



Haoyu Chen

St. Cross College

Supervisors

Paul N. Watton
Mark S. Thompson

INTRACRANIAL ANEURYSM DISEASE:
**Novel Modelling of Inception and the
Microstructural Adaption of Collagen
Fabric**

**A thesis submitted for the degree of
Doctor of Philosophy**

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To mum & dad - for raising me and supporting me all the time.

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*IA Disease: Novel Modelling of Inception and the Microstructural Adaption of
Collagen Fabric*

By Haoyu Chen, St. Cross College.

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Abstract

An intracranial aneurysm (IA) is a balloon-like focal lesion on the cerebral arterial wall. IAs are poorly understood, but are commonly considered to be a disease caused by multiple factors. Current interventional treatments are accompanied with risks. Given the low incidence of rupture, it would be ideal to only treat aneurysms identified with rupture risk. Numerical models of aneurysm development may provide insight into the disease mechanisms, and contribute to the prediction of disease progression. Better understanding of the disease aetiology will also guide clinical decision making.

Different hypotheses have been proposed on the influence of haemodynamic stimuli on IA inception. We investigate this influence by examining the haemodynamic stimuli of the ‘pre-aneurysmal’ vasculature in the locations of IA formation in 22 clinical cases. The ‘pre-aneurysmal’ geometries are obtained by applying a novel numerical vessel reconstruction method on the aneurysmal geometries. This automated reconstruction method propagates a closed curve along the vessel skeleton using the local Frenet frames to smoothly morph the upstream boundary into the downstream boundary. We observe that locally elevated wall shear stress (WSS) and gradient oscillatory number (GON) are highly correlated with regions susceptible to sidewall IA formation, whilst haemodynamic indices associated with the oscillation of the WSS vectors have much lower correlations.

A common assumption made in the literature on arterial growth and remodelling (G&R) is that the ‘state of stretch’ (denoted as the *attachment stretch*) at which collagen fibres are configured in the extracellular matrix (ECM) is assumed to be constant. This will lead to an unrealistically thickened arterial wall in modelling aneurysm evolution. We propose a novel 1D mathematical model of collagen microstructural adaption during IA evolution. We assume new collagen fibres are con-

figured into the ECM in a state of attachment stretch distribution which can be temporally adaptive. We explicitly define the functional form of this distribution and model its temporal adaption during IA evolution. This model is then implemented into two 3D models of IA evolution: a solid structural model and Fluid-Solid-Growth (FSG) model. In the solid structural model, the artery is modelled as a two-layer, nonlinear elastic cylindrical membrane using a physiologically realistic constitutive model. The development of the aneurysm is considered as a consequence of the growth and remodelling of its material constituents: elastinous constituents are prescribed to degrade in a localised circular patch; collagen concentration and recruitment variables enable the growth and remodelling of collagen fabric to be simulated; adaption of the attachment stretch distribution is confined locally within the region of aneurysm evolution. The sophisticated solid model predicts stabilised saccular IAs with realistic sizes and wall thicknesses. The FSG model simulates the IA development on patient-specific vasculature: the updated 3D solid structural model is integrated into a patient-specific geometry of the vasculature and the growth and remodelling of the constituents is now linked to the local haemodynamic stimuli obtained from a rigid-wall computational fluid dynamics analysis. Adaption of the attachment stretch distribution is also confined locally in the region where the constituents degrade. An illustrative case of IA development on patient-specific geometry is provided.

Based on our study, we conclude that incorporating the adaption of attachment stretch distribution is necessary to simulate IA evolution with physiological evolving wall thicknesses. However, how vascular cells confine this adaption heterogeneously needs further investigation. Improved understanding and modeling of the biology of the arterial wall is needed for more sophisticated models of aneurysm evolution. It will in turn assist in understanding the aetiology of IA formation. Ultimately we hope to have a patient-specific growth model that could have the potential be used to assist diagnostic decisions.

Statement of Originality

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the University of Oxford or any other educational institution, except where due acknowledgement is made in the thesis.

Any contribution made to the research by others, with whom I have worked at the University of Oxford or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

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ACRONYMS

AAA	Abdominal aortic aneurysms
AFI	Aneurysm formation indicator
BSI	Biaxial stretch index
CFD	Computational fluid dynamics
CTA	Computed tomography angiography
DICOM	Digital imaging and communications in medicine
EC	Endothelial cell
ECM	Extracellular matrix
eNOS	Endothelial nitric oxide synthase
FSG	Fluid-solid-growth
G&R	Growth and remodelling
GON	Gradient oscillatory number
IA	Intracranial aneurysm
ICA	Internal carotid artery
ICAM-1	Intercellular Adhesion Molecule 1
IEL	Internal elastic lamina
ILT	Intraluminal thrombus
MCP-1	Monocyte Chemotactic Protein 1
MMP	Matrix metalloproteinases
NO	Nitric oxide
OSI	Oscillatory shear index
PDF	Probability density function
RBC	Red blood cell
RMF	Rotation minimising frame
SEF	Strain energy function
VSMC	Vascular smooth muscle cell
WSS	Wall shear stress
WSSG	Wall shear stress gradient



INTRODUCTION

An intracranial aneurysm (IA) is an arterial disease in which a localised distension can be observed on the surface of the wall. Given a relatively high incidence rate in the adult population, the rupture risk of IAs is not high at all, with less than 1% of detected aneurysms rupturing per year (Juvela, 2004). However, a severe secondary incident to the rupture of an IA is subarachnoid haemorrhage, which is accompanied by a very high mortality and morbidity rates (Brisman et al., 2006). Treatments of the disease is also associated with high morbidity and mortality rates.

Based on the facts above, one question immediately arises: if a patient is detected with an unruptured IA, should treatments be carried out or not? Given such a low risk of rupture, and the fact that the current interventional procedures for treating an unruptured aneurysm are not without risk, economically it would be best to only treat those aneurysms which have the potential to rupture and leave those which will not rupture untouched. This requires a criterion to help to identify which aneurysms are likely to rupture and which are not. The current criterion used to assess clinical interventions is predominantly based on the sizes (or more specifically, the diameters) of the aneurysms, which apparently do not account for patient specific variabilities including family history and life style, as well as haemodynamic variabilities (Ventikos et al., 2009). In addition, while it may seem intuitive that larger aneurysms are at greater risk of rupture, some small aneurysms do rupture (Lasheras, 2007). Hence there is an urgent need for a more rigorous criterion to

emerge.

The proposal of a better criterion requires improved understandings of the pathogenesis of the disease and the cause of its subsequent progression. These understandings will also assist the development of more sophisticated models of aneurysm growth, which will help to improve the prediction of growth and rupture risk of IAs, and help to determine the interventional treatment on a patient-specific basis. Unfortunately, although IAs have been studied for decades, the exact cause is still unknown. However, given the fact that IAs commonly occur in specific regions of the arteries, particularly regions of high curvature and bifurcations where blood flow is complex, it may be a reasonable argument that haemodynamics plays a significant role in the disease inception and progression. Hence understanding of which specific type of haemodynamic environment can trigger vascular cell response, and how exactly cells are responding to these haemodynamic stimuli, becomes particularly important.

In this chapter, the disease is generally overviewed first, before introducing the biological background of the arterial wall structure and constituents, including vascular cells. Following this, findings on arterial biomechanics and mechanobiology are summarised. Recently findings on the role of haemodynamics and mechanobiology on IA inception and growth is also reviewed in detail. Finally we outline the entire DPhil research, as well as the organisation of the thesis.

1.1 GENERAL OVERVIEW OF THE DISEASE

An intracranial aneurysm is a cerebrovascular disorder in which a localised dilation occurs to the cerebral blood vessel. Inflated by the blood pressure, these aneurysms usually appear as sac-like out-pouchings of the arterial wall. The estimated prevalence rates range between 0.4% and 6% (Rinkel et al., 1998; Wolfe et al., 2006) and the overall prevalence rate in a population without comorbidity is estimated to be about 3.2% (Vlak et al., 2011). Most remain asymptomatic; however, there is a small but inherent risk of rupture: 0.1% to 1% of detected IAs rupture every year (Juvela, 2004). If rupture occurs, there is a 30% to 50% chance of fatality (Brisman et al., 2006).

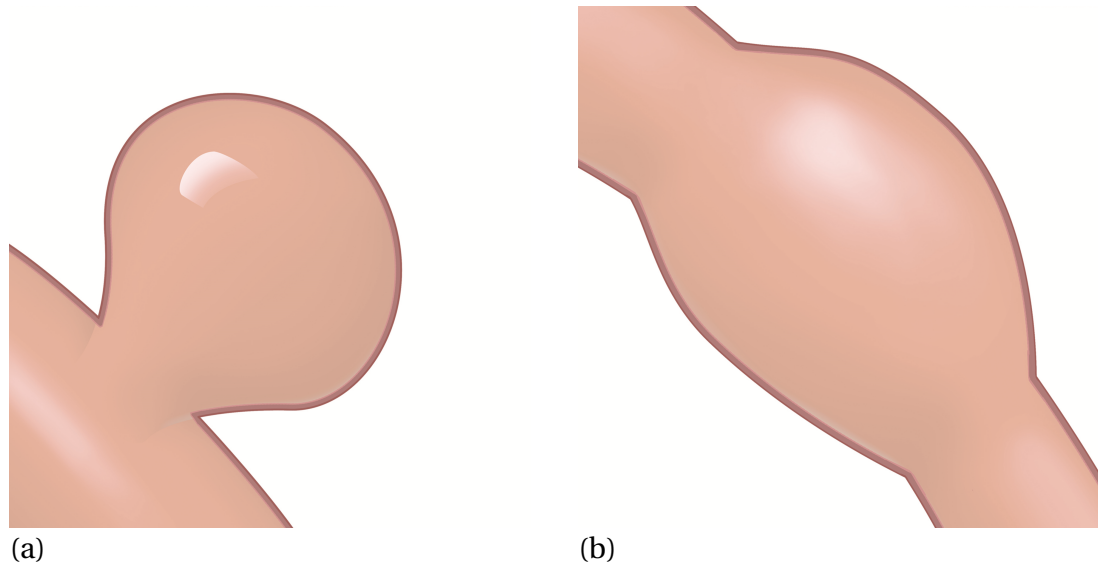


Figure 1.1: Saccular and fusiform aneurysms. (a) a saccular aneurysm, (b) a fusiform aneurysm

1.1.1 Classification

Morphologically, aneurysms can be generally categorised into two types: saccular aneurysms and fusiform aneurysms. A saccular aneurysm is a pouch on one side of the wall, whereas a fusiform aneurysm is spindle-shaped and usually develops when the arterial wall weakens along its entire circumference (See Fig. 1.1). Saccular aneurysms are most prevalently found on cerebral arteries, while fusiform ones are rarely seen among IAs but more commonly diagnosed in other parts of human body. The pathogenesis, symptoms and treatments greatly vary between these two types (Lasheras, 2007). Consequently these two types of aneurysms are usually distinguished and studied separately.

1.1.2 Locations

IAs generally occur at bifurcations, origins of branching and zones of sharp curvature. Approximately 85–95% of saccular IAs develop in the anterior part of the Circle of Willis.¹ The remaining 5–15% cases of IAs occur in the vertebra-basilar part in the brain known as the posterior circulation. Fig. 1.3 highlights the most prevalent sites

¹The Circle of Willis is an anastomotic system of arteries that sits at the base of the brain. All the principal arteries that supply blood to the cerebral hemispheres of the brain branch off from the Circle of Willis.

of IA formation around the Circle of Willis (Brisman et al., 2006).

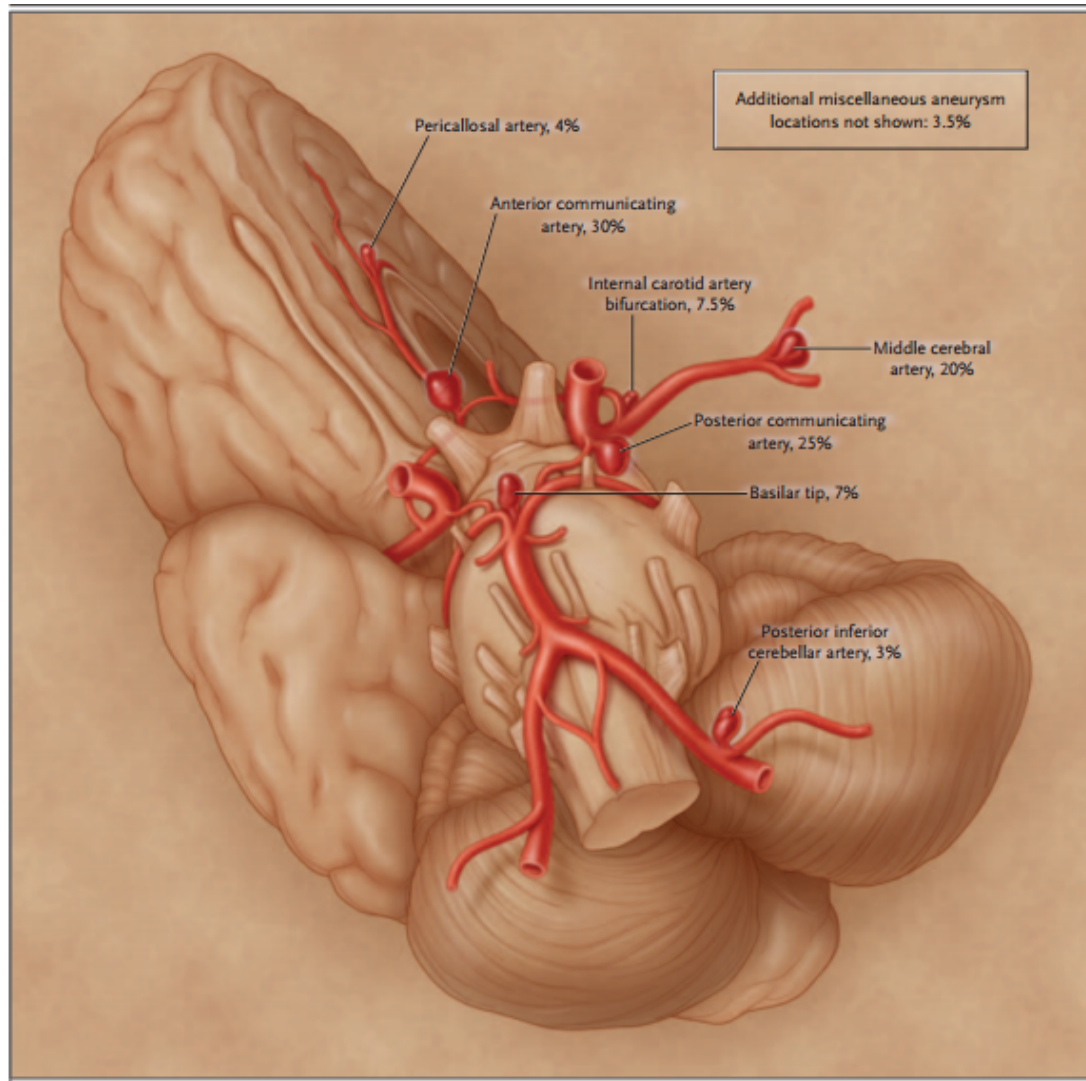


Figure 1.2: Most prevalent locations of IA formation (Brisman et al., 2006).

1.1.3 Identification of treatment

The identification and diagnosis of an IA is achieved by modern imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) or intracranial angiography (Forsting and Wanke, 2008). Relevant treatments for individuals with either a ruptured or unruptured cerebral aneurysm aim at stopping the blood supply to the aneurysm. Currently there are three major treatment options for cerebral aneurysms: surgical clipping of the aneurysmal neck, coil embolisation and flow diverter. During surgical clipping an MRI-compatible alloy clip is placed

across the base of the aneurysm neck after it has been exposed by craniotomy (Brisman et al., 2006); this will exclude the aneurysm from the blood circulation in the brain. A different approach is coil embolisation, where Guglielmi Detachable Coils are carried by a microcatheter and deployed in to the aneurysm to induce stagnation zones at the neck of the aneurysm (Viñuela et al., 1997; Murayama et al., 2003). Subsequently local thrombosis will initiate at the aneurysmal neck and occlude the blood flow into the aneurysm (Brisman et al., 2006). A third approach to treat an IA is the use of a flow diverter, which is a stent-like device deployed endovascularly. As opposed to coil embolisation, flow diverters are placed within the parent arteries rather than the IA sacs. They take advantage of changing the haemodynamics at the parent artery/aneurysm sac interface, altering in-flow and out-flow jets. Intracapsular thrombosis occurs over time after the deployment of the flow diverters. Subsequent inflammatory response, healing, and endothelial growth shrink the aneurysm and reconstruct the parent artery/aneurysm sac interface (Alderazi et al., 2014). In comparison with coil embolisation, flow diverters cause aneurysms to occlude over time rather than immediately at the end of the procedure (Alderazi et al., 2014). In addition to their individual use during IA treatment, flow diverters can be used in combination with coil embolisation, enhancing the function of coiling and prevent the coil from becoming displaced or uncoiled, which is a common problem for wide necked aneurysms (Akpek et al., 2005). This further expands the options of treatments available to clinicians and patients.

Studies have shown that the morbidity and mortality rates for surgical clipping range from 4.0–10.9% and 1–3%, whereas the rates for coiling are 3.7–5.3% and 1.1–1.5% respectively (Brisman et al., 2006). Risks of these two treatments involve cerebral artery occlusion, brain tissue damage, subarachnoid haemorrhage due to arterial and aneurysmal wall perforation and so forth. Flow diverters are also associated with risks, which include in-stent thrombosis, peri-aneurysmal edema, distant and delayed hemorrhages, and perforator occlusions (Berge et al., 2012). The choice of treatment depends on various factors such as the morphology of the aneurysm and its parent artery, operator availability and expertise, and of course, patient preference (Brisman et al., 2006). However, an estimated 80% of all aneurysms do not rupture during the course of a person's lifetime (Brisman et al., 2006). Ideally, we would only treat those IAs at risk of rupture. This would have both health and economic benefits. Unfortunately, the aetiology of this disease is still poorly understood, hence the great need for research in this field.

1.2 ARCHITECTURE OF THE HEALTHY ARTERY

Given that IAs evolve from a healthy cerebral artery, the starting point for understanding the aetiology of this disease is to have an appreciation for the biology of the healthy arterial wall structure. The arteries generally consist of three concentric layers: tunica intima, tunica media and tunica adventitia. Outside the adventitia there is also a network of small blood vessels called vasa vasorum which penetrate the vessel wall and secure blood supply to the large vessels. However, note that cerebral arteries have no vasa vasorum. An overview of the layered structure of an artery is shown in Fig. 1.3. Details of each layer is given below, with emphasis on the vascular cells in each layer.

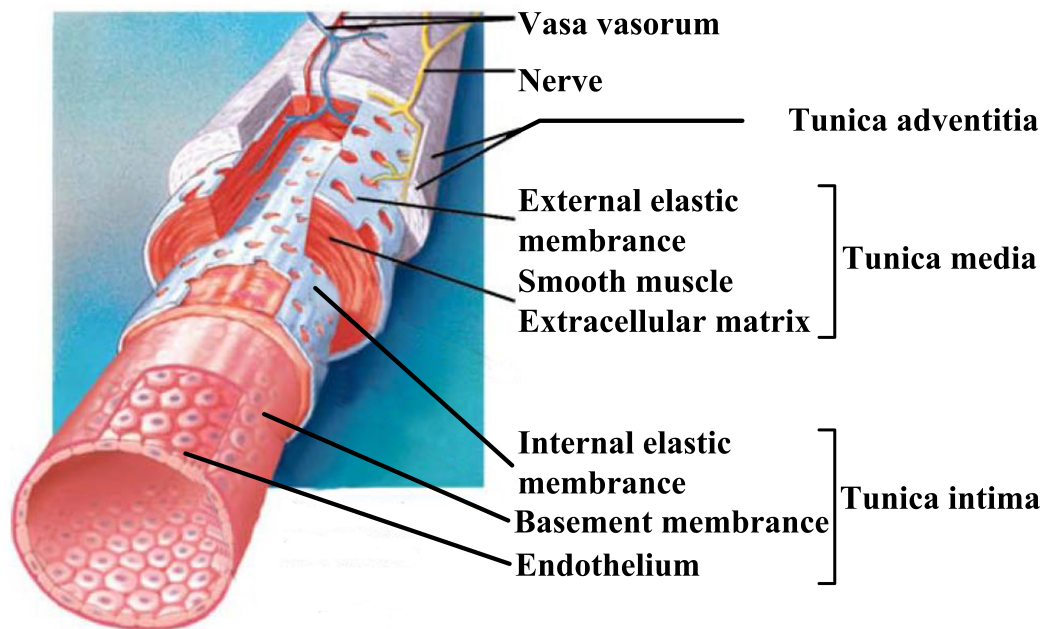


Figure 1.3: An overview of the layered structure of an artery (adapted from (Lasheras, 2007)).

1.2.1 The tunica intima

The tunica intima is the innermost layer of the vascular wall. It basically consists of a single smooth and ‘silky’ layer of endothelial cells (ECs) and is supported by the internal elastic lamina (IEL), which separates the intima from the media. These ECs are in direct contact with the lumen. In straight sections of a blood vessel, these ECs

typically align and elongate in the direction of fluid flow (Langille and Adamson, 1981). They act as a selective barrier between the vessel lumen and the surrounding tissue, controlling the passage of material and the transit of white blood cells into and out of the bloodstream. These cells also regulate various biochemical pathways such as vaso-constriction and vaso-dilation, blood clotting, reaction to inflammation, angiogenesis in wound healing and so forth (Eroschenko and Mariano, 2013).

1.2.2 The tunica media

The tunica media is the middle layer of the vascular wall. It is generally the thickest one of the three layers and contributes to the mechanical stretch of the vessel. It mainly consists of the vascular smooth muscle cells (VSMCs), elastic connective tissues and various types of collagen. The VSMCs are oriented helically about the vessel axis with a small pitch. The main function of these cells is to regulate the diameters of the blood vessels in human body. They contract or relax to change the volume of the artery and hence the local pressure. This regulating mechanism is responsible for the redistribution of the blood within the body to the areas where needed. In addition, due to their function of synthesising and secreting the elastic connective tissue, matrix degrading enzymes as well as proteoglycans, VSMCs are also deemed very critical in the process of aneurysm formation and growth (Kondo et al., 1998; Lee et al., 2001). The elastic connective tissue, which is bundles of elastic fibres, are very high in elasticity. These fibres can stretch up to several times of their original length, and then snap back when relaxed. This high elasticity is considered to be a result of the crosslinks formed among the protein molecules in the matrix.

1.2.3 The tunica adventitia

Separated from the tunica media by the external elastic lamina, the tunica adventitia is the outermost layer of the vascular wall. It is composed primarily of fibroblast cells (FCs), ground substance and collagen fibres. Anchoring the vessel to the surrounding tissue, the adventitia gives the entire vessel stability. The adventitia has no distinct outer border and its mechanical function is to prevent over-distension of the blood vessel wall (Eroschenko and Mariano, 2013). Fibroblasts synthesise the extracellular matrix and the collagen fibres, which help to maintain the structural integrity of the connective tissues. Hence fibroblasts are also known to play a critical role in wound healing.

1.3 BIOMECHANICS OF THE ARTERY

Being considered as a type of material supporting the pulsatile blood pressure, the artery has mechanical properties that are very different from common daily materials such as steel or glass. This difference is mainly attributed to the living organic structural constituents in the arterial wall, such as elastins, collagens, as well as some vascular cells, which are not only involved in bearing load, but also continuously degrade and deposit these structural constituents. Some salient mechanical properties of the arteries include:

1. *Nonlinearity.* One predominant mechanical property of the artery is its non-linear mechanical response, which is a result of the compound contribution from different vascular constituents. At low blood pressures, the load in the artery is mainly borne by the elastinous constituents as the collagen fibres are initially crimped, hence at this stage the artery behaves more like a linearly elastic material. With increasing pressures, due to the progressively straightening and recruitment of the collagen fibres, the artery presents an exponential stiffening effect (Shadwick, 1999; Holzapfel et al., 2000).
2. *Axial in situ stretch.* It is observed that when the artery is removed from the body it will become shortened. Hence arteries are known to be subjected to an axial in situ stretch within the physiological environment.
3. *Residual stress.* Experiments show that if an unloaded arterial ring is cut in the radial-axial plane then it will open and bend away from the axis of the artery. This implies that the stress-free state of the artery is different from its load-free state (Holzapfel et al., 2000), i.e. there exists a residual stress in the arterial wall.
4. *Heterogeneity.* Heterogeneity of the arteries mainly relates to their layer-specific mechanical properties. Experiments show that under lower pressures, the adventitia is less stiff than the media, due to the unloaded wavy adventitial collagen fibres. However, as the pressure increases, these fibres are stretched and the stiffness of adventitia grows very rapidly. Hence, under high pressures, the mechanical response of the media and adventitia is found to be very similar (Sommer, 2008). This also indicates that the collagen fibres are the main constituents which are responsible for the arterial stiffness in this

range. In addition to the layer-specific heterogeneity, the arterial mechanical properties are also known to be different among different arteries, and among different individuals. They can also adapt with physical exercise, age and disease.

5. *Anisotropy*. It is commonly acknowledged that the mechanical response of the artery is anisotropic with respect to the circumferential and axial directions. This has been evidenced by experiments on both animals and humans, although some disparities exist. The cause of arterial anisotropy may be linked to the distribution of collagen fibre orientations with respect to the circumferential axis, as well as the alignment of VSMCs along the circumferential direction.
6. *Incompressibility*. A common assumption for the arterial wall is its incompressibility, due to its high water content (70%–80%). Experimental studies supporting this assumption claim that, although due to the stress gradient there is some transportation of small portions of fluids within the tissue, the incompressibility condition is maintained at least globally (Sommer, 2008).
7. *Viscoelasticity*. Due to the fluid transportation within arterial wall and the friction between the fluids and solid constituents, arteries also present a certain level of viscoelastic behaviour. This is evidenced by experiments of arterial creep and stress relaxation, as well as hysteresis in arteries under cyclic loads (Gasser et al., 2006).
8. *Active mechanical response*. In addition to all the passive mechanical responses detailed above, vascular smooth muscle cells (VSMCs) also actively contract or relax to help maintain the local blood pressure by changing the volume of the lumen.

To summarise, arteries generally exhibit a nonlinear, heterogeneous, anisotropic and even viscoelastic character that is temporally, spatially and individually different. Fig. 1.4 below shows the overall mechanical response of the arterial tissue, together with the linear response of elastinous constituents and the non-linear response of collagenous constituents.

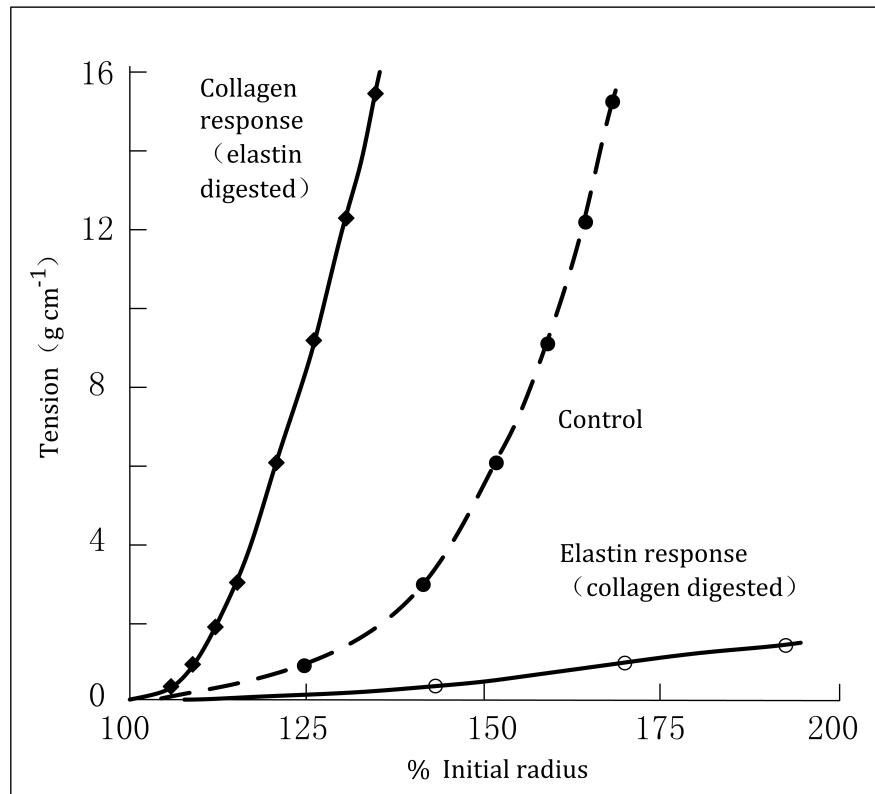


Figure 1.4: The tension-length response of human iliac arteries with contributions from the elastins and collagens. The elastin-only response is shown as the line with unfilled circles. The collagen-only response is shown as the curve with diamonds. The ‘control’ curve shows the overall response of the artery (adapted from Shadwick (1999)).

1.4 ARTERIAL TISSUE MECHANOBIOLOGY

Mechanobiology is usually referred to as the interdisciplinary field of biology and engineering, focusing on the study of how physical forces acting on the cells contribute to the tissue physiological development, daily functionality, and even disease progression. In our real life, there have already been many practical application of this subject, such as the use of tissue expanders to increase the skin area during reconstructive surgery, the use of surgical tension devices to heal bone fracture etc. Nevertheless, it seems that both the understanding and application of mechanobiology in the environment of arterial tissues are limited. The current consensus regarding the underlying mechanisms that provoke the inception of an IA and drive its successive growth appear to be the complex interplay between the patho-physiological process triggered by inherited biochemical or structural defects, aging, infection or disease and the arterial tissue *patho-mechanobiological*

factors (Lasheras, 2007, 2010). Hence understanding of relevant knowledge in arterial mechanobiology and appropriate representation of the knowledge within models of arterial tissue will provide insight into the mechanisms behind the IA disease.

In general, mechanobiology can be considered from the following two aspects:

- the mechanical stimuli that cells sense and the associated physical/chemical/electrical response that cells exhibit under these mechanical stimuli;
- the exact molecular mechanism through which cells can sense the mechanical signals and respond accordingly (this is also known as mechanotransduction).

For arterial tissue, cells are embedded in a complex mechanical environment and acted on by various types of forces (for example, see Fig. 1.5). It is obvious that these cells can respond differently under distinct types of forces, such as axial and circumferential stresses in the tissue, blood pressure, the cyclic strain due to distension of the artery, and the shear stress induced by the blood flow, i.e. the wall shear stress (WSS) (Wang and Thampatty, 2006). For example, the endothelial cells lying on the intimal layer of the arterial wall are in direct contact with the lumen and are able to sense the WSS and convert it to biochemical signals. Moreover, vascular cells even seem to respond differently under the same type of force but with distinct magnitudes (Hoffman et al., 2011). It has been hypothesised that these ECs can also sense the gradient of the magnitude of the WSS, i.e. wall shear stress gradient (WSSG), and can distinguish between positive and negative gradients, i.e. whether the magnitude of the gradient increases or decreases in the direction of the flow (Meng et al., 2011). As Chien (2007) discusses, directed mechanical forces acting on ECs influence the regulation of inflammatory and proliferative pathways. Mechanical forces with a clear direction such as the pulsatile shear stress resulting from strong forward or the laminar flow in straight arteries, cause a transient activation of pro-inflammatory and proliferative signalling pathways, which become down-regulated when such forces are sustained. In contrast, mechanical forces without a definitive direction, e.g. disturbed flow observed at branching regions, result in a sustained activation of pro-inflammatory and proliferative pathways. While ECs are primarily affected by the blood flow due to their direct contact, VSMCs seem to be primarily affected by the cyclic stretch which is caused by the pulsatile changes in blood pressure (Haga et al., 2007; Li and Xu, 2007). The influence of cyclic stretches on

VSMCs has only received more attention recently, however, it has been shown that cyclic stretches affect the orientation, alignment, signaling, proliferation and even the phenotype of VSMCs (Birukov et al., 1995; Nguyen et al., 2000; Standley et al., 2002). For example, it has been observed that in the diseased arteries VSMCs switch from a normal *contractile* phenotype to a *proliferative* phenotype (Opitz et al., 2007). As for the fibroblast cells in the adventitia, since they attach themselves to the surrounding ECM, they tend to be affected more by the strains that they experience during the cardiac cycle. An increase in strain usually results in an increase in the rate of ECM material synthesis, and a decrease in the rate of matrix-degrading enzymes production, consequently an increase in the ECM production. On the contrary, a decrease in strain will produce an opposite result (Wang and Thampatty, 2006).

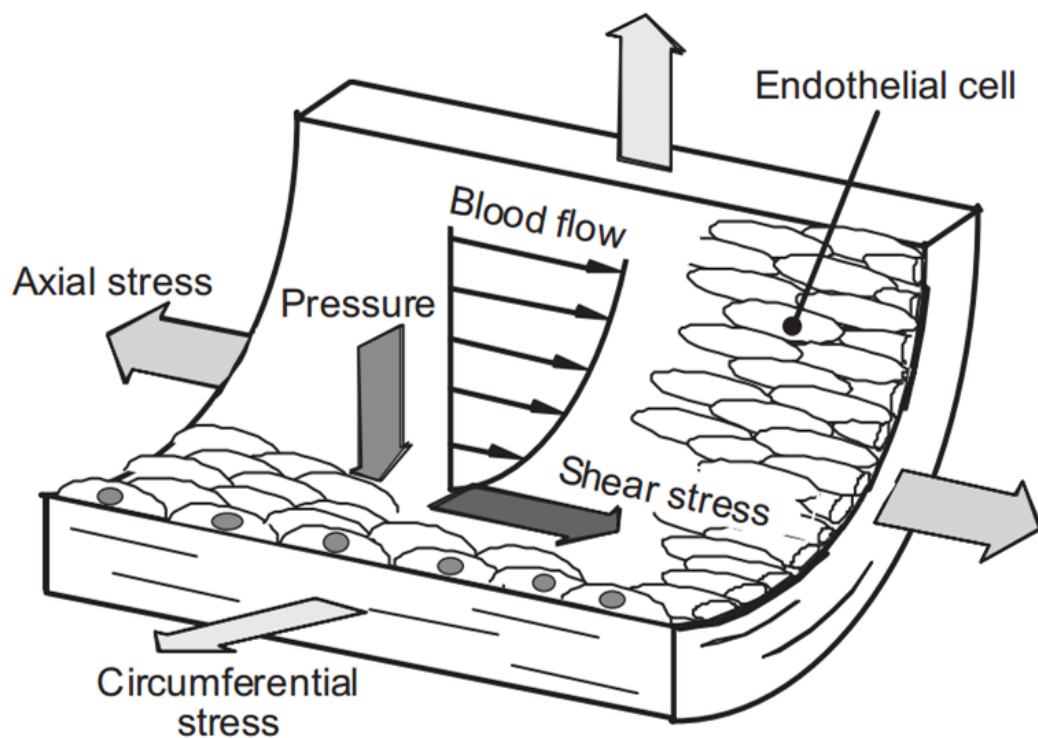


Figure 1.5: Endothelial cells are embedded in a complex mechanical environment and exerted on by various types of forces, including axial and circumferential stresses, pressure, and shear stresses induced by the blood flow (Ohashi and Sato, 2005).

The cooperation and coordination among different vascular cells are so important in non-pathophysiological arterial wall remodelling that together they consti-

tute an auto-regulation system which is vital in our daily life and protects the artery from the onset of many diseases such as atherosclerosis. For example, in response to an increase in the blood flow (and thereby WSS) which can be sensed by the ECs, the release of nitric oxide (NO) is up-regulated. NO is known to be involved in the activation of matrix metalloproteinases (MMPs) (Metaxa et al., 2008), which act to degrade the ECM and IEL. The degradation of the ECM and IEL then allows the expansion of the arterial wall scaffold (Hashimoto et al., 2006; Kolega et al., 2011). NO can also relax the VSMCs to cause vasodilation. Additionally, increase in the blood flow also results in down-regulation of endothelin-1 production, which act on VSMCs to constrict the vessel (Black et al., 2000). The consequence of this complex physiological process is the dilation of the artery, and the dilated arterial lumen restores WSS to a homeostatic level. Meanwhile, synthesis of additional ECM, and proliferation of ECs and VSMCs also occur to cover the newly enlarged surface (Hashimoto et al., 2006; Kolega et al., 2011). However, in the case where the artery is exposed to a prolonged increase in flow, the arterial wall constituents may remodel to achieve an entirely new state of homeostasis (Humphrey, 1999).

As stated at the beginning of this section, the other aspect of arterial mechanobiology that we should consider is the exact molecular mechanism through which vascular cells can sense the mechanical signals and respond accordingly, i.e. how exactly mechanical stimuli activate cellular mechanosensors, signaling pathways, as well as gene and protein expressions (see Fig. 1.6). This process is commonly referred to as ‘mechanotransduction’. A key component of the mechanotransduction process is the cellular cytoskeleton, which is a network of protein fibers contained within the cells’ cytoplasm. The cytoskeleton is usually described as a dynamic stress-bearing structure, as it governs cell shape, and parts of it can be constantly destroyed, renewed or newly constructed (Alberts et al., 2008; Kolahi and Mofrad, 2010). Additionally, the cytoskeleton also provides a mechanical link between the intracellular and extracellular environments. It can bind either directly or indirectly to the shear stress receptors of the ECs, hence can undergo rapid changes in response to flow, cellular movement or shape change (Resnick et al., 2003; Kolahi and Mofrad, 2010). For example, ECs seem to be able to response to the directed mechanical stimuli by remodelling the cytoskeleton structure to minimise the change in intracellular stress/strain from the homeostatic levels, and induce adaptive changes in EC signalling (Chien, 2007). The deformation of the ECM by mechanical forces can also be transduced into the cells by stretch-activated ion

channels and by some transmembrane receptors, such as integrins, which attach the cells to the ECM (Salameh and Dhein, 2013). These integrins couple the ECM outside the cells to the cytoskeleton inside the cell, and their interactions lead to transmission of mechanical loads into the cell, resulting in both intracellular and extracellular responses (Okada et al., 1998).

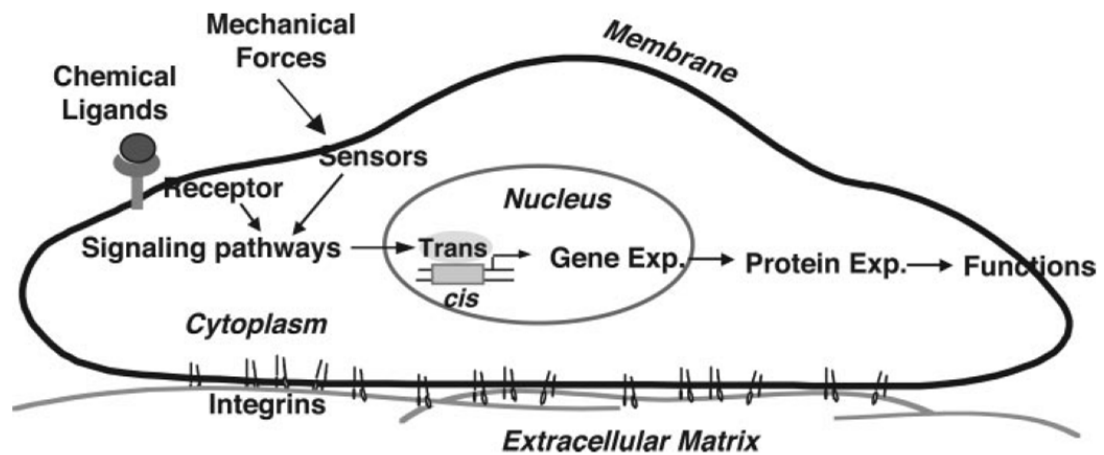


Figure 1.6: The activation of a complex chain of cellular signalling pathways in response to the extracellular mechanical stimuli (Chien, 2007).

To summarise this section, we see that, although these vascular cells may not contribute highly to the bulk mechanical response of the arterial wall, understanding the relevant knowledge of the mechanobiology of these cells and appropriate representation of them within arterial models are obviously helpful in gaining more insight into the mechanisms behind the IA disease.

1.5 IA INCEPTION AND GROWTH: THE ROLE OF BIOMECHANICS AND MECHANOBIOLOGY

In general, the aetiology of IA development has been investigated for decades but is still not clearly understood. The current consensus appears to be that the cause is more likely due to a complex interplay among the pathophysiological processes triggered by inherited biochemical or structural defects, ageing, infection or disease and specific haemodynamic factors (see Fig. 1.7). In spite of this, how each factor exactly contributes to the aneurysm initiation is poorly understood (Lasheras, 2007, 2010).

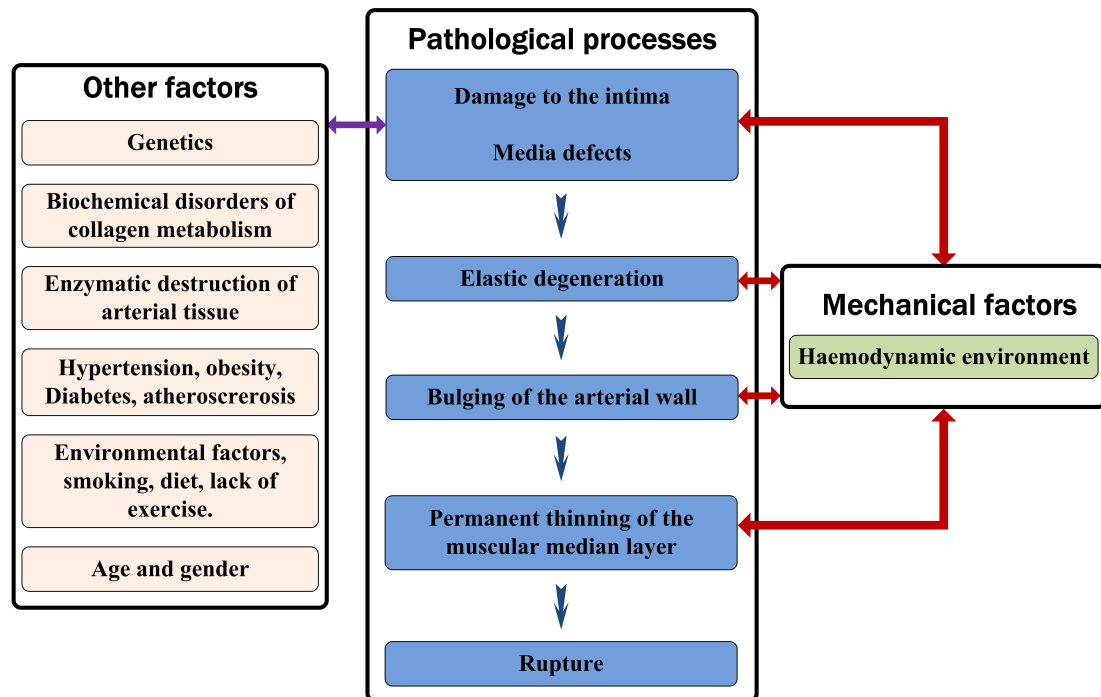


Figure 1.7: Interplay between mechanical stimuli and other physiological processes on the inception of IAs. The inception of an IA is more likely to be triggered by a complex interplay among different pathophysiological processes (adapted from Lasheras (2010)).

The influence of arterial haemodynamics on the initiation and progression of aneurysms has been suggested by many studies both experimentally and computationally (Meng et al., 2007; Shimogonya et al., 2009a; Meng et al., 2011; Chen et al., 2013 et. al.). In the following sub-sections, we briefly overview some important finding and conclusion from these previous studies.

1.5.1 The role of biomechanics and mechanobiology on IA inception

As introduced in Sec. 1.4, ECs lying on the intima layer of the vessel wall are in direct contact with the lumen and are able to sense the wall shear stress induced by blood flow and convert it into biochemical signals such as nitric oxide (NO) (Lasheras, 2007, 2010). These biochemical signals have been shown to activate signalling pathways which control the functionality of the artery, such as vasodilation and vasoconstriction. One significant result of this complex biochemical process is the recovery of WSS to its homeostatic level in response to either short time changes caused by,

for example, exercise, or chronic changes in the arteries. This entire process functions as a feedback controlling system which is essential to the human body's auto-regulation. In addition, these signalling pathways may also facilitate a change in the constitution and the structural integrity of the arterial wall (Freese, 2005). During normal ageing, the cerebral arteries gradually undergo morphological changes in their geometry, which may in some cases lead to the formation of bend, kinks, or other types of geometric irregularities. These geometric irregularities may create 'disturbed flow' conditions inside the lumen. It may be argued that these disturbed haemodynamic conditions may trigger some anomalous response in vascular endothelial cells, resulting in abnormality in the signalling pathway. This may destabilise the aforementioned feedback controlling system which is usually stable, and lead to irreversible destructive remodelling in the constitution. These factors together could contribute to an unstable progressive weakening of the structural integrity of the arterial wall and eventually result in the initiation of the aneurysm (Lasheras, 2010).

Histological observations have revealed that, during the inception of an IA, it seems that the loss of the IEL is the first prominent change in the wall (Meng et al., 2011; Frösen et al., 2012). This is followed by the apoptosis of VSMCs, which appears to be the key difference between normal and destructive arterial wall remodelling (Frösen et al., 2012). Due to the loss of the IEL and VSMCs, the weakened arterial wall is prone to be influenced by the blood pressure and protrude out to form a bulge on the surface. An infiltration of inflammatory cells into the arterial wall then follows (Frösen et al., 2012).

Both experimental and computational studies have focused on investigating the role of haemodynamics in cerebral aneurysm inception. To quantify the haemodynamic environment in the lumen, several haemodynamic indices have been proposed in the literature, for example, wall shear stress (WSS), wall shear stress gradient (WSSG), the Oscillatory Shear Index (OSI), the Aneurysm Formation Indicator (AFI) and the Gradient Oscillatory Number (GON). More details regarding the definitions and the calculations of these will be provided in Sec. 3.3. These indices focus on different aspects of the flow and are supported by different studies in the literature dedicated to investigating which is the most prominent index related to aneurysm inception. However, as later will be discussed in details, the most acceptable hypothesis on the role of haemodynamic indices on aneurysm inception is that

of the WSS and its combination with WSSG.

In the study led by Meng et al. (2007), results of the CFD studies are compared with the histological examinations of the arterial wall at artificially created bifurcations in six dogs. Three regions were reported: an impingement region (with high WSS and WSSG) where normal remodelling occurs, an acceleration region (with even higher WSS but slightly lower WSSG) where destructive remodelling is observed resembling early histological observations of the aneurysmal wall, as well as a recovery region (with baseline level of WSS) where no change to the wall is observed. Based on these observations, it is concluded that the combination of high WSS and high WSSG form a dangerous haemodynamic environment, which may induce aneurysmal remodelling. Follow-up studies from the same research group conducted on rabbits also show similar results, i.e. an initial insult of high WSS and high WSSG triggers early destructive remodelling, which leads to aneurysm development (Meng et al., 2011; Kolega et al., 2011).

As ECs are the main type of vascular cell of the arterial wall that sense the WSS, many in-vitro studies have also been performed using EC-embedded flow chambers to investigate the effect of WSS and its possible combination with WSSG on EC shape, alignment and their biochemical production. In a healthy artery, ECs are usually elongated and aligned with the direction of flow (Chien, 2007). Depaola et al. (1992) found that under the condition of elevated WSS, ECs tend to be both elongated and aligned with direction of flow. They also found lower cell density in regions of high WSS and high WSSG compared with regions of high WSS and low WSSG. However, surprisingly, cell divisions are observed to occur in the regions of high WSS and high WSSG, which implies that high WSSG induces cell division but drives them to migrate away. Metaxa et al. (2008) shows that an increased production of endothelial nitric oxide synthase (eNOS) occurs in bovine ECs at elevated WSS. Interestingly, they also claim that the integrity of ECs can be maintained for a very high level of WSS as long as the flow is laminar. Consistently, LaMack and Friedman (2007) also found that expression of eNOS transcriptional factors increases with WSS magnitude, but was independent of WSSG. In addition, they found that the expressions of MCP-1 (short for Monocyte Chemotactic Protein 1 which is a key molecule facilitating the binding of monocytes to the arterial wall) and ICAM-1 (short for Intercellular Adhesion Molecule 1 which is a molecule involved in the maintaining of tight junctions between adjacent ECs), are dependent on the inter-

action of WSS and WSSG. However, the former one has the highest expression when both WSS and WSSG are high whereas the latter one has the highest expression when WSS is high but WSSG is low. Sakamoto et al. (2010) found that ECs will always eventually align themselves in the direction of flow regardless of the magnitude of WSS if no WSSG is present. However, if WSSG is present, ECs tend to remain polygonal without a preferred alignment. Most recently, Ostrowski et al. (2014) found that at high confluency ECs migrate against the direction of the flow and concentrate in the region of high WSS, whereas at low confluency they migrate in the flow direction. However, inconsistent to the findings of Sakamoto et al. (2010), they found at low WSS ECs tend to align parallel to the flow but when the local WSS arises above a critical threshold, then ECs will orient perpendicularly to the flow direction. To conclude, the consistent finding among the studies above is that ECs seem to respond to elevated WSS over time. However the effect of WSSG on the ECs is uncertain, not to mention the combination of these two indices. The interaction of WSS and WSSG might be of significance only if their magnitudes reach a certain level. A more detailed discussion of the magnitudes of haemodynamic indices is provided in Sec. 3.6.

