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Author(s): Conway, Claire

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The Development of a Computational Test-Bed
to Assess Coronary Stent Implantation

Claire Conway
B.E., National University of Ireland, Galway

A thesis submitted to the National University of Ireland as fulfilment of the requirements for the Degree of Doctor of Philosophy

Department of Mechanical and Biomedical Engineering
National University of Ireland, Galway

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Supervisors of Research: Professor Peter McHugh & Dr. Patrick McGarry

Director of Research: Professor Peter McHugh
Abstract

The implantation behaviour of coronary stents is of great interest to clinicians and engineers alike as in-stent restenosis (ISR) remains a critical issue with the community. ISR is hypothesized to occur for reasons that include injury to the vessel wall caused by stent placement. To reduce the incidence of ISR, improved design and testing of coronary stents is needed. This research aims to facilitate more comprehensive evaluation of stents in the design phase, by generating more realistic arterial environments and corresponding stress states than have been considered heretofore, as a step towards reducing the prevalence of ISR. Furthermore, it proposes improvements to the current requirements for coronary stent computational stress analyses as set out by the Food and Drug Administration (FDA).

A systematic geometric test-bed with varying levels of arterial curvature and stenosis severity is developed and used to evaluate the implantation behaviour of two stent designs using finite element analysis. A parameter study on atherosclerotic tissue behaviour is also carried out. Results are analysed using tissue damage estimates and lumen gain comparisons for each design. Results indicate that stent design does not have a major impact on lumen gain behaviour but may have an influence on the potential for tissue damage. The level of stenosis in the arterial segments is seen to have a strong impact on the results while the effects of arterial curvature appear to be design dependent.

The greatest variable in any stenting analysis is the representation of the atherosclerotic tissue and this was the focus of the second phase of work. This research explores the direct stenting technique versus the predilation technique, the effects of variation of the material model for the atherosclerotic tissue matrix, the
effects of inclusion of calcifications and a lipid pool and finally the effects of inclusion of the Mullins effect on the atherosclerotic tissue matrix in stenting applications. One major finding is that the stiffness of the base elasticity model and the strength of the tissue are key parameters in these analyses.

In conclusion, the use of finite element modeling in this thesis to assess the biomechanics of coronary stent implantation has yielded the development of a novel computational test-bed. This work has generated considerable new insight into the mechanics of coronary stenting, and has created the basis for more effective and efficient stent design in the future.
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Abstract

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1 Introduction

1.1 The Heart and Coronary Arteries

The heart is the driving force of the circulatory system in the human body. From an engineering perspective, it is the pump which delivers healthy oxygenated blood to all parts of the body including the heart muscle. The delivery of healthy oxygenated blood to the heart muscle is vital for its normal operation. Arteries are the predominant delivery vessels, and the three main coronary arteries which serve the heart muscle are the right coronary artery, the left anterior descending artery and the left circumflex artery. An illustration of the position of these arteries relative to the heart is shown in Figure 1.1.

In their normal healthy state, each of these arteries typically is composed of three layers. The innermost layer is known as the intima, the outer layer is known as the adventitia and the central layer is known as the media. An illustration of the structure of a typical artery is shown in Figure 1.2 [1]. The intimal layer consists of a single layer of endothelial cells which line the arterial wall. The medial layer consists of a complex arrangement of smooth muscle cells, and elastin and collagen fibrils. This layer can typically be subdivided into a number of well-defined concentric fibre-reinforced medial layers separated by elastic laminae [2]. The media is separated from the intimal and adventitial layers by the internal and external elastic laminae respectively. The adventitial layer mainly consists of fibroblasts and fibrocytes (cells which produce collagen and elastin), histological ground substance and thick bundles of collagen fibrils. In the medial and adventitial layer the wavy collagen fibrils are generally arranged in helical patterns. These collagen fibrils are the load bearing
structures in each of the layers. For further information on the arterial wall the reader is referred to the work of Holzapfel et al. [1]. However the healthy arterial wall is not the primary motivation for this work. It is the diseased state which is of particular interest and this is discussed in section 1.2 of this chapter.

1.2 Heart Disease & Atherosclerosis

Ischemic heart disease is the leading cause of death in the world. In 2004, an estimated 12.3% of deaths in men and an estimated 12.2% of deaths in women were attributed to ischemic heart disease. According to World Health Organisation (WHO) statistics, this is predicted to remain one of the top four leading causes of death in 2030 [3].

Ischemic heart disease is characterised by reduced blood supply to the heart muscle, typically caused by atherosclerosis of the coronary arteries. Atherosclerosis is the thickening of the arterial wall due to an accumulation of necrotic waste, fat, cholesterol and other substances which lead to the formation of plaque structures. This reduction of blood flow to the heart muscle can lead to angina (chest pains), myocardial infarction (heart attack) and death. The progression of coronary atherosclerosis has been shown to be linked to factors such as family history, obesity, history of cigarette smoking, hypertension and diabetes [4].

According to Stary's classification [5], atherosclerosis typically progresses in a particular order, from Type I to Type VIII. A summary of the classifications of atherosclerotic lesions adapted from Stary is given in Table 1-1. According to this progression, the disease starts as an accumulation of macrophage foam cells, (fat cells) within the intimal wall, Type I. These foam cells can then coalesce and form multiple layers, Type II. The lesion then advances to preatheroma stage, Type III,
and onto atheroma stage IV, where an atheroma is a swelling of the arterial wall made up mostly of macrophage foam cells, lipid and connective tissue. The next stage in the progression is a Type V fibroatheroma lesion classification, in which prominent new fibrous connective tissue has formed. The next stages, Types VI to VIII, are characterised by fissuring, ulcerating and haemorrhaging of the vessel wall. Calcifications and fibrotic connective tissue also tend to develop in these more complicated lesion types. Figure 1.3 is an illustration which shows the progression of the disease from stages I to VI.

The progression of this disease is also not confined to the later stages of life, as illustrated by the graph in Figure 1.4. This graph shows that, for a total sample population of 691, by puberty 69% of subjects had some type of coronary lesion and by late thirties this figure rises to 95%.

### 1.3 Evolution of Treatments

Today the gold standard for treating atherosclerotic coronary vessels is the insertion of a small tubular scaffold called a stent as part of the angioplasty procedure (technique of mechanically widening narrowed or obstructed arteries via inflation of a balloon). This minimally invasive procedure has largely replaced the highly invasive and traumatic coronary artery bypass graft (CABG) procedures that are carried out to allow blood flow to bypass the stenotic region through attachment of a saphenous vein graft around the restricted site.

The CABG procedure first involves removal of a portion of the saphenous vein from the upper thigh, leaving a sizeable scar. The breast bone in the chest then is opened to access the heart organ and the procedure is carried out on a beating heart (Off-Pump Coronary Artery Bypass Graft) or on a heart organ that is still (Traditional
Coronary Artery Bypass Graft). For the latter the heart muscle is typically injected with cardioplegia (a drug to stop the heart and slow its metabolism). A heart-lung bypass machine keeps the blood and oxygen moving throughout the body during the surgery. This procedure typically requires on average two weeks of recovery in hospital [6].

However, the minimally invasive procedure of stenting has now largely replaced CABG surgeries, where possible, due to its high success rate, minimal scarring and quicker recovery times. However, if more than three coronary arteries are narrowed or if the patient is diabetic CABG may be recommended [7].

There are two general categories of stents: self expanding stents (SES) and balloon expandable stents (BES). These can be bare-metal or drug-coated, and permanent or biodegradable. Of particular interest to this work is the assessment of BES but the computational framework that is presented in the later stages of the thesis could also be readily utilised for the assessment of SES.

According to Kay et al. [8], the insertion of a stent typically involves the following steps.

First the femoral artery is localised by the cardiologist with the middle and index fingers of the left hand. With the fingers stable the area distal is anaesthetised using 10-20 ml of lignocaine. A discrete cut (3-5mm) is made in the skin using a scalpel blade over the femoral artery as shown in Figure 1.5. The vessel is then punctured with a needle, known as percutaneous access. The cardiologist may sense the artery at the tip of the needle though the transmitted palpation. Once pulsatile flow is confirmed a 0.035 inch wire can be introduced into the vessel toward the heart.
Fluoroscopic confirmation of the position of the wire is mandatory. The needle is then withdrawn.

A guiding catheter is then directed to a position in the ascending aorta (see Figure 1.1) such that its tip is coaxial with the opening of the diseased coronary vessel. To ensure that there is no air or clot present within the catheter a syringe is connected to aspirate and discard approximately 5ml of blood. The catheter is then connected to a three-port manifold (see Figure 1.6). This is a closed system manifold which allows pressure monitoring, catheter flushing with saline, and radiographic contrast administration.

The injection syringe, full of contrast dye, is held with the handle elevated so that any bubbles present rise to the plunger. This reduces the risk of bubbles being injected into the patient. Contrast is injected at a sufficient rate to briefly replace the blood in the coronary artery to reveal the atherosclerotic lesion.

The guidewire is then advanced through the guiding catheter to the diseased site, typically with a monorail catheter. The monorail catheter is a catheter where only the distal 15–25 cm of the balloon catheter tracks over the guidewire (see Figure 1.7). The advantages of this system are less procedural time, a single operator, reduced fluoroscopy time, and no additional devices for the exchange.

It is usually not difficult to advance the balloon catheter over the guidewire. However, very cumbersome lesions such as those that are tortuous, diffusely calcified, or chronically occluded need additional techniques. In order to cross such difficult lesions, the following techniques can be applied: the use of stronger back-up catheters, deep insertion of the guiding catheter, adding vibration, pushing the
balloon while pulling the guidewire or the use of a stiff guidewire (so-called ‘extra-
support type’).

The stent mounted on the catheter is then positioned at the site of stenosis. The
central part of the stent should cover the most severe segment of the stenosis,
especially in the case of hard calcified lesions. The stent is then deployed to expand
the stenosed vessel. Further details on the delivery of the device can be found in the
work of Kay et al. [8].

Depending on the stent type different methods of deployment are utilised. BES, as
the name implies are expanded via inflation of a folded balloon. The stent is crimped
onto the folded balloon, which is mounted on a catheter assembly. Once the catheter
is in place the balloon is expanded with a saline solution and this inflates the stent.
The balloon inflation period at the appropriate site should be 30–120 s. The balloon
is then deflated and removed leaving the stent in place as a scaffold maintaining
lumen patency. With a SES, the stent is manufactured at a desired diameter and then
constrained to a smaller diameter before insertion in the body. Upon positioning at
the site of the blockage the constraint (typically a sheath) is removed and the SES
expands to its original diameter.

For coronary applications typically a BES is used as opposed to a SES. One reason
for this is that the radial stiffness of a BES are generally much higher than a SES,
due to the materials from which they are manufactured. This has the implication that
SES often do not have sufficient stiffness to open calcified lesions which makes a
BES preferred in coronary and renal applications [9]. However, self expanding stents
are usually manufactured from super elastic materials such as nitinol which
elastically recover even after complete flattening or radial crushing making them suitable for peripheral applications [9].

1.4 History of Angioplasty and Stenting

In 1977, Andreas Gruentzig and colleagues performed the first coronary angioplasty in a living human [8]. The equipment used in this procedure was quite primitive and bulky, compared to modern day systems. In the early 1980’s guiding catheters and introducer sheaths were improved for the angioplasty procedure. First generation balloon catheters were fixed to the guidewire which made it difficult to traverse tight or tortuous lesions. The next major development in the procedure was the introduction of steerable guidewires [10] which allowed the operator better control. Further progression in balloon technology has included the use of different types of balloons, improved materials, better coatings and lower profile narrower systems.

The inclusion of a scaffolding device to improve upon balloon angioplasty results was first proposed in 1964 by Charles Dotter [11]. But it took nearly two decades before Jacques Puel and colleagues implanted the first balloon expandable stent in a human coronary artery in Toulouse, France [12]. The inclusion of this metallic scaffold acted against the elastic recoil of the artery, which improved lumen gain outcomes when compared to balloon angioplasty alone.

The term stent has become associated with a device that held a skin graft in position, a support for tubular structures and then an endovascular scaffold which relieved and prevented vascular obstructions [13]. But the original name is attributed to Charles Stent, a 19th century English dentist, who developed a mould with which to form an impression of the teeth and the oral cavity. Little did he know that his name would
become synonymous with the management of coronary artery disease in today’s world.

The first implantation of a balloon expandable stent was reported by Schatz et al. [14] in 1987. The implantation was in the peripheral artery of a canine and represented a significant milestone in the treatment of atherosclerotic vessels. The first implantation of a coronary stent in humans was carried out by Sigwart [15], in 1986, using the WallStent design; see Figure 1.8 for an image of first generation stents including the WallStent.

However it was 1991 before the first balloon-expandable stent, the Palmaz-Schatz slotted tube design (see Figure 1.8), was approved by the FDA (Food and Drug Administration). The results from the BENESTENT clinical trial, using the Palmaz-Schatz stent, were published in 1994 [16]. This trial showed that, for 540 patients with new lesions in the main coronary arteries, the clinical and angiographic outcomes were better in patients who received a stent than in those who received standard coronary angioplasty. A few years later it was reported that stent use as a percentage of total percutaneous angioplasty procedures had increased from 5.4% in 1994 to 69% in 1997 [17].

1.5 Issues with Coronary Stenting

The evolution of the stenting procedure has significantly improved the clinical treatment of atherosclerosis. However it is not a panacea in the treatment of the disease. First generation stents were typically bare metal stents and while they had a high success rate it was found that in-stent restenosis, when the stented vessel lumen becomes reblocked, was a key problem [18–23].
A second generation of stents emerged which were termed drug-eluting stents due to the coating of drug on their surface, typically embedded in a polymer matrix to control elution rates. The purpose of the drug (common types include sirolimus, paxitaxel, everolimus, and zotarolimus) is generally to suppress the vessel’s natural response to the stent implant through delayed healing of the intimal tissue forming around stent struts. These drug coatings have contributed significantly to the prevention of restenosis [24], however it has emerged recently that higher rates of late stent thrombosis (formation of blood clots within the stent) have been reported for drug eluting stents [25] (see Figure 1.9, adapted from [26]) causing a renewed interest in stent geometrical design to address the restenosis issue.

Contributing factors to restenosis are thought to include stresses within the arterial vessel wall [27,28] caused by stent implantation, or in some cases stent fracture [29–31]. The placement of a stent within a diseased vessel ultimately induces some level of arterial injury due to the supra-physiological loading involved in implantation of the device [32–34], even with drug eluting stents [35]. This injury to the vessel wall induces a biological response that leads to the development of neointimal hyperplasia. This is the natural response to damage to the endothelium, the lining of the arterial wall (see Figure 1.2). Endothelial cells release inflammatory mediators that trigger platelet aggregation, fibrin deposition and recruitment of leukocytes to the area. These cells then express growth factors that promote smooth muscle cell migration from the media to the intima. These smooth muscle cells proliferate in the intima and deposit extracellular matrix, in a process similar to scar formation, resulting in a partial or complete remodelling of the lumen.
1.6 Coronary Stent Design

To deal with the issues with coronary stenting discussed in Section 1.5 a renewed interest in stent geometrical design is emerging [36]. The use of numerical models to improve stent geometrical design is now a well-recognised and widely adopted approach. Such models allow one to easily assess physical quantities that are difficult to assess experimentally or in vivo.

The main design requirements of coronary stents are outlined below:

- **Deliverability** – this is prerequisite for any stent as it cannot treat a diseased vessel if it cannot be delivered to the site. Flexibility in a design is crucial to allow it to transverse the tortuous path to the coronary arteries.

- **Crimping on the balloon** – a good stent design must be securely crimped onto the balloon until it reaches the deployment site. Failure to maintain this feature could result in the stent slipping off the balloon in a blood vessel.

- **Radiopacity** – this is visibility of the stent once implanted and is related to the material the stent is manufactured from. It is vital for the cardiologist to be able see the stent once implanted to assess the success of the procedure. This also relates to the geometry of the design, while it might be desirable to reduce strut width of a design it can have an adverse effect on the visibility of the device so a balance must be reached.

- **Radial strength** – this is the ability of the stent to resist the tendency of the artery to naturally recoil. A design should have sufficient radial strength to prevent arterial wall collapse.

- **Scaffolding** – the capacity of a stent to prevent arterial tissue prolapsing between it gaps. The metal to artery ratio is an important quantity in this
regard; there should be sufficient metal to support the artery but no too much
to encourage thrombosis formation.

- **Conformability** – the stent should be able to take the shape of the artery upon expansion, particularly in stenosed tortuous sites where straightening of the stented vessel is undesirable.

- **Good apposition** – there should be uniform contact between the stent and the arterial wall upon deployment. If one or more stent struts protrude project into the arterial lumen it would prove difficult to advance a balloon or second stent to treat a lesion further along the same artery. Also protrusion of struts into the lumen can induce irregular blood flow patterns around the struts leading to undesirable physiological effects.

- **Biocompatibility** – the material from which the stent is manufactured must be biocompatible with the artery to minimise the risk of physiological immune responses such as thrombosis formation.

With the utilisation of numerical modelling one can design stents to better manage the physiological environment to which to they are exposed. The potential clinical and anatomical situations and the equivalent desired stent features are given in Table 1-2 [8]. To assess the performance of design several criteria can be examined using computational modelling. For instance in deployment simulations the level of elastic recoil (springback), foreshortening (longitudinal recoil) and flexibility of the device can all be assessed.

Using numerical simulations one can ultimately relate the design of a stent to the degree of stress to which the arterial vessel is exposed. Variations in design of a stent can lead to alterations in the stress distribution within the arterial wall. High levels of
arterial stress have been shown to be linked to issues such as in-stent restenosis as discussed previously in Section 1.5. This calls for a more accurate depiction and assessment of the arterial stress state to be modelled in silico (a computational simulation) with the aim that this depiction will lead to improved stent designs that injure the arterial vessel wall to a lesser extent. If the arterial wall is subject to a lower level of injury, due to improved geometrically designed stents, the risk of the biological response of neointimal hyperplasia formation will be reduced. Therefore a tool that allows stent designers to more accurately depict the arterial vessel response, to new and emerging designs, needs to be developed. The development of this tool will be the particular focus application area for this thesis.

1.7 Regulatory Requirements for Coronary Stents

There are two governing guidance documents for coronary stents provided by the FDA in the United States. These are “Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies” [37] and “Nonclinical Engineering Tests and Recommended Labelling for Intravascular Stents and Associated Delivery Systems”[38].

The first document focuses on a coronary drug-eluting stent as a combination product; in that it is a device being inserted in the body that is also delivering a drug. This document focuses mostly on the effects of the drug delivered by the stent scaffold. Potential site toxicity due to the drug is one of the first things required to be established in nonclinical (animal) trials. If the drug that is to be delivered by the stent is well validated then the main focus is on the device performance, which is outlined in the second document.

Included in this second document are requirements for characterisation of the stent material, from its composition to its corrosive resistance. Also required are stent
dimensional and functional attributes such as dimensional verification, percent surface area, foreshortening, radial stiffness and radial strength, mechanical properties, recoil for balloon expandable stents, particulate evaluation and others. A complete description of the delivery system dimensional and functional attributes is required along with shelf life and biocompatibility assessments.

Portions of the second document outlining non-clinical engineering tests applied to the stent will be referred to during the presentation of this thesis. In particular, Section IV, part B-9 “Stress-Strain Analysis” will be examined. This section of the document aims to analyse, in combination with a fatigue assessment and accelerated durability testing, the potential for failure of the device. This device failure can be classified as loss of radial support or perforation of the vessel wall by the stent struts. These analyses may also to provide an indication of device durability.

As stress-strain analyses of the performance of new stent designs are required by the FDA, it is imperative that these computational models are representative of the in vivo situation. In order to appropriately assess device performance a representative physiological environment needs to be modelled from a geometrical and material perspective. It is the contention of this work that the specificity of the blood vessel needs to be investigated within the guideline documentation of Section IV, part B-9. Currently all that is requested is a “justification for the physiological relevance of your vessel model parameters” and a description of vessel geometry. If this is to be a thorough examination of predicted in vivo performance a more systematic approach is required and this shall be discussed further of the course of this work.

Also to be mentioned here are the European regulatory requirements for medical devices such as coronary stents. To attain approval for distribution of a medical
device the CE mark is required. To attain the CE mark for a medical device, such as a stent, two particular directives apply; these are the “Medical Devices Directive (93/42/EEC)” and the “Active Implantable Medical Devices Directive (90/385/EEC)”. From a careful examination of these directives, it is clear that even less specification is required from a stress-strain analysis point of view. Therefore, the recommendations that arise from this thesis are considered applicable to the European guideline documentation also.

1.8 Objectives of thesis

The assessment of coronary stent implantation in silico is the primary research topic of this thesis. Its motivation is derived directly from the clinical issue of in-stent restenosis that is attributed to high stresses in the arterial wall. Using computational modelling the assessment of the stress state within the vessel wall and the scaffolding ability and recoil of the device is of interest to this work.

Particular attention will also be given to the regulatory requirements for stress/strain analyses involving coronary stents. The physiological environment simulated will be examined in detail. Recommendations will be given on the degree of specificity of the blood vessel that should be required in computational simulations of stenting procedures.

This work also enters the realm of personalised medicine. It introduces the idea of population specific categories for assessing stent designs. This differs significantly from current approaches which look at either a single idealised geometry or a single patient specific geometry.

Finally an in-depth analysis of the representation of atherosclerotic tissue used in stenting simulations will be presented. The purpose of this is to decipher what level
of detail should be presented in modelling this tissue type given the current available experimental data.

The specific objectives of this work are as follows:

- To develop and implement a new framework for more comprehensive evaluation of coronary stent implantation with the aim of reducing the risk of in-stent restenosis due to arterial stress related factors.
- To assess the importance of blood vessel geometry in stent stress/strain analyses and to provide recommendations to the FDA on the degree to which blood vessel geometry should be specified in stent assessment standards.
- To show that a practical computational framework for assessing stent performance that captures a range of population categories, which is more general than patient specific, yet more realistic than a single idealised arterial structure is required for a more accurate depiction of in silico stent behaviour. This computational framework will be referred to as the computational arterial test-bed, with each category of artery representing a specific population type.
- To introduce a new representation of atherosclerotic tissue, more representative of physiological tissue than current approaches, and to apply this new representation to stenting simulations.

1.9 Thesis Structure

In Chapter Two a review of the fundamental theory of continuum mechanics, in particular non linear hyperelasticity and damage modelling, and the finite element method is presented. Chapter Three provides a comprehensive literature review of computational approaches taken to model coronary stents. Also detailed in Chapter
Three is a review of approaches taken to model damage of soft fibrous biological material with particular attention paid to arterial tissue.

The development of a computational arterial test-bed including initial studies on stent loading, mesh sensitivity, element type and arterial constitutive modelling comparisons are described in Chapter Four. The arterial test-bed developed is applied to assess two stent designs also in Chapter Four. This chapter presents the results in terms of overall stent performance metrics and specific tissue deformation analyses.

Chapter Five presents an investigation into the representation of atherosclerotic tissue used in stenting simulations. The application of different approaches to modelling the response of this tissue to loading and unloading cycles is reported in terms of overall stent performance metrics and specific tissue deformation analyses.

Finally Chapter Six provides a discussion on the findings of the thesis, implications for regulatory requirements for computational analyses of coronary stents, conclusions and future work.
References


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 devices/deviceregulationandguidance/guidancedocuments/ucm071863.htm
Table 1-1  Classifications of atherosclerotic lesions used in pathology [5].

<table>
<thead>
<tr>
<th>Histological Classification of Lesions</th>
<th>Additional Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Isolated macrophage foam cells</td>
</tr>
<tr>
<td></td>
<td>Early lesion, minimal lesion</td>
</tr>
<tr>
<td></td>
<td>Fatty dot, fatty streak</td>
</tr>
<tr>
<td>Type II</td>
<td>Multiple foam cell layers</td>
</tr>
<tr>
<td>Type III</td>
<td>Preatheroma, intermediate lesion</td>
</tr>
<tr>
<td>Type IV</td>
<td>Atheroma</td>
</tr>
<tr>
<td></td>
<td>Fibrolipid plaque, fibrous plaque, plaque</td>
</tr>
<tr>
<td>Type V</td>
<td>Fibroatheroma</td>
</tr>
<tr>
<td>Type VI</td>
<td>Fissured, ulcerated, hemorrhagic, thrombotic lesion</td>
</tr>
<tr>
<td>Type VII</td>
<td>Calcific lesion</td>
</tr>
<tr>
<td>Type VIII</td>
<td>Fibrotic lesion</td>
</tr>
</tbody>
</table>
Table 1-2  Desirable stent characteristics for given physiological conditions, adapted from [8].

<table>
<thead>
<tr>
<th>Clinical and Anatomical Situations</th>
<th>Desirable Stent Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcified Lesions</td>
<td>Good radial support, low friction</td>
</tr>
<tr>
<td>Calcified Vessels</td>
<td>Low friction, high flexibility, low crossing profile, good radial support</td>
</tr>
<tr>
<td>Lesion located on a curve (&gt;90°)</td>
<td>High conformability and flexibility</td>
</tr>
<tr>
<td>Proximal vessel tortuosity</td>
<td>High flexibility, low friction, low crossing profile</td>
</tr>
<tr>
<td>Bifurcation involving large side branch</td>
<td>Open cell design</td>
</tr>
<tr>
<td>Ostial lesions</td>
<td>Good radial support, good radiopacity</td>
</tr>
<tr>
<td>Vein grafts, thrombus-containing lesion, total occlusions</td>
<td>Good lesion coverage and radial support</td>
</tr>
<tr>
<td>Small vessels</td>
<td>Thin stent strut, high flexibility</td>
</tr>
<tr>
<td>Diffuse disease</td>
<td>Minimal balloon overhang</td>
</tr>
<tr>
<td>Significant vessel tapering</td>
<td>Minimal balloon overhang</td>
</tr>
<tr>
<td>Direct stenting</td>
<td>Low crossing profile, low friction, high flexibility</td>
</tr>
<tr>
<td>Vessel perforation</td>
<td>Covered stents</td>
</tr>
</tbody>
</table>
Figure 1.1  Coronary arteries responsible for delivery of healthy oxygenated blood to the heart.
Figure 1.2   Components of the healthy arterial wall [1].
Figure 1.3 Progression of atherosclerosis according to Stary's classification [5].
Figure 1.4  Development of atherosclerotic lesions in age groups up to 40, adapted from [5].

Figure 1.5  Schematic of the femoral access site [8].
Figure 1.6  Schematic of a three-port manifold typically attached to an angiographic catheter [8].

Figure 1.7  Construction of a monorail balloon catheter.
Figure 1.8 Seven coronary stents, clockwise from bottom left: Wallstent, Palmaz-Schatz stent, Wiktor stent, Gianturco-Roubin stent, Cordis stent, AVE stent, and Multilink stent [13].
Possible complications due to the use of drug-eluting stents and bare metal stents [26].
2 Theory & Numerical Implementation

This chapter describes some of the theoretical formulations employed in this work. The theory described is used, either directly or indirectly, though finite element modelling. The finite element models developed apply the principles of continuum mechanics and finite deformation kinematics, which are discussed in section 2.1. The fundamentals of hyperelastic material behaviour are discussed in section 2.2. The phenomenon of stress softening in rubber-like materials is then presented in section 2.3. The concepts of how permanent deformations are represented are discussed in sections 2.4 and 2.5. Finally the implementation of the finite element models through different solver approaches is discussed in sections 2.6 and 2.7.

2.1. Fundamental Principles

The fundamental principles of continuum mechanics that are relevant to this work are presented here. Figure 2.1 shows an arbitrary body in space, $B_r$, which undergoes kinematic deformation to become $B_{\text{curr}}$. An infinitesimal material “fibre” is described by $dx$ in the reference configuration and by $dy$ in the current configuration.

The motion from $B_r$ to $B_{\text{curr}}$ is described by the deformation gradient, $F$, defined as follows in equation (2.1)

$$ F = \frac{\partial y}{\partial x} $$  \hspace{1cm} (2.1)

such that,

$$ dy = F \cdot dx. $$  \hspace{1cm} (2.2)
From the deformation gradient, \( \boldsymbol{F} \), two particular measures of strain can be ascertained, known as the left and right Cauchy-Green Strain Tensors, \( \mathbf{B} \) and \( \mathbf{C} \). These are defined by the following equations

\[
\mathbf{B} = \boldsymbol{F} \cdot \boldsymbol{F}^T \\
\mathbf{C} = \boldsymbol{F}^T \cdot \boldsymbol{F}.
\]  

The first three invariants of tensors \( \mathbf{B} \) and \( \mathbf{C} \), are equivalent for both of the tensors and are defined as follows

\[
I_1 = \text{tr} (\mathbf{C}) = \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \\
I_2 = \frac{1}{2} [I_1^2 - \text{tr} (\mathbf{C}^2)] = \lambda_1^2 \lambda_2^2 + \lambda_2^2 \lambda_3^2 + \lambda_3^2 \lambda_1^2 \\
I_3 = \det(\mathbf{C}) = [\det(\mathbf{F})]^2 = J^2 = \lambda_1^2 \lambda_2^2 \lambda_3^2
\]

where the determinant of the deformation gradient, \( \mathbf{F} \), is also known as the Jacobian, \( J \) and \( \lambda_i \) are the stretches.

Cauchy (true) stress describes the force per unit area on the current configuration. It is a symmetric tensor and is related to the traction, \( \mathbf{t} \), on a surface (internal or external) in the current configuration and a unit normal vector to the surface, \( \mathbf{n} \)

\[
\mathbf{t} = \mathbf{\sigma} \cdot \mathbf{n}.
\]

The Cauchy stress can generally be considered as having two components: a hydrostatic stress component which causes volume change, and a deviatoric stress which causes shape change. These components become significant in the description of constitutive laws which are used to define specific material behaviour. It can be broken down as follows
where \( \mathbf{S} \) is the deviatoric stress and \( \mathbf{I} \) is the identity tensor. \( p \) is the hydrostatic pressure which is defined as follows

\[
p = -\text{tr}(\mathbf{\sigma})/3.
\]

In the elastic-plastic analysis of materials, the von Mises equivalent stress, \( \bar{\sigma} \), is commonly used. This can be regarded as a scalar uniaxial equivalent of a multi-axial stress state. It can be defined as follows

\[
\bar{\sigma} = \sqrt{\frac{3}{2}S_{ij}S_{ij}}.
\]

Other important stress tensors are the Kirchoff stress (symmetric), \( \mathbf{K} \), the first Piola-Kirchoff stress or nominal stress (unsymmetric), \( \mathbf{P} \), which is the force per unit area in the reference configuration, and the Second Piola Kirchoff stress (symmetric), \( \mathbf{\tau} \). They are defined as follows

\[
\mathbf{K} = j\mathbf{\sigma}
\]

\[
\mathbf{P} = \mathbf{F}^{-1} \cdot \mathbf{K}
\]

\[
\mathbf{\tau} = \mathbf{F}^{-1} \cdot \mathbf{K} \cdot \mathbf{F}^{-T}.
\]

A summary of the relevant fundamental principles of continuum mechanics has been given above. As regards material constitutive descriptions, this thesis is primarily concerned with elasticity and elasto-plasticity, both in the context of finite deformation kinematics. For further information the reader is referred to [1,2]. As the finite element programme Abaqus (V.6.10 Dassault Systems, Providence, RI, USA) [3] is used for all of the simulations in the thesis it is logical to discuss
elasticity and elasto-plasticity in terms of the descriptions of these theories provided by Abaqus.

2.2. Hyperelasticity

Hyperelastic materials are types of materials that are a special case of elastic materials, where the stress-strain relationship derives from a strain energy density potential, $U$. Hyperelastic materials typically exhibit a non-linear stress-strain relationship that usually cannot be adequately captured by assuming a linear stress-strain response (even if one assumes linearity between finite deformation kinematic measures as discussed above). The most common example of this is rubber, whose stress-strain relationship is highly non-linear. Soft biological tissue, such as the arterial vessel, also has a highly non-linear stress-strain relationship. This non-linearity has been observed by many researchers and in particular its first investigation was by Fung in 1967 [4].

