoses invariably have a more complex shape. Since LDL transport has been shown to be very sensitive to geometrical changes, an interesting extension of this work would be to explore the effects of different stenotic geometries on the concentration of LDL in the lumen and the wall. To fully exploit this opportunity the existing mass transport code would need to be extended to accommodate three-dimensional studies. Although the FEM formulations could be expanded relatively easily, the existing code uses a direct solver, which, though efficient for two-dimensional problems, would be prohibitively memory-intensive for three-dimensional problems. This would require the implementation of an iterative solver. In addition, the current quadrilateral elements, while convenient for two-dimensional geometries, do not provide ample flexibility in meshing more complex three-dimensional geometries. In three-dimensions the elements are rectangular bricks,
which can be limiting in the definition of three-dimensional meshes. The use of
tetrahedral elements would be preferred.

- Atherosclerotic-prone sites in the arterial tree are not restricted to regions of luminal
  constriction (stenoses). Arterial bends and bifurcations have also been exposed as
  “hot spots” for atherosclerotic plaque formation. Another interesting extension of this
  work would be to study the LDL mass transport in the lumen and wall of these
  regions. However, as a result of the significant secondary flow patterns that occur in
  such regions, two-dimensional geometries prove insufficient to capture the important
  flow features. Again, three-dimensional models would be needed, thereby requiring
  the modifications discussed in the previous point.

- The impact of enhanced endothelial LDL permeability when exposed to elevated
  concentrations of LDL is potentially devastating. However, it is not clear how
  reliably data for $M'(c_w)$ can be extrapolated from Guretzki’s cell culture studies to the
  in vivo situation. An experimental study of the effect of LDL concentration on
  endothelial LDL permeability using a more physiologically realistic approach would
  be very valuable.

- The current FEM formulation of Brinkman’s model is based on the penalty method.
  Although the penalty method is very efficient, it does introduce an error of order $\varepsilon^{3/2}$
  into the solution of the velocity field, where $\varepsilon$ is the penalty parameter. The use of a
  pressure-correction method would improve on the accuracy of the velocity solution.
This could be of particular value since the use of the SUPG method introduces an additional error of order $h^2$, where $h$ is the grid-size.

- The semi-coupled approach used in this research is considered acceptable since the lumenal LDL concentration field appears to be only very weakly affected by the uptake of LDL into the wall. This assumption would no longer be valid if the physical parameters of the problem were to change such that the wall uptake began to exert a measurable effect on the lumenal concentration field. To improve the robustness of the dual-region model, it would be desirable to develop a fully coupled model in which the lumen and wall concentration fields are solved simultaneously.

- The SUPG method used in this work represents a significant improvement over standard finite element methods when applied to convection dominated transport problems. However, SUPG does not preclude overshooting and undershooting about sharp layers. To address this issue, an extension to SUPG has been developed that involves the addition of a 'discontinuity-capturing' term to the SUPG weighting function \cite{44}. This term has a form similar to the streamline term, but acts in the solution gradient direction instead of the streamline direction. The drawback of this method is that the dependence of the discontinuity-capturing term on the solution gradient results in a nonlinear discrete method. Nevertheless, this method should be incorporated, especially if three-dimensional models are to be considered that have limited capacity for extensive mesh resolution near boundaries.
APPENDIX A - GURETZKI FACTOR

In Chapter 5, the function used to calculate the "Guretzki factor" was presented. The fit of this function to Guretzki et al.'s experimental data was also shown. Since Guretzki et al.'s study was conducted using cultured endothelial cells rather than an in vitro or in vivo arterial endothelium, the dimensional values of the endothelial LDL permeability could not be used directly. Instead, a ratio was calculated (the Guretzki factor) that represents the amount by which the permeability of the endothelial cells is increased when exposed to an LDL concentration of \( c_\omega C_0 \) (in mg/mL). For example, at a base concentration of 1 mg/mL the permeability was found to be \( 5.7 \times 10^{-7} \pm 1.3 \times 10^{-7} \text{cm/s} \) \((p_1)\). When the concentration was increased to 1.5mg/mL, the permeability was found to be \( 20.2 \times 10^{-7} \pm 5.3 \times 10^{-7} \text{cm/s} \) \((p_2)\). The Guretzki factor \((G_f)\) at a concentration of 1.5mg/mL was then simply the ratio \( G_f = \frac{p_2}{p_1} = 3.54 \). The corresponding error, \( e_{G_f} \), was calculated using the following relation from Holmon [40]:

\[
e_{G_f} = \left[ \left( \frac{\partial G_f}{\partial p_1} e_1 \right)^2 + \left( \frac{\partial G_f}{\partial p_2} e_2 \right)^2 \right]^{1/2}
\]

where \( e_1 \) and \( e_2 \) are the errors (SEM) associated with \( p_1 \) and \( p_2 \), respectively, as published by Guretzki et al. Based on the definition of \( G_f (= \frac{p_2}{p_1}) \):

\[
\frac{\partial G_f}{\partial p_1} = -\frac{p_2}{p_1^2} \quad \text{and} \quad \frac{\partial G_f}{\partial p_2} = \frac{1}{p_1}
\]
APPENDIX B - TIME TO STEADY-STATE