Then the final question arises: mechanobiologically, how exactly does a combination of high WSS and high WSSG trigger the inception of an aneurysm? As introduced in Sec. 1.4, ECs exposed to elevated WSS release vasodilation factors such as NO to remodel the wall (Hoi et al., 2004). NO is known to be involved in the activation of MMPs, which degrade the ECM and dilate the arterial wall by relaxing VSMCs (Metaxa et al., 2008). Under sustained high WSS conditions, the degradation of the ECM is also sustained, so is the degradation of the ECM. This may be the potential factor that decreases the mechanical strength of the wall (Hoi et al., 2004). Interestingly, however, under high WSSG conditions, the loss of intercellular adhesion may occur, resulting in dysfunction of the ECs which further leads to a loss of eNOS activity. This leads to a reduction in NO production, and hence reduction in VSMCs relaxation, and finally inhibits vasodilation (Hahn and Schwartz, 2008; Nixon et al., 2010). In addition, high WSSG also increases EC migration, resulting in a decrease in MMP inhibitors (Meng et al., 2007; Tanoue et al., 2011). On this aspect, high WSSG actually seems to play a protective role to prevent the wall from being further destructed. Consequently, under high WSS/high WSSG conditions, it seems more likely to be a combination of normal and abnormal remodelling that starts to destruct the IEL. The initial bulge forms on the wall leads to the forma-

tion of a region of reduced WSS but elevated WSSG. The migration of ECs begins and the intracellular gaps become wider in the initial bulging region. The locally low WSS encourages the adhesion of inflammatory cells, which may more easily penetrate the wall and induce apoptosis of the VSMCs (Tanoue et al., 2011; Hosaka and Hoh, 2014). In return, the thinning of the media layer due to VSMC apoptosis may even facilitate more inflammatory cell infiltration (Aoki and Nishimura, 2010; Tanoue et al., 2011).

The hypothesis regarding the role of combinations of high WSS and high WSSG is also supported by several computational fluid dynamics (CFD) studies (Baek et al., 2009; Singh et al., 2010; Chen et al., 2013). One similarity among these studies is that the original aneurysm was virtually removed and a healthy ‘pre-aneurysmal’ artery was analytically reconstructed. Subsequently CFD simulations are performed on the reconstructed arteries to calculate the indices of interest, and the correlation between these indices and known locations of the aneurysms is finally analysed.

Beyond disruption of the IEL, another common pathological feature of early aneurysm formation or early aneurysmal change seems to be the atherosclerotic change within aneurysm wall (Chalouhi et al., 2012). According to Kosierkiewicz et al. (1994) and Killer-Oberpfalzer et al. (2012), atherosclerotic lesions are present in all saccular IAs. Kosierkiewicz et al. (1994) observed diffuse intimal thickening and macrophages/lymphocytes in the smallest aneurysms, as well as more advanced atherosclerotic lesions with phenotypically modulated VSMCs, lipid-laden macrophages, and lymphocytes in the largest aneurysms. In fact, atherosclerosis is a disorder in which chronic inflammation is a critical pathogenic feature. Therefore, the possible association of IA with atherosclerosis implies that the critical role of inflammation in the pathogenesis of atherosclerosis may also underlie IA formation (Chalouhi et al., 2012). Haemodynamic conditions such as stagnation blood flow with oscillatory WSS can prolong the residence time of atherogenic particles near the wall. This induces more focal lipid exchange and recruitment of macrophages, and may activate atherogenic and proinflammatory signaling pathways in ECs that support the inflammatory process resulting in atherogenesis (Sugiyama et al., 2013). This hypothesis suggests that stagnant and oscillatory blood flow may be one of the key conditions for atherosclerotic lesion formation in IA. Based on this hypothesis, one specific haemodynamic index, the OSI, which relates to the oscillatory nature of the flow and has well-established relationships to atherosclerosis (Mantha et al.,

2006), is believed to have a similarly pathogenic effect on the initiation of IAs (Watton et al., 2011a). Other similar indices, such as AFI and GON, are also supported by some studies, in particular computational studies, to have potential relationships with the inception of IA (Mantha et al., 2006; Ford et al., 2009; Shimogonya et al., 2009a). More details on these indices, as well as their supporting studies, are introduced in Chapter 3.

As introduced in Sec. 1.2.2, the media layer of the artery mainly consists of an integrated assembly of VSMCs, elastic connective tissues and various types of collagen fibres. Crosslinks between the ECM components and the VSMC-ECM interactions endow the artery with adequate mechanical properties to bear the blood pressure. However, the media layer degenerates in aging arteries: it gradually thins out, and the elastic connective tissues become fragmented and unorganized. This degeneration is accompanied by an increase of a much stiffer structural collagenous substance. In addition, these collagenous substance tends to bind to glucose molecules, forming crosslinks known as advanced glycation end products (AGEs). The accumulation of the AGEs alters the physical properties of the collagen fibres, causing them become less supple but even stiffer (Lee and Oh, 2010). As a result, the vessel progressively stiffens and loses its elasticity (Lasheras, 2007). Vascular calcification due to aging may also contribute to the stiffening of the arteries as well as their loss of distensibility (Blacher et al., 2001; London et al., 2013). Atherosclerosis is also closely related to arterial aging. Decreased availability of nitric oxide in the endothelium is considered as one of the earliest signs of arterial aging and a pathological sign of atherosclerosis (Glasser et al., 1996; Brandes et al., 2005; Yildiz, 2007). In the aging arteries, endothelial nitric oxide synthase (eNOS), which is necessary in producing nitric oxide in the ECs, is often in short supply. This can prevent the ECs from functioning properly. These aging ECs tend to cause leukocytes to adhere to themselves, weakening the barrier between the endothelium and other layers of the artery, and allowing fats, cholesterol, platelets as well as other substances to accumulate in the artery walls. This accumulation can in turn stimulate other arterial wall changes, leading to the additional thickening of the endothelium and the formation of plaques (Hansson, 2005). Atherosclerotic deposits of plaques could massively decrease the cross-sectional area of the lumen of the arteries. In some arteries, together with the stiffening of the wall, the decrease of the arterial lumen may result in an increase in the arterial pulsation. Over time, this increased arterial pulsation can have a direct effect on the structural elastic connective tissues, reorgan-

ising their polymerised structure and causing the already fragmented elastic fibres to further fatigue and fracture at levels of tensional stresses much lower than which they were previously able to withstand (Lasheras, 2007; Lee and Oh, 2010). This initiates and propagates cracks in the elastic sheets, causing a progressive permanent focal dilatation of the vessel. The permanent stretching of VSMCs then up-regulates the content of the collagenous substances, further stiffening the arterial wall. The entire age-related changes in the arterial structure may create a vicious cycle of arterial properties which renders the artery more vulnerable to the inception of an IA. Certainly, this process can be compounded and accelerated by any other various comorbid risk factors, which are invariably highly prevalent among the elderly. (Lasheras, 2007).

To summarise this section, the predominant model for IA formation based on many studies in the literature is: (1) EC damage and degeneration of the elastic lamina, (2) infiltration of the inflammatory cells and (3) chronic deterioration of the arterial wall. EC damage can be caused by changes in the haemodynamic environment, in particularly elevated WSS and its possible combination with high WSSG. This results in sustained degradation of the ECM. Subsequently, infiltration of various inflammatory cells follow, inducing apoptosis of the VSMCs and further destructive remodeling of the artery wall. This possibly leads to the formation of an IA (Hosaka and Hoh, 2014). In addition, IA inception seems to be usually accompanied by atherosclerotic changes within the aneurysm wall, and is more prone to occurring in aging arteries.

1.5.2 The role of biomechanics and mechanobiology on IA growth

In general, the major hypotheses regarding the haemodynamic condition that drives the successive growth of IA can be divided into two categories: the high WSS theory and the low WSS theory.

In the high WSS theory, it is assumed that similar processes which are responsible for aneurysm inception, as introduced in Sec. 1.5.1, are also involved in subsequent aneurysm growth. In this case, the major studies within the literature that support this theory involve taking follow-up images of patient aneurysms and performing CFD simulations, or running CFD simulations on multiple cases of segmented aneurysm geometries directly (Shojima et al., 2004; Tateshima et al., 2007; Sforza et al., 2012).

On the other hand, in the low WSS theory, a common thought is that low WSS may result in inflammatory cell infiltration, which is the main factor that drives the successive growth of IAs. It is hypothesised that low WSS can induce an inflammatory response from the ECs, which involves the release of MMPs by macrophages. These MMPs continue to degrade the ECM, resulting in structural deterioration of the arterial wall (Aoki and Nishimura, 2010; Kanematsu et al., 2011; Cebal and Meng, 2012). In addition, it seems that low WSS can also increase both the proliferation and apoptosis rates of ECs, leading to a high turnover of the cell, which may further render the wall vulnerable to inflammatory cell infiltration (Malek et al., 1999; Paszkowiak and Dardik, 2003; Boussel et al., 2008).

As an IA enlarges, the flow patterns in the aneurysmal vessel diverge away from the healthy artery due to an alteration of local geometry. In general, blood flows into the aneurysm dome along the proximal wall of the dome and leaves this section along the distal wall during the acceleration period of systole. However, due to the low pressure during the deceleration period of systole and diastole, blood changes its flow direction, entering along the distal wall of the cavity and leaving along the proximal cavity wall (Rossitti, 1998). These jets and recirculations of the blood flow occurring in the aneurysm dome may cause prolonged residence times. Although low WSS has been shown to cause endothelial dysfunction, several studies hypothesise that it is mainly the presence of a high WSSG that triggers the destructive remodelling and inflammation process (Jou et al., 2005; Doenitz et al., 2010; Tanoue et al., 2011; Sugiyama et al., 2012). The explanation for this is somewhat similar to the aforementioned mechanism of how high WSSG is related to aneurysm inception: under disturbed flow conditions, ECs show no preferential alignment and exhibit a polygonal shape (Chien, 2007). This results in widened junctional gaps between adjacent endothelial cells and may affect permeability of the endothelium to allow monocytes to penetrate. It seems that transendothelial permeability is more likely to elevate in low WSS conditions, especially in the presence of large WSSG field (LaMack et al., 2005). The residence time of inflammatory cells near the arterial wall is increased due to the disturbed flow, and monocyte adhesion to ECs also seems to be increased under conditions of high WSSG (Hashimoto et al., 2006; Szymanski et al., 2008; Wang et al., 2009; Tanoue et al., 2011). As a result, together with the more permeable endothelium layer, these inflammatory cells are much easier to attach to and penetrate the arterial wall. In addition to all of this, as discussed in Sec. 1.5.1, high WSSG can also induce EC migration away from the region of high

WSSG, which could further facilitate the infiltration of inflammatory cells into the wall, resulting in a weakened wall strength.

Due to the pulsatile nature of the blood flow, the arterial wall is subjected to a perpetual cyclic stretching. The long-term influence of this cyclic stretching on IA evolution is still poorly understood. One possible direct influence is that an increased frequency of cyclic stretching may lead to hastened fatiguing of the wall, eventually resulting in IA rupture (Meng et al., 2014). However, more importantly, cyclic stretching may influence the IAs by regulating the vascular cells embedded in the arterial wall. In fact, the three primary vascular cells (ECs, VSMCs and fibroblast cells) are all known to be exquisitely sensitive to the cyclic stretching. It has been observed that the alignment, activity, biochemical production, functionality and even apoptosis of these cells can be affected by the alteration of the cyclic stretches to which they are subjected. For example, Sotoudeh et al. (1998) observed that EC activity increases significantly when these cells are subjected to 15% or more cyclic stretches. Their production of endothelin 1 (a vasoconstrictor protein) and eNOS are also increased under elevated cyclic stretches (Humphrey, 2009). Hayakawa et al. (2001) reported that cyclic stretching on rat VSMCs *in vitro* could produce rapid reorganisation of the stress fibers perpendicular to the stretching direction. Albinsson et al. (2004) observed that longitudinal cyclic stretching of the vascular wall can lead to actin polymerisation. Both Cunningham et al. (2002) and Na et al. (2007) found that increased cyclic stretching imposed on VSMCs resulted in a rapid but transient increase in the expression level of focal contact-associated components (vinculin and paxillin), suggesting that cyclic stretching may strengthen the number and size of focal adhesion complexes. Humphrey (2008) noted that increased cyclic stretch can increase VSMCs' secretion of angiotensin II production and AT₁ receptor (angiotensin II receptor, type 1) sensitivity, which, in turn, can stimulate the production of TGF- β (transforming growth factor beta), eventually causing an increased production of collagen. Rubbens et al. (2009) found that *in vitro* cells align perpendicular to the direction of cyclic stretching in monolayers whereas align in the direction of cyclic stretch in three-dimensional environments. Shin et al. (2002) and Humphrey (2008) observed that cyclic pressure can also modulate the apoptosis and proliferation of the vascular cells. Apart from these researches, there are also other studies investigating the combined effect of cyclic stretch and WSS, which seems to work either synergistically or antagonistically on EC response (Dolan et al., 2013). For example, alignment (Moore et al., 1994) and

stress fiber formation (Zhao et al., 1995) in ECs subjected to WSS appear to be enhanced by the addition of cyclic stretch. However, if WSS is applied to counteract the orientation responses of the ECs due to cyclic stretch, then WSS and cyclic stretch are observed to cancel each other's effects on ECs (Owatverot et al., 2005). For more details of how cyclic stretching can influence the functionality of the vascular cells, interested readers are suggested to refer to (Qiu et al., 2014). Clearly, the evolving cyclic stretching of the arterial tissue has significant consequences for vascular cells, and thus evolution of IAs (Watton et al., 2011a). Consequently, when modelling IA evolution, ideally, these consequences should be considered.

Similar to abdominal aortic aneurysms (AAA), the formation of intraluminal thrombus (ILT) is also one of the common complications during IA growth (Workman et al., 2002; Cohen et al., 2010), though ILT in IAs has not been investigated as extensively as that in AAAs. It is observed that in comparison with small IAs, thrombus formation seems more likely to occur in the giant ones (Nagata et al., 1990; Gerber et al., 1994). ILT acts as a double-edged sword during IA growth. On one hand, ILT formation is the first step leading to permanent aneurysm repair through cicatrization and reverse remodelling of the vessel wall. Coil embolisation and flow diverter treatment of IAs have demonstrated well their great potential to induce this pathway of cure through thrombosis. On the other hand, the presence of fresh and organising ILT is considered to be a key factor which may lead to aneurysm wall degradation and contribute to the pathophysiologic cascade ending in IA rupture (Kulcsár et al., 2011a). Moreover, the occurrence of ILT in IAs can also present an additional risk of thromboembolism (Rayz et al., 2010; Castro, 2013). Nevertheless, the reason is still unclear why in some cases ILT may lead to cure, whereas in others cases it leads to rupture (Kulcsár et al., 2011a). In AAAs, mural thrombus is in permanent contact with the blood flow and undergoes continuous thrombolysis and renewal. By aggregating platelets which continuously entrap circulating white blood cells and absorbing plasma components, the mural thrombus acts as a source of secreted proteases within the aneurysm. Its existence can lead to further chemical degradation and weakening of the aneurysm wall with subsequent evolution of the AAA (Kulcsár et al., 2011a). In IAs, one possible hypothesis to explain the double-edged sword role of ILT is that the aneurysmal wall might be exposed to varying thrombus-induced autolytic activities, depending on the quality, quantity, and growth rate of the ILT. Whether cicatrization and reverse remodeling or rupture occur may depend on the balance between pro-autolytic and anti-autolytic ac-

tivities in the aneurysm wall (Kulcsár et al., 2011a). Clearly, more investigation is needed to gain better explanations for this paradoxical role of ILT in IA growth.

In general, the thrombus cascade can be divided mainly into two stages: initiation through platelet activation and deposition as well as aggregation majorly through fibrinogen polymerisation into fibrin fibres (Moiseyev et al., 2013). During the platelet activation stage, it has been suggested that the activation of platelets is dependent on the high WSS and the time that platelets are exposed to such stresses (Rayz et al., 2010). Activated platelets are carried by the flow, and may accumulate in zones of recirculation and stagnation. Low WSS observed in these regions may disrupt the endothelial layer, decreasing anti-thrombotic factor production and exposing collagen fibres to the circulating platelets. Increased residence time in the near-wall regions together with low WSS is also likely to facilitate platelet adhesion to the collagen with collagen-specific surface receptors (Pallister and Watson, 2010; Rayz et al., 2010). During the following fibrin aggregation stage, the fibrinogens are converted into fibrin strands by thrombins. Factor XIII (the fibrin stabilising factor) is also activated by thrombins, and then crosslinks the fibrin strands to form thrombus (Pallister and Watson, 2010). Several models have been proposed to study the thrombus formation process, including both models focusing on these two different stages as well as overall comprehensive coagulation models. To give the readers a general perception, here we briefly summarise the models of thrombus formation proposed in the most recent two years' time. For the platelet activation stage, Affeld et al. (2013) designed an experimental model to investigate the influence of shear rates on the platelet deposition onto collagens, accompanied by a numerical model to reproduce and interpret the results obtained from the experimental model. Their findings suggested that a certain range of shear rates seem to be favourable for the deposition of platelets. Wang and King (2012) briefly reviewed the computational methods used to simulate the process of platelet adhesion with a focus on the method proposed by their group called platelet adhesive dynamics, which combines a Monte-Carlo simulation of receptor-ligand binding and hydrodynamic calculations with a complete double-layer boundary integral equation method. Reasor et al. (2013) investigated the dependence of platelet margination on other critical parameters through modelling the blood as a suspension of deformable red blood cells (RBCs) and rigid platelets in a viscous liquid. The RBC membranes were modelled with a coarse-grained spectrin-link method whereas the dynamics of platelets were updated using Newton's equations of motion for axisymmetric shapes. Their

results emphasised that the haematocrit, viscosity ratio of plasma to cytoplasm and the shape of platelet will all influence the rate of platelet margination (Reasor et al., 2013). Shadden and Sahar (2013) studied the potential fluid mechanic pathways of platelet activation by introducing a new haemodynamic-based parameter called activation potential, which was derived from a Lagrangian integral of the strain rate magnitude. This activation potential was then illustrated to be generally maximised along, and near to distinguished material surfaces in their stenotic flow simulation (Shadden and Sahar, 2013). For the fibrin aggregation stage, Moiseyev et al. (2013) proposed a statistical model for the growth of fibrin clots based on the description of the polymerisation process underlying the formation of the fibrin polymeric network. This study aimed at providing insights to the role of different factors, such as the concentration of thrombin and plasmin as well as shear rate on the mechanical properties of thrombus during the coagulation process. For overall comprehensive coagulation models, Efremov et al. (2013) integrates quartz crystal microbalance data obtained in the laboratory with mathematical modelling of acoustic interactions between quartz crystal surfaces and coagulating blood. More approaches of modelling thrombus formation can be found in Efremov et al. (2013). In the review paper of Moiseyev and Bar-Yoseph (2013), the authors classified the current modelling schemes of haemodynamically-induced thrombus into three categories: continuum-based methods, multi-scale methods as well as mesoscopic-like methods. The major difference among these methods lies in the way of modelling individual particles, such as platelets, RBCs and thrombins (Moiseyev and Bar-Yoseph, 2013). In the continuum methods, individual particles are modelled as solutes undergoing convection and diffusion, whereas the agents of biochemical reactions are modelled by continuous distributions due to their much smaller sizes. In the multi-scale methods, the particles and their interactions are modelled at the micro-scale, while the blood flow and biochemistry interactions are still modelled at the macro-scale. Finally, in the mesoscopic-like methods, continuous distributions are used to describe how the particle population changes statistically over time (Moiseyev and Bar-Yoseph, 2013). For a more comprehensive review of different models of thrombus under these categories, interested readers can refer to Moiseyev and Bar-Yoseph (2013) and Flamm and Diamond (2012) which also includes an detailed introduction to the biology and physics of thrombus formation under flow.

It might also be of interest to briefly review the studies on correlations between the formation of ILT and the flow pattern as well as the WSS distribution of the IA,

though the amount of studies is still limited. Rayz et al. (2008) used rigid wall models to predict regions prone to thrombus formation. In a later study of Rayz et al. (2010), Patient-specific CFD simulations were performed from MRI data for three patients with thrombus-free IAs who proceeded to develop ILT detected in follow-up MR studies. Results show either an increased residence time or a low WSS at the locations where ILT formed. Xiang et al. (2012) analysed three patient-specific models with rigid walls and found that non-Newtonian rheology overestimates wall shear stress in IA domes, therefore underestimate the risk of ILT formation (Castro, 2013). Wang and Li (2013) utilised a fluid-structure interaction approach to study thrombus formation in patient-specific models, where the aneurysmal wall was considered isotropic and linear elastic. Simulation result showed that the regions occupied by the ILT coincide with regions where slow rotating vortices were formed, both of which locate in the aneurysm bulges. Low WSS values were also detected at those locations. In addition, it is observed that the maximum WSS predicted by the simulations was lower than the previous studies where the cerebral aneurysmal wall was considered rigid. The authors explained that the flexibility of the wall enabled the aneurysm cavity to dilate, and hence, the direct impact coming from the pulsatile blood flow acting on the wall was weakened, thus resulting in lower WSS (Wang and Li, 2013; Castro, 2013).

Lastly, we would like to point out that, when the vessel tissue strength is weakened to a certain level below the tissue stress due to tissue deformation, the aneurysm tends to rupture. To predict aneurysm rupture, the real challenge is to predict the strength of the tissue which changes temporally and calculate the tissue stress induced by the enlargement of the aneurysm. Unfortunately, the strength of the tissue may be spatially heterogeneous and vary individually, also cannot be determined non-invasively. Furthermore, the thickness of the aneurysmal tissue and mechanical properties of the tissue may also vary between patients and cannot be determined non-invasively. Consequently, accurate structural analyses present significant challenges. This is also a reason why research has focused mainly on the influence of haemodynamic flow pattern on aneurysm growth.

1.6 RESEARCH OUTLINE AND THESIS ORGANISATION

The entire DPhil research forms one picture: computational modelling of intracranial aneurysm disease. The ultimate objective of this research is to sophisticate a

state-of-the-art 3D Fluid-Solid-Growth (FSG) model to incorporate the microstructural adaption of collagen fabrics so that IA evolution can be simulated on patient specific arteries with more realistic results. Specific tasks include:

- development of automated numerical methods to reconstruct pre-diseased healthy vasculature from medical imaging depicting sidewall IAs;
- gaining insight into the current hypotheses on the influence of haemodynamic environment on IA inception;
- development of a novel mathematical model for the microstructural adaption of collagen fabrics during aneurysm evolution;
- implementation of the collagen adaption model into the 3D solid structural model of IA evolution;
- implementation of the collagen model into the state-of-the-art FSG model of IA evolution;

During the study, different stages of aneurysm development is examined including the inception, enlargement and stabilisation. For aneurysm inception, in order to explore the influence of the haemodynamic environment on the initiation of IAs, a correlation of locations of aneurysm formation with different local haemodynamic indices is investigated. For aneurysm growth and stabilisation, a novel 1D conceptual model is developed to incorporate a more sophisticated representation of the microstructural aspects of the arterial collagens and their adaption during IA development. Following this, the conceptual collagen microstructural adaption model is further integrated into a 3D solid IA growth model as well as a 3D FSG modelling framework, which accounts for both fluid mechanics and solid mechanics. This enables us to simulate evolution of an aneurysm on 3D patient specific arteries with more sophisticated representation of the microstructural adaption of the tissue. Details about the structure of the thesis are provided as follows:

Chapter 1 overviews the IA disease and introduces relevant biological, biomechanical as well as mechanobiological backgrounds of the arterial tissue. Up-to-date hypotheses of the role of biomechanics and mechanobiology in the inception and growth of IAs is also reviewed.

Chapter 2 introduces a novel method to reconstruct the hypothetical geometry of the healthy vasculature prior to intracranial aneurysm formation from segmented geometries depicting evolved cerebral aneurysms. This method takes into account the tortuosity of the arterial vasculature and requires minimal user subjectivity.

Chapter 3 investigates the correlation between aneurysm inception and local haemodynamic stimuli which are associated with the transient wall shear stress acting locally on the vascular wall, including WSS, WSSG, OSI, min(AFI) and GON.

Chapter 4 presents a novel 1D conceptual model of microstructural aspects of the collagen fabrics and their adaption. This model is applied to simulate the evolution of conceptual 1D IAs. Key concepts of collagen attachment stretch and recruitment stretch distributions are introduced; governing equations of the mechanical equilibrium of the arterial wall, as well as the Strain Energy Functions (SEFs) of the arterial constituents are derived; the approach taken to model the growth and remodelling of the arterial tissue, as well as the temporal adaption of the collagen microstructure is presented; finally the influence of different approaches for adapting the collagen microstructures on the growth of the aneurysms is examined.

Chapter 5 illustrates the implementation of the novel 1D conceptual collagen microstructure adaption model into two aneurysm growth models: the 3D solid model to simulate IA development on idealised cylindrical arteries, as well as the state-of-the-art FSG model to simulate IA development on patient-specific geometries embedded in a realistic haemodynamic environment. For the solid model, 3D non-linear elasticity is utilised to derive the equation that governs the mechanical response of the arterial wall; 3D SEFs for the heterogeneous arterial constituents and the particular approach for modelling the growth and remodelling of the constituents are described; numerical implementation of the model is also briefly introduced. Results are compared between four simulation cases to show the advantages of the new model. The FSG model integrates the research findings of previous chapters: a novel numerical approach is used to reconstruct the healthy pre-aneurysmal geometry of the vasculature; a realistic constitutive model of the arterial wall incorporating distributions of collagen fibres is utilised to model the mechanical re-

sponse of wall; adaption of the microstructure of the collagen fibres are considered; growth and remodelling of the arterial constituents is explicitly linked to the local haemodynamic stimuli acting on the surface of the aneurysm domain. Finally an aneurysm is observed to develop on physiological vasculature.

Chapter 6 summarises the whole thesis and discusses the main shortcomings of the research. Future research directions are also suggested, including the development of an automated method to reconstruct pre-diseased healthy vasculature depicting *bifurcating* IAs, sophistication of the 3D model so that it can be applied to *arbitrary* geometry, application of the current modelling framework to an experimental rabbit model of elastase induced cerebral aneurysms as well as the integration of the collagen adaption model into a thick-wall model of arterial growth and remodelling.



A NOVEL AUTOMATED METHOD TO RECONSTRUCT HEALTHY VASCULATURE FROM MEDICAL IMAGING DEPICTING IAS

The pathogenesis of IAs is a complex process that combines biological, biochemical as well as mechanobiological factors together. It has been investigated for decades but is still not clearly understood. As we have reviewed in Chapter 1, the mechanisms that give rise to the initiation of an IA involve the complex interplay between the local mechanical stimuli acting on the arterial wall, the biological processes occurring at the cellular level, as well as the response of the wall to these stimuli and biochemical reactions. A better understanding of the IA pathogenesis will not only allow better decisions with regard to disease management, but also, more importantly, help to improve prevention measures.

Currently, it is impossible to predict whether and where an IA will occur. However, given that aneurysms are more prone to develop at certain regions in the Circle of Willis, we may question whether there is any common haemodynamic environment associated with these regions that triggers the inception of an aneurysm. To investigate this, one thought is to examine whether there is any correlation between the haemodynamic factors of the original ‘healthy’ artery and the locations where the aneurysms form, which we already know from clinical imagings. Nevertheless, the geometries of the healthy arteries prior to aneurysm formation are usu-

ally unavailable. As a result, several methods have been developed to numerically remove the aneurysms and reconstruct the surface of the artery from imagings, and these reconstructed surfaces are considered to be the pre-aneurysmal hypothetical ‘healthy’ geometries of the arteries. Ideally, such methods need to be repeatable, have reasonable user-independence in regards to the geometries of the reconstructed arteries, and be sufficiently robust to be applied to aneurysms growing in a variety of locations.

The main objective of this chapter is to present a novel automated numerical method to remove *sidewall* IAs and reconstruct the vasculature. In the following sections, firstly the existing vessel reconstruction methods proposed in the literature are reviewed; secondly the mathematical preliminaries on which our novel method is based is introduced; thirdly the procedures of this method and the some practical problems that we encountered during the implementation of the method are detailed; finally the advantages and shortcomings of our method are discussed in comparison with other previous methods.

2.1 A REVIEW OF EXISTING VESSEL RECONSTRUCTION METHODS

In order to investigate the influence of haemodynamic environment on IA inception, several computational approaches which are utilised to obtain the hypothetical pre-diseased healthy vasculature from medical imagings of IAs have been proposed within the literature (Mantha et al. 2006; Ford et al. 2009; Shimogonya et al. 2009a; Baek et al. 2009; Cebal et al. 2010; Le et al. 2013 and et al.); some being relatively simple and straightforward, and some being quite complicated to understand. At the beginning of this chapter, we briefly summarise these approaches so that the readers can make straight comparisons with our approach which will be introduced later.

2.1.1 The circular section method

The circular section method generally means creating a smooth surface comprised of circular cross sections to replace the aneurysmal segment in the parent artery. This method usually consists of the following procedures:

1. Sample the 3D vessel model into a contiguous set of 2D cross sections.
2. Manually define the aneurysmal segment and remove the cross sections within the aneurysmal segment.
3. Reconstruct the parent artery with a new set of circular cross sections.
4. Transform the new cross sections into a smooth surface.
5. Optional: apply a smoothing algorithm to eliminate any geometric discontinuity on the new geometry.

This method has been applied in several studies to obtain the hypothetically healthy artery before aneurysm formation (Karmonik et al. 2004; Mantha et al. 2006; Shimogonya et al. 2009a,b, 2012). The difference between methods lies in the generation of new circular cross sections. In the first two studies, for cross sections within the aneurysm segment, only the boundary points belonging to the normal arterial wall were selected excluding any point associated with the aneurysm ostium. Subsequently the radial centres of these sections were determined using a single value decomposition algorithm, and the arterial radii were calculated as the average distance between the centre points and the reduced set of boundary points. Contrarily, in the latter studies (Shimogonya et al. 2009a,b, 2012), centre points, as well as arterial radii of the new cross sections, were interpolated using the corresponding data at several selected cross sections extracted from both remaining parts of the original geometry. The general process of the method is provided in Fig. 2.1.

2.1.2 The Voronoi diagram method

Ford et al. (2009) developed an entirely different technique to digitally remove sacular aneurysms and reconstruct the artery. The core concept of this method is the application of the Voronoi diagram to tessellate the vascular lumen geometry. The method can be summarised by the following procedures (see Fig. 2.2 for visual illustration):

1. Partition the lumen by a set of maximally inscribed spheres of different sizes so that no sphere contains a sphere within it. The centres of these spheres are called the Voronoi seeds (Fig. 2.2-a, b).

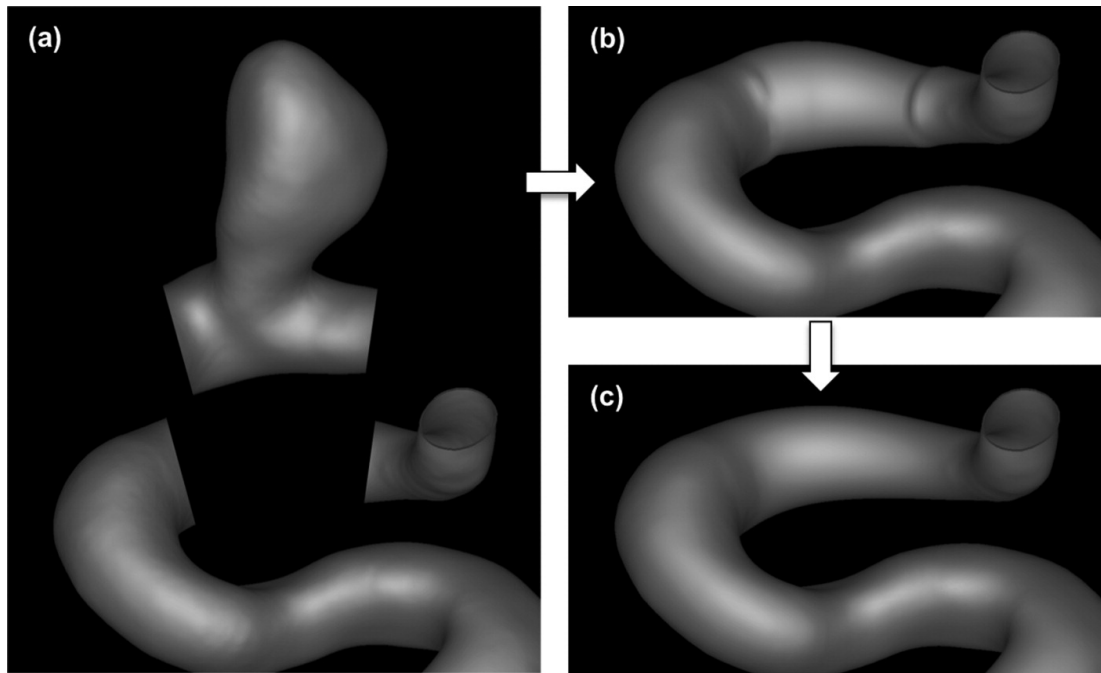


Figure 2.1: Numerical removal of the aneurysm and reconstruction of the artery geometry with the circular section method: (a) Removal of the aneurysmal segment, (b) Reconstruct the parent artery with a new set of circular cross sections and transform the new sections into a smooth surface, (c) Smoothing of the parent artery to eliminate any kink in the new geometry (adapted from Shimogonya et al. (2009b)).

2. Clip the lumen centreline and the corresponding Voronoi seeds are between two manually selected clipping points on the centreline (Fig. 2.2-c).
3. Interpolate a new centreline between the clipping points. Interpolate a new set of Voronoi seeds along the new centreline within a certain distance (Fig. 2.2-d, e).
4. Transform the new Voronoi seeds to a new surface (Fig. 2.2-f).

An obvious advantage of this method is that it can also be applied to reconstruct arterial bifurcations. The procedures of this method have already been implemented in an open source project for vascular modelling called VMTK, short for Vascular Modeling ToolKit (Antiga et al., 2008).

2.1.3 The smoothing method

Another vessel reconstruction method was proposed by Cebal et al. (2010) in their study on the associations between haemodynamics and the formation of blebs in

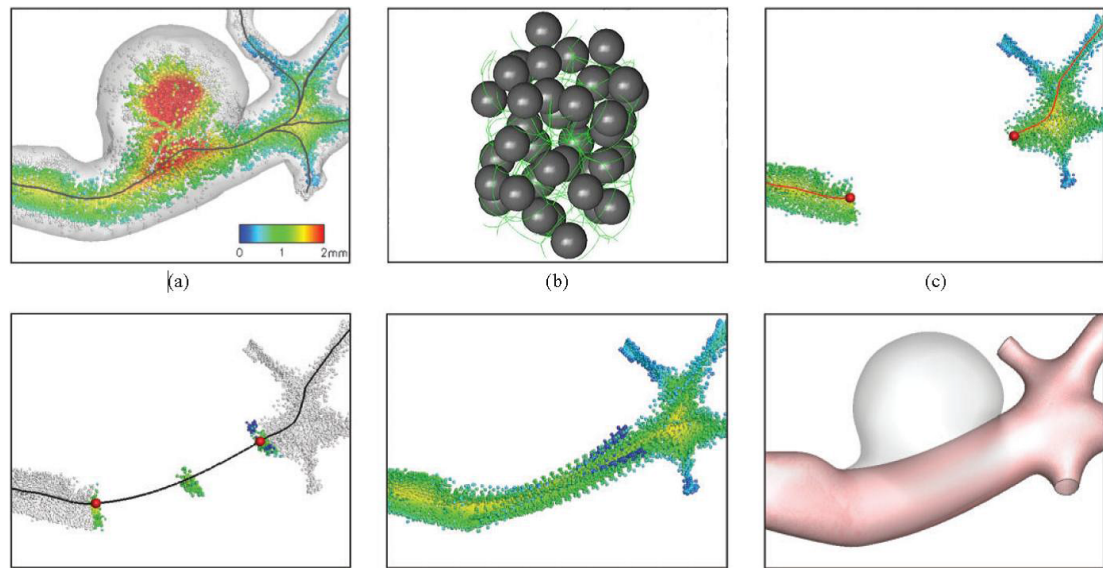


Figure 2.2: Numerical removal of the aneurysm and reconstruction of the artery geometry with the Voronoi diagram method: (a) Partition of the lumen by a Voronoi diagram. (b) A close-up of the Voronoi seeds. (c) Clipping of the lumen centreline and the corresponding Voronoi seeds within the aneurysmal segment. (d) Interpolation of a new centreline. (e) Interpolation of a new set of Voronoi seeds along the new centreline. (f) Transformation of the new Voronoi seeds to a new surface (adapted from Ford et al. (2009)).

cerebral aneurysms, here named as the smoothing method. This method is based on applying a smoothing algorithm (usually Laplacian or Gaussian smoothing) to the bulging region manually delineated on the original geometry. Fixing the boundaries of the bulging region is required as a smoothing procedure tends to shrink the surface being smoothed. Iteratively applying the procedure smooths out the bulging and eventually generates a smooth surface, which is considered to represent the pre-bulging arterial geometry (see Fig. 2.3). This method has been applied successively to remove blebs on aneurysms as well as aneurysms on arterial bifurcations (Cebal et al. 2010; Castro et al. 2012).

2.1.4 The patching method

The patching method generally means the utilisation of certain commercial packages to numerically remove the aneurysm and repair the geometry. For instance, Baek et al. (2009) utilised the surface generation tools in Gridgen (Pointwise Inc., Fort Worth, Texas, USA) to remove the aneurysm and generate surface patches bounded by user-defined splines on the removed surface. Le et al. (2013) used the

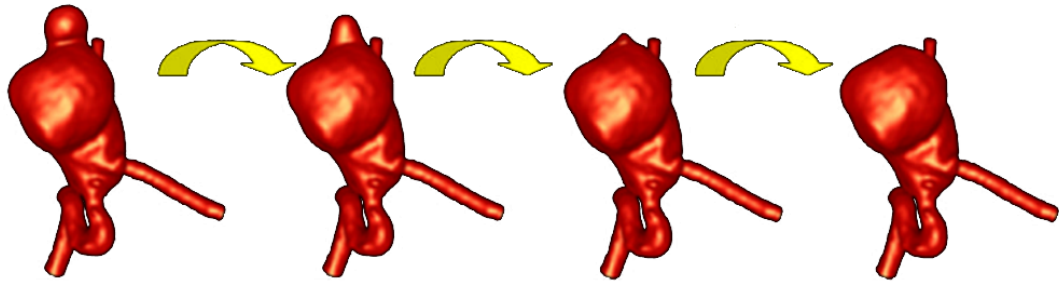


Figure 2.3: Iteratively apply the smoothing algorithm on the bulging to generate a smooth surface (Adapted from Cebal et al. (2010)).

software package Geomagic studio (Geomagic, Research Triangle Park, North Carolina, USA) to clip the aneurysm and repair the modified surface. After first removing the aneurysm segment, Selimovic (2013) used ANSYS ICEM CFD (ANSYS Inc., Cecil Township, Pennsylvania, USA) to embed the cylinder model within patient-specific arterial geometries by creating surfaces that smoothly connects the cylinder to the parent artery. Details of these procedures can be found in the cited documents respectively.

2.2 MATHEMATICAL PRELIMINARIES FOR THE VESSEL RECONSTRUCTION METHOD

This section introduces the mathematical preliminaries needed for developing this novel vessel reconstruction method, including some concepts regarding the differential geometry of curves (curve parameterisation, Frenet frame, curvature, torsion), a novel method to interpolate cubic Hermite spline over a series of points as well as determination of the plane-Hermite spline intersection point. In the next section, the novel Hermite spline interpolation method will be utilised to create a new skeletonisation for the aneurysmal segment. The method to determine plane-Hermite spline intersection point will be used to determine the intersection points between the new skeletonisation and the upstream as well as downstream boundaries. The computed Frenet frame is then used to the guide the propagation of a closed curve from the upstream boundary to the downstream boundary.

2.2.1 Curve parameterisation and the Frenet frame

A curve in the Euclidean space $\mathbb{R}^3$ can be defined as a parametric differentiable function with one independent parameter t , i.e. $\mathcal{C}(t): [a, b] \rightarrow \mathbb{R}^3$, with the starting point $\mathcal{C}(a)$ and the endpoint $\mathcal{C}(b)$. The general form used to express the parametric function of a 3D space curve is:

$$x = f(t) \quad (2.1a)$$

$$y = g(t) \quad (2.1b)$$

$$z = h(t) \quad (2.1c)$$

where (x, y, z) are the three Cartesian coordinates of the points on the curve and $f(t)$, $g(t)$ and $h(t)$ are three parametric equations used to represent each coordinate of the points.

A Frenet frame is a local orthonormal basis spanning $\mathbb{R}^3$ and consisting collectively of the unit tangent, normal and binormal vectors $\mathbf{T}$, $\mathbf{N}$ and $\mathbf{B}$ (see Fig. 2.4). Using the parametric function for a 3D space curve, we introduce the notations $\dot{\mathcal{C}}(t) = \frac{d\mathcal{C}(t)}{dt}$ and $\ddot{\mathcal{C}}(t) = \frac{d^2\mathcal{C}(t)}{dt^2}$ to denote the first and second derivatives of the curve. The unit tangent vector determines the orientation and the forward direction of the curve, and can be defined as:

$$\mathbf{T}(t) = \frac{\dot{\mathcal{C}}(t)}{|\dot{\mathcal{C}}(t)|} \quad (2.2)$$

The unit normal vector indicates the deviation of the curve from being a straight line and takes the form:

$$\mathbf{N}(t) = \frac{\dot{\mathbf{T}}(t)}{|\dot{\mathbf{T}}(t)|} = \frac{\dot{\mathcal{C}}(t) \times (\ddot{\mathcal{C}}(t) \times \dot{\mathcal{C}}(t))}{|\dot{\mathcal{C}}(t)| \cdot |\ddot{\mathcal{C}}(t) \times \dot{\mathcal{C}}(t)|} \quad (2.3)$$

Lastly, the binormal vector is defined as the cross product of $\mathbf{T}$ and $\mathbf{N}$, i.e.:

$$\mathbf{B}(t) = \mathbf{T}(t) \times \mathbf{N}(t). \quad (2.4)$$

providing the coordinates system is right-handed.