As stated above, hyperelastic material behaviour is captured by a strain energy density potential, $U$. This potential can be related to the first Piola-Kirchoff stress and Cauchy stress, respectively

$$ P = \left( \frac{\partial U(F)}{\partial F} \right) $$ \hspace{1cm} (2.15)

$$ \sigma = \frac{1}{J} F \cdot \left( \frac{\partial U(F)}{\partial F} \right) . $$ \hspace{1cm} (2.16)

A broad range of material constitutive definitions are provided in the finite element software Abaqus [3] which is employed in this research. Several different approaches to modelling healthy and diseased arterial tissue are investigated within
this work and the various hyperelastic constitutive models available within Abaqus that are used are now presented, in terms of the strain energy density potential.

Hyperelastic models are generally of two types: phenomenological, where the model describes macroscopically observed behaviour, or mechanistic, where the model is developed from considerations of the underlying structure of the material. Sometimes a combination of both can be used.

A very common type of hyperelastic model is the polynomial form of strain energy density potential. This is a phenomenological model and is described by equation (2.17).

$$U = \sum_{i+j=1}^{N} C_{ij}(\tilde{I}_1 - 3)^i(\tilde{I}_2 - 3)^j + \sum_{i=1}^{N} \frac{1}{D_i} (J - 1)^{2i}$$  (2.17)

$U$ is the strain energy density per unit reference volume, $N$ is the number of polynomial terms used in the series, for each polynomial term $C_{ij}$, $D_i$ are material parameters. $\tilde{I}_1$ and $\tilde{I}_2$ are the first and second invariants of the modified right Cauchy-Green strain tensor, $\bar{C}$ and $J$ is as defined previously in equation (2.7). The modified right Cauchy-Green strain tensor, $\bar{C}$, is defined as follows

$$\bar{C} = J^{-2/3}C.$$  (2.18)

Another form of this phenomenological model is the reduced polynomial form of strain energy density potential
Also available is the Ogden form of strain energy density potential defined as follows

\[
U = \sum_{i=1}^{N} C_{i0} (I_1 - 3)^i + \sum_{i=1}^{N} \frac{1}{D_i} (J - 1)^{2i}.
\]  

(2.19)

where \( \lambda_j \) are the deviatoric principal stretches, \( \tilde{\lambda}_j = J^{-1/3} \lambda_j \) and \( \lambda_j \) are the principal stretches. The Ogden potential is made up of a series of \( N \) terms. For each term, \( \mu_i, \alpha_i \) and \( D_i \) are material parameters.

All the above mentioned models are isotropic, however arterial tissue is highly anisotropic [5]. For the case of modelling the material as anisotropic the Holzapfel-Gasser-Ogden hyperelastic model is considered in this work, as it has been shown to generate an excellent fit to experimentally derived data for arterial tissue mechanical testing [6]. This model has the following form

\[
U = U_{iso} + U_{aniso}
\]  

(2.21)

where \( U_{iso} \) is the isotropic portion of the strain energy density potential, typically relating to the matrix of the material, and \( U_{aniso} \) is the anisotropic portion of the strain energy density potential, typically relating to the embedded fibres. Both components of the overall strain energy response are defined as follows

\[
U_{iso} = \mu (I_1 - 3)
\]  

(2.22)
\[ U_{aniso} = \frac{k_1}{k_2} \sum_{i=1,2} \left( \exp[k_2(\kappa I_1 + (1 - 3\kappa)I_4 - 1)^2] - 1 \right) \] (2.23)

where \( k_2 \) and \( \kappa \in [0, 1/3] \) are dimensionless material parameters and \( k_1 \) and \( \mu \) are material parameters with the dimensions of stress. The fourth invariant of the modified right Cauchy-Green tensor, \( I_{4i} = a_{0i} \otimes a_{0i} : \bar{C} \), is a tensor invariant equal to the square of the stretch in the direction of a unit vector \( a_{0i} \).

To assist in understanding the formulation of the model, Figure 2.2 shows an illustration of the inflation of the adventitial layer of the artery [7]. The structure illustrated contains two embedded families of collagen fibres. The mean orientation of each family of fibres is characterised by the vectors \( a_{01} \) and \( a_{02} \), respectively, both subtending an angle \( \gamma \) with the horizontal, as illustrated in Figure 2.2. In a cylindrical polar coordinate system the components of \( a_{01} \) and \( a_{02} \) are

\[
a_{01} = \begin{bmatrix} 0 \\ \cos(\gamma) \\ \sin(\gamma) \end{bmatrix}; \quad a_{02} = \begin{bmatrix} 0 \\ -\cos(\gamma) \\ \sin(\gamma) \end{bmatrix}
\] (2.24)

The dispersion of fibres around the mean is characterised by the parameter, \( \kappa \), which is defined as follows

\[
\kappa = \int_0^\pi \rho(\theta)\sin^3\theta d\theta
\] (2.25)

where \( \theta \) is the angle between the local fibre to the mean fibre direction, \( a_{0i} \), and \( \rho \) is the orientation density distribution and is defined below as

\[
\rho(\theta) = 4 \frac{b}{\sqrt{2\pi}} \frac{\exp[b(\cos2\theta)+1]}{\text{erfi}(\sqrt{2b})}
\] (2.26)
where \( b \) is a positive concentration parameter and \( \text{erfi}(x) = -i\text{erf}(ix) \) is the imaginary error function. The error function is given by the standard formula below.

\[
\text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_{0}^{x} \exp(-t^2) dt \tag{2.27}
\]

### 2.3 Stress Softening of Rubbery Materials

In 1969, Mullins first wrote the review on stress softening of rubber under cyclic loading [8]. The so-called Mullins effect is characterised by the following features: when a virgin material is stretched from undeformed state to a certain deformation, the stress-stretch curve follows a primary loading path. On unloading from this deformation, softening (reduced stress compared to the primary loading stress) is observed. Subsequent reloading follows the former unloading curve until the previous maximum stretch is reached. At this point the material returns to the primary loading curve up to a new maximum. For an illustration of the stress-strain response of a material exhibiting the Mullins effect see Figure 2.3.

Stress softening been observed in many types of soft fibrous biological tissue exposed to cyclic loading. Also to be mentioned here are the other main phenomenon observed during cyclic loading of soft tissue apart from the Mullins effect. This observed phenomenon is preconditioning, characterised by continuous softening during the early cycles until achieving a certain “saturated” state [9]. The area enclosed by the loading unloading curves, which reflects the dissipated energy, decreases with every cycle. Finally in steady state the loading unloading paths almost coincide.
Any given strain energy density potential, $U$, can be broken down into two components: volumetric (dilatational) and isochoric (volume preserving or non-dilatational) which can be expressed as

$$U = U_{vol}(f) + U_{isch}(\mathbf{C}, \mathbf{M}_f).$$

(2.28)

In the above $\mathbf{M}_f$ is the cross product of the unit vectors, $\mathbf{a}_{0i}$, defining the predominant fibre directions, see Figure 2.2. It is generally assumed under continuum damage mechanics theory that damage occurring in the material affects only the isochoric portion of the strain energy density function (see [10–12] for examples).

Continuum damage mechanics constitutive theory when applied to soft tissue typically falls into one of two categories: continuous or discontinuous type damage. To succinctly describe the difference between the two approaches the following definitions from Miehe [13] are adapted.

A discontinuous evolution of damage assumes that damage accumulation only occurs within the first cycle of a strain-controlled loading process and does not occur again until a new maximum effective strain energy is reached. With this type of damage, further strain cycles below a maximum effective strain energy do not have an effect on the material response. The model of Ogden and Roxburgh [14] which describes the Mullins effect phenomenon is an example of a discontinuous type damage model.

Conversely, a continuous damage model takes into account the whole strain history of the deformation process to allow continuous damage accumulation. This means that damage can accumulate during loading and unloading and during all strain
cycles at the same amplitude. With a discontinuous damage model, typically damage only accumulates on unloading and only during the first cycle for a series of strain cycles at the same amplitude.

Expressed mathematically, the discontinuous damage model is assumed to be governed by a variable

$$\alpha(t) = \max_{s \in [0,t]} \sqrt{2U^0_{isch}(\bar{C}(s))}$$

(2.29)

where $\alpha(t)$ is the maximum effective strain energy which has been achieved within the time interval [0,\(t\)] achieved by the isochoric (volume preserving or non-dilatational) portion of the undamaged strain energy density function, $U^0_{isch}(\bar{C}(s))$. The whole time history is expressed in terms of a variable $s \in [0, t]$.

Any damage criterion in the strain space can be defined by the condition that, at any time, $t$, of the loading process the following is satisfied [10]

$$\Phi(\bar{C}(t), \Xi_t) = \sqrt{2U^0_{isch}(\bar{C}(t))} - \alpha(t) = \Xi_t - \alpha(t) \leq 0$$

(2.30)

where the term $\Xi_t = \sqrt{2U^0_{isch}(\bar{C}(t))}$, is used for succinctness in future definitions. The equation $\Phi(\bar{C}(t), \Xi_t) = 0$ defines a damage surface in the strain space. Finally, the evolution of the damage parameter, $D$, is characterised by an irreversible equation of evolution such as [12]

$$\frac{dD}{dt} = \begin{cases} \tilde{h}(\Xi, \alpha)\dot{\Xi} & \text{if } \Phi = 0 \text{ and } \mathbf{N} \cdot \dot{\bar{C}} > 0 \\ 0 & \text{otherwise} \end{cases}$$

(2.31)

in the above, $\mathbf{N} = \frac{\partial \Phi}{\partial \bar{C}}$ is the normal to the damage surface in strain space, $\Xi$ is defined at the current time $t$ and $\tilde{h}(\Xi, \alpha)$ is a function that characterises the damage
evolution in the material. This underlies the discontinuous nature of the damage effect, i.e. there is no damage accumulation if the force lies inside the undamaged domain.

Also expressed mathematically, the continuous type damage evolution is assumed to be governed by the arclength of the effective strain energy rate. Expressed mathematically this is captured by the following

\[ \beta(t) = \int_0^t \text{sign}[\dot{U}_{\text{isch}}(\bar{C}(s))]ds \] \hspace{1cm} (2.32)

where \( \beta(t) \) is the arclength of the effective strain energy rate and \( s \) a point in the time history \([0,t]\).

The continuous type damage evolution method was not adopted in this thesis as this approach does not allow the fitting of material parameters to experimental data independent of the fitting of the damage parameters. However, with the discontinuous approach the material parameters can be fit independent of the fitting of the damage parameters. Later in this work a discontinuous damage model is adopted through use of the Mullins effect to model damage in atherosclerotic tissue.

### 2.4 Elasto-Plasticity

To define the material behaviour of a metallic stent within the Abaqus finite element code the material is assumed to be homogenous, isotropic, rate-independent and elastic-plastic. The kinematical framework used to define this type of material model splits the deformation into an elastic part, \( el \), which is recoverable, and a plastic part, \( pl \), which is unrecoverable. The deformation gradient is decomposed as follows [3,15,16]
where $F^{el}$ is the elastic component of the deformation gradient and $F^{pl}$ is the plastic component of the deformation gradient.

In the metals used in stenting the elastic strain developed, before the metal yields, amounts to a few percent. When elastic strains are small the above multiplicative decomposition of the deformation gradient, $F$, can be approximated in terms of an additive decomposition of strain rates [15]. The total strain rate is defined as follows

$$\dot{\varepsilon} = \dot{\varepsilon}^{el} + \dot{\varepsilon}^{pl}. \quad (2.34)$$

In the above, the elastic strain rate is denoted by $\dot{\varepsilon}^{el}$ and the plastic strain rate is denoted by $\dot{\varepsilon}^{pl}$. When this equation is integrated with respect to time the following equation is obtained giving the respective elastic and plastic strains.

$$\varepsilon = \varepsilon^{el} + \varepsilon^{pl} \quad (2.35)$$

The elastic component of the deformation can be related to the stress through the Bulk modulus, $K$, and the Shear modulus, $G$, which are functions of the Young’s Modulus, $E$, and Poisson’s Ratio, $v$,

$$K = \frac{E}{3(1-2v)} \quad \text{and} \quad G = \frac{E}{2(1+v)}. \quad (2.36)$$

Specifically, the elastic strain can be decomposed into volumetric and deviatoric parts and these can be related to the hydrostatic pressure and deviatoric stress respectively. The volumetric elastic strain, $\varepsilon^{el}_{[\text{vol}]}$, can be defined as;

$$\varepsilon^{el}_{[\text{vol}]} = tr(\varepsilon^{el}) = -\frac{p}{K} \quad (2.37)$$

and the deviatoric elastic strain, $\varepsilon^{el}$, can be defined as
This is related to the deviatoric stress through the following

$$S = 2G\varepsilon^{el}.$$  \hspace{1cm} (2.39)

### 2.5 $J_2$ Flow Theory

Permanent plastic deformation occurs in metallic materials when the stresses due to the deformation exceed the material’s yield stress. The criterion by which metallic stents yield considered here is $J_2$ flow theory [15,16].

According to $J_2$ flow theory a material yields when the material stress state is on the yield surface of the material. The yield surface is the surface in stress space that bounds the domain of elastic straining in the material. The yield criterion proposed by von Mises is defined as follows

$$J_2 = k^2$$ \hspace{1cm} (2.40)

where $k^2$ is a constant. $J_2$ is defined by the following

$$J_2 = S_{ij}S_{ij}$$ \hspace{1cm} (2.41)

where $S_{ij}$ is the deviatoric stress within the material as defined in equation (2.9). The flow rule governs the way plasticity is computed, so an increment of plastic strain is determined by the following equation

$$d\varepsilon^{pl}_{ij} = S_{ij}d\lambda$$ \hspace{1cm} (2.42)

where $d\lambda$ is a positive scalar that depends on the stress increment. From this equation the equivalent plastic strain, $\varepsilon^{pl}$, is also defined.
To define the stress and increment of plastic strain in terms of work, the increment of plastic work done per unit volume is

\[ dW^{pl} = \sigma_{ij} d\varepsilon_{ij}^{pl}. \quad (2.44) \]

The von Mises equivalent stress defined in equation (2.11) can be applied to redefine the work in terms of the equivalent stress and equivalent plastic strain increment,

\[ dW^{pl} = \frac{2}{3} \sigma^2 d\lambda = \bar{\sigma} d\varepsilon^{pl} \quad (2.45) \]

From equation (2.45) the positive scalar, \( d\lambda \), can be defined as

\[ d\lambda = \frac{3}{2} \frac{d\varepsilon^{pl}}{\bar{\sigma}}. \quad (2.46) \]

Therefore the definition for the increment of plastic strain can be rewritten in terms of equivalent stress and plastic strain increment using equation (2.42),

\[ d\varepsilon_{ij}^{pl} = S_{ij} \frac{3}{2} \frac{d\varepsilon^{pl}}{\bar{\sigma}}. \quad (2.47) \]

Within Abaqus, this incremental plastic constitutive law is combined with elasticity (through equations (2.37) and (2.39)) to generate a combined elasto-plastic incremental constitutive law, and integrated through time using the backward Euler method [3].

### 2.6 Implicit Finite Element Method

In the commercial finite element code Abaqus/Standard, non-linear systems are solved using implicit integration techniques. The body making up the system is first
broken down into discrete sections called elements which are connected together at points called nodes. The full collection of elements and nodes which represent the body is known as the finite element mesh. The governing constitutive equations, which are calculated for each element, assemble to form a system of algebraic equations to describe the behaviour of the body as a whole. By applying boundary conditions to the system of equations, the stress and strain can be calculated for each element incrementally. The principle of virtual work is a fundamental equation upon which this method is based

\[
\int_V \delta \varepsilon^T \sigma \, dV = \int_S \delta \mathbf{u}^T \mathbf{t} \, dS
\]

(2.48)

In equation (2.48) the equilibrium is enforced on a reference volume, \( V \), which is bounded by a surface, \( S \). \( \sigma \) and \( \mathbf{t} \) are the stress and surface traction vectors respectively, while \( \delta \varepsilon \) and \( \delta \mathbf{u} \) are the virtual strain and virtual displacement vectors. For each element, “\( e \)”, in the finite element mesh the following interpolation holds true

\[
\delta \varepsilon = \mathbf{B}_e \delta \mathbf{u}_e
\]

(2.49)

\[
\delta \mathbf{u} = \mathbf{N}_e \delta \mathbf{u}_e
\]

(2.50)

where \( \mathbf{N}_e \) and \( \mathbf{B}_e \) are the element shape function and shape function gradient matrices respectively. Substituting these into equation (2.53) and rearranging yields the following

\[
\sum_e \int_{V_e} \delta \mathbf{u}_e^T \mathbf{B}_e^T \sigma(\mathbf{u}_e) \, dV = \sum_e \int_{S_e} \delta \mathbf{u}_e^T \mathbf{N}_e^T \mathbf{t} \, dS
\]

(2.51)
where the summation is over all the elements “e” in the finite element mesh. Performing the summation, which in effect means assembling element quantities into global quantities, and removing the arbitrary virtual quantities yields the following global expression

\[ \int_V B^T \sigma(u) dV = \int_S N^T t dS \]  

(2.52)

where \( u \) is the global nodal displacement vector the mesh. This set of global equations in \( u \) for the out of balance force, \( G \), can then be assembled

\[ G(u) = \int_V B^T \sigma(u) dV - \int_S N^T t dS = 0 \]  

(2.53)

In Abaqus/Standard, a range of implicit solution procedures are available. For a static structural analysis a form of the Newton-Raphson iterative solution solves the equations. Using the combination of Newton-Raphson iterations and incremental steps in time, the implicit integration results in definition of the nodal displacements as the following

\[
\mathbf{u}_{n+1}^{t+\Delta t} = \mathbf{u}_n^{t+\Delta t} - \left[ \frac{\partial G(u_n^{t+\Delta t})}{\partial \mathbf{u}} \right]^{-1} \cdot G(u_n^{t+\Delta t})
\]  

(2.54)

where \( t \) is the time at the start of the increment, \( \Delta t \) represents the value of the time increment in use and \( n \) is the iteration count. With the Newton-Raphson method, \( \mathbf{u}_n^{t+\Delta t} \) is the initial estimate of the nodal displacements, \( \mathbf{u}_{n+1}^{t+\Delta t} \) is the improved estimate after the iteration.

The Newton-Raphson method solves the equations iteratively where the boundary conditions are applied incrementally over the course of the deformation history. This
method ensures equilibrium is achieved at the end of each time step, providing a robust and accurate solution.

### 2.7 Explicit Finite Element Method

The explicit method was originally developed to solve dynamic problems involving deformable bodies. Accelerations and velocities at a particular point in time are assumed to be constant during a time increment and are used to solve for the next point in time. To perform an explicit dynamic analysis the commercial finite element code Abaqus/Explicit can be implemented. This code utilises an explicit integration rule together with a lumped element mass matrices for the system. The governing equations for the motion of a body are given by the following

\[
\mathbf{u}^{n+1} = \mathbf{u}^n + \Delta t^{n+1} \dot{\mathbf{u}}^{n+1/2} \quad (2.55)
\]

\[
\dot{\mathbf{u}}^{n+1/2} = \dot{\mathbf{u}}^{n-1/2} + \frac{\Delta t^{n+1} + \Delta t^n}{2} \ddot{\mathbf{u}}^n. \quad (2.56)
\]

In the above equations, \( \dot{\mathbf{u}} \) and \( \ddot{\mathbf{u}} \) represent velocity and acceleration, \( n \) is the increment number with \( n - 1/2 \) and \( n + 1/2 \) being the half increment values before and after the \( n \text{th} \) increment. It is important to distinguish between the use of \( n \) in this section and its use in the previous section. In the implicit finite element method \( n \) refers to the iteration number within a certain time increment. However in the explicit finite element method, no iteration takes place; \( n \) refers to the time increment number.

The explicit technique utilises inversion of the diagonal element mass matrix to reduce computational cost. This results in the following expression for the system’s acceleration
\[ \ddot{u}^n = M^{-1} \cdot (F^n - I^n) \]  

with,

\[ F^n = \int_S N^T t^n \, dS + \int_V N^T P^n \, dV \]  

\[ I^n = \int_V B^T \sigma^n \, dV \]  

\[ M = \int_V \rho \, dV \]  

where \( F^n \) is the total applied nodal force vector, \( M \) is the diagonal element mass matrix, and \( I^n \) is the internal force vector. In equation (2.58) \( P^n \) is the vector of nodal forces. In equation (2.60) \( \rho \) is the current density of the material. All other quantities are defined through equation (2.52).

It is important when performing a quasi-static analysis simulation using the explicit finite element method that the inertial forces do not affect the mechanical response and provide unrealistic dynamic results. It has been shown that by keeping the ratio of kinetic energy to total internal strain energy at <5% dynamic effects in the model are negligible [17,18]. This is the criterion for the quasi-static behaviour that is employed in the explicit analyses in this thesis.

The major difference between explicit and implicit solvers is that the explicit procedure requires no iterations and no stiffness matrix. A summary of implicit and explicit finite element methods that are relevant to the work of this thesis has been given. For further information the reader is referred to [3].
References


Figure 2.1  Schematic of finite deformation kinematics.
Figure 2.2 Thin-wall approximation of the inflation of the adventitial layer with two embedded families of fibres. The mean orientations and the dispersion of the collagen fibres are characterized by $\gamma$ and $\kappa$, respectively [7].
Figure 2.3  Stress/strain response of a material showing idealised Mullins effect.
3 Literature Review

This literature review is dedicated to describing the key works in the modelling of coronary and peripheral stents. Also included is a review of soft tissue damage models, as these are investigated with a view to applying such models to atherosclerotic tissue in this work.

As one of the aims of this chapter is to thoroughly review stent modelling approaches, Figure 3.1 has been included to familiarise the reader with the typical features of different types of stent geometry. In Figure 3.1-A, a stent geometry is shown that contains six rings along its length axially. The insert labels the main features of one of the rings. In Figure 3.1-B, a schematic is shown of a slotted tube design stent. The top image shows a “rolled out” undeployed geometry and the lower image shows the geometry in its deployed state. In Figure 3.1-C the difference between an open cell design and a closed cell design stent is illustrated. To elaborate further, a stent is typically classified as closed cell if every adjacent ring segment is connected at every possible junction. If some or all of the connecting junction points are removed the design is typically classified as an open cell design.

The first section of this chapter (Section 3.1) details developments in unconfined stent expansions (no arterial vessel present) and the second section (Section 3.2) details the confined expansion simulations (artery present). In the second section, a review of developments in arterial modelling is presented. The developments and trends in arterial modelling are discussed with respect to stenting simulations. This section also includes a review of existing experimental data for mechanical characterisation of atherosclerotic plaque tissue. Simulations involving the loading of
this tissue are then discussed, both those with and without a stent present, as they are of interest to this work.

In the third section of this chapter (Section 3.3) a review of the existing experimental data for soft tissue undergoing damage is presented. Also included in this section is a review of the damage modelling approaches that attempt to capture this behaviour in soft tissue. A further section on other approaches taken in modelling stents is presented in Section 3.4. The final section in this chapter (Section 3.5), details the limitations of current approaches to stent modelling and where this work introduces advances in the area.

3.1 Unconfined Deployment Methods for Coronary and Peripheral Stent Modelling
In the context of this literature review, the term unconfined deployment is used to describe numerical simulations investigating the expansion of vascular stents without an exterior confinement, i.e. no artery is included in the analysis. The following section details these works.

In 1997, Whitcher [1] was one of the first researchers to investigate the expansion performance of vascular stents in silico. The focus of the work was nitinol stents for peripheral application. The actual simulations were simple by today’s standard but pioneering none the less. A fatigue loading simulation, on a one eighth section of the stent geometry, due to pulsatile blood flow, was carried out on an expanded geometry and stresses due to this loading were discussed. It was found that the model predictions agreed well with destructive fatigue testing data in both quantitative and qualitative terms.
Brauer et al. [2] in 1999 investigated the dilatational properties of metallic stents both experimentally and computationally for different stent materials. A partial axial stent segment mounted on a cylindrical balloon was modelled to simulate expansion of the device. In pressure vs. change in diameter curves, good agreement was found between the simulation and experiment up to a certain diameter. Also captured was the “bone effect” of the balloon during expansion or what is now more commonly termed “dogboning”.

Another early study of note is that of Dumoulin and Cochelin [3] in 2000 where the mechanical behaviour of balloon-expandable stents was investigated. A repeating unit cell, representative of the Palmaz-Schatz design, was expanded using a pressure load applied to the inner surface. Also investigated was the response of the device to buckling and fatigue loads. It showed the unsuitability of this design for peripheral applications that exerted severe compressions as this was predicted to produce permanent collapse.

In 2001, Tan et al. [4] examined the performance of the Palmaz-Schatz and Freedom stent geometry designs using finite element analysis. The geometry, stent wire diameter and contact with an external hemispherical surface were varied. The external hemispherical surface is representative of a lesion in the analyses and was found to produce large distortions both stent designs. These findings are the earliest showing the capability of finite element analysis as a comparative tool for analysing stent designs.

Also in 2001, Etave et al. [5] examined the behaviour of two different types of stents, tubular and coil. Seven mechanical performance measures were studied, including deployment pressure, recoil, resistance to compressive forces,
foreshortening, coverage area of the stent, flexibility and stress distribution. They concluded that tubular stents are very rigid, foreshorten with increasing diameter and require higher deployment pressures than coil stents. They found that coil stents are quite flexible, lengthen during deployment and exhibit less recoil than tubular stents.

There are several papers from Chua and co-workers [6–8] that investigated unconfined stent expansion using the finite element method. In the first of the series in 2002, Chua et al. [6] simulated the expansion of a slotted tube type stent design using a mechanical pressure applied to the inner surface of the device. Two different types of pressure loading were investigated. In 2003, Chua et al. [7] investigated the deployment behaviour of a similar stent geometry, this time the balloon was explicitly represented as a straight cylindrical body. The resulting deformations and stresses within the stent were reported. Another paper in 2004 by Chua et al. [8] investigated the effects of varying the slotted stent geometry on the expansion behaviour of the device. It was found that increasing the length rather than the width of the slots achieved a higher expansion rate with minimum effect on foreshortening. Symmetry was utilised in all three papers to minimise finite element model size.

In 2004, Gong et al. [9] presented a study that compared experimentally evaluated radial resistive forces of a Nitinol stent to finite element predictions. The results compared the radial resistive force, chronic outwards force and the crush resistance of the device. These first two parameters give an indication of the forces exerted by self expanding stents in an arterial vessel and the crush resistance parameter indicates the ability of the device to resist forces exerted physiologically on the device. The results of this study indicated that radial resistive forces and mechanical response of Nitinol stents evaluated experimentally compared well to those predicted in a finite element model.
Given that stent struts can be on the order of 100 microns in thickness, knowledge of the microstructure of the device is important. In 2003, Stolpmann et al. [10] investigated different constitutive laws for stent materials and also included void initiation as a criterion for mechanical failure. It was concluded that a Cauchy stress-strain material model should be used within simulations. McGarry et al. [11] also analysed the microstructure of the device, this time through the use of classical plasticity theory, which was compared to the physically based crystal plasticity theory. A 2D unit cell model of the NIR stent (Medinol/Boston Scientific) geometry was utilised in the finite element analyses. The results indicated that crystal plasticity theory predicted non-uniform stress and strain fields within the material microstructure, which are a real feature of microscale mechanical behaviour of polycrystalline metals used in stents. Savage et al. [12] investigated the micromechanical behaviour of individual 316L stainless steel coronary stent struts using crystal plasticity theory. Their results showed the relationship between the size of a stent strut and its mechanical performance, and in particular they demonstrated the significant reduction in tensile ductility of a strut with reduction in strut thickness.

Stent strut size effects were further explored computationally in Murphy et al. [13], in 2006, and Harewood & McHugh [14], in 2007. Most recently, Grogan et al. [15] investigated size effects for a range of metallic stent materials. It was demonstrated that size effects are more significant the more ductile the metal.

Donnelly et al. [16], in 2007, analysed the residual stresses associated with deployment and recoil for different stent geometries with a view to establishing an appropriate stress state for fatigue loading of stents. The maximum, minimum and mean stresses induced were reported and also radial and longitudinal recoil. A more
recent study from Sweeney et al. [17] presented a framework for predicting the fatigue life of coronary stents. The methodology combined the use of a three-dimensional stent-artery model, modelled using $J_2$ plasticity theory, with a micromechanical stent model, modelled with crystal plasticity theory and $J_2$ plasticity theory. Under cyclic deformation, fatigue life predictions for the crystal plasticity model and the $J_2$ plasticity model were compared with the predictions of conventional fatigue life estimation techniques. From the results, it was concluded that micromechanical fatigue analysis of stents is necessary to achieve accurate life estimates due to the significant predicted effects of material inhomogeneity on micro-plasticity and micro-crack initiation.

In 2002 Migliavacca et al. [18] investigated the effects of different geometrical features on the mechanical performance of three stent designs. The performance of the stents were analysed in terms of radial recoil, longitudinal recoil, foreshortening and dogboning. It was found that ratio between the angle described by the stent surface, $\alpha_p$ (see Figure 3.2), to the angle described by the stent slot, $\alpha_f$ (see Figure 3.2), reduced radial and longitudinal recoil but increased the foreshortening and dogboning. It was also shown that decreasing the strut thickness had an unfavourable outcome on longitudinal recoil, foreshortening and dogboning. Finally, it was shown that increasing the slot length (see Figure 3.2) increased the radial recoil. In 2005, Migliavacca et al. [19] compared the computed mechanical behaviour of a new generation coronary stent to the observed experimental mechanical behaviour. It was found that agreement between the different results was quite satisfactory but some discrepancies did exist that were attributed to the lack of explicit balloon modelling in the computational model.
The expansion process for different stent designs and balloon lengths was the focus of the work of Wang et al. [20] in 2006. One objective of the work was to investigate the dogboning phenomenon and it was found that it could be eliminated through improved stent geometry and/or varying balloon length relative to stent length. In particular, increasing the strut width of the end rings in conjunction with reducing the balloon overlength minimised the dogboning effect.

In 2007, Xia et al. [21] reported a general finite element method for the analysis of balloon expandable stents. The method was applied to three different stent geometries and utilised the repeated unit cell approach, including periodic boundary conditions, to analyse deployment with a cylindrical balloon. The advantages of the method are that a much smaller finite element model is required resulting in a much less expensive computational analysis. In 2008, the same group [22] developed on this work using three types of models, the panel, the repeated unit cell and the repeated unit cell with a free end. This time the boundary conditions applied incorporated symmetry, periodicity and free edge conditions. One of the main conclusions of this work was that the repeated unit cell with a free end could capture the behaviour of the ends of the stent (dogboning) as well as the inner region of the stent using the specified boundary conditions representing a significant improvement on the previous work.

In 2008, Lim et al. [23] analysed the foreshortening and dogboning behaviour of seven types of coronary stents mounted on folded balloons using the finite element method. They found that by using stents composed of opened unit cells connected by bend-shaped link structures and by controlling the geometrical features of the unit cells struts and link structures at the ends of the stent, the dogboning and
foreshortening behaviour was reduced. This was hypothesised to reduce the risk of restenosis that could be attributed to dogboning or foreshortening of the stent.

Shape optimisation of coronary stents was the focus of the study by Li *et al.* [24] in 2009. This study used finite element analysis in conjunction with optimisation of an objective function to formulate an optimised design. The objective function was generated to minimise intrinsic elastic recoil, radial loss and dogboning, while maximising radial gain. The optimisation process resulted in 41 iterations and a design with improved mechanical properties.

In 2008, De Beule *et al.* [25] investigated different methods of deployment of a stent *in silico*. Free expansion simulations were carried out where the stent was expanded via a mechanical pressure applied to its inner surface, expansion of an unwrapped cylindrical balloon and expansion of a tri-folded balloon. It was concluded that the simulations with the tri-folded balloon explicitly modelled were the most representative, as there was good qualitative and quantitative agreement with both manufacturer’s data and experiments, in terms of pressure vs. inner stent diameter measurements. Further developing on this approach, Mortier *et al.* [26] analysed the impact on deployment of inaccuracies in stent placement on the balloon. Several parameters such as: balloon length, folding pattern and relative position of the stent with respect to the balloon catheter were investigated. The analyses showed that balloon length and folding pattern had a significant influence on the uniformity and symmetry of transient stent expansion. It was also shown that small positioning inaccuracies can change the behaviour of the stent. For example a non-centrally placed stent results in a strongly asymmetric expansion.
3.2 Representation of the Artery in Deployment Methods for Coronary and Peripheral Stent Modelling

The arterial geometry has been represented using a variety of approaches in stent modelling analyses. These methods can be loosely categorised as being either idealised or patient specific. In the idealised case, simple geometrical cylindrical arterial shapes are typically considered; whereas the patient specific geometries are very realistic portrayals of particular arteries, typically derived from CT imaging of a particular vessel. Idealised representations of the artery can be either straight or curved (where curved is taken to including bifurcated vessels). The representation of arteries and the evolution of material modelling for the tissue are discussed in the following sections.