In Section 6.2 several *in vitro* hypertension studies were discussed. In order to verify that steady-state had not been reached during these experiments the time required to reach steady-state was estimated. To aid in this estimation, an *in vitro* arterial albumin transport experiment was used, which measured the albumin concentration profiles in the arterial walls of rabbit thoracic aortas at different times throughout the experiment [88]. It was found that steady-state (defined when the albumin concentration profile no longer exhibited any change) was reached after approximately 3 hours. The time to reach steady-state can also be obtained through a straightforward calculation. This is done by assuming that the speed at which macromolecules are transported into the wall is the primary factor controlling how quickly steady-state is achieved. If it is further assumed, based on the analysis from Section 1.4 that the transport of macromolecules in the wall is dominated by convection, then an approximation of the time to reach steady-state can be determined by dividing the wall thickness (approximately 200 µm) by the macromolecular convective velocity. The hindered convective velocity of albumin through the wall was calculated using Equation 1.2 and the studies by Laurent et al. [51, 52], and found to be approximately 1.7x10⁻⁶ cm/s. This yielded a time to reach steady-state of about 3 hours, which is the same as the value found by Tedgui et al. Thus it appears that the assumption that the convective speed of macromolecules through the wall controls the time to reach steady-state was reasonable. Using this result, the time to reach steady-state for LDL transport was calculated. Again, the wall thickness was divided by the hindered convective velocity (1x10⁻⁷ cm/s from Section 1.4), which yielded a value of about 55 hours.
**APPENDIX C - TABLE OF MODEL PARAMETERS**

The following table lists the origins of the model parameters used in this work. The values listed in the table were obtained from various experimental and computational studies, as indicated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value Used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial LDL permeability</td>
<td>$M$</td>
<td>$2 \times 10^{-8}$ cm/s</td>
<td>$1.9 \pm 0.8 \times 10^{-8}$ cm/s [92]</td>
</tr>
<tr>
<td>LDL permeability at vasa vasorum</td>
<td>$M_{vv}$</td>
<td>$2 \times 10^{-9}$ cm/s</td>
<td>$1.7 \times 10^{-3}$ cm/s [67]</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>$\varepsilon_s$</td>
<td>0.15</td>
<td>0.17 [89] 0.15 [32] 0.1 [63]</td>
</tr>
<tr>
<td>Binding and degradation rate</td>
<td>$H$</td>
<td>$2 \times 10^{-5}$ s$^{-1}$</td>
<td>$2.4 \times 10^{-5}$ s$^{-1}$ [91]</td>
</tr>
<tr>
<td>Diffusivity of LDL</td>
<td>$D$</td>
<td>$5 \times 10^{-8}$ cm$^2$/s</td>
<td>$10^{-7}$-$10^{-8}$ cm$^2$/s [5]</td>
</tr>
<tr>
<td>Effective diffusivity of LDL</td>
<td>$D_{eff}$</td>
<td>$5 \times 10^{-10}$ cm$^2$/s</td>
<td>$6.2 \pm 3.7 \times 10^{-10}$ cm$^2$/s [89] 5.4$\pm$3.1$\times$10$^{-10}$ cm$^2$/s [92]</td>
</tr>
<tr>
<td>Transmural velocity</td>
<td>$v_w$</td>
<td>$4 \times 10^{-6}$ cm/s</td>
<td>$2.8$-$4.4 \times 10^{-6}$ cm/s [87] 4.1-$6.4 \times 10^{-6}$ cm/s [99]</td>
</tr>
</tbody>
</table>
Recall from Section 2.1.2 that the modified $Q_2^+-P_1$ Crouzeix-Raviart element [16] is used for this work. This element is recommended as one of the best incompressible finite elements for use with the penalty method [18]. The $Q_2^+-P_1$ notation indicates that the element is enriched (*), i.e. it has a velocity node at the element’s centroid, that it is quadrilateral (Q), and that it uses second order velocity shape functions ($2$) and first order pressure shape functions ($1$). The important features of the $Q_2^+-P_1$ element are [24]:

- The Brezzi-Babushka condition is satisfied, which essentially means that mass can be conserved element-wise.
- The pressure is continuous and differentiable within a single element; however, it is discontinuous between elements.
- Due to the discontinuous pressure feature, the product $[L]^T[D]^{-1}[L]$ can be computed on an elemental basis.
- The matrix $D$ can be easily inverted since the pressure shape functions are only employed at the element centroids.