2.2.2 Curvature and torsion of a space parametric curve

For a space parametric curve $\mathcal{C}(t)$, $t \in [a, b]$, the curvature κ measures the deviance of $\mathcal{C}(t)$ from being flat in the osculating plane. Physically, it is defined as the magnitude of the rate of change of the unit tangent vector $\mathbf{T}(s)$ with respect to the arc

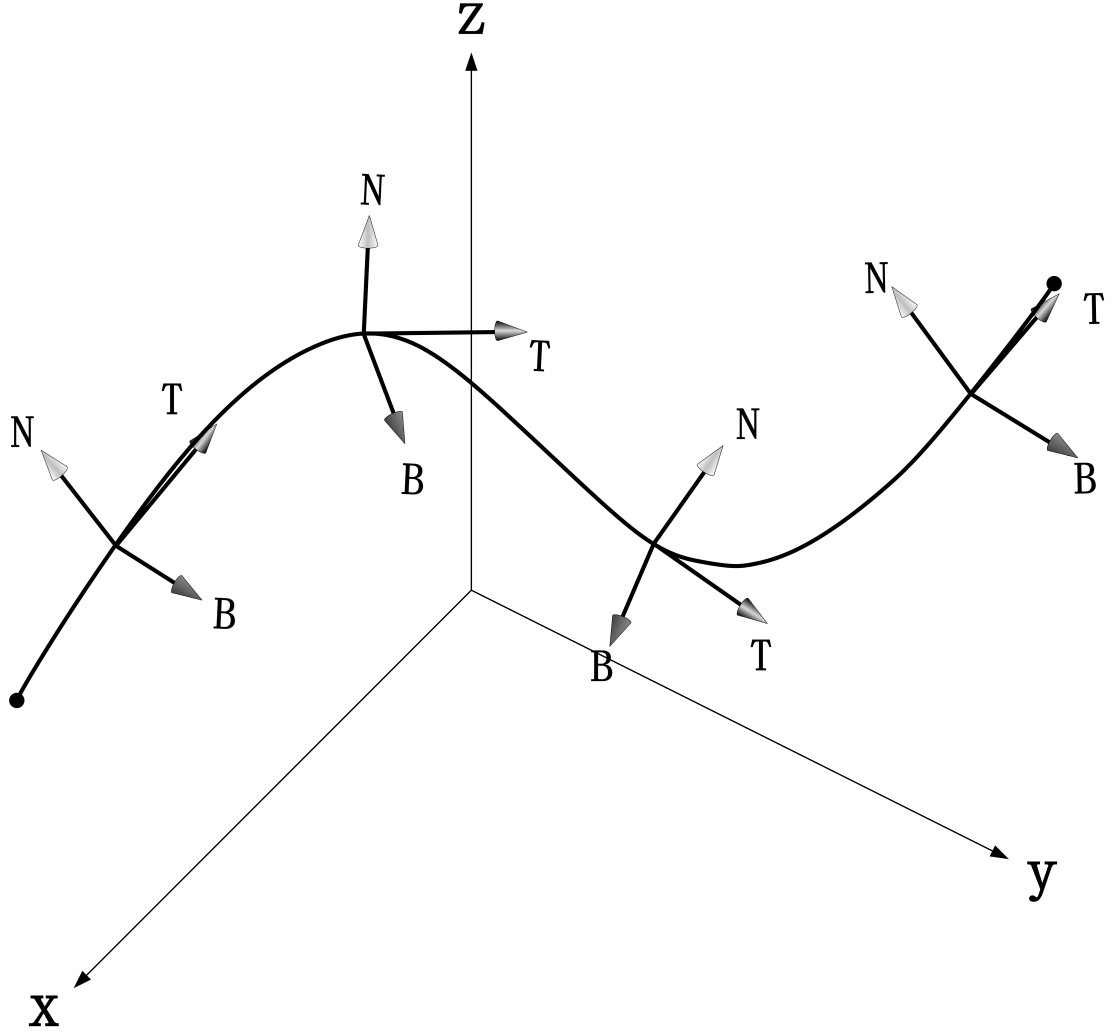


Figure 2.4: The 3D Frenet frame along a space curve, which consists the unit tangent, normal and binormal vectors $\mathbf{T}$, $\mathbf{N}$ and $\mathbf{B}$.

length s :

$$\kappa(s) = \left| \frac{d\mathbf{T}(s)}{ds} \right| = \left| \frac{d^2\mathcal{C}(s)}{ds^2} \right| \quad (2.5)$$

where $\mathcal{C}(s)$ is the same curve reparameterised with respect to s . The differential of arc length ds can be expressed in terms of the lengths of the elements in three directions:

$$ds = \sqrt{(dx)^2 + (dy)^2 + (dz)^2} = |\dot{\mathcal{C}}(t)| dt \quad (2.6)$$

For the original curve $\mathcal{C}(t)$, the curvature κ can be computed directly from the following equation:

$$\kappa(t) = \frac{|\dot{\mathcal{C}}(t) \times \ddot{\mathcal{C}}(t)|}{|\dot{\mathcal{C}}(t)|^3} \quad (2.7)$$

The torsion of a curve, denoted as τ , measures the extent to which a curve twists out of the osculating plane. Geometrically, it is defined as the magnitude of the rate of change of the unit binormal vector $\mathbf{B}(s)$ with respect to the arc length s . To be more specific, for a curve that is reparameterised by s :

1. Imagine two close points on the curve $\mathbf{P}^1 = \mathcal{C}(s)$ and $\mathbf{P}^2 = \mathcal{C}(s + \Delta s)$, where Δs is the curve arc length between $\mathbf{P}^1$ and $\mathbf{P}^2$. Denote the angle between the two binormal vectors $\mathbf{B}(s)$ and $\mathbf{B}(s + \Delta s)$ at $\mathbf{P}^1$ and $\mathbf{P}^2$ as $\Delta\theta$. $\Delta\theta$ is considered to be positive if its measurement obeys the right-hand rule of the local Frenet frame.
2. Define the torsion τ of the curve at point $\mathbf{P}^1$ as the limit of $\frac{\Delta\theta}{\Delta s}$ when Δs approaches 0:

$$\tau(s) = \lim_{\Delta s \rightarrow 0} \frac{\Delta\theta}{\Delta s} = \frac{d\theta}{ds} = -\frac{d\mathbf{B}(s)}{ds} \cdot \mathbf{N}(s) \quad (2.8)$$

Since $\frac{d\mathbf{B}(s)}{ds}$ is always colinear with $\mathbf{N}(s)$, the minus sign in the preceding equation simply implies that $\tau(s)$ is positive if the twisting of the curve is consistent with the right-hand rule of the local Frenet frame, and negative if being inconsistent (see Fig. 2.5). For the original curve $\mathcal{C}(t)$, the torsion τ can be computed by:

$$\tau(t) = \frac{[\dot{\mathcal{C}}(t) \times \ddot{\mathcal{C}}(t)] \cdot \ddot{\ddot{\mathcal{C}}}(t)}{|\dot{\mathcal{C}}(t) \times \ddot{\mathcal{C}}(t)|^2} \quad (2.9)$$

where $\ddot{\ddot{\mathcal{C}}}(t) = \frac{d^3\mathcal{C}(t)}{dt^3}$. Eq. 2.7 and 2.9 show that κ describes the second order behavior of a curve, whereas τ describes the third order behavior. κ and τ are related by the famous Frenet-Serret formulas for a curve $\mathcal{C}(t)$:

$$\frac{d}{dt} \begin{bmatrix} \mathbf{T} \\ \mathbf{N} \\ \mathbf{B} \end{bmatrix} = |\dot{\mathcal{C}}(t)| \begin{bmatrix} 0 & \kappa & 0 \\ -\kappa & 0 & \tau \\ 0 & -\tau & 0 \end{bmatrix} \begin{bmatrix} \mathbf{T} \\ \mathbf{N} \\ \mathbf{B} \end{bmatrix} \quad (2.10)$$

where the additional factor $|\dot{\mathcal{C}}(t)|$ comes from the chain rule $|\dot{\mathcal{C}}(t)| = \frac{ds}{dt}$. Eq. 2.10 shows more clearly that the curvature κ is a measurement of how fast $\mathbf{T}$ rotates

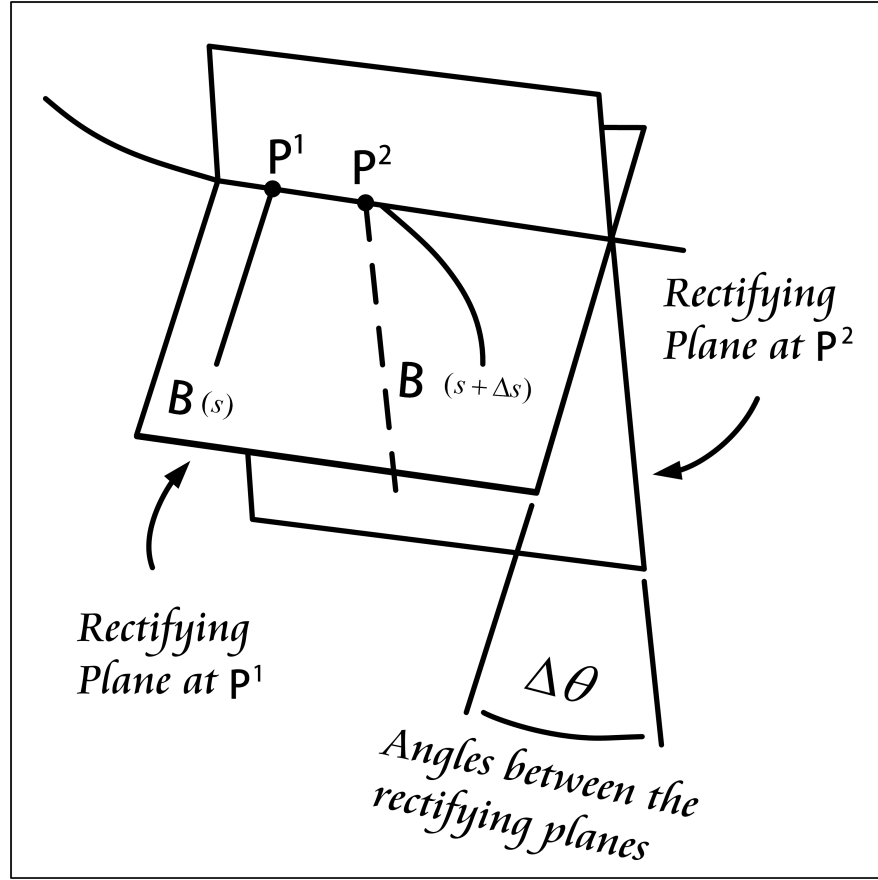


Figure 2.5: Torsion of a space curve $\mathcal{C}(s)$ parameterised by s between two points $\mathbf{P}^1 = \mathcal{C}(s)$ and $\mathbf{P}^2 = \mathcal{C}(s + \Delta s)$.

around $\mathbf{B}$, whereas the torsion τ is a measurement of how fast $\mathbf{B}$ rotates around $\mathbf{T}$. The rate of change of $\mathbf{N}$ is more complex, which is affected by both κ and τ . Note if a curve has $\tau = 0$ everywhere on the curve with non-vanishing κ , then this curve belongs to a fixed plane.

2.2.3 Cubic Hermite spline interpolation over a series of points

In this section, we present a novel method to construct a cubic Hermite spline over a series of points. We first illustrate this method with the simplest case of a single-interval spline interpolated between two endpoints, then move onto a more complicated case of multi-interval spline interpolated through a series of points. The method introduced in this section serves to create a Hermite spline through the points on the old skeletonisation of the aneurysmal segment, as well as to construct new skeletonisation between the upstream and downstream boundaries.

Given a series of N distinct points $\mathbf{P}^1, \mathbf{P}^2, \dots, \mathbf{P}^N$ in the Euclidean space $\mathbb{R}^3$, we can always construct a smooth continuous spline curve consecutively passing through each point. Among the many choices of types of spline curves, the cubic Hermite spline is selected for its unique characteristics. For instance, for only two points $\mathbf{P}^1$ and $\mathbf{P}^2$, given the two position vectors $\mathbf{P}^1, \mathbf{P}^2$ as well as two additional vectors $\mathbf{T}^1, \mathbf{T}^2$ at these points, a single-interval Hermite spline, starting from point $\mathbf{P}^1$ with tangent vector $\mathbf{T}^1$ and ending at point $\mathbf{P}^2$ with tangent vector $\mathbf{T}^2$, can be constructed by applying the standard Hermite formula using these boundary conditions. For multiple points, a classic method for constructing a multi-interval spline is to apply the standard Hermite formula in each single interval following the point order, where the tangent vectors at the points are chosen in a sensible manner. However, splines constructed by this method only have C^1 continuity. A novel method to construct a multi-interval Hermite spline which has C^2 continuity is presented below. This assures the continuity of the entire Frenet frame along the whole interpolated Hermite spline (except for the twisting points, discussed later).

2.2.3.1 Single-interval Hermite spline interpolation

We start from the simplest case ($N = 2$), where two points $\mathbf{P}^n = (P_1^m, P_2^m, P_3^m)$, $m = 1, 2$ and two tangent vectors $\mathbf{T}^n = (T_1^m, T_2^m, T_3^m)$ at these two points are given. We use $\mathcal{C}^1 = (x_1^1, x_2^1, x_3^1)$ to denote the cubic Hermite spline, with 1 implying the 1st interval of the spline (to be consistent with the following context). The general form of a single-interval Hermite spline $\mathcal{C}^1$ parameterised by $t \in [0, 1]$ can be written as:

$$x_1^1 = a_{01}^1 + a_{11}^1 t + a_{21}^1 t^2 + a_{31}^1 t^3 \quad (2.11a)$$

$$x_2^1 = a_{02}^1 + a_{12}^1 t + a_{22}^1 t^2 + a_{32}^1 t^3 \quad (2.11b)$$

$$x_3^1 = a_{03}^1 + a_{13}^1 t + a_{23}^1 t^2 + a_{33}^1 t^3 \quad (2.11c)$$

Using the Einstein notation, the preceding equation can be alternatively written in a more concise form:

$$x_j^1 = a_{ij}^1 t^i \quad (2.12)$$

where $i = 0, 1, 2, 3$, $j = 1, 2, 3$. An alternative option is to use the matrix notation, then the preceding equation can be written as:

$$\begin{bmatrix} x_1^1 & x_2^1 & x_3^1 \end{bmatrix} = \begin{bmatrix} 1 & t & t^2 & t^3 \end{bmatrix} \begin{bmatrix} a_{01}^1 & a_{02}^1 & a_{03}^1 \\ a_{11}^1 & a_{12}^1 & a_{13}^1 \\ a_{21}^1 & a_{22}^1 & a_{23}^1 \\ a_{31}^1 & a_{32}^1 & a_{33}^1 \end{bmatrix} \quad (2.13)$$

The coefficients a_{ij}^1 are determined such that the boundary conditions are fulfilled:

$$\mathcal{C}^1(0) = \mathbf{P}^1 \quad (2.14a)$$

$$\mathcal{C}^1(1) = \mathbf{P}^2 \quad (2.14b)$$

$$\dot{\mathcal{C}}^1(0) = \mathbf{T}^1 \quad (2.14c)$$

$$\dot{\mathcal{C}}^1(1) = \mathbf{T}^2 \quad (2.14d)$$

This yields 12 linear equations for the 12 unknowns a_{ij}^1 . This system of linear equations can be written compactly using matrix notation:

$$\mathbf{M}_1 \mathbf{A}_1 = \mathbf{Q}_1 \quad (2.15)$$

where

$$\mathbf{M}_1 = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 2 & 3 \end{bmatrix} \quad (2.16)$$

and

$$\mathbf{A}_1 = \begin{bmatrix} a_{01}^1 & a_{02}^1 & a_{03}^1 \\ a_{11}^1 & a_{12}^1 & a_{13}^1 \\ a_{21}^1 & a_{22}^1 & a_{23}^1 \\ a_{31}^1 & a_{32}^1 & a_{33}^1 \end{bmatrix} \quad (2.17)$$

is the coefficient matrix storing the 12 unknown coefficients a_{ij}^1 , and

$$\mathbf{Q}_1 = \begin{bmatrix} \mathbf{P}^1 \\ \mathbf{P}^2 \\ \mathbf{T}^1 \\ \mathbf{T}^2 \end{bmatrix} \quad (2.18)$$

is the matrix storing the boundary conditions. The solution to the coefficient matrix $\mathbf{A}_1$, namely the 12 unknown coefficients a_{ij}^1 , can be simply calculated by $\mathbf{A}_1 = \mathbf{M}_1^{-1} \mathbf{Q}_1$.

2.2.3.2 Multi-interval Hermite spline interpolation

Now let us look at a slightly more complicated case: a multi-interval spline, i.e. $N \geq 3$. Given a series of N distinct points $\mathbf{P}^1, \mathbf{P}^2, \dots, \mathbf{P}^N$ where $\mathbf{P}^m = (P_1^m, P_2^m, P_3^m)$, $m =$

$1, 2, \dots, N$, and two tangent vectors, $\mathbf{T}^1 = (T_1^1, T_2^1, T_3^1)$ and $\mathbf{T}^N = (T_1^N, T_2^N, T_3^N)$, at the boundary points $\mathbf{P}^1$ and $\mathbf{P}^N$, we can interpolate an $N - 1$ interval cubic Hermite spline. The n th interval of the spline, connecting the two adjacent points $\mathbf{P}^n$ and $\mathbf{P}^{n+1}$ and parameterised by $t \in [0, 1]$, is denoted as $\mathcal{C}^n = (x_1^n, x_2^n, x_3^n)$, $n = 1, 2, \dots, N - 1$. Using the Einstein notation, the general form of $\mathcal{C}^n$ can be written as: $x_j^n = a_{ij}^n t^i$, $i = 0, 1, 2, 3$, $j = 1, 2, 3$. Alternatively, using the matrix notation, the preceding equation reads:

$$\begin{bmatrix} x_1^n & x_2^n & x_3^n \end{bmatrix} = \begin{bmatrix} 1 & t & t^2 & t^3 \end{bmatrix} \begin{bmatrix} a_{01}^n & a_{02}^n & a_{03}^n \\ a_{11}^n & a_{12}^n & a_{13}^n \\ a_{21}^n & a_{22}^n & a_{23}^n \\ a_{31}^n & a_{32}^n & a_{33}^n \end{bmatrix} \quad (2.19)$$

The coefficients a_{ij}^n for the n th interval $\mathcal{C}^n$ are determined to satisfy both the boundary conditions at the boundary points $\mathbf{P}^1$ and $\mathbf{P}^N$, as well as the C^0 , C^1 and C^2 continuity conditions at all other points:

Boundary conditions at $\mathbf{P}^1$ and $\mathbf{P}^N$:

$$\mathcal{C}^1(0) = \mathbf{P}^1 \quad (2.20a)$$

$$\mathcal{C}^{N-1}(1) = \mathbf{P}^N \quad (2.20b)$$

$$\dot{\mathcal{C}}^1(0) = \mathbf{T}^1 \quad (2.20c)$$

$$\dot{\mathcal{C}}^{N-1}(1) = \mathbf{T}^N \quad (2.20d)$$

C^0 continuity conditions at $\mathbf{P}^n$, $n = 2, 3, \dots, N - 1$:

$$\mathcal{C}^{n-1}(1) = \mathbf{P}^n \quad (2.21a)$$

$$\mathcal{C}^n(0) = \mathbf{P}^n \quad (2.21b)$$

C^1 continuity conditions at $\mathbf{P}^n$:

$$\dot{\mathcal{C}}^{n-1}(1) - \dot{\mathcal{C}}^n(0) = 0 \quad (2.22)$$

C^2 continuity conditions at $\mathbf{P}^n$:

$$\ddot{\mathcal{C}}^{n-1}(1) - \ddot{\mathcal{C}}^n(0) = 0 \quad (2.23)$$

Together the conditions detailed in Eq. 2.20a to 2.23 yield $12(N - 1)$ linear equations for the $12(N - 1)$ unknowns. This system of linear equations can be written compactly using the matrix notation:

$$\mathbf{MA} = \mathbf{B} \quad (2.24)$$

where $\mathbf{M}$ is a $4(N-1) \times 4(N-1)$ matrix, $\mathbf{A}$ is a $4(N-1) \times 3$ matrix storing all the coefficients of each interval of the spline a_{ij}^n . $\mathbf{B}$ is a $4(N-1) \times 3$ matrix storing the coordinates of all of the $\mathbf{P}^m$, $m = 1, 2, \dots, N$ as well as two tangent vectors $\mathbf{T}^1$ and $\mathbf{T}^N$ at points $\mathbf{P}^1$ and $\mathbf{P}^N$. These three matrices $\mathbf{M}$, $\mathbf{A}$ and $\mathbf{B}$ can be written in the form of block matrix. More specifically, $\mathbf{M}$ can be written as:

$$\mathbf{M} = \begin{bmatrix} \mathbf{M}_2 & \mathbf{M}_3 & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_2 & \mathbf{M}_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \mathbf{0} \\ \mathbf{0} & \cdots & \mathbf{0} & \mathbf{M}_2 & \mathbf{M}_3 \\ \mathbf{M}_4 & \mathbf{0} & \cdots & \mathbf{0} & \mathbf{M}_5 \end{bmatrix} \quad (2.25)$$

i.e., for every row downwards except for the last row, blocks $\mathbf{M}_2$ and $\mathbf{M}_3$ are moving a column rightwards. In this large block matrix of $\mathbf{M}$, we have:

$$\mathbf{M}_2 = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 \\ 0 & 0 & 2 & 6 \end{bmatrix} \quad \mathbf{M}_3 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & -2 & 0 \end{bmatrix} \quad (2.26a)$$

$$\mathbf{M}_4 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \mathbf{M}_5 = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 \\ 0 & 1 & 2 & 3 \end{bmatrix} \quad (2.26b)$$

and the block $\mathbf{0}$ is a 4×4 zero matrix. The matrix $\mathbf{A}$ in Eq. 2.24 can be written as:

$$\mathbf{A} = \begin{bmatrix} \mathbf{A}_1 \\ \mathbf{A}_2 \\ \vdots \\ \mathbf{A}_{N-2} \\ \mathbf{A}_{N-1} \end{bmatrix} \quad (2.27)$$

where

$$\mathbf{A}_n = \begin{bmatrix} a_{01}^n & a_{02}^n & a_{03}^n \\ a_{11}^n & a_{12}^n & a_{13}^n \\ a_{21}^n & a_{22}^n & a_{23}^n \\ a_{31}^n & a_{32}^n & a_{33}^n \end{bmatrix} \quad (2.28)$$

Finally, the matrix $\mathbf{B}$ takes the form of:

$$\mathbf{B} = \begin{bmatrix} \mathbf{B}_0 \\ \mathbf{B}_1 \\ \vdots \\ \mathbf{B}_{N-2} \\ \mathbf{Q} \end{bmatrix} \quad (2.29)$$

where

$$\mathbf{B}_0 = \begin{bmatrix} \end{bmatrix} \quad \text{and} \quad \mathbf{B}_n = \begin{bmatrix} \mathbf{p}^n \\ \mathbf{p}^{n+1} \\ \mathbf{0} \\ \mathbf{0} \end{bmatrix} \quad \text{and} \quad \mathbf{Q} = \begin{bmatrix} \mathbf{p}^{N-1} \\ \mathbf{p}^N \\ \mathbf{T}^1 \\ \mathbf{T}^N \end{bmatrix} \quad (2.30)$$

We note that $\mathbf{B}_0$ is intentionally defined to be an empty matrix which enables us to group together the equations of computing the coefficient matrices of both single-interval and multi-interval splines into a more generalised form. Otherwise when $N = 2$, the matrix $\mathbf{B}_{N-2} = \mathbf{B}_0$ will be undefined. $\mathbf{B}_n$ stores the position vectors of the first $N - 1$ points as well as null vectors. $\mathbf{Q}$ stores the position vectors of the last two points $\mathbf{p}^{N-1}$ and $\mathbf{p}^N$, as well as the two tangent vectors $\mathbf{T}^1$ and $\mathbf{T}^N$ at the boundary points $\mathbf{p}^1$ and $\mathbf{p}^N$. Now return to Eq. 2.24: $\mathbf{MA} = \mathbf{B}$. The solution to the coefficient matrix $\mathbf{A}$ can be simply computed by $\mathbf{A} = \mathbf{M}^{-1}\mathbf{B}$ in any mathematical computing environment such as MATLAB (MathWorks, Natick, Massachusetts, USA).

Of particular note is that when $N = 2$, matrix $\mathbf{A}$ in Eq. 2.27 reduces to $\mathbf{A}_1$ in Eq. 2.17, whereas matrices $\mathbf{B}$ and $\mathbf{Q}$ in Eqs. 2.29 and 2.30 reduce to $\mathbf{Q}_1$ in Eq. 2.18. Hence, it is reasonable to write that the equation of computing the coefficient matrix of any interval spline in a general form is simply $\mathbf{MA} = \mathbf{B}$. When a single interval spline ($N = 2$) is needed, $\mathbf{M} = \mathbf{M}_1$ as in Eq. 2.16. When a multi-interval spline ($N \geq 3$) is required, $\mathbf{M}$ takes the form of Eq. 2.25. In both cases, $\mathbf{A}$ and $\mathbf{B}$ take the forms of Eqs. 2.27 and 2.29 respectively. The coefficient matrix $\mathbf{A}$ is computed by $\mathbf{A} = \mathbf{M}^{-1}\mathbf{B}$.

2.2.4 General form of the plane equation and plane-Hermite spline intersection

Here we derive the general form of the plane equation as well as the intersection point of a plane and a Hermite spline in the Euclidean space $\mathbb{R}^3$. This provides the mathematical solution to a problem encountered in the vessel reconstruction

method which will be introduced later: finding the intersection points between the skeletonisation of the vasculature and the clipping boundaries.

Let the general form of the plane equation to be defined as:

$$ex + fy + gz + h = 0 \quad (2.31)$$

Also let $\mathbf{P}_n = (x_n, y_n, z_n)$, $n = 1, 2, 3$ to be three non-collinear points on the plane. These points should satisfy the following system of three equations:

$$ex_n + fy_n + gz_n + h = 0 \quad (2.32)$$

This system can be solved by applying the Cramer's Rule. Let

$$D = \begin{vmatrix} x_1 & y_1 & z_1 \\ x_2 & y_2 & z_2 \\ x_3 & y_3 & z_3 \end{vmatrix} \quad (2.33)$$

If $D = 0$, this means the volume of the parallelepiped taking $\mathbf{P}_1, \mathbf{P}_2, \mathbf{P}_3$ and the origin as four vertices is zero. In other words, the plane passes through the origin, hence we have $d = 0$ as well. In this case, this system has infinite sets of solutions for e, f, g . One set can be obtained by giving an arbitrary non-zero number to any of e, f and g , and the other two parameters will be easily determined. In the more common case when $D \neq 0$, the values of e, f and g can be calculated as follows:

$$e = -\frac{h}{D} \begin{vmatrix} 1 & y_1 & z_1 \\ 1 & y_2 & z_2 \\ 1 & y_3 & z_3 \end{vmatrix} \quad f = -\frac{h}{D} \begin{vmatrix} x_1 & 1 & z_1 \\ x_2 & 1 & z_2 \\ x_3 & 1 & z_3 \end{vmatrix} \quad g = -\frac{h}{D} \begin{vmatrix} x_1 & y_1 & 1 \\ x_2 & y_2 & 1 \\ x_3 & y_3 & 1 \end{vmatrix} \quad (2.34)$$

Here the values of e, f and g are dependent on the value of h . They are uniquely determined if h is set equal to any non-zero number. Substituting these parameters into Eq. 2.32 yields the general form of the plane equation.

Now we want to find the intersection of a plane and a cubic Hermite spline. Suppose that the interval of the Hermite spline $\mathcal{C}$ that intersects with the plane is parameterised by $t \in [0, 1]$ and can be represented by:

$$x(t) = a_{01} + a_{11}t + a_{21}t^2 + a_{31}t^3 \quad (2.35a)$$

$$y(t) = a_{02} + a_{12}t + a_{22}t^2 + a_{32}t^3 \quad (2.35b)$$

$$z(t) = a_{03} + a_{13}t + a_{23}t^2 + a_{33}t^3 \quad (2.35c)$$

We also have the plane represented by $ex + fy + gz + h = 0$. Substituting Eqs. 2.35a - 2.35c into the plane equation yields the following cubic equation:

$$\begin{bmatrix} 1 & t & t^2 & t^3 \end{bmatrix} \begin{bmatrix} a_{01} & a_{02} & a_{03} \\ a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} e \\ f \\ g \end{bmatrix} + h = 0 \quad (2.36)$$

Now the problem of finding the intersection point of a plane and a cubic Hermite spline becomes finding the roots to the preceding equation which fall in the domain $t \in [0, 1]$. In general a cubic function can have 0–3 real roots in the domain $t \in [0, 1]$. However, in our case where the Hermite spline is the skeletonisation of the vasculature and the plane is one of the clipping boundaries (introduced in Sec. 2.3), there is always one and only one real root t_0 that satisfies $0 \leq t_0 \leq 1$. This root can be easily computed using any computational software. The intersection point is simply given by substituting t_0 into the spline equations, i.e. $(x(t_0), y(t_0), z(t_0))$.

2.3 A NOVEL METHOD TO NUMERICALLY RECONSTRUCT THE VASCULAR GEOMETRY

In this section we present a novel and simple method to reconstruct the hypothetical geometry of the healthy vasculature prior to intracranial aneurysm (IA) formation. The basic assumption for the vasculature is that the blood vessel is tapering from one end to the other without any abrupt change in the radii. The method can be summarised as follows: a Frenet frame is calculated along the skeletonisation of the arterial geometry; upstream and downstream boundaries of the aneurysmal segment are expressed in terms of the local Frenet frame basis vectors; the hypothetical healthy geometry is then reconstructed by propagating a closed curve along the skeleton using the local Frenet frames so that the upstream boundary is smoothly morphed into the downstream boundary. This methodology takes into account the natural tortuosity of the arterial vasculature and requires minimal user subjectivity. The procedures of this method are summarised as follows:

1. Clinical imaging data (see Fig. 2.6(a)) depicting an aneurysmal vessel is first segmented using @neufuse (a segmentation-registration-visualisation software suite developed for the European project @neurIST, <http://www.>

aneurist.org: Integrated Biomedical Informatics in the Management of Cerebral Aneurysms, see Villa-Uriol et al. (2011)).

2. A skeleton of the vasculature is generated in @neufuse.
3. The aneurysmal segment is clipped from the blood vessel so that the vessel is divided into three segments: upstream, aneurysm and downstream (see Fig. 2.6(b)). The clipping planes are normal to the vascular skeleton. The positions of the clipping planes are chosen visually so that they do not include any of the neck geometry and (subjectively) where the local curvature of the vessel has not been influenced by the presence of the aneurysm. This is done whilst also attempting to minimise the amount of vessel removed.
4. The boundary curves of the upstream and downstream segments are extracted in Tecplot (Tecplot, Inc, Bellevue, Washington, USA).
5. Both the skeleton and the two boundary curves are exported into MATLAB (Mathworks, Natick, Massachusetts, USA) in the form of discrete points. Points of the skeleton are interpolated by a multi-interval cubic Hermite spline using the method introduced in Sec. 2.2.3.2. The boundary tangent vectors are taken to be the vectors connecting the first two points as well as the last points on the skeleton respectively.
6. The position vectors of the two intersection points of the interpolated Hermite spline and the two boundary planes are calculated using the method introduced in Sec. 2.2.4. Two normal vectors of the boundary planes in the flow direction are also determined.
7. Neither the skeleton nor the interpolated Hermite spline based on the skeleton can be used again for reconstructing a healthy geometry since the skeleton may have already been reshaped due to the growth of the aneurysm. Hence a new skeleton is interpolated between the two boundary planes using the computed vectors based on the single-interval cubic Hermite spline interpolation scheme introduced in Sec. 2.2.3.1. A Frenet frame composed of the $\mathbf{T}$, $\mathbf{N}$ and $\mathbf{B}$ vectors is then calculated along the newly interpolated skeletonisation using the equations introduced in Sec. 2.2.1 (see Fig. 2.6(c)).
8. Once the Frenet frame is defined, upstream and downstream boundaries are defined in terms of the local Frenet frame basis vectors (see Fig. 2.6(d)).

The hypothetical healthy geometry is then reconstructed by propagating a closed curve along the skeletonisation in the normal planes, i.e. the planes spanned by the $\mathbf{N}$ and $\mathbf{B}$ vectors, so that the upstream boundary morphs smoothly into the downstream boundary. The propagating boundary curve $\mathbf{r}(t, \theta)$, $\theta \in [0, 2\pi)$, $t \in [0, 1]$, is constructed from the skeletonisation curve $\mathbf{c}(t)$ and the radial vectors $\mathbf{l}(t, \theta)$ which lie in the $\mathbf{N}$ - $\mathbf{B}$ planes, i.e.

$$\mathbf{r}(t, \theta) = \mathbf{c}(t) + \mathbf{l}(t, \theta) \quad (2.37)$$

where t is a parameterisation of $\mathbf{c}(t)$ and θ is the angle of $\mathbf{l}(t, \theta)$ counted from the local normal vector $\mathbf{N}$ in the direction that obeys the right-hand rule.

9. $\mathbf{l}(t, \theta)$ is expressed in a combination of local Frenet frame basis vectors:

$$\begin{aligned} \mathbf{l}(t, \theta) = & (|\mathbf{l}(0, \theta)| \cdot (1 - \omega(t)) + |\mathbf{l}(1, \theta)| \cdot \omega(t)) \\ & \cdot (\cos(\theta) \cdot \mathbf{N}(t) + \sin(\theta) \cdot \mathbf{B}(t)) \end{aligned} \quad (2.38)$$

where $\omega(t)$ is an interpolation function based on some specific property of the skeleton such as the parameterisation t or the arc-length, and should satisfy:

$$\omega(t) = \begin{cases} 0 & t = 0 \\ 1 & t = 1 \end{cases} \quad (2.39)$$

Different interpolation functions will provide boundaries with different shapes. In our study, we select a simple, linear function: $\omega(t) = t$, which is suitable for reconstructing a short arterial segment.

10. By considering a discrete range of values for t and θ , we can generate a contiguous set of boundaries (see Fig. 2.6(e)).
11. These boundaries are triangulated and converted into a smooth surface, which is considered as the reconstructed, hypothetical healthy segment (introduced in Sec. 2.5).

The procedures of the method are summarised in Fig. 2.6.

2.4 PRACTICAL PROBLEMS DURING METHOD IMPLEMENTATION

During the implementation of this novel vessel reconstruction method we encountered several problems, including reinterpolation of the points on the boundary

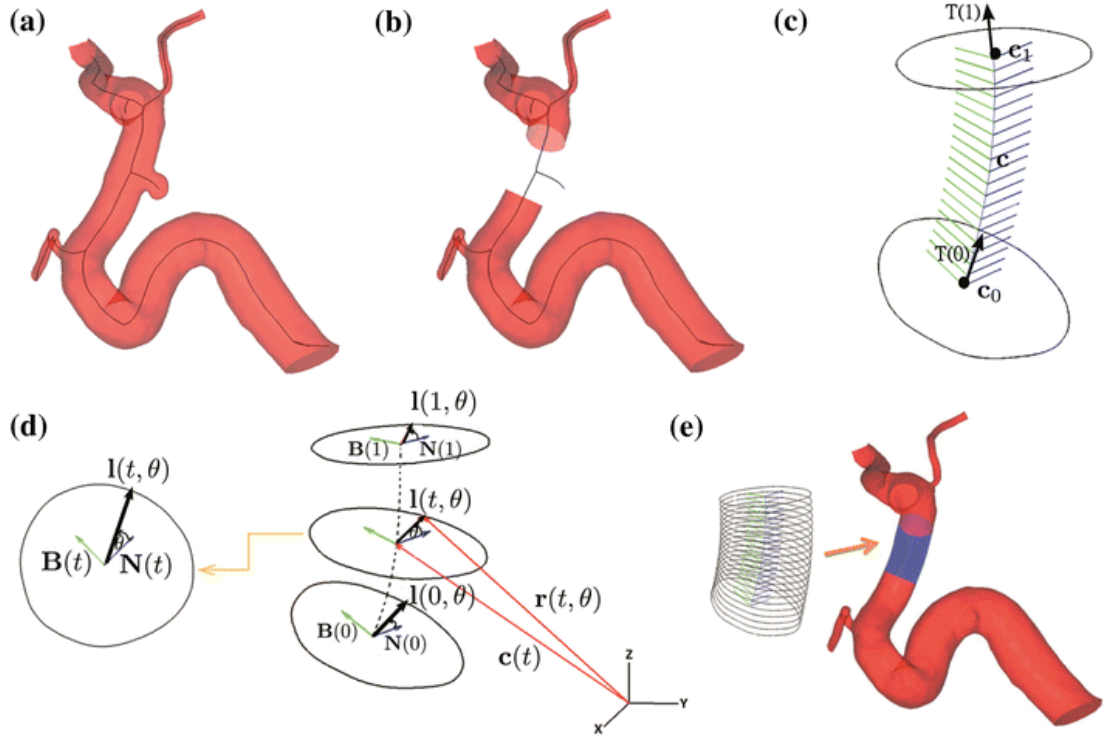


Figure 2.6: Some key procedures of the novel vessel reconstruction methodology. (a) Segmented clinical image of vasculature depicting an IA and the skeletonization of the arterial vasculature. (b) Aneurysmal segment removal. (c) Extraction of the boundaries, interpolation of a new skeleton using a cubic polynomial and computation of the Frenet frame along the interpolated skeleton (tangent vector not shown). (d) Morphing the inlet boundary into the outlet boundary. Position vectors of reconstructed surface section $\mathbf{r}(t, \theta)$ computed by adding the position vectors of the skeleton curve $\mathbf{c}(t)$ to radial vectors in the local $\mathbf{N}$ - $\mathbf{B}$ plane, i.e., $\mathbf{I}(t, \theta)$. The magnitude of $\mathbf{I}(t, \theta)$ is defined using an interpolation of the radial vector magnitudes of the inlet and outlet boundaries. (e) Transformation of the boundaries into a smooth surface and reconnecting this surface into the parent geometry reconstruction method.

curves, specifying the magnitude of the boundary vectors for the interpolation of the new skeleton, as well as twisting points on the new skeletonisation of the aneurysmal segment.

2.4.1 Reinterpolation of the points on the boundary curves

When this method is numerically implemented, the parameter t of the skeleton and the angle θ of the radial vectors $\mathbf{I}(t, \theta)$ should first be discretised. The upstream and downstream boundary curves can be represented by radial vectors $\mathbf{I}(0, \theta)$ and $\mathbf{I}(1, \theta)$. For these radial vectors θ must be identically discretised so that $\mathbf{I}(t, \theta)$ of

other boundary curves are correctly interpolated. However, these upstream and downstream boundary curves are extracted in the format of discrete points from the imaging data. Neither the numbers of points on these boundary curves are equal, nor the angle between any two adjacent points on one boundary curve is same. In other words, θ is not identically discretised for these two boundary curves. Hence these boundaries curves must be processed before being applied to interpolate the radial vectors on other cross sections. A simple method is developed to solve this problem, which is based on the application of an equidistant angle interpolation to the radial vectors on these two boundary curves. Taking the upstream boundary curve ($t = 0$) as an example and assume it is extracted into the format of N discrete points, we summarise the procedures of this method as follows:

1. Compute all the radial vectors $\mathbf{l}(0, \theta_n)$, $n = 1, 2, \dots, N$ in this boundary curve by subtracting the position vectors of the boundary points with the local skeleton point $\mathbf{c}(0)$. Here θ_n is defined as the angle between the local normal vector of the skeleton $\mathbf{N}(0)$ and the radial vector $\mathbf{l}(0, \theta_n)$, measured following the right-hand rule of the Frenet frame.
2. We define a new angular function $\varphi(i) = i$, $i \in (0, 2\pi]$, where the associated new radial vectors $\mathbf{l}(0, \varphi)$ will be interpolated based on the values of φ .
3. We linearly interpolate $\mathbf{l}(0, \varphi)$ using the radial vectors of the discrete boundary points $\mathbf{l}(0, \theta_n)$. For any angle of φ , we interpolate $\mathbf{l}(0, \varphi)$ as:

$$\mathbf{l}(0, \varphi) = \begin{cases} \mathbf{l}(0, \theta_N) + [\mathbf{l}(0, \theta_1) - \mathbf{l}(0, \theta_N)] \cdot \frac{\varphi - \theta_N + 2\pi}{\theta_1 - \theta_N + 2\pi} & 0 < \varphi \leq \theta_1 \\ \mathbf{l}(0, \theta_n) + [\mathbf{l}(0, \theta_{n+1}) - \mathbf{l}(0, \theta_n)] \cdot \frac{\varphi - \theta_n}{\theta_{n+1} - \theta_n} & \theta_n < \varphi \leq \theta_{n+1} \\ \mathbf{l}(0, \theta_N) + [\mathbf{l}(0, \theta_1) - \mathbf{l}(0, \theta_N)] \cdot \frac{\varphi - \theta_N}{\theta_1 - \theta_N + 2\pi} & \theta_N < \varphi \leq 2\pi \end{cases} \quad (2.40)$$

4. By considering discrete values of i following a finite arithmetic progression, we can have equidistant angles of φ , as well as an equidistant angle interpolation of the radial vectors $\mathbf{l}(0, \varphi)$ in this boundary curve. An example would be letting $i = \frac{m\pi}{180}$ where $m = 1, 2, \dots, 360$, then we would have discretised $\mathbf{l}(0, \varphi_m)$ whereby $\varphi_m = \frac{m\pi}{180}$.

Fig. 2.7 visualises the reinterpolation of the points on the upstream boundary. After repeating the preceding procedures for the downstream boundary curve, we now

have both upstream and downstream boundary curves whose radial vectors are discretised in an identical way with respect to the angle φ . This enables us to correctly proceed to the interpolation of the radial vectors of other boundary curves.

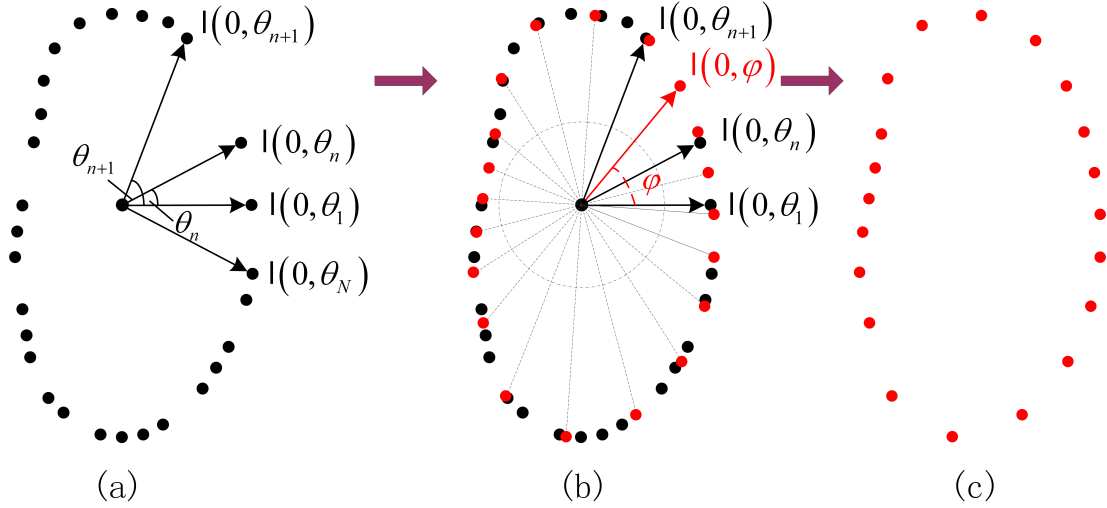


Figure 2.7: Reinterpolation of the upstream boundary points based on the existing points on the boundary. (a) Upstream boundary represented by the original points. (b) Reinterpolation of new boundary points whose radial vectors have equidistant angles around the boundary based on the original points. (c) Upstream boundary represented by the newly reinterpolated points.

2.4.2 Specifying the boundary tangent vectors for interpolating the new vascular skeleton

In this vessel reconstruction method, a new single-interval cubic Hermite spline is created to be taken as the skeleton of the reconstructed arterial segment. The boundary conditions needed to create this spline, i.e. the matrix $\mathbf{Q}_1$ in Eq. 2.18, consist of two endpoints $\mathbf{P}^1$ and $\mathbf{P}^2$, as well as two tangent vectors $\mathbf{T}^1$ and $\mathbf{T}^2$ at $\mathbf{P}^1$ and $\mathbf{P}^2$. $\mathbf{P}^1$ and $\mathbf{P}^2$ are the intersection points of the old skeleton and the clipping planes, hence are determined boundary conditions for interpolating the new spline. However, the tangent vectors still have yet to be determined. Each tangent vector has three degrees of freedom (DOFs): two supplied by the direction cosines to specify the direction of the vector and one supplied by the magnitude of the vector. The directions of $\mathbf{T}^1$ and $\mathbf{T}^2$ are taken to be normal to the clipping planes, together occupying 4 DOFs. This leaves two DOFs undetermined, i.e. the magnitudes of the vectors. Here the magnitude of $\mathbf{T}^1$ is denoted as κ_1 and that of $\mathbf{T}^2$ is denoted as κ_2 .

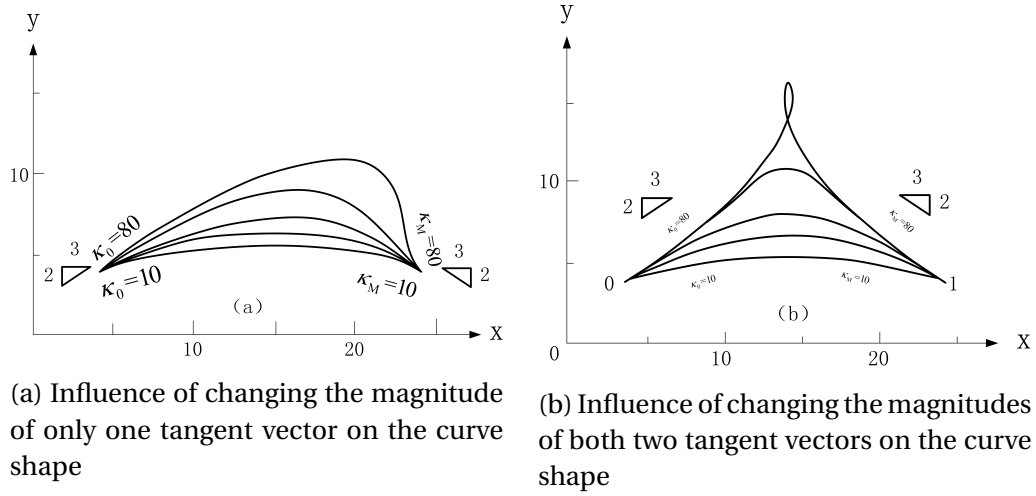


Figure 2.8: Influence of the magnitudes of the tangent vectors on the shape of the interpolated single-interval Hermite spline. In the left case, the right tangent magnitude remains unchanged. Increasing the left tangent magnitude makes the curve travel a longer distance before bending towards the right endpoint. In the right case, both tangent magnitudes are changed equally. Increasing the magnitudes makes the curve rise in the middle and even form a loop (adapted from Mortenson 2006).

Interestingly, values of κ_1 and κ_2 affect the shape of the curve. Fig. 2.8 shows the effect of adjusting the values of κ_1 and κ_2 on the shape of an interpolated two dimensional curve with the endpoints and the directions of the curve at the endpoints fixed. It can be seen that the magnitudes of the tangent vector affect the curve shape by adjusting the entire arc length as well as its trend of how it travels from one end to the other. In general, increasing the values of κ_1 and κ_2 will result in longer curves, even generating loops. Varying κ_1 and κ_2 will yield an infinite family of curves, all of which have the same endpoints and same directions at the endpoints yet entirely different interior shapes; thus the vessels reconstructed using these curves as the new skeletons will all be different. In the literature, several methods have been suggested to determine κ_1 and κ_2 (Barsky and Beatty 1983; Kochanek and Bartels 1984; Manning 1974); some being quite complicated, some being easier to implement. A simple method is adopted in our study: we set the magnitudes of both tangent vectors to be the distance between the two endpoints, i.e. $\kappa_1 = \kappa_2 = \|\mathbf{P}^2 - \mathbf{P}^1\|$. New vessel skeletons were interpolated using this method in 22 cases of physiological vasculatures. Results show that the vessels reconstructed based on these skeletons look realistic in all cases.

2.4.3 Twisting points on the new vascular skeleton

One intrinsic feature that associates with a space Hermite spline, or more generally, any cubic curve, is the presence of abrupt twists of the spline at certain locations on the curve (Wang et al., 2008). We call them the twisting points in general. At these locations, due to the abrupt twists of the curve, the normal and binormal vectors $\mathbf{N}$ and $\mathbf{B}$ of the Frenet frame will also exhibit a very sudden spin along the tangent vector $\mathbf{T}$ (see Fig. 2.9). If this Frenet frame is employed to reconstruct the cross

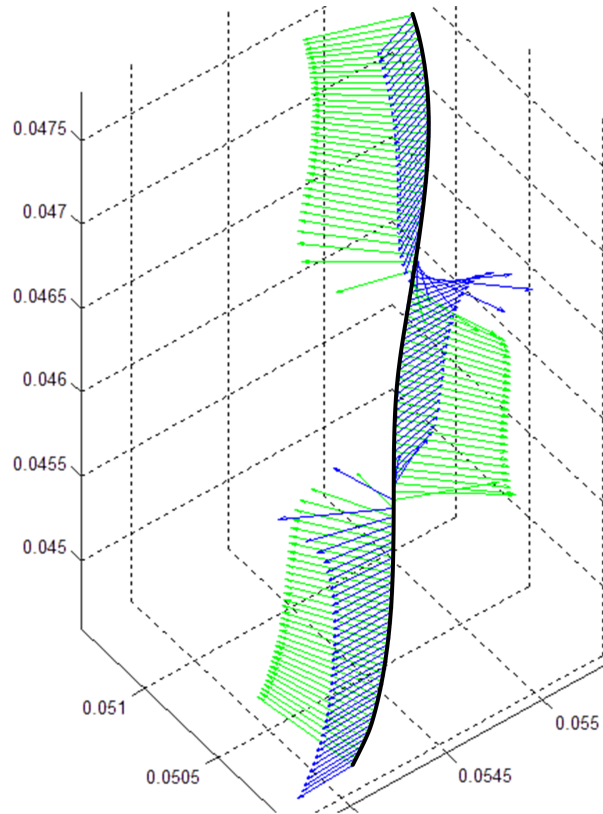


Figure 2.9: An illustration of two twisting points on a space curve. Notice the rapid spinning of the Frenet frame in the neighbourhood of the twisting points.

sections of the artery (as detailed in Sec. 2.3), the final surface transformed from the cross sections will be discontinuous (See Fig. 2.10). Hence before applying the vessel reconstruction method, we need to determine whether the new skeleton has any twisting points, and where these points are if they exist. In addition, the rapidly spinning Frenet frame caused by the twisting points also needs to be processed.