3.2.1 Idealised Straight Artery Models

In an idealised straight artery, the vessel is usually cylindrical in nature [27–40]. This approach accounts for the bulk of stent-artery modelling analyses. It is the simplest approach utilised in stent modelling as the positioning of the device is easily achievable because no bending of the stent-catheter assembly is required, which can represent a significant challenge.

In 2004, Migliavacca et al. [27] were one of the first groups to use an idealised straight arterial vessel to study the interaction of balloon expandable and self expandable stents with the vessel wall. In this study, the stress state induced in the vascular wall due to the implantation of different stents was analysed. The effects of coronary stenosis, atherosclerotic plaque stiffness and stent design were investigated. It was found that the balloon-expandable stent induced higher stress in the arterial wall, although the balloon was not explicitly modelled, compared to the self-expandable stent. A parameter study suggested that increasing the stiffness of the
plaque increased the required opening pressures and hence induced higher stresses. The degree of stenosis also altered the pressure requirements and hence the induced arterial stress. The metal-to-artery ratio was also investigated and a higher ratio required a lower opening pressure. This study was also based on perfectly symmetrical geometries and one twelfth of the stent geometry was modelled in the circumferential direction and one half in the longitudinal direction.

Petrini et al. [28] developed upon this work in 2005 by performing similar analyses to investigate the effects of stent geometry on stent recoil, dogboning and foreshortening, by varying parameters such as strut thickness, strut length and metal-to-artery ratio. In their previous arterial analyses [27], they considered the stress state in a partial arterial geometry, a one twelfth unit circumferentially, at various stages of the procedure for both a self expandable stent and a balloon expandable stent, although again the balloon was not explicitly modelled. The results showed that a self expandable stent induced lower stresses and lower damage to the vessel when compared to the balloon expandable stent. However, the lower stiffness of the self expandable stent material meant that the design was less capable of restoring the lumen of the vessel.

Gervaso et al. [29], in 2008, studied the effects of different deployment strategies in modelling balloon expandable stents for both free expansion and confined expansion simulations, where a straight unstenosed artery was included. This work explicitly modelled the expansion of the balloon, although it was not in a folded configuration at the start of their deployment analysis as would occur in reality. Three deployment strategies for balloon expandable stents were examined: pressure expansion, utilisation of cylinder to expand the stent and a balloon expansion. They concluded
that the modelling of the balloon is mandatory to reliably estimate the level of injury caused on the arterial wall during stent expansion.

The deformations of the arterial wall during stenting are also related to the prolapse of the arterial tissue between stent struts. This feature alters the local blood flow patterns which have been found to contribute to in-stent restenosis [41]. The arterial wall stress state and tissue prolapse were investigated by Capelli et al. in 2009 [30] for five different balloon-expandable stent designs. These designs were expanded in straight unstenosed vessels and the stress state determined. Additionally, a prolapse index (PI) was defined and evaluated. It was found that in comparing the computational results to clinical data, where available, there was a correlation between the PI values and restenosis rates. Though admittedly, other aspects of the designs such as flexibility and metal-to-artery ratio could be having an effect.

The effects of stent design on the stress state in the arterial wall were investigated by Bedoya et al. in 2006 [31] by varying three key parameters of a generic stent design. These parameters included strut spacing, radius of curvature at the crown junctions and the axial amplitude of the crowns (see Figure 3.3). In this work, it was found from the computational analyses that stents with low strut spacing and low crown amplitude induced higher stresses over larger areas of the artery than other designs. Also, stents with large strut spacing, a non-zero radius of curvature and a large amplitude imposed the lowest circumferential stresses compared to the other designs considered. All analyses were carried out in straight unstenosed vessels.

Within the same research group in 2008, two of the stent geometries were selected for further analysis (Timmins et al. [32]). This time the effects of material properties were of significant concern. Specifically, the effects of stent material stiffness and
stent design on the response of a straight atherosclerotic vessel with 20% stenosis were investigated. The stiffness of the atherosclerotic tissue was also varied in the simulations. It was found that appropriate stent design can minimise arterial stress while maintaining an acceptable lumen size in atherosclerotic vessels. A significant limitation of this work was that stent expansion was not simulated so elastic recoil of the device was not captured and the typical high stresses due to balloon inflation were not represented.

Chua et al. in 2004 [33] also investigated the response of atherosclerotic tissue to a slotted-tube type stent expansion. The expansion method was via an unfolded balloon and symmetry was assumed, with only a circumferential quadrant of the straight stenotic vessel and two axial units of the stent being modelled. The authors did successfully demonstrate the capability to model the expansion of a slotted tube design within an artery, showing also the potential areas of high stress in the tissue during and after deployment.

The response of a straight stenosed arterial vessel to two particular commercial stent designs, the S7 (Medtronic AVE) and NIR (Medinol/Boston Scientific), were investigated by Lally et al. [34] in 2005. The simulation method involved pressurising the artery to a diameter greater than that of the expanded stents and then reducing that pressure to correspond to mean blood pressure to simulate implantation. This approach meant that the elastic recoil of the stent designs could not be captured and also the high stresses generated by balloon inflation could not be represented as with [33]. However, it was shown that there were higher arterial stresses generated by the NIR stent compared to the S7 design.
In 2009, Pericevic et al. [35] investigated the effect of varying plaque properties on the underlying arterial wall stress during stent expansion in straight idealised vessels. The response of three different plaque types to stent expansion was modelled. Symmetry was assumed in the circumferential and axial directions, with one circumferential quadrant of the straight stenotic vessel and two axial units of the stent being modelled. The stent was expanded via a pressure applied to the inner surface of the implant geometry. It was found that higher stresses were predicted in the arterial wall for cellular plaques, while stiffer calcified plaques appeared to play a protective role by producing lower stresses in the healthy arterial wall.

Within the same research group in 2009, Zahedmanesh and Lally [36] examined the role of stent strut thickness, with a focus on linking the mechanical stress state induced by stent placement to in-stent restenosis rates. One stent design was modelled with both thin and thick struts producing two separate geometries. The balloon was not explicitly modelled and to simulate deployment a pressure was applied to the inner surface of the device. For two loading cases the arterial stress state was investigated. For the first loading case, the stents were expanded to the same initial maximum diameter and for the second case the stents were expanded to the same final diameter, taking recoil into consideration. The thinner strut stent was found to induce less stress in the arterial wall for the first loading case and it also resulted in less lumen gain. The second case study showed that the expansion of the thinner strut stent resulted in acutely higher intimal stresses during loading. The study concluded that an optimal stent design should recoil sufficiently to prevent overstressing the vessel whilst maintaining an optimal lumen size.

In 2009, Early et al. [42] developed a balloon expandable stent-artery model to simulate deployment of the device in a peripheral artery. Symmetry was assumed
and only a quarter circumferential section was modelled. The stent geometry was based on a slotted tube Palmaz design (see Figure 1.8). As device failure has been reported in peripheral arteries, joint flexion was simulated by bending the arterial vessel post deployment to investigate the effects of bending. Results indicated that high peak stresses in the artery are located at the distal/proximal end of the stent both before and after bending. The authors concluded that the slotted tube design gave a flexibility lower than open cell designs and, despite its previous use in peripheral arteries, is not best suited for placement in an environment where bending will occur.

Another work of note is that of Early and Kelly [37] in 2010, where the authors investigated the role of stent geometry and mechanical properties on the arterial stress state in both coronary and peripheral arteries and for balloon expandable and self expandable stents. In their analyses, it was shown that the balloon expandable stents induced higher stresses in coronary arteries compared to peripheral arteries. It was also predicted that self expandable stents induced higher intimal and medial stresses in peripheral arteries than in coronary arteries. Both approaches assumed symmetry within the systems and the balloon expandable stents were expanded via a mechanical pressure applied to the inner surface of the device as the balloon was not explicitly modelled.

An interesting study from Takashima et al. [38] investigated the contact conditions between two different stents and two arteries, one stenosed one unstenosed, using finite element and experimental approaches. In the finite element analysis, the stress states due to expansion of the stent designs were examined. The contact area ratio (the ratio between the area of all elements of the stent surface in contact with the artery and the area of the stent surface) for both stent models within the straight arteries was reported and compared with the ratios calculated from the experimental
measurements. The experimental results were consistently higher than the finite element results. This was attributed to the method of calculating the experimental contact area and possibly to the fact that a straight cylinder was modelled instead of a folded balloon.

In the work of Gu et al. [39], the relationship between arterial stress due to stent implantation and restenosis rate was investigated. Two stent designs were selected and deployed in stenosed straight vessels. The balloon was not explicitly modelled and displacement constraints were used to simulate expansion of the stents. The results of this work demonstrated that the two stent designs induced different levels of stress concentrations in the healthy arterial wall. The stress concentration results also correlated well with reported clinical data for restenosis rates for each design.

A stent geometry parameterisation study was carried out by Pant et al. [40] in 2011. This detailed work included many variations of stent design such as changes in strut width, axial strut length, and link curvature. However, the one geometric constant was the stented environment, the stenotic vessel. The main objectives of this work were to assess recoil, stress distribution, drug distribution and flexibility. The authors successfully showed how different variations of stent design could be used, for example, to minimise stresses and maximise drug delivery.

In 2012, Azaouzi et al. [43] modelled the deployment of a self expanding stent inside an unstentosed artery that was then subjected to pulsatile loading. Levels of stress and strain in the stent were calculated and could potentially be used to estimate for fatigue life of the device. The effect of oversizing (the difference between the artery inner diameter and nominal stent diameter) was also considered. From the results of
the study, the authors concluded that the strain recovery of the stent depended on the amount of oversizing which would in turn affect the fatigue life of the stent.

3.2.2 Idealised Curved Artery Models
Though arteries can be highly complex and tortuous, relatively few researchers have included curvature in their analyses, with the vast majority representing the arterial environment as a straight cylinder as discussed in the previous section. This section presents a summary of works that included idealised curvature or idealised bifurcations in their analyses.

In 2007, Wu et al. [44] were one of the first groups to model stent expansion in a curved vessel. A symmetrical model was assumed and half of a stenotic curved vessel was modelled. Also modelled for comparison was a straight stenotic vessel, one eighth of which was modelled due to symmetry assumptions. Stent expansion was simulated by applying displacement constraints to the inner surface of the device, as the balloon was not explicitly modelled. No bending simulation of the stent for the curved vessel was carried out. In reality, the stent would not be delivered into a curved vessel completely straight, due to the tortuous path to the coronary arteries. To accurately present the stress state of the device in the stenosed region, bending along the delivery path should be modelled. Despite this limitation, the authors were able to successfully model straightening of the vessel and noted that stress was higher along the inner curvature of the curved vessel model.

Also in 2007, Wu et al. [45] were one the first groups to examine the behaviour of a self expanding nitinol stent in an idealised carotid bifurcation. Two stent designs were modelled in their analyses. The first represented a segmented stent with six units and the second had shorter strut lengths and nine units. Results indicated that
the shorter stent struts resulted in higher radial force levels on the arterial tissue. Shorter struts also allowed more conformation of the stent with the tortuous vessel geometry.

Another work that examined the behaviour of stents in a curved vessel is that of Kaisiri and Kelly [46]. In this study, an evaluation of the effectiveness of using a multiple segment stent rather than a single long stent in a curved artery was carried out. A double stented segment was shown to be more flexible and to result in less recoil than the single long stent. However, in the models the stents were assumed to be straight as no bending simulation was carried out. Also the balloon was not modelled; the vessel modelled was unstentosed and the curvature was quite slight.

In the work of Mortier et al. [47], the focus was on evaluating a technique for modelling balloon expandable stents in the bifurcated vessel. The impact of using different balloon sizes and stent designs was also investigated. The evaluated technique involved stenting the main branch and then using a balloon, positioned through the side of the stent, to inflate the side branch. The authors concluded that a different technique might be more suitable for the stent designs considered. In this work, no lesion was included in the analyses.

Another work dealing with idealised bifurcations is that of Gastaldi et al. [48]. In this work, different balloon inflation strategies were analysed and also the effects of strut positioning for accessing the side branch of the bifurcation were examined. The effects of strut positioning correlated well with in vitro tests carried out by Ormiston et al. [49] which illustrates the accuracy of finite element predictions. However, the geometry of the lesions represented was not diffuse along the bifurcation, as would
be expected, and there was no smoothing or tapering at the edges which could lead to unrealistic stresses at the stenotic edges.

### 3.2.3 Patient Specific Arterial Models

The final category of arterial models to be discussed is that of patient specific. These are typically generated from CT scans of a particular patient’s vasculature and a finite element mesh of the vessel in question is then created. While this represents a significant area of research, it still only captures the response of one particular individual to the implantation procedure. In this section, the advances in this area of modelling are summarised.

One of the earliest published studies in this area is from Holzapfel et al. [50] in 2005. The vessel in question was an iliac artery which was broken down into eight vascular tissues, forming a fundamentally straight stenotic vessel, into which different stent designs were deployed. Many factors were varied, such as stent design, strut thickness and stent-artery radial mismatch. A very detailed arterial model was created but the balloon expansion was not explicitly modelled as a mechanical pressure was applied to the inner stent surface to simulate deployment. The authors defined scalar indicators which allowed for a better judgement of the performance of stents used for a specific artery. Numerical studies allowed for changes of these indicators as a function of certain parameters such as stent cell type, geometry of stent strut and stent cell, and the mismatch between the smallest lumen diameter in the stenosis and the expanded stent diameter, a crucial parameter in clinical practice. The indicators were essentially measures of the mechanical stresses produced during the expansion, which should be as small as possible, and of the lumen gain, which should be as large as possible.
Kiousis et al. [51] in 2007 also used a patient specific arterial vessel in their study of different stent implantations. The vessel was divided into four material sections. In their simulations, an unfolded cylindrical balloon was inflated for stent implantation, however, only one unit cell along the axial direction was modelled so the results were limited to this section. The performance of each stent was characterised by scalar quantities relating to stress changes in the artery, contact forces, and changes in lumen area after stenting. The study concluded by suggesting two optimal stent designs for two different clinically relevant parameters: lumen gain and the induced stress level in the tissue.

Another work in this area is that of Gijsen et al. [52] in 2008 who simulated stent deployment in a mildly curved mildly stenosed arterial vessel. The balloon was not explicitly modelled and a mechanical pressure was applied to simulate expansion of the device in silico. The stent was placed in the straightest section of the vessel so that no bending simulation was required. The results showed the deformed configurations, the pressure-lumen area relationship and stress distribution in the arterial wall and stent struts. The method presented in this work could be applied to predict stresses in the stent struts and the vessel wall, and thus used to evaluate whether a specific stent design is optimal for a specific patient.

Harewood et al. [53] used a multiscale methodology to assess failure in the deployment of coronary stents. In this work, the macroscale simulations carried out compared the implantation behaviour of a particular stent design in an idealised straight vessel and a highly curved arterial vessel generated from a healthy right coronary vessel. A bending simulation was carried out to allow the stent to be positioned within the curved vessel, unlike previous works which typically placed a straight stent in the most convenient section of the realistic geometry. The main
limitations of the macroscale simulations were that the balloon was not explicitly modelled and the choice of a healthy coronary vessel meant no stenosis was modelled. The results gave an insight into failure risks for different stent implantation scenarios: stent failure was considered to be unlikely in deployment in tortuous vessels, however, there may be risks associated with certain bifurcational stenting techniques such as “crush” stenting. In this procedure, a stent is initially deployed in the side branch with its proximal end remaining in the main artery. A second balloon is then inflated in the main artery, crushing the portion of original stent that remains in the main artery and allowing the deployment of a second stent in the main branch. In the “crush” simulation, the region with the risk of failure is a straight strut that was not designed for bending, but undergoes bending and stretching during the distortion of the stent.

Zahedmanesh et al. [54] compared different deployment strategies for balloon expandable stents in a realistic coronary vessel to determine an optimum modelling strategy. This work compared the explicit use of a folded balloon to the use of a mechanical load applied to the inner surface of the stent and also proposed an alternative pressure deployment method that utilised connector elements that restrained the stent as the desired diameter was achieved. It was concluded that the balloon should be explicitly modelled to predict the stresses during implantation but that the final stress state could be predicted using the restraining element approach.

In one of the most advanced simulations in the area of patient specific modelling, Mortier et al. [55], in 2010, presented a deployment strategy used to simulate implantation in a realistic unstenosed arterial vessel with significant curvature. The simulation involved a bending/positioning stage prior to inflation of the balloon-catheter-stent assembly in the complex vessel. Three stent designs were investigated
using the methodology. The study found that vessel straightening occurred and that the compliance mismatch at the stent ends induced stress concentrations which it was concluded that this may be a cause of adverse biological responses. However, the main limitation of the work was that an unstenosed vessel was selected so the response of a stenotic vessel was not captured.

### 3.2.4 Evolution of Material Models used for the Healthy Arterial Wall

In the confined expansion simulations discussed in sections 3.2.1-3, the healthy arterial wall has typically ranged from being a single layer, isotropic, homogenous, hyperelastic material [27,28,31–33,35,37–39,44,47,52,53], to a multi-layer isotropic material structure [29,30,36,40,46,48,54] and onto a multilayer anisotropic material structure accounting for the presence of collagen fibres [50,51,55].

Modelling the arterial wall as a single homogenous material for stent simulation purposes has been the most common starting point for arterial representations in the literature [27,28,31–33,35,37–39,44,47,52,53]. However, this approach does not capture the individual mechanical stress-strain response of each layer. It has been shown experimentally that the stress-strain responses of each layer are very different [56]. This approach therefore cannot accurately predict the arterial stress state during a virtual implantation.

The next main advance in arterial constitutive modelling in stenting simulations was the representation of the individual layers in the arterial wall, the intima, media and adventitia, as isotropic hyperelastic materials [29,30,36,40,46,48,54]. These authors typically adopted constitutive laws that had been fitted to experimental data, for example the works of Loree et al.[57] and Lee et al. [58], to derive the necessary material properties describing the laws. However, it has been shown that the
behaviour of the individual healthy arterial layers is highly anisotropic [56] due to the presence of fibrous tissue, consisting mainly of elastin and collagen fibrils. State-of-the-art studies, in the context of stent-artery interactions during implantation, use material models that account for the anisotropic nature of the arterial wall [50,51,55].

3.2.5 Experimental Testing of Atherosclerotic Tissue
In contrast to the healthy arterial wall, the characterisation of atherosclerotic plaque tissue has received less attention. Reports of experimental test results for the mechanical properties of atherosclerotic tissue are infrequent in the literature. This can typically be due to the difficulty in obtaining the tissue and the lack of a robust animal model that is representative of the disease in humans. Since the representation of atherosclerotic tissue is of significant interest to this thesis, a brief review of experimental characterisation of the tissue is presented here.

In 1991, Lee et al. [58] published a study on the cyclic compressive behaviour of human aortic atherosclerotic fibrous caps. The fibrous cap of atherosclerotic tissue is the component responsible for separating the necrotic core from the blood stream. Some studies suggest that fissuring or fracture of this fibrous cap is what leads to unstable coronary artery disease [59–61]. This can cause a cascade of events such as thrombus formation and myocardial infarction. Lee and co-workers examined the mechanical properties of 27 fibrous caps obtained from the abdominal aorta. The fibrous caps were taken from atherosclerotic lesions, which were classified as cellular, hypocellular or calcified. It was found that hypocellular fibrous caps were 1-2 times stiffer than cellular caps and calcified caps were 4-5 times stiffer than cellular caps. All 27 fibrous caps demonstrated an increase in radial stiffness with increasing frequencies of stress. It was concluded that the stiffness of fibrous caps
from human atherosclerotic plaques is related to the underlying histological structure of the specimen.

The mechanical properties of whole atherosclerotic human plaques, which were classified as either cellular, hypocellular or calcified, were examined by Loree et al. [57] in 1994. The static circumferential tangent moduli of 26 aortic plaques were studied. The response of the tangent modulus of each specimen to variation in increasing applied circumferential tensile load was investigated. It was found that there was great variation in the calculated tangential moduli from all samples at a 25kPa applied stress. All 26 specimens demonstrated a statistically significant increase in tangential modulus with increasing applied stress. It was concluded that the static circumferential tangential modulus of atherosclerotic plaque is not affected by the degree of cellularity and calcification as determined by histological characterisation. It was also concluded that all the specimens exhibited strong anisotropic and non-linear properties when comparing the tensile circumferential moduli to that of the radial compressive moduli reported by Lee et al [58].

Also in 1994, Loree et al. [62] investigated the mechanical properties of model atherosclerotic lipid pools. The contention of this research was that the mechanical properties of the lipid pool are critical in determining the stress in the lesion and that variation in the composition of the lipid pool can occur in the atherosclerotic regression process. The mechanical properties of different lipid combinations, similar to those observed in atherosclerotic lesions, were examined. The dynamic shear moduli of combinations of cholesterol monohydrate crystals, phospholipids and triglycerides were measured. It was found that increasing the cholesterol monohydrate concentration from 0% to 50% increased the real component of the dynamic shear modulus by 4.5. It was also found that all specimens demonstrated an
increase in stiffness with increasing frequencies of stress. It was concluded that the stiffness of the model pool is related to the concentration of the cholesterol monohydrate crystals. It was thought that the increase in relative content of these crystals, which typically occurs during early regression, may result in stiffening of the lipid pool and in reducing the stresses in the fibrous plaque cap.

In 1997, Topoleski et al. [63] examined the different mechanical responses exhibited by atherosclerotic aortic plaques with different compositions, and focussed specifically on radial compressive behaviour. The specimens were characterised as fibrous, calcified or atheromatous (lipid-rich). Specimens were subjected to monotonic and cyclic compressive loading. From their data, it was concluded that the atherosclerotic plaques exhibited composition- and history-dependent nonlinear and inelastic responses under finite deformations.

In 2001, Salunke et al. [64] investigated the time-dependent response of excised human atherosclerotic plaques subjected to uniaxial relaxation tests in radial compression. This was a development on the previous paper by Topoleski and co-workers [63]. The specimens were characterised as fibrous, calcified or atheromatous. The mode of loading was hypothesised to be similar to what the tissue is subjected to during inflation of a balloon catheter. It was found that, despite differences in plaque type, the overall responses during relaxation were qualitatively similar. It was also found that relaxation is significant and differs for different classes of lesion. It was concluded that this was evidence for treating plaques clinically based on composition and not just the degree of obstruction.

The nanomechanical properties of calcification, fibrous tissue, partially calcified tissue, and hematoma from atherosclerotic plaques was the focus of the study carried
out by Ebenstein et al. [65] in 2008. Fourier transform infrared (FTIR) spectroscopy was used to quantify the amount of mineral and lipid in each tissue region tested with a nanoindenter. It was found that the stiffness of the plaque tissue increased with increasing mineral content. Importantly, this was the first reported experimental data on the mechanical properties of atherosclerotic calcifications, and it showed that the estimated modulus values commonly used in computational models greatly underestimate the stiffness of fully calcified tissue.

In 2009, Barrett et al. [66] investigated the mechanical properties of carotid atherothrombotic fibrous plaque caps using indentation techniques. The elastic properties of the specimens were estimated by fitting the measured indentation response to finite element simulations. It was found that the measurements were comparable to the static radial compression tests of Lee et al. [58] discussed previously.

Also in 2009, Maher et al. [67] investigated the tensile and compressive properties of fresh human carotid atherosclerotic plaques. The majority of previous studies mentioned report the properties of the tissue removed following autopsy. This work used fresh human carotid plaques removed during endarterectomy that were tested within 2 hours. A total of 50 radial compressive and 17 circumferential tensile uniaxial tests were performed on samples taken from 14 patients. Plaques were classified as calcified, mixed or echolucent (lipid-rich). The data indicated that the tissue was highly heterogeneous and that the mechanical properties varied significantly between specimens obtained from individual donors and between donors. The results of this study showed that calcified plaques had the stiffest response and that echolucent plaques were least stiff. It was also found that there
may be a difference in behaviour of samples taken from different anatomical locations (common, internal and external carotid artery).

In 2011 Lawlor *et al.* [68] also investigated the circumferential tensile properties of fresh carotid plaques. A total of 14 specimens were obtained from the endarterectomy procedure and separated into three grades of stiffness, hard, mixed and soft, according to their mechanical response. Individual and group material coefficients were then generated analytically using a Yeoh strain energy density potential. The ultimate tensile strength of each sample was also recorded. A large variation in ultimate tensile strength was found for the specimens. It was hoped that the data might be used in the design optimisation of next generation medical devices for the treatment of diseased arteries at the carotid bifurcation.

Also in 2011, Maher *et al.* [69] published a constitutive model to describe the inelastic behaviour of atherosclerotic plaque based on experimental testing of plaque specimens. The mathematical model derived will be discussed later in this chapter. Fresh human carotid atherosclerotic plaque specimens were subjected to cyclic radial compressive loading. These specimens were classified as mixed, calcified or echolucent. From the results of this study it was found that there was an approximately linear increase in plastic deformation with increase in the peak applied strain for all plaque types. While calcified plaques were the generally the stiffest, it was also found that the clinical classification of plaques had no significant effect on the magnitude of plastic deformation on unloading.

### 3.2.6 Computational Modelling of Atherosclerotic Tissue

Discussed above was the available experimental data that is in the public domain for atherosclerotic plaque tissue. It is studies like these that aid us on the quest for
understanding of the complex disease that is atherosclerosis. Having the most up-to-date and representative data is crucial with regards computational modelling of the biomechanical response to procedures such as intravascular stenting, as it is this modelling that allows us to further our insight into the biomechanics of this diseased tissue. These computational models have developed significantly in previous years and the following is a summary of the achievements to date in this area and also the limitations of the analyses carried out.

There are typically two classes of simulation carried out involving atherosclerotic tissue. These are simulations involving analysing the effects of the stenting procedure on the tissue or simulations of the effects of blood flow on the diseased tissue. The latter will be presented in terms of the geometry utilised and the material models used (even though these studies do not explicitly model the stenting procedure, they are included in this section as they are also of interest to this thesis). The former has been discussed in previous sections with the focus on stent behaviour and arterial shape. These works with atherosclerotic tissue present will be summarised here; this time with a focus on the geometry and material models used for atherosclerotic tissue. The developments and trends observed in both classes of simulations will then be discussed.

In 1989, Richardson et al. [70] were the first group to model atherosclerotic plaque using finite element techniques. To investigate the types of atherosclerotic plaques that fissure and where they fissure, plaques from 85 patients who had died from coronary thrombosis were examined histologically. Several 2D idealised parametric cross-sections of atherosclerotic vessels were then developed, containing varying quantities of lipid pool and calcifications. A pressure loading was then applied to the vessel interior. The results indicated that when eccentric lipid pools were present,
stresses were concentrated at the plaque cap, especially near the edge (or shoulder) of the plaque. When the lipid pool occupied less than 15% of the vessel circumference, and when the plaque cap was less stiff than the adjacent normal intima, the point of maximum stress was over the centre of the plaque. It was also shown that the distribution of circumferential tensile stress across the intima was significantly altered by atherosclerotic plaques. Regions of high circumferential stress correlated well with the site of intimal tears found at necropsy.

In 1992, Loree et al. [71] investigated the effects of variation of fibrous cap thickness on peak circumferential stress in finite element models of atherosclerotic vessels. It was the intention of this study to investigate the mechanisms behind plaque rupture. The geometrical models used were 2D idealised cross-sections of atherosclerotic lesions containing plaque tissue and a lipid pool surrounded by a healthy arterial wall. Linear elastic properties were assigned to the plaque and artery, which assumed to be orthotropic. The lipid pool was modelled as isotropic and with a Young’s modulus 1/100th of the arterial circumferential Young’s modulus. Ten idealised models were designed to test the effects of plaque geometry on circumferential stress fields in the diseased vessel. Also, a sensitivity analysis was carried out to examine the effect of varying the orthotropic material parameters on the maximum circumferential stress. From the results of the study, it was found that reducing the fibrous cap thickness dramatically increased peak circumferential stress in the plaque, whereas increasing the stenosis severity decreased the peak stress in the atherosclerotic tissue.

In 1993, Cheng et al. [72] examined the distribution of circumferential stress in ruptured and stable atherosclerotic lesions using the finite element method. Their intention was to test the hypothesis that plaque rupture occurs at sites of high
circumferential stress in the diseased vessel. Histological specimens from 12 coronary artery lesions that caused lethal myocardial infarction were compared with those from 12 stable control lesions. The 2D geometries used in the analyses were generated from digitised tracings of the specimens. The geometries were broken down into fibrous, calcified and lipid sections. The material properties were the same as those used in Loree et al. [71]. The calcifications were modelled using a Young’s modulus that was ten times higher than the circumferential Young’s modulus of the plaque. It was found that the maximum circumferential stress in the plaques that ruptured was significantly higher than the maximum stress in the stable lesions. It was also found that plaque rupture might not always occur in the region of highest stress, suggesting that local variations in the plaque material properties could contribute to plaque rupture.

Over a decade later in 2006, Li et al. [73] performed finite element stress analyses of five vulnerable carotid plaques based on geometries derived from in vivo magnetic resonance imaging (MRI). A vulnerable plaque was defined as a large soft lipid pool covered by a thin fibrous cap. The 2D models were assigned material properties representative of the fibrous cap, lipid pool and vessel wall properties and the region properties assigned correlated with histology for plaque characterisation. The components of the plaque were modelled as isotropic, incompressible and hyperelastic materials undergoing large deformations under pulsatile pressure loading. The results of the simulations predicted high stress concentrations at the shoulders and the thinnest fibrous cap regions of the plaque. It was also shown that larger relative stiffness of the fibrous cap to the lipid pool resulted in higher stress within in the cap region.
In 2009, Tang et al. [74] published a study investigating if local critical stress correlated better than global maximum stress with features linked to atherosclerotic plaque vulnerability. Critical stress was defined as the greatest of the maximum principal stress values. 206 2D slices of in vivo MRI’s of carotid atherosclerotic plaques from 20 patients were acquired for model construction. Each slice was segmented into vessel wall, fibrous cap, lipid pool and calcified regions, which were modelled as non-linear, isotropic and hyperelastic. A modified Mooney-Rivlin strain energy density potential was used for the material model. The results from the study showed that the localised critical stress value had a much better correlation with plaque morphological features, known to be linked to plaque rupture risk, compared to global maximum stress conditions.

Also in 2009, Tang et al. [75] tested the hypothesis that high structural stress in atherosclerotic carotid plaques may contribute to plaque disruption using 3D fluid-structure interaction (FSI) models. The computational models were developed from in vivo MRI data from 12 patients scheduled for endarterectomy procedures. Histology confirmed that five of the 12 plaques had ruptured. The vessel properties were modelled using the same approach as the above work [74]. The results of the study showed that plaques with prior ruptures were associated with higher critical stress conditions, both at ulcer sites and when compared with nonruptured plaques. It was concluded that, with further validation, plaque stress analysis might provide additional stress indicators helpful for image-based plaque vulnerability assessment.

In 2012, Wong et al. [76] studied the effects of calcifications, lipid core elasticity, and fibrous cap thickness on the mechanical stability of plaque, using 2D and 3D numerical models. The constituents of the vessel wall were assigned orthotropic linear elastic material properties. Finite element analyses showed that the distance
between the calcium agglomerate and the fibrous cap should be small to maintain plaque stability. It was also demonstrated that increases in calcium content, which are typically coupled with a decrease in lipid core volume, can stabilise plaque structurally.

Also in 2012, Cilla et al. [77] performed 3D parametric finite element analyses to investigate the role of axial and circumferential residual stresses in plaque rupture. Geometrical parameters studied included lipid core length, stenosis ratio, fibrous cap thickness and lipid core ratio. The plaque constituents were modelled as isotropic materials and the healthy wall was considered as anisotropic with two families of fibres. The results predicted that the fibrous cap thickness, lipid core length and the lipid core width were key morphological parameters in determining the maximum principal stress (MPS). It was also predicted that the stenosis ratio did not have a significant role in vulnerability related to the MPS. To examine vulnerability, results were compared with a threshold stress value that was adopted from the results of Loree et al. [57].