The $Q_2^+-P_1$ element has nine nodes oriented as follows:
The biquadratic velocity and coordinate interpolation, and the linear pressure interpolation take the form:

\[\begin{align*}
    x &= \sum_{i=1}^{9} \phi_i x_i \\
    y &= \sum_{i=1}^{9} \phi_i y_i \\
    u &= \sum_{i=1}^{9} \phi_i u_i \\
    v &= \sum_{i=1}^{9} \phi_i v_i \\
    p &= \psi_1 p_9 + \psi_2 \frac{\partial p}{\partial x} \bigg|_{x=x_9} + \psi_3 \frac{\partial p}{\partial y} \bigg|_{y=y_9}
\end{align*}\]

An important feature of this element is that the velocity components and the pressure gradient in the centroid may be eliminated, thus reducing the independent degrees-of-freedom from 21 (18 velocity, 3 pressure) to 17 (16 velocity, 1 pressure) without a loss of accuracy [18].
# Appendix E - Table of Models

The following table lists the different models used throughout this work. The section number within which the model first appears is identified followed by a statement of the model’s purpose and important assumptions.

<table>
<thead>
<tr>
<th>Section</th>
<th>Purpose</th>
<th>Assumptions</th>
</tr>
</thead>
</table>
| 4.2     | Two models of a stenotic artery. The first model has one region (lumen) and the second model has two regions (lumen and wall). The lumenal LDL concentration fields of these models can be compared to ensure that Brinkman’s model and SUPG are running accurately together. Only the lumenal concentration field is solved in these models. | • A constant filtration velocity of $4 \times 10^{-6}$ cm/s is applied at the outer boundary of each model.  
• The distance from the lumen to the vasa vasorum is 4% of the lumenal diameter away from the stenosis and 12.5% of the lumenal diameter at the center of the stenosis. |
| 5.2     | Model of a stenotic artery with two regions (lumen and wall). Used to generate lumenal LDL concentration profiles along the lumen/wall interface and to calculate the net LDL transport into the wall. Results obtained under hypertensive conditions and with the presence of plaque in the artery wall. Only the lumenal concentration field is solved in this model. | • Same geometry as two-region model described in Section 4.2.  
• Constant pressure boundary condition applied at outer boundary of model (location of adventitial vasa vasorum). 120mmHg and 160mmHg represent normal and hypertensive conditions, respectively.  
• Plaque region occupies entire stenosis section of arterial geometry (from $x/R=6$ to $x/R=8$) and has a uniform Darcian permeability of 5 or 10 times greater than that of the normal wall.  
• Assumes an exponential relationship between the lumenal LDL concentration at the lumen/wall interface and the endothelial LDL permeability. |
| 6.3.1   | Unsteady two-region model with zero axial flow. Used to determine the mechanism underlying the experimentally observed increase in LDL wall concentration at elevated pressures. Both the lumenal and wall concentration fields are solved in this model. | • Mimics an experimental set-up in which an arterial wall segment is exposed to a solution containing LDL. This model mimics an experiment with no axial flow.  
• At time=0 the simulated run commences and LDL is transported into the wall from the simulated solution, containing LDL, in the lumenal region.  
• At time=30 minutes the simulation is stopped and snapshots of the LDL concentration profiles across the wall are taken.  
• A constant filtration velocity is applied at the outer wall. Two values are tested, which represent normal and hypertensive conditions. |
<table>
<thead>
<tr>
<th>Section</th>
<th>Purpose</th>
<th>Assumptions</th>
</tr>
</thead>
</table>
| 6.3.2   | Steady two-region model with flow. Also used to determine the mechanism underlying the experimentally observed increase in LDL wall concentration at elevated pressures. Both the lumenal and wall concentration fields are solved in this model. | - Uses straight portion of two-region stenotic artery model described in Section 5.2.  
- Mimics a perfusion experiment in which a solution containing LDL is passed through an arterial segment. The resulting LDL profiles across the wall are measured.  
- Constant pressure applied at outer boundary (location of adventitial vasa vasorum). 120mmHg and 160mmHg represent normal and hypertensive conditions, respectively |
| 6.4.2   | Model of a stenotic artery with two regions (lumen and wall). Used to study impact of plaque region on LDL wall concentration. Both the lumenal and wall concentration fields are solved in this model. | - Same assumptions as those listed for the model used in Section 5.2.  
- Plaque region has a uniform Darcian permeability of 5 times greater than that of the normal wall. |
| 6.5     | Model of a stenotic artery with two regions (lumen and wall). Used to study impact of plaque region with the presence of a necrotic core on LDL wall concentration. Both the lumenal and wall concentration fields are solved in this model. | - Same assumptions as those listed for the model used in Section 5.2.  
- A necrotic core is added to the plaque region in the artery wall. The necrotic core has a uniform Darcian permeability that is 25 times lower than that of the plaque region. |
BIBLIOGRAPHY