Generally speaking, a cubic Hermite spline can have a maximum of two twisting points. For a plane spline in which the torsion τ equals to 0 everywhere on the curve,

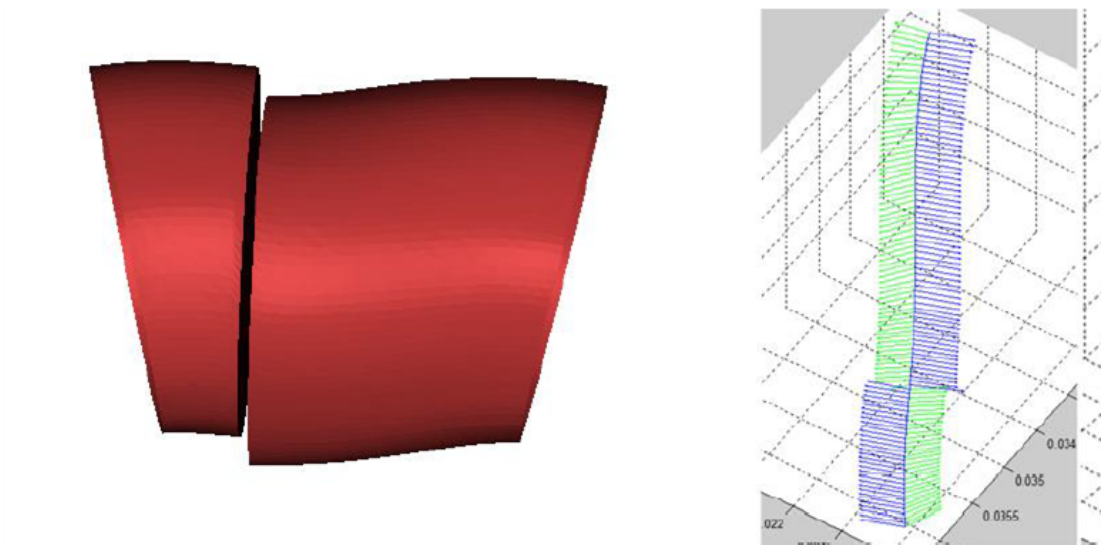


Figure 2.10: Reconstructed geometry using Frenet frames with a twisting point.

the twisting points coincide with the inflection points, i.e. points where the curvature κ vanishes and the curve concavity changes sign. For a space spline, the definition of a twisting point becomes ambiguous since κ can never be exactly equal to 0 (see below for proof). The fast spin of the Frenet frame happens within a very short segment of the curve where κ nearly vanishes rather than a single point, namely in very short segments where the spline is relatively straight. In this case locating the ‘twisting segment’ and processing the Frenet frame accordingly becomes very important. Here we present a simple and practical method to detect the general twisting points and to process the affected Frenet frame of the vascular skeleton $\mathcal{C}(t)$, $t \in [0, 1]$, which has the same form as in Eq. 2.35a to 2.35c. Two scenarios are considered: (1) Plane curve, (2) Space curve. In order to determine whether $\mathcal{C}(t)$ is a plane spline or a space spline, we compute the determinant of the following coefficient matrix:

$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} \quad (2.41)$$

If $\det(\mathbf{A}) = 0$, then $\mathcal{C}(t)$ is a plane spline, otherwise $\mathcal{C}(t)$ is a space spline. To prove this, we know that $\det(\mathbf{A}) = 0$ means that the three column vectors of $\mathbf{A}$ are linearly dependent, i.e.:

$$\begin{bmatrix} a_{13} \\ a_{23} \\ a_{33} \end{bmatrix} = k_1 \begin{bmatrix} a_{11} \\ a_{21} \\ a_{31} \end{bmatrix} + k_2 \begin{bmatrix} a_{12} \\ a_{22} \\ a_{32} \end{bmatrix} \quad (2.42)$$

The parameters k_1 and k_2 are not both 0. Substituting Eq. 2.42 into the spline equations 2.35a to 2.35c, we have:

$$k_1x + k_2y - z + p = 0 \quad (2.43)$$

where $p = a_{03} - k_1a_{01} - k_2a_{02}$. Comparing this equation with Eq. 2.31, we see that Eq. 2.43 satisfies the general form of a plane equation. Hence we have proven that this spline is a plane curve. On the contrary, if $\det(\mathbf{A}) \neq 0$, then the equation of the spline does not satisfy the general form of a plane equation. Hence the spline is a space curve. Now we summarise our method to detect the general twisting points and to process the affected Frenet frame of the vascular skeleton as follows:

1. If $\mathcal{C}(t)$ is a plane spline, the problem of finding twisting points becomes finding the inflection points of a plane spline. This is done by letting the curvature κ vanish:

$$\kappa(t) = \frac{|\dot{\mathcal{C}}(t) \times \ddot{\mathcal{C}}(t)|}{|\dot{\mathcal{C}}(t)|^3} = 0 \quad (2.44)$$

which implies that the numerator must be 0. Eq. 2.44 can be further decomposed into three separate equations:

$$\begin{vmatrix} 3t^2 & a_{12} & a_{13} \\ -3t & a_{22} & a_{23} \\ 1 & a_{32} & a_{33} \end{vmatrix} = \begin{vmatrix} a_{11} & 3t^2 & a_{13} \\ a_{21} & -3t & a_{23} \\ a_{31} & 1 & a_{33} \end{vmatrix} = \begin{vmatrix} a_{11} & a_{12} & 3t^2 \\ a_{21} & a_{22} & -3t \\ a_{31} & a_{32} & 1 \end{vmatrix} = 0 \quad (2.45)$$

This means the vector $(3t^2, -3t, 1)^T$ $t \in [0, 1]$ lies in the same plane as the three vectors $(a_{11}, a_{21}, a_{31})^T$, $(a_{12}, a_{22}, a_{32})^T$ and $(a_{13}, a_{23}, a_{33})^T$ composed of the spline coefficients. Since these three vectors are coplanar for a plane spline, the solution to any of these three equations automatically satisfies the other two. Now the problem of finding the twisting points of a plane spline $\mathcal{C}(t)$ has become finding the solution to a quadratic equation (or a linear equation if the quadratic coefficient is 0) within the range $[0, 1]$. No solution implies no twisting point (or inflection point) on the spline, one solution represents a single twisting point, whereas two solutions corresponds to double twisting points. Having determined the twisting points, we need to process the Frenet frame. Assume the skeleton is discretised by N points, denoted as $\mathbf{P}_n$, $n = 1, 2, \dots, N$:

- a) If no twisting point presents on the spline, nothing needs to be done to the Frenet frame.

- b) If a single twisting point exists, here denoted as $\mathbf{P}_{M_1}$, then we reverse the normal and binormal vectors $\mathbf{N}_n$ and $\mathbf{B}_n$, $n = 1, \dots, M_1$, between the initial endpoint $\mathbf{P}_1$ and $\mathbf{P}_{M_1}$ if $M_1 \leq \frac{N}{2}$, or reverse $\mathbf{N}_n$ and $\mathbf{B}_n$, $n = M_1, \dots, N$, between $\mathbf{P}_{M_1}$ and the last endpoint $\mathbf{P}_N$ if $M_1 \geq \frac{N}{2}$.
- c) If double twisting points presents, denoted as $\mathbf{P}_{M_1}$ and $\mathbf{P}_{M_2}$, $M_1 \leq M_2$, respectively, then we simply reverse $\mathbf{N}_n$ and $\mathbf{B}_n$, $n = M_1, \dots, M_2$, between $\mathbf{P}_{M_1}$ and $\mathbf{P}_{M_2}$.

This will yield a continuous Frenet frame along the spline.

2. If $\mathcal{C}(t)$ is a space curve, then the three vectors $(a_{11}, a_{21}, a_{31})^T$, $(a_{12}, a_{22}, a_{32})^T$ and $(a_{13}, a_{23}, a_{33})^T$ are not coplanar. Hence the twisting points cannot be found by simply setting $\kappa = 0$ since Eq. 2.45 can never be satisfied. In addition, the method we have used to process the Frenet frame for a plane spline fails as for a space curve the Frenet frame usually spins rapidly in the ‘twisting segment’ rather than at one point. Hence we have used a different numerical method of detecting the twisting points (twisting segments), based on the computation of the spinning angle of the Frenet frame. In order to process to Frenet frame, a modified Frenet frame (also called rotation minimising frames) is used (Bloomenthal, 1990). The details of this method is as follows:

- a) Determine if the spline contains a twisting point. To do this, firstly, compute the absolute value of the torsion $|\tau|$ at all points on the curve $\mathbf{P}_n$, $n = 1, 2, \dots, N$, and assume the point $\mathbf{P}_{M_1}$ which has the maximum $|\tau|$ is a twisting point. Secondly, specify another two points $\mathbf{P}_A$ and $\mathbf{P}_B$ on the curve on each side of $\mathbf{P}_{M_1}$, satisfying $A = \max(M_1 - Q, 1)$ and $B = \min(M_1 + Q, N)$, $Q \in \mathbb{Z}^+$. In our cases, given each skeleton consists of around 100 points, we choose $Q = \lceil N/50 \rceil$. Now the curve arc $\widehat{\mathbf{P}_A \mathbf{P}_B}$ is assumed to be the segment in which the Frenet frame rapidly spins. Thirdly, calculate the total spinning angle of the binormal vector $\mathbf{B}$ within the segment based on the definition of τ (i.e. Eq. 2.8):

$$\theta = \int_{s(\mathbf{P}_A)}^{s(\mathbf{P}_B)} \tau(s) ds = \int_{t(\mathbf{P}_A)}^{t(\mathbf{P}_B)} \tau(t) |\dot{\mathcal{C}}(t)| dt \quad (2.46)$$

Lastly, define a critical spinning angle θ_C : if $\theta \geq \theta_C$, then the assumption is accepted, i.e. $\mathbf{P}_{M_1}$ is a twisting point and $\widehat{\mathbf{P}_A \mathbf{P}_B}$ is a segment in which the Frenet frame rapidly spins; otherwise the assumption is rejected, $\mathbf{P}_{M_1}$ is a normal point. For a plane spline, the inflection points

cause a complete reverse of $\mathbf{B}$. This can be regarded as a spinning angle of π . For numerical purposes, after many trials, we set $\theta_C = \frac{3\pi}{4}$ to detect the existence of a twisting point for a space curve. If $\mathbf{P}_{M_1}$ is not a twisting point, then the spline is considered to have no twisting point at all. However, if $\mathbf{P}_{M_1}$ is a twisting point, then we apply this method on the skeleton points again $\mathbf{P}_n$, $n = 1, \dots, A-1$ and $n = B+1, \dots, N$ excluding the points bounded by $\widehat{\mathbf{P}_A \mathbf{P}_B}$ to check if the spline has a second twisting point. If it exists, we denoted as $\mathbf{P}_{M_2}$, and the corresponding twisting segment as $\widehat{\mathbf{P}_C \mathbf{P}_D}$, where $\mathbf{P}_C$ is closer to the upstream boundary and $\mathbf{P}_D$ is closer to the downstream boundary.

- b) If no twisting point exists on the spline, nothing needs to be done to the Frenet frame. If a single twisting point $\mathbf{P}_{M_1}$ presents together with the twisting segment $\widehat{\mathbf{P}_A \mathbf{P}_B}$, then we reverse the normal and binormal vectors $\mathbf{N}_n$ and $\mathbf{B}_n$, $n = B, \dots, N$, between $\mathbf{P}_B$ and the last endpoint $\mathbf{P}_N$, i.e. $\widehat{\mathbf{N}}_n = -\mathbf{N}_n$ and $\widehat{\mathbf{B}}_n = -\mathbf{B}_n$ where $\widehat{\mathbf{N}}_n$ and $\widehat{\mathbf{B}}_n$ are the new frame vectors. For the Frenet frame between $\mathbf{P}_A$ and $\mathbf{P}_B$, we use a simple interpolation scheme proposed by Bloomenthal (1990) (introduced later). Finally, if double twisting point $\mathbf{P}_{M_1}$ and $\mathbf{P}_{M_2}$ presents together with the two twisting segment $\widehat{\mathbf{P}_A \mathbf{P}_B}$ and $\widehat{\mathbf{P}_C \mathbf{P}_D}$, assuming $m_1 < m_2$, we simply interpolate a new set of Frenet frame between points $\mathbf{P}_A$ and $\mathbf{P}_D$.
- c) We use the concept called rotation minimising frame (RMF) (Bloomenthal, 1990) to interpolate a new set of Frenet frame between $\mathbf{P}_A$ and $\mathbf{P}_X$ where $X = B$ for a single twisting point spline and $X = D$ for a double twisting point spline. The interpolation of a new frame is based on its previous frame: the new frame $(\mathbf{T}_n, \widehat{\mathbf{N}}_n, \widehat{\mathbf{B}}_n)$ at $\mathbf{P}_n$ is computed by transforming $(\mathbf{T}_{n-1}, \widehat{\mathbf{N}}_{n-1}, \widehat{\mathbf{B}}_{n-1})$ from $\mathbf{P}_{n-1}$ to $\mathbf{P}_n$, and then rotating it so that $\mathbf{T}_{n-1}$ aligns itself with $\mathbf{T}_n$, $n = A+1, \dots, X-1$. Then the rotated frame is considered as the new frame $(\mathbf{T}_n, \widehat{\mathbf{N}}_n, \widehat{\mathbf{B}}_n)$ at point $\mathbf{P}_n$. To be more specific, the axis of rotation at $\mathbf{P}_n$ can be represented by a unit vector $\mathbf{u}^n = (u_x^n, u_y^n, u_z^n)$ computed by:

$$\mathbf{u}^n = \frac{\mathbf{T}^{n-1} \times \mathbf{T}^n}{|\mathbf{T}^{n-1} \times \mathbf{T}^n|} \quad (2.47)$$

The rotation angle α^n is given by:

$$\alpha^n = \arccos\left(\frac{\mathbf{T}^{n-1} \cdot \mathbf{T}^n}{|\mathbf{T}^{n-1}| |\mathbf{T}^n|}\right) \quad (2.48)$$

The rotation matrix $\mathbf{R}^n$ can be written concisely in Rodrigues' rotation formula:

$$\mathbf{R}^n = \cos \alpha^n \mathbf{I} + \sin \alpha^n [\mathbf{u}^n]_{\times} + (1 - \cos \alpha^n) \mathbf{u}^n \otimes \mathbf{u}^n \quad (2.49)$$

where $\mathbf{I}$ is the 3×3 identity matrix, $[\mathbf{u}^n]_{\times}$ is the skew-symmetric matrix of $\mathbf{u}^n$ and $\mathbf{u}^n \otimes \mathbf{u}^n$ is the tensor product of $\mathbf{u}^n$ with itself, i.e.:

$$[\mathbf{u}^n]_{\times} = \begin{bmatrix} 0 & -u_z^n & u_y^n \\ u_z^n & 0 & -u_x^n \\ -u_y^n & u_x^n & 0 \end{bmatrix} \quad \mathbf{u}^n \otimes \mathbf{u}^n = \begin{bmatrix} (u_x^n)^2 & u_x^n u_y^n & u_x^n u_z^n \\ u_x^n u_y^n & (u_y^n)^2 & u_y^n u_z^n \\ u_x^n u_z^n & u_y^n u_z^n & (u_z^n)^2 \end{bmatrix} \quad (2.50)$$

Hence given the frame $(\mathbf{T}^{n-1}, \hat{\mathbf{N}}^{n-1}, \hat{\mathbf{B}}^{n-1})$ at point $\mathbf{P}^{n-1}$, we can compute the new frame $(\mathbf{T}^n, \hat{\mathbf{N}}^n, \hat{\mathbf{B}}^n)$ at point $\mathbf{P}^n$:

$$\hat{\mathbf{N}}^n = \mathbf{R}^n \hat{\mathbf{N}}^{n-1} \quad \text{and} \quad \hat{\mathbf{B}}^n = \mathbf{R}^n \hat{\mathbf{B}}^{n-1} \quad (2.51)$$

and $\mathbf{T}^n$ is just taken to be the tangent vector of the old Frenet frame. An extreme case is when $\mathbf{T}^n = \mathbf{T}^{n-1}$, Eq. 2.47 becomes undefined hence no axis is available to perform the rotation. In this case we simply assume that there is no rotation of the frame and set the rotation matrix $\mathbf{R} = \mathbf{I}$, hence $\hat{\mathbf{N}}^n = \hat{\mathbf{N}}^{n-1}$, $\hat{\mathbf{B}}^n = \hat{\mathbf{B}}^{n-1}$. Fig. 2.11 shows the approach to create the RMFs: the frame $(\mathbf{T}^{n-1}, \hat{\mathbf{N}}^{n-1}, \hat{\mathbf{B}}^{n-1})$ is first transformed from point $\mathbf{P}^{n-1}$ to point $\mathbf{P}^n$ then rotated into $(\mathbf{T}^n, \hat{\mathbf{N}}^n, \hat{\mathbf{B}}^n)$. Starting from point $\mathbf{P}_{A+1}$, repeating this approach in order and finishing at point $\mathbf{P}_{X-1}$, we finally have a new set of frames interpolated in order between points $\mathbf{P}_A$ and $\mathbf{P}_X$.

The reconstructed geometry using a smooth processed Frenet frame is compared with the reconstructed geometry using the original Frenet frame in Fig. 2.12.

2.5 TRANSFORMING BOUNDARY CURVES INTO A SURFACE

During the implementation of this method, the boundary curve functions $\mathbf{r}(t, \theta)$ are discretised by t_n where $n = 1, 2, \dots, N$ and by θ_m where $m = 1, 2, \dots, M$. This yields N boundary curves and M points on each of these boundary curves. Hence the total amount of points on the reconstructed segment is $N \times M$. These points need to be

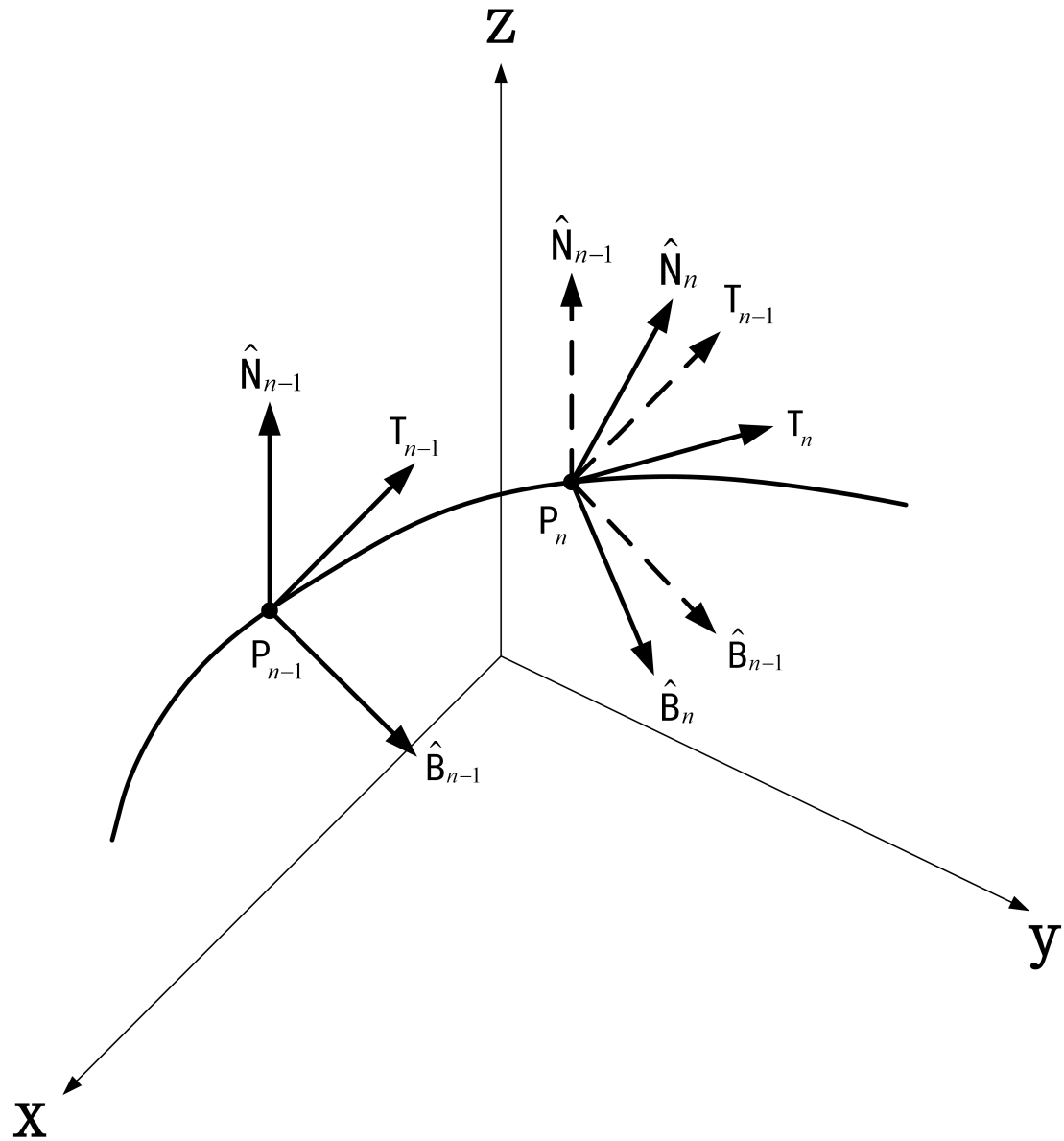


Figure 2.11: The approach to create a rotation minimising frame. The interpolation of a new frame is based on its previous frame.

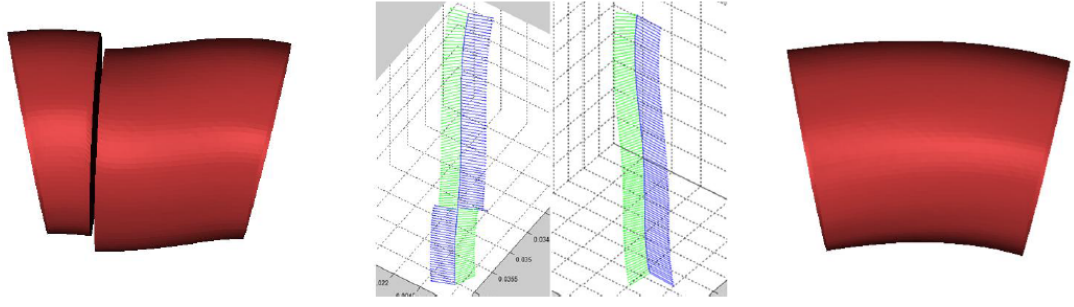


Figure 2.12: This compares the reconstructed geometries using original Frenet frame which includes one twisting point and the processed Frenet frame without twisting point.

transformed into a surface so that the reconstructed surface geometry can be connected back to the parent artery. The method we adopted to achieve this is based on creating triangular facets from these points, and a natural way to triangulate the points is to write standard STL files. STL, which is short for STereoLithography, is a file format that describes a raw unstructured triangulated surface by the unit normal vectors and the vertices of the triangles using a three-dimensional Cartesian coordinate system. A standard STL file can be specified in either ASCII or binary representations, the first one of which is adopted in our study. An STL file is built up by many blocks each of which is used to represent a single triangular facet. For three points $\mathbf{P}^i = (P_x^i, P_y^i, P_z^i)$, $i = 1, 2, 3$, a general triangular facet can be created, denoted as $\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3$. The corresponding STL block representing this facet has the following shape:

Listing 2.1: A general STL block used to represent a triangular facet

```
facet normal  $n_x(\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3)$   $n_y(\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3)$   $n_z(\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3)$ 
  outer loop
    vertex  $P_x^1$   $P_y^1$   $P_z^1$ 
    vertex  $P_x^2$   $P_y^2$   $P_z^2$ 
    vertex  $P_x^3$   $P_y^3$   $P_z^3$ 
  endloop
endfacet
```

where $n_x(\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3)$, $n_y(\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3)$, $n_z(\Delta\mathbf{P}^1\mathbf{P}^2\mathbf{P}^3)$ are the coordinates of the outward unit normal vector $\mathbf{n}$ of the facet. Note that the direction of $\mathbf{n}$ should be consistent with the order of the points $\mathbf{P}^1 \rightarrow \mathbf{P}^2 \rightarrow \mathbf{P}^3$ by the right-hand rule. Now in our method, in order to transform the generated boundary points into a sur-

face, we still need to sort out the correct order of the points that are used to write the facet blocks in the STL file. We denote four adjacent points, two on the n th boundary curve as $\mathbf{P}(t_n, \theta_m)$ and $\mathbf{P}(t_n, \theta_{m+1})$, and the other two on the $(n+1)$ th boundary curve as $\mathbf{P}(t_{n+1}, \theta_m)$ and $\mathbf{P}(t_{n+1}, \theta_{m+1})$, where $n = 1, 2, \dots, N-1$ and $m = 1, 2, \dots, M-1$. Using these four points, we can generate two triangular facets: $\triangle \mathbf{P}(t_n, \theta_m) \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m)$ and $\triangle \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m)$. Each of these facets shares one common edge (or two common vertices) with each of its three adjacent facets. The STL blocks for representing $\triangle \mathbf{P}(t_n, \theta_m) \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m)$ and $\triangle \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m)$ should be written following the point order $\mathbf{P}(t_n, \theta_m) \rightarrow \mathbf{P}(t_n, \theta_{m+1}) \rightarrow \mathbf{P}(t_{n+1}, \theta_m)$ and $\mathbf{P}(t_n, \theta_{m+1}) \rightarrow \mathbf{P}(t_{n+1}, \theta_{m+1}) \rightarrow \mathbf{P}(t_{n+1}, \theta_m)$ respectively:

Listing 2.2: Two consecutive blocks used to represent two adjacent triangular facets composed of vettices θ_m

```

facet normal  $n_x(\triangle \mathbf{P}(t_n, \theta_m) \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m))$   $n_y(\triangle \mathbf{P}(t_n, \theta_m) \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m))$ 
» $n_z(\triangle \mathbf{P}(t_n, \theta_m) \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m))$ 
  outer loop
    vertex  $P_x(t_n, \theta_m)$   $P_y(t_n, \theta_m)$   $P_z(t_n, \theta_m)$ 
    vertex  $P_x(t_n, \theta_{m+1})$   $P_y(t_n, \theta_{m+1})$   $P_z(t_n, \theta_{m+1})$ 
    vertex  $P_x(t_{n+1}, \theta_m)$   $P_y(t_{n+1}, \theta_m)$   $P_z(t_{n+1}, \theta_m)$ 
  endloop
endfacet

facet normal  $n_x(\triangle \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m))$ 
» $n_y(\triangle \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m))$   $n_z(\triangle \mathbf{P}(t_n, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_{m+1}) \mathbf{P}(t_{n+1}, \theta_m))$ 
  outer loop
    vertex  $P_x(t_n, \theta_{m+1})$   $P_y(t_n, \theta_{m+1})$   $P_z(t_n, \theta_{m+1})$ 
    vertex  $P_x(t_{n+1}, \theta_{m+1})$   $P_y(t_{n+1}, \theta_{m+1})$   $P_z(t_{n+1}, \theta_{m+1})$ 
    vertex  $P_x(t_{n+1}, \theta_m)$   $P_y(t_{n+1}, \theta_m)$   $P_z(t_{n+1}, \theta_m)$ 
  endloop
endfacet

```

where the subscripts x , y and z denote the x , y and z components of the vectors respectively. A special case will be $m = M$, which corresponds to the last point $\mathbf{P}(t_n, \theta_M)$ on the n th boundary and the last point $\mathbf{P}(t_{n+1}, \theta_M)$ on the $(n+1)$ th boundary curves. These points should also be triangulated together with the first points $\mathbf{P}(t_n, \theta_1)$ and $\mathbf{P}(t_{n+1}, \theta_1)$ on these boundary curves. Hence another two facets are generated based on these four points following the point order $\mathbf{P}(t_n, \theta_M) \rightarrow \mathbf{P}(t_n, \theta_1) \rightarrow \mathbf{P}(t_{n+1}, \theta_M)$ and $\mathbf{P}(t_n, \theta_1) \rightarrow \mathbf{P}(t_{n+1}, \theta_1) \rightarrow \mathbf{P}(t_{n+1}, \theta_M)$, here denoted

as $\Delta \mathbf{P}(t_n, \theta_M) \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_M)$ and $\Delta \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_1) \mathbf{P}(t_{n+1}, \theta_M)$ respectively. The STL blocks corresponding to these two facets have the following form:

Listing 2.3: Two consecutive blocks used to represent two adjacent triangular facets composed of vettices θ_m

```

facet normal  $n_x(\Delta \mathbf{P}(t_n, \theta_M) \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_M))$   $n_y(\Delta \mathbf{P}(t_n, \theta_M) \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_M))$ 
»  $n_z(\Delta \mathbf{P}(t_n, \theta_M) \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_M))$ 
  outer loop
    vertex  $P_x(t_n, \theta_M)$   $P_y(t_n, \theta_M)$   $P_z(t_n, \theta_M)$ 
    vertex  $P_x(t_n, \theta_1)$   $P_y(t_n, \theta_1)$   $P_z(t_n, \theta_1)$ 
    vertex  $P_x(t_{n+1}, \theta_M)$   $P_y(t_{n+1}, \theta_M)$   $P_z(t_{n+1}, \theta_M)$ 
  endloop
endfacet

facet normal  $n_x(\Delta \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_1) \mathbf{P}(t_{n+1}, \theta_M))$   $n_y(\Delta \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_1) \mathbf{P}(t_{n+1}, \theta_M))$ 
»  $n_z(\Delta \mathbf{P}(t_n, \theta_1) \mathbf{P}(t_{n+1}, \theta_1) \mathbf{P}(t_{n+1}, \theta_M))$ 
  outer loop
    vertex  $P_x(t_n, \theta_1)$   $P_y(t_n, \theta_1)$   $P_z(t_n, \theta_1)$ 
    vertex  $P_x(t_{n+1}, \theta_1)$   $P_y(t_{n+1}, \theta_1)$   $P_z(t_{n+1}, \theta_1)$ 
    vertex  $P_x(t_{n+1}, \theta_M)$   $P_y(t_{n+1}, \theta_M)$   $P_z(t_{n+1}, \theta_M)$ 
  endloop
endfacet

```

After all the points on the n th and $(n+1)$ th boundary curves have been triangulated into facets, the same process starts again from the first points on the $(n+1)$ th and $(n+2)$ th boundary curves and continues until the tessellation for the last two points on the $(N-1)$ th and N th boundary curves is finished. The entire reconstructed segment containing $N \times M$ points will have $(N-1) \times 2M$ facets (see Fig. 2.13). The STL file containing all the facets of the reconstructed geometry is then imported into ANSYS ICEM CFD (ANSYS Inc, Cecil Township, Pennsylvania, United States) with the geometry of the parent vessel. These geometries are remeshed together with unstructured tetrahedral elements. Now a new continuous surface geometry is finally obtained representing the hypothetically healthy vasculature prior to aneurysm formation.

2.6 DISCUSSION

To investigate the haemodynamic environment prior to IA formation it is necessary to obtain the pre-aneurysmal arterial geometry. Generally, the pre-aneurysmal

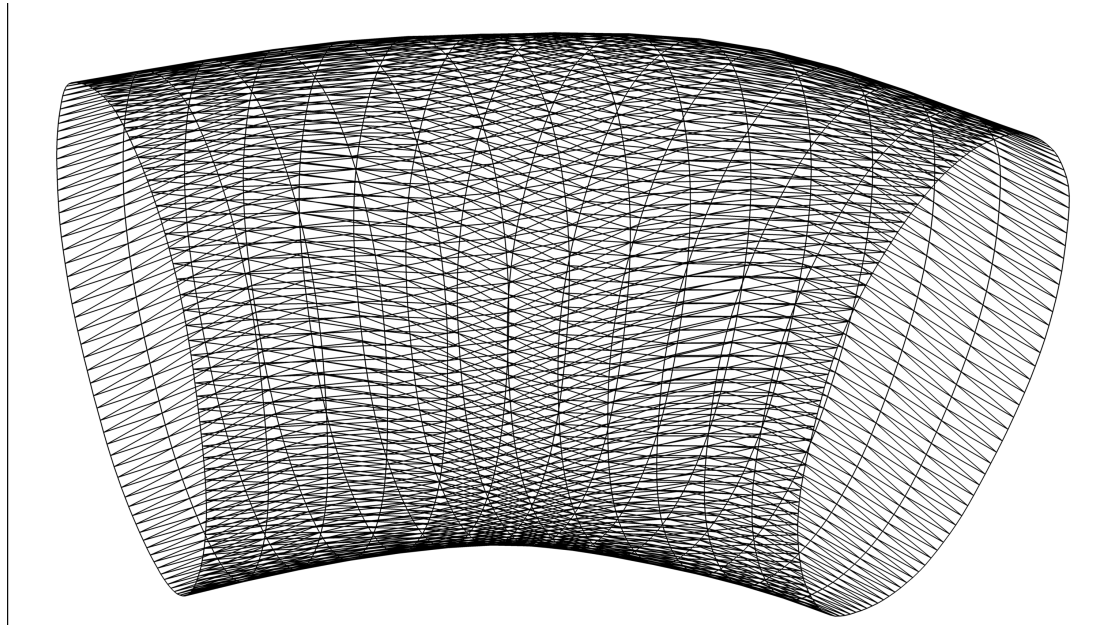


Figure 2.13: The generated STL mesh of the geometry with triangular facets.

geometry is not available and hence numerical methods have been developed to estimate it. For instance, Karmonik et al. (2004), Mantha et al. (2006) and Shimogonya et al. (2009a) reconstructed the healthy arteries from circular segments; Ford et al. (2009) developed a reconstruction technique based on the digitisation of the arterial vessel by Voronoi diagrams; Baek et al. (2009) utilised commercial surface generation tools to generate surface patches bounded by user-defined splines on the arterial surface; Cebal et al. (2010) applied a smoothing algorithm to the bulging region manually delineated on the original geometry to smooth out the bulging and generate a smooth surface. One obvious limitation of these vessel reconstruction methods is the strong user dependence: all of these methods require plenty of manual intervention. To overcome this shortcoming, we propose a novel, simple yet effective methodology: a local Frenet frame is defined along the skeletonisation of the vasculature; upstream and downstream boundaries of the aneurysmal segment are expressed in terms of the local Frenet frame basis vectors; the hypothetically ‘healthy’ geometry is then reconstructed by propagating a closed curve along the skeletonisation using the local Frenet frames so that the upstream boundary is smoothly morphed into the downstream boundary. Our method takes into consideration the tortuosity of vasculature and requires minimum user dependence. However, an inherent problem to all of these methodologies is that as the aneurysm grows, the local geometry of the vessel may be distorted, particularly for large aneurysms.

Consequently, the accuracy with which the reconstructed geometry reflects the real vasculature prior to IA formation may be reduced. Inaccurate geometry reconstructions would affect the computational fluid dynamics, spatial distributions of haemodynamic indices (introduced in the next chapter) and thus the conclusions of our study. In order to avoid such inaccuracies the ideal would be to find a proper approach to validate the reconstruction results. However, in order to do this, the actual pre-aneurysmal arterial geometry is needed for comparison. Unfortunately, this is currently impossible since most clinical collections of aneurysm data do not contain pre-aneurysmal healthy blood vessel images, as it is impractical, costly and ethically dubious to routinely capture images of subjects without the presence of due clinical concern. Nevertheless, despite this fact, the above mentioned studies still have the potential to guide hypotheses relating to the mechanobiology of IA inception.

2.7 CONCLUSION

In this chapter, a novel method is presented to reconstruct the hypothetical geometry of the healthy vasculature prior to IA formation, based on the propagation of a closed curve along the skeletonisation using the local Frenet frames to morph the upstream boundary into the downstream boundary. In the next chapter, this method will be applied to 22 clinical cases depicting IAs and computational fluid dynamic simulations of the reconstructed vasculature without the presence of IA will be performed.



INVESTIGATION OF THE INFLUENCE OF HAEMODYNAMIC FACTORS ON THE INCEPTION OF IAS

As introduced in Chapter 2, several recent numerical investigations (Mantha et al., 2006; Shimogonya et al., 2009a; Ford et al., 2009; Baek et al., 2009; Singh et al., 2010 et al.) have attempted to estimate the pre-aneurysmal, ‘healthy’ geometry of the vasculature from the diseased one. For sidewall IAs, the general approach involves removal of the arterial section containing the IA from the segmented geometry and reconstructing the healthy geometry in this region. Computational fluid dynamic (CFD) studies on the hypothetical healthy geometry are then used to investigate whether patterns of haemodynamic stimuli on the healthy vasculature correlate with the *known* location of IA formation. However, these studies to date have been relatively small, i.e. examined between only 1 and 5 clinical cases, and consequently inconsistencies in conclusions are apparent. For example, it has been concluded (from such studies) that local elevations in wall shear stress (WSS), wall shear stress gradient (WSSG), oscillatory shear index (OSI), aneurysm formation indicator (AFI) and/or gradient oscillatory number (GON) may be suggestive of a region that is susceptible to IA formation. Table 3.1 illustrates the disparities in conclusions of previous studies. Whilst these are not studies of causality *per se*, they may give rise to novel hypotheses that can be tested in vivo, in vitro or in-silico, using aneurysm

Table 3.1: Summary of the previous IA inception studies. Specific patterns of these haemodynamic indices have been observed to correspond to the location of aneurysm formation (LAF). Note that conclusions are sometimes inconsistent among different studies and that the number of cases considered is small.

Study	Conclusions (supporting indices)	Positive corre- lations
Mantha et al. (2006)	Low AFI	3/3
Shimogonya et al. (2009a)	GON	1/1
Ford et al. (2009)	GON	4/5
Baek et al. (2009)	High WSS	2/2
Singh et al. (2010)	High WSS	2/2
	High OSI	1/2

evolution models. However, given the divergence in the conclusions of previous studies, there is a need for further investigations using larger databases to provide guidance on which indices are most relevant with respect to IA inception.

In this chapter, we present a study that is conducted on 22 (segmented) clinical cases depicting sidewall IAs. The original, pre-aneurysmal vascular geometry is numerically reconstructed using the novel method introduced in Chapter 2 and CFD simulations on these ‘hypothetically healthy’ geometry are performed. The first sections of this Chapter cover the following: an introduction to CFD, including basic assumptions, determination of boundary conditions and meshing of surface geometries; clear definitions of the aforementioned haemodynamic indices; a means of objectively defining the positive correlation between various indices at locations of IA formation; an analysis of haemodynamic index distributions in the region where the IA is known, *a priori*, to develop. Finally, our findings are compared and discussed with the observations from previous studies in the literature.

3.1 CASE SELECTION AND APPLICATION OF THE VESSEL RECONSTRUCTION METHOD

The sidewall IA cases used in this study are pre-selected from a database of approximately 200 segmented aneurysm geometries collected and processed during the European project @neurist. To assist in the pre-selection, we exclude: IAs with perforating arteries, IAs immediately adjacent to small side-branching arteries, IAs which incorporate a branching artery on the segment to be reconstructed, as well as terminal IAs. Several sidewall aneurysms which develop close to (but not at) bifurcations were included. This is done by visual inspection of the segmented geometry and skeletonisation to identify if the aneurysm section could be clipped. Using this approach, a subset of 22 sidewall IA cases was identified for this study. The age of the patients ranges between 40 and 77 years, with an average age of 58 years; 14 of the aneurysms are from females and 8 are from males. The locations are summarised in Table 3.2. We successfully applied the novel vessel reconstruction method (de-

Table 3.2: Locations of the IAs in this study.

Locations	Number
carotid bifurcation	1
posterior communicating artery	10
ophthalmic artery	3
anterior choroidal artery	1
A1 segment of anterior cerebral artery	2
anterior communicating artery	2
sylvian bifurcation	1
basilar artery	2

tailed in Chapter 2) to all 22 of the pre-selected sidewall IA cases: the aneurysm sections are removed and the arterial segments are reconstructed. Twenty geometries are illustrated in Fig. 2 with the original aneurysms superimposed onto the reconstructed segment.

3.2 COMPUTATIONAL FLUID DYNAMICS INITIATION

To investigate the haemodynamic environment in the arteries, computational fluid dynamics (CFD) is employed. The main assumptions adopted in this study are:

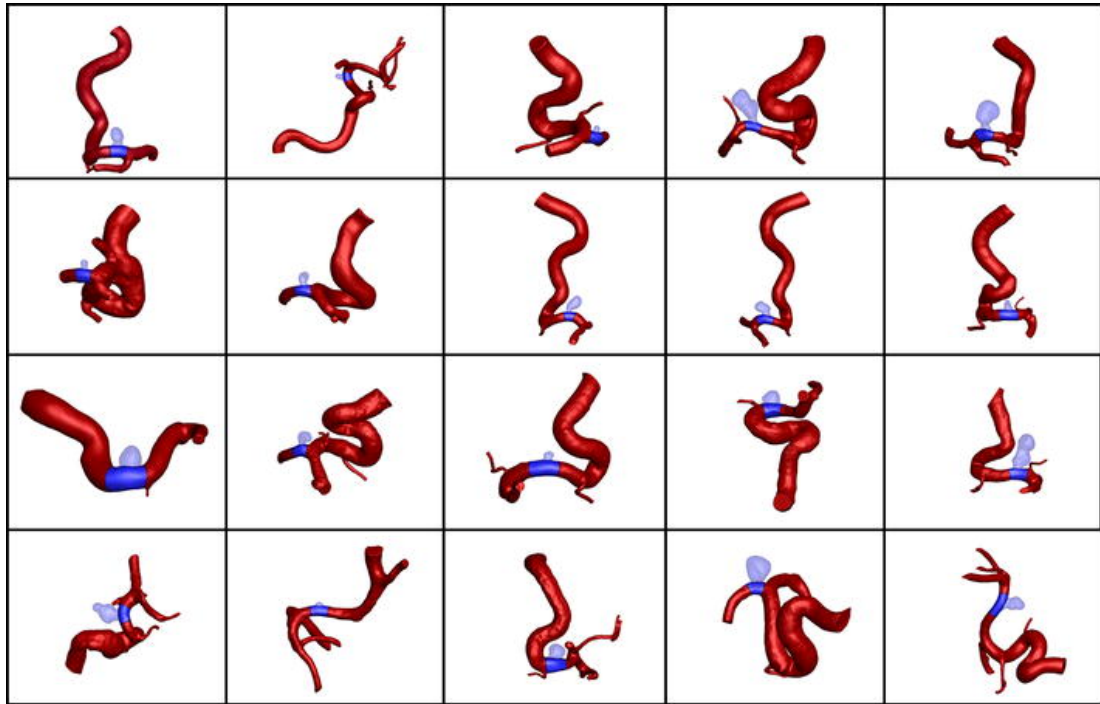


Figure 3.1: Illustration of the application of the vessel reconstruction method to 20 (out of 22) clinical cases depicting sidewall IAs. The reconstructed segments are depicted in dark blue whilst IAs are superimposed on the reconstructed geometries and depicted in light blue (Chen et al., 2013).

- Blood is modelled as incompressible Newtonian fluid. One factor that affects the viscosity property of blood is the shear stress. Blood only shows an obvious non-Newtonian nature at low shear stress level, which usually occurs in small vessels such as arterioles and capillaries. Of the arteries being analysed here, only the ophthalmic and posterior communicating artery are relatively narrow, however, the average diameter for these is approximately 1.5mm, which is deemed wide enough for the blood to be considered as a Newtonian fluid. Therefore in the simulations the blood is assumed to have a constant viscosity of $0.0035\text{Pa}\cdot\text{s}$ and a constant density of 1069kg/m^3 , both taken from the literature.
- Arteries are modelled as rigid-wall vessels. We do not consider the pulsatile nature of the arterial wall, since coupling the deformation of the wall and the blood flow is computationally-demanding as it required to continuously remesh the fluid domain as the wall boundary deforms. Previous studies also prove this assumption to be reasonable. For example, Perktold et al.

(1984) demonstrated that, for cerebral vasculature with aneurysms, the radial Cauchy strain of the parent vessel and aneurysm is only 0.02–0.05 as a consequence of pulsatile flow, which results in a negligible change to the WSS distribution.

- No-slip condition is assumed at the wall of the vessels. This assumption is considered to be applicable due to the fact that, although blood contains red blood cells which may ‘bounce along’ down the surface, the red blood cells tend to concentrate at the centre of the vessel due to their spinning behaviour in the vessel. Hence a small cell-free flow boundary layer exists at the wall of the vessels.

These assumptions have also been adopted in many other computational studies on arterial haemodynamics within the literature, and have been proven to be reliable (Mantha et al. 2006; Watton et al. 2009a; Shimogonya et al. 2009a; Ford et al. 2009; Doenitz et al. 2010; Kulcsár et al. 2011b; Chen et al. 2013; Aparício et al. 2014 and et al.).

Navier-Stokes equations for incompressible flow of a Newtonian fluid govern the motion of the fluid:

$$\rho\left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v}\right) = -\nabla p + \mu \nabla^2 \mathbf{v} + \mathbf{f} \quad (3.1)$$

where ρ is the density of the fluid, $\mathbf{v}$ is the flow velocity and $\nabla \mathbf{v}$ is the velocity gradient tensor, p is pressure, μ is fluid viscosity and $\mathbf{f}$ is the body force per unit volume acting on the fluid. These equations are solved using ANSYS CFX (ANSYS Inc., Canonsburg, Pennsylvania).

Realistic temporal profiles are used to model the flow and pressure variation during the cardiac cycle. These were obtained directly from @neufuse, in which a 1D model of the human circulatory system is incorporated. In this 1D model, the inlet pulsatile flow rates are obtained from phase contrast MR measurement on normal subjects, whereas the outlet pulsatile pressure profiles are obtained by numerically solving the 1D form of the momentum and continuity equations derived from the Navier-Stokes equations. Elastic properties of the vessel in this 1D model were taken from previous studies and dimensions of the vessels were taken from previous 1D models. The outlet pressure profiles have been validated by Reymond et al. (2009) and Reymond et al. (2011) in which non-invasive pressure measurements

using tonometry is performed on volunteers. The velocity profiles are applied perpendicularly to the inlet boundary and pressure profiles are imposed on the outlet surfaces (see Fig. 3.2 for an illustrative case of the applied boundary conditions in one simulation).

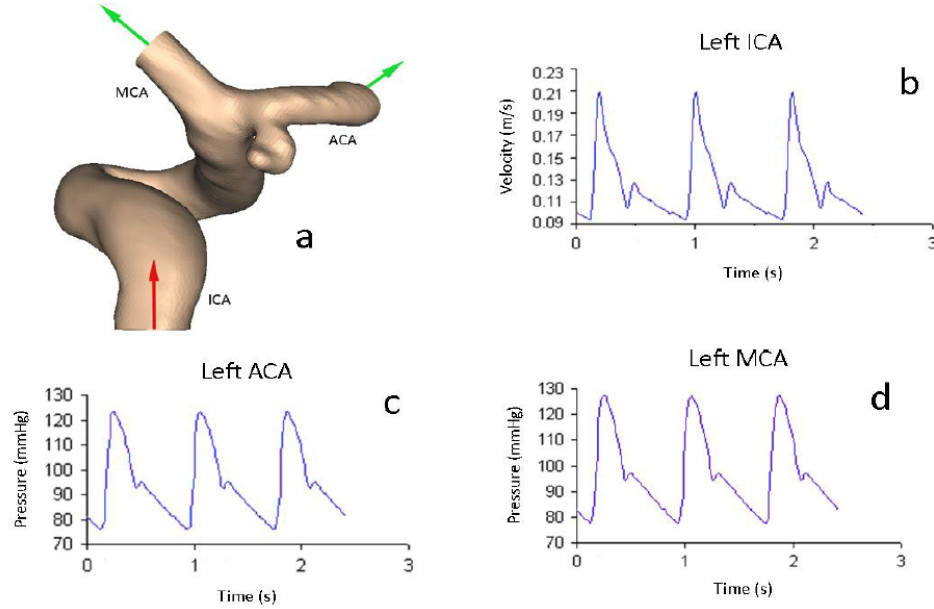


Figure 3.2: The boundary conditions applied on the geometry for one simulation. (a) Arterial geometry with boundary normals, (b) Internal carotid artery (ICA) velocity profile, (c) Anterior communicating artery (ACA) pressure profile, (d) Middle cerebral artery (MCA) pressure profile.

ANSYS ICEM (ANSYS Inc., Canonsburg, Pennsylvania) is used to construct a tetrahedral mesh of the vessel volume; prism mesh layers are specified near the arterial wall, which can help to enhance grid quality near the wall and give rise to more accurate solutions and better convergence for our study (Fig. 3.3). In order to exclude the initialisation artefacts in the early stages, three cardiac cycles were simulated and only the last cycle is used for analysis. Haemodynamic comparison results were exported into ANSYS CFD-Post (ANSYS Inc., Canonsburg, Pennsylvania) for further analysis.