The second class of simulations, involving the effects of stenting on atherosclerotic tissue modelling, will now be presented. Many of these papers have been discussed in previous sections with a focus on the stenting approach and the material modelling method for the healthy arterial wall. However, these studies are reintroduced with the focus now on the atherosclerotic tissue geometry and material models used, as the representation of the stenosis is of significant concern to this thesis.

In 2004, Chua et al. [33] were one of the first to model stent deployment in a stenosed vessel. The idealised plaque and artery were assumed to be linear elastic
and isotropic materials. Symmetry was assumed within the model and a half length axially and a quarter unit circumferentially were simulated.

Also in 2004, Migliavacca et al. [27] improved on [33] by comparing the performance of a balloon expandable stent and a self expandable stent in a diseased vessel with different stiffnesses associated with the plaque tissue material model. The idealised plaque was assumed to be a hyperelastic and isotropic material. Symmetry was assumed within the model and a half length axially and a one twelfth circumferentially. The parameter study to alter the stiffness involved changing the coefficients of the polynomial hyperelastic constitutive law. It was found that increasing the stiffness of the plaque required a higher pressure to expand the stent and consequently higher stresses were predicted in the vessel wall.

In 2005, Petrini et al. [28] compared the performance of a balloon expandable stent and a self expanding stent in a stenosed vessel. The idealised plaque and artery were assumed to be hyperelastic and isotropic materials and, again, geometrical symmetry was assumed.

Also in 2005, Holzapfel et al. [50] analysed the changes in the mechanical environment of a stenotic artery during stent implantation. The patient specific model generated is, in the author’s opinion, one of the most advanced physiological representations of a diseased vessel to be stented in silico. High resolution MRI was used to generated the 3D geometrical model. The vessel wall was divided into eight layers representing the adventitia, the non-diseased media, the non-diseased intima, the fibrous cap, the lipid pool, the calcifications, the diseased intima and the diseased media. These eight regions corresponded to histological examination of the diseased
vessel section. The material parameters used were obtained by fitting the Holzapfel-
Gasser-Ogden anisotropic hyperelastic model [78] to experimental data [79].

In 2007, Migliavacca et al. [80] investigated the expansion and drug elution of a
coronary stent in a diseased artery. The idealised plaque and artery were assumed to
be hyperelastic and isotropic materials. Symmetry was assumed again, this time with
a half circumferential vessel modelled. The deformed artery and stent were then used
as input geometries for a drug elution analysis.

Also in 2007, Kiousis et al. [51] published a study on the interaction of vascular
stents with human atherosclerotic lesions. The diseased vessel was divided into four
sections representing the adventitia, the media, the intima and a lipid pool. The
arterial wall was modelled as anisotropic and hyperelastic, while the lipid pool was
assumed to isotropic. The geometry was generated from MRI scans of a diseased
vessel. Two initial tears in the intimal shoulder of the geometry were introduced to
investigate fissuring and dissection of the plaque, which is thought to occur
sometimes in balloon angioplasty and stenting. From the results, it was predicted that
the highest stresses were reported in the vicinity of the tears.

In 2008, Timmins et al. [32] investigated the effects of stent design and
atherosclerotic plaque stiffness on artery wall biomechanics. The stenotic artery was
modelled as an axisymmetric diseased vessel. The plaque was modelled as
hyperelastic and the coefficients of the strain energy density potential were scaled to
produce a material that was 0.5, 1.0, and 2.0 times as stiff as the arterial material
model. The results indicated that the stress in the arterial wall depended on both stent
design and plaque properties, with the differences between stents being more
pronounced for the stiffer plaques.
In 2009, Pericevic et al. [35] examined the influence of plaque composition on underlying arterial wall stress during stent analysis. Three types of plaque were investigated: cellular, hypocellular and calcified. The coefficients of the polynomial strain energy density potential were fitted to the experimental data generated by Loree et al. [57] for each classification of plaque. Symmetry was assumed within the arterial model with a third section circumferentially and half section axially simulated. The results indicated that the variation in plaque properties caused significant difference in the stress distribution in the healthy arterial wall, suggesting the need for lesion specific stents.

In 2010, Gastaldi et al. [48] investigated the effects of stent positioning in a stenosed coronary bifurcation. For the first time, the plaque was assumed to behave as a hyperelastic and perfectly plastic (where a stress plateau is reached at a certain strain value) material. This method aimed to limit the load carried by the atherosclerotic tissue, allowing a more representative stress distribution in the healthy arterial wall. The stress plateau, or yield stress, was fixed at 0.4 MPa supposedly according to the rupture stress value reported by in Loree et al. [57] in 1994. However, this value is not explicitly reported from Loree’s study and the effect of its variation was not investigated.

Also in 2010, Gu et al. [39] examined the relationship between arterial stress and restenosis rate after stenting with two different stent designs. The plaque and artery were assumed to behave as hyperelastic and isotropic materials. Symmetry was assumed in the idealised geometries, with a half unit axially and a half unit circumferentially modelled. Three levels of stenosis were simulated. The results showed that as the stenosis level increased the maximum stress and its gradient on the arterial wall varied significantly, more than doubling for both stent designs. For a
constant stenosis level, it was found that the stress concentrations in the arterial wall
due to deployment of one stent design were more than twice than those induced by
the other design. This correlated well with reported restenosis rates for the respective
stent designs.

Zahedmanesh et al. [54] published a study simulating a balloon expandable stent in a
realistic stenosed coronary artery in 2010. The aim of this study was to determine an
optimum modelling strategy for stent deployment. The patient specific coronary
vessel was created from digitised 3D angiography images. The plaque was assumed
to be a hyperelastic and isotropic material.

In 2011, Pant et al. [40] performed a parametric study for the optimisation of
coronary stents. The geometry of the idealised stenosed vessel was kept constant for
the analyses. The plaque was assumed to be a hyperelastic and isotropic material.

In 2012, Garcia et al. [81] investigated the influence of geometrical parameters on
the radial force of two self expanding stents in a stenosed vessel. The idealised
stenosed vessel was modelled containing a lipid core and also a calcified core. The
plaque properties were modelled using the anisotropic Holzapfel-Gasser-Ogden
hyperelastic potential.

From the above summarised studies the following trends and developments in
atherosclerotic lesion modelling have become apparent:

- The geometry of the atherosclerotic models has moved from 2D to more
  advanced 3D representations.
- The geometries generated have varied from highly idealised to patient
  specific models of the atherosclerotic tissue.
• The atherosclerotic tissue has changed from being represented as a homogenous continuum to heterogeneous tissue consisting of constituents such as a lipid pool, calcifications, fibrous cap and connective tissue.

• The stress-strain relationship for the plaque tissue has developed from being linear elastic and isotropic to non-linear elastic and anisotropic.

The implications of this will be discussed in reference to this thesis in the final section of this chapter.

3.3 Soft Tissue Damage Models

As mentioned previously in section 3 of Chapter Two, stress softening has been observed experimentally in various types of soft fibrous biological tissue including atherosclerotic plaque. Franceschini et al. [82] showed that human brain tissue deforms similarly to filled elastomers under uniaxial cyclic loading, exhibiting the Mullins effect. A study by Peña et al. [83] investigated the mechanical softening process of prolapsed human vaginal tissue. The softening associated with large strains and loading-unloading scenarios was attributed to the Mullins effect. Ciarletta et al. [84] developed a pseudo-hyperelastic model to represent the hysteresis observed experimentally in cyclic tensile loading of porcine tendons. This hysteresis may be attributed to the Mullins effect. In a study by Maher et al. [69], cyclic compressive tests, in strain-control mode, were carried out on human atherosclerotic tissue. On unloading, significant stress softening and permanent deformation were observed in the tissue which may be attributable to a combination of the Mullins effect and permanent set. This section of the literature review is dedicated to describing the various constitutive models that have been developed to describe this softening phenomenon.
In recent years, there has been an increased interest in the modelling of the soft tissue in the supra-physiological domain. Several authors have developed constitutive theories to represent the damaged behaviour of soft biological tissue in this domain. Typically coming from a continuum damage mechanics framework, much of the work in this area has developed from research into the modelling of large-strain elastic rubbery materials. The following sections, 3.3.1-3, are devoted to discussing representations of soft tissue damage models and relevant large strain elastic damage material models. The core differences between continuous and discontinuous modelling approaches that are used will be examined and the reviews dedicated to their comparison discussed.

3.3.1 Discontinuous Damage Evolution Models
As defined in Chapter Two, discontinuous damage model assumes that damage accumulation only occurs within the first cycle of a strain-controlled loading process. With this type of damage model, further strain cycles below a maximum effective strain energy do not have an effect on the material response.

One of the earliest models for the representation of discontinuous damage, in particular the Mullins effect, is that of Ogden and Roxburgh from 1999 [85]. This model was developed for particular application to filled rubbers which under cyclic loading exhibit a stress softening behaviour referred to as the Mullins effect. The model was termed “pseudo-elastic” as the material response is governed by different forms of strain-energy function on primary loading and unloading. This terminology was also used by Fung for similar observations in the context of biological tissue [86].
Within this formulation the constitutive model is based on the strain energy density potential and has the following form

\[ U(\lambda_1, \lambda_2, \eta) = \eta U^0(\lambda_1, \lambda_2) + \phi(\eta) \] (3.1)

where \( U \), the strain energy density potential, is a function of the damage parameter, \( \eta \), and the principal stretches \( \lambda_1 \) and \( \lambda_2 \). \( U^0 \) is the strain energy density potential for the initial virgin or “undamaged” material. \( \phi(\eta) \), referred to as the damage function, is a smooth function of its argument and satisfies the following condition

\[ \phi(1) = 0. \] (3.2)

The condition of Equation (3.2) means that for an undamaged material the response of the material is that of the initial virgin material. Ogden and Roxburgh suggested the following for the evolution of the damage function

\[ -\phi'(\eta) = m \text{erf}^{-1}(r(\eta - 1)) + U_m \] (3.3)

where \( U_m \) represents the strain energy density function at a point \( m \) at which unloading has most recently been initiated from a primary loading path, \( m \) and \( r \) are positive material constants and \( \text{erf}^{-1}(\cdot) \) is the inverse of the error function. The physical interpretations for \( m \) and \( r \) are as follows: the parameter \( r \) is a measure of the extent of the damage relative to the virgin state and \( m \) controls the dependence of the damage on the extent of deformation.

Numerical simulations of simple shear and tension tests, using the model, exhibited the main qualitative features of the Mullins effect. The model, though subjected to only uniaxial numerical testing, is applicable to multiaxial states of stress and strain.
Although the Ogden and Roxburgh model [85] was introduced in 1999 for application to stress softening in rubber, there were attempts made prior to this to model stress softening in biological tissue. One of the first constitutive theories incorporating damage with application to arteries was developed by Hokanson and Yazdani in 1997 [87]. In this work, a damage model was applied to an isotropic strain energy potential that was fitted to experimental data for bovine coronary artery tissue. The evolution of the damage function, $\phi$, proposed is given in Equation (3.4)

$$\phi(D) = 1 - \left( \alpha \exp \left( \frac{\beta G(D)}{\varepsilon_f} \right) \right)$$  \hspace{1cm} (3.4)

where $\alpha$ and $\beta$ are experimentally determined parameters, $D$ is a scalar cumulative damage term, $G(D)$ is a hardening-softening function and $\varepsilon_f$ is the dissection equivalent strain magnitude. Below a threshold strain, $\varepsilon_r$, no damage is assumed to occur so $\phi$ has a value of unity. When the strain is equal to dissection equivalent strain $\phi$ has a value of zero indicating complete failure. However, in reality, failure would occur below this threshold strain.

A model for anisotropic damage was developed by Balzani et al. [88] with applications to soft tissue in 2004. Damage was assumed to occur only in the fibre direction. It was biomechanically motivated by the breakage of collagen cross-links during over-expansion of arterial vessels. The damage variable, $D$, was shown to be a function of the orthotropic undamaged component, $U_i^0$, of the free energy. It was proposed to have the following form

$$D_i(U_i^0) = \gamma_1 \left[ 1 - \exp \left( -\frac{\beta_i}{\gamma_2} \right) \right]$$  \hspace{1cm} (3.5)
where $\gamma_1$ and $\gamma_2$ are material constants and the subscript $i$ refers to values for each fibre. The internal variable $\beta_i$ has the following form

$$\beta_i = \sup \{U_i^0(C, M_i, s)\}$$  \hspace{1cm} (3.6)

where the sup function represents the least upper bound of the set $U_i^0$. Numerical simulations of cyclic tensile tests showed the main characteristics observed in experiments.

Further developments on this model were carried out by the same authors in 2006 [89] to include residual stresses with application to circumferentially overstretched atherosclerotic arteries. When axial segments of arteries are slit, two phenomena are generally observed. If they are cut transverse to the axial direction they shrink and when they are sliced in the radial direction they spring open. Hence, due to these observations there must be some residual stresses in the closed unloaded configuration. Balzani et al. [89] worked to include these residual stresses in their damage model as a better representation of the arterial stress state. In their numerical approach, a radially sliced artery was closed in order to obtain the deformation gradient at each integration point associated with the residual stresses. Then the nodal coordinates and the deformation gradient at each integration point were stored. The second part of the analysis used a closed axial segment with the same nodal coordinates and deformation gradient as was stored. This was then loaded in the supra-physiological domain to attain a realistic stress state. The authors successfully showed that their damage model could be utilised in 2D representations of arterial overstretch.

An extension of the work of Ogden and Roxburgh [85] was carried out by Peña and Doblaré [90] in 2009. Their model used the approach of Ogden and Roxburgh but
was capable of reproducing the softening behaviour of anisotropic soft biological tissue. Their claim was that the model combines simplicity and applicability, making it a good candidate for modelling stress softening of tissue.

The softening variable, $\eta_k$, presented in [90] is given in Equation (3.7)

$$\eta_k = 1 - \frac{1}{\beta_k} \text{erf} \left( \frac{U_{isch(k)(p)}^0 - U_k^0}{\alpha_k + \gamma_k U_{isch(k)(p)}^0} \right). \quad (3.7)$$

In Equation (3.7), $\alpha_k \geq 0$, $\beta_k \geq 0$, and $\gamma_k \geq 0$ are material parameters with the following physical meaning: $\alpha_k$ measures the damage suffered by the material, a value of zero means the material suffers the largest amount, $\beta_k$ is a measure of the extent of the damage relative to the virgin state, similar to the constant $r$ in Equation (3.3), and for $\gamma_k$ a zero value returns the model to the original model of Ogden and Roxburgh [85], and a non-zero value reduces the stiffness of the unloading path. The subscript, $k$, indicates the parameters for the various components of the tissue, i.e. matrix and each family of fibres. Peña and Doblaré [90] also carried out experimental tests of human vaginal tissue and ovine vena cava tissue to test their model. The comparison of experiment and simulation showed good agreement in both cases.

Another approach following the pseudo-elastic basis was that of Maher et al. in 2011 [69]. This research examined the response of carotid plaque tissue to cyclic compressive loading. The test data was characterised using a constitutive model that accounts for both permanent deformation and stress softening. The fundamental form of the constitutive relationship expressed in terms of Cauchy stress, $\sigma$, was given as follows
\[ \sigma = (1 - D)(\sigma_{IL} - \sigma_{IN}). \]  

(3.8)

In Equation (3.8), \( \sigma_{IL} \) is the initial loading stress and \( \sigma_{IN} \) is the inelastic stress which is activated only upon certain criteria being fulfilled. The evolution of the damage variable, \( D \), is given by the following equation

\[ D(\alpha(t), U_{IL}(C)) = \zeta_\infty \left[ 1 - \exp \left( \frac{-(\alpha(t) - U_{IL}(C))}{i} \right) \right] \]  

(3.9)

where \( \zeta_\infty \) and \( i \) are material constants and \( \alpha(t) \) is the maximum value of the initial loading strain energy density function, \( U_{IL} \), in the loading history. The constitutive model proposed in the study resulted in a consistent quality fit with experimental data. However, several limitations were acknowledged [69], such as lack of tensile testing of the specimens.

A further work by Peña [91] introduced a rate dependent anisotropic damage model for fibred materials for application to soft biological tissue. The rate of damage evolution is given as follows

\[ \dot{D}_k = \begin{cases} \mu_k \bar{Y}(\Phi_k)\bar{h}_k(\Xi_k, D_k) & \text{if } \Phi_k = 0 \text{ and } N_k; \hat{\mathbf{C}} > 0, \\ 0 & \text{otherwise} \end{cases} \]  

(3.10)

In Equation (3.10) \( \mu_k \) is the damage viscosity coefficient, \( \bar{Y}(\Phi_k) \) is the viscous damage flow function and \( \Phi_k \) is defined in Danto and Woo [92] for the matrix and fibres, \( \bar{h}_k(\Xi_k, D_k) \) is the function that characterises the damage evolution, with \( \Xi_k \) being the damaged energy release rate (please refer to section 2.3 for further definitions). Finally, the subscript, \( k \), indicates the parameters for the various components of the tissue, i.e. matrix and each family of fibres. The model was evaluated in several numerical applications and it was found that it was able to capture the typical stress-strain behaviour of soft biological tissue.
A recent study by Weisbecker et al. [93] reported the results of layer-specific damage experiments and modelling of human aortic tissue. The damage modelling approach was based on the pseudo-elastic method and damage accumulation was considered in the matrix and fibres. For the case that considered damage accumulating in both matrix and fibres, it was found that hysteresis was not produced in the non-collagenous matrix. Hence, for the first time, this study showed evidence that the predominant mechanism of damage accumulation in human aortic tissue is in the fibre direction. This has important implications for other soft biological fibrous tissue. A good agreement was found between the model predictions and the experimental data when damage was considered in the collagen fibre fabric.

3.3.2 Continuous Damage Evolution Models
As defined in Chapter Two, continuous damage models take into account the whole strain history of the deformation process to allow continuous damage accumulation. In 2006, Rodríguez et al. [94] published a stochastic-structurally based continuous damage model for fibrous soft tissue. The model used a simple isotropic damage mechanism to describe the softening behaviour of the matrix material and also included statistical aspects related to the length distribution of the reinforcing fibres to describe the damage model for the reinforcing material. The equivalent strain within the collagen fibres was considered a random variable and assigned a Beta probability density function. The model contained nine parameters, four of which are related to the structure of the tissue and five to the mechanical properties of the constituents. The model was applied to a biaxial test and a torsion-extension test, which illustrated the potential of the model for capturing soft fibrous biological tissue behaviour.
Calvo et al. [95] developed an uncoupled deterministic directional damage model for fibred soft biological tissue in 2007. The evolution of their damage variable, $\bar{g}_k$, was defined as follows

$$\bar{g}_k(\bar{z}_t) = \begin{cases} \frac{1}{1 - \exp(\beta^k(\bar{z}_t - \psi^k_{\text{min}}))} & \text{if } \bar{z}_t^m \leq \psi^k_{\text{min}} \\ \frac{1}{1 - \exp(\beta^k(\psi^k_{\text{min}} - \psi^k_{\text{max}}))} & \text{if } \psi^k_{\text{min}} \leq \bar{z}_t^m \leq \psi^k_{\text{max}} \\ 0 & \text{if } \psi^k_{\text{max}} \leq \bar{z}_t^m \end{cases}$$ (3.11)

In Equation (3.11) the subscript and superscript, $k$, can refer to either the matrix or fibres, $\psi^k_{\text{min}}$ is the strain energy at initial damage for the constituent material and $\psi^k_{\text{max}}$ is the strain energy at total damage for the constituent material, and $\beta^k$ is a material coefficient. Numerical simulations were carried out using the model which included stretching of a thin perforated square plate, damage of human medial collateral ligament during valgus knee loading, damage of arteries after balloon angioplasty and damage after arterial clamping. Good qualitative agreement was found between the simulation results and experimental results for the medial collateral ligament and arterial examples.

Alastrué et al. [96] compared the two previous models [94,95] just described in a study in 2007. In numerical simulations a uniaxial test, stretching of a thin perforated square plate and damage of arteries after balloon angioplasty were carried out. The simulations showed a similar performance for both models. It was also noted that due to the number of parameters involved in fitting the stochastic model of Rodríguez et al. [94], the numerical fit was laborious and the computational cost in finite element simulations was expensive.

In 2009, Ehret et al. [97] published a model to describe the anisotropic softening phenomenon associated with cyclic loading of soft biological tissue. In numerical
examples, the model was applied to simulate the preconditioning behaviour of soft tissue exposed to cyclic loading, where preconditioning is usually characterised by pronounced softening and hysteresis even in quasi-static experiments; after some cycles the response stabilises and approaches a steady-state. The results suggested that the general characteristics of preconditioning with different upper load limits are well captured including hysteresis and residual deformations. A model for the Mullins effect was obtained as a special case and showed good agreement with experimental results on mouse skin.

Also in 2009, Brinkhues et al. [98] published a model for the simulation of damage hysteresis in soft biological tissues. With their approach the damage variable, $D$, was incorporated into the strain energy density function, enabling them to obtain remanent strains after unloading. The model results were compared with experimental data for cyclic uniaxial tensile tests on carotid artery medial tissue. A good correlation between the experimental data and model predictions was achieved.

More recently, Balzani et al. [99] introduced a constitutive framework for the modelling of damage in collagenous soft tissue with application to arterial walls. It is known that residual deformations are obtained due to supra-physiological loading if a certain load level is exceeded in soft tissue. The main goal of the work was to define a construction principle for damage models that accounts for residual strains after unloading. Similar to the approach of Brinkhues et al. [98], the damage variable, $D$, was incorporated directly into the strain energy density function to obtain residual strains after unloading. The damage variable, $D$, was assumed to have the following form
where $D_s \in [0,1]$, $r_s \in [0,1]$, $\beta_s > 0$. The only material parameter $\beta_s$ is the value of the internal variable, $\beta$, which is reached at a certain fraction, $r_s$, of the maximal damage variable, $D_s$, for a fixed maximum load level. The internal variable, $\beta$, is defined by the following equation

$$D(\beta) = D_s \left[ 1 - \exp \left( \frac{\ln(1 - r_s)}{\beta_s} \beta \right) \right]$$

(3.12)

where $\beta^{ini}$ is the internal variable at an initial damage state in order to make sure that the damage evolution starts when entering the supra-physiological domain, the Macaulay brackets, $\langle x \rangle$, are a notation used to describe the ramp function. The time associated with the loading history is denoted by $s \in \mathbb{R}^+$; $t \in \mathbb{R}^+$ defines the current loading situation. The model represented the experimental response with reasonable accuracy. Numerical modelling of overstretching of an axial segment of atherosclerotic vessel was also carried out. It was noted that although the quantitative results were not to be determined as realistic, due to lack of experimental data, a significant influence of axial residual strains was identified.

Also published in 2012 was the work of Martin and Sun [100] that looked at modelling of long-term fatigue damage of soft tissue including stress softening and permanent set effects. The particular application was bio-prosthetic heart valves that are prone to structural deterioration due to fatigue. In this model damage due to the number of loading cycles was considered, in contrast to other models described in this literature review, where equivalent strain is generally only considered. The unfatigued material properties were assumed to follow a Fung-type strain energy
function. It was also noted that during the fatigue process, irreversible un-crimping of collagen fibres induced a permanent set in the tissue. Two parameters were introduced to define the boundaries of the fatigue evolution zone and a distribution of the number of cycles to failure was presented. The permanent set within the tissue was assumed to linearly accumulate during each loading cycle, at a given equivalent strain. The model predictions were compared with experimental data for uniaxial fatigue testing of glutaraldehyde-treated bovine pericardium. A good correlation was achieved with the experimental results.

3.3.3 Reviews Comparing Continuous and Discontinuous Damage Models
Miehe [101] looked at discontinuous and continuous damage evolution in Ogden-type large strain elastic materials in 1995. The author explained the discontinuous damage effect as being related to the maximum effective strain energy. In this approach, no damage accumulation occurs for values of the strain-energy inside a damaged domain. However, Miehe mentions that experimental investigations of filled polymers indicate that a damage accumulation also occurs for strain cycles which have values of effective free energy below the maximum value of the past history.

The major aim of this study was to take into account experimental observations and propose an additional contribution to the damage evolution (Mullins type discontinuous damage evolution), governed by the arclength of effective strain energy. This part of the damage was assumed to accumulate continuously during a cyclic loading history. The second aim of the work was to formulate the damage model for general Ogden-type elastic materials. The total damage was described by the following expression
In Equation (3.14), \( \hat{d}_\alpha \) and \( \hat{d}_\beta \) are monotonically increasing smooth functions with the properties \( \hat{d}_\alpha(0) = 0, \hat{d}_\beta(0) = 0 \) and \( \hat{d}_\alpha(\infty) + \hat{d}_\beta(\infty) \in [0,1] \). They can be considered as shape functions that relate the damage variable, \( d \), to the new variables, \( \alpha \) and \( \beta \), which describe the discontinuous and continuous damage, respectively.

Using numerical simulations of simple tension, pure shear and equibiaxial tension, the differences between discontinuous and continuous modelling was shown. Hysteresis was apparent with both approaches but the reloading path differed from the unloading path with continuous damage. As would be expected also, the continuous damage model tended to result in a softer modulus than the discontinuous approach.

In 2009, Peña et al. [102] published a study on continuous and discontinuous damage modelling, discussing the Mullins effect and hysteresis observed in fibred biological tissues. Their model was an extension of the approach of Miehe [101], see Equation (3.11) and following discussion. Using numerical simulations, three approaches were compared: discontinuous, continuous, and mixed (continuous and discontinuous). For a biaxial tension example, it was found that in the purely discontinuous damage case it was easy to detect the characteristic Mullins effect with damage only occurring during the unloading process. On the contrary, in a purely continuous damage case, damage occurred in both loading and unloading that increased faster in the initial loading history than at the end. Finally, in the mixed damage case, damage strongly increased under loading, whereas during unloading damage was lower when it became close to a stabilised value. In another numerical
example, examining the softening behaviour of arteries, the comparison between experimental test and simulation showed a good agreement for the mixed model, where hysteretic and Mullins behaviour was produced. However, continuous and discontinuous models were not able to reproduce the inelastic response of the aorta. The discontinuous model reproduced the Mullins effect and not the hysteretic behaviour while the continuous model was able to model the hysteretic response but not the Mullins effect. Overall, the mixed model produced a good qualitative agreement between numerical and experimental results.

3.4 Current Trends in Stent Modelling
This literature review has been dedicated to reviewing solid mechanics approaches to modelling coronary and peripheral stent implantation techniques. Also presented has been a review of damage models that characterise the phenomenon of stress softening in soft biological tissue. However, the area of stent modelling is vast and not confined to the above objectives and approaches. A number of other areas in stent modelling are touched upon here, for completeness of the discussion.

Advanced computational fluid dynamics techniques have been utilised by several authors, for examples see [103–107], to capture the complex blood flow patterns in stented regions and also to examine the wall shear stress. It has been shown that disruptions to the normal blood flow pattern and also a low wall shear stress can be associated with in-stent restenosis [108,109].

A new generation of commercial stents are emerging today that are classified as biodegradable stents. These can be composed of absorbable metals or polymers. The characterisation of these new materials has been investigated by several authors and applied to stenting simulations, for examples see [110–112].
Drug eluting stents, biodegradable or permanent, can have issues of coating (which elutes the therapeutic drug compound) debonding. If this happens in vivo and a piece of coating breaks away from the stent, it leaves the patient at risk of a microembolism and potential thrombus formation. Hopkins et al. [113] used finite element modelling to simulate how different coatings debonded from stent geometries. The results showed good correlation with experimental images of the debonding process.

Finally researchers have also investigated the elution of drugs from coated stents into the arterial wall and surrounding blood flow, for examples see [114–116]. The aim of these studies has been to characterise drug elution rates and design compounds that optimised elution times clinically.

### 3.5 Current limitations of Stent Modelling Approaches

This chapter has presented a thorough review of stent modelling approaches for two distinct categories: unconfined expansions (no artery modelled) and confined expansions (artery modelled). However, from the review of this literature, it is obvious that there are certain limitations in these approaches to stent modelling.

The main limitation of the unconfined expansion of stents is the lack of a physiologically representative environment, i.e. the artery is not modelled. The purpose of the stenting procedure is to expand blocked arterial vessels and the absence of the vessel itself in simulations does not capture the realistic deployment characteristics of the device. However in saying this, there is valuable information to be ascertained from free expansion simulations such as the axial foreshortening, dogboning, radial recoil and flexibility, amongst others. These are important parameters to be aware of but fully capture the predicted in vivo response to implantation an arterial vessel needs to be included in the analyses.
There are also several limitations to existing approaches that have included the arterial vessel in their analyses. The predominant limitation in the analyses is the lack of comparison between different arterial vessel model representations. This is a critical point as no two humans or their vasculature systems are identical; so why should one arterial model be enough to capture the implantation of the device? This is a question to be asked of arterial models that are patient specific or idealised. To ascertain a representative picture of device performance, it is the contention of this thesis that it should be assessed across a range of arterial vessels that capture variation across the population.

Another significant limitation in many studies is the lack of stenosis present in the arterial vessel model. In reality a healthy vessel is not stented \textit{in vivo} so the \textit{in silico} representation should account for the presence of atherosclerotic tissue.

To achieve a representative physiological environment in simulations there is the requirement that the constitutive material models used should capture the true material response. Often arterial tissue is considered as isotropic, however, due to the presence of collagen fibres, it is known to be highly anisotropic.

The lack of explicit representation of a balloon within the analyses can also be considered a significant limitation within certain studies. The lack of an explicit balloon model means that an accurate depiction of arterial stress state is not captured.

While the limitations of current studies have been listed above, it must also be acknowledged that these studies have made significant breakthroughs in the world of stenting through thorough examinations of different aspects of device performance. However, this thesis aims to integrate the shortcomings of previous works and
address them in a new approach for device assessment. This framework that addresses all the previously discussed issues, will be presented in the Chapter Four.

Also to be considered is the representation of the atherosclerotic tissue in the analyses. No comprehensive assessment has been carried out on the effects of the elasticity model used for the atherosclerotic tissue in a stenting simulation. Damage modelling techniques have been reported within this chapter but they have not been applied to atherosclerotic tissue behaviour in an advanced *in silico* representation of stent deployment in a stenosed vessel. In this work, a discontinuous damage model will be applied to the behaviour of atherosclerotic tissue. This is selected over a continuous damage modelling approach as it can be readily fit to experimental data for this tissue type. Finally, the inclusion of the typical constituents of the plaque, a lipid pool and calcifications, has not been thoroughly investigated in the context of stent modelling. These limitations in current research will be addressed in Chapter Five.

It is the aim of this thesis to build upon previous studies and address their limitations to develop a framework that gives new insight into the biomechanics of coronary stent implantation and present a methodology for assessing new and emerging stent designs.
References


40. Pant S, Bressloff NW, Limbert G: Geometry parameterization and multidisciplinary constrained optimization of coronary stents 2011;


Figure 3.1  A) Axial cut through stent geometry. Insert labels the main features of the geometry, B) slotted tube stent geometry in unexpanded and expanded states, C-i) open cell stent design and C-ii) closed cell stent design.
Figure 3.2: Example of an unexpanded slotted stent; l: length of the slot, s: thickness, $\alpha_p$: angle described by the metallic surface, $\alpha_v$: angle described by the slot and D: outer diameter; finite element mesh for a quarter of model slotted stent also shown [18].
Figure 3.3  
Generic stent showing the three parameters of interest: h is the connector bar length (or strut spacing), \( \rho \) is the radius of curvature at the crown junctions, and f is the axial amplitude. These three parameters were varied to test their effects on artery wall stress [31].
Chapter Four

4 Computational Test-Bed

4.1 Introduction

As stated previously in Chapter One, ischaemic heart disease is the major international cause of death [1]. The reduced blood supply to the heart muscle, characteristic of the disease, is usually caused by atherosclerosis of the coronary arteries. The evolution of the stenting procedure has significantly improved the clinical treatment of atherosclerosis. However in-stent restenosis, when the stented vessel lumen becomes reblocked, has been a significant issue with coronary stents [2–7]. Drug eluting stents (DES) have contributed significantly to the prevention of restenosis [8], however, recently high instances of late stent thrombosis have been reported for DES [9], causing a renewed interest in stent geometrical design to address the restenosis issue.