3.3 CALCULATION OF THE HAEMODYNAMIC INDICES

We briefly overview the definitions of the haemodynamic indices used in this study. For an incompressible and isotropic Newtonian fluid, the total stress tensor σ at any

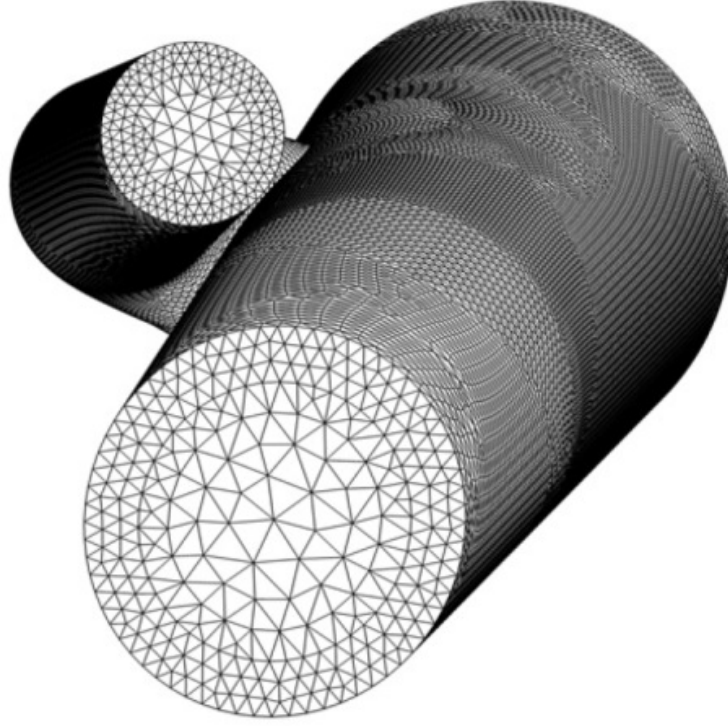


Figure 3.3: Tetrahedral mesh of the volume with prism layers specified near the arterial wall.

point is given by:

$$\boldsymbol{\sigma} = -p\mathbf{I} + 2\mu\mathbf{D} = -p\mathbf{I} + \mu[\nabla\mathbf{v} + (\nabla\mathbf{v})^T] \quad (3.2)$$

where again, p is the hydrostatic pressure, $\mathbf{I}$ is the identity tensor, μ is the blood viscosity, $\mathbf{D}$ is the rate of deformation tensor and $\nabla\mathbf{v}$ is the velocity gradient tensor. If we denote as $\mathbf{n}$ the unit normal vector at any point on the vessel wall pointing towards the lumen; then the traction force vector at the same point can be defined as $\mathbf{t} = \boldsymbol{\sigma}\mathbf{n}$. The shearing component of this traction vector, the wall shear stress vector $\mathbf{t}_s$, is given by Cheng et al. (2002):

$$\mathbf{t}_s = \mathbf{t} - (\mathbf{t} \cdot \mathbf{n})\mathbf{n} = (\mathbf{I} - \mathbf{n} \otimes \mathbf{n})\mathbf{t} \quad (3.3)$$

We denote the magnitude of $\mathbf{t}_s$ as $\tau(t)$ and compute its time-averaged value τ_{av} ,

$$\text{WSS} \equiv \tau_{av} = \frac{1}{T} \int_0^T \tau \, dt \quad (3.4)$$

and refer to this in the text as the wall shear stress (WSS), where T is the length of a cardiac cycle.

We calculate the wall shear stress gradient (WSSG) in a similar manner to the WSS. First, the tangential component of the gradient of WSS on the vessel surface is computed:

$$\mathbf{g}_s = \nabla \tau - (\nabla \tau \cdot \mathbf{n})\mathbf{n} = (\mathbf{I} - \mathbf{n} \otimes \mathbf{n}) \nabla \tau \quad (3.5)$$

and the time-averaged WSSG, γ_{av} , is computed as

$$\gamma_{av} = \frac{1}{T} \int_0^T |\mathbf{g}_s| dt \quad (3.6)$$

We compute two measures associated with the oscillation in direction of the wall shear stress vectors during the cardiac cycle, i.e. the oscillatory shear index (OSI) and minimum Aneurysm Formation Indicator (min(AFI)). If we define $\bar{\mathbf{t}}_s$ as the mean wall shear stress vector during one cardiac cycle:

$$\bar{\mathbf{t}}_s = \frac{1}{T} \int_0^T \mathbf{t}_s dt \quad (3.7)$$

Then the OSI is calculated as Ku et al. (1985); He and Ku (1996):

$$\text{OSI} = \frac{1}{2} \left(1 - \frac{|\bar{\mathbf{t}}_s|}{\tau_{av}} \right) \quad (3.8)$$

The values of OSI vary from 0 to 0.5, where OSI = 0 corresponds to the case in which the direction of the WSS vector $\mathbf{t}_s$ is constant and OSI = 0.5 corresponds to the case in which the direction of $\mathbf{t}_s$ is continuously rotating during the cardiac cycle.

The aneurysm formation indicator (AFI) proposed by Mantha et al. (2006) is a quantification of the cosine of the angle between the instantaneous and mean wall shear stress vectors at any time point:

$$\text{AFI} = \frac{\mathbf{t}_s \cdot \bar{\mathbf{t}}_s}{\tau \cdot |\bar{\mathbf{t}}_s|} \quad (3.9)$$

However, as AFI is an instantaneous quantity, we compute the minimum value of AFI during a cardiac cycle and denote it as min(AFI). This index quantifies the maximum deviation of the wall shear stress vector from its mean direction during the cardiac cycle. Hence each value of min(AFI) has a unique geometrical interpretation, e.g. min(AFI) = 1, 0, -1 implies the maximum deviation of the wall shear stress vector from its mean direction during the cardiac cycle is 0, 90, 180 degrees, respectively. Given that there is ambiguity in interpreting values of OSI other than 0 and 0.5, the index min(AFI) may offer some advantages in characterising the flow.

Lastly, in order to define the gradient oscillatory number (GON) index, at every surface point we define a local instantaneous right-hand Cartesian coordinate system pqr : p axis has the same direction as the local mean WSS vector $\bar{\mathbf{t}}_s$; q axis is perpendicular to $\bar{\mathbf{t}}_s$; r axis has the same direction as the local surface normal vector $\mathbf{n}$. The components of $\mathbf{t}_s$ in this coordinate system are $((t_s)_p, (t_s)_q, 0)$. If we define $\mathbf{G} = (\frac{\partial(t_s)_p}{\partial p}, \frac{\partial(t_s)_q}{\partial q}, 0)$, then the gradient oscillatory number (GON), recently proposed by Shimogonya et al. (2009a), is defined as:

$$\text{GON} = 1 - \frac{|\int_0^T \mathbf{G} dt|}{\int_0^T |\mathbf{G}| dt} \quad (3.10)$$

The values of GON vary from 0 to 1. Similarly to OSI, the minimum value $\text{GON} = 0$ corresponds to the case in which the direction of $\mathbf{G}$ is constant and the maximum value $\text{GON} = 1$ corresponds to the case in which the direction of $\mathbf{G}$ is continuously rotating during the cardiac cycle.

3.4 DEFINITION OF POSITIVE CORRELATIONS BETWEEN HAEMODYNAMIC INDICES AND LOCATIONS OF IA FORMATION

In an attempt to reduce the subjectivity of result analysis, we consider three distinct scenarios in which a correlation between a local elevation in a haemodynamic index and the location of aneurysm formation (LAF) can exist. More specifically, a correlation may be deemed positive if the region of local elevation of a haemodynamic index:

1. is within the ostium boundary
2. overlaps the ostium boundary
3. is within the vicinity of the ostium

where ‘the vicinity of the ostium’ refers to the half-section of the reconstructed artery segment that includes the aneurysm ostium. The third condition relaxes the definition of a positive correlation so that we have an upper bound on the number of positively correlated cases. Fig. 3.4 illustrates examples of these three criteria.

We consider two definitions of correlations: definition I contains all three scenarios (1,2,3), whereas definition II considers the first two scenarios (1,2). Note that we take care to use the word ‘elevated’ as opposed to using the word ‘high’ to describe a local increase in a haemodynamic index, since there is ambiguity with regards to what magnitude can be actually defined as ‘high’ (see Sec. 3.6). Given these definitions, the results are inspected independently by three observers. For each case of geometry, if a possible correlation is agreed by two or more observers, then the correlation is taken to be positive; otherwise negative. This criterion is utilised for analysing the spatial distributions of the five indices considered (WSS, WSSG, GON, OSI, min(AFI)) for all 22 cases.

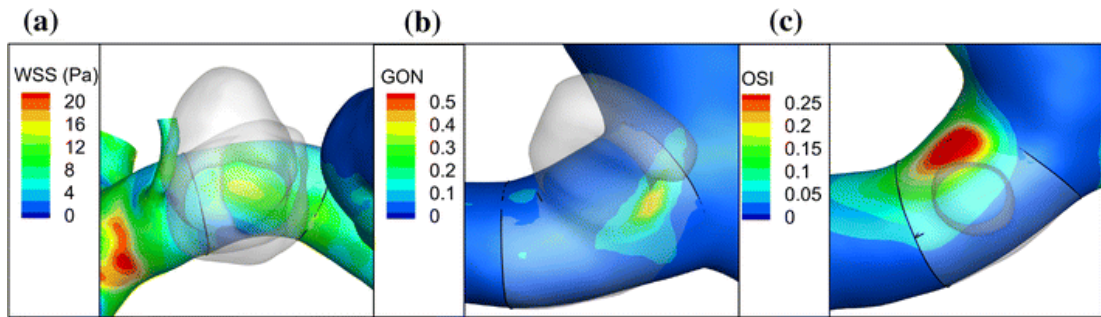


Figure 3.4: Three scenarios of relative positions between the elevation regions of the indices and the aneurysm ostium which can possibly be considered as positive correlations. (a) Elevation region of WSS (Pa) inside aneurysm ostium. (b) Elevation region of GON partially overlaps the ostium. (c) Elevation region of OSI locating in the vicinity of the ostium.

In this study, it is the local elevations of a haemodynamic index that are of primary interest to us, not the absolute magnitudes. However, to determine a visual correlation between a local elevation of a haemodynamic indice and the LAF, the range of each colourmap needs to be specified. Consequently, the identification of a local elevation is partly dependent on the choice of the upper and lower limits of the colourmap. The approach we have taken in this numerical study is as follows. For all cases, the number of intervals of the colourmap legend is set to 10. For OSI, min(AFI) and GON, we use the same colourmap ranges for all cases, i.e. $OSI \in [0, 0.25]$; $\min(AFI) \in [-1, 1]$; $GON \in [0, 0.5]$. Magnitudes of OSI above 0.1 and GON above 0.2 can easily be visually distinguished by looking for contours on the artery that are green, yellow or red, i.e. not blue. $\min(AFI) \leq 0.2$ can also be easily distinguished as green, yellow or red contours (the colourmap is reversed). The magnitudes of WSS and WSSG in the region of the LAF may vary significantly be-

tween different cases and thus it is difficult to utilise a universal colourmap range that applies to all cases. To proceed, we set the minimum values of the colourmap ranges for WSS and WSSG to be 0 Pa and 0 Pa/m respectively. The upper magnitude of the colourmap range, denoted as $L^{\max}$, is specified as follows. Initially $L^{\max}$ is set to be the global maximum value of the WSS/WSSG on the entire geometry (the default setting in ANSYS CFX). However, as the global maximum value can be much greater than the local maximum value of WSS/WSSG in the LAF, this results in no local elevation being identified due to monotonous blue colour in the region. In this case, we successively reduce $L^{\max}$ to see if a local elevation can be identified. However, we do specify a greatest lower bound (glb) for $L^{\max}$ so that we have a minimum threshold of WSS/WSSG that can be considered to be an elevation. For WSS, $\text{glb}(L^{\max}) = 5 \text{ Pa}$, this enables local elevations of WSS exceeding 2 Pa to be identified. For WSSG, $\text{glb}(L^{\max}) = 10000 \text{ Pa/m}$, this enables WSSG exceeding 4000 Pa/m to be identified as an elevation. For the 22 cases considered in this study, the ranges for the WSS colourmap vary between $[0, 5] \text{ Pa}$ and $[0, 70] \text{ Pa}$ whilst for WSSG they vary between $[0, 10000] \text{ Pa/m}$ and $[0, 50000] \text{ Pa/m}$.

3.5 SIMULATION RESULTS

Fig. 3.5 illustrates the spatial distributions of (a) WSS, (b) WSSG, (c) OSI, (d) min(AFI) and (e) GON; Fig. 3.6 illustrates the distributions of all the indices on one geometry. It can be seen that the OSI and min(AFI) tend to maximise locally in specific zones on the vessel, such as bifurcations, roots of branching arteries and large bends. However, the GON index appears more noisy with elevation regions appearing throughout the vessel in small patches.

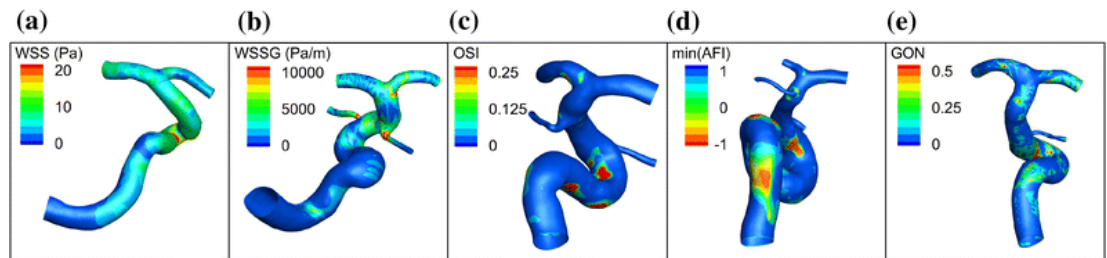


Figure 3.5: Illustration of spatial distribution patterns of the five investigated haemodynamic indices: (a) WSS, (b) WSSG, (c) OSI, (d) min(AFI) and (e) GON.

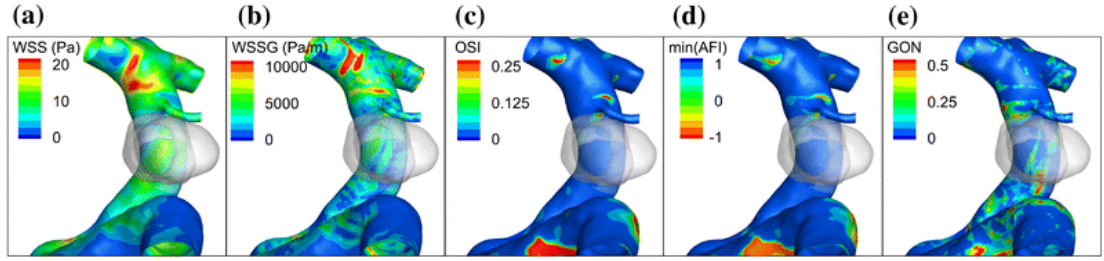


Figure 3.6: Spatial distributions of indices on one geometry: (a) WSS, (b) WSSG, (c) OSI, (d) min(AFI) and (e) GON.

The spatial distributions of WSS, WSSG, OSI, min(AFI) and GON were analysed and compared with respect to the aneurysm ostium using the two definitions for a positive correlation (see Sec. 3.4). Table 3.3 summarises the observations for all 22 cases. We observed that the magnitudes of the local elevations for the correlated cases varied, more specifically, magnitudes for local elevations were in the following ranges: $WSS \in [8, 50]$ Pa; $WSSG \in [7000, 45000]$ Pa/m; $OSI \in [0.3, 0.5]$; $\min(AFI) \in [-1.0, -0.8]$; $GON \in [0.4, 0.8]$; we will return to this in the Sec. 3.6.

Table 3.3: Summary of positive correlations between haemodynamic indices and LAFs. Results are based on the relative locations of the elevation region with respect to the aneurysm ostium. P, D, L, R denote the proximal, distal, left and right regions of the ostium and the suffixes E and V denote edge and vicinity, respectively.

	Ostium	P _E	P _V	D _E	D _V	L _E	L _V	R _E	R _V	I	II
WSS	14	4	1	1				1		20/22	20/22
WSSG	1	2	1		2				1	7/22	3/22
OSI				1	2		2		2	7/22	1/22
AFI	1			1	2		1		2	7/22	2/22
GON	8	2		9						19/22	19/22

Examples of both positive correlations (upper row) and non-correlations (lower row) of local elevations of haemodynamic indices with respect to the aneurysm ostium are depicted in Fig. 3.7. We observed a strong correlation between a local elevation of WSS and the LAF. Of the 22 geometries considered, 20 geometries witnessed WSS elevations in regions of IAs: 14/22 elevations occurred within the aneurysm ostium, whereas 6/22 elevations occurred on the edge of the ostium (4/22 proximal region, 1/22 distal edge, 1/22 lateral edge). Fig. 3.7a shows examples of correlation and non-correlation for the WSS index. Note that although a significant hot spot occurs on the downstream section of artery away from the location where the

aneurysm develops, a local elevation of WSS does occur in the aneurysm orifice; hence it is taken to be a positive correlation.

The correlations between WSSG and LAF appear to be low (see Fig. 3.7b for examples of positive and negative correlations for WSSG). By definition I of a positive correlation, 7/22 positive correlation cases are observed; 1/22 within the ostium; 2/22 on the proximal edge, 4/22 in the vicinity (1/22 proximal side, 2/22 distal side, 1/22 lateral side). Consequently, by definition II, there are only 3/22 positive correlations.

The indices OSI and min(AFI) quantify the oscillatory nature of the WSS vectors and hence have similar distribution patterns on the vessel wall. For both indices, low correlations with the LAF (OSI: 7/22, min(AFI): 7/22) were observed by definition I. By definition II, the correlations are further reduced (OSI: 1/22, min(AFI): 2/22). For OSI (see Fig. 3.7c), 1/22 elevation occurred on the distal edge of the aneurysm, whereas 6/22 elevations occurred in the vicinity (2/22 distal side, 4/22 lateral side). For min(AFI) (Fig. 3.7d), 1/22 elevation was observed to fully coincide with LAF, and another 1/22 elevation occurred on the distal edge the LAF. 5/22 elevations were observed in the vicinity of LAF (2/22 distal side, 3/22 lateral side).

Lastly, the GON index was observed to have a high level of correlation with the LAF in our study: 19/22 by both definitions for a positive correlation. However, note that regions of elevation are distributed throughout the artery (see Fig. 3.7e) and hence a high number of positive correlations is to be expected.

3.6 DISCUSSION

Consistent with previous studies such as Shimogonya et al. (2009a) and Ford et al. (2009) (see Table 3.1), we observed that elevated WSS and elevated GON were found to have the highest positive correlation with the LAF (20/22 for WSS and 19/22 for GON). For 17 out of 19 positively correlated cases of GON, the WSS was also elevated; consequently, in this study, GON offers little additional benefit in identifying the LAF. Interestingly, it can be seen in Figs. 3.5, 3.6 and 3.7 that all indices have elevations in the non-aneurysm regions as well. For example, in the upper figure of Fig. 3.7(a), a significant hot spot of WSS occurs on the downstream section of artery away from the location where the IA develops. Another good case to be considered is the GON index. Given that the accuracy of GON is two orders lower than

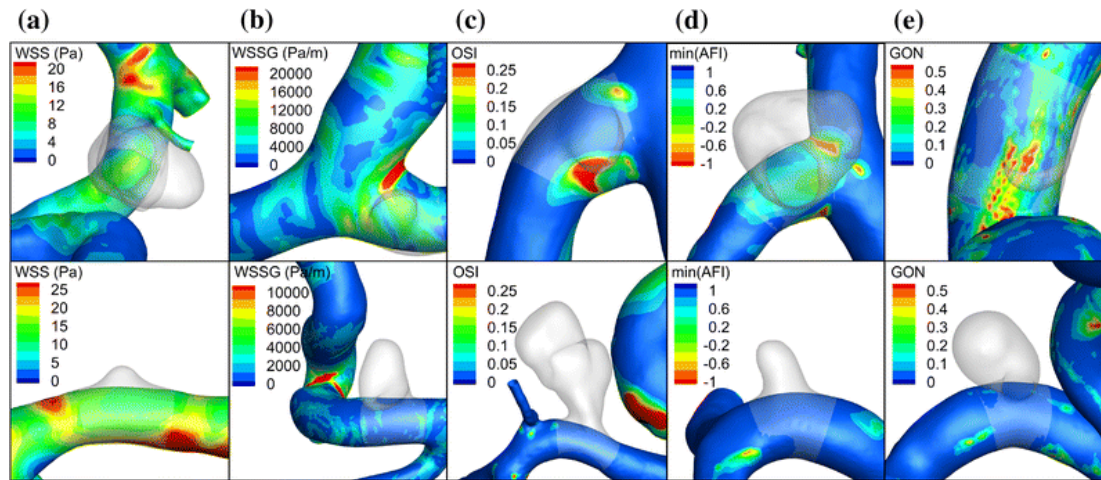


Figure 3.7: Examples of positive and negative correlations of elevations of haemodynamic indices and locations of aneurysm formation: (a) WSS, (b) WSSG, (c) OSI, (d) min(AFI) and (e) GON. The upper row depicts positive correlations whilst the lower row depicts negative correlations. Note that for the positive correlations we used a top view to highlight the relationship between the elevation region and the aneurysm ostium more clearly; for negative correlations, we used lateral view to illustrate that even in the vicinity of the aneurysm ostium, no index elevation is observed.

the velocity, it is understandable why GON appears noisy that it elevates at many non-aneurysmal sites. These false positive correlations obviously reduce the prediction qualities of all the proposed haemodynamic indices, especially of the ones which have high positive correlations, i.e. WSS and GON. However, while certain geometric features (e.g. bifurcations and sharp bends of the arteries) exhibit such haemodynamic conditions which are believed to be more ‘dangerous’, these geometric features are actually common both among individuals as well as across the population. In fact, only approximately 40% of the population has a ‘textbook’ Circle of Willis (Nixon et al., 2010). Despite of these facts, only minor population develops aneurysms whereas major does not. Hence these elevations of indices at the non-aneurysm regions clearly demonstrate that only they alone cannot account for the inception of IAs. Given the inter-person variability in arterial geometries and the incidence of IAs at certain regions in the Circle of Willis, it appears to be more likely that, IA formation is an unfortunate coincidence of multiple factors. In addition, we would like to remind the readers that the aim of this study is not to find a haemodynamic index which can be utilised to predict the locations where IAs will initiate. It is to examine one of current hypotheses regarding IA inception that spe-

cific haemodynamic patterns can possibly lead to the inception of IAs. Bearing this aim in mind, we consider that it is natural and actually meaningful to have these false positive correlations in our study where elevations of the indices are observed at non-aneurysm regions.

We observed low correlations between indices associated with the oscillatory nature of the flow and the LAF: by definition I, OSI (7/22) and min(AFI) (7/22); by definition II, OSI (1/22) and min(AFI) (2/22). These findings differ significantly from Mantha et al. (2006) in which a strong correlation for min(AFI) was observed (3/3). However, they are consistent with the observations from Singh et al. (2010) where OSI (1/2).

We observed locally elevated WSSG to be correlated to the LAF in only 7/22 cases by definition I, and merely 3/22 cases by definition II. This seems low compared to recent findings, e.g. in a recent clinical study, for which the vasculature geometry prior to aneurysm formation was known, Kulcsár et al. (2011b) observed that 3/3 bifurcation IAs evolved in regions of high WSS and high WSSG. Given that the spatial distributions of these indices at bifurcations usually differs from that for non-branched vessels, it is beneficial to distinguish between these two categories to avoid selection bias. If we consider only those IAs that occur near a bifurcation, the correlation with WSSG is much stronger, i.e. 3/5 cases (see Table 3.4). Interestingly, we observed that for the 6/7 cases with a positive correlation between WSSG and the LAF, elevations of WSS in the aneurysmal regions were also observed.

Table 3.4: Correlations for the IA cases close to a bifurcation (5 cases) and away from bifurcation (17 cases).

Indices	Bifurcation definition I	Bifurcation definition II	Sidewall definition I	Sidewall definition II
WSS	4/5	4/5	16/17	16/17
WSSG	3/5	0/5	4/17	3/17
OSI	5/5	1/5	2/17	0/17
min(AFI)	5/5	2/5	2/17	0/17
GON	5/5	5/5	14/17	14/17

It is not the role of this numerical study to provide guidance on the threshold values of haemodynamic indices that should be considered to be elevated. Moreover, thresholds should also be considered in conjunction with the cell exposure

time (Glor et al., 2004). In this respect, it may be beneficial to consider a range of flow/pressure profiles to reflect the activity of a person during a day, week or month. However, it is of interest to compare the magnitudes of elevations observed in this study with other studies in the literature; particularly given the wide variations proposed.

Thresholds for OSI observed and/or suggested in the literature vary considerably. Cebal et al. (2003) observed that regions of vessel branching and high curvature that are often associated with localisation of atherosclerotic plaque formation and aneurysm development exhibit OSI magnitudes between 0.3 and 0.4. Similar magnitudes are reported by Baek et al. (2009). However, Jou and Mawad (2011a) utilise a threshold of $OSI > 0.1$ to identify regions subject to intimal hyperplasia and thrombosis for aneurysms treated with stenting. Singh et al. (2010) suggest a threshold for OSI of 0.2; this follows from the studies of Glor et al. (2003, 2004) where it is suggested that $OSI > 0.2$ is the threshold above which endothelial alignment is perturbed. For our study, the colourmap range had 10 intervals between 0 and 0.25. This enables magnitudes of $OSI \geq 0.2$ to be easily visually identified. However, the actual magnitudes of the local elevations range between 0.30 and 0.50. This is consistent with the values obtained by Cebal et al. (2003) and Baek et al. (2009). An inherent difficulty with the OSI index is that values other than 0 and 0.5 do not have a clear interpretation; this is perhaps why there is difficulty in defining a unique threshold value. Another problem is that some research groups appear to put too much emphasis on local elevations: it is not uncommon to see presentations at international conferences where a locally elevated $OSI < 0.05$ is referred to as high; spatial distributions of this index are sometimes presented with a small colour bar range, i.e. up to 0.01 in Singh et al. (2010). Such low values of OSI reflect negligible oscillation of the WSS vectors and thus it is questionable whether they would be of mechanobiological significance. Experimental guidance may assist in defining a minimum threshold of OSI that can be considered elevated.

Mantha et al. (2006) first proposed the AFI index. Recall, it quantifies the instantaneous deviation of the WSS vector from its mean direction (during the cardiac cycle). They observe positive correlations between this index and the LAF in 3/3 cases. A critical threshold value for AFI is not given; however, the highest value of AFI considered to be a correlation in their study is approximately 0 and hence a threshold of 0 is implicitly implied. For our analysis, we considered the minimum of the AFI in-

dex over the cardiac cycle and denoted it $\min(\text{AFI})$. We adopted a colourmap range between -1 and 1 which enables $\text{AFI} \leq 0.2$ to be easily (visually) identified. Interestingly, for all 7/22 positive correlations the magnitude of the local minimum of $\min(\text{AFI})$ ranged between -0.8 and -1 . From a mechanobiological point of view it may be beneficial to quantify both the maximum deviation and the mean deviation of the WSS vector from its mean direction during the cardiac cycle, i.e. $\min(\text{AFI})$ and $\text{mean}(\text{AFI})$. As with OSI, experimental guidance is needed to determine threshold magnitudes which correspond to altered functionality of endothelial cells (ECs).

Shimogonya et al. (2009a) proposed the novel index GON. In their initial study, the maximum value of GON reached 1 in the aneurysm region. In a subsequent study led by Shimogonya et al. (2009b), in which the same geometry is adopted, a threshold of 0.6 was utilised to drive aneurysm growth. A more recent study by Shimogonya et al. (2012), investigating the sensitivity of GON to inlet flow waveforms, considered a colourmap range up to 0.5. Ford et al. (2009) observed 4/5 correlations between elevations of GON and the LAF; the magnitudes of the elevations being approximately 0.25. In our study, for the correlated cases, the GON index ranged between 0.4 and 0.8. These values are higher than the results of Ford et al. (2009); however, these are consistent with the magnitudes observed in other studies (Shimogonya et al., 2009a,b, 2012).

The magnitude of a high WSS threshold has a broad range among previous studies. Glor et al. (2003, 2004) considered 2.5Pa as the threshold above which they found endothelial alignment to be perturbed. This is the also the value up to which the WSS is plotted in Ford et al. (2009). However, greater magnitudes are frequently interpreted as high, i.e. 5.6Pa in Augst et al. (2007), 15Pa in Singh et al. (2010), 40–60Pa in Baek et al. (2009) and Kulcsár et al. (2011b). Dolan et al. (2011) proposed two categories of high WSS under the assumption that different thresholds may elicit unique transcriptional profiles that favour particular cell functions; magnitudes greater than 5Pa and 10Pa were referred to as *high* and *very high* WSS respectively. In our study, the local elevations of WSS in the correlation cases have magnitudes in the range of 8Pa to 50Pa. Interestingly, magnitudes of WSS that have been considered to be *high* may be referred to as low WSS (Doenitz et al., 2010); however, this is actually attributed to the magnitudes being associated with a local minima of WSS. Hence it appears there is not a clear consensus with regards to what magnitude of WSS should be considered ‘high’. However, perhaps some clarity is possible if we

take into account that the endothelium is spatially and temporally heterogeneous, i.e. the properties of ECs not only vary between different sites of the vasculature, they may adapt from one moment in time to the next, responding to the unique needs of the underlying tissue (Aird, 2005; Regan and Aird, 2012). Hence we suggest care is needed when proposing absolute thresholds for high WSS, i.e. thresholds may be dependent on the species, the individual, the spatial location within the arterial tree and the time of observation.

The role of WSSG with respect to aneurysm inception is supported by animal (Meng et al., 2006, 2007; Tremmel et al., 2010; Metaxa et al., 2010; Dolan et al., 2011) as well as human studies (Kulcsár et al., 2011b). However, magnitudes of critical thresholds can vary considerably between species due to allometric scaling (Tremmel et al., 2010). For example, 10kPa/m is considered as high WSSG for dogs (Meng et al., 2007) whereas for rabbits, two thresholds of WSSG for internal elastic laminar damage have been recently proposed: optimal threshold at 146 kPa/m and conservative threshold at 530kPa/m (Metaxa et al., 2010). In a recent clinical study in which the vasculature geometry prior to aneurysm formation was actually known, 3/3 IAs evolved in locations of high WSS and high WSSG; the peaks of the WSSG are between 40–90kPa/m (Kulcsár et al., 2011b). The values of local elevations of WSSG observed in the correlation cases in our study were in between 7kPa/m and 45kPa/m; broadly consistent with the clinical findings of Kulcsár et al. (2011b). However, note that much lower magnitudes are observed in flow chamber studies: Dolan et al. (2011) observe that positive WSSG (1kPa/m) will inhibit endothelial alignment and stimulate proliferation and apoptosis under high WSS condition, whereas negative WSSG (-1kPa/m) has the opposite effect. From the above discussion, it can be seen that challenges remain in defining a precise threshold.

Many studies can be found in the literature where the definition of WSSG utilised is not given. When definitions are available, inconsistencies in the definitions can also be found. For instance, WSSG has been defined to be the magnitude of the gradient of the WSS (Jou and Mawad, 2011b) or the gradient of the WSS resolved in the flow direction (Tremmel et al., 2010); a more recent definition distinguishes between positive WSSG and negative WSSG, i.e. it is defined to be the spatial derivative of WSS along the flow direction with respect to the streamwise distance (Meng et al., 2011). In this study, we considered the magnitude of the tangential component of gradient of the magnitude of the wall shear stress vector. From a purely

phenomenological perspective, we desire to find an index which gives strong correspondence to the location at which inception occurs and thus one could debate which is most appropriate. However, from a mechanobiological perspective, the index that relates to what the endothelial cell actually senses is preferable. For instance, given that ECs can differentiate between positive and negative WSSG, it is desirable for the definition of WSSG to account for this and thus the recent definition proposed by Meng et al. (2011) may be most appropriate.

The reconstruction algorithm we have developed is applicable only to sidewall aneurysms. Out of a set of 200 segmented aneurysm geometries, we pre-selected 22 sidewall IAs which were suitable for its application. However, whilst these nicely illustrate the application of the algorithm, they are from a variety of locations in the Circle of Willis. We point out that computational fluid dynamic investigations which focus on aneurysms from specific locations may offer improved insight with respect to the aetiology of different categories of aneurysms. In this study correlations between elevations of the haemodynamic indices and LAF were evaluated by visual observations. In an attempt to minimise subjectivity we used multiple observers; however, subjectivity remains. For future research, a fully automated method to inspect for correlations may be beneficial; particularly if larger datasets are analysed.

In response to elevated WSS, ECs release vasodilation factors such as nitric oxide (NO) to relax vascular smooth muscle cells (VSMCs) resulting in a dilatation of the arterial wall and a return of WSS to baseline levels (Hoi et al., 2004). In sustained, elevated WSS conditions, it is suggested that the degradation of the ECM is also sustained, leading to a decrease in strength of the wall (Hoi et al., 2004) and thus to the potential for aneurysm inception. However, as discussed above, a clear definition of a supra-physiological level of WSS is yet to emerge. In fact, some studies suggest that such a threshold may only be defined in conjunction with a high WSSG. For example, in the series of animal studies (Meng et al., 2006, 2007, 2011), Meng and colleagues observed a very high correlation between a combination of high WSS and high WSSG with the LAF. In contrast, other research groups observe a locally *low* WSS in the region of aneurysm formation (Doenitz et al., 2010). It appears that a common element of many hypotheses of low-WSS-induced IA formation is inflammatory cell infiltration. For instance, Cebal and Meng (2012) hypothesise that low WSS induces an inflammatory response from the endothelium, which involves the release of MMPs by macrophages (Aoki and Nishimura, 2010; Kanematsu et al.,

2011), which in turn acts to degrade the arterial wall.

Our study is merely a computational investigation of the spatial correlations between local patterns of certain haemodynamic indices and locations where IAs tend to form. The physiological mechanisms that give rise to the development of an IA involve the complex interplay between the local mechanical forces acting on the arterial wall and the biological processes occurring at the cellular level. Consequently, to gain further insight into IA inception, enlargement, stabilisation and rupture, CFD alone is insufficient; improved understanding and modelling of the biology of the arterial wall is also needed (Robertson and Watton, 2012). We must take into consideration: (i) the biomechanics of the arterial wall; (ii) the biology of the arterial wall and (iii) the complex interplay between (i) and (ii), i.e. the mechanobiology of the arterial wall. *Fluid-Solid-Growth* (FSG) models (Humphrey and Taylor, 2008) which incorporate fluid and solid mechanics analysis of the vascular wall in combination with algorithmic representations of the vascular mechanobiology may play a vital role. However, such models are still in their infancy and there is a need for experimental models to guide the theoretical representation of the mechanobiology: the application of *Fluid-Solid-Growth* models (Watton et al., 2011, 2013) to in vitro models and animal models (Meng et al., 2011; Zeng et al., 2011) may be an important step in this direction.

3.7 CONCLUSION

In this chapter, CFD simulations are performed on 22 clinical sidewall IAs, whose hypothetical pre-diseased geometries are estimated using the novel vessel reconstruction methodology introduced in Chapter 2. It is observed that locally elevated wall shear stress (WSS) and gradient oscillatory number (GON) are highly correlated with regions susceptible to sidewall IA formation, whilst haemodynamic indices associated with the oscillation of the wall shear stress vectors have much lower correlations with the locations of IA formation. To gain insight into IA growth, in the next chapter, we will introduce a novel 1D model of the microstructural aspects of the arterial collagen fabrics as well as their adaption during IA evolution.



A NOVEL MATHEMATICAL MODEL FOR MICROSTRUCTURAL ADAPTION OF THE COLLAGEN FABRIC DURING ANEURYSM EVOLUTION

As we have discussed in Chapter 1, the current consensus regarding aneurysm growth is that the growth and remodelling (G&R) of the arterial tissue regulated by biochemical and biomechanical factors play a key role in the disease progression. Mathematical models of aneurysm growth are proposed with the potential to test different hypotheses and gain insight into the disease (Watton et al., 2004; Watton and Hill, 2009; Kroon and Holzapfel, 2009; Baek et al., 2006). One common assumption among these models, as well as other models of arterial G&R, is that new collagen fibres are assumed to be deposited and configured into the extant matrix under certain mechanical stretch (stress). According to Humphrey and Rajagopal (2002), although this stretch has not been identified experimentally, there are increasing biological observations supporting this assumption (Eastwood et al., 1998; Alberts et al., 2008). Both experimental and computational studies have demonstrated that cells contract the matrix by compaction strain with order of 15% - 20% during deposition or reorganisation of collagen network, which might be the potential the cause of this ‘attachment stretch’ of newly deposited constituents (En-

gler et al., 2004; Meshel et al., 2005; Grinnell and Petroll, 2010; Nagel and Kelly, 2012). Different names have been used throughout the literature to denote this stretch state, e.g. attachment stretch, homeostatic stretch, deposition stretch, equilibrium stretch, preferred stretch, pre-stretch etc (Watton et al., 2004; Gleason and Humphrey, 2005; Eriksson et al., 2009; Machyshyn et al., 2010). In this thesis the terminology *attachment stretch* will be used for consistency. Previous studies on modelling arterial G&R show that the attachment stretch is of great significance in determining the mechanical behavior of the arterial wall. For example, Valentín and Humphrey (2009a) believed that the attachment stretch is one of the important fundamental mechanisms in arterial G&R in maintaining a stable and optimal geometry under normal conditions as well as enabling effective adaptations to altered loads; and Kroon and Holzapfel (2009) concluded that the attachment stretch determines the growth speed and stability of the aneurysm. However, the current understanding of this stretch (or stress) state is still very limited. Although understanding has been developed from single and discrete values to statistical distributions (see Sec. 4.9 for the review of the development history), no explicit functional form of the attachment stretch distribution has been suggested in the literature. More importantly, all of the studies assume that the attachment stretch is invariant of time. This may lead to unrealistic results in the mathematical models of arterial G&R. For example, based on the results of their model, Baek et al. (2006) concluded that the ability of the lesion to thicken quickly is critical to arresting the enlargement and thus yielding a stable growth. Results showing thickening of the arterial wall can be found in other similar studies on modelling aneurysm growth as well (Kroon and Holzapfel, 2009). However, in many of the histological observations of the aneurysmal tissue, thinning of the lesion wall is usually present (Kondo et al., 1997). This makes us reassess the correctness of the current assumption that the attachment stretch is always constant.

In this Chapter we make the assumption that the attachment stretches are temporally adaptable during the growth of an IA. The aneurysm evolution modelling framework proposed by Watton et al. (2004) is adopted. Concepts of collagen recruitment, in vivo and attachment stretch distributions are detailed, modelling mechanical response of the arterial wall as well as arterial G&R are introduced; some variables for analysing the growth of aneurysms are defined; different approaches utilised to adapt the attachment stretch distribution are also compared. Finally, simulation results in different scenarios obtained using these approaches are anal-

ysed and the influence of the adaption of attachment stretches on arterial G&R is discussed. Limitations of this model and its further development are also discussed.

4.1 BRIEF REVIEW OF THE EVOLUTIONARY HISTORY OF THE CONCEPT OF ATTACHMENT STRETCH

Due to the important role of the attachment stretch in arterial G&R, here we first briefly review the evolutionary history of this concept so that the readers can have a better appreciation of its chronological development. However, before starting, readers should first be aware that the concept of attachment stretch is not confined to collagen fibres in some of the studies in the literature. It is also used to refer the ‘born stretch states’ of the new elastinous constituents as well the smooth muscle cells (SMCs), despite of the fact that the half life of some elastinous constituents (such as elastins) can be extremely long. The initial formulation of this concept can be traced back to the study of Humphrey (1999), where a new approach of modelling tissue G&R was proposed which serves as the basis for many subsequent arterial G&R models, including our study. This approach assumes that the deposition and degradation of the arterial constituents occur at different configurations. To be more specific, deformation and mechanical response of the old constituents are measured relative to the initial natural configuration, whereas deformation and mechanical response of the newly deposited constituents are measured relative to an altered configuration which is different from both the initial natural configuration as well as the current deformed configuration. However, new constituents are assumed to be laid down stress-free in the altered configuration, i.e. their attachment stretch equals to unity. Later Humphrey and Rajagopal (2002) realised that the new constituents are likely to be deposited under stress. As this stress had not been identified in the literature, they hypothesised it to be the ‘deposition stress’ of the constituents. However, no actual value of the deposition stress is suggested in this study. Watton et al. (2004) and Gleason et al. (2004) seem to be the first people to formulate the pre-loading of the new collagen fibres in terms of deformation (stretch) rather than force (stress). In Watton et al. (2004)’s study, the attachment stretch is linked to the cyclic pulsations of the artery: the time that fibroblast cells need to configure new collagens into the matrix is assumed to be much longer than the duration of a pulse. This implies a range of attachment stretches with a maximum value that the fibroblasts can achieve, which is equal to the maximum stretch

of the fibres which occur at the systole of the cardiac cycle. This concept of maximum attachment stretch is utilised throughout the researchers' subsequent studies on modelling aneurysm growth (Watton and Hill, 2009; Watton et al., 2009b). Gleason et al. (2004) suggested that the attachment stretches can be anisotropic, i.e. different values of attachment stretches were used for the constituents aligning in radial and axial directions respectively. In their succeeding study, Gleason and Humphrey (2005) also utilised the concept of range (distribution) of attachment stretches and assumed that attachment stretches in the radial and axial directions form a 2D distribution function. However, rather than prescribing any functional form of the attachment stretch distribution, they only specified the mean values and prescribe the functional form of distribution of the natural configurations instead. Similar approaches based on prescribing the functional forms of the natural configurations, as well as their evolution, have been utilised in several other studies in the literature (Wan et al., 2010; Martufi and Gasser, 2012). Recently, Karšaj and Humphrey (2012) considered the heterogeneity of the attachment stretches of the elastinous constituents by linearly varying its single discrete values along the radial direction in their model. On the contrary, the attachment stretches of the collagenous constituents, as well as of the smooth muscle cells, are assumed to be homogeneous.

4.2 MODEL OVERVIEW

As one of the first sections of this chapter, we would like to first overview the model so that the readers can have a general impression. We model the artery as a 1D two-layer (media and adventitia) non-linear elastic cylindrical membrane subject to internal blood pressure and a constant axial stretch. The media is modelled as a membrane composed of both elastic and collagen fibres, whereas the adventitia is simply modelled as a collagenous membrane. Collagen fibres are assumed to align *circumferentially* in both layers. We model elastic fibres using the isotropic Neo-Hookean constitutive model. We also assume that the strain energy function (SEF) of an individual collagen fibre has a simple quadratic functional form and the mechanical nonlinearity of collagens results from the gradual fibre recruitment during load bearing, which is represented by a distribution of collagen recruitment stretches. Initially the media is the main load bearing layer and the adventitia acts as a protective sheath bearing no load in the physiological state. Different distributions of col-

lagen attachment stretches are adopted to represent the distinct mechanical roles of the medial and adventitial collagens: both are simplified as triangular distributions but have different values. Gradual degradation of the media layer is prescribed to drive the development of an aneurysm. Continual growth and remodelling of the adventitial collagens is captured by modelling the change of mass density and modelling the evolution of natural configurations through modelling the distribution of recruitment stretches. The change of the mechanical role of the adventitia layer from a protective sheath to the primary load bearer during media degradation is explicitly captured by considering the temporal adaption of adventitial collagen attachment stretch distribution, whose functional form remains triangular but values adapt. Influences of different prescribed adaptations of the attachment stretch distributions on the aneurysm development are examined.

4.3 CONCEPTS OF COLLAGEN RECRUITMENT AND ATTACHMENT STRETCH DISTRIBUTIONS

In the previous studies, Watton et al. (2004) defined the recruitment stretch λ_R as the stretch that the unloaded tissue needs to be tensioned in order to straighten the initially wavy (hypothetical) collagen fibres and recruit them for load bearing. Given a 1D tissue under stretch λ , λ_R is related to λ by the collagen fibre stretch λ_C (see Fig. 4.1). In other words, λ_C is measured from the own natural configuration of the collagen fibre:

$$\lambda_C = \frac{\lambda}{\lambda_R} \quad (4.1)$$

In vitro experimental observations demonstrate that real collagen fibres exhibit a distribution of waviness in the unloaded configuration (Schrauwen et al., 2012) (see Fig. 4.2). This implies that the natural configurations of the fibres are in a manner of statistical distribution, so are their recruitment stretches. We define the statistical distribution of the collagen recruitment stretches as the *recruitment stretch distribution*, denoted as $Pr(\Lambda_R)$. $Pr(\Lambda_R)$ describes the distributional manner of the natural reference configurations of the arterial constituents and similar concepts can be found in the literature (Gleason and Humphrey, 2005; Wan et al., 2010; Martufi and Gasser, 2012). The direct consequence of $Pr(\Lambda_R)$ is that the in vivo stretches of the collagen fibres should also be in a manner of statistical distribution

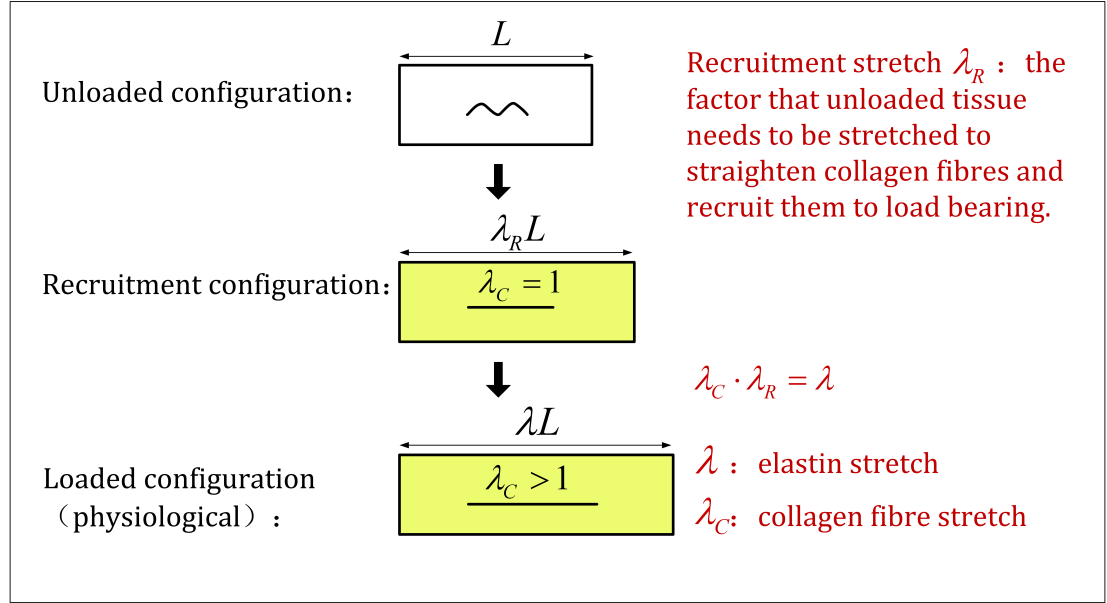


Figure 4.1: The recruitment stretch λ_R is defined as the stretch that the unloaded tissue needs to be tensioned in order to straighten the initially wavy collagen fibre and recruit it for load bearing. The actual stretch of the collagen fibre λ_C is measured from its own configuration.

when the tissue is at physiological stretch λ . We name this stretch distribution the *in vivo stretch distribution*, denoted as $Pr(\Lambda_C)$. Having $Pr(\Lambda_R)$ and $Pr(\Lambda_C)$ defined, Eq. 4.1 can be rewritten as:

$$\Lambda_C = \frac{\lambda}{\Lambda_R} \quad (4.2)$$

where Λ_C and Λ_R are any corresponding single values of in vivo stretches in $Pr(\Lambda_C)$ and recruitment stretches in $Pr(\Lambda_R)$.

Watton et al. (2004) defined the attachment stretch λ_{AT} as the state of stretch in which collagen fibres are configured to the arterial extracellular matrix (ECM) in the physiological (loaded) configuration. Considering the distributional manner of collagen waviness in the physiological configuration (Schrauwen et al., 2012), it is reasonable to assume that human arterial collagen fibres are actually configured into the ECM in a state of stretch distribution, referred as the *attachment stretch distribution* and denoted as $Pr(\Lambda_{AT})$. We assume that $Pr(\Lambda_{AT})$ can be simplified by a triangular distribution whose probability density function (PDF) $f_{\Lambda_{AT}}(\lambda_{AT})$ is

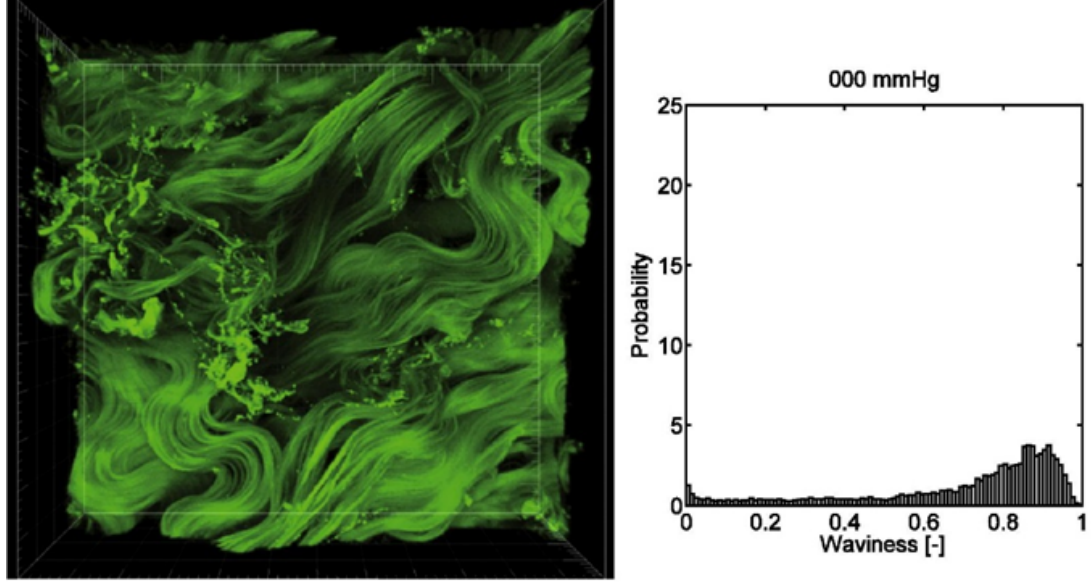


Figure 4.2: Experimental observation of distribution of collagen waviness in the unloaded configuration (Schrauwen et al., 2012).

represented by the triangular function:

$$f_{\Lambda_{AT}}(\lambda_{AT}) = \begin{cases} 0 & \lambda_{AT} < \lambda_{AT}^{min} \\ \frac{2(\lambda_{AT} - \lambda_{AT}^{min})}{(\lambda_{AT}^{max} - \lambda_{AT}^{min})(\lambda_{AT}^{mod} - \lambda_{AT}^{min})} & \lambda_{AT}^{min} \leq \lambda_{AT} \leq \lambda_{AT}^{mod} \\ \frac{2(\lambda_{AT}^{max} - \lambda_{AT})}{(\lambda_{AT}^{max} - \lambda_{AT}^{min})(\lambda_{AT}^{max} - \lambda_{AT}^{mod})} & \lambda_{AT}^{mod} < \lambda_{AT} \leq \lambda_{AT}^{max} \\ 0 & \lambda_{AT} > \lambda_{AT}^{max} \end{cases} \quad (4.3)$$

As shown in the equation above as well as in Fig. 4.3 (the left distribution), $f_{\Lambda_{AT}}(\lambda_{AT})$ is uniquely defined by the three variables: minimum attachment stretch λ_{AT}^{min} , maximum attachment stretch λ_{AT}^{max} and mode attachment stretch λ_{AT}^{mod} . Collagen fibres with λ_{AT}^{min} are recruited last as the tissue is stretched, thus having the maximum recruitment stretch, here denoted as λ_R^{max} . Fibres achieving λ_{AT}^{max} are recruited first, thus having the minimum recruitment stretch, denoted as λ_R^{min} . Similarly, fibres with λ_{AT}^{mod} are all simultaneously recruited for load bearing, hence have the same mode recruitment stretch, denoted as λ_R^{mod} . Therefore the collagen recruitment stretch distribution $Pr(\Lambda_R)$, which is due to the variation in fibre waviness/ undulations in the unloaded tissue, is indeed a natural consequence of the attachment stretch distribution $Pr(\Lambda_{AT})$.

Now we want to determine the recruitment stretch distribution when the arterial wall is in initial homeostasis at time $t = 0$. In this situation, the collagen in vivo

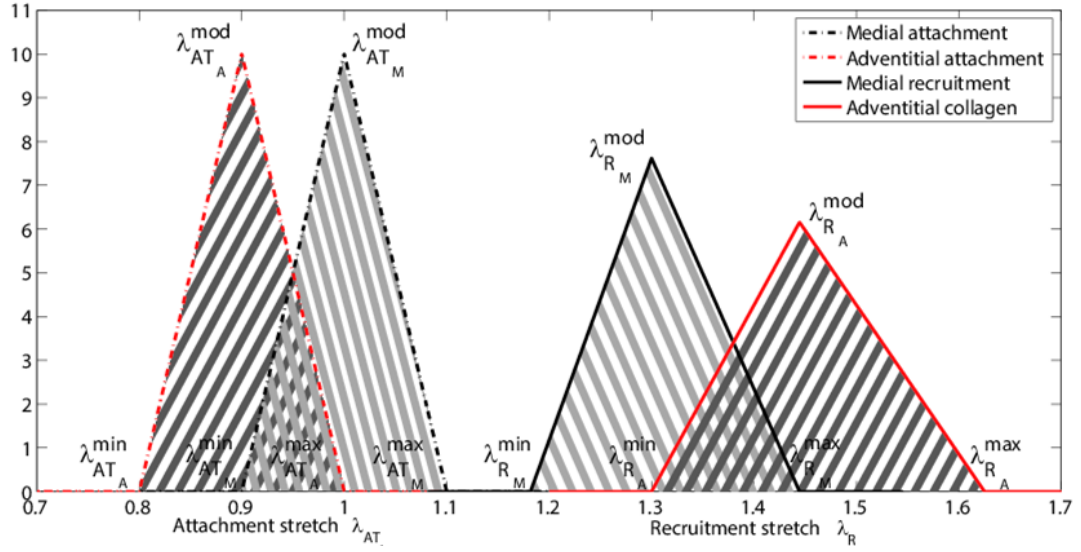


Figure 4.3: This figure shows the attachment stretch and recruitment stretch distributions of medial and adventitial collagens at time $t = 0$ with tissue circumferential stretch $\lambda = 1.3$. Both the attachment and the recruitment stretch distributions are determined by three salient points: minimum attachment and recruitment stretches ($\lambda_{AT_L}^{min}$ and $\lambda_{R_L}^{min}$), maximum attachment and recruitment stretches ($\lambda_{AT_L}^{max}$ and $\lambda_{R_L}^{max}$), as well as mode attachment and recruitment stretches ($\lambda_{AT_L}^{mod}$ and $\lambda_{R_L}^{mod}$). Here L can take either M representing medial collagens or A representing adventitial collagens. Different values of attachment and recruitment stretch distributions are used to represent the medial and adventitial collagen fibres. In the left attachment stretch distributions, collagens with attachment stretches whose values are bigger than 1 are bearing load. This portion of collagens corresponds to the collagens whose recruitment stretches are smaller than the tissue stretch $\lambda = 1.3$ in the right recruitment stretch distributions.

stretch distribution should be identical to its attachment stretch distribution, i.e. $Pr(\Lambda_C) = Pr(\Lambda_{AT})$. Equivalently, for any single collagen fibre, its in vivo stretch is same as its attachment stretch, i.e. $\Lambda_C = \Lambda_{AT}$. Substituting this equation into Eqn. 4.2 immediately yields the following relationship:

$$\lambda_{AT}^{min} \cdot \lambda_R^{max} = \lambda_{AT}^{max} \cdot \lambda_R^{min} = \lambda_{AT}^{mod} \cdot \lambda_R^{mod} = \Lambda_{AT} \cdot \Lambda_R = \lambda \quad (4.4)$$

This equation implies that the PDF $f_{\Lambda_R}(\lambda_R)$ of the recruitment stretch distribution $Pr(\Lambda_R)$ can be determined from the PDF $f_{\Lambda_{AT}}(\lambda_{AT})$ of the attachment stretch distribution $Pr(\Lambda_{AT})$. As $f_{\Lambda_{AT}}(\lambda_{AT})$ is a piecewise triangular function described by Eq. 4.3, $f_{\Lambda_R}(\lambda_R)$ is also a piecewise function. The explicit functional form of $f_{\Lambda_R}(\lambda_R)$ when the tissue is at initial homeostatic stretch λ can be written as (see Appendix A

for the full derivation):

$$f_{\Lambda_R}(\lambda_R) = \begin{cases} 0 & \lambda_R < a \\ \frac{2(\lambda_R - a)}{(b - a)(c - a)} \cdot \frac{abc}{\lambda_R^3} & a \leq \lambda_R < c \\ \frac{2(b - \lambda_R)}{(b - a)(b - c)} \cdot \frac{abc}{\lambda_R^3} & c \leq \lambda_R < b \\ 0 & \lambda_R \geq b \end{cases} \quad (4.5)$$

where a , b and c are used to denote λ_R^{min} , λ_R^{max} and λ_R^{mod} respectively for convenience. One thing worth noting is that $f_{\Lambda_R}(\lambda_R)$ is not a triangular function due to the extra nonlinear term $\frac{abc}{\lambda_R^3}$. In other words, given the attachment stretch distribution $Pr(\Lambda_R)$ a triangular distribution, the recruitment stretch distribution $Pr(\Lambda_R)$ is not triangular. However, for simplicity reasons, we simplify $Pr(\Lambda_R)$ by a triangular distribution and use triangular functions for $f_{\Lambda_R}(\lambda_R)$, i.e. taking out the nonlinear term $\frac{abc}{\lambda_R^3}$ in Eq. 4.5. This gives the $f_{\Lambda_R}(\lambda_R)$ that we have used in the model when the arterial wall is in initial homeostasis at time $t = 0$ under tissue circumferential stretch λ :

$$f_{\Lambda_R}(\lambda_R) = \begin{cases} 0 & \lambda_R < a \\ \frac{2(\lambda_R - a)}{(b - a)(c - a)} & a \leq \lambda_R < c \\ \frac{2(b - \lambda_R)}{(b - a)(b - c)} & c \leq \lambda_R < b \\ 0 & \lambda_R \geq b \end{cases} \quad (4.6)$$

where a , b and c (i.e. λ_R^{min} , λ_R^{max} and λ_R^{mod}) can be determined from Eq. 4.4 if the corresponding attachment stretches are given. The difference of $f_{\Lambda_R}(\lambda_R)$ between the real functional form (Eq. 4.5) and simplified triangular functional form (Eq. 4.6) can be evaluated by performing a Kolmogorov-Smirnov test (Massey, 1951). Fig. 4.4 illustrates both of these two functional forms of medial and adventitial collagens recruitment stretch distributions at time $t = 0$. In the figure we have used the subscript L to denote the layer to which the collagen fibres belong. L can be either M representing media layer or A representing adventitia layer, e.g. $\lambda_{R_L}^{min}$ means the minimum recruitment stretch of collagens in the L layer. Determination of the initial values of the minimum, maximum and mode recruitment stretches for the model are introduced in Sec. 4.7. Adaption of $f_{\Lambda_R}(\lambda_R)$ is used for modelling collagen remodelling during aneurysm growth. This is introduced in Sec. 4.5.

As introduced above, when the arterial wall is in initial homeostasis, we also have $Pr(\Lambda_C) = Pr(\Lambda_{AT})$. Hence it is reasonable to assume that the collagen in vivo stretch distribution $Pr(\Lambda_C)$ follows triangular distribution as well, i.e. the PDF

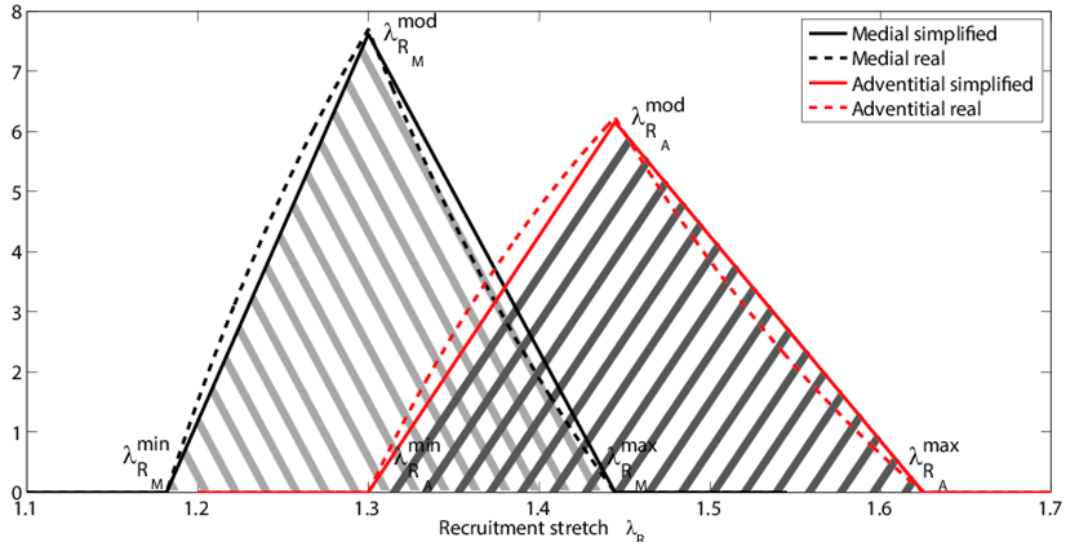


Figure 4.4: This figure shows the real functional forms as well as simplified triangular functional forms of the PDF $f_{\Lambda_R}(\lambda_R)$ of medial and adventitial collagen recruitment stretch distributions at time $t = 0$ with tissue circumferential stretch $\lambda = 1.3$. The real functional forms represented by the dashed lines are calculated by Eq. 4.5. The simplified triangular functional forms represented by solid lines are the ones that are determined by Eqn. 4.6. These are the ones which are actually used in this study. Medial and adventitial collagens are also distinguished by different filling patterns. Salient points of the distributions are illustrated as well, i.e. the minimum ($\lambda_{R_M}^{min}, \lambda_{R_A}^{min}$), maximum ($\lambda_{R_M}^{max}, \lambda_{R_A}^{max}$) and mode ($\lambda_{R_M}^{mod}, \lambda_{R_A}^{mod}$) recruitment stretches.

$f_{\Lambda_C}(\lambda_C)$ can be simplified as a triangular function and uniquely determined by the three key variables λ_C^{min} , λ_C^{max} and λ_C^{mod} , which are the minimum, maximum and mode in vivo stretches. At initial homeostasis we have $\lambda_C^{min} = \lambda_{AT}^{min}$, $\lambda_C^{max} = \lambda_{AT}^{max}$ and $\lambda_C^{mod} = \lambda_{AT}^{mod}$. During aneurysm growth, we assume that the functional form of $f_{\Lambda_C}(\lambda_C)$ maintains a triangular function though in reality its functional function may not be. Values of λ_C^{min} , λ_C^{max} and λ_C^{mod} are computed using Eq. 4.2.

As opposed to all of previous studies in the literature, in this study we assume that $f_{\Lambda_{AT}}(\lambda_{AT})$ can adapt temporally during aneurysm growth but remains a triangular function. $f_{\Lambda_{AT}}(\lambda_{AT})$ is applied to model collagen fibres having different mechanical roles, whereas its temporal adaption is utilised to represent the adaption of these mechanical roles. Details are given below. We assume that initially the media acts as the main load bearer with some of the collagens recruited to bear load, whereas the adventitial collagens act as a protective sheath bearing no load. This is achieved by letting $f_{\Lambda_{AT}}(\lambda_{AT_M})$ and $f_{\Lambda_{AT}}(\lambda_{AT_A})$ have different initial values: we let

$\lambda_{AT_M}^{min}$, $\lambda_{AT_M}^{max}$ and $\lambda_{AT_M}^{mod}$ take values of 0.9, 1.1 and 1 (see Sec. 4.7 for justification), whereas $\lambda_{AT_A}^{min}$, $\lambda_{AT_A}^{max}$ and $\lambda_{AT_A}^{mod}$ take values of 0.8, 1.0 and 0.9 so that both $f_{\Lambda_{AT}}(\lambda_{AT_M})$ and $f_{\Lambda_{AT}}(\lambda_{AT_A})$ are symmetric. Collagens whose attachment stretches are smaller than 1 indicate that they are deposited crimpedly, hence bearing no load. Because $\lambda_{C_A}^{max} = \lambda_{AT_A}^{max} \leq 1$ in initial homeostasis, this means these adventitial collagen are borne without taking load. But they will take load if the artery further dilates, i.e. $\lambda_{C_A}^{max} \geq 1$. Hence their mechanical role is a protective sheath. Fig. 4.3 illustrates the use of $Pr(\Lambda_{AT_L})$ to represent the medial and adventitial collagen fibres at time $t = 0$ respectively, with the stretch of the tissue set to be $\lambda = 1.3$. The recruitment stretches can also be determined accordingly (see Sec. 4.7). The use of the temporal adaption of $f_{\Lambda_{AT}}(\lambda_{AT})$ to represent the change of the mechanical role of the collagen fibres are introduced in Sec. 4.5.

4.4 MECHANICAL RESPONSE OF THE ARTERIAL WALL

We consider a hollow cylindrical elastic membranal tube to represent the artery in 1D, with length l (not to be confused with L used to denote each layer), radius R and wall thickness H in the unloaded configuration. The tube is subject to internal pressure p acting normal to the midplane and a constant axial stretch λ_z . The procedures to derive the mechanical governing equation is detailed in Watton et al. (2004) and Watton et al. (2009b). Here we give an outline of the derivation to avoid unnecessary repetition. Deformation of the arterial wall is governed by the principle of virtual displacement. The principle of stationary potential energy requires that the first variation of the total potential energy vanishes:

$$\delta\Pi_{int} - \delta\Pi_{ext} = 0 \quad (4.7)$$

where $\delta\Pi_{int}$ is the variation of the internal potential energy stored in the arterial wall and $\delta\Pi_{ext}$ is the variation of the external potential energy caused by the normal pressure p acting on the membrane. Given that the membrane is relatively thin, the area elements as well as the virtual displacement field of the upper and lower surfaces are approximated to be equal to those of the midplane. So Eq. 4.7 can be written as:

$$\int_V \delta\Psi dV - \int_S p(\hat{\mathbf{a}}_3 \cdot \delta\mathbf{u}) dS = 0 \quad (4.8)$$

where S is the portion of the boundary surface on which the internal pressure p is applied and Ψ is the SEF per unit volume, $\hat{\mathbf{a}}_3$ is the unit normal vector of the deformed midplane, $\mathbf{u}$ is the displacement field of the midplane. The assumption that

the strain field is uniform through the thickness of the arterial wall equating that of the midplane implies that the SEF Ψ is constant in each layer along the direction of $\hat{\mathbf{a}}_3$. This converts the volume integral in Eq. 4.8 into a surface integral and enables an immediate integration yielding:

$$\int_0^{2\pi R} \int_0^l (H_M \delta \Psi_M + H_A \delta \Psi_A - p \hat{\mathbf{a}}_3 \cdot \delta \mathbf{u}) dX_1 dX_2 = 0 \quad (4.9)$$

where H_M and H_A are the thicknesses of the media and adventitia layers respectively, and $H_M + H_A = H$. Ψ_M and Ψ_A are the SEFs per unit volume in the media and adventitia layers.

For 1D deformations of the cylindrical membranes, the deformation field can be further described by one independent stretch variable, i.e. the circumferential stretch of the tissue λ . Applying the geometric constraints of symmetric deformation of a cylinder (see Watton et al. (2004) and Watton et al. (2009b) for details), Eq. 4.9 can be eventually written as the following form:

$$p = \frac{H_M}{\lambda \lambda_z R} \frac{\partial \Psi_M}{\partial \lambda} + \frac{H_A}{\lambda \lambda_z R} \frac{\partial \Psi_A}{\partial \lambda} \quad (4.10)$$

The SEF of the media layer Ψ_M is considered to be an additive contribution from both the elastinous and collagenous constituents, whereas the SEF of the adventitia Ψ_A is only contributed to by the collagenous constituents:

$$\Psi_M = \Psi_{E_M} + \Psi_{C_M} \quad (4.11)$$

and

$$\Psi_A = \Psi_{C_A} \quad (4.12)$$

where Ψ_{J_L} denotes the SEF of the elastin ($J = E$) or collagen ($J = C$) constituent in the L layer (M for the media or A for the adventitia). Substituting Eq. 4.11 and 4.12 into Eq. 4.9 yields the governing equation Eq. 4.13 which describes the gross mechanical response of the artery under pressure p and axial stretch λ_z :

$$p = \frac{H_M}{\lambda \lambda_z R} \frac{\partial}{\partial \lambda} (\Psi_{E_M} + \Psi_{C_M}) + \frac{H_A}{\lambda \lambda_z R} \frac{\partial \Psi_{C_A}}{\partial \lambda} \quad (4.13)$$

Now the SEF of each constituent needs to be specified. We model arterial elastins as an isotropic Neo-Hookean solid, utilising the model proposed by Holzapfel et al. (2000), with an extra degradation function of the elastin mass density:

$$\Psi_{E_M} = m_{E_M}(t) K_{E_M} (I_1(\mathbf{C}) - 3) \quad (4.14)$$

where $m_{EM}(t)$ is the mass density of elastin at time t normalised with respect to the initial mass density at $t = 0$, i.e. $m_{EM}(0) = 1$. K_{EM} is the elastin material constant. I_1 is the first invariant of the right Cauchy-Green deformation tensor $\mathbf{C}$. For a 1D cylindrical axially pre-stretched tube, $I_1(\mathbf{C})$ can be calculated by:

$$I_1(\mathbf{C}) = \lambda^2 + \lambda_z^2 + \frac{1}{\lambda^2 \lambda_z^2}, \quad (4.15)$$

where the radial stretch is implied by applying the incompressibility constraint.

The approach proposed by Hill et al. (2012) is modified for modelling the mechanical response of collagen fibres. We assume that the SEF Ψ_{CL}^* of an individual collagen fibre in the L layer has a simple quadratic functional form, described by the following equation:

$$\Psi_{CL}^* = \frac{K_{CL}}{2} (\lambda_{CL} - 1)^2 \quad (4.16)$$

where K_{CL} is the collagen material constant and λ_{CL} is the stretch of the individual collagen fibre measured from its own natural configuration. λ_{CL} is related to the stretch of the tissue λ by the recruitment stretch λ_{RL} of the fibre, i.e. via Eq. 4.2. Eq. 4.16 implies a linear relationship between the 1st Piola-Kirchhoff stress P_{CL}^* and the stretch λ_{CL} of the fibre.

As introduced in Sec. 4.3, the recruitment of collagen fibres for load bearing is assumed to be in a manner of statistical distribution, represented by the recruitment stretch distribution $Pr(\Lambda_{RL})$. Hence the SEF Ψ_{CL} of all the collagen fibres per unit volume at tissue stretch λ can be computed by integrating the SEF Ψ_{CL}^* of a single fibre with respect to the proportion of the recruited fibres, multiplied by the collagen mass density :

$$\Psi_{CL}(\lambda) = m_{CL}(t) \int_1^\lambda \Psi_{CL}^* \left(\frac{\lambda}{\lambda_{RL}} \right) f_{\Lambda_R}(\lambda_{RL}) d\lambda_{RL} \quad (4.17)$$

Again, λ_{RL} is the recruitment stretch and $f_{\Lambda_R}(\lambda_{RL})$ is the PDF of $Pr(\Lambda_{RL})$. $m_{CL}(t)$ is the mass density of collagen fibres normalised with respect to its initial mass density at $t = 0$, i.e. $m_{CL}(0) = 1$. As shown in Eq. 4.6, $f_{\Lambda_R}(\lambda_{RL})$ is assumed to be a piecewise triangular function, hence $\Psi_{CL}(\lambda)$ is a piecewise function as well. For 1D deformation, if we differentiate $\Psi_{CL}(\lambda)$ with respect to the tissue stretch λ , then we obtain the average 1st Piola-Kirchhoff stress P_{CL} of all the collagen fibres within a unit vol-

ume at tissue stretch λ , which is also a piecewise function:

$$P_{C_L} = \frac{d\Psi_{C_L}(\lambda)}{d\lambda} = \begin{cases} 0 & \lambda < a_L \\ f(\lambda) & a_L \leq \lambda \leq c_L \\ g(\lambda) & c_L < \lambda \leq b_L \\ h(\lambda) & \lambda > b_L \end{cases} \quad (4.18)$$

where

$$f(\lambda) = \gamma_L \cdot (b_L - c_L) \left[(\lambda + a_L) \ln \frac{\lambda}{a_L} + 2a_L - 2\lambda \right] \quad (4.19a)$$

$$g(\lambda) = \gamma_L \cdot [(b_L - c_L)(\lambda + a_L) \ln \frac{c_L}{a_L} - (c_L - a_L)(\lambda + b_L) \ln \frac{\lambda}{c_L} + 2(c_L - a_L)(\lambda - b_L)] \quad (4.19b)$$

$$h(\lambda) = \gamma_L \cdot [(b_L - a_L)(\lambda + c_L) \ln \frac{c_L}{a_L} - (c_L - a_L)(\lambda + b_L) \ln \frac{b_L}{a_L}] \quad (4.19c)$$

where $\gamma_L = m_{C_L} K_{C_L} / ((b_L - a_L)(c_L - a_L)(b_L - c_L))$. For convenience, a_L , b_L and c_L are used to denote the minimum, maximum and mode recruitment stretches of $f_{\Lambda_R}(\lambda_{R_L})$ respectively, i.e. $a_L = \lambda_{R_L}^{min}$, $b_L = \lambda_{R_L}^{max}$, $c_L = \lambda_{R_L}^{mod}$. Fig. 4.5 shows the mechanical responses between tissue gross circumferential stretches λ and the average 1st Piola-Kirchhoff stresses P_{C_L} of the medial and adventitial collagens within a unit volume. The recruitment stretch distributions of the collagens $f_{\Lambda_R}(\lambda_{R_M})$ and $f_{\Lambda_R}(\lambda_{R_A})$ are also shown. Both Eq. 4.16 - 4.19c as well as Fig. 4.5 show that nonlinearity of the mechanical response of collagenous constituents can be obtained by assuming a linear response for each single collagen fibre and gradual recruitment of the fibres.

4.5 GROWTH AND REMODELLING OF THE ARTERIAL TISSUES

In a healthy artery, elastins are known to be one of the most stable proteins in the body, with a half-life approximately 40-70 years (Langille, 1993; Martyn and Greenwald, 1997; Franklin, 2006), whereas collagen fibres are always in a state of continual deposition by the cells and degradation by the collagenase, with a much shorter half-life of around only 2-3 months (Langille, 1993). In an aneurysm artery, histological observations of the aneurysmal wall usually involve thinning/loss of the media layer as well as thickening of the adventitia layer. More specifically, loss of internal

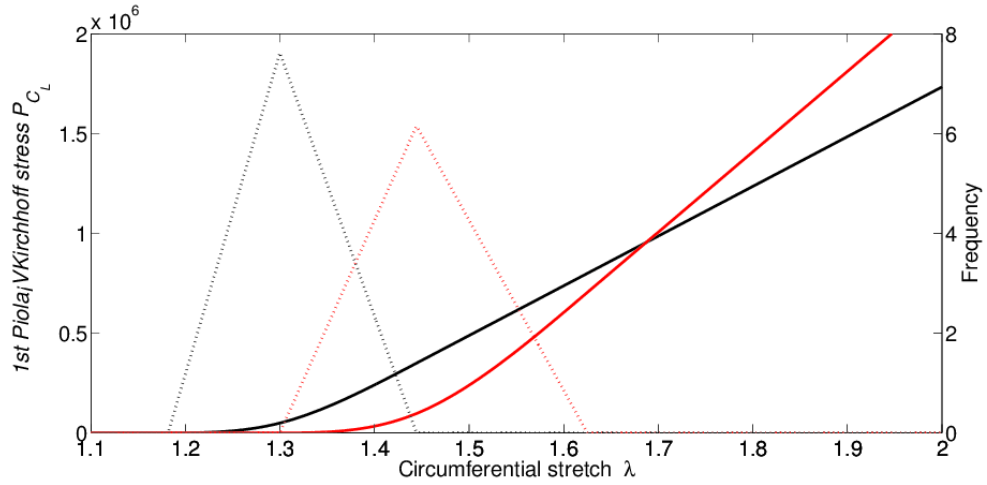


Figure 4.5: The non-linear mechanical response of the medial and adventitial collagen fibres can be considered by assuming a linear response for each single collagen fibre and gradual recruitment of the fibres. Mechanical response between the tissue circumferential stretches and average 1st Piola-Kirchhoff stresses of the medial (black) and adventitial (red) collagens within a unit volume is illustrated with solid curves (left y axis). The recruitment stretch distributions for the collagen fibres are also shown with dotted lines (right y axis).

elastic lamina, apoptosis of vascular smooth muscle cells (VSMC), as well as fragmentation of the elastic fibres have been observed in the media layer; whereas in the adventitia highly organised collagen fibres are commonly present (Canham et al., 1991). However, the pathological processes leading to the histological changes of the arterial layers which may incorporate various signaling pathways are still poorly understood.

With limited understanding of underlying biological cause, we degrade the medial fibres to initiate an aneurysm on the artery and impel its following growth. This is done by prescribing the change of medial elastin and collagen mass densities m_{E_M} and m_{C_M} using an exponential decay function during the time span of n years:

$$m_{J_M}(t) = (\varrho_{J_M})^{\frac{t}{n}} m_{J_M}(0) \quad (4.20)$$

where ϱ_{J_M} is the percentage of the J ($J = E, C$) constituents which remain in the media after n years and $m_{J_M}(0)$ is the mass density of the J constituents at $t = 0$ (before aneurysm formation). In the study we assume a loss of the entire media layer after 5 years. For this reason ϱ_{J_M} is set to be 0.01 for numerical implementation and n set to be 5, which means only 1% of the medial constituents remain in the media after 5 years. From Year 5 onwards m_{E_M} and m_{C_M} are set to 0.

The loss of medial constituents is compensated by the growth and remodelling (G&R) of the collagen fibres to prevent over-dilation of the artery due to internal blood pressure. Adventitial collagen growth is related to the mass change of the adventitial collagenous constituents and is simulated by evolving its mass density m_{C_A} . Based on the fact that adventitial collagens are exclusively degraded and deposited by the fibroblast cells, we assume that:

1. The rate of change of m_{C_A} is proportional to the amount of fibroblast cells and the level that these fibroblast cells are mechanically deviated from their homeostatic states.
2. The amount of fibroblast cells is equal to the amount of adventitial collagens.
3. The level that these fibroblast cells are mechanically deviated from their homeostatic states is evaluated by the deviations of the current average stretch of the fibroblast cells from their homeostatic average stretch.
4. Fibroblast cells have the same natural reference configurations as the adventitial collagens, i.e., the current average stretch of the fibroblast cells is equal to the mean stretch of the collagen in vivo stretch distribution $Pr(\Lambda_{C_A})$, denoted as $\lambda_{C_A}^{mean}$, whereas the homeostatic average stretch of the fibroblast cells is equal to the mean attachment stretch of collagen attachment stretch distribution $Pr(\Lambda_{AT_A})$, denoted as $\lambda_{AT_A}^{mean}$.

Then the evolution of m_{C_A} , i.e. the growth of adventitial collagen is modelled using a simple stretch-based evolution law:

$$\frac{dm_{C_A}}{dt} = \beta m_{C_A} \left(\frac{\lambda_{C_A}^{mean} - \lambda_{AT_A}^{mean}}{\lambda_{AT_A}^{mean}} \right) \quad (4.21)$$

where β is a growth rate parameter relating to the rate at which additional adventitial collagen is deposited and configured. It is numerically determined that $\beta = 3$ so that the dilation is physiologically consistent over a typical timescale of aneurysm growth: we assume that the diameter increases by a factor of 2–3 over a period of 10 years (Watton et al., 2004; Watton and Hill, 2009). However, it is noted that some IAs may grow very fast (Doenitz et al., 2010). $\lambda_{C_A}^{mean}$ and $\lambda_{AT_A}^{mean}$ are the expected values of the collagen in vivo and attachment stretch distributions $Pr(\Lambda_{C_A})$ and $Pr(\Lambda_{AT_A})$ respectively. For triangular distributions, they are simply calculated by

$\lambda_{C_A}^{mean} = (\lambda_{C_A}^{min} + \lambda_{C_A}^{max} + \lambda_{C_A}^{mod})/3$ and $\lambda_{AT_A}^{mean} = (\lambda_{AT_A}^{min} + \lambda_{AT_A}^{max} + \lambda_{AT_A}^{mod})/3$. Here, again $\lambda_{C_A}^{max}$, $\lambda_{C_A}^{min}$ and $\lambda_{C_A}^{mod}$ are the maximum, minimum and mode in vivo stretches of $Pr(\Lambda_{C_A})$ in the adventitia layer during the cardiac cycle, whereas $\lambda_{AT_A}^{max}$, $\lambda_{AT_A}^{min}$ and $\lambda_{AT_A}^{mod}$ are the maximum, minimum and mode attachment stretches of $Pr(\Lambda_{AT_A})$, as introduced in Sec. 4.3.

Remodelling of the medial and adventitial collagen fibres generally refers to the natural physiological processes occurring in the tissue that change the gross microstructure of the fibres without changing their total mass. To be more specific, this includes the degradation of old fibres and deposition of new fibres with altered microstructure, natural configurations and orientation angles. As mentioned previously, during aneurysm development, old collagen fibres are continuously replaced by the new collagen fibres, with attachment stretches measured relative to their new natural configurations. This naturally implies that the collagen natural configurations are evolving so that the collagen in vivo stretch distribution $Pr(\Lambda_{C_L})$ is continuously remodelled into its attachment stretch distribution $Pr(\Lambda_{AT_L})$. This phenomenon is generally captured by modelling the evolution of the recruitment stretch distributions $Pr(\Lambda_{R_L})$ of the fibres: we assume that $Pr(\Lambda_{R_L})$ always maintains a triangular distribution during its evolution, and propose three linear differential equations to remodel the three salient variables $\lambda_{R_L}^{min}$, $\lambda_{R_L}^{max}$ and $\lambda_{R_L}^{mod}$ in its PDF $f_{\Lambda_R}(\lambda_{R_L})$:

$$\frac{d\lambda_{R_L}^{min}}{dt} = \alpha \left(\frac{\lambda_{C_L}^{max} - \lambda_{AT_L}^{max}}{\lambda_{AT_L}^{max}} \right) \quad (4.22a)$$

$$\frac{d\lambda_{R_L}^{max}}{dt} = \alpha \left(\frac{\lambda_{C_L}^{min} - \lambda_{AT_L}^{min}}{\lambda_{AT_L}^{min}} \right) \quad (4.22b)$$

$$\frac{d\lambda_{R_L}^{mod}}{dt} = \alpha \left(\frac{\lambda_{C_L}^{mod} - \lambda_{AT_L}^{mod}}{\lambda_{AT_L}^{mod}} \right) \quad (4.22c)$$

where α is the collagen remodelling rate parameter which can be determined numerically so that the remodelling rate of the recruitment stretches is physiologically realistic. Watton (2002) presented a method to correspond α to a prescribed collagen half-life. For more explanations on this method please refer to Sec. 2.3.3 of Watton (2002). Given that collagen in the arterial wall typically has a half-life of 60 days, we assume a default value of $\alpha = 2$ is determined for this study.

Now we want to emphasise that we assume the adventitial collagen attachment stretch distribution $Pr(\Lambda_{AT_A})$ can adapt temporally during aneurysm growth. The

change of the mechanical role of the adventitia from a protective sheath in a normal arterial wall to the primary load bearer in the aneurysmal arterial wall implies that some newly deposited collagens must have attachment stretches $\lambda_{AT_A} > 1$ so that they take load in the homeostatic state. Since for the initial healthy artery we have $\lambda_{AT_A}^{min}(0) = 0.8$, $\lambda_{AT_A}^{max}(0) = 1.0$ and $\lambda_{AT_A}^{mod}(0) = 0.9$, this indicates that an augmenting adaption of $f_{\Lambda_{AT}}(\lambda_{AT_A})$ is needed to represent the transition of the mechanical role of adventitia to the primary load bearer. However, due to the lack of biological data on this, currently we analytically prescribe the adaption $f_{\Lambda_{AT}}(\lambda_{AT_A})$: we assume that $f_{\Lambda_{AT}}(\lambda_{AT_A})$ adapts but its functional form always remains triangular. Then we prescribe the adaption of $f_{\Lambda_{AT}}(\lambda_{AT_A})$ by prescribing the evolution of $\lambda_{AT_A}^{min}$, $\lambda_{AT_A}^{max}$ and $\lambda_{AT_A}^{mod}$. A simplified Richards' growth function (Richards, 1959) is adopted to evolve the adventitial collagen maximum attachment stretch $\lambda_{AT_A}^{max}(t)$:

$$\lambda_{AT_A}^{max}(t) = \lambda_{AT_A}^{max}(0) + \frac{\lambda_{AT_A}^{max}|_f - \lambda_{AT_A}^{max}(0)}{1 + e^{-B(t-n/2)}} \quad (4.23)$$

where n is the duration of media degradation, same as the one in Eq. 4.20. B relates to the growth rate of the curve and is numerically determined, $B = 3$, so that the evolution curve of $\lambda_{AT_A}^{max}(t)$ is relatively flat near $t = 0$ and $t = n$ while not too steep in the middle. $\lambda_{AT_A}^{max}|_f$ is the maximum attachment stretch of adventitial collagens after the entire media layer has been degraded. This variable describes the maximum ability of the fibroblast cells to stretch the newly synthesised collagen fibres and attach them to the extracellular matrix. Again, due to the lack of biological understanding on this, the only justification we can take into consideration is that adventitial collagens are known to be stiff and act to prevent over-dilation of the artery. Hence we simply assume that the maximum strain of the adventitial collagens is same as the value of media $\lambda_{AT_M}^{max}$, i.e. $\lambda_{AT_A}^{max}|_f = 1.10$. Fig. 4.6 shows the prescribed evolution of the maximum attachment stretch $\lambda_{AT_A}^{max}(t)$ during aneurysm evolution.

In order to explore the influence of $f_{\Lambda_{AT}}(\lambda_{AT_A})$ evolution on the aneurysm growth, we modelled five scenarios with different variances to evolve minimum and mode attachment stretches $\lambda_{AT_A}^{min}$ and $\lambda_{AT_A}^{mod}$, including one scenario in which $f_{\Lambda_{AT}}(\lambda_{AT_A})$ is assumed to be constant for comparison:

1. $f_{\Lambda_{AT}}(\lambda_{AT_A})$ is constant, i.e. $\lambda_{AT_M}^{min}(t) = 0.8$, $\lambda_{AT_M}^{max}(t) = 1.0$ and $\lambda_{AT_M}^{mod}(t) = 0.9$.
2. $\lambda_{AT_A}^{min}(t) = \lambda_{AT_A}^{max}(t) - 0.2$ and $\lambda_{AT_A}^{mod}(t) = 0.5 \cdot [\lambda_{AT_A}^{min}(t) + \lambda_{AT_A}^{max}(t)]$, i.e. the range and skewness of $f_{\Lambda_{AT}}(\lambda_{AT_A})$ are constant ($\text{Range}(\Lambda_{AT_A}) = 0.2$, $\text{Skew}(\Lambda_{AT_A}) =$

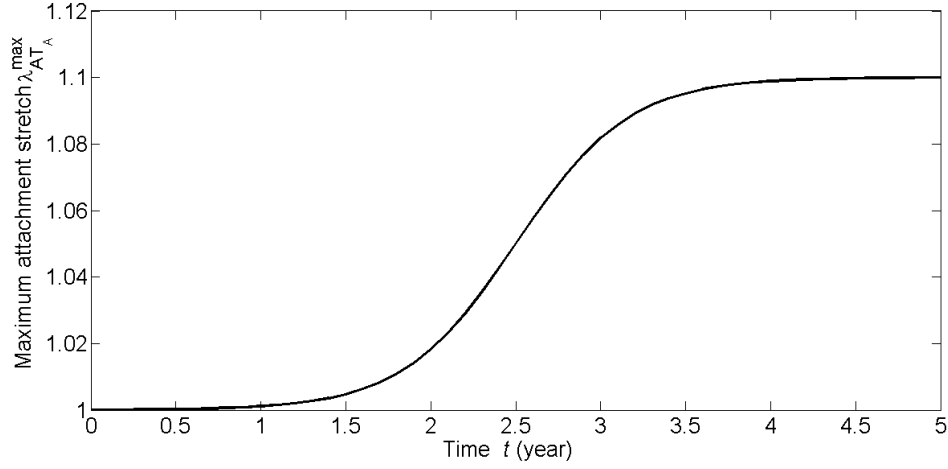


Figure 4.6: This figure shows the evolution of the maximum attachment stretch $\lambda_{AT_A}^{max}(t)$ during aneurysm evolution. The evolution is prescribed during the period of elastin degradation in the first 5 years. After $t = 5$, $\lambda_{AT_A}^{max}(t)$ is set to be constant.

0). This scenario represents the only shifting of $f_{\Lambda_{AT}}(\lambda_{AT_A})$ during aneurysm growth.

3. $\lambda_{AT_A}^{min}(t) = \lambda_{AT_A}^{max}(t) - 0.2$ and $\lambda_{AT_A}^{mod}(t) = 0.5 \cdot [\lambda_{AT_A}^{min}(t) + \lambda_{AT_A}^{max}(t)] + \gamma \cdot q(t)[\lambda_{AT_A}^{max}(t) - \lambda_{AT_A}^{min}(t)]$, i.e. $f_{\Lambda_{AT}}(\lambda_{AT_A})$ is gradually skewed negatively. $q(t)$ is the interpolation parameter defined as:

$$q(t) = \begin{cases} t/n & t \leq n \\ 1 & t > n \end{cases} \quad (4.24)$$

and $0 \leq \gamma \leq 0.5$ is the parameter that controls the speed of skewing the distribution. The bigger γ is, the faster the distribution is skewed. In this study, we choose $\gamma = 0.3$. This scenario represents shifting and skewing of $f_{\Lambda_{AT}}(\lambda_{AT_A})$.

4. $\lambda_{AT_A}^{min}(t) = \lambda_{AT_A}^{max}(t) + 0.1 \cdot q(t) - 0.2$ and $\lambda_{AT_A}^{mod}(t) = 0.5 \cdot [\lambda_{AT_A}^{min}(t) + \lambda_{AT_A}^{max}(t)]$, i.e. $f_{\Lambda_{AT}}(\lambda_{AT_A})$ is gradually narrowed as the range is linearly approaching the value of 0.1. This scenario represents the shifting and narrowing of $f_{\Lambda_{AT}}(\lambda_{AT_A})$.
5. $\lambda_{AT_A}^{min}(t) = \lambda_{AT_A}^{max}(t) + 0.1 \cdot q(t) - 0.2$ and $\lambda_{AT_A}^{mod}(t) = 0.5 \cdot [\lambda_{AT_A}^{min}(t) + \lambda_{AT_A}^{max}(t)] + \gamma \cdot q(t)[\lambda_{AT_A}^{max}(t) - \lambda_{AT_A}^{min}(t)]$, i.e. $f_{\Lambda_{AT}}(\lambda_{AT_A})$ is both gradually narrowed and skewed negatively. This scenario represents the combination of shifting, narrowing as well as skewing of $f_{\Lambda_{AT}}(\lambda_{AT_A})$.

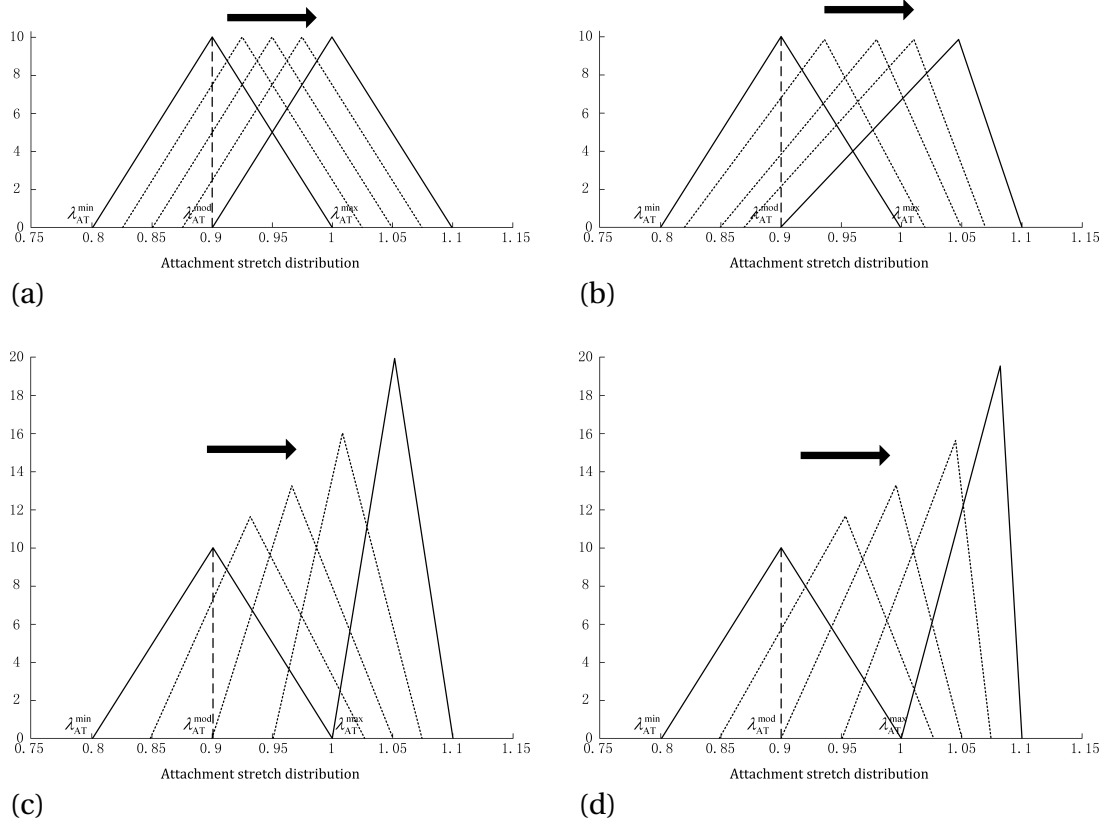


Figure 4.7: Four simulations using different approaches to adapt the attachment stretch distribution. (a) Only shifting, (b) Shifting accompanied by skewing, (c) shifting accompanied by narrowing, (d) a combination of shifting, skewing and narrowing

These five scenarios of using different variances to evolve $f_{\Lambda_{AT}}(\lambda_{AT_A})$ are simulated in order to investigate the influence of its evolution on the aneurysm growth. In all of these scenarios, the three variables $\lambda_{AT_A}^{min}$, $\lambda_{AT_A}^{max}$ and $\lambda_{AT_A}^{mod}$ determine the adaption of $f_{\Lambda_{AT}}(\lambda_{AT_A})$. Fig. 4.7 shows the evolution of the attachment stretch distribution in the last four scenarios.

However, the above is for adventitial collagens. For medial collagens, as they have already participated in load bearing in a healthy artery and are eventually degraded during aneurysm evolution, we simply assume $f_{\Lambda_{AT}}(\lambda_{AT_M})$ is constant, i.e:

$$f_{\Lambda_{AT}}(\lambda_{AT_M}(t)) = f_{\Lambda_{AT}}(\lambda_{AT_M}(0)) \quad (4.25)$$

The minimum, maximum and mode attachment stretches are set as $\lambda_{AT_M}^{min}(t) = 0.9$, $\lambda_{AT_M}^{max}(t) = 1.1$ and $\lambda_{AT_M}^{mod}(t) = 1.0$ throughout the simulation.

4.6 ANALYSIS OF ANEURYSM GROWTH

This section introduces some additional variables that are used to analyse the evolution of the aneurysm, including the cyclic stretch, the remodelled wall thickness, as well as ratio of remodelled thickness to evolving radius.

The cyclic stretch λ_{cyc} is defined as the ratio of the systolic circumferential stretch to the diastolic circumferential stretch:

$$\lambda_{cyc} = \frac{\lambda}{\lambda_{dias}} \quad (4.26)$$

where λ and λ_{dias} are the systolic and diastolic circumferential stretches computed from Eq. 4.13 with p being the systolic p and diastolic blood pressures p_{dias} respectively.

We define the remodelled thickness h_{rem} to be the thickness of the arterial wall incorporating the volumetric growth of the tissue (including both degradation of the medial constituents and growth of the adventitial collagen). The remodelled wall thickness h_{rem} can be approximated by (see Appendix B):

$$h_{rem}(t) \approx \kappa_{rem}(t) \cdot \frac{H}{\lambda(t)\lambda_Z} \quad (4.27)$$

where the first term $\kappa_{rem}(t)$ accounts for the volumetric growth of the wall constituents, whereas the second term after the dot is the thickness only considering the incompressibility condition of the wall. The inference of $\kappa_{rem}(t)$ is based on the assumption that the volumetric growth of the tissue is proportional to the mass growth of the constituents. We have (see Appendix B for the derivation):

$$\kappa_{rem}(t) \approx \frac{2m_{EM}(t) + 2m_{CM}(t) + m_{CA}(t)}{5} \quad (4.28)$$

Now let us assume the total loss of medial layer at $t = 10$, i.e. $m_{EM}(10) = m_{CM}(10) = 0$. Substituting Eq. 4.28 into Eq. 4.27 and evaluating $h_{rem}(t)$ at $t = 10$, we have:

$$h_{rem}(10) \approx \frac{H}{5\lambda_Z} \cdot \frac{m_{CA}(10)}{\lambda(10)} \quad (4.29)$$

Eq. 4.29 shows that the remodelled wall thickness h_{rem} is proportional to m_{CA} and inversely proportional to λ after the medial layer is totally degraded.