It is well documented clinically that placement of a stent can injure the vessel it is treating, which can lead to the formation of neointimal hyperplasia and in-stent restenosis, for examples see [10–12]. Engineers who have modelled the implantation of stents in silico have noted high mechanical stresses within the arterial vessel beings stented [13], a thorough review of which has been presented in Chapter Three. Another contributing factor to restenosis is thought to be stent fracture [14–16]. To reduce the risk of in-stent restenosis due to arterial stress related factors, more comprehensive evaluation of coronary stent mechanical performance in the design phase is necessary. The generation of a computational framework to facilitate such an evaluation provides the first motivation for work presented in this chapter.
In April 2010, the United States’ Food and Drug Administration (FDA) released a report entitled “Non-clinical engineering tests and recommended labelling for intravascular stents and associated delivery systems” [17]. The report supersedes the guidance of a previous report with the same title released in 2005. This previous report was critiqued by Lanzer et al. [18] who gave suggestions for the improvement of these standards. Of particular interest to this work is Section 9 of the current report which outlines the stress-strain analyses to be performed for approval of a new stent design. Despite improvements in the 2010 report relative to the 2005 version, the standards are still relatively imprecise in relation to the role of blood vessel geometry in stent stress-strain analyses, and the range of geometries that should be considered in these analyses, to generate an accurate depiction of device performance in vivo. This provides the second motivation for the present work; in particular, the generated computational framework will be used to assess the importance of blood vessel geometry in stent stress-strain analyses, and to give insight into the degree to which vessel geometry should be specified in stent assessment standards.

The use of computational modelling in the clinical domain is well established for coronary stents. It has been developed as a viable alternative to the difficult and expensive experimental analysis and evaluation of stent deployment for assessing performance [19]. Computational modelling of the deployment procedure can provide valuable insights into the mechanical behaviour and performance of a given stent design. A review of such modelling is given in Martin and Boyle [20] and a discussion has also been presented in Chapter Three of this thesis.
As described previously, for coronary applications there are typically two types of stent: self expanding stents (SES) and balloon expandable stents (BES). These can be bare-metal or drug-coated, and permanent or biodegradable. Of particular interest to this work is the assessment of BES but the computational framework presented here could also be utilised for the assessment of SES.

While significant advances in stent deployment simulations have been realised in recent years, as discussed in Chapter Three, there still is a need for a practical computational framework for assessing stent performance that captures a range of population categories, which is more general than patient specific, yet more realistic than a single idealised arterial structure. The generation of these population-specific, enhanced realism arterial geometries is a third motivation for the present work.

Against this backdrop what is proposed here is to generate a computational test-bed that has the following features:

- A systematic, purposefully chosen, variation in arterial curvature
- A range of realistic stenosis sizes
- A choice of mechanical properties for the representation of the stenosis
- A selection of material parameters for representation of the healthy artery

This will allow for a systematic assessment of stent mechanical performance \textit{in silico} that is reasonably representative of the expected performance in a range of anatomical geometries. The computational test-bed is then used to investigate the mechanical performance of coronary stents, with a focus on BES. Two stent designs representative of the closed-cell Cypher stent (stent A) and the open-cell Multi-Link
stent (stent B) are considered. The issues of population-specific geometries, effects of stenosis severity, yield behaviour of atherosclerotic tissue, and effects of arterial curvature are considered. The resulting new insights for stent modelling are discussed and implications for FDA guidelines are considered.

4.2 Computational Model Formulation
The models and methods implemented are discussed in the following sections with the specific geometries and meshes for the major components of the assemblies being discussed first and then the constitutive material models used for each assembly component. The commercially available Abaqus/Explicit solver is used for the finite element simulations. The finite element mesh densities quoted below were arrived at following mesh design and convergence studies, within the constraints of numerical problem size practicality. Significant development studies were also carried out and are presented here.

4.2.1 Geometrical Models

4.2.1.1 Non-Atherosclerotic Arterial Tissue
Three levels of arterial curvature are modelled in the test-bed; straight, moderately curved with a tortuosity index, TI, of 0.1 and a severely curved segment with a TI equal to 0.3. The TI of a segment is calculated as shown in Figure 4.1(a), where ‘‘A’’ represents the curved arc length and ‘‘B’’ represents the chord length of the arc [21]. A TI varying between zero and 0.1 represents natural curvature and a TI of 0.3 or higher represents arterial tortuosity.

For further information on the calculation of the TI the reader is referred to Figure 4.2, which shows angiographic images of a diseased arterial vessel pre- and post-stenting [21]. Illustrated in Figure 4.2 is how the calculations of radius of curvature,
angulation and TI of a vessel are performed. It is important to note also that due to the 2D nature of the image, no out of plane curvature is considered in the calculation.

It is assumed that the wall thickness of each segment is 0.5 mm and this is equally divided into three sections representing the intimal, medial and adventitial layers. These dimensions fall within the range of experimentally measured wall thicknesses, as reported by Holzapfel et al. [22]. The inner diameter of each unstenosed segment is assumed to be 3.0 mm.

To create the curved geometries, the straight segments were mapped from a Cartesian to a cylindrical coordinate system. The x, y, and z components were mapped to r, θ and z components, respectively. The resultant geometries are depicted in Figure 4.1(b), with each row representing an increasing level of curvature from top to bottom. Each segment was meshed with 3D reduced integration linear continuum elements, C3D8R, with the mesh density varying between 80000 and 180000 for the healthy arterial wall. A thin outer layer of shell elements, S4R, is also included in the arterial models to represent the physiological environment in which an artery would be embedded.

4.2.1.2 Atherosclerotic Arterial Tissue
The plaque tissue is idealised as semi-ellipsoidal in shape with the point of maximum blockage reaching two levels of arterial cross-sectional area stenosis: 50% and 60%, at the mid-section. These values were chosen as key stenosis levels for the study. Gould et al. [23] found that coronary flow begins to decrease with stenosis greater than 50%. Another study by Jasti et al. [24] found correlations between fractional flow reserve (FFR) and stenosis level. FFR measurement is an established
method of deciding if a lesion mass has reached a critical value. It relates the pressure differences across the stenosis, and once an FFR value of 0.75 [24] or less is attained a stent is usually implanted. Jasti found that an FFR value of 0.75 correlated to a range of area stenoses: mean 49% ± SD 19%, as measured by intravascular ultrasound (IVUS). These two studies [23,24] have motivated the choice of key stenosis levels for the present work, i.e. 50%, corresponding to the measurements in Gould et al. [23] and approximately the mean in Jasti et al. [24], and 60%, corresponding to an area stenosis in the higher range of that reported in [24]. Each plaque section was meshed with 3D reduced integration linear continuum elements, C3D8R, with the mesh density varying between 50000 and 70000 for the diseased arterial wall. The final arterial geometries generated are shown in Figure 4.1(b), with each column representing an increase in stenosis level.

4.2.1.3 Mesh Sensitivity Study
In the initial creation of the arterial meshes used in the test-bed a “free” meshing approach was utilised, due to the complexity of the geometry involved, when the lesion was present. This involved the use of tetrahedral elements, C3D4, in the mesh. However, it is generally advised to avoid first order tetrahedral elements as much as possible in stress analysis problems; the elements can be over stiff and exhibit low convergence with mesh refinement [25]. This is especially a problem with first-order tetrahedral elements. If used, an extremely fine mesh may be needed to obtain results of sufficient accuracy. For this reason a different meshing approach was investigated. By partitioning the complex geometry into smaller more regular shapes, see Figure 4.2, a structured mesh which uses hexahedral elements, C3D8R, could be implemented.
Another distinct advantage of using hexahedral elements is that reduced integration type elements could be utilised. With this type of element, the strains and stresses are calculated at the locations that provide optimal accuracy. They also decrease CPU time and storage requirements due to a reduced number of integration points being utilised. However, one disadvantage of this type of element is the phenomenon of “hourglassing”. This means that deformation models that cause no straining at the integration points can occur. This can propagate throughout a mesh and result in inaccurate solutions. To prevent this problem, in the Abaqus finite element software, an additional artificial stiffness is added to the element, as part of the hourglass control procedure, that is associated with zero-energy deformation modes [26].

Although second-order elements can provide higher accuracy in Abaqus/Standard than first-order elements, this is generally for analyses that do not involve complex contact conditions, impact or severe element distortions. In the case of balloon expandable stent deployments the contact problems encountered are indeed complex and for this reason first-order elements were selected. Also in Abaqus/Explicit only reduced integration first order elements are available for the hexahedral geometry.

Various mesh densities were examined to find a converged solution for the pressure expanded stent simulations (to be discussed below). Shown in Figure 4.4 are the final three structured meshes, HX3 with 38994 elements, HX6 with 119168 elements and HX9 with 130064 elements. The von Mises stress distribution for a pressure expanded stent is shown for each of the three structured meshes. The convergence criterion was that the maximum von Mises stresses converge within 5%. This was obtained with the HX9 mesh, relative to the HX6 mesh, and thus became the SAL50 (straight artery with a 50% lesion) model for the test-bed.
Strain based convergence criteria were also implemented. The convergence criteria were that the maximum and minimum principal strains (logarithmic strains) converge within 5%. Using the same three meshes as above, this was obtained with the HX9 mesh, relative to the HX6 mesh, with an even closer agreement: the strains were within 2% agreement in both the maximum and the minimum principal strain comparisons.

A similar approach was taken to achieve the SAL60 (straight artery with a 60% lesion) and the SA (straight artery) arterial models. In the initial stages of this work another higher level of stenosis was used in the straight arterial section of the test-bed, SAL70 (straight artery with a 70% lesion). However due to difficulties in placement of the stent-catheter assembly in a curved 70% stenosed model a stenosis of 60% was introduced in its place at later stages in this work. As a 60% stenosis was in the upper range of the area stenoses reported by Jasti et al. [24] for a critical masses of lesions needing intervention, it was felt the use of this model was justified.

The meshes for the curved geometries (MCA, MCAL50, MCAL60, SCA, SCAL50 and SCAL60) were created by the mapping of nodes from a cartesian coordinate system to a cylindrical coordinate system. The mesh densities were deemed acceptable based on the mesh sensitivity studies carried out on the equivalent straight meshes.

4.2.1.4 Stent
Two generic stent geometries are used in this study representative of different classes of commercially available stent geometries, and which are based on the Cypher closed-cell and Multi-Link open-cell commercial stents. The Cypher-like stent is
referred to as stent A and the Multi-Link-like stent is referred to as stent B. Figure 4.5 shows an illustration of the geometries of each stent design. The geometries were meshed with 3D reduced integration linear continuum elements, C3D8R, with the total mesh densities reaching approximately 200000 elements. The meshes generated were compared with published mesh densities [27,28] for similar stent designs and were deemed acceptable based on these comparisons.

4.2.1.5 Stent Delivery System

The balloon catheter and guidewire delivery system are based on designs presented in the work of Mortier et al. [28]. The guidewire has a diameter of 0.2 mm and the catheter is modelled with a diameter of 0.22 mm. The balloon in its unwrapped configuration reaches a diameter of 3 mm. The wrapping of the balloon is simulated by the method outlined in Laroche et al. [29].

In this method, the mesh configuration of the wrapped balloon is constructed by mapping the nodes of the deployed balloon onto a wrapped configuration, as illustrated in Figure 4.6. Points $P_i$ on the deployed balloon of radius $c$ are mapped onto points $\hat{P}_i$ of the folded balloon of inner radius $a$ and outer radius $b$. Points $P_i$ can be expressed in polar coordinates $(c, \theta)$ and points $\hat{P}_i$ as $(\hat{r}, \hat{\theta})$. A fold starts at point $\hat{P}_1$ and finishes at point $\hat{P}_2$, this is for a typical fold, or any one fold. The angle $\beta$ between $P_1$ and $P_2$ is calculated by the following equation

$$\beta = \frac{\phi}{2} \left( \frac{b + a + 2c}{b + a} \right)$$

where $\phi = 2\pi/n$ and $n$ is the number of folds. The angle between $\hat{P}_1$ and $\hat{P}_2$ is given by
\[ \alpha = \frac{b + a}{2c} \beta. \quad (4.2) \]

The angles and radii of points \( P_i \) are mapped onto points \( \hat{P}_i \) using the following rule:

If \( \theta \in [0, \alpha] \) then

\[ \hat{\theta} = \frac{\beta}{\phi} \theta \quad (4.3) \]

\[ \hat{r}(\hat{\theta}) = a + \frac{b - a}{\beta} \hat{\theta}. \quad (4.4) \]

If \( \theta \in [\alpha, \beta] \) then

\[ \hat{\theta} = \left( \frac{\beta - \phi}{\phi - \alpha} \right) (\phi - \theta) + \phi \quad (4.5) \]

\[ \hat{r}(\hat{\theta}) = a + \frac{b - a}{\beta - \phi} (\hat{\theta} - \phi) \quad (4.6) \]

Using the above methodology a trifoliated balloon (n=3) was generated and positioned on the catheter assembly.

4.2.2 Constitutive Models and Numerical Implementation

4.2.2.1 Non-atherosclerotic Arterial Tissue Material Model

Each layer of the arterial vessel, which consists of the intima, media and adventitia, is modelled as an anisotropic homogenous body following the model proposed by Gasser et al. [30].

This model has been shown to capture the strong stiffening effect of the collagen fibres, observed experimentally [22] within each layer at high levels of loading, which is captured by the exponential function in equation (4.9). This model has also
been shown to generate a very good correlation with experimental test data for non-atherosclerotic tissue [22].

The behaviour of each can be broken down into two terms and the strain energy potential may be written as

\[ U = U_{iso} + U_{aniso} \] (4.7)

which is the sum of an isotropic term, \( U_{iso} \), related to the matrix material of the tissue and an anisotropic term, \( U_{aniso} \), related to the embedded families of collagen fibres. The model was described in Chapter Two but the strain energy density potential is presented here again as a reminder to the reader. The isotropic and anisotropic components are defined as follows

\[ U_{iso} = \mu(I_1 - 3) \] (4.8)

\[ U_{aniso} = \frac{k_1}{2k_2} \sum_{i=1,2} \left( \exp[k_2(\kappa I_1 + (1 - 3\kappa)I_{4i} - 1)^2 - 1] \right) \] (4.9)

where \( I_1 = tr \bar{C} \) is the first invariant of the modified Cauchy-Green tensor \( \bar{C} = J^{-2/3}C \), with volume ratio \( J = (\det C)^{1/2} > 0 \) and \( C \) is the Cauchy-Green tensor, and \( I_{4i} = a_{0i} \otimes a_{0i} : C \) is a tensor invariant equal to the square of the stretch in the direction of \( a_{0i} \), as defined previously in Chapter Two. The material parameters \( k_2 \) and \( \kappa \in [0, 1/3] \) are dimensionless, whereas \( k_1 \) and \( \mu \) have the dimensions of stress.

Table 4-1 summarises the values used [31] and the uniaxial tensile responses of the individual layers, in the circumferential and axial directions, are illustrated in Figure 4.7.
A thin outer layer of shell elements is also included in the arterial models to represent the physiological environment in which an artery would be embedded. This outer layer is considered to be isotropic and to be linear elastic in terms of finite deformation strain and stress measures. It is given a Young's Modulus of $E = 50$ kPa and a Poisson's Ratio of $\nu = 0.3$ and assigned a thickness of 0.1 mm. A similar approach was applied by Harewood et al. [32] so that physiologically representative boundary conditions could be applied to the artery.

### 4.2.2.2 Atherosclerotic Arterial Tissue Material Model

The three types of plaque: cellular, being soft and fibrous, hypocellular being lipid rich and calcified, typically being very stiff, are modelled as isotropic homogenous bodies. It was assumed that they followed a third order Mooney-Rivlin hyperelastic constitutive representation. This theory was introduced in Chapter Two; the specific form of this equation is repeated here to remind the reader and is as follows

$$ U = C_{10} (I_1 - 3) + C_{01} (I_2 - 3) + C_{20} (I_1 - 3)^2 + C_{11} (I_1 - 3)(I_2 - 3) + C_{30} (I_1 - 3)^2 $$

(4.10)

where $I_1 = \text{tr}C$ and $I_2 = 0.5\{\text{tr}(C)^2 - (\text{tr}C)^2\}$ are the first and second invariants of the Cauchy-Green tensor and $C_{ij}$ are the hyperelastic constants. The hyperelastic constants used are those fitted by Pericevic et al. [33] to the experimental tensile data for each plaque type by Loree et al. [34]. These constants are given in Table 4-2 and the uniaxial tensile responses of each plaque type are illustrated in Figure 4.8.

For reference, the reader is also directed toward Figure 4.9 which gives the original stress-strain plot published by Loree et al. [34]. One can observe that in the low-strain range (0-10%) the individual data points for each category of atherosclerotic tissue are difficult to distinguish. The implications of this with regards fitting
material models and the impact on the simulation results analysis are discussed in section 4.3.3.1.

A parameter study was carried out to investigate the effect of inclusion of a yield stress on the results. From the work of Loree et al. [34], a large variation in failure stress was observed within each plaque type. For this reason a range of yield stresses was investigated to represent the wide range in physiological behaviour of the tissue. Perfect plasticity was assumed as a first approximation of damage within the tissue and also to act as a stress limiter within the region. The yield stresses investigated were 0.2, 0.4 and 0.8 MPa and the results for these are compared to the response of a pure hyperelastic atherosclerotic tissue.

The inclusion of a yield stress in the model was to limit the load carried by the atherosclerotic tissue and improve stress redistribution in the healthy arterial wall. This was assumed to be more representative of the in vivo behaviour of the vessel wall; as the load that can be supported by the diseased atherosclerotic tissue will be limited. This method is a straightforward approach at this point and a more focussed study on atherosclerotic plaque modelling will be presented in Chapter Five. Based on the substantial review of damage modelling for soft tissue, a discontinuous damage modelling approach for atherosclerotic tissue will be presented in Chapter Five. As a first step in this process the inclusion of a yield stress was deemed acceptable for the work presented in this chapter.

To facilitate the analysis and the reporting of the results, the above atherosclerotic tissue descriptions are classified as constitutive law categories: “non-linear elastic-0.2” which refers to a hyperelastic material with a yield stress of $\sigma_y=0.2$MPa; “non-linear elastic-0.4” which refers to a hyperelastic material with a yield stress of
\( \sigma_y = 0.4 \text{MPa}; \) “non-linear elastic-0.8” which refers to a hyperelastic material with a yield stress of \( \sigma_y = 0.8 \text{MPa}; \) and “hyperelastic” which is pure hyperelasticity with no plastic yield included. Within each category the percent vessel recoil, (a definition of which is given later in this chapter) of the three lesion types (cellular, hypocellular and calcified) was investigated.

4.2.2.3 Numerical Implementation: Incompressibility of Hyperelastic Materials

In modelling studies, arterial tissue is generally considered to be hyperelastic and incompressible, for examples see [31,35,36]. However in reality its behaviour can be viscoelastic (strain rate-dependent) [37] and can display compressibility [38].

In Abaqus/Standard, through the use of hybrid elements, fully incompressible materials can be modelled. In Abaqus/Explicit however, it is not possible to assume that the material is fully incompressible as the program has no mechanism for imposing such a constraint, with the exception of plane stress and uniaxial cases. As Abaqus/Explicit was the solver used in the finite element simulations presented for balloon expandable stent analyses the compressibility assumption was deemed acceptable in this context. However the extent of compressibility is investigated in this section to examine the differences in material response.

In Abaqus/Explicit, if no value of compressibility is specified by default the program assumes an initial bulk modulus, \( K_0 \), to an initial shear modulus, \( \mu_0 \), ratio, \( R \), (see equation (4.11)) of 20.

\[
R = \frac{K_0}{\mu_0}
\]  
(4.11)

\[
v = \frac{3R - 2}{6R + 2}
\]  
(4.12)
An $R$ value of 20 corresponds to a Poisson’s ratio, $\nu$, of 0.475 as given by equation (4.12). However unfilled elastomers have $R$ values in the range of 1,000 to 10,000 ($\nu = 0.4995$ to 0.49995) and filled elastomers have $R$ values in the range of 50 to 200 ($\nu = 0.490$ to 0.497), this default can therefore provide much more compressibility than is available in most elastomers.

The Abaqus documentation [25] recommends when using non-default values of the ratio, $R$, that an upper limit of 100 should be used. Larger ratios introduce high frequency noise into the dynamic solution and require the use of excessively small time increments leading to drastic increases in simulation run times. The effects of the variation of the ratio, $R$, were investigated for a third order hyperelastic polynomial material model for cellular atherosclerotic tissue, and the results are presented in section 4.3.

### 4.2.2.4 Stent Material Model

The elastic behaviour of both stents is considered to be linear and isotropic in terms of finite deformation stress and strain measures as discussed in Chapter Two, with a Young’s Modulus of $E = 200$ GPa and Poisson’s Ratio of $\nu = 0.28$. Plasticity is described by isotropic hardening $J_2$ flow theory, where the specific form of the strain hardening curve is taken from McGarry et al. [39], including a yield strength of 264 MPa and a UTS of 584 MPa at an engineering plastic strain of 0.247. Both stents are modelled as the biomedical grade stainless steel alloy 316L. This methodology is consistent with the general approach taken in the literature for stent deformation, for examples see [40–42].

### 4.2.2.5 Numerical Implementation: Damping Parameter Study

The mass proportional Rayleigh damping coefficient, $\alpha$, has been used in previous balloon expandable stent analyses [43]. This damping coefficient defines mass
proportional damping; it gives a damping contribution proportional to the mass matrix for an element. The use of this parameter means that unrealistic diameter fluctuations during the unfolding and expansion of the balloon are avoided through energy dissipation. These fluctuations can also occur in the arterial wall when the Abaqus/Explicit solver is used, due to numerical issues. To avoid this in the analysis the Rayleigh damping coefficient can be applied to the arterial wall.

A parameter study to investigate the effects of using this coefficient and to select a final value was carried out using a reduced arterial mesh (47112 C3D8R elements), with no lesion present, and a reduced stent model (one circumferential unit with 2808 elements), which was expanded by the direct pressure method. The ends of the artery were pinned in all three directions. A pressure was applied to the inner surface of the stent and three nodes on a axially central plane were constrained to prevent rotation circumferentially and translation axially (highlighted in yellow in Figure 4.10). The geometries used and the stages of expansion of the model are depicted in Figure 4.10. The inner diameter of the stent segment was expanded to 3 mm using the same pressure in all cases. Three Rayleigh damping coefficients were investigated and compared with the results for no damping in the arterial wall. The coefficients utilised were 300, 400 and 500, and the results are presented in section 4.3.

4.2.2.6 Stent Delivery System Material Models
In the balloon expandable stenting simulations, a semi-compliant nylon balloon mounted on a high density polyethylene catheter positioned using a nitinol guidewire is used. Each are modelled as behaving as linear and isotropic in terms of finite deformation stress and strain measures, similar to the approach documented in Mortier et al. [28]. The guidewire deformations are assumed to be small and
superelastic properties of nitinol are neglected. Table 4-3 summarises the elastic constants for each component. Included also in Table 4-3 is the mass proportional Rayleigh damping coefficient, $\alpha$, used for each component in the delivery system. As stated earlier, for the balloon in particular, this means that unrealistic diameter fluctuations during the inflating and unfolding of the balloon are avoided through energy dissipation.

4.2.3 Boundary Conditions & Loading

4.2.3.1 Magnitudes of Pressures used in Loading Simulations

The deployment pressures used in this work were determined by free expansion simulations (straight stent and no artery) with the condition that an inner stent diameter of 3 mm be reached. This was required so that the inner diameter of the stent would be the same as the inner diameter of the unstenosed sections of the arterial vessels, modelled later in this work.

Two methods of expansion were investigated for stent A: the direct pressure method, where a pressure was applied directly to the inner surface of the stent, and the balloon method, where a pressure was applied to the inner surface of the folded balloon. For stent A to reach a diameter of 3 mm, the direct pressure method required a pressure load of 1.44 MPa and the balloon method required a pressure load of 1.1 MPa. For stent B to reach the required 3 mm diameter a pressure load of 1.82 MPa was necessary using the balloon method.

This affords an initial comparison of the performance of both stents with stent B requiring 1.82 MPa versus Stent A requiring 1.1 MPa to reach the same level of deployment. Also noted during the free expansion simulations were foreshortening (difference in axial length of stent before and after deployment relative to
undeployed stent length) percentages for each stent and are given here as preliminary information for the reader. Predicted foreshortening for stent A is 8.3% and for stent B is 9.2%.

Stent A was deployed in all categories of the test-bed shown in Figure 4.1(b) and stent B in selected categories for comparison. The stents were positioned in the centre of the available lumen cross-section, and along the longitudinal axis.

An amplitude curve (allows arbitrary time variations of load to be applied during an analysis) was applied to all loading simulations for stent A. The amplitude curve selected was a smooth step and this curve has the form shown in the series labelled “Original” in Figure 4.11, which is defined explicitly below in equation (4.13)

\[ t_0 = 0.0, \quad \text{Amp}_0 = 0.0 \]  
\[ t_1 = 1.0, \quad \text{Amp}_1 = 1.0 \]  

For \( t_0 < t < t_1 \), \[ \text{Amp}_t = \text{Amp}_0 + (\text{Amp}_1 - \text{Amp}_0) \cdot \xi^3 \cdot (10 - 15\xi + 6\xi^2) \]  
where \( \xi = \frac{t - t_0}{t_1 - t_0} \)

where the current amplitude, \( \text{Amp}_t \), at time, \( t \), is defined by the difference between the maximum amplitude, \( \text{Amp}_1 \), and the initial amplitude, \( \text{Amp}_0 \), multiplied by the time proportionality constant, \( \xi \), as defined in equation (4.13).

For stent B a modified amplitude curve was applied as the kinetic energy was found to spike at certain stages during the free expansion simulation. To counteract the spikes in kinetic energy the loading amplitude was reduced at these points. The
modified amplitude curve is shown in blue in Figure 4.11. The modification of the amplitude curve means also that the amplitude is applied over a longer time step. This time step is 50% longer than the time step for stent A. The run time for the free expansion of stent A was approximately 12 hours on 36 CPUs. Due to the longer time step and denser mesh on stent B the run time was approximately 405 hours on 36 CPUs. Despite the longer run time, dictated by computational practicality, this approach was deemed acceptable as the stent material was modelled as rate-independent and the length of loading duration would not affect the final stress or deformation state.

The high performance computing cluster provided by ICHEC was used for the balloon expandable stent analyses. The computer accessed was an SGI Altix ICE 8200EX cluster with 320 compute nodes. Each compute node has two Intel (Westmere) Xeon E5650 hex-core processors and 24GB of RAM.

4.2.3.2 Balloon versus Pressure Deployment
In 2008, Gervaso et al. [44] published a study on different modelling deployment strategies for balloon expandable stents in a straight unstented arterial vessel. The three methods investigated were the application of pressure directly to the inner surface of the stent, the utilisation of a cylinder to expand the stent and finally the explicit inclusion of a balloon to expand the stent. They concluded that the inclusion of the balloon was the most appropriate method of expansion for their analysis. However it has not been verified that this method is most appropriate for straight stenosed vessels or for curved vessels.

To address this, the application of pressure directly, with the inclusion of an additional pressure at the ends to account for dogboning as per the work of
Harewood et al. [32], was carried out in straight and curved stenosed vessels and compared to the results of equivalent balloon expanded stenting simulations. The results of these simulations were compared in terms of lumen gain at the axial cross-section of the arterial segments and also in terms of a percent tissue damage risk indicator. The results are presented in section 4.3.

### 4.2.3.3 Bending Simulations

In order to position the stent A and B in the curved arterial vessels, a preliminary bending simulation needed to be performed. For stent A an approach similar to that of Mortier et al. [28] was utilised. In this approach the stent and balloon-catheter assembly were traversed along a rigid guidewire to position the assembly. The nodes at the ends of the balloon were tied to the mating surface of the catheter. The stent itself was constrained using beam elements at each of its crowns tying it to the nearest balloon nodes. A displacement boundary condition was then applied to the proximal end of the catheter to position the entire assembly in the curved vessel. For an illustration of the geometries and boundary conditions involved see Figure 4.12.

Due to the stiffness of the stent relative to the balloon and the motion involved in the simulation, it was found that it was necessary to increase the stiffness of the balloon tenfold for the simulations to be completed successfully. The deformed geometries of the balloon, catheter and stent were then imported into a second analysis and the stress state of the stent was also included. In this second analysis the balloon was inflated to deploy the stent in an arterial vessel. As it was only the deformed shape of the balloon and not the stress state that was of interest, the increase in Young’s Modulus for the bending simulation was deemed acceptable. The Young’s Modulus of the balloon was then returned to its original value for the stent deployment analysis.
In the case of stent B, due to numerical complexities and the increased mesh density, a second method of bending was investigated and adopted. This involved the use of the VDISP (vectorised displacement) subroutine within Abaqus. This subroutine permits the application of boundary conditions of varying magnitudes to a region of interest. In the case of stent B, it allowed the bending of the stent and balloon-catheter assembly onto an arc corresponding to the axial mid-section curvature of the arterial vessel. As before, the stress state of the stent was included in the second analysis and the deformed geometries of the assembly were also imported.

Two sets of simulations were carried out in the case of stents A and B. The first set of simulations allowed bending of the stent assemblies for the tortuosity of the moderately curved vessels and the second set allowed bending of the stent assemblies to correspond to the tortuosity of the severely curved vessels.

Stent A was deployed in all categories of the test-bed shown in Figure 4.1(b) and stent B in selected categories for comparison. The analyses were carried out in two phases in each case where deployment was in a curved arterial vessel. The first phase simulation was a bending analysis to position the stent balloon and catheter assembly into a radius of curvature that matched the artery’s radius of curvature. The first phase bending simulation was assumed to be frictionless. The second phase simulation was the deployment analyses where the balloon was inflated to expand the stent in the vessel. In the straight arteries only a deployment analysis was performed.

To allow application of appropriate boundary conditions to the arterial segments, a 10mm length of straight three layer arterial mesh was added to both ends of each arterial segment shown in Figure 4.1(b) (see Figure 4.13 for a full assembly
depiction for a severely curved case). The proximal and distal extremities of the extended arterial model were then pinned. This was to allow more representative arterial behaviour during the balloon inflation and deflation. The proximal and distal ends of the layer of shell elements surrounding the arterial vessel were also pinned. The inclusion of this layer of elements added more stability to the analyses as this material was assigned a mass proportional Rayleigh damping coefficient similar to that used for the balloon-catheter assembly components. A coefficient of friction of 0.2 was applied to all contacting surfaces during balloon inflation analyses, as per the approach of Mortier et al. [28]. Examples of the stent deployment simulations are illustrated in Figure 4.14.

The Abaqus/Explicit solver was used for the large deformation analyses with the condition that the kinetic energy of the simulation remain below 5% of the total internal energy for each analysis. Contact between all parts of the model was defined according the general contact algorithm available in Abaqus/Explicit.

4.3 Results

4.3.1 Analysis of Results

The results of this chapter are presented in two sections: the developmental study results and the arterial test-bed simulation results. From the results relating to both model development studies and the arterial test-bed simulations, the following are examined:

- The von Mises stress distribution contour plots in the healthy arterial wall
- The deformed lumen geometry post balloon deflation or removal of direct pressure
- The percent vessel recoil
• The scaffolding potential of a stent design

• The percent risk of tissue damage caused by stent placement

The second set of results from the test-bed simulations reported in this chapter are analysed in terms of the third, fourth and fifth parameters. The third is percent vessel recoil and is defined as follows

\[
\text{% Vessel Recoil} = \frac{\text{Lumen CSA}_{\text{max}} - \text{Lumen CSA}_{\text{deflation}}}{\text{Lumen CSA}_{\text{max}}} \times 100
\]  

(4.14)

where lumen CSA is the cross-sectional area of the lumen, \((\text{CSA})_{\text{max}}\) denotes the area at maximum balloon inflation and \((\text{CSA})_{\text{deflation}}\) denotes the area post balloon deflation. This parameter is used to examine the effects of changing the material response of the atherosclerotic tissue. Each measurement is taken at the axial mid-section of the vessel, where the greatest change in lumen area is observed.