We also define a dimensionless variable χ for comparison reasons: ratio of remodelled thickness to remodelled radius, which is computed by (see Appendix B for the derivation):

$$\chi(t) = \frac{h_{rem}(t)}{r_{rem}(t)} \approx \frac{H}{R\lambda_Z} \frac{\kappa_{rem}(t)}{[\lambda(t)]^2} \quad (4.30)$$

where the remodelled radius $r_{rem}(t)$ is the radius of the remodelled geometry considering volumetric growth of the wall constituents.

4.7 MODELLING VARIABLES

Variables used in this study are summarised in Table 4.1. The unloaded geometry of our artery model has a radius $R = 2$ mm and wall thickness $H = 0.4$ mm. We assume that the media occupies $2/3$ of the thickness of the arterial wall whereas the adventitia occupies the remaining $1/3$, i.e. $H_M = 0.27$ mm and $H_A = 0.13$ mm. In the systolic configuration, the artery has a radius $r(0) = 2.6$ mm, an axial pre-stretch $\lambda_z = 1.3$, and a circumferential stretch $\lambda(0) = 1.3$. These data are consistent with previous reports on geometry of cerebral arteries: Kroon and Holzapfel (2007) reported that basilar and internal carotid arteries usually have radii in the range 1.5–2.5 mm, whereas Monson et al. (2003) found that the wall thickness of an unloaded middle cerebral artery is approximately $1/5$ of the thickness of the outer radius and the average in vivo axial stretch of fresh human cerebral blood vessels is about 1.31. Additionally, we also assume that the artery has a 10% pulsation at $t = 0$, i.e. the initial cyclic stretch $\lambda_{cyc}(0) = 1.1$. This implies a diastolic radius $r_{dias}(0) = 2.36$ mm and a diastolic stretch $\lambda_{dias}(0) = 1.18$. The systolic and diastolic pressures in the artery are assumed to be $p = 120$ mmHg and $p_{dias} = 80$ mmHg respectively, i.e. 16 kPa and 10.7 kPa. These values have been used in the literature (Watton et al., 2009a) and are consistent with subjects in the supine position (Hansen et al., 1995).

The orientations of both medial and adventitial collagen fibres are assumed to be only in the circumferential direction of the artery. We assume that the medial collagens start to be recruited to load bearing from the diastolic configuration, whereas the adventitia collagens initially act as a protective sheath starting to bear load from the systolic configuration at $t = 0$. These assumptions imply the initial values of the minimum recruitment stretches of medial and adventitial collagens, i.e. $\lambda_{RM}^{min}(0) = \lambda_{dias}(0) = 1.18$ and $\lambda_{RA}^{min}(0) = \lambda(0) = 1.3$. Values of the maximum in vivo stretches of medial and adventitial collagens can also be determined, i.e. $\lambda_{CM}^{max}(0) = \lambda(0)/\lambda_{RM}^{min}(0) = 1.1$ and $\lambda_{CA}^{max}(0) = \lambda(0)/\lambda_{RA}^{min}(0) = 1$. When the artery is initial homeostasis, the collagen attachment stretches are equal to the in vivo stretches, hence we have $\lambda_{ATM}^{max}(0) = \lambda_{CM}^{max}(0) = 1.1$ and $\lambda_{ATA}^{max}(0) = \lambda_{CA}^{max}(0) = 1$. Another constraint of the initial values of the medial collagen attachment stretch distribution $f_{\Lambda_{AT}}(\lambda_{ATM})$ is that, since some collagens are still wavy when the artery is

in the physiological state, we should have $\lambda_{AT_M}^{min}(0) < 1$. Due to the lack of biological data on the values of attachment stretch distributions, we assume that initially both of the distributions are symmetric. We set $\lambda_{AT_M}^{min} = 0.9$, $\lambda_{AT_M}^{max} = 1.1$, $\lambda_{AT_M}^{mod} = 1.0$ for medial collagen, and $\lambda_{AT_A}^{min} = 0.8$, $\lambda_{AT_A}^{max} = 1.0$, $\lambda_{AT_A}^{mod} = 0.9$ for adventitia. Finally, initial values of other salient points of the recruitment stretch distributions $f_{\Lambda_R}(\lambda_{R_M})$ and $f_{\Lambda_R}(\lambda_{R_A})$ can be determined by Eq. 4.4, see Table 4.1 for the values.

The material constants of the elastic and collagenous constituents still need to be determined. Given the systolic and diastolic circumferential stretches of the artery $\lambda(0)$ and $\lambda_{dias}(0)$ at the systolic and diastolic pressures p and p_{dias} respectively, we can determine the material parameters of the medial constituents K_{E_M} and K_{C_M} . These values yield a condition that around 77% of the blood pressure is borne by the elastic constituents during the initial systolic configuration. This is very close to the value used in the literature, i.e. 80% (Watton and Hill, 2009). For adventitia collagen material constant K_{C_A} , we simply set $K_{C_A} = 2K_{C_M}$. However, we note this is just a purely arbitrary choice. More accurate determination of the parameters requires mechanical testing of the individual layers of the cerebral arteries.

The pressure-diameter curve of our artery model is shown in Fig. 4.8. We note that during the dilation of the artery due to the increase of the total blood pressure, collagen fibres are bearing gradually larger proportion of the total pressure.

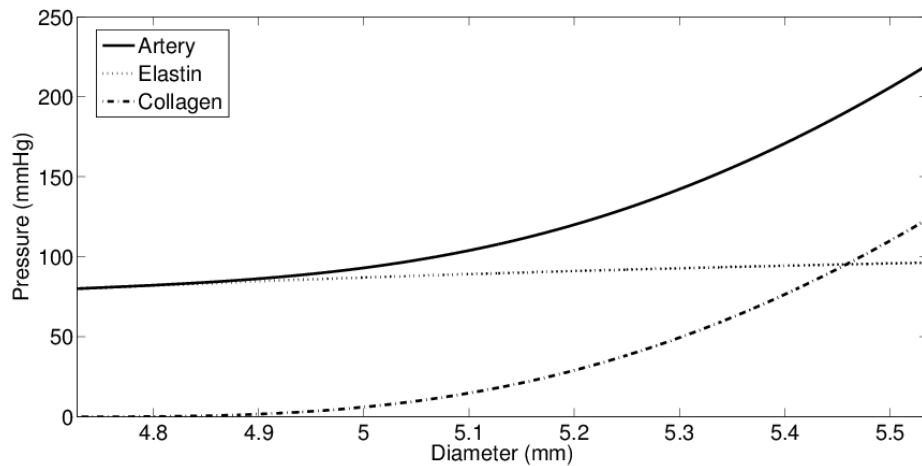


Figure 4.8: The pressure-diameter curve captures the mechanical response of our artery model during radial dilation due to the increase of blood pressure. The increase of the load borne by the elastins due to pressure increase is very limited. On the contrary, the proportion of total pressure borne by the collagen fibres are gradually increasing as a result of the gradual recruitment of fibres for load bearing.

Table 4.1: The initial values of some modelling variables and material constants used in the model

Undeformed wall thickness:		
Media	H_M	0.27 mm
Adventitia	H_A	0.13 mm
Undeformed radius	R	2 mm
Pressures:		
Systolic	p	120 mmHg
Diastolic	p_{dias}	80 mmHg
Axial pre-stretch	λ_z	1.3
Deformed radius:		
Systole	r	2.60 mm
Diastole	r_{dias}	2.36 mm
Circumferential stretches:		
Systole	λ	1.3
Diastole	λ_{dias}	1.18
Cyclic stretch	λ_{cyc}	1.1
Medial collagen		
Attachment stretches	$\lambda_{AT_M}^{max}, \lambda_{AT_M}^{min}, \lambda_{AT_M}^{mod}$	1.1, 0.9, 1.0
Recruitment stretches	$\lambda_{R_M}^{max}, \lambda_{R_M}^{min}, \lambda_{R_M}^{mod}$	1.44, 1.18, 1.30
Adventitial collagen		
Attachment stretches	$\lambda_{AT_A}^{max}, \lambda_{AT_A}^{min}, \lambda_{AT_A}^{mod}$	1.0, 0.8, 0.9
Recruitment stretches	$\lambda_{R_A}^{max}, \lambda_{R_A}^{min}, \lambda_{R_A}^{mod}$	1.63, 1.30, 1.44
Material Parameters:		
Elastin	K_{E_M}	0.15 MPa
Medial collagen	K_{C_M}	4.25 MPa
Adventitial collagen	K_{C_A}	8.50 MPa

4.8 RESULTS

MATLAB (Mathworks, Natick, Massachusetts) was used to run this model. Five cases of simulations were performed in total, using different variances to temporally adapt the adventitial collagen attachment stretch distribution: ①case 1: constant, unchanged; ②case 2: only shifting; ③case 3: shifting and skewing; ④case 4: shifting and narrowing; ⑤case 5: shifting, skewing and narrowing. Details about these variances are introduced in Sec. 4.5. Results including evolution of the medial and adventitial fibre mass densities, collagen maximum in vivo stretches, cyclic stretches, remodelled wall thickness as well as ratio of remodelled wall thickness to remodelled radius are illustrated over a time span of 10 years.

Fig. 4.9 illustrates the prescribed degradation of the mass densities of the medial elastinous and collagenous constituents m_{J_M} using Eq. 4.20. Here J can be either E representing elastins or C representing collagens. In the initial five years, the degradation of m_{J_M} is prescribed to follow an exponential decay function. The media layer is assumed to totally disappear after the end of fifth year.

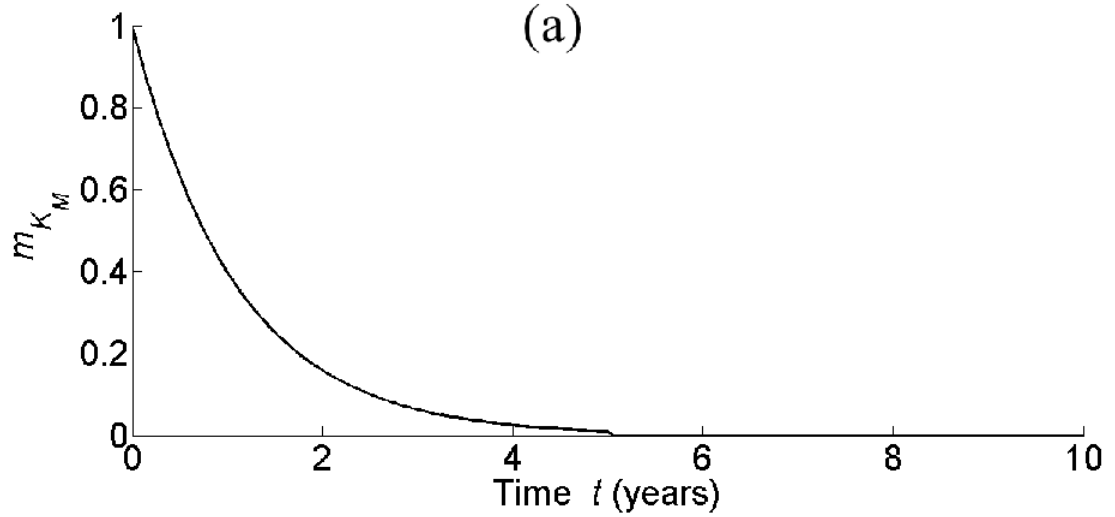


Figure 4.9: Degradation of the medial elastin and collagen fibres drives the continuous growth of the aneurysm. The change of mass density m_{J_M} of medial constituent J is prescribed using an exponential decay function over the first five years' time. After the end of fifth year, the media layer is assumed to be totally lost so $m_{J_M} = 0$. Here J can be either E representing the elastins or C representing the collagens.

Fig. 4.10 depicts the evolution of adventitial collagen mass densities m_{C_A} . We notice that in the first year and a half the growth of adventitial collagen mass densities in all cases are very similar to each other. If we refer back to Fig. 4.9, this time point corresponds to when more than 30% of medial constituents still remain within the artery wall. However, after the first year these curves start to divert from each other. The largest collagen growth is achieved in case 1, where the collagen mass density increases uncontrollably. Case 5 has the smallest growth rate and tends to stabilise fastest.

Fig. 4.11 shows the evolution of elastin stretch λ , which is also the circumferential stretch of the artery. It measures the increase in size of the aneurysms. We observe that λ is very similar in all of the five cases in the first year and a half. After that, different trends of evolution of λ can be observed. The aneurysm with largest size occurs in Case 1 whereas the aneurysm with smallest size occurs in Case 5. The

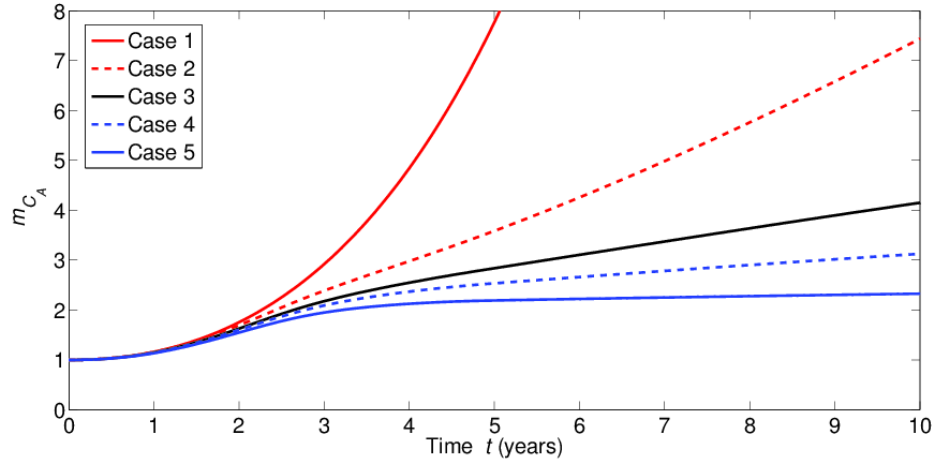


Figure 4.10: The growth of adventitial collagen is modelled by the change of adventitial collagen mass density m_{CA} . The rates of change of m_{CA} in the five cases in the first year and a half are very similar to each other. After that, the change of m_{CA} begins to have different trends in different cases: in Case 1, m_{CA} grows uncontrollably; in Case 2, m_{CA} grows with an almost constant rate; in Case 3, 4 and 5, the growth of m_{CA} gradually slow down during the later years. At the end of the simulations (ten years), m_{CA} is observe to only stabilise in Case 5.

final arterial radii of these five cases are approximately $4.1/1.3 \approx 3.2$, $2.9/1.3 \approx 2.2$, $2.5/1.3 \approx 1.9$, $2.4/1.3 \approx 1.8$ and $2.2/1.3 \approx 1.7$ times of the original arterial radii respectively.

Fig. 4.12 shows the evolution of adventitial collagen maximum in vivo stretch λ_{CA}^{max} . Starting from a value of 1, λ_{CA}^{max} first increases in a similar manner in all these five cases in the first year, reaching the peak values between 1.14 and 1.17 in the middle of the third year, and decreases again and tends to stabilise at the values of maximum attachment stretch λ_{ATA}^{max} , which is set to be 1.0 in Case 1 and 1.1 in other cases. However, note that the stabilisation of λ_{CA}^{max} towards λ_{ATA}^{max} in these cases is relatively slow so that λ_{CA}^{max} is still decreasing at the end of the simulations.

Fig. 4.13 shows the evolution of the cyclic stretch λ_{cyc} , which is defined as the ratio of tissue systolic stretch λ to diastolic stretch λ_{dias} . In all of the cases, λ_{cyc} decreases rapidly within the first two years, from the initial value of 1.1 to about 1.03 at the end of the second year. After this, Case 1 λ_{cyc} continues to decrease and eventually stabilise at around 1.01, whereas in the other cases λ_{cyc} only decreases slightly and tends to finally stabilise at the values around 1.02.

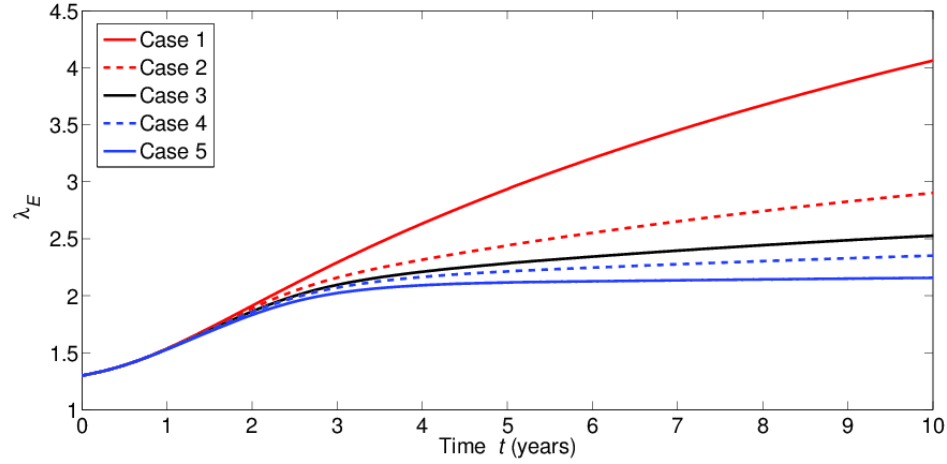


Figure 4.11: The elastin stretch λ_{EM} , which is also the circumferential stretch of the artery, measures the change of sizes of the aneurysms. The rates of change of λ_{EM} in the five cases in the first year and a half are very similar to each other. After that, different trends of evolution can be seen: λ_{EM} grows fastest in Case 1, in which it eventually reaches the level of 4.1 after 10 years; whereas in other cases, λ_{EM} grows slower in the following years than Case 1. The aneurysm in Case 5 has the smallest growth rate among the five cases, hence stabilises fastest. Aneurysms in other cases have bigger growth rates, hence have larger dilations. However they are still enlarging at the end of simulations.

Fig. 4.14 illustrates the evolution of remodelled wall thickness h_{rem} considering volumetric growth of the tissue. It can be seen that h_{rem} decreases in similar ways in all cases during the initial two years. From the beginning of the third year, Case 1 h_{rem} increases again and eventually reaches about 3.4 times its initial value. In Case 2, h_{rem} only increases slightly in the following years. In Case 3 and 4, the increase of h_{rem} is trivial compared with Case 1, whereas in Case 5, h_{rem} finally stabilises at about 1/4 of its initial value.

Lastly, Fig. 4.15 illustrates the evolution of the newly defined dimensionless variable χ , which is the ratio of remodelled thickness h_{rem} to remodelled radius r_{rem} (see Appendix B). The trends of χ curves are similar to those of h_{rem} . Starting from the initial value of 0.09, χ decreases in almost identical ways in all of the five cases during the first two years. From the beginning of the third year, Case 1 χ increases again and eventually returns to approximately the same level as the initial value at the end of the simulation. In Case 2, χ only increases slightly in the following years. In Case 3 and 4, the increase of χ is also trivial compared with that of Case 1. In Case 5, χ eventually stabilises to around 1/5 of its initial value.

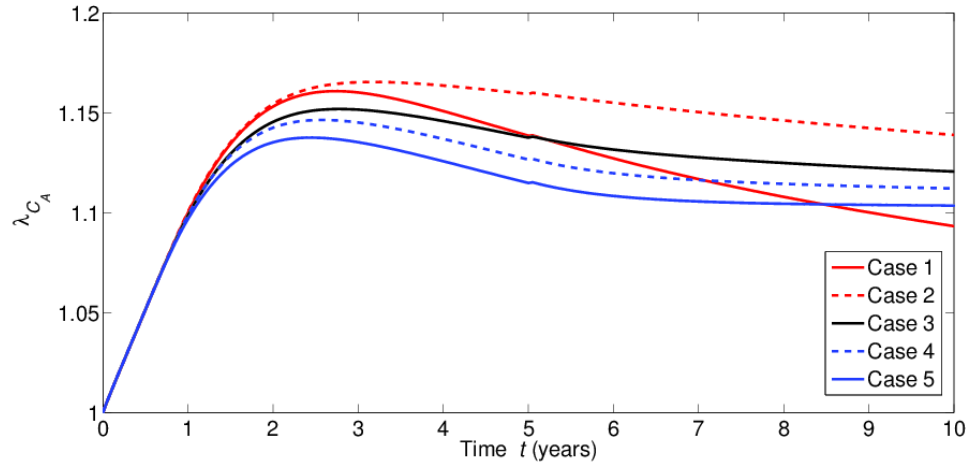


Figure 4.12: The maximum in vivo stretch of adventitial collagen $\lambda_{C_A}^{max}$ measures the maximum deformation of the adventitial collagen fibres from their own natural reference configurations. The rates of change of $\lambda_{C_A}^{max}$ in the five cases in the first year are almost identical. After the end of the first year, different trends of $\lambda_{C_A}^{max}$ can be seen. However, in general, in all cases $\lambda_{C_A}^{max}$ reaches the maximum values in the middle of the third year, and then decreases and tends to stabilise towards the values of $\lambda_{AT_A}^{max}$. Note the rate of stabilisation are slow, hence at the end of the simulations, $\lambda_{C_A}^{max}$ is still decreasing in all cases. $\lambda_{C_A}^{max}$ stabilises towards $\lambda_{AT_A}^{max} = 1.0$ in Case 1, and towards $\lambda_{AT_A}^{max} = 1.1$ in the other four cases.

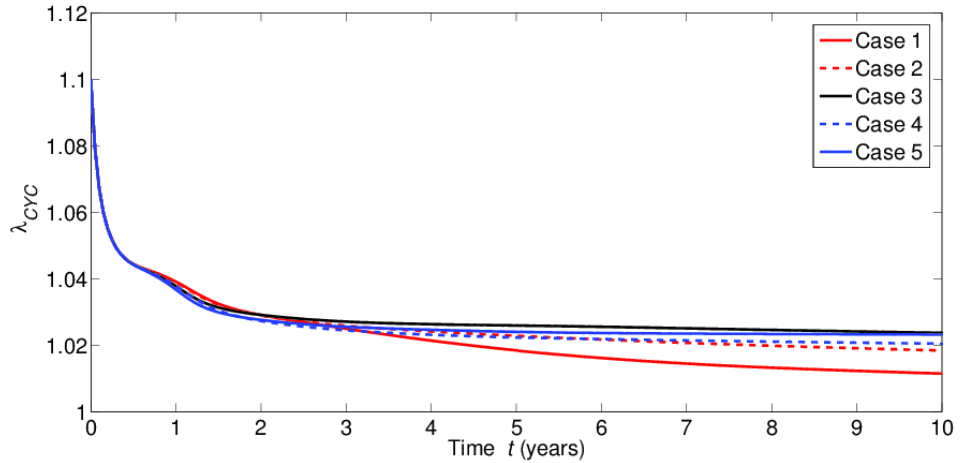


Figure 4.13: The cyclic stretch λ_{cyc} measures the cyclic deformation of the arterial tissue and is defined as the ratio of tissue systolic circumferential stretch to the diastolic circumferential stretch. Starting from the value of 1.1, λ_{cyc} experiences rapid decrease during the first two years in all cases. After this, λ_{cyc} continues to decrease and eventually stabilise at around 1.01 in Case 1, whereas in the other cases, λ_{cyc} only decreases slightly and tends to stabilise eventually.

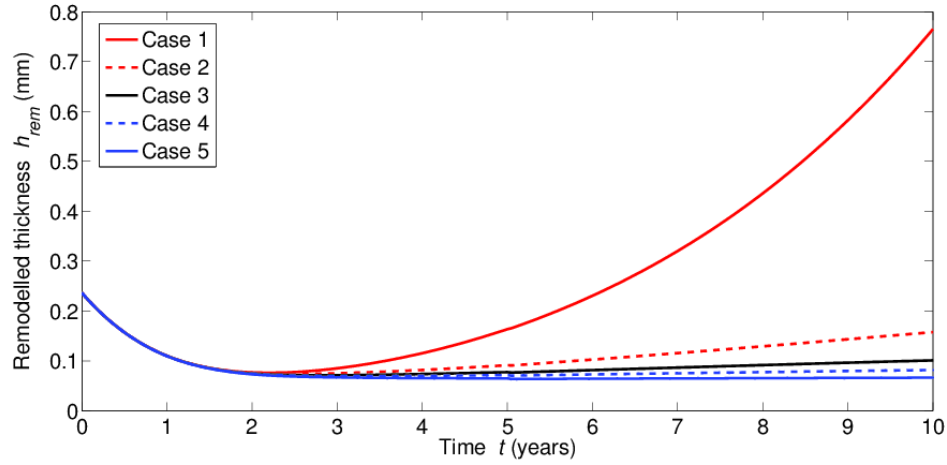


Figure 4.14: The remodelled wall thickness h_{rem} takes into consideration the volumetric growth of the wall constituents. Starting from the initial value 0.24 mm, h_{rem} decreases to about 0.08 mm in similar patterns in all of the five cases during the first two years. After that, Case 1 h_{rem} increases dramatically and finally reaches 0.78 mm at the end of the simulation, i.e. 3.3 times of its initial value, whereas in Case 2 h_{rem} only increases slightly in the following years. In Case 3 and 4, the increase of h_{rem} is trivial compared with Case 1. In Case 5, h_{rem} eventually stabilises at around 0.06 mm, i.e. 1/4 of its initial value.

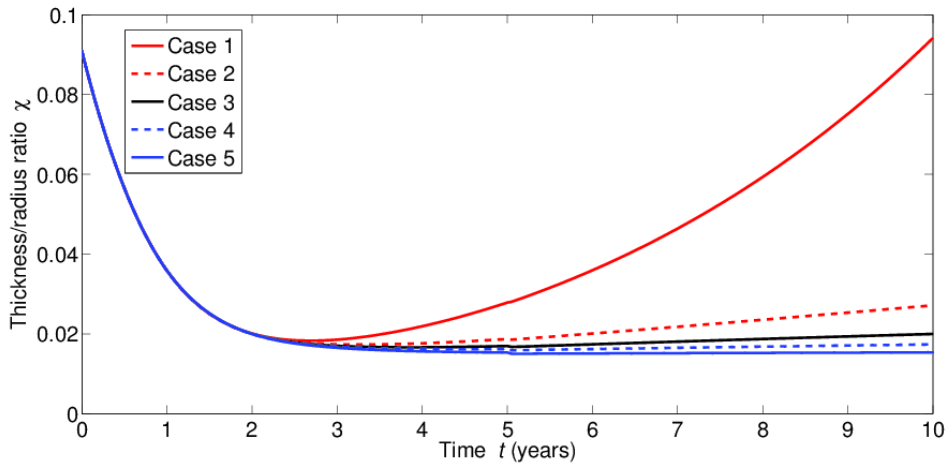


Figure 4.15: The ratio of remodelled thickness to remodelled radius is a dimensionless variable denoted as χ . The evolution patterns of χ in the five cases are similar to those of h_{rem} . Starting from the initial value of 0.09, χ decreases in almost identical ways in all of the five cases during the first two years. After that, Case 1 χ increases rapidly and finally returns to approximately the same level as the initial value at the end of the simulation, whereas in Case 2, χ only increases slightly in the following years. In Case 3 and 4, the increase of χ is trivial compared with Case 1. In Case 5, χ eventually stabilises at value of 0.018, i.e. about 1/5 of its initial value.

4.9 DISCUSSION

In Sec. 4.1, we briefly reviewed the evolutionary history of the concept of attachment stretch prior to this study. In our study, the attachment stretches are assumed to be in the form of 1D distribution. This 1D distribution is homogeneous in each layer, but heterogeneous between different layers. More importantly, it is assumed to be able to adapt temporally. Considering Sec. 4.1, here we can summarise that the concept of statistical distributions of attachment stretches is gradually becoming a consensus in this field of modelling arterial G&R. The distribution itself may also be anisotropic (i.e. multivariate distribution) and spatially heterogeneous. Additionally, this attachment stretch distribution is not temporally constant. It should be able to adapt if the mechanical environments surrounding the fibroblast cells, or the mechanical properties of the fibroblast cells themselves have changed. This is where many things are currently unknown and more experimental investigations are needed.

In this study we investigated the influence of temporal adaption of the attachment stretch distribution on the growth of an aneurysm. Due to the lack of relevant biological information on the ‘born stretch states’ of the newly deposited collagen fibres at the moment, different variances are tested to evolve the attachment stretch distribution, including only shifting, shifting and skewing, shifting and narrowing, as well as shifting and skewing and narrowing of the distribution. We also include one case in which the attachment stretch distribution is assumed to be constant for comparison reasons. Results show that a constant attachment stretch distribution yields an unrealistic thickened arterial wall, which is much thicker than the original wall in initial homeostasis. If shifting of the distribution is considered, the result for the remodelled wall thickness h_{rem} is improved. However, h_{rem} is still observed to increase in the final years. When skewing or/and narrowing of the distribution is incorporated, the results for the remodelled wall thickness become more realistic, i.e. the wall gradually becomes thinner and eventually stabilises. However, in these cases the dilation of the aneurysm is also smaller than the cases of constant attachment distribution and only shifting the distribution. In general, if larger proportions of collagen fibres are configured into the matrix with bigger attachment stretches, then both the amount of collagens required to balance the blood pressure and the tissue circumferential stretch of the tissue will be smaller. The remodelled wall thickness, as well as the ratio of wall thickness to remodelled radius, will also

be reduced. Given that the remodelled thickness is proportional to the collagen mass density and inversely proportional to the circumferential stretch after the media layer is totally degraded (see Eq. 4.29), this implies that larger proportions of collagen fibres with bigger attachment stretches have greater influence on the collagen mass density than on the tissue circumferential stretch. Based on previous histological observations of the aneurysmal tissue, whereby a much thinned arterial wall is usually present, our simulation results suggest that, in order to achieve a reduced wall thickness, it seems that more and more collagen fibres are gradually configured into the matrix with bigger attachment stretches during aneurysm evolution, i.e. the attachment stretches are temporally variant in a way that the attachment stretch distribution is continuously shifted positively before it reaches an upper bound. Additionally, it is very possible that narrowing, as well as negative skewing of the distribution, are also present.

It might be of interest to have a quick review of the actual values of the attachment stretches used in the literature. Table 4.2 summaries some of the latest studies from different research groups in which values of the attachment stretches are provided. From this table we can see that, except for the studies conducted by the researchers Gleason et al. in which comparatively large values of attachment stretches are used, the values of the collagen attachment stretches are always less or equal to 1.10. Surprisingly, however, in many of the studies, no information as to which criteria led to the choice of value was provided. In one of the few studies in which the criteria were actually introduced, Watton et al. (2004) determined the value of maximum attachment stretch by assuming that collagen fibres begin to be recruited to load bearing at diastolic pressure. Hence the maximum attachment stretch is just equal to the initial maximum stretch of the collagen fibres, which is also equal to the initial cyclic stretch of the artery, i.e. approximately 1.1. Valentín and Humphrey (2009b) suggested that the values of the attachment stretches could be determined by comparing with observations from purely collagenous tissues such as tendons and intracranial aneurysms. Hence values between 1.05 and 1.1 are recommended by the researchers, with 1.08 being the choice for their study. In the two studies conducted by Kroon and Holzapfel (2007, 2009), values between 1.012 and 1.10 were tested in an aneurysm growth model and, based on the results, values roughly of the order 1.02 - 1.04 were suggested by the authors. In our study, we assume the medial collagen attachment stretch distribution initially ranges from 0.9 to 1.1, whereas the adventitial distribution initially ranges from 0.8 to 1.0. These values are selected due

to their mechanical roles as the primary load bearer and as a protective sheath respectively in the initial homeostasis. During the aneurysm growth, the medial distribution remains constant whereas the adventitial distribution shifts positively. The maximum attachment stretch increases to 1.1 whereas the minimum attachment stretch increases to no less than 0.9 but no more than 1.0. These values are chosen to represent the change of the mechanical role of the adventitial collagen from a protective sheath to the main load bearer. As the minimum attachment stretch is no more than unity, this represents the assumption that there are always some collagen fibres bearing no load when being deposited and configured into the matrix. The values used here are fairly consistent with the ones used in other studies in the literature. To conclude briefly, the values of the collagen attachment stretches are subjectively prescribed in all of the studies in the literature. However, as the physiological cause of the attachment stretches is considered to be related to the compaction of the matrix by cells in order to achieve certain level of strain or stress, we suggest that these attachment stretches can possibly be linked to the mechanical environment outside the cells, including cyclic stretches of the wall, stretch/stress of the ECM, matrix stiffness, as well as the mechanical environment inside the cells, which specifically means the architecture as well as mechanical property of the cytoskeleton.

In this 1D study, all of the collagen fibres are simply assumed to align perfectly in the circumferential direction. Due to this reason we only consider 1D single-variate attachment stretch distribution for the fibres deposited along the circumferential direction. However, collagen fibres are known to align in two distinct principal directions, with some dispersions in the orientations in both the media and adventitia layers of normal arteries (Rezakhaniha et al., 2012; Schriefl et al., 2012). Under abnormal physiological conditions, these fibre orientations also remodel as the arterial G&R process. This includes the deposition of the new fibres with different orientations, as well as reorientation of the existent fibres. Several studies have been focusing on modelling the arterial fibre orientations, as well as their remodelling, via certain distribution functions (Hariton et al., 2007; Driessen et al., 2008; Baaijens et al., 2010; Nagel and Kelly, 2012). In more realistic arterial G&R models where fibre orientations, as well as the remodelling of the orientations are incorporated, the anisotropic behaviour of the attachment stretch distribution should then be taken into consideration. Multivariate distributions might be of use if the attachment stretch is proven to be anisotropic.

Table 4.2: Types and values of collagen attachment stretches used in some selected studies in the literature. Note in Gleason and Humphrey (2005) and Wan et al. (2010), that although distributions of attachment stretches are proposed in theory, in practice only mean values of the distributions are used.

Studies	Type	Actual value(s)
Humphrey (1999)	Single	1
Watton et al. (2004)	Single	1.10
Gleason and Humphrey (2005)	Distribution	1.259 (circumferential) 1.334 (axial)
Baek et al. (2006)	Single	1.10
Valentín and Humphrey (2009b)	Single	1.08
Figueroa et al. (2009)	Single	1.07
Kroon and Holzapfel (2009)	Single	1.02–1.04 suggested
Eriksson et al. (2009)	Single	1.02
Watton et al. (2009a)	Single	1.07
Machyshyn et al. (2010)	Single	1.10
Wan et al. (2010)	Distribution	1.340 (isotropic)
Nagel and Kelly (2012)	Single	1.05
Karšaj and Humphrey (2012)	Single	1.08

The formulation of this 1D model is based on a thin membrane assumption, where the arterial tissue is assumed to be incompressible, i.e. $\text{def}(\mathbf{F}) = 1$. When deriving the mechanical equilibrium equation Eq. 4.13, the constituents are assumed to turn over in a way that the mass density changes and the volume of the arterial wall preserves, i.e. constant volume of the wall is maintained during aneurysm growth. However, in order to infer the remodelled wall thickness considering volumetric growth using Eq. 4.27 and Eq. 4.28, we approximate the volumetric growth of the constituents by assuming that the volumetric growth is proportional to the mass growth of the constituents. In other words, the constituents are assumed to turn over in a way that the volume changes and the mass density preserves, i.e. constant mass density of the arterial wall is maintained during aneurysm growth. The need to make these two different assumptions in this study is attributed to the impossibility of quantitatively measuring the dynamic change of the masses of the constituents in the artery wall during aneurysm growth. Actually, if the wall itself is considered as an isolated system of interest, then the total mass of this system may not even be conserved during aneurysm growth. Hence, other principles in the field of continuum mechanics which are derived based on the principle of mass conservation may also be challenged. In reality, it is biologically unclear whether the

constituents are turned over to maintain constant volume or constant mass density. Most likely it happens in a combined way of changing the volume and mass density at the same time. Hence better understanding this mechanism may provide insight into the formulation of more realistic models on arterial G&R, and is also imperative for the calculation of actual remodelled wall thickness, as well as other calculations that are based on the wall thickness.

In this study we only modelled the mechanobiology of the fibroblast cells in a simple and phenomenological way. The mechanobiology of the endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) are not modelled. However, these two types of cells are also known to play important roles in tissue G&R as well. For instance, ECs sense the haemodynamic environment near the vessel wall and release certain chemical substance into the media. This is considered to possibly have an impact on aneurysm initiation as well as subsequent growth (Chien, 2007; Chiu and Chien, 2011; Chen et al., 2013). VSMCs actively help to bear the mechanical load within the arterial wall caused by the local blood pressure, and are involved in regulating the blood pressure through vasodilation and vasoconstriction. They are also responsible for synthesising and degrading medial constituents. Ideally the effects of ECs and VSMCs on arterial G&R should be taken into consideration in a more realistic model.

Currently the model presented here is in 1D form. It has been fully integrated into the 3D solid aneurysm growth model, as well as the *Fluid-Solid-Growth* (FSG) computational framework for modelling aneurysm evolution on patient-specific geometries of the vasculature. The FSG framework represents the functionality of the ECs by linking the degradation of the elastinous constituents within the arterial wall to the haemodynamic stimuli obtained from computational fluid dynamics analysis. Spatial heterogeneity of the ECs is also considered (Aparício et al., 2014). In addition, a quasistatic structural analysis quantifies the cyclic deformation of the arterial wall so that collagen G&R is explicitly linked to the cyclic deformation of vascular cells. Implementing this collagen microstructure adaption model into the 3D solid model, as well as the FSG framework requires the incorporation of collagens with different orientations. The current formulations for modelling the mechanical response of the artery, as well as the G&R of the arterial constituents, are sophisticated when implemented into both the 3D solid model and the FSG framework. More realistic simulation results, especially regarding the remodelled wall thickness

and the Cauchy stress within wall, will be presented in the next chapter.

4.10 CONCLUSION

In this chapter, a novel mathematical model is presented for microstructural adaption of the collagen fabric during aneurysm evolution. In this 1D model we assume that the ‘born stretch states’ of the new collagen fibres, which is referred to here as the attachment stretch distribution, can temporally adapt when the external mechanical environment of the cells alters. We investigated the influence of temporal adaption of the attachment stretch distribution on the growth of an aneurysm. Different variances are utilised to adapt the attachment stretch distribution, including only shifting, shifting and skewing, shifting and narrowing, as well as shifting and skewing and narrowing of the attachment stretch distribution. One extra scenario in which the attachment stretch distribution is assumed to be constant is also included for comparison reason. Results show that in general, if larger proportions of collagen fibres are configured into the matrix with bigger attachment stretches, then the collagen mass density, size of the aneurysm, remodelled wall thickness as well as ratio of remodelled wall thickness to evolving radius will all be reduced. Based on our results, as well as on histological observations, we concluded that in order to achieve a thinned wall, the attachment stretches should be temporally variant in a way that the attachment stretch distribution is continuously shifted positively before it reaches an upper bound. Narrowing as well as negative skewing of the distribution may be also present. Our model is the first collagen microstructural adaption model that explicitly defines the functional form of the attachment stretch distribution and incorporates the temporal adaption of the distribution. Although this model is proposed based on an aneurysm evolution model to simulate the growth of an IA, it can be also implemented into other models on arterial growth and remodelling.

In the next chapter, we will present the full integration of this collagen microstructure model into the 3D solid model as well as a novel Fluid-Solid-Growth modelling framework of aneurysm evolution.



THE 3D SOLID MODEL AND THE FLUID-SOLID-GROWTH MODEL OF IA EVOLUTION

In the previous chapter, a novel 1D model of the microstructural adaption of the collagen fabrics during IA evolution is presented. Simulation results of a 1D conceptual aneurysm development show that thinning of the remodelled wall thickness and reduction of the thickness to radius ratio can be achieved if new collagens are configured into the ECM by the vascular cells with a positive adaption of the attachment stretch distribution.

3D computational models have been developed to address the evolution of aneurysms. For example, Watton et al. (2004) developed a computational framework to model the evolution of abdominal aortic aneurysms (AAAs). In their model, spatially and temporally dependent microstructural variables are introduced into a realistic constitutive model of the arterial wall (Holzapfel et al., 2000). This enables the G&R of the arterial tissue to be simulated during the evolution of an AAA, including the degradation of elastinous constituents, growth/atrophy of the mass of collagenous constituents as well as remodelling of the natural reference configurations with respect to which collagen fibres are recruited to load bearing. Subsequently, this model was updated to model the evolution of intracranial aneurysms (Watton and Ventikos, 2009). Other models of IA evolution can also be seen within the

literature (Baek et al., 2005, 2006; Kroon and Holzapfel, 2007, 2008, 2009). Most recently, the aforementioned model was further sophisticated to model the evolution of IAs in patient-specific geometries (Watton et al., 2011a), where G&R of the arterial constituents is explicitly linked to the local haemodynamic environment in the aneurysm region as well as the mechanical environment of the vascular cells (in particular the cyclic deformations).

In this chapter, we illustrate the integration of our 1D model of collagen microstructural adaption into two 3D models of IA evolution: the solid structural model presented in Watton and Ventikos (2009), as well as the Fluid-Solid-Growth (FSG) model presented in Watton et al. (2011a). Mechanical response of the arterial wall with the strain energy functions for the heterogeneous arterial tissue in the 3D environment is first introduced. The approach to model G&R of the arterial constituents with the adaption of the collagen microstructure is also presented. Results are compared to show the influence of incorporating the 1D collagen adaption model on the evolution of the aneurysm. Finally, the implementation of the 1D collagen adaption model into the state-of-the-art 3D FSG model is briefly introduced. One illustrative case is presented to show the successful implementation and its influence on simulated IA evolution.

5.1 NON-LINEAR ELASTICITY

To model the gradual development of the arterial wall during aneurysm evolution, a geometric non-linear membrane theory (Heil, 1996) is adopted. The internal carotid artery in the unloaded reference configuration, here denoted as Ω_0 , is modelled as a thin cylinder of undeformed radius R , length L_1 , and thickness H . The thickness of the media layer H_M is assumed to be $2/3$ of the thickness of the arterial wall, whilst the thickness of the adventitia H_A is assumed to be $1/3$. In the initially loaded configuration Ω_0^t , the artery is subject to a physiological axial pre-stretch λ_z , and a constant systolic pressure $p = 16kPa$ which leads to a circumferential stretch of λ_0 . Hence in Ω_0^t the cylindrical artery has dimensions of length $L = \lambda_z L_1$, radius $r = \lambda_0 R$ and thickness $h = H/(\lambda_0 \lambda_z)$ (see Fig. 5.1). During the evolution of the aneurysm, both the proximal and distal ends are considered to be fixed.

The membrane is described by a 3D body-fitted Lagrangian coordinate system, where coordinates θ_1 , θ_2 and θ_3 initially lie in the axial, circumferential and radial

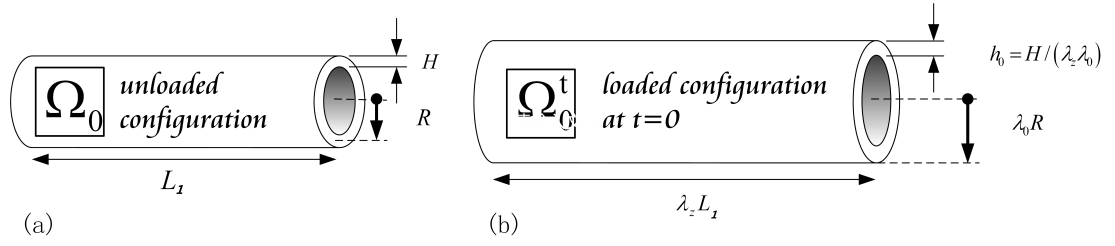


Figure 5.1: Different reference configurations of the arterial model: (a) unloaded configuration Ω_0 ; (b) initially loaded configuration Ω_0^t (adapted from (Watton et al., 2009a)).

directions of the cylinder respectively (see Fig. 5.2). The midplane of the arterial wall is positioned at $\theta_3 = 0$ so that the upper and lower surfaces of the arterial wall have coordinates $\theta_3 = \pm H/2$. Here we note that the coordinate system we adopt is a material coordinate system which deforms with the development of the aneurysm, i.e. θ_1 and θ_2 always sit in the midplane, whereas θ_3 is always perpendicular to the midplane. In the following numerical description of the deformation, the Einstein notation is used throughout. Upper case letters are used to refer to the undeformed configuration, whereas lower case letters are used to refer to the deformed configuration.

In general, a material point on the midplane of the membrane is described by its position vector $\mathbf{X}(\theta_1, \theta_2)$. At this point, a pair of covariant basis vectors is defined as the tangents to the coordinate curves θ_α ($\alpha = 1, 2$):

$$\mathbf{A}_\alpha = \mathbf{X}_{,\alpha} = \frac{\partial \mathbf{X}}{\partial \theta_\alpha} \quad (5.1)$$

where the comma denotes partial derivatives with respect to θ_α . The third basis vector is defined as the unit normal vector to the two midplane basis vectors:

$$\mathbf{A}_3 = \frac{\mathbf{A}_1 \times \mathbf{A}_2}{|\mathbf{A}_1 \times \mathbf{A}_2|} \quad (5.2)$$

Hence, in the undeformed configuration, the covariant midplane metric tensors can be defined as $A_{ij} = \mathbf{A}_i \cdot \mathbf{A}_j$ ($i, j = 1, 2, 3$).

During the deformation, the material point which originally lies at position $\mathbf{X}(\theta_1, \theta_2)$ in the undeformed configuration is displaced to its new position given by:

$$\mathbf{x}(\theta_1, \theta_2) = \mathbf{X}(\theta_1, \theta_2) + \mathbf{u}(\theta_1, \theta_2) \quad (5.3)$$

where $\mathbf{u}(\theta_1, \theta_2)$ gives the midplane displacement field. A pair of basis vectors of the deformed midplane $\mathbf{a}_\alpha$ ($\alpha = 1, 2$) can be defined as the tangent vectors to the

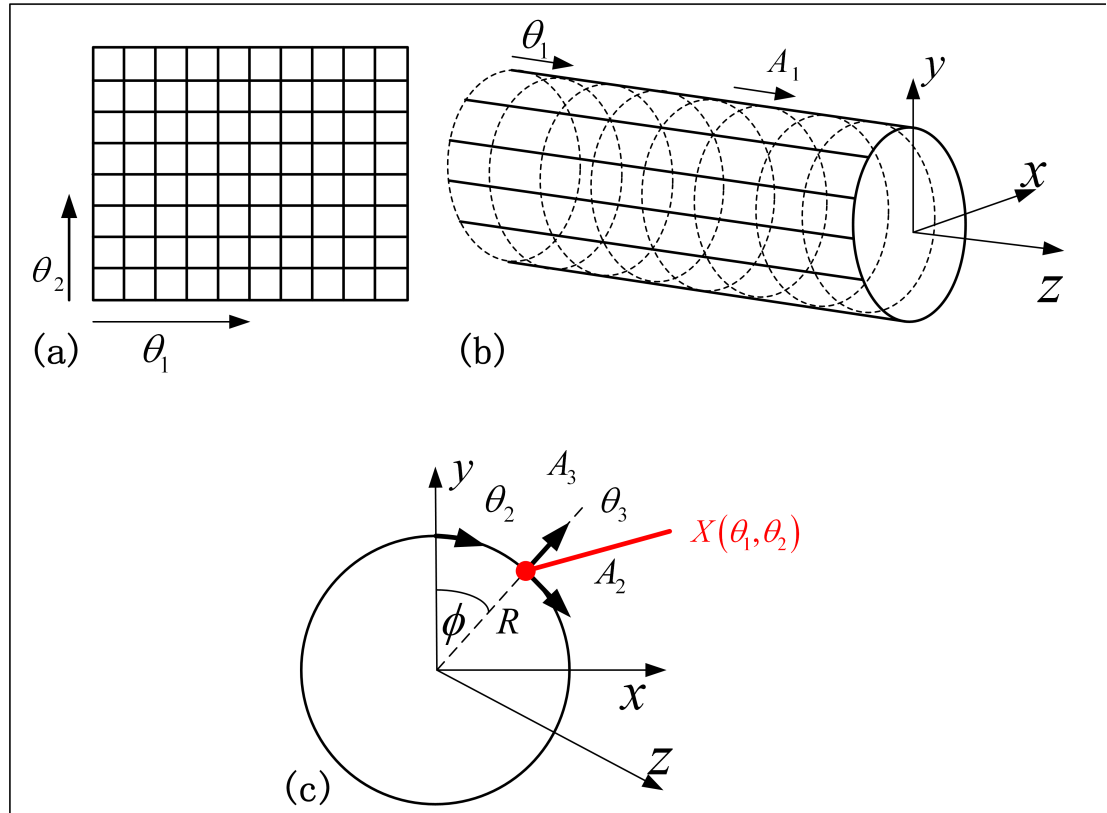


Figure 5.2: A body-fitted Lagrangian coordinate system is adopted to describe the deformation of the arterial membrane (showing the midplane of the arterial wall). (a) and (b): Coordinates θ_1 and θ_2 are parallel to the midplane of the arterial wall; (c) coordinate θ_3 is perpendicular to the midplane. The position vector $\mathbf{X}$ of any point on the membrane is defined with respect to the coordinates θ_1 and θ_2 . At each point, a set of covariant basis vectors is defined as tangents to θ_1 and θ_2 (adapted from (Watton, 2002)).

coordinate curves in the deformed midplane:

$$\mathbf{a}_\alpha = \mathbf{x}_{,\alpha} = \frac{\partial \mathbf{x}}{\partial \theta_\alpha} = \mathbf{A}_\alpha + \mathbf{u}_{,\alpha} \quad (5.4)$$

The third midplane basis vector $\mathbf{a}_3$ is chosen as the normal vector to $\mathbf{a}_1$ and $\mathbf{a}_2$. In addition, the condition of incompressibility on the midplane needs to be satisfied. To achieve this, $\mathbf{a}_3$ is defined as:

$$\mathbf{a}_3 = \frac{(\mathbf{a}_1 \times \mathbf{a}_2) |\mathbf{A}_1 \times \mathbf{A}_2|}{(|\mathbf{a}_1 \times \mathbf{a}_2|)^2} \quad (5.5)$$

Similarly, in the deformed configuration, the covariant midplane metric tensors can be defined as $a_{ij} = \mathbf{a}_i \cdot \mathbf{a}_j$ ($i, j = 1, 2, 3$).