The fourth parameter used is a measure of the scaffolding potential of a stent design and it compares the lumen area achieved to the reference unstenosed lumen area. This reference area is the area of an unstenosed cross-section with an inner vessel diameter of 3 mm. Figure 4.15 illustrates the relevant areas, which again are taken at the axial mid-section of the vessel.

The final parameter estimates the risk of tissue damage caused by stent placement. A straightforward stress-based approach is taken, where the von Mises stresses in each arterial layer are compared to reported UTS values [45] for each layer.

\[
\text{% Tissue Damage Risk} = \frac{\#\text{Elements exceeding UTS}_{\text{arterial layer}}}{\#\text{Elements}_{\text{arterial layer}}} \times 100
\]  

(4.15)
Equation (4.15) details the calculation of the percent tissue damage risk parameter for each arterial layer. This parameter is used as a comparative measure between stent designs deployed in the test-bed.

A second version of the tissue damage risk parameter is also considered, viz. a stretch based percent tissue damage risk, where the maximum principal stretch is compared to reported Ultimate Tensile Stretch values for each arterial layer [43]. The comparison is made in terms of logarithmic strain, i.e. computed logarithmic strain output from Abaqus, and Ultimate Tensile Stretch values from [43] converted to logarithmic strain.

4.3.2 Results from Developmental Study

4.3.2.1 Damping Parameter Study
The von Mises stress value was used as the basis for comparison of the results with the maximum value being of interest. The results of the four simulations, involving the reduced stent artery model described in section 4.2.2.5, are shown in Figure 4.16. It can be seen that the lowest maximum von Mises stress occurs in the undamped arterial model. The respective percent increases in the maximum von Mises stress in the Rayleigh damped models of 300, 400 and 500 are 6.7, 6.3 and 5.4.

This leads to the conclusion that direct inclusion of Rayleigh damping coefficient in the arterial model may lead to an artificial stiffening of the material which can result in higher predicted stresses within the tissue wall. From this study it was decided to apply no damping to the arterial wall during subsequent simulations.

4.3.2.2 Incompressibility of Hyperelastic Materials
As stated earlier in section 4.2.2.3, the Abaqus documentation recommends an upper limit of 100 to be used in analyses with non-default values of the ratio $R$. The effects
of variation of this $R$ value are shown in Figure 4.17 for the stress-strain response of atherosclerotic tissue. The material model used was the third-order hyperelastic polynomial model for a cellular type atherosclerotic tissue. For the analyses considered the recommended upper limit of 100 was used and the difference in the stress-strain response compared to a fully incompressible material was deemed acceptable (see Figure 4.17).

4.3.2.3 Balloon versus Pressure Deployment

Figure 4.18 shows the resultant lumen area expressed as a fraction of the reference lumen area for two different arterial geometries, SAL50 and SAL70, and a cellular atherosclerotic tissue type. The direct pressure expansion method failed to capture lumen gains similar to that of the balloon expansion method in straight stenosed vessels. A similar result was found in curved vessels. Figure 4.19 shows the resultant luminal shape due to both methods of expansion. It is observed that not only is the lumen gain significantly less but that vessel straightening is not captured to the same extent as the balloon expansion method.

When the tissue damage risk was calculated for each healthy arterial layer in the direct pressure analyses it was found there were no elements exceeding the respective UTS values of each tissue layer. This was in great contrast to the balloon expansion analyses where significant volumes of the tissue were predicted to be damaged (see results below).

Following these results it was decided that the direct pressure expansion method was not appropriate for the analyses as it did not capture lumen gain correctly or depict a realistic stress state within the arterial wall. Consequently, the balloon expansion method was used for the test-bed simulations.
4.3.3 Results from the Arterial Test-Bed Simulations

4.3.3.1 Plaque Constitutive Models

One important result to be established is the effect of inclusion of plasticity, in the constitutive behaviour of the atherosclerotic tissue, on the percent vessel recoil. Also to be investigated is the effect of variation of the yield stress value on the percent vessel recoil. Using a straight 50% stenosed vessel (SAL50, see Figure 4.1(b)) stent A was deployed by inflation of the tri-folded balloon which was then deflated. All four lesion constitutive law categories, for all three types of lesion, cellular, hypocellular and calcified, were investigated. Based on the findings of this, the most appropriate lesion type to include in the suite of models is established.

One of the most apparent outcomes of this study is that plasticity has a definite effect on vessel recoil for all lesion types. Overall it reduces the percent vessel recoil for all lesion types, as illustrated in Figure 4.20. Within each category of constitutive law, the stiffer lesion type exhibits higher levels of percent vessel recoil than the more compliant. Typically, calcified lesions are stiffer than hypocellular lesions, with cellular being the most compliant. The trend is similar within each category except for a yield of 0.2 MPa. This is due to the fact that the instantaneous (tangential) modulus, in the material model fit, for the calcified lesion is lower than that for the cellular lesion at low stretch, as shown in the stress-stretch curve in Pericevic et al. [33] and reproduced in Figure 4.8. If this is true of the behaviours of the calcified and cellular lesions in reality is difficult to establish due to the limited data available, please refer to Figure 4.9 which shows the original published data from work of Loree et al. [34]. As can be seen also in Figure 4.9 is the difficulty in determining the individual data points at low levels of stretch which may have had an effect on the material model fit imposed by Pericevic et al. [33].
Overall the results suggest that the actual value of lesion yield stress is not that significant, and that the introduction of plasticity at all, irrespective of the yield stress value, is the dominant factor. Specifically, the variation in percent vessel recoil for all of the cases shown in Figure 4.20 is between 6.9 and 20.7%, whereas when the plasticity cases alone are considered, irrespective of the value of the yield stress, the variation is only in the range 6.9 to 12.5%. The grey arrows in Figure 4.20 indicate these ranges.

Based on the above, to proceed with the remainder of the analyses, the yield was chosen to be 0.4 MPa and a cellular type plaque was chosen. The reason for this is two-fold. Firstly at this value of yield the vessel recoil is similar for all three plaque types, and secondly a cellular type plaque is the most homogenous physiologically so one can justify its selection as most appropriate for a homogenous material description.

4.3.3.2 Scaffolding Assessment
For each stent design a comparison of scaffolding potential was made using the test-bed, where the scaffolding potential is indicated by the lumen area, achieved at maximum balloon inflation and after balloon deflation, relative to the reference unstenosed lumen area. Figure 4.21 shows the scaffolding potential of stent A for all nine arterial geometries (see Figure 4.1). It can be seen that the level of stenosis has a definite effect on the lumen area achieved by stent A and that it also affects the level of recoil of the device after balloon deflation. The recoil of the device is indicated by the difference in the heights of the solid columns relative to their respective hatched columns.
It should be noted in Figure 4.21 that there is slight over-inflation of the unstenosed vessels, and of the 50% stenosed vessels at maximum inflation. This is due to the nature of the loading conditions, which were determined, as described above, to ensure that the inner diameter of the stent reaches 3 mm to be the same as the reference diameter of the arterial vessel. For the 60% stenosed vessels, the reference lumen area is almost reached at maximum balloon inflation but after balloon inflation significant recoil of the device occurs at all levels of curvature.

Results for the comparison of the scaffolding potential of stent A and stent B in selected arterial models are shown in Figure 4.22 and Figure 4.23. These arterial models were chosen to show the effect of varying the level of curvature for no stenosis and the most severe level of stenosis. A stenosis level of 60% was selected as this is when the scaffolding potential is most affected, as shown in Figure 4.21.

In Figure 4.22 it can be seen that the scaffolding results for stent A and stent B are very similar in both straight and severely curved vessels. This is true at both maximum balloon inflation and post balloon deflation. In the severely curved unstenosed case stent B reaches a slightly higher lumen area than stent A.

In Figure 4.23, for the straight 60% stenosed vessel the scaffolding results for both designs are similar at maximum balloon inflation and after balloon deflation. In the severely curved 60% stenosed vessel the scaffolding results are similar at maximum balloon deflation but with less recoil observed in stent B post balloon deflation. This would suggest that the level of curvature in the arterial segment does not have a major effect on stent A but its effect is somewhat more noticeable in the case of stent B, in particular in a severely curved severely stenosed region.
This implies that there is a very weak dependence on curvature in the analyses overall. However, for the case when a stenosis is present there does appear to be stent design dependence.

4.3.3.3 Predicted Tissue Damage Risk
The stresses due to implantation of each stent design were analysed in each arterial layer and compared to that of reported UTS values [45] of each layer, with the results interpreted in terms of the tissue damage risk parameter defined above. For stent A the tissue damage risk results for all three arterial layers in the straight vessels are shown in Figure 4.24. The unstenosed vessel has a tissue damage risk of 80% for the intimal layer only, whereas the stenosed vessels have predicted tissue damage throughout all three layers.

The maximum principal stretches, at maximum balloon inflation, in each arterial layer due to the implantation of stent A were also compared with Ultimate Tensile Stretch values for each arterial layer, in terms of the stretch based percent tissue damage risk defined above. Figure 4.25 shows the tissue damage risk results based on the stretch comparison for each arterial layer for the straight vessels in the test-bed due to implantation of stent A.

Comparing Figure 4.24 and Figure 4.25, the most significant observation is that both approaches do indicate a risk of tissue damage, although there are certain differences in the details of the predictions, as would be expected due to the differences in the formulations. For example, no predicted tissue damage occurs in the intimal layer of the unstenosed vessel in the stretch based analysis compared to the stress based analysis. However, for the arguably more realistic situations where stenoses are present, similar trends are observed in tissue damage risk prediction; in particular,
and significantly, both the intimal and medial layers are predicated to be at greater risk for 60% stenosis in comparison to 50% stenosis (the SAL50 and SAL60 models (see Figure 4.1(b)). Due primarily to the ability of the currently implemented stress based approach to capture stress-state multi-axiality, and the broadly similar tissue damage risk prediction of the two approaches, it was decided to implement a stress based analysis for assessing tissue damage risk in the remainder of the thesis. This is further discussed in Section 4.4.2.

Figure 4.26 shows the tissue damage risk results for each arterial layer for the straight vessels due to implantation of stent B. The unstenosed vessels show a slightly lower tissue damage risk of 71% for the intimal layer only (as compared to deployment of stent A in the same vessel), whereas again the stenosed vessels have predicted tissue damage throughout all three layers. Interestingly, stent B implantation generates a tissue damage risk of 57% in the intimal layer in SAL50 (see Figure 4.1(b)) compared to the 39% for stent A in the same vessel. However in a straight 60% stenosed vessel (SAL60 - see Figure 4.1(b)) stent B performs better than stent A, with a tissue damage risk of 65% versus the 72% intimal tissue damage risk for stent A.

Figure 4.27 and Figure 4.28 show the predicted distribution of equivalent plastic strain within the lesion material in SAL50 and SAL60 respectively. The top panels in each show the response due to inflation of stent A and the bottom panels show the response due to inflation of stent B. In SAL50, more regions of high plastic strain are developed due to implantation of stent B than stent A; whereas in SAL60 there are slightly more regions of high plastic strain due to implantation of stent A than stent B. This is in agreement with the tissue damage risk results for the intimal layer due to implantation of stents A and B in the 50% and 60% stenosed vessels. These results
would appear to indicate that the stenosis level may interact strongly with the stent design to generate the arterial stress state during deployment, and consequently stenosis level may be a very important parameter in stent selection.

**4.4 Discussion & Conclusions**

**4.4.1 Discussion on Developmental Study Results**

The initial section of the work presented in this chapter was dedicated to performing mesh sensitivity analyses, investigating the effects of various material parameters on the analyses, and examining the different deployment methodologies for stent expansion in stenosed and curved vessels.

It was found that an arterial mesh density of over 130,000 elements for the SAL50 model was necessary to reach a converged solution. This lead to an increased run time of the analyses but with access to the high performance computing cluster provided by ICHEC this was manageable.

The effect of inclusion of a damping parameter on the arterial wall was next investigated. It was concluded that the utilisation of this damping coefficient lead to an artificially high increase in the stiffness of the arterial wall and was hence excluded from further simulations.

With the use of the Abaqus/Explicit solver for the simulations the effect of compressibility in the soft tissue material models was investigated. As the Abaqus/Explicit solver cannot model a completely incompressible material this was deemed necessary. It was shown that the recommended upper limit of the ratio, $R$, of 100 gave a significant improvement over the default value of 20. It decided that it was an acceptable approach for modelling the near incompressibility of the arterial wall.
Finally, as stated earlier, Gervaso et al. [44] investigated the effects of different deployment strategies for balloon expandable stents in straight unstenosed vessels. This was further investigated in this work for stenosed vessels and curved vessels. Based on the results for the tissue damage risk indicator and the scaffolding potential, it was concluded that the direct pressure method was not appropriate for modelling balloon expandable stents in stenosed vessels and also in curved vessels. This is in agreement with the findings of Gervaso for straight unstenosed vessels.

The findings from the developmental studies were then applied to the full balloon stent artery simulations presented as the computational test-bed framework results.

4.4.2 Discussion on Arterial Test-Bed Simulations
One of the main objectives of the present study was to examine the mechanical behaviour of two generic stent designs during their implantation in purposefully selected arterial geometries, that form a comprehensive computational test-bed, with a view to getting a more generally representative characterisation of the arterial stress state due to stent implantation than has been reported to date, and this has been presented.

A motivation of the work presented in this chapter was the need to investigate the degree of specificity of the blood vessel geometry in the stent stress analyses of the FDA guidelines. The current guidelines [17] for stent analyses recommend a 15 mm radius of curvature for coronary applications. This curvature is much less than the moderately curved (radius of curvature, 12.85 mm) and severely curved (radius of curvature, 8 mm) vessels used in the test-bed. The results presented here are interesting in that they indicate that these more severe conditions do not have a significant effect on the implantation behaviour for both of the generic stent designs.
considered, at least in terms of the performance measures considered. However, this may not be true of all stent designs so the author believes that it is important to adhere to the guidelines as a minimum to examine curvature effects for any new designs.

Another motivation for this work was the need to generate a practical computational framework capable of assessing stent performance in a range of population-specific categories. Previous research in the area of personalised medicine and stenting has focussed on using patient specific arterial geometries for computationally deploying stents. This research is significant but does not capture the effects of stent deployment in population-specific categories. A computational framework capable of this assessment has been presented here. It is accepted of course that the computational framework in overall terms is only useful as part of a process that includes experimental analysis to generate any final conclusions on the performance of an engineering design.

One of the major observations of the present study is that the level of stenosis present in an arterial segment has a significant effect on the scaffolding potential of a stent design, and also on the tissue damage risk for the plaque itself and for the surrounding arterial tissue. It is shown that increasing the level of stenosis increases the intimal tissue damage risk, as highlighted in Figure 4.24 and Figure 4.26. The two generic stent designs modelled are shown to have similar scaffolding potential at each level of stenosis but the tissue damage risk is different for both at each level of stenosis, with stent A inducing less damage in a SAL50 but stent B inducing less damage in SAL60. This leads to the suggestion that stenosis level could be a critical parameter in stent selection for the clinician. It should be emphasised that the tissue damage risk, as defined here based on a straightforward critical stress criterion, is
used purely as a means of comparing the predicted arterial stress states generated by
different stents, and consequently comparing different stent behaviours. However, it
is not a direct quantification of actual in vivo physiological tissue damage due to
angioplasty, which will depend on a range of in vivo environmental factors. It is also
important to emphasise that high arterial stresses due to stent deployment have been
predicted many times previously in the literature (e.g. [33,46]) and arterial wall
stresses have been associated with the formation of neointimal hyperplasia and in-
stent restenosis [47].

As described above, a stretch based approach to assess predicted tissue damage risk
was also considered. The stretch based approach compares the maximum principal
stretch with Ultimate Tensile Stretch. The comparison of the stress and stretch based
approaches to tissue damage risk prediction generated interesting results (in terms of
the test cases considered: straight arteries with varying degrees of stenosis).
Fundamentally, both approaches indicate a risk of tissue damage for a stented artery,
and are broadly consistent in terms of the assessment of the effects of stenosis level;
in particular both indicate that a 60% stenosis is at higher risk than a 50% stenosis
for the intimal and medial layers (see Figure 4.24 and Figure 4.25). Certainly there
are some differences in the details of the predictions that are due to the differences in
the respective formulations. For example, the stretch based approach does not predict
tissue damage for the intimal layer for the unstenosed artery; however this is
arguably not that significant a result as an unstenosed artery is unlikely to be stented
anyway and such cases are included in this thesis primarily for comparison purposes.
One interesting result is the relatively high tissue damage risk predicted for both the
media layer and the intimal layer using the stretch based approach, in comparison to
the stress based approach. This would indicate the need for future experimental
studies to establish damage accurate limits and failure points (in terms of both strains and stresses) for arterial tissue, in order to enhance the reliability and usefulness of the computational test-bed developed here.

One advantage of the stretch based approach in the context of the present work is that, fundamentally, strains are easier to measure experimentally than stresses, and it might be possible for example to infer critical stretch/strain levels directly from medical image data of arteries undergoing deformation and rupture [48]. One advantage of the stress based approach, when using the von Mises stress, in terms of simplicity of application and implementation, is that the multi-axiality of the stress state, including both tensile and compressive stresses, is naturally incorporated into a single scalar quantity (the von Mises stress). By contrast, a critical principal stress, or indeed strain, approach would potentially require a different damage/failure criterion to be developed and implemented for local tensile vs. compressive loading of the tissue. One potential disadvantage of using the von Mises stress is that it was originally developed for metal plasticity and so there is always a question mark over its applicability for soft tissue deformation.

Notwithstanding the above, given that both the stress and stretch based approaches as implemented here give broadly similar predictions, and that the use of a von Mises stress based approach is consistent with other reported studies (e.g. Pericevic et al. [33]), it was decided to implement a stress based (von Mises) tissue damage risk assessment for the remainder of this work.

Surprisingly, the level of curvature present in an arterial segment does not appear to have a significant effect on the implantation behaviour of stent A. However the open cell design of stent B performs slightly better in a curved stenosed vessel, in terms of
lower recoil. This may indicate that, as regards scaffolding potential, the open cell type design maybe more suitable for use in a tortuous vessel.

Also investigated was the effect of the inclusion and variation of plasticity within the atherosclerotic tissue. The inclusion of plasticity has a significant effect on vessel recoil for all three types of lesion tested. It is shown that the stiffer the material the greater the vessel recoil, which is not surprising. It can be explained by the fact that, for a given radial deformation, a stiffer lesion has a greater circumferential stress and hence on load removal, in this case balloon deflation, there is a greater tendency for stent recoil. However it is also observed that the actual value of the yield stress chosen, once within the range of 0.2 – 0.8 MPa, is not that significant. This could be because once permanent deformation occurs elastic deformation is limited and hence the tendency of the vessel to recoil is reduced.

Also to be considered are the limitations of this work. One limitation is the representation of the lesion in the analyses as a homogenous continuum when in reality atherosclerotic tissue is highly heterogeneous. Improvement of the work could be achieved through explicit representation of the individual components of plaque such as the fibrous cap, lipid rich necrotic core and calcifications. However, as the focus of the work was a generic population specific test-bed, the use of a homogenous type plaque was considered acceptable. A second limitation is the simplified assumption of damage within the atherosclerotic tissue through the application of perfect plasticity. A more advanced constitutive model that incorporates damage within this region is needed, however experimental data for such behaviour is lacking. Also predicted from the analyses is the tissue damage risk in the individual arterial layers but this is not directly coupled with the arterial layer constitutive law in terms of the inducement of softening. Again experimental data for
the response of arterial layers to high levels of loading is lacking and as such a 
constitutive model for the damage response cannot yet be complete without this data. 
The effects of arterial pre-stretch, residual stresses, specific stent positioning and 
luminal blood pressure were not considered in these analyses.

In conclusion, the results presented in this chapter show that computational 
modelling is a very useful tool in predictive analyses of coronary stent behaviour and 
can allow for direct comparison to be made between stent designs in a controlled 
environment. A practical computational framework has been presented that varies 
stenosis level and arterial curvature. It is found that the presence of a stenosis and the 
variation of this stenosis level have a significant effect on the stress induced in the 
underlying arterial tissue and also on the ability of the stent to maintain the lumen 
cross-sectional area. Moreover, it is found that the scaffolding potential of a given 
design is affected by the level of curvature in an arterial segment; though this is very 
much a design dependent effect.

In the current FDA guidelines there is no specific requirement to include a stenosis 
or to vary its presence in computational simulations of stent deployment. However 
from the results of this study the following is recommended:

- In the representation of the arterial environment to be stented, a stenosis 
  should be included for a more accurate depiction of the in vivo setting.

- Stent performance should be investigated for a range of stenoses, to see if 
  there is an optimum design for a given stenosis level.

- Vessel curvature should be included in the analyses, adhering to the 
guidelines as a minimum.
As stated previously, one of the major limitations of the work was the representation of the atherosclerotic tissue material. The work presented in the forthcoming chapter will aim to deal with these limitations through the inclusion of a damage model for the atherosclerotic tissue material and also include explicit representation of the various components of this tissue, such as calcifications and a lipid pool.
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<th>( k_2 ) (-)</th>
<th>( \Phi ) (°)</th>
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Table 4-3  Elastic constants, $E$ and $v$, mass proportional damping factor, $\alpha$, characterising the behaviour of stent and delivery system

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<td>Stent</td>
<td>200,000</td>
<td>0.28</td>
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Figure 4.1 Schematic of actual geometries used in computational test bed; a) calculation of Tortuosity Index (TI), b) test bed geometries with respective Tortuosity Indices and insert showing mesh density.
Figure 4.2 Angiogram images of an arterial vessel pre- and post-stenting, showing calculation of curvature, angulation and tortuosity indices (adapted from [21]).
Figure 4.3 Use of partitioning to create structured mesh. A) Front View of partitioned geometry, B) Iso View of partitioned geometry with some layers removed, C) Resultant Hexahedral Mesh.
Figure 4.4  
Mesh sensitivity results for three hexahedral meshes, HX3, HX6 and HX9, increasing in element density from top to bottom. Contour plot shows von Mises stress distribution due to a pressure expanded stent.
Figure 4.5  Geometries of the closed cell Stent A and the open cell Stent B. Full stent and segment of pattern to illustrate the structure are shown in each case.

Figure 4.6  Cross-section of balloon showing mapping of points from deployed configuration to wrapped configuration according to method outlined by Laroche et al. [29].
Figure 4.7  Uniaxial tensile stress-stretch responses of individual arterial layers in the circumferential (Circ) and axial directions, coefficients taken from [31].
Figure 4.8  Uniaxial tensile stress-stretch response of different atherosclerotic tissue materials, reproduced from [33].

Figure 4.9  Original stress-strain data for uniaxial tensile testing of different categories of atherosclerotic plaque [34].
Figure 4.10  Stages of deployment in model used for damping parameter study.
Figure 4.11 Amplitude curves applied to loading of stent B. The "Original" smooth step function is shown in the dashed red line and the “Modified” smooth step function is shown in the solid blue line.
Figure 4.12  Bending simulation results for stent A being traversed along a rigid guidewire, to suit the tortuosity of a moderately curved vessel. Insert shows schematic of location of beam elements at the crown of stent A.
Figure 4.13 Various stages of bending stent A balloon catheter assembly along guidewire, full arterial model geometries also shown.
Figure 4.14 Stages of implantation of stent A in 60% stenosed vessels; A: Pre-deployment, B: Mid-deployment, C: Full deployment, D: Final configuration. Section X-X shows where cross-sectional areas are measured.
Figure 4.15  Illustration of A: Reference unstenosed lumen area; B: Unstented lumen area; C: Final stented lumen area. Cross-sectional areas are taken at the mid-section of the vessel.

Figure 4.16  von Mises stress distribution for different applied damping values, inserts show increases in stress compared to undamped arterial segment.
Figure 4.17  
Stress strain plots for variation in bulk to shear modulus ratio, $R$.  

Figure 4.18 Resultant lumen area as a fraction of reference lumen area at axial mid-section of arterial segments for direct pressure deployment strategy and balloon deployment strategy, in straight stenosed vessels.
Figure 4.19 Comparison of resulting luminal curvatures due to expansion of stent A in a moderately curved 50% stenosed vessel by two methods, direct pressure method shown in the black dashed line and explicit balloon modelling method shown in the solid red line.
Figure 4.20  Effect of changing the atherosclerotic tissue yield stress on vessel recoil using 50% stenosed straight vessel, and stent A. Results for all four constitutive law categories, and three lesion types, are shown. Ranges for variation in constitutive law are shown by the grey arrows.
Figure 4.21  Stent A: Resultant lumen area as a fraction of reference lumen area (see Figure 4.15) at mid section of vessels with varying stenosis level. Solid columns indicate results at point of maximum balloon inflation and hatched columns indicate vessel response after balloon deflation.
Figure 4.22 Comparison between resultant lumen area as a fraction of reference lumen area (see Figure 4.15) for stent A and B at mid section of unstenosed vessels with varying curvature level. Solid columns indicate results at point of maximum balloon deployment and hatched columns indicate vessel response after recoil of balloon.
Comparison between resultant lumen area as a fraction of reference lumen area (see Figure 4.15) for stent A and B at mid section of 60% stenosed vessels with varying curvature level. Solid columns indicate results at point of maximum balloon deployment and hatched columns indicate vessel response after recoil of balloon.
Figure 4.24 Predicted tissue damage risk for individual arterial layers in straight vessels due to implantation of stent A; based on comparison of von Mises stress with UTS of individual arterial layers.
Figure 4.25 Predicted tissue damage risk for individual arterial layers in straight vessels due to implantation of stent A, using a stretch based approach; based on comparison of maximum principal stretch with ultimate tensile stretch of individual arterial layers. Asterisks indicate zero values of relevant terms.
Figure 4.26 Predicted tissue damage risk for individual arterial layers in straight vessels due to implantation stent B; based on comparison of von Mises stress with UTS of individual arterial layers.
Figure 4.27 Distribution of PEEQ in a 50% stenosed straight vessel at maximum balloon inflation for both stent designs.

Figure 4.28 Distribution of PEEQ in a 60% stenosed straight vessel at maximum balloon inflation for both stent designs.
5 Atherosclerotic Plaque Modelling for Stenting Applications

5.1 Introduction

Atherosclerotic tissue is highly heterogeneous and can be comprised of a lipid core, calcifications, cellular debris, and fibrous tissue. However, its representation computationally in stenting simulations has often been as a homogenous continuum; apart from the work of Holzapfel et al. [1], where the properties of the calcification and lipid were estimated, and the work of García et al. [2] where again the properties of the calcification and lipid were estimated. An example of a histological cross-section of a diseased arterial vessel is shown in Figure 5.1 [3] and the variation in tissue content within the diseased atherosclerotic region is apparent. A homogenous representation of atherosclerotic tissue is by far the most common assumption used in arterial computational models in general, and in particular in arterial models used in stenting analyses, for examples see [4–6].

In conjunction with geometrical simplifications, the behaviour of atherosclerotic tissue is generally considered as hyperelastic and that it follows the low loading regime (representative of physiological loading that exerts relatively low stresses and strains on tissue in comparison to device implantation) behaviour, despite the fact that loading due to stent placement introduces supra-physiological forces within the tissue.

This computational simplicity is based on the fact that there is currently a dearth of experimental data for the properties of atherosclerotic tissue as discussed in Chapter Three. The limited data that exists deals mostly with the behaviour of the tissue in the physiological loading range and most of this is for tissue tested as a continuum with little information on its constituents, apart from the work of Ebenstein et al. [7]
who used nanoindentation to investigate the mechanical properties of the individual constituents in the physiological domain. However due to the nature of the loading, in the work of Ebenstein et al. [7] the mechanical properties determined are related to linear elasticity which may be appropriate for a very stiff calcified particle but is not representative for softer tissue, knowing the non-linearity, in terms of the stress-strain relationship, associated with the rest of the arterial wall.

The primary aim of this chapter is to investigate the level of detail that is appropriate when modelling atherosclerotic tissue response to stenting. An additional motivation is to provide recommendations to the FDA for the stress-strain analysis section of their guideline document on non-clinical engineering tests for coronary stents [8] for modelling the physiological environment.

The focus of this work thus far has been the computational modelling of the direct stenting procedure, however the standard stent implantation technique often involves predilation with a balloon to open the blocked vessel and facilitate passage and positioning of the stent [9]. Also presented in this chapter is a study on the effect of variation of the material models for atherosclerotic tissue, for two-phase expansion simulations – where the stenosed vessel is inflated and re-inflated with a stent to represent this predilation technique. Recommendations on the direct stenting approach versus the predilation technique are then given.

A 50% stenosed three layer arterial model is used as a basis for the analyses. Atherosclerotic tissue is varied from being a homogenous continuum to having a lipid rich core, to also having diffuse calcifications throughout. Several material models are also investigated as the base atherosclerotic tissue matrix in the analyses. This includes applying different elastic models to describe the physiological
response and then including damage models which account for the response of the tissue to supra-physiological loading (high non-physiological loads).

For the two-phase expansion simulations, a very stiff cylinder is used to expand the 50% stenosed straight arterial vessel; it is then retracted and deployed again, with a stent inflated on the second deployment. The effect of inclusion of the Mullins effect within the atherosclerotic tissue material model is then discussed.

In summary, this chapter explores the direct stenting technique versus the predilation technique, the effects of variation of the material model for the atherosclerotic tissue matrix, the effects of inclusion of calcifications and a lipid pool and finally the effects of inclusion of the Mullins effect on the atherosclerotic tissue matrix in stenting applications.

5.2 Materials & Methods

5.2.1 Geometry & Meshes

For the analyses, the 50% stenosed three layer arterial model geometry, SAL50, (please refer to Figure 4.1-b in Chapter Four) is used. To recap, this geometry consists of a 0.5 mm thick healthy arterial wall equally divided into three layers representing the intima, media and adventitia. The stenosis is considered semi-ellipsoidal in shape and blocks 50% of the available lumen by area, at the maximum axial cross-section. Each section was meshed with 3D reduced integration linear continuum hexahedral elements, C3D8R. The mesh consisted of 130064 elements for the SAL50 geometry. A thin outer layer of shell elements, S4R, is also included in the arterial models to represent the physiological environment in which an artery would be embedded.
To examine the response of inhomogeneous atherosclerotic tissue to stenting, two further modifications are included in the SAL50 model. The first is the inclusion of a lipid pool section as shown in Figure 5.2 and the second is the inclusion of diffuse calcified particles as shown in Figure 5.3. The volume of lipid included represents 9.3% of the total atherosclerotic tissue volume. The calcified particles are randomly distributed in the atherosclerotic bulk as shown in Figure 5.3. The assignment of calcified regions is performed using a python script (Appendix A). The 630 calcified particles represent 0.5% of the total atherosclerotic tissue volume and the volume of a single particle is approximately 0.0002 mm$^3$. To allow assignment of the calcified regions the element size had to be reduced to represent an individual calcified particle. The inclusion of diffuse calcified particles requires a significant increase in mesh density and this mesh consisted of 726958 elements. The resulting mesh density was deemed acceptable within the confines of computational practicality.

A generic stent geometry is used in this study that is representative of the Cypher closed-cell stent, as described previously in Chapter Four. As a reminder to the reader, the mesh generated was compared with published mesh densities [10,11] for similar stent designs and was deemed acceptable based on these comparisons. As described previously in Chapter Four, the balloon catheter and guidewire delivery system are based on designs presented in the work of Mortier et al. [11]. The guidewire has a diameter of 0.2 mm and the catheter is modelled with a diameter of 0.22 mm. The balloon in its unwrapped configuration reaches a diameter of 3 mm. The wrapping of the balloon is simulated by the method outlined in Laroche et al. [12].
To investigate the effects of the choice of atherosclerotic tissue constitutive theory on a two-phase expansion, a stiff tube, meshed with 6580 shell elements, is also modelled. The purpose of the stiff tube is to simplify the balloon deployment simulation, using the tube to expand the stent instead of the balloon. This also allows a comparison with a two-phase deployment simulation with the tube inflated and deflated twice.

5.2.2 Constitutive Models

As before, each layer of the healthy arterial wall is considered anisotropic and the model proposed by Gasser et al. [13] is applied. The same material parameters are applied as listed in Table 4.1 of Chapter Four. The thin outer layer of shell elements is considered to be isotropic and to be linear elastic in terms of finite deformation strain and stress measures. It has a Young's Modulus of $E = 50 \text{kPa}$ and a Poisson's Ratio of $\nu = 0.3$ and has a thickness of 0.1 mm. As described in Chapter Four, a similar approach was applied by Harewood et al. [14] so that physiologically representative boundary conditions could be applied to the artery.

For the atherosclerotic tissue several material models are investigated. The first approach utilises the polynomial hyperelastic form published by Pericevic et al. [4], which is based on the tensile testing response of atherosclerotic tissue carried out by Loree et al. [15] in 1994. The second approach utilises the data published by Maher et al. [16], which resulted from the testing of atherosclerotic tissue in compression. A first order Ogden model was fitted to this compressive test data. The third approach combined the Loree tensile data [15] with the Maher compressive data [16] to fit a sixth order Ogden model describing the response of the tissue in tension and compression. Figure 5.4 shows the uniaxial responses of the three models in tension and compression.
The polynomial model fit in Figure 5.4 shows that the tissue is quite stiff in tension and also in compression. However, as this tissue was only tested in tension [15] it is unknown if the compressive response should be as stiff. The first order Ogden model is very soft in compression and also in tension. However, as this tissue was only tested in compression [16] it is unknown if the tensile response should be as soft. As a compromise between the two sets of data, the sixth order Ogden was fit to the soft compressive data [16] and stiff tensile data [15] to produce the resulting fit in Figure 5.4. For clarity, the reader is referred to Figure 5.5 where the three material models are plotted separately and the stress responses in tension (+) and compression (−) are indicated.

The three approaches described only give the response of the tissue to physiological loading. However the implantation of a stent introduces supra-physiological forces within the tissue. To account for this, the elasticity models are combined with different damage modelling approaches to describe the behaviour of the tissue in the supra-physiological domain. The polynomial model is combined with a perfect plasticity model, as per the approach of Gastaldi et al. [5], and as used in Chapter Four, to limit the stresses supported by the atherosclerotic tissue, and a yield stress of 0.4 MPa was assumed. The compressive data published by Maher et al. [16] gave the cyclic response of the tissue to loading. In that paper the authors fitted their own damage model to capture the stress softening and permanent set observed within the tissue during loading. Here, using the cyclic response data [16] the Mullins effect model is calibrated to the Maher data and combined with the Ogden first order model. A similar procedure is carried out for the Ogden sixth order model. The response of the Ogden models to strain controlled cyclic loading is illustrated graphically in Figure 5.6. In this figure the materials models are stretched to 50%
and 60% strain in tension and compressed by 50% and 60% strain in compression, as shown in the insert. The response of the polynomial with perfect plasticity to monotonic loading is also shown and a stress plateau on loading can be observed in tension and in compression. The responses of the Ogden models (N=1 and N=6) combined with the Mullins effect show that the unloading path differs from the loading path in tension and in compression.

To fit the Mullins effect damage model the material response to cyclic strain controlled loading is required. In the data of Loree et al. [15] only monotonic loading was performed. This means that the resulting polynomial model could not be combined with the Mullins effect. As cyclic strain control loading data was available for the Maher data [16] the Mullins effect model could be applied to the Ogden models. However due to the general softness of these models (for both models in compression, and in tension for the first order Ogden model), where stresses lower than the assumed plastic yield stress (0.4 MPa) would be experienced for the most part during loading, it was decided not to include the perfect plasticity assumption in these models.

The calcifications are considered to be isotropic and to be linear elastic in terms of finite deformation strain and stress measures. They have a Young's Modulus of $E = 1\text{GPa}$ and a Poisson's Ratio of $\nu = 0.3$. The stiffness of the particles is taken from the experimental data of Ebenstein et al. [7] using the calculated Young’s Modulus derived from the indentation unloading curves. The lipid pool is considered to be isotropic, to behave as a very soft solid and is modelled using the same approach as Holzapfel et al. [1]. It is modelled using the isotropic portion of the material model proposed by Gasser et al. [13] and is assigned a $\mu$ of 0.05 kPa. The reader is referred to Chapter Two (Equation 2.22) for a reminder of its formulation.
The stiff tube modelled in the two-phase expansion simulations is modelled as elastic and has a Young’s Modulus of 200 GPa and a Poisson’s Ratio of 0.3.

As described previously in Chapter Four, the elastic behaviour of the stent is considered to be linear and isotropic in terms of finite deformation stress and strain measures as discussed in Chapter Two, with a Young’s Modulus of $E = 200$ GPa and Poisson’s Ratio of $\nu = 0.28$. Plasticity is described by isotropic hardening $J_2$ flow theory, where the specific form of the strain hardening curve is taken from McGarry et al. [17], including a yield strength of 264 MPa and a UTS of 584 MPa at an engineering plastic strain of 0.247. The stent is modelled as the biomedical grade stainless steel alloy 316L. This methodology is consistent with the general approach taken in the literature for stent deformation, for examples see [18–20].

In the balloon expandable stenting simulations, a semi-compliant nylon balloon mounted on a high density polyethylene catheter positioned using a nitinol guidewire is used. As described previously in Chapter Four, each are modelled as behaving as linear and isotropic in terms of finite deformation stress and strain measures, similar to the approach documented in Mortier et al. [11]. The guidewire deformations are assumed to be small and superelastic properties of nitinol are neglected. Table 4-3 of Chapter Four summarises the elastic constants for each component. Included also in Table 4-3 is the mass proportional Rayleigh damping coefficient, $\alpha$, used for each component in the delivery system. As stated earlier, for the balloon in particular, this means that unrealistic diameter fluctuations during the inflating and unfolding of the balloon are avoided through energy dissipation.
5.2.3 Boundary Conditions & Loading

To allow application of appropriate boundary conditions to the arterial segments, a 10 mm length of straight three layer arterial mesh is added to both ends of each arterial segment, as described previously in Chapter Four. The proximal and distal extremities of the extended arterial model are then pinned. This is to allow for more representative arterial behaviour during the balloon inflation and deflation. The proximal and distal ends of the layer of shell elements surrounding the arterial vessel are also pinned. The inclusion of this layer of elements adds more stability to the analyses as this material is assigned a mass proportional Rayleigh damping coefficient similar to that used for the balloon-catheter assembly components. A coefficient of friction of 0.2 is applied to all contacting surfaces during deployment analyses, as per the approach of Mortier et al. [11]. As described previously (Chapter Four) the pressure applied to the inner surface of the folded balloon is 1.1 MPa which was determined from a free expansion simulation.

For the two-phase expansion simulations, a uniform radial displacement is applied to all nodes of the stiff tube. All other degrees of freedom are fully constrained. The amplitude curve applied to the radial displacement of the nodes is shown in Figure 5.7. The tube is expanded first, with contact between the stent and tube switched off for the first inflation. The tube is then deflated and re-inflated, with contact between the stent and tube switched on for the second inflation. The tube is then deflated leaving the stent in place as a scaffold for the artery. Its purpose is to observe the effects of inclusion of the Mullins effect on the atherosclerotic tissue response. For this reason the maximum amplitude of the second loading cycle is 10% higher than the first loading cycle for the Mullins effect to become active. For comparison, two-phase expansion simulations are performed with the tube only to compare with the
two-phase stent expansion simulations. An illustration of the two-phase expansion of a stent is shown in Figure 5.8.

5.3 Results

5.3.1 Analysis of Results

The use of computational modelling gives great insight into the predicted behaviour of tissue and implants *in vivo*, once the input parameters are realistic and representative. But once the simulation has run there are many evaluated quantities to be considered. For the simulations presented in this section of the work, it was decided to look in detail at the deformed lumen shape as this can show how the tissue is responding to the stent and also how the stent is performing as a scaffold. To examine the deformed lumen shape a python script (Appendix B) was utilised which calculated the lumen cross-sectional area based on the deformed nodal coordinates in the Abaqus output data for each circumferential path along the length of the lesion. For each material model investigated the lumen cross-sectional area along the length of the atherosclerotic tissue is plotted. To compare each model in general, an average lumen cross-sectional area is calculated and compared with the reference lumen area. All the above are evaluated at two time points for each model, at maximum balloon inflation and post balloon deflation.

The second measurement of interest is the stress state in the healthy arterial wall. The variation of the constitutive behaviour of the atherosclerotic tissue has an effect on the stresses transferred to the healthy arterial wall. The percent tissue damage risk (as defined in Chapter Four) is calculated in each healthy arterial layer for each variation in constitutive model. To recap, this value shows the proportion of elements
exceeding reported UTS values for each arterial layer compared to the total number of elements.

Finally, the third measure of interest is the stress state in the diseased atherosclerotic tissue and for this several sets of stress contour plots were examined at two time points, maximum balloon inflation and post deflation.

Also to be mentioned are the simulation run times for these analyses. These were on the order of 400 CPU hours each, and the run time more than doubled when the mesh density was increased to include calcifications in the analyses. Also the number of runs required was significant due to the number of variables involved in the parameter studies. This also included significant numbers of development and trial simulations to generate working models, given the complexity of the analyses performed.

5.3.2 Direct Stenting Analyses

In the forthcoming sections, the results for lumen cross-sectional area measurement, predicted tissue damage risk and stress state in the diseased tissue will be presented for the direct stenting analyses. These simulations are performed with deployment of the stent via balloon inflation.

Several parameters are varied during the simulations. The response of the tissue is examined when a lipid pool and calcifications are included in the analyses and the inclusion of supra-physiological loading response is investigated. Then the base elasticity model is varied for the atherosclerotic tissue, i.e. the Ogden N=1, Ogden N=6 and Polynomial N=2 material models are applied.
5.3.2.1 Deformed Lumen Measurements

The first atherosclerotic tissue model to be examined in terms of deformed lumen measurements, due to a direct stenting approach, is the Ogden N=1 hyperelastic model. Figure 5.9 shows the results for the cross-sectional area along the length of the lesion for the Ogden N=1 model (OgN1) on its own, the solid purple lines, and with the Mullins effect included, the solid orange lines. Two time points were examined, maximum balloon inflation, the respective lighter purple and orange lines, and post balloon deflation, the respective darker purple and orange lines. The solid lines indicate the results for a homogenous lesion tissue and the dotted lines indicate the results for when a lipid pool is incorporated into the analyses.

The lines in Figure 5.9 indicate the change in cross-sectional area along the length of the lesion. As seen in this figure there are many “jagged” regions along these lines and this is indicative of the general compliance of the lesion material that is allowing localised indentation around the stent struts.

The first point to note is that the behaviour at the two time points is different due to vessel recoil, and this is manifested in terms of two distinct tiers in Figure 5.9. The Mullins effect should only be activated on unloading of the material and in the top tier the four curves show that the lumen deformations are in agreement at maximum inflation, within the bounds of numerical accuracy for models of such complexity.

The Mullins effect should be active on unloading but in the bottom tier of results in Figure 5.9 there is little difference when including the Mullins effect on the Ogden N=1 model; comparing for example the dark purple and orange lines. The inclusion of a lipid pool in the analyses (the matching dotted lines) does seem to generate quite a noticable effect, on deflation, most significantly in terms of a redistribution of the
lesion deformation along the length of the lesion, in particular local to the stent struts.

Figure 5.10 shows the results for the inclusion of diffuse calcifications in conjunction with the Ogden N=1 model for atherosclerotic tissue. The dashed lines show the results for calcifications in the Ogden N=1 model, with no Mullins effect present (purple) and with the Mullins effect present (orange), respectively.

There is a significant difference when calcifications are included if Figure 5.9 and Figure 5.10 are compared. The calcifications not only affect the unloaded configuration and the distribution of lesion deformation along the length of the lesion but also the maximum cross-sectional area achieved by the stented lumen. In general the presence of calcifications – indicated by the dashed lines – appears to lower the lumen cross-sectional area.

The next atherosclerotic tissue model to be examined in terms of lumen cross-sectional area is the Ogden N=6 model. As a reminder to the reader, this material model is stiff in tension and soft in compression. Figure 5.11 shows the results for the cross-sectional area along the length of the lesion for the Ogden N=6 model (OgN6) on its own, the solid blue lines, with the Mullins effect included, the solid red lines. Two time points were examined, maximum balloon inflation, the respective lighter blue and red lines, and post balloon deflation, the respective darker blue and red lines. The solid lines indicate the results for a homogenous lesion tissue and the dotted lines indicate the results for when a lipid pool is incorporated into the analyses.

In Figure 5.11 the results at maximum balloon inflation are very similar, as expected. However on unloading of the balloon the results remain quite similar in contrast to
the Ogden N=1 case. Again, the inclusion of the Mullins effect produces little
difference on the luminal measures, however the analyses also appear to be not that
sensitive to the presence of a lipid pool.

The next case to be examined is that for the Polynomial N=2 model (P2) for the
lesion, again at two time points inflation and deflation, with and without plasticity
and with and without a lipid pool present. Figure 5.12 shows the results for lumen
cross sectional area along the length of the lesion. The light pink and green lines
show the results at maximum balloon inflation and the dark pink and green lines
show the results post balloon deflation. The results for the Polynomial N=2 model on
its own are shown in green and the results for the inclusion of plasticity are shown in
pink. The results for inclusion of a lipid pool are shown by the dotted curves.

To remind the reader, the Polynomial N=2 model is much stiffer in tension and in
compression than the Ogden N=1 model (as shown in Figure 5.4) so the lumen
deformations are much smoother around the stent struts due to this increase in
stiffness. Secondly there is significant difference at maximum balloon inflation
between pure hyperelastic polynomial (solid pink curve) and hyperelastic in
combination with plasticity (solid light green curve). There is more lumen gain
when plasticity model is used, as due to its characteristics the stress is limited which
encourages straining within the tissue.

The difference between the respective curves on deflation of the balloon is also
significant. The difference between the light and dark green curves (plasticity
included) is less than the difference between the light and dark pink curves (pure
hyperelastic). This indicates that vessel recoil is less on inclusion of plasticity (an
effect noted in the previous chapter). Finally, the inclusion of a lipid pool in this set
of analyses tends to increase the lumen gain in the middle region of the lesion in all cases. This is most likely due to a softening effect on its inclusion, relative to the stiffness of the Polynomial N=2 material, which means it is easier to deform the tissue. However, the effect is much less than the effect of plasticity on its own.

Figure 5.13 shows the results for the percentage difference in the average lumen area compared with the reference lumen area, at maximum balloon inflation, shown in red, and post balloon deflation, shown in blue, for all models discussed above.

A value of zero on this graph indicates that the overall average cross-sectional area is the same as the required reference lumen area, i.e. no net difference between the overall deformed cross-sectional area and the reference lumen area. A positive value on this graph indicates that the average cross-sectional area is greater than the reference lumen area and conversely a negative value indicates that the average lumen cross-sectional area is less than the reference lumen area.

One of the clearest observations from Figure 5.12 is that, in terms of this overall quantity, all models produce generally similar results. At maximum balloon inflation (the red columns) the percent change varies only between 7 to 11 percent for all material models.

Differences post balloon deflation are more significant (blue columns), where the percent change varies between -5 to 4.5 percent for all material models. Differences are negative, i.e. less than the reference lumen area (least lumen gain), when calcifications are included and when the polynomial model is used. In these cases the stent design is being more challenged in its scaffolding ability due to the stiffness of the lesion material. While, from Figure 5.12, the inclusion of calcifications does
appear to have a noticeable overall effect of stiffening the lesion material, the effect of the lipid pool is less significant for all of the base elasticity models used.

Overall, the results shown in Figures 5.8 to 5.12, suggest that the stiffness of the base elasticity model may be the most important parameter in determining the luminal measures considered here. The lipid pool does appear to have an effect locally in the lesion, which is dependent on the base elasticity model, but not significantly in terms of the overall average behaviour. The calcifications do have a noticeable effect, both locally and on average. Finally, the inclusion of the Mullins effect may not be that important, at least for the range of base elasticity models for the lesion considered here.

5.3.2.2 Tissue Damage Risk

The next step in post-processing the analyses is to examine the stress state in the healthy arterial wall at two time points, maximum balloon inflation and post balloon deflation. The values can then be compared with UTS values for each healthy arterial layer.

Figure 5.14 shows the predicted percent tissue damage risk results in each arterial layer, for all atherosclerotic tissue models previously discussed, in the SAL50 model, with a homogenous lesion representation. The grey columns indicate the results at maximum balloon inflation and the coloured columns show the results post balloon deflation. As expected the predominant percent tissue damage risk occurs in the innermost layer, the intima, with substantially less damage likely in the outer two layers. The stiffer lesion as represented by the P2 model seems to inflict the greatest damage in all three layers. The least stiff model, Ogden N=1, results in less damage to the intimal layer and negligible damage to the other two layers by comparison.
The grey columns indicate in all cases that damage is greater at maximum balloon inflation as would be expected. The inclusion of the Mullins effect has a negligible effect also, and similarly for the inclusion of plasticity, for this particular performance measure.

The effect of including a lipid pool is shown in the percent tissue damage risk results in Figure 5.15 for all six types of atherosclerotic lesion modelled. A very similar trend can be observed when compared with Figure 5.14 but on the whole the percent tissue damage risk is slightly less in all cases. This suggests an overall softening effect due to the presence of the lipid pool, which is consistent with the general trend observed for the luminal cross-sectional area results.

Finally, the effects of including a lipid pool and including calcifications in the base atherosclerotic matrix, on the percent tissue damage risk are compared in Figure 5.16. The base atherosclerotic matrix is modelled using the Ogden N=1 model and results for each case are shown with and without the Mullins effect. The inclusion of the lipid pool as before has a softening effect and reduces percent tissue damage risk. The inclusion of a small percentage of calcifications results in a stiffening and an increase in percent tissue damage risk, and it even becomes apparent in the medial layer.

5.3.2.3 Stress Distribution in Atherosclerotic Tissue

The reader is referred to Figure 5.17 for examples of the stress state in the deformed atherosclerotic tissue modelled with the Ogden N=1 material model. Figure 5.17-A,B show the von Mises stress state at maximum balloon inflation and post balloon deflation respectively. Figure 5.17-C,D show the von Mises stress state when a lipid pool is included at maximum balloon inflation and post balloon deflation,
respectively, and finally Figure 5.17-E,F show the von Mises stress state in the deformed tissue when calcifications are present at maximum balloon inflation and post balloon deflation respectively. As a note to the reader the stresses presented in this and all forthcoming stress plots are in presented in MPa.

The first point to note is the overall differences in stress level between the respective pairs in the two columns. At maximum balloon inflation (left column) the atherosclerotic tissue is more highly stressed than after balloon deflation (right column). This is to be expected as after the balloon is deflated it is only the stent that is exerting a load on the artery, as the vessel attempts to return to its original stress state. The inclusion of a lipid pool lowers the overall stress in the atherosclerotic tissue whereas the inclusion of calcified particles increases the overall stress in the tissue. Interestingly, when calcifications are present the von Mises stress in the non-calcified tissue is increased around the stent struts.

This examination of the von Mises stress state in atherosclerotic tissue raises the question of how these stresses compare with stresses in ruptured plaques. As a reminder to the reader, the study of Li et al. [21] created 2D finite element models derived from MRI imaging of vulnerable plaques that had ruptured and vulnerable plaques that had not ruptured. In the finite element simulations the 2D models were subjected to pulsatile loading and the resulting von Mises stress state examined. It was found that the mean maximal von Mises stresses were higher in the ruptured plaques (683.3 kPa) than those in the unruptured plaques (226.9 kPa). The results of the stenting simulations shown in Figure 5.17-E,F indicate several regions of stress exceeding those rupture stresses reported [21]. The implications of this shall be discussed in the final section.
However, the von Mises stress measure is a positive scalar quantity that gives a good indication of multi-axial stress state but does not capture whether the material is in tension or compression (the reader is referred to Chapter Two for a definition of the von Mises stress measure). For this reason, the maximum and minimum principal stresses at maximum balloon inflation are also examined. In Figure 5.18-A,B the minimum and maximum principal stresses in atherosclerotic tissue modelling with the Ogden N=1 material model are shown. In Figure 5.18-C,D the effects of inclusion of a lipid pool on the minimum and maximum principal stresses in atherosclerotic tissue are plotted. Finally, in Figure 5.18-E,F the effects of inclusion of calcified particles on the minimum and maximum principal stresses are shown.

In the minimum principal stress plots (left column), the predominant stresses are compressive and in the magnitude range 0 to 1.9 MPa (dark and light orange regions). However there are several tensile regions in the magnitude range 0 to 0.2 MPa (red regions) when calcifications are present. In the maximum principal stress plots the predominant stresses are tensile and in the magnitude range 0 to 0.12 MPa (dark cyan regions).

The von Mises stress state of atherosclerotic tissue modelled with the Ogden N=6 material model is shown in Figure 5.19. The stress state at maximum balloon inflation and post balloon deflation are shown in Figure 5.19-A,B respectively. The effects of inclusion of a lipid pool on the diseased tissue stress state are shown in Figure 5.19-C,D at maximum balloon inflation and post balloon deflation respectively.

As before for similar stress plots for the Ogden N=1 material model, the overall von Mises stresses are higher at maximum balloon inflation (left column) than after
balloon deflation (right columns). The inclusion of a lipid pool also appears to lower the overall resulting stress in the tissue. Comparing the values determined in Figure 5.19 with rupture stress reported by Li et al. [21] (683.3 kPa) it can be seen that there are again several regions exceeding this value. However, they are less concentrated than those in Figure 5.17 and are more diffuse.

The minimum and maximum principal stresses in atherosclerotic tissue, at maximum balloon inflation, modelled with the Ogden N=6 material model are shown in Figure 5.20. For a homogeneous lesion representation, the minimum and maximum principal stresses are shown in Figure 5.20-A,B respectively. The effects of inclusion of a lipid pool on the minimum and maximum principal stresses are shown in Figure 5.20-C,D respectively.

In the minimum principal stress plots (left column) the stresses are predominantly compressive and are in the range 0 to 0.47 MPa (dark orange regions). In the maximum principal stress plots the predominant stresses are tensile and in the range 0 to 0.12 MPa (light blue regions).

The stress state of atherosclerotic tissue modelled with the Polynomial N=2 material model is shown in Figure 5.21. The stress state at maximum balloon inflation and post balloon deflation are shown in Figure 5.21-A,B respectively. The effects of inclusion of a lipid pool on the atherosclerotic tissue stress state are shown in Figure 5.21-C,D at maximum balloon inflation and post balloon deflation respectively.

As before for similar stress plots for the Ogden N=1 and N=6 material models, the overall von Mises stresses are higher at maximum balloon inflation (left column) than after balloon deflation (right columns). The inclusion of a lipid pool also appears to lower the overall resulting stress in the tissue. However, as with similar
stress plots for the Ogden N=1 and N=6 material models, there are many regions exceeding the rupture stresses reported by Li et al. [21]. The regions exceeding the rupture stresses are greater this time and very pronounced.

Finally, the minimum and maximum principal stresses in atherosclerotic tissue, at maximum balloon inflation, modelled with the Polynomial N=2 material model are shown in Figure 5.22. For a homogeneous lesion representation, the minimum and maximum principal stresses are shown in Figure 5.22-A,B respectively. The effects of inclusion of a lipid pool on the minimum and maximum principal stresses are shown in Figure 5.22-C,D respectively.

In the minimum principal stress plots (left column) the stresses are predominantly compressive and are in the range 0 to 0.84 MPa (dark and light orange regions). In the maximum principal stress plots the predominant stresses are tensile and in the range 0 to 1.27 MPa (light blue and green regions).

5.3.3 Two-Phase Expansion Simulations
As discussed above, a straight stiff tube is used as the deployment mechanism in the two-phase expansion simulations; this represents a simplified version of some approaches to stenting implantation presented previously. The results are analysed in terms of lumen gain measurements along the lesion length and in terms of percent tissue damage risk. An illustration of the stages of deployment of a two-phase expansion simulation is shown in Figure 5.8.

5.3.3.1 Deformed Lumen Measurements
Figure 5.23 shows the response of the deformed lumen to the expansion process at two time points, Inflation Two and Deflation Two (please refer to Figure 5.7), for two material modelling approaches for the atherosclerotic tissue, the first order
Ogden model with and without the Mullins effect and for a tube deployment only and a tube-stent deployment.

The time points Inflation One and Deflation One were not included in the plot as they produced identical results in terms of lumen gain. For the first cycle, each arterial model was inflated with a tube and the atherosclerotic material model was also varied from pure hyperelastic to including the Mullins effect. All four curves were identical and hence not included in the figure. This was to be expected as the Mullins effect only becomes active on unloading during the first cycle. Since the first unloading was with the tube and no scaffold was remaining in place the arterial vessel would become fully unloaded and reach the same undeformed state regardless of the whether the Mullins effect was included, and the analyses verified this.

At the maximum of the second loading cycle, the same lumen cross-sectional area pattern is observed for the tube-only deployment analyses both with and without the Mullins effect. The same lumen cross-sectional area pattern is observed for the stent deployment analyses both with and without the Mullins effect. This is to be expected as the material should return to its original loading path on loading to a new maximum strain, as is the case in the loading of the tube during the second inflation.

At the final time point, Deflation Two, the same lumen cross-sectional area pattern is observed for the tube-only deployment. This is expected as the tissue becomes fully unloaded and should return to same state, both with and without the Mullins effect. However the results were not as expected for the stent deployment simulations. Essentially, the same lumen cross-sectional area pattern is observed both with and without the Mullins effect. The tissue is not reaching a fully unloaded state in this case, due to the presence of the stent, and it was thought that the unloading of the
tissue would follow a different path when the Mullins effect was included. However as shown in Figure 5.6 with the first order Ogden model the load-unload path difference is very minor. This is most likely due to the softness in general of the atherosclerotic tissue model selected.

\textbf{5.3.3.2 Tissue Damage Risk}

The results for the predicted intimal tissue damage risk are shown in Figure 5.24 for the four time points, Inflation One, Deflation Two, Inflation Two and Deflation Two. The results are shown only for the intimal layer as there was no significant damage predicted in the medial or adventitial layers for all analyses.

At the maximum of the first loading cycle, Inflation One, there is no significant difference in predicted intimal tissue damage risk both with and without the Mullins effect, the solid red and yellow columns respectively. This is true for both the stent and tube-only analyses. Similarly at the minimum of the first loading cycle, Deflation One, there is no significant difference in the results as the tissue reaches an unloaded state in both deployment cases.

At the maximum of the second loading cycle, Inflation Two, there are differences between the tube-only deployment results. When the Mullins effect is included there is less predicted intimal tissue damage risk, the height of the green column on the left of the graph is less than the height of the purple column on the left of the graph. This is most likely due to the different reloading curve followed on the second cycle when the Mullins effect is included. For the stent deployment analyses there is no significant difference in the predicted intimal tissue damage risk at Inflation Two, the heights of the solid purple and solid green columns are essentially the same on the
right of the graph. This may be due to the presence of the stent having a more
dominant effect that the inclusion of the Mullins effect.

At the final time point, Deflation Two, there is no difference between the tube-only
results. This is to be expected as the tissue reaches a fully unloaded state regardless
of the unloading path followed. However for the stent deployment simulations the
unloading results are slightly different. There is less predicted intimal tissue damage
risk when the Mullins effect is included, the height of the hatched green column is
less than the height of the hatched purple column. Bearing in mind that that in the
stented case the tissue does not fully unload, this shows that the different unloading
path followed when the Mullins effect is included does have an effect, albeit slight,
on the residual arterial stress state.

5.4 Discussion & Conclusions

The focus of this chapter is to examine the different approaches to modelling
atherosclerotic tissue response to stenting, and then to use these results to generate
recommendations for the FDA for their guideline document for non-clinical
engineering tests for coronary stents [8].

5.4.1 Discussion of Results from Direct Stenting Simulations

Three different hyperelastic models for the base matrix of the atherosclerotic lesion
were investigated in the direct stenting simulations. The inclusion of a lipid pool and
the inclusion of calcifications in the lesion were investigated. Finally the response of
the models to the inclusion of plasticity within the base lesion material and the
response of the models to the inclusion of the Mullins effect within the base lesion
material were also investigated. The results were examined in terms of deformed
lumen measurements, percent tissue damage risk in the healthy arterial wall and the
atherosclerotic tissue stress state. All results were examined at maximum balloon inflation and post balloon deflation.

A detailed examination of the deformed lumen was given in Figure 5.9, Figure 5.10, Figure 5.11, and Figure 5.12. Looking at the results overall in these figures, one major conclusion is that the inclusion of the Mullins effect on the base atherosclerotic tissue behaviour does not have significant effect on the deformed shape of the tissue in a direct stenting simulation. The inclusion of plasticity, as found in Chapter Four, does have a significant effect on the results for deformed lumen measurements. The inclusion of the Mullins effect does not limit the stress the tissue can support on loading. On the contrary, the inclusion of perfect plasticity does limit the stress the tissue can support. This means that straining is encouraged when plasticity becomes active and then affects the deformed lumen measures.

Looking at the results locally, i.e. the deformations around the stent struts, one can see that in Figure 5.9 for example that the inclusion of a lipid pool with surrounding matrix of tissue modelled with the Ogden N=1 model induces a redistribution of lesion deformation along its length, and in particular a lower cross-sectional area around the struts post balloon deflation; on deflation, the lipid pool, representing 9% of the lesion by volume, reduced the cross-sectional area local to the stent struts by up to 3%. However, when the surrounding matrix is modelled with the much stiffer Ogden N=6 model the local deformation distribution results are very similar, with and without a lipid pool. This is also the case for the Polynomial N=2 model. This indicates that presence of a lipid pool may only have an effect on a very soft surrounding matrix and less so on a stiff surrounding tissue.
Looking at the inclusion of calcifications surrounded by a tissue matrix represented by the Ogden N=1 model in Figure 5.10, the results locally vary greatly. The presence of the calcifications affects the local deformation both at inflation and on deflation. For the same given applied pressure to the balloon expanding the stent, the same deformed lumen is not achieved when calcifications are present. On deflation, the inclusion of 0.5% calcifications, by volume, reduces the range in lumen cross-sectional area by 0.2 mm$^2$ or 3%. This implies that for even a small volume of calcifications present in a lesion (in this case 0.5% of the total lesion volume) the cardiologist may have to inflate to a higher pressure to gain the desired lumen cross-sectional area. This is evident clinically also, as when calcifications are present sometimes a subsequent balloon inflation (with pressures up to 20 atm) have been reported if adequate stent expansion is not achieved [22]. From a macroscopic perspective, the results in Figure 5.13 show that the overall performance of the stent is being challenged when calcifications are present, as it does not achieve the reference lumen area on deflation of the balloon.

From a percent tissue damage risk perspective, the inclusion of the Mullins effect on the base atherosclerotic tissue behaviour does not have a significant effect, as seen in Figure 5.14. The inclusion of plasticity has a slight effect on the percent tissue damage risk results. Therefore, the inclusion of advanced damage modelling, such as the inclusion of the Mullins effect, may not be necessary for modelling the response of a soft atherosclerotic tissue to stenting. However, as a step toward representation of supra-physiological loading response the inclusion of plasticity could be recommended. As the inclusion of plasticity in the atherosclerotic tissue limits the stress supported by the tissue, it encourages redistribution of the stress in the healthy arterial wall thus resulting in higher predicted tissue damage risk.
The results for the presence of a lipid pool indicate a softer overall atherosclerotic body in the simulations. This reduces the percent tissue damage risk in all cases, on average by 2%, whereas the presence of diffuse calcifications increases the percent tissue damage risk in the Ogden N=1 case modelled by 7%, as seen in Figure 5.16. The presence of the calcifications results in a stiffer overall atherosclerotic body.

Taking all of the above into account, i.e. the examination of the deformed lumen areas and the predicted tissue damage risk in the healthy arterial wall, one is led to the critical conclusion that, for stenting applications, the base elasticity model for atherosclerotic tissue is the key aspect of the lesion modelling (for a given stenosis level) that determines the overall computational test-bed predictions.

Focusing on the micromechanical stress state in the lesion, presented in Figure 5.17 to Figure 5.22 were the stress states of the atherosclerotic tissue for inclusion of a lipid pool, diffuse calcifications, and variation of the base elasticity material model in terms of von Mises stresses and the maximum and minimum principal stresses.

An interesting result from examination of the von Mises stress plots is that stresses greater that the rupture stress levels reported by Li et al. [21] can be observed in these plots, both at maximum balloon inflation and post balloon deflation, and when the tissue is homogeneous or inhomogeneous. This is also the case if one looks at the maximum principal stresses (from Figures 5.17, 5.19 and 5.21), and is true for all of the base elasticity models, including the very soft Ogden N=1 model. This indicates that the expansion of this particular stent design may generate a rupture risk, for the atherosclerotic tissue associated with it. It also has a broader implication that accurate knowledge of the local strength of the lesion material is critically important in the further development of models such as those developed here for the test-bed,
so that the lesion rupture risk of different stent designs can be accurately assessed as part of the stent design process.

Looking at the results for the minimum and maximum principal stresses it can be seen for the Ogden N=1 material model that the compressive minimum principal stress range is an order of magnitude greater than the tensile maximum principal stress range. For the Ogden N=6 material model the compressive minimum principal stress range is twice that of the tensile maximum principal stress range. However for the Polynomial N=2 material model, the tensile maximum principal stress range is nearly twice the compressive minimum principal stress range.

Consideration of these stress ranges generates the implication that for an atherosclerotic plaque with soft compression properties, such as the Ogden N=1 and N=6 material models (see Figure 5.4), the predominant mode of loading is radial compression. However if the atherosclerotic tissue is stiff in compression, the Polynomial N=2 material model (Figure 5.4), the predominant mode of loading is circumferential tension. This indicates the importance of mechanically testing atherosclerotic tissue in tension and in compression to fully capture the tissue behaviour, as this has important effects on the in vivo stress state of the tissue during loading.

Based on all of the above (deformed lumen areas, predicted tissue damage risk and lesion microscale stress state) one can conclude that, for stenting applications, the choice of the base elasticity model for the lesion, combined with an accurate knowledge of lesion material strength, are the key drivers in determining the overall computational test-bed predictions.
5.4.2 Discussion of Results from Two-Phase Expansion Simulations

The second study examined the response of the tissue to a two-phase expansion simulation with a stiff tube acting as the deploying mechanism. A detailed examination of the lumen cross-sectional area on the second loading cycle for two time points, Inflation Two and Deflation Two, in Figure 5.23 shows that the Mullins effect has no significant effect on the resulting deformed lumen geometry. As expected the stent deployment versus the tube deployment produced different cross-sectional area patterns due to the nature of the geometries involved.

The results for the percent predicted tissue damage risk shown in Figure 5.24 indicate that for the stent deployment case, the stresses within the tissue are the very similar for both approaches (with and without Mullins effect), with only a slightly lower tissue damage risk being observed for the Mullins effect case on unloading. In the tube only case, a noticeably lower tissue damage risk is observed on Inflation 2 (reinflation) when the Mullins effect is included that is not seen in the stent deployment case. This is most likely due to the nature of the tissue damage risk evaluation, i.e. as a percentage of the tissue above a stress threshold. In the tube only case stresses are lower in general so that it is quite possible that the percentage of the tissue above the threshold is quite sensitive to small changes in stress state, as would be generated by the inclusion of the Mullins effect, whereas in the stent deployment case, stresses are much higher overall, as driven by the presence of the stiff stent, and hence the percentage of tissue over the threshold is much less sensitive to small stress changes.

Overall however, the clinical situation of most interest is when a stent is being deployed, and what is shown here is that the use of the Mullins effect to take account of the loading history (i.e. that there was a predilation), is insufficient to generate any
noticeable predilation effect, at least in the context of the soft lesion case (Ogden N=1) considered here. To depict the stress-state and the response of the vessel to a two-phase expansion technique a model accounting for permanent damage, i.e. the generation of permanent inelastic strains (damage or plastic strains) within the atherosclerotic tissue may be a better approach in these circumstances. This appears to be the case for the very soft lesion case, however even though not directly considered here, based on the results of the direct stenting simulations considered above, one would not expect the situation to be significantly different however the situation may be different for stiffer lesion material, e.g. Ogden N=6.

### 5.4.3 Closing Remarks

The current FDA guidelines for non-clinical engineering tests do not require the modelling of a lesion in their stress-strain analysis section in relation to stent deployment modelling. From Chapter Four it was strongly recommended that for assessing device performance the presence of a lesion should be accounted for in computational models, and also that the quantity of lesion tissue should be varied. Continuing on these recommendations, from the results of this study the following is also recommended:

- The elastic behaviour of the atherosclerotic tissue represented in the models should be within experimental ranges reported in the literature, and also the local (microscale) strength of the tissue should be considered, as these have been determined to be the key factors in controlling stent performance predictions in the computational models (computational test-bed predictions).
- The inclusion of calcifications should be accounted for through either explicit representation or a significant increase in stiffness in the elasticity model for the base matrix of atherosclerotic tissue.
The inclusion of advanced damage modelling is not absolutely necessary for stent assessment simulations, when a soft atherosclerotic tissue is to be modelled, but plasticity can be included to account for the supra-physiological response of the atherosclerotic tissue, in particular when the tissue is stiffer.

The FDA guidelines are aimed at assessing device performance overall and the recommendations above generally relate to this. However the study and assessment of local deformation and stress measures in the tissue are of critical importance in a range of areas of research. This includes, for example, detailed investigations of drug deposition rate around stent struts and vulnerable plaque analyses, which examine closely the stress distributions in the tissue and in particular around the fibrous plaque cap. The risk of plaque rupture is an important quantity to be assessed and the stress distribution and deformations due to the presence of a lipid pool and/or calcifications are of paramount concern in this area. From the detailed examinations of the von Mises stress state in the atherosclerotic tissue performed here it is observed that the stress levels may indeed induce a risk of plaque rupture. This indicates that the expansion of this particular stent design may generate a lesion rupture risk, with the implication that accurate knowledge of the local strength of the lesion material is critically important in the further development of the computational test-bed presented here, so that performance of different stent designs can be more accurately and more completely assessed.

The work presented in this chapter has primarily focused on the lesion material representation, for one of the population categories of the test-bed introduced in Chapter Four (SAL50, see Figure 4.1-B), and the performance measures chosen have the ability to capture the local and global deformation and stress states. The full
arterial test-bed presented in Chapter Four, that covers a wide range of population categories, combined with the ability to vary lesion material representation within each of these categories (as illustrated here for SAL50), has the definite potential to quantify the effects of stent implantation in a useful way that can guide stent assessment and design and it can be used to explore variable variations beyond the scope presented here.
References


Figure 5.1  Histological cross-section of a lipid rich atherosclerotic arterial vessel taken from the work of Stary [3]. Labels indicate the following: A – adventitia, M – media, core – confluent extracellular lipid core, fo – foam cells.
Figure 5.2  Schematic of lipid pool with SAL50 arterial model, with insert showing mesh density.

Figure 5.3  Schematic of calcified regions in SAL50 arterial model, with insert showing mesh density.
Figure 5.4  Uniaxial responses of material models for atherosclerotic tissue to monotonic loading in tension and compression.

Figure 5.5  Uniaxial responses of the three material models plotted separately with stress behaviour indicated for compression (−) and tension (+).
Figure 5.6 Responses of Ogden models to cyclic loading in tension and compression (insert shows strain loading amplitude) and response of Polynomial model to monotonic loading.
Figure 5.7 Amplitude loading curve for two-phase stiff tube expansion simulations. This amplitude curve is applied to the radial displacement of all nodes on the stiff tube with the amplitude of Inflation 2 being 10% higher than Inflation 1.
Figure 5.8  Example of stages of stent deployment with a stiff elastic tube.
A) Pre-deployment, B) Maximum inflation one, with contact between the stent and tube turned off, C) Post tube deflation one, D) Maximum inflation two, with contact between stent and tube turned on, E) Post tube deflation two.
Figure 5.9 Cross-sectional measurements along the length of the atherosclerotic tissue geometry, Z position along axis (please refer to Figure 5.8-A), for variations in constitutive behaviour and inclusions within the atherosclerotic tissue. Two time points are shown, lumen cross-sectional area at maximum balloon inflation, light purple and light orange curves, and lumen cross-sectional area post balloon deflation, dark purple and orange curves. Results for the Ogden N=1 model only are shown in solid purple curves and results for inclusion of the Mullins effect are shown in solid orange curves. The results for inclusion of a lipid are shown by the respective dotted curves.
Figure 5.10 Cross-sectional measurements along the length of the atherosclerotic tissue geometry, Z position along axis (please refer to Figure 5.8-A), for variations in constitutive behaviour and inclusions within the atherosclerotic tissue. Two time points are shown, lumen cross-sectional area at maximum balloon inflation, light purple and light orange curves, and lumen cross-sectional area post balloon deflation, dark purple and orange curves. Results for the Ogden N=1 model only are shown in solid purple curves and results for inclusion of the Mullins effect are shown in solid orange curves. The results for inclusion of a calcifications are shown by the respective dashed curves.
Figure 5.11 Cross-sectional measurements along the length of the atherosclerotic tissue geometry, Z position along axis (please refer to Figure 5.8-A), for variations in constitutive behaviour and inclusions within the atherosclerotic tissue. Two time points are shown, lumen cross-sectional area at maximum balloon inflation, light red and light blue curves, and lumen cross-sectional area post balloon deflation, dark red and blue curves. Results for the Ogden N=6 model only are shown in solid blue curves and results for inclusion of the Mullins effect are shown in solid red curves. The results for inclusion of a lipid are shown by the respective dotted curves.
Cross-sectional measurements along the length of the atherosclerotic tissue geometry, Z position along axis (please refer to Figure 5.8-A), for variations in constitutive behaviour and inclusions within the atherosclerotic tissue. Two time points are shown, lumen cross-sectional area at maximum balloon inflation, light pink and light green curves, and lumen cross-sectional area post balloon deflation, dark pink and green curves. Results for the Polynomial N=2 model only are shown in solid pink curves and results for inclusion of plasticity are shown in solid green curves. The results for inclusion of a lipid are shown by the respective dotted curves.
Figure 5.13 Results for % change in average lumen cross-sectional area with respective to reference lumen area (please refer to Figure 4.13) for all types of atherosclerotic tissue models discussed in text. Data was analysed at two time points, max balloon inflation (red “inflation” series) and post balloon deflation (blue “deflation” series).
Figure 5.14 Predicted percent tissue damage risk results in each arterial layer, for each atherosclerotic tissue model discussed in the text at two time points, maximum balloon inflation shown in grey and post balloon deflation indicated by the coloured columns.
Figure 5.15  Predicted percent tissue damage risk results in each arterial layer, for each atherosclerotic tissue model discussed in the text with a lipid pool present at two time points, maximum balloon inflation shown in grey and post balloon deflation indicated by the coloured columns.
Figure 5.16  Predicted percent tissue damage risk results in each arterial layer, for Ogden N=1 atherosclerotic tissue model modelled with calcifications, with a lipid pool and as homogenous continuum at two time points, maximum balloon inflation shown in grey and post balloon deflation indicated by the coloured columns.
Figure 5.17  von Mises stress distribution in atherosclerotic tissue, A) Max inflation for Ogden N=1 material model, B) Deflation for Ogden N=1 material model, C) Max inflation for Ogden N=1 material model with lipid pool, D) Deflation for Ogden N=1 material model with lipid pool, E) Max inflation for Ogden N=1 material model with calcifications and F) Deflation for Ogden N=1 material model with calcifications.
Figure 5.18 Principal stress distribution in atherosclerotic tissue at maximum balloon inflation, A) Minimum principal stress for Ogden N=1 material model, B) Maximum principal stress for Ogden N=1 material model, C) Minimum principal stress for Ogden N=1 material model with lipid pool, D) Maximum principal stress for Ogden N=1 material model with lipid pool, E) Minimum principal stress for Ogden N=1 material model with calcifications and F) Maximum principal stress for Ogden N=1 material model with calcifications.
Figure 5.19 von Mises stress distribution in atherosclerotic tissue, A) Max inflation for Ogden N=6 material model, B) Deflation for Ogden N=6 material model, C) Max inflation for Ogden N=6 material model with lipid pool and D) Deflation for Ogden N=6 material model with lipid pool.
Figure 5.20 Principal stress distribution in atherosclerotic tissue at maximum balloon inflation, A) Minimum principal stress for Ogden N=6 material model, B) Maximum principal stress for Ogden N=6 material model, C) Minimum principal stress for Ogden N=6 material model with lipid pool, D) Maximum principal stress for Ogden N=6 material model with lipid pool.
Figure 5.21 von Mises stress distribution in atherosclerotic tissue, A) Max inflation for Polynomial N=2 material model and B) Deflation Polynomial N=2 material model, C) Max inflation for Polynomial N=2 material model with lipid pool and D) Deflation for Polynomial N=2 material model with lipid pool.
Figure 5.22 Principal stress distribution in atherosclerotic tissue at maximum balloon inflation, A) Minimum principal stress for Polynomial N=2 material model, B) Maximum principal stress for Polynomial N=2 material model, C) Minimum principal stress for Polynomial N=2 material model with lipid pool, D) Maximum principal stress for Polynomial N=2 material model with lipid pool.
Cross-sectional measurements along the length of the atherosclerotic tissue geometry, Z position along axis (please refer to Figure 5.8-A), for variations in constitutive behaviour at each significant time point in the two-phase expansion simulations, Inflation 1, Deflation 1, Inflation 2 and Deflation 2 (please refer to Figure 5.7).
Chapter Five

Figure 5.24  Predicted percent tissue damage risk in the intimal layer results for two-phase expansion simulations, at four time points: Inflation One, Deflation One, Inflation Two, Deflation Two (refer to Figure 5.7). Additional symbols indicate zero values of relevant terms.
6 Conclusions & Recommendations

6.1 Introduction

The assessment of coronary stent implantation in silico was the primary research topic of this thesis. Its motivation was derived directly from the clinical issue of in-stent restenosis that is attributed to high stresses in the arterial wall. Through the use of finite element modelling several studies were performed to investigate the biomechanics of the stent implantation process and the sensitivity of these analyses to variations in vessel geometry and material properties.

In this chapter a summary of the work presented in this thesis is given (section 6.2) along with recommendations for the FDA on their guideline documentation (section 6.3) for non-clinical engineering tests for coronary stents [1]. In section 6.2 the motivation behind each study is given along with a summary of methodology and results from Chapters Four and Five. Main limitations of the work are summarised in section 6.4. Proposals of future work leading on from this thesis are presented in section 6.5. Finally, overall conclusions from the work are summarised in section 6.6.

6.2 Summary of Work

The development of a computational framework constituted the first phase of work reported in this thesis, and was presented in Chapter Four. It was motivated by three key factors:

1. The need for an accurate depiction of arterial stress state in stenting simulations to better understand ISR.
2. The lack of specificity with regards to the physiological environment for stenting simulations in the FDA guideline documentation [1].

3. The need for a population specific arterial test-bed to characterise the response of different population groups to stenting as the bulk of current research either focuses on a patient specific vessel or an overly idealised vessel.

The development of a nine arterial model test-bed of varying tortuosity and stenosis severity was presented in Chapter Four. To show the capacity of the test-bed as a virtual analysis design tool the performance of two generic stent designs was investigated. The response of the arterial vessels to the deployment of each of the two stents, the closed cell stent A and the open cell stent B, were examined. The chosen performance metrics were the percent tissue damage risk, as an indicator of the potential damage to the healthy arterial wall, and the scaffolding ability of each stent design.

Several parameter studies were also carried out; including mesh sensitivity analyses, damping parameter study, sensitivity of hyperelastic materials to incompressibility and sensitivity of the analyses to variation in material model for the atherosclerotic tissue.

From the results of Chapter Four it was found that a key parameter in the analyses was the quantity of atherosclerotic tissue present. It was found that the level of stenosis present had a significant effect on the scaffolding potential of a stent design and also on the tissue damage risk for the surrounding arterial tissue.

Surprisingly it was found that the level of curvature present in an arterial vessel did not have a major influence on the results. However the open cell design of stent B
was found to perform slightly better in a curved stenosed vessel, in terms of lower recoil. This may indicate that, as regards scaffolding potential, the open cell type design maybe more suitable for use in a tortuous vessel.

Thirdly, from the results of the parameter study on variation of the atherosclerotic tissue material model, it was found that for a hyperelastic-plastic material model the value of yield stress selected (once within the range of 200-800kPa) did not have a huge effect on the recoil of the arterial vessel. To capture the response of an atherosclerotic tissue to stenting it is vital to know the sensitivity of the simulations to various parameters. It is known that there is significant variability in the behaviour of atherosclerotic tissue. However, the behaviour in the failure domain – in this case when it can no longer support load, represented in this case by perfect plasticity – is not that sensitive to the yield values selected. This is an important point, as with the enormous variability in biological tissue, from the perspective of modeling the overall or macroscale performance of the stent in the artery, the lack of sensitivity to yield is worth noting.

Following on from the work reported in Chapter Four, the second phase of work reported in this thesis was presented in Chapter Five, and focussed on the modelling of perhaps the biggest unknown in a stenting simulation, the modelling of the atherosclerotic tissue. Using a straight 50% stenosed arterial vessel, the responses of the test-bed due to direct stenting and two-phase deployments, representing the predilation technique, were investigated.

The results from the direct stenting approach gave many useful insights into the modelling of atherosclerotic tissue response. One major finding is that the stiffness of the base elasticity model is perhaps the most significant parameter in these
analyses controlling the overall or macroscale behaviour of the stent during deployment in the artery. This stiffness can cause the percent tissue damage risk and the deformed lumen geometry profile to be greatly altered. Having said this, it is also the case that the inclusion of a small proportion of calcifications can have a significant effect on the results for deformed lumen geometry and stress distribution, when embedded in a matrix of soft atherosclerotic tissue. This is due to the stiffening effect of the particles, and to the author’s knowledge, it is the first time they have been modelled, with the values reported by Ebenstein et al. [2], in a stenting simulation. This has the implication for device designers, that they will need to account for the stiffening effect of calcified particles, if present.

From the detailed examinations of the predicted change in local lumen cross-sectional area, the results indicate that presence of a lipid pool may only have a significant effect for a very soft surrounding matrix and less so for stiff surrounding tissue. Overall, in terms of average lumen cross-sectional area (and lumen gain) for all base elasticity models, the lipid pool has a noticeable effect, but weaker and therefore less important than the effect of the inclusion of calcifications. From a tissue damage risk perspective the inclusion of a lipid pool reduces the predicted damage in the healthy arterial wall. Therefore for research examining the detailed deformation of atherosclerotic plaque (in particular soft atherosclerotic tissue), such as that examining vulnerable plaque and tissue prolapse within devices, accounting for the presence of the lipid pool is important. For research concerned with overall device performance a device, in terms of scaffolding ability, the inclusion of a lipid pool may not be necessary.

Another major finding is that for direct stenting simulations the inclusion of a pseudo-elastic damage model, in particular the inclusion of the Mullins effect, to
capture the atherosclerotic tissue behaviour does not have a significant effect on the results for lumen geometry profile or on the predicted percent tissue damage risk for the healthy arterial wall, for the range of elasticities considered here for the atherosclerotic material. This particular damage model is classified as discontinuous and only becomes active on unloading of the material.

The results from the two phase deployment simulations indicate that the Mullins effect does not have a significant effect on the results for deformed lumen measures or predicted tissue damage risk. This suggests that the pseudo-elastic approach, represented here by the Mullins effect, is not appropriate for modelling a soft atherosclerotic tissue response, in the context of the models considered here. Although there is a representation of loading history “memory” in terms of damage parameter that controls the progressive elastic response of the material (see section 2.3, equation 2.31), the theory does not allow for the representation of a permanent/non recoverable inelastic strain that would represent permanent damage or plastic deformation, as may be necessary in the present application. This has that the implication that, unless using a model accounting for permanent deformation in the diseased tissue (data for which is lacking), the response of the vessel to stenting can be captured by the direct stenting simulation regardless of whether or not predilation with an angioplasty balloon took place.

The Mullins effect is a discontinuous damage model as defined in Chapter Two. A continuous damage model which becomes active on loading could induce a different response through softening on loading, though no such model has been applied to atherosclerotic tissue previously, most likely due to the difficulty in extrapolating an experimental data fit for these particular models. If the material model were to become active, i.e. soften on loading, the deformation of the tissue would be altered
and the load supported by the tissue would be less, which would have an effect on the scaffolding of the device and the tissue damage risk. The various material model formulations for atherosclerotic plaque presented in Chapter Five have paid particular attention to existing experimental data and produced models that were more accurate than previous approaches. However with the introduction of more experimental data for this tissue type further improvements could be made.

From the detailed micromechanical analyses of the atherosclerotic tissue stress state in Chapter Five, it was observed that stresses above the rupture stress values reported by Li et al. [3] were present. This has the important implication that accurate knowledge of the local strength of the lesion material is critically important in the further development of models such as those developed here for the test-bed, so that the lesion rupture risk of different stent designs can be accurately assessed as part of the stent design process.

Also based on the stress ranges observed in the atherosclerotic tissue, the implication is that for an atherosclerotic plaque with soft compression properties, the predominant mode of loading is radial compression. However if the atherosclerotic tissue is stiff in compression, the predominant mode of loading is circumferential tension. This indicates the importance of mechanically testing atherosclerotic tissue in tension and in compression to fully capture the tissue behaviour, as this has important effects on the in vivo stress state of the tissue during loading.

### 6.3 Recommendations to the FDA

In the current FDA guidelines for non-clinical engineering tests for intravascular stents [1] the section on stress-strain analysis has been of interest to this work. In this section of the document, the recommendations do not require the inclusion of a
stenosis or the variation of its presence in computational simulations of stent deployment. However, from the results of the present work, the following recommendations should be considered:

- In the representation of the arterial environment to be stented, a stenosis should be included for a more accurate depiction of the in vivo setting.
- Stent performance should be investigated for a range of stenoses, to see if there is an optimum design for a given stenosis level.
- Vessel curvature should be included in the analyses, adhering to the guidelines as a minimum.

As regards the single greatest unknown currently in stenting simulations, the atherosclerotic tissue, an investigation into variations in constitutive theory and inclusion of the constituents of the plaque were considered here. Continuing on from the previous recommendations, from the results of the present work the following is also recommended:

- The elastic behaviour of the atherosclerotic tissue represented in the models should be within experimental ranges reported in the literature, and also the local (microscale) strength of the tissue should be considered, as these have been determined to be the key factors in controlling stent performance predictions in computational models.
- The inclusion of calcifications should be accounted for through either explicit representation or a significant increase in stiffness in the elasticity model for the base matrix of atherosclerotic tissue.
- The inclusion of advanced damage modelling is not absolutely necessary for stent assessment simulations, when a soft atherosclerotic tissue is to be modelled, but plasticity can be included to account for the supra-
physiological response of the atherosclerotic tissue, in particular when the tissue is stiffer.

6.4 Limitations

Also to be addressed are the limitations of the work presented in this thesis. The first assumption within the work was that the atherosclerotic tissue is isotropic, when in reality it is probably anisotropic due to the presence of collagen fibres. Experimental data for this point is currently lacking. Another assumption with regards soft tissue is that all soft tissues modelled are considered rate independent although these tissues are most likely rate dependent and viscoelastic. Again, experimental data for this behaviour is currently lacking.

A third assumption is with regard to the representation of the lipid pool as a soft solid when it may be more appropriate to model it as a viscous liquid. For such representations, the use of fluid-structure interaction (FSI) techniques should be explored in future developments of the computational test-bed. Another limitation of the work is that the curved arterial vessels modelled are curved in one plane only. In reality, out of plane curvature exists in the coronary vasculature system and an investigation into stent performance in an arterial vessel with curvature in more than one plane would be suggested as a step to further develop the test-bed presented in this thesis.

One main limitation of the work is the lack of direct experimental validation of many of the computational results generated here. This was primarily due to the difficulty in setting up appropriate and sufficiently accurate experiments. However, in the future, using synthetic materials such as silicone to represent the arterial wall and gels with a range of stiffnesses to represent the atherosclerotic plaque, useful
experimental representations of the test-bed could be generated that would help in direct validation. For example, the scaffolding ability of different stent designs could be compared with computational predictions and the deformed lumen measures validated.

6.5 Future Research

Over 20% of deaths in 2004 were attributable to ischaemic heart disease or cerebrovascular disease [4]. These diseases, predominantly caused by presence of atherosclerotic plaque in the coronary and carotid arteries respectively, are of serious concern to clinicians, scientists and biomedical engineers. There is a wide variation in atherosclerotic plaque type due to its heterogeneous nature, which can include the presence of a fibrous cap, lipid rich necrotic core, dense fibrous tissue and calcifications. However, relatively little is known about the heterogeneous nature of atherosclerotic plaques and its constituents. Future work in this area would be to carry out a thorough investigation of atherosclerotic tissue biomechanics, including vulnerable plaque (defined as unstable plaque and “prone to thrombose” [5]), through experimental and computational methods with the aim of increasing our knowledge of the diseased tissue and give recommendations on its treatment. This would enable computational studies, such as those in this thesis, to further develop upon material model formulations, using the framework presented, for a more accurate depiction of in silico device performance.

Clinically adverse events are often associated with rupture of the fibrous cap [6] resulting in exposure of the necrotic plaque core and thrombus formation. The mechanical properties of this region and more specifically the thickness of the cap are also thought to be critical to whether or not rupture occurs. This is particularly
true of vulnerable plaques which are recognised through imaging, such as optical
coeherence tomography, as plaques with a thin fibrous cap (<150μm) and a large
atheromatous core (>40% lesion volume) [7]. Some experimental data exists on
fibrous cap mechanical behaviour from nanoindentation testing [8] and cyclic
compression testing [9] but these studies are limited to behaviour of the tissue in the
physiological loading regime and do not account for the damage progression
response or the anisotropic nature of the tissue due to the presence of collagen fibres.

Research to mechanically test atherosclerotic tissues specimens, in particular fresh
samples harvested from carotid endarterectomy surgeries, would provide invaluable
information to those designing implants and clinicians. On-going studies within
research groups in the University of Limerick and Dublin City University, and other
centres world-wide, are mechanically testing atherosclerotic plaque tissue [8,10,11],
but the focus thus far has been on the behaviour of the plaque as a whole. Future
research that takes the classification and the constituents of the tissue into account
could improve on current approaches.

With the assistance of a pathologist, plaque samples could be tested according to
classification (hypocellular, cellular and calcified). Tissue samples could be
examined by micrography after staining, with either Hematoxylin and Eosin or von
Kossa’s reagent. The classified samples could then be loaded in tension and
compression. Particular attention should be paid to the behaviour of the
atherosclerotic fibrous plaque cap. The orientations of the collagen fibres within the
cap should also be considered as this is a key determinant in the strength of the
tissue.
Using this experimental failure data it would be proposed to develop a constitutive model to account for the non-linear anisotropic nature of the material and its behaviour when damaged. This data could be implemented in a computational framework, such as that presented in this thesis, to assess whether this material model could improve on current indicators for device performance.

From the computational framework presented here, the test-bed could be used to calculate accurate boundary and loading conditions for micro-mechanical fatigue loading analyses, such as those presented in the work of Sweeney et al. [12]. It could also be utilised for the assessment of the performance of biodegradable stents, both metallic and polymeric, and to represent biodegradation.

Also the test-bed could be used to give very accurate representations of stent strut deformation during deployment. This could be linked with a formula, such as the one presented in the work of Grogan et al. [13] for strut failure as a function of strut size and grain size, to evaluate stent failure risk. Experimental work to validate the results of the test-bed as regards the effects of arterial curvature, stenosis size and type could also be performed.

6.6 Concluding Remarks

In conclusion, the use of finite element modelling in this thesis to assess the biomechanics of coronary stent implantation has yielded the development of a novel computational test-bed which may assist device designers in their evaluation of new and emerging stent designs. The detailed investigation into different approaches to modelling atherosclerotic tissue response to stenting has provided invaluable information on the suitability of certain modelling techniques. Finally this work has
generated considerable new insight into the mechanics of coronary stenting, and has created the basis for more effective and efficient stent design in the future.
References


Appendix A

Below is the python script used to randomly assign elements to a set that represents calcified regions (from a specified region of interest) within the arterial model.

The output from the below script is an element set to which the material properties of calcifications can be applied.

# Python script for Assigning Calcified Regions
# Import Abaqus Modules
from abaqusConstants import *
from abaqus import *
import random

# Create Model, Assembly objects
modelNames= mdb.models.keys()
currModel= mdb.models['<model_name>']
currAssembly= currModel.rootAssembly
currPart= currModel.parts[ '<part_name>']
Bulk= currPart.sets['<part_region_of_interest_set_name>'].elements
BulkLabel= list()
i=0

for eachElem in Bulk:
    label= eachElem.label
    BulkLabel.insert(i,(label))
    i=i+1

labels= random.sample(BulkLabel, 630)
CalcDiffuse=currPart.SetFromElementLabels(name='Calcified_Region_Set_name', ElementLabels=labels)
Presented in this appendix, is the python script used to measure the cross-sectional area of the deformed lumen of the artery along the axial length of the lesion.

The output of this script is the print-to-screen values of the axial position along the length of the lesion and the cross-sectional area values at each axial position.

```python
# Import Necessary Abaqus Modules
from abaqusConstants import *
from abaqus import *
from miscUtils import sorted

# Open CAE file
File=openMdb(pathName="path to file/<file_name.cae>")
OptModel=File.models['<model_name>']
OptAssembly=OptModel.rootAssembly
UnDefPart=OptModel.parts['<Reference_Undeformed_Part_name>']
DefPart=OptModel.parts['<Deformed_Part_name>']
areaList=list()

# Create sets of rings of nodes along Z axis of lumen
for i in range(0, 119):
    lumen=UnDefPart.sets['lumen'+str(i)].nodes
    j=0
    labelList=list()
    for eachNode in lumen:
        label=eachNode.label
        labelList.append(label)
```

```
labelList.insert(j,(label))

j=j+1

DefPart.SetFromNodeLabels(name='Lumen'+str(i),nodeLabels=(labelList),)

#Find central node of each set of rings

lumen=DefPart.sets["Lumen"+str(i)].nodes

j=0

labelList=list()

sumX=0

sumY=0

sumZ=0

for eachNode in lumen:

   label=eachNode.label

   xCoord=eachNode.coordinates[0]

   yCoord=eachNode.coordinates[1]

   zCoord=eachNode.coordinates[2]

   sumX=sumX+xCoord

   sumY=sumY+yCoord

   sumZ=sumZ+zCoord

   labelList.insert(j,(label))

   j=j+1

   centreX=sumX/j

   centreY=sumY/j

   centreZ=sumZ/j

   centreNode=DefPart.Node(coordinates=(centreX,centreY,centreZ),)

   label=lumen[0].label
xCoord1=lumen[0].coordinates[0]
yCoord2=lumen[0].coordinates[1]
xC=centreNode.coordinates[0]
yC=centreNode.coordinates[1]
zCoord=centreNode.coordinates[2]
startNode=lumen[0]
edges=lumen[0].getElemEdges()
for eachEdge in edges:
    nodes=eachEdge.getNodes()
    x=nodes.index(startNode)
    if x==0:
        y=1
    else:
        y=0
    node1=nodes[y]
    if node1 in lumen:
        label1=node1.label
        break
areaTotal=0
for eachNode in lumen:
    label1=node1.label
    edges1=node1.getElemEdges()
    for eachCommEdge in edges1:
        nodesComm=eachCommEdge.getNodes()
        x=nodesComm.index(node1)
if x==0:
    y=1
else:
    y=0
node2=nodesComm[y]
if node2 in lumen:
    if node2==startNode:
        continue
    else:
        break

# Do area calculation

x1=node1.coordinates[0]
y1=node1.coordinates[1]
x2=node2.coordinates[0]
y2=node2.coordinates[1]
a=sqrt((x2-xC)**2+(y2-yC)**2)
b=sqrt((x1-xC)**2+(y1-yC)**2)
c=sqrt((x2-x1)**2+(y2-y1)**2)
p=(a+b+c)/2
area=sqrt(p*(p-a)*(p-b)*(p-c))
areaTotal=areaTotal+area

# Then Node 2 becomes Node 1 and Node 1 becomes startNode
startNode=node1
node1=node2
areaList.insert(i, areaTotal)

# Print Output to Screen

print zCoord

print areaList