The membrane theory assumes that the off-midplane and midplane strain fields are equal, i.e. the strain field is uniform along the direction normal to the midplane. Therefore, the Green-Lagrangian (GL) strain tensor can be defined as the difference between the deformed and undeformed midplane metrics:

$$E_{ij} = \frac{1}{2}(a_{ij} - A_{ij}) \quad (5.6)$$

In our model, cylindrical polar Lagrangian coordinates θ_i ($i = 1, 2, 3$) are used to denote the arc lengths in the axial, circumferential and radial directions respectively. Hence, the position vector of a material point on the undeformed midplane with respect to a Cartesian coordinate system is given by:

$$[\mathbf{X}] = [R \sin(\theta_2/R), R \cos(\theta_2/R), \theta_1] \quad (5.7)$$

for $\theta_1 \in [0, L_1]$ and $\theta_2 \in [0, 2\pi R]$. The position vector of the point after deformation is then given by:

$$[\mathbf{x}] = [(R + u_3) \sin(\theta_2/R) + u_2 \cos(\theta_2/R), (R + u_3) \cos(\theta_2/R) - u_2 \sin(\theta_2/R), \theta_1 + u_1] \quad (5.8)$$

where u_1 , u_2 and u_3 are the components of the displacement field in the axial, circumferential as well as radial directions respectively. Now the strain field can be calculated through Eq. 5.1 to Eq. 5.6.

5.2 OVERVIEW OF THE SOPHISTICATED SOLID STRUCTURAL MODEL OF IA EVOLUTION

We begin by first overviewing the 3D solid structural model of IA evolution sophisticated with the implementation of the 1D collagen microstructural adaption model. The artery is modelled as a two-layer, nonlinear elastic cylindrical membrane subject to a constant systolic pressure and a physiological axial pre-stretch. Both the media and the adventitia layers are modelled as composites of elastinous constituents and two sets of normal collagen fibres (positively and negatively wound). Two sets of additional protective collagen fibres (positively and negatively wound) are also added to the adventitia layer. These additional collagen fibres are assumed to bear no load in the normal physiological regime, hence acting as a protective sheath to prevent the artery from over-dilation. Elastinous constituents

are modelled using an isotropic Neo-Hookean constitutive model. Normal collagens are modelled using a highly non-linear (exponential) model, whereas the additional protective collagens are modelled by aggregating the mechanical contributions of individual collagen fibres which are successively recruited for load bearing, represented by the distribution of collagen recruitment stretches. IA evolution is assumed to be a consequence of the growth and remodelling of the arterial constituents. To localise the aneurysm, the degradation of the elastinous and the normal collagenous constituents are prescribed within a circular patch. Remodelling of the collagen recruitment stretch distributions allow the degradation and deposition of the collagen fabrics in altered configurations to be simulated. The temporal adaption of the attachment stretch distribution of the additional protective collagen fibres is also incorporated to model their transition from a protective sheath to the primary load bearer during IA evolution. This adaption is confined to the aneurysm domain. One simulation under this modelling scheme is compared with three other simulations, including: 1. model with no additional protective collagens; 2. model with no remodelling of the additional protective collagens; 3. model with collagen attachment stretch distribution adapted throughout the artery. It is observed that the sophisticated solid structural model incorporating collagen microstructural adaption predicts stabilised saccular IAs with more realistic evolution of wall thicknesses and stresses in the wall. We also observe that confining the attachment stretch adaption in the aneurysm region is necessary.

5.3 MECHANICAL RESPONSE OF THE ARTERIAL WALL

In this model, the inception and growth of the IA is assumed to be a consequence of the growth and remodelling of the material constituents of the artery. The principal of stationary potential energy governs the steady deformation of the arterial wall. For mechanical equilibrium of the system, it requires that the first variation of the total potential energy vanishes (Holzapfel, 2000; Bower, 2010):

$$\delta\Pi_{\text{int}} - \delta\Pi_{\text{ext}} = 0 \quad (5.9)$$

where $\delta\Pi_{\text{int}}$ represents the variation of the internal potential energy stored in the arterial wall, whilst $\delta\Pi_{\text{ext}}$ represents the variation of the external potential energy caused by the normal pressure acting on the artery. To evaluate the steady deformation of the arterial wall, $\delta\Pi_{\text{int}}$ must be computed. The stored internal potential

energy can be expressed in the form of the SEFs of the arterial constituents. Given that the membrane is relatively thin, the area elements as well as the virtual displacement field of the upper and lower surfaces are approximated to be equal to those of the midplane. So Eq. 5.9 can be written as:

$$\int_V \delta\Psi dV - \int_S p(\hat{\mathbf{a}}_3 \cdot \delta\mathbf{u}) dS = 0 \quad (5.10)$$

where S is the portion of the boundary surface on which the internal pressure p is applied and $dS = |\mathbf{a}_1 \times \mathbf{a}_2| d\theta_1 d\theta_2$. Ψ is the SEF per unit volume, $\hat{\mathbf{a}}_3$ is unit normal vector of the deformed midplane and $\hat{\mathbf{a}}_3 = (\mathbf{a}_1 \times \mathbf{a}_2)/|\mathbf{a}_1 \times \mathbf{a}_2|$, $\mathbf{u}$ is the displacement field of the midplane and $\mathbf{u} = u_i \mathbf{A}_i$. The assumption that the strain field is uniform through the thickness of the arterial wall equating that of the midplane implies the SEF Ψ is constant in each layer along the direction of $\hat{\mathbf{a}}_3$. This converts the volume integral in Eq. 5.10 into a surface integral. Substituting these equations into Eq. 5.10 enables an immediate integration yielding:

$$\int_0^{2\pi R} \int_0^{L_1} [H_M \delta\Psi_M + H_A \delta\Psi_A - p(\mathbf{a}_1 \times \mathbf{a}_2) \cdot \delta u_i \mathbf{A}_i] d\theta_1 d\theta_2 = 0 \quad (5.11)$$

where again H_M and H_A are the thicknesses of the media and adventitia layers respectively, and $H_M + H_A = H$. Ψ_M and Ψ_A are the SEFs per unit volume in the media and adventitia layers.

5.4 STRAIN ENERGY FUNCTIONS FOR THE ANEURYSMAL TISSUES

Appropriate functional forms for the spatially and temporally heterogeneous strain energy functions (SEFs) for the media Ψ_M , and the adventitia Ψ_A need to be specified. Structurally, the arterial wall is modelled as a two-layered, non-linear cylindrical membrane. The inner layer models the mechanical response of the medial elastinous constituents (ground substance, elastic fibres and passive VSMCs) and two sets of collagen fibres helically wound around the artery at an angle of γ_{M_p} to circumferential axis. The outer layer models the mechanical response of the adventitia, which comprises a small amount of elastinous constituents and two sets of helically wound collagen fibres oriented at an angle of γ_{A_p} to the circumferential axis. Here p can be either '+' or '-', denoting the positive or negative pitch of the collagen fibre γ_{J_p} relative to the circumferential axis of the unloaded artery, where the

subscript J denotes either the media M or the adventitia layer A . Hence $\gamma_{M+} = +\gamma_M$, $\gamma_{M-} = -\gamma_M$ and $\gamma_{A+} = +\gamma_A$, $\gamma_{A-} = -\gamma_A$. Two sets of *additional protective collagen fibres* helically wound around the artery at an angle of γ_{S_p} are added onto the adventitia layer to simulate the role of the adventitia as a protective sheath to prevent the over-dilation of the artery, where $\gamma_{S+} = +\gamma_S$, $\gamma_{S-} = -\gamma_S$. Fig. 5.3 illustrates the orientations of the collagen fibres in the media and adventitia layers. By implementing the 1D model in this way, we can minimise the change to the original model while being able to examine the functional role of the adventitia as a protective sheath on the aneurysm growth.

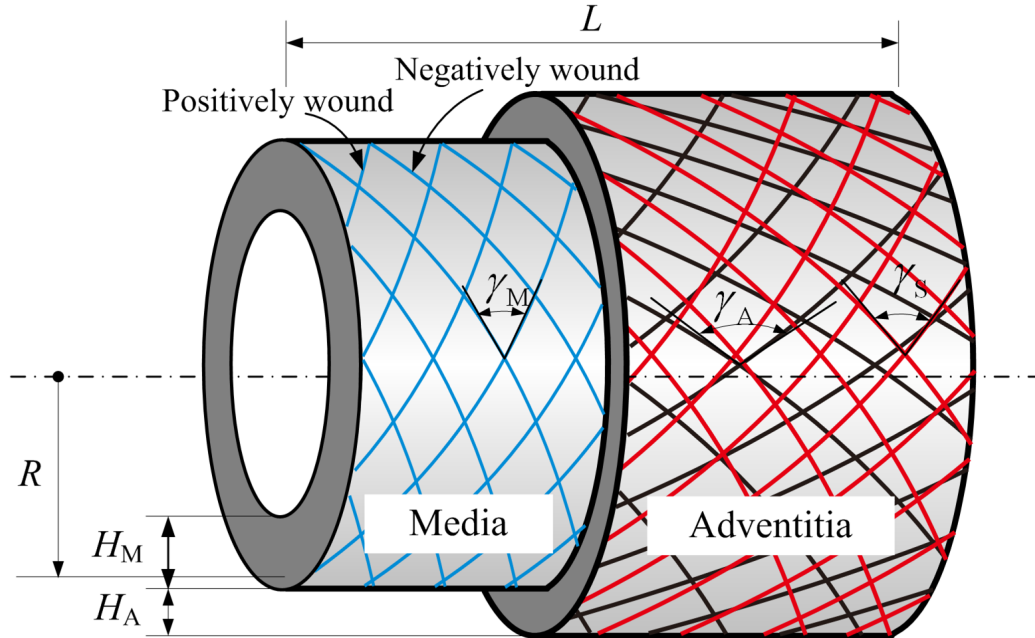


Figure 5.3: Illustration of the orientation of the collagen fibres in the media and adventitia layers. Blue: medial normal collagen; black: adventitial normal collagens; red: adventitial protective collagens. Fibres positively and negatively wound around the artery are both shown.

The total mechanical response of the artery is modelled as the sum of the mechanical responses of each layer, which is considered to be the sum of the contributions from the individual constituents in the layer. Three different SEFs are used to model the mechanical contributions of the elastinous and collagenous constituents respectively. Spatially and temporally dependent functions are introduced for the concentration of these constituents, as well as the configurations in which the collagen fibres are recruited to load bearing, i.e. the recruitment stretches. The

dimensionless concentration functions of the constituents define the ratio of the mass density of a constituent at time t to its mass density at time $t = 0$. This enables to model the growth and atrophy of the constituents. We have utilised the concept of recruitment stretch many time is Chapter 4. However, in the 3D environment, it needs to be redefined: we define the recruitment stretch function as the factor by which the tissue must be stretched relative to the unloaded configuration, *in the direction of a collagen fibre*, for the fibre to begin to be recruited for load bearing. Remodelling the recruitment stretches enables us to model the remodelling of the collagenous constituents during aneurysm development. To model the mechanical response of different constituents, the following is applied:

1. for the elastinous constituents in the media and adventitia, classical neo-Hookean SEFs are used (Watton et al., 2009c). These SEFs are multiplied by a normalised spatially and temporally dependent concentration function $m^E(\theta_1, \theta_2, t)$, where initially $m^E(\theta_1, \theta_2, t = 0) = 1$. This function is employed to prescribe the degradation of the elastinous constituents.
2. for the collagen fibres that are included in the old model (here denoted as the normal collagens) in the media and adventitia layers, a highly nonlinear SEF is used (Holzapfel et al., 2000). Fields of spatially and temporally dependent fibre concentration variables $m_{J_p}^C(\theta_1, \theta_2, t)$ as well as fibre recruitment stretches $\lambda_{J_p}^R(\theta_1, \theta_2, t)$ are defined throughout the midplane of the arterial wall, where initially $m_{J_p}^C(\theta_1, \theta_2, t = 0) = 1$. Again, $p = \pm$ so $m_{J_+}^C(\theta_1, \theta_2, t)$ and $m_{J_-}^C(\theta_1, \theta_2, t)$ are the concentration variables and $\lambda_{J_+}^R(\theta_1, \theta_2, t)$ and $\lambda_{J_-}^R(\theta_1, \theta_2, t)$ are the recruitment stretches of the positive and negative wound collagens fibres in the J layer respectively.
3. for the added additional protective collagen fibres, the approach proposed by Hill et al. (2012) is adopted and modified (which is also introduced in the 1D model in Chapter 4, however, collagen orientation needs to be incorporated now). The SEF of an individual collagen fibre Ψ_S^{C*} is assumed to have a simple quadratic functional form:

$$\Psi_{S_p}^{C*} = K_S^C (E_{S_p}^C)^2 \quad (5.12)$$

where K_S^C is the collagen material constant and $E_{S_p}^C$ is the Green-Lagrange (GL) strains in the collagen fibres with pitch p defined relative to their own

natural reference configurations. The highly nonlinear mechanical response of the collagen ensemble is considered to be a consequence of the gradual recruitment of the fibres during load bearing. The recruitment of collagen fibres is assumed to be in a manner of statistical distribution, represented by the recruitment stretch distribution $Pr(\Lambda_{S_p}^R)$ whose probability density function $f_{\Lambda_{S_p}^R}[\lambda_{S_p}^R(\theta_1, \theta_2, t)]$ is also spatially and temporally dependent. Hence the SEF $\Psi_{S_p}^C$ of all the collagen fibres per unit volume when the stretch of the elastin resolved in the direction of the collagen fibres is λ_{S_p} can be determined by integrating the SEF $\Psi_{S_p}^{C*}$ of a single fibre with respect to the proportion of the recruited fibres, multiplied by a normalised spatially and temporally dependent collagen concentration function $m_{S_p}^C(\theta_1, \theta_2, t)$, where initially $m_{S_p}^C(\theta_1, \theta_2, t = 0) = 1$:

$$\Psi_{S_p}^C(\lambda_{S_p}^C) = m_{S_p}^C \int_1^{\lambda_{S_p}} \Psi_{S_p}^{C*}(E_{S_p}^C) f_{\Lambda_{S_p}^R}(\lambda_{S_p}^R) d\lambda_{S_p}^R \quad (5.13)$$

where we have

$$\lambda_{S_p}^C = \frac{\lambda_{S_p}}{\lambda_{S_p}^R} \quad (5.14)$$

The PDF of the collagen recruitment stretch distribution $f_{\Lambda_{S_p}^R}(\lambda_{S_p}^R)$ is still assumed to be a piecewise triangular function, hence $\Psi_{S_p}^{C*}$ is also a piecewise function.

Consequently, the SEF for the media layer is:

$$\Psi_M = m^E K_M^E (E_{11} + E_{22} + E_{33}) + \sum_{p=\pm, E_{M_p}^C > 0} m_{M_p}^C K_M^C \{\exp[A^C (E_{M_p}^C)^2] - 1\} \quad (5.15)$$

and the SEF for the adventitia layer is:

$$\Psi_A = m^E K_A^E (E_{11} + E_{22} + E_{33}) + \sum_{p=\pm, E_{A_p}^C > 0} m_{A_p}^C K_A^C \{\exp[A^C (E_{A_p}^C)^2] - 1\} + \sum_{p=\pm, E_{S_p}^C > 0} \Psi_{S_p}^C(\lambda_{S_p}^C) \quad (5.16)$$

where K_J^E is the material parameters for the elastinous constituents and K_J^C and A^C are parameters related to the normal collagen fabrics, where $J = M$ represents the media and $J = A$ represents the adventitia. The GL strains of the elastin, i.e. E_{11}, E_{22} and E_{33} are defined relative to the unloaded configuration. They represent strains in the axial, circumferential as well as radial directions respectively in the initial cylindrical configuration. The GL strains in the collagen fibres are denoted

by $E_{J_p}^C(\theta_1, \theta_2, t)$ and $E_{S_p}^C(\theta_1, \theta_2, t)$. They are defined relative to the configuration in which the collagen fibres are recruited to load bearing. More specifically, the GL strains $E_{J_p}^C$ and $E_{S_p}^C$ of the collagen fibres are a function of the GL strains of the elastin resolved in the directions of the collagen fibres, denoted as E_{J_p} and E_{S_p} , and can be computed from the components of the GL strain tensor:

$$E_{J_p} = E_{11} \sin^2 \gamma_{J_p} + E_{22} \cos^2 \gamma_{J_p} + 2E_{12} \sin \gamma_{J_p} \cos \gamma_{J_p} \quad (5.17a)$$

$$E_{S_p} = E_{11} \sin^2 \gamma_{S_p} + E_{22} \cos^2 \gamma_{S_p} + 2E_{12} \sin \gamma_{S_p} \cos \gamma_{S_p} \quad (5.17b)$$

They are related to the elasin stretches resolved in the directions of the collagen fibres λ_{J_p} and λ_{S_p} respectively by:

$$E_{J_p} = ((\lambda_{J_p})^2 - 1)/2 \quad \text{and} \quad E_{S_p} = ((\lambda_{S_p})^2 - 1)/2 \quad (5.18)$$

Hence, $E_{J_p}^C$ and $E_{S_p}^C$ are calculated by:

$$E_{J_p}^C = \frac{E_{J_p} - E_{J_p}^R}{1 + 2E_{J_p}^R} \quad \text{and} \quad E_{S_p}^C = \frac{E_{S_p} - E_{S_p}^R}{1 + 2E_{S_p}^R} \quad (5.19)$$

where

$$E_{J_p}^R = ((\lambda_{J_p}^R)^2 - 1)/2 \quad \text{and} \quad E_{S_p}^R = ((\lambda_{S_p}^R)^2 - 1)/2 \quad (5.20)$$

can be interpreted as the recruitment strains and $\lambda_{J_p}^R(\theta_1, \theta_2, t)$ and $\lambda_{S_p}^R(\theta_1, \theta_2, t)$ are the recruitment stretch functions.

In addition, to calculate the average stresses in the wall based on the remodelled wall thickness, we recall that the 2nd Piola-Kirchhoff (PK) stress tensor $\mathbf{S}$ is energy conjugate to the GL strain tensor $\mathbf{E}$. Hence the average 2nd PK stresses S_{ij} in the arterial wall can be computed by taking the partial differentiation of the SEF of the entire wall with respect to the components of the GL strain tensor E_{ij} .

$$S_{ij} = \frac{1}{H_{rem}} \frac{\partial(H_M \Psi_M + H_A \Psi_A)}{\partial E_{ij}} \quad (5.21)$$

where H_{rem} is the remodelled thickness inferred from the volumetric change of the wall (see Appendix B). Also notice that as the SEFs in Eq. 5.15 and Eq. 5.16 are expressed in terms of not only the GL strains of the elasin, but also the GL strains of collagen fibres $E_{J_p}^C$, as well as the stretches of the additional collagen fibres $\lambda_{J_p}^C$, hence variations of these variables are also needed and the chain rule needs to be applied. In addition, since the recruitment stretch distribution of adventitial protective collagens is a piecewise function, each components of the 2nd PK stress tensor will also be piecewise.

The average Cauchy stress in the wall based on the remodelled thickness is computed by:

$$\sigma_{ij} = J^{-1} F_{ik} S_{kl} F_{jl} \quad (5.22)$$

where $\mathbf{F}$ is the deformation gradient tensor and $J = \det(\mathbf{F})$. In our case where membrane incompressibility is adopted, $J = 1$.

Lastly, we note that during aneurysm evolution, although the orientations of the collagen fibres (i.e. the γ_{J_p} and γ_{S_p}) distort with the material coordinates, these orientations with respect to the unloaded reference configuration are constant. In other words, in our model the reorientation of the collagen fibres as a result of the tissue growth and remodelling during aneurysm evolution is not modelled.

5.5 GEOMETRY, PHYSIOLOGICAL DATA AND MATERIAL PARAMETERS

In the initial systolic configuration, the modelled artery has a radius of r_s , an axial pre-stretch of λ_z and a circumferential stretch of λ_0 . The additional adventitia collagen acts as a protective sheath bearing no load and the elastinous constituents are assumed to bear 80% of the total load in the physiological configuration. The elastinous response of the adventitia is assumed to be an order of magnitude weaker than that of the media, i.e. $K_A^E = K_M^E / 10$, and the ratio of the medial and adventitial collagen material parameters is specified to be $K_A^C = K_M^C / 4$ (Watton and Ventikos, 2009). Values of K_M^E , K_M^C , A^C are also obtained from the literature (Watton and Ventikos, 2009). Finally the value for the additional protective collagen K_P^C is taken from the 1D model with some rounding. A few simulations are also run to make sure this value of K_P^C will not over-stiffen the adventitia, i.e. IAs can still evolve with realistic sizes.

To keep the model simple and minimise the change to the original model, we still give single and *constant* value of attachment stretch to the normal medial and adventitial collagens instead of variable distribution. The magnitude of the attachment stretch λ_{AT}^C is defined to be the stretch in the medial collagen fibres at systole at $t = 0$. We note that in the initial reference configuration when $t = 0$, the arterial geometry is still cylindrical. Hence the initial values of the variables associated with the collagen fibres are independent on their pitches, for example, $\lambda_{M+}^C|_{t=0} = \lambda_{M-}^C|_{t=0}$. For the healthy artery, the medial collagen fibres do not bear

significant load until the upper end of physiological pressures. The value of λ_{AT}^C is taken directly from the literature. It is computed by assuming that the medial collagen fibres which are predominantly orientated circumferentially are recruited to load bearing at diastole, i.e. when the circumferential stretch is λ_0/λ_D^S , where λ_D^S denotes the ratio of systolic to diastolic diameters. This implies an initial value $\lambda_M^R|_{t=0}$ for the medial recruitment stretches $\lambda_{M_p}^R$ where $p = \pm$:

$$\lambda_M^R|_{t=0} = \lambda_{M_p}^R|_{t=0} = \sqrt{(\lambda_0/\lambda_D^S)^2 \cos^2 \gamma_{M_p} + (\lambda_z)^2 \sin^2 \gamma_{M_p}} \quad (5.23)$$

Consequently, the attachment stretch λ_{AT}^C , which is defined to be equivalent to the stretch of the medial collagen fibres at systole at $t = 0$, i.e. $\lambda_{M_p}^C|_{t=0}$, can be computed by:

$$\lambda_{AT}^C = \lambda_{M_p}^C|_{t=0} = (\sqrt{(\lambda_0)^2 \cos^2 \gamma_{M_p} + (\lambda_z)^2 \sin^2 \gamma_{M_p}}) / \lambda_M^R|_{t=0} \quad (5.24)$$

Finally, the initial value of the recruitment stretch of the normal adventitial collagen fibres $\lambda_A^R|_{t=0}$ is determined so that the stretch of the adventitial collagen fibres at systole at $t = 0$ equals its attachment stretch, i.e.

$$\lambda_A^R|_{t=0} = \lambda_{A_p}^R|_{t=0} = (\sqrt{(\lambda_0)^2 \cos^2 \gamma_{A_p} + (\lambda_z)^2 \sin^2 \gamma_{A_p}}) / \lambda_{AT}^C \quad (5.25)$$

As for the additional adventitial protective collagen fibres, triangular distributions of attachment stretches and recruitment stretches from the 1D model are used. Since these fibres are assumed to be deposited crimpedly and bear no load in the initial systolic configuration, values of the minimum, maximum and mode attachment stretches are set to be no more than 1. Initial values of the attachment stretches are assumed to be $\lambda_S^{AT}|_{t=0}^{min} = 0.9$, $\lambda_S^{AT}|_{t=0}^{max} = 1.0$ and $\lambda_S^{AT}|_{t=0}^{mod} = 0.95$, i.e. a symmetric distribution independent on collagen pitches. If the artery further dilates, these additional collagen fibres will be recruited to load bearing. Hence their mechanical role is that of a protective sheath. Here we note that being different from the normal collagen fibres, the attachment stretch distribution of these additional collagen fibres are assumed to adapt temporally during aneurysm growth. Details about the use of temporal adaption of the attachment stretch distribution to represent the change of the mechanical role of the collagen fibres are introduced in Sec. 5.6. The initial values of the salient points $\lambda_S^R|_{t=0}$ of the distribution of recruitment

stretches can also be determined by:

$$\lambda_S^R|_{t=0}^{min} = \lambda_{S_p}^R|_{t=0}^{min} = (\sqrt{(\lambda_0)^2 \cos^2 \gamma_{S_p} + (\lambda_z)^2 \sin^2 \gamma_{S_p}}) / \lambda_S^{AT}|_{t=0}^{max} \quad (5.26a)$$

$$\lambda_S^R|_{t=0}^{max} = \lambda_{S_p}^R|_{t=0}^{max} = (\sqrt{(\lambda_0)^2 \cos^2 \gamma_{S_p} + (\lambda_z)^2 \sin^2 \gamma_{S_p}}) / \lambda_S^{AT}|_{t=0}^{min} \quad (5.26b)$$

$$\lambda_S^R|_{t=0}^{mod} = \lambda_{S_p}^R|_{t=0}^{mod} = (\sqrt{(\lambda_0)^2 \cos^2 \gamma_{S_p} + (\lambda_z)^2 \sin^2 \gamma_{S_p}}) / \lambda_S^{AT}|_{t=0}^{mod} \quad (5.26c)$$

Table 5.1 summarised the arterial geometry and physiological data, as well as the material parameters for the medial and adventitial constituents, which serve the basis for this 3D model.

5.6 GROWTH AND REMODELLING OF THE ARTERIAL TISSUES

In this chapter the framework applied to model the growth and remodelling of the arterial tissue including the adaption of the collagen microstructure is explicitly detailed.

5.6.1 Degradation of the elastinous constituents

As we discussed in Sec. 4.5, in a healthy artery, elastins are known to be one of the most stable proteins in the body with a half-life approximately 40–70 years (Langille, 1993; Martyn and Greenwald, 1997; Franklin, 2006), whereas collagen fibres are always in a state of continual deposition by the cells and degradation by the collagenase, with a much shorter half-life of only 2–3 months (Langille, 1993). A saccular IA usually appears as a thin collagenous structure in the aneurysm dome, whilst the parent artery still has a well-defined structure with an intact medial layer. To be more specific, loss of internal elastic lamina, apoptosis of vascular smooth muscle cells (VSMCs), fragmentation of the elastic fibres, as well as highly organised collagen fibres have been observed (Canham et al., 1991). There is also a relatively abrupt transition from healthy tissue to aneurysmal tissue in the neck region of the aneurysm (Watton and Ventikos, 2009).

Although it is thought and widely accepted that the inception and development of the aneurysm is strongly related to the complex haemodynamic environment at the aneurysm site, in this 3D solid structural model, we still prescribe a loss of the

Table 5.1: Geometry, physiological data and some parameters used in this model

Radii			
Reference configuration	R		1.50 mm
At systole	r_S		1.87 mm
At diastole	r_D		1.70 mm
Wall thickness			
Total	H		0.375 mm
Media	H_M		0.25 mm
Adventitia	H_A		0.125 mm
Fibre orientation			
Media normal	γ_M		30°
Adventitia normal	γ_A		60°
Adventitia protective	γ_S		45°
Applied pressure, kinematics			
Systolic pressure	p		16 kPa
Axial pre-stretch	λ_z		1.3
Ratio of systolic to diastolic circumferential diameters	λ_D^S		1.1
Attachment stretches ($t = 0$)			
Medial normal	λ_{AT}^C		1.07
Adventitial normal	λ_{AT}^C		1.07
Adventitial protective minimum	$\lambda_{S AT}^{min}$		0.90
Adventitial protective maximum	$\lambda_{S AT}^{max}$		1.00
Adventitial protective mode	$\lambda_{S AT}^{mod}$		0.95
Recruitment stretches ($t = 0$)			
Medial normal	$\lambda_{M_p}^R$		1.18
Adventitial normal	$\lambda_{A_p}^R$		1.20
Adventitial protective minimum	$\lambda_{S_p}^R ^{min}$		1.28
Adventitial protective maximum	$\lambda_{S_p}^R ^{max}$		1.42
Adventitial protective mode	$\lambda_{S_p}^R ^{mod}$		1.34
Modulus parameters			
Medial elastin	K_M^E		133.8 kPa
Adventitial elastin	K_A^E		13.38 kPa
Medial normal collagen	K_M^C		1.964 kPa
Adventitial normal collagen	K_A^C		0.491 kPa
Adventitia protective collagen	K_S^C		8 MPa
Normal collagen exponential constant	A^C		60

elastinous constituents to initiate an aneurysm on the artery and impel its following growth. The degradation of the elastinous constituents are prescribed to occur within a circular patch in the centre of the Lagrangian computational domain. The circular patch is split into an inner circle of radius R_i^E and a thin outer concentric annulus with an outer radius R_o^E (see Fig. 5.4). We prescribe the elastin degradation within the inner circle and assume that there is no degradation outside the outer circular annulus. The elastin concentration is linearly interpolated using radial splines between its values on the inner and outer circular annuli so that it is a continuous function throughout the domain. Within the central circular patch, the concentration of elastin is defined as:

$$m^E(\theta_1, \theta_2, t) = 1 - (1 - m_{MIN}^E(t)) \times \left\{ \exp\left[-\omega_1 \left(\frac{\theta_1 - L_1/2}{L_1/2}\right)^2\right] \cdot \exp\left[-\omega_2 \left(\frac{\theta_2 - L_2/2}{L_2/2}\right)^2\right] \right\} \quad (5.27)$$

where $\theta_1 \in [0, L_1]$, $\theta_2 \in [0, L_2]$ and $(\theta_1 - L_1/2)^2 + (\theta_2 - L_1/2)^2 \leq R_E^i$. Here θ_1 and θ_2 are the Lagrangian coordinates of the computational domain. The parameters ω_1 and ω_2 control the degree of localisation of the degradation function; values used in the literature are adopted $\omega_1 = \omega_2 = 1$ (Watton and Ventiokos, 2009). m_{MIN}^E represents the minimum concentration of elastin located at the centre of the inner circle: $(\theta_1, \theta_2) = (L_1/2, L_2/2)$. The concentration of elastin at the point $(L_1/2, L_2/2)$ at time T is specified and denoted as m_T^E . It is assumed that the minimum concentration m_{MIN}^E decays exponentially at $0 \leq t < T$ and is constant at $t \geq T$, i.e.:

$$m_{MIN}^E(t) = \begin{cases} (m_T^E)^{(t/T)} & 0 \leq t < T \\ m_T^E & t \geq T \end{cases} \quad (5.28)$$

Note that we have $m_{MIN}^E(t = 0) = 1$. In the 3D model presented in this chapter, we use $m_T^E = 0.1$ and $T = 10$ years.

Now for all θ_1 and θ_2 satisfying $\sqrt{(\theta_1 - L_1/2)^2 + (\theta_2 - L_1/2)^2} \geq R_E^o$, it is specified that $m^E(\theta_1, \theta_2, t) = 1$. For the domain between the inner and outer annulus, the elastin concentration is linearly interpolated between its values on the inner radius to its values on the outer radius using radial splines with origin $(\theta_1, \theta_2) = (L_1/2, L_2/2)$.

5.6.2 Growth and atrophy of the collagen fabric

As discussed in Sec. 1.4, fibroblast cells adhere to the ECM via specialised cell surface receptors, in particular integrins (Wang and Thampatty, 2006). These integrins

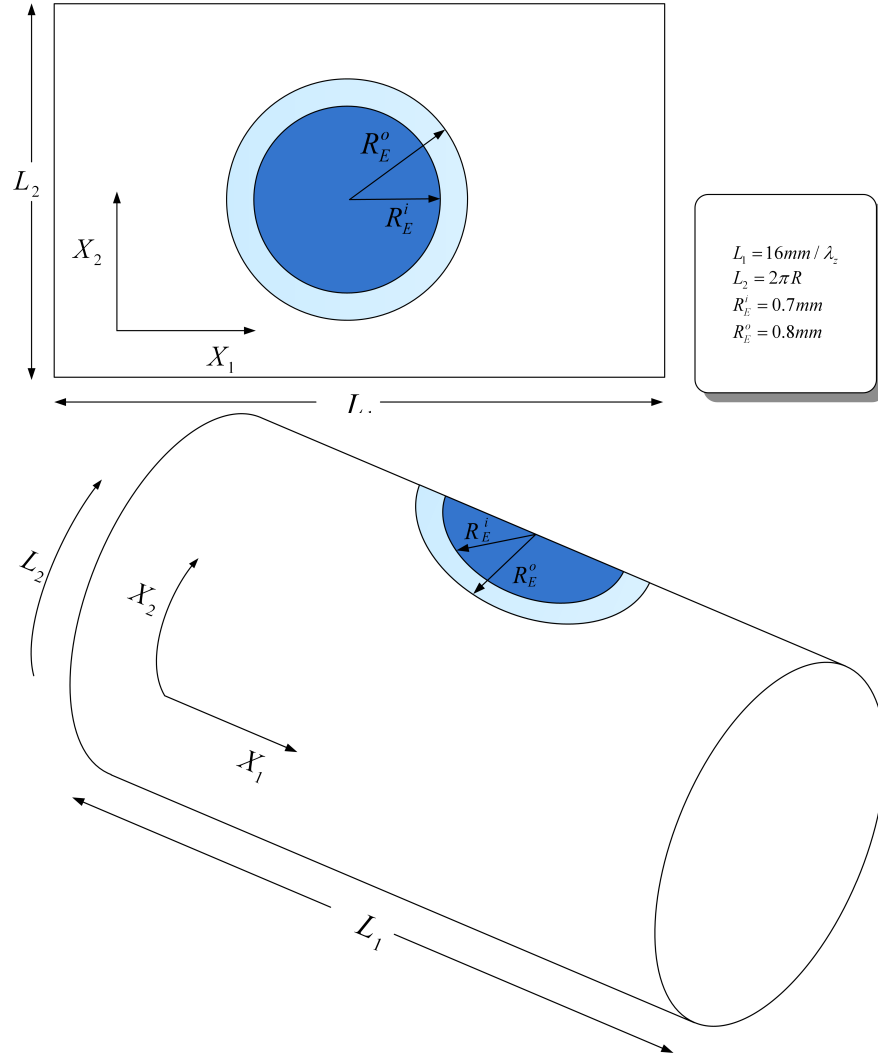


Figure 5.4: The elastinous constituents are prescribed to degrade in a circular patch in the central region of the computational domain to initiate the development of an IA. The degradation within the inner circular patch of radius R_E^i is prescribed. The degradation between the inner and outer circular annulus is linearly interpolated using radial splines between the values on the inner annulus and the outer annulus where no degradation occurs. No degradation of the elastinous constituents occurs throughout the rest of the computational domain (adapted from Watton and Venti-
 tikos (2009)).

physically link the ECM to the cytoskeleton of the fibroblasts, and transduce exterior mechanical signals into the cells (Gupta and Grande-Allen, 2006). Experimental evidences suggest that these integrins act as mechanical stretch sensors and enable the fibroblasts to sense changes in the mechanical strains applied to them (Chiquet et al., 2003, 2009). In case of increased stretch, for example, fibroblasts attempt to reduce their stretches and reach new levels of equilibrium by restructuring their cytoskeleton and contracting the ECM that they are attached to. In other words, fibroblasts reconfigure their natural reference configurations in response of increased stretch (Watton and Ventikos, 2009).

In addition, fibroblasts also deposit collagen fabrics and secrete proteases to degrade them. Hence the growth/atrophy of the collagens is directly related to the functionality of the fibroblast cells. In this study we use different modelling approaches to simulate the growth/atrophy of the normal collagen fibres and the additional protective collagen fibres. For normal collagen fibres in the media and adventitia layer, the approach proposed by Watton (2002) is utilised. Here we first have a general review of this approach. In this approach, we assume that

1. the fibroblasts' rates of depositing and degrading the collagenous constituent are proportional to the amount of fibroblast cells in the arterial wall, denoted as $N_{J_p}^F$ and the strains of fibroblast cells, denoted as $E_{J_p}^F$.
2. $N_{J_p}^F$ is proportional to the mass concentration of the collagenous constituents, i.e. $N_{J_p}^F = \xi_0 m_{J_p}^C$, $\xi_0 > 0$.
3. the local reference configuration of the fibroblast cell is identical to that of the collagen fabric which it is maintaining. Under this assumption, the GL strain of the fibroblasts, denoted as $E_{J_p}^F$, is equal to the GL strain of the collagen fibre, i.e. $E_{J_p}^F = E_{J_p}^C$.

These assumptions imply that the rate of change of the collagen concentration $m_{J_p}^C$ can be expressed in terms of the current fibre concentration:

$$\begin{aligned}
 \frac{\partial m_{J_p}^C}{\partial t} &= N_{J_p}^F \mathcal{F}_S(E_{J_p}^F) - N_{J_p}^F \mathcal{F}_D(E_{J_p}^F) \\
 &= m_{J_p}^C \xi_0 [\mathcal{F}_S(E_{J_p}^C) - \mathcal{F}_D(E_{J_p}^C)] \\
 &= m_{J_p}^C \mathcal{F}_G(E_{J_p}^C)
 \end{aligned} \tag{5.29}$$

where $\mathcal{F}_G(E_{J_p}^C) = \xi_0[\mathcal{F}_S(E_{J_p}^C) - \mathcal{F}_D(E_{J_p}^C)]$, $\mathcal{F}_S(E_{J_p}^F)$ is a function to depict how collagen synthesis is related to the strain of the fibroblast cell, and similarly $\mathcal{F}_D(E_{J_p}^F)$ is a function to depict how the production of matrix metalloproteases (MMP) is related to the stretch of the fibroblast cell (Watton and Ventikos, 2009). Now the functional form of $\mathcal{F}_G(E_{J_p}^C)$ needs to be determined as it is currently unknown. However, when the collagen fabric is in homeostasis, we have $E_{J_p}^C = E_{AT}^C$, and the secretion of ECM is balanced by the degradation and there is no change in concentration. Hence if $E_{J_p}^C = E_{AT}^C$ it is required that $\mathcal{F}_G(E_{J_p}^C) = 0$. In addition, stretching the ECM results in an up-regulation of ECM protein expression and a down-regulation of collagenase expression. Conversely, relaxing the ECM can trigger a reversed pattern of protein expression, i.e. down regulation of ECM protein expression and up-regulation of collagenase expression Chiquet et al. (2003). Although we do not explicitly model protein synthesis and enzymatic degradation of the ECM, the net result is to stimulate upregulation/downregulation of the ECM proteins (Watton and Ventikos, 2009). The simplest functional form for $\mathcal{F}_G$ that satisfies these requirements is linear, i.e.:

$$\mathcal{F}_G = \beta(E_{J_p}^C - E_{AT}^C)/E_{AT}^C \quad (5.30)$$

Substituting Eq. 5.30 into 5.29, we use the following equation for evolving the collagen fibre concentration:

$$\frac{\partial m_{J_p}^C}{\partial t} = \beta m_{J_p}^C \frac{E_{J_p}^C - E_{AT}^C}{E_{AT}^C}, \quad (5.31)$$

where β is a phenomenological growth parameter that relates to the rate at which the fibroblasts increase or decrease the mass of the collagenous constituents in response to deviations of stretch from normotensive levels (Watton and Ventikos, 2009). It can be numerically determined so that the enlargement of the geometry is physiologically consistent over a typical timescale of aneurysm growth (Watton et al., 2004; Watton and Hill, 2009). In this study, we consider $\beta = 0.1$ for the cases where the additional protective collagen is absent so that in that particular simulation case the aneurysms can enlarge to a realistic size at the end of the simulation (10 years). However, some IAs may grow very fast (Doenitz et al., 2010). We also note that we increase the value of β by a factor of 100 in the last simulation year, otherwise the aneurysm will keep enlarging without stabilisation and the computation will eventually collapse.

Above is the general approach utilised to model the evolution of mass concentration of the normal collagens in the arterial wall when the additional protective

collagen is absent. However, we note that in the simulated cases where the additional protective collagen fibre is present, we actually decrease the mass concentration of the normal medial and adventitial collagen fibres to model gross effect of collagen atrophy, using the exact same method that was introduced in Sec. 5.6.1 to degrade the elastin fibres. The reason for doing this is to allow the additional collagen fibres to bear most of the load in the aneurysmal artery to show the conversion of its mechanical role from a protective sheath to the main load bearer.

For the additional protective collagen fibres, in order to investigate the influence of adapting the attachment stretch distribution on the growth of an aneurysm, we eliminate the contribution of load bearing from the increased mass concentration of these fibres by simply assuming that the mass concentration $m_{S_p}^C$ is constant during aneurysm growth, i.e.:

$$m_{S_p}^C(t) = m_{S_p}^C(0) = 1 \quad (5.32)$$

To simplify the presentation of the results, we define the average fibre concentration m^C of the medial and adventitial layers (excluding the additional protective collagen fibres as their mass concentration is constantly unity), where:

$$m^C = \frac{1}{H} \left(H_M \frac{(m_{M_+}^C + m_{M_-}^C)}{2} + H_A \frac{(m_{A_+}^C + m_{A_-}^C)}{2} \right) \quad (5.33)$$

5.6.3 Collagen remodelling

We first briefly revisit the concepts of the recruitment stretch and attachment stretch distributions. For the understanding of these concepts as well as the remodelling of collagen natural reference configurations, it is sufficient to visualise the idea with regard to a uniaxial stretching of a strip of arterial tissue in which the collagen fibres are arranged parallel to the direction of tension (Watton and Ventikos, 2009).

The stretches in the collagen fibres are defined with respect to the reference configurations in which the fibres are recruited to load bearing whilst the stretch in the elastin is always defined with respect to the initial unloaded reference configuration. Now consider a strip of tissue with collagen fibres aligned along its length. These collagen fibres are recruited to load bearing when they are fully straightened out. For a single collagen fibre, if it becomes straight when the unstrained tissue is stretched by a factor λ^R , then λ^R is defined as the recruitment stretch of this fibre

and its actual stretch is defined with respect to this recruitment configuration. A simple relationship between the elastin stretch λ and the collagen stretch λ^C exists:

$$\lambda^C = \frac{\lambda}{\lambda^R} \quad (5.34)$$

Given that collagen fibres exhibit different waviness in the tissue, this implies that there should be a distribution of recruitment stretches and a distribution of actual stretches. However, we can still use Eq. 5.34 to represent the relationship between single values of the corresponding collagen recruitment stretches and the actual stretches within the distributions. The significance of Eq. 5.34 is that the recruitment stretch distribution can be remodeled to maintain the actual stretch distribution in the collagen fibres to an equilibrium distribution whilst the stretch in the elastin increases as the tissue is stretched (Watton and Ventikos, 2009).

Collagen fibres are in a continual state of deposition and degradation (Humphrey, 1999). We define the state of stretch distribution in which these fibres are synthesised and attached to the ECM to be the attachment stretch distribution, and denoted as λ_{AT}^C . For more details regarding the recruitment stretch and attachment stretch distributions and their motivations, see Sec. 4.3.

The remodelling of the recruitment stretch distribution is subtle and it may be more helpful to visualise what is occurring on the scale of the collagen fibres using simpler representations. In order to explain the motivation for this concept more clearly, we further simplify the problem in the following illustrative case by assuming that:

1. all the collagen fibres have the same waviness, i.e. the same recruitment and attachment stretches.
2. the state of the stretch with which new fibres are attached to the tissue, i.e. the attachment stretch, is constant.

These are actually the common assumptions that are widely made in the past studies found in the literature (including the old 3D solid aneurysm growth model). Under these assumptions, the recruitment stretch and attachment stretch distributions become single values (or in other words, Dirac delta distributions). Fig. 5.5 illustrates the 1D representation of the effects of fibre deposition and degradation for a tissue that is stretched and held at fixed length whilst remodelling occurs. From

this figure we can see that the gross effect of the continual turnover of collagen fibres that are attached to the matrix with the attachment stretch λ_{AT}^C can be captured by remodelling the recruitment stretch λ^R of the fibre.

In reality, collagen fibres do have different waviness in the unloaded tissue that may follow certain statistical distributions (Rezakhaniha et al., 2012; Schrauwen et al., 2012), which implies distributions of recruitment stretch and attachment stretch of the collagen fibres. These facts must be accounted for when modelling the remodelling of collagen fibres. The turnover of collagen and the consequence of fibre attachment is simulated by proposing remodelling equations that act to maintain the actual stretch distribution of the collagen fibres to the equilibrium distribution. This is achieved by remodelling the reference configurations in which the fibres are recruited to load bearing throughout the arterial domain, i.e. remodelling the fields of recruitment stretches distributions. Triangular distributions are once again used here to represent the recruitment, attachment, and actual stretch distributions for their simple analytical functional form. The simplest way to remodel the triangular recruitment stretch distribution is to remodel the three salient values in the distribution, i.e. the minimum, maximum and mode recruitment stretches $\lambda_{S_p}^R|^{min}$, $\lambda_{S_p}^R|^{max}$ and $\lambda_{S_p}^R|^{mod}$ of the adventitial protective collagens either positively wound ($p = +$) or negatively wound ($p = -$) respectively. Linear differential equations are proposed for the remodelling of the recruitment stretches:

$$\frac{\partial \lambda_{S_p}^R|^{min}}{\partial t} = \alpha \left(\frac{\lambda_{S_p}^C|^{max} - \lambda_S^{AT}|^{max}}{\lambda_S^{AT}|^{max}} \right) \quad (5.35a)$$

$$\frac{\partial \lambda_{S_p}^R|^{max}}{\partial t} = \alpha \left(\frac{\lambda_{S_p}^C|^{min} - \lambda_S^{AT}|^{min}}{\lambda_S^{AT}|^{min}} \right) \quad (5.35b)$$

$$\frac{\partial \lambda_{S_p}^R|^{mod}}{\partial t} = \alpha \left(\frac{\lambda_{S_p}^C|^{mod} - \lambda_S^{AT}|^{mod}}{\lambda_S^{AT}|^{mod}} \right) \quad (5.35c)$$

where again $\lambda_S^{AT}|^{min}$, $\lambda_S^{AT}|^{max}$ and $\lambda_S^{AT}|^{mod}$ are the minimum, maximum and mode attachment stretches of the adventitial protective collagens and $\lambda_{S_p}^C|^{min}$, $\lambda_{S_p}^C|^{max}$ and $\lambda_{S_p}^C|^{mod}$ are their minimum, maximum and mode in vivo stretches. $\alpha > 0$ is the collagen remodelling rate parameter which is numerically determined so that the remodelling rate of the collagen recruitment stretches is physiologically realistic and can correspond to a prescribed half-life of the collagen fibres. α is computed by specifying the kinetics of the amount of collagen laid down in altered configurations and the amount of collagen which remains from the original configuration as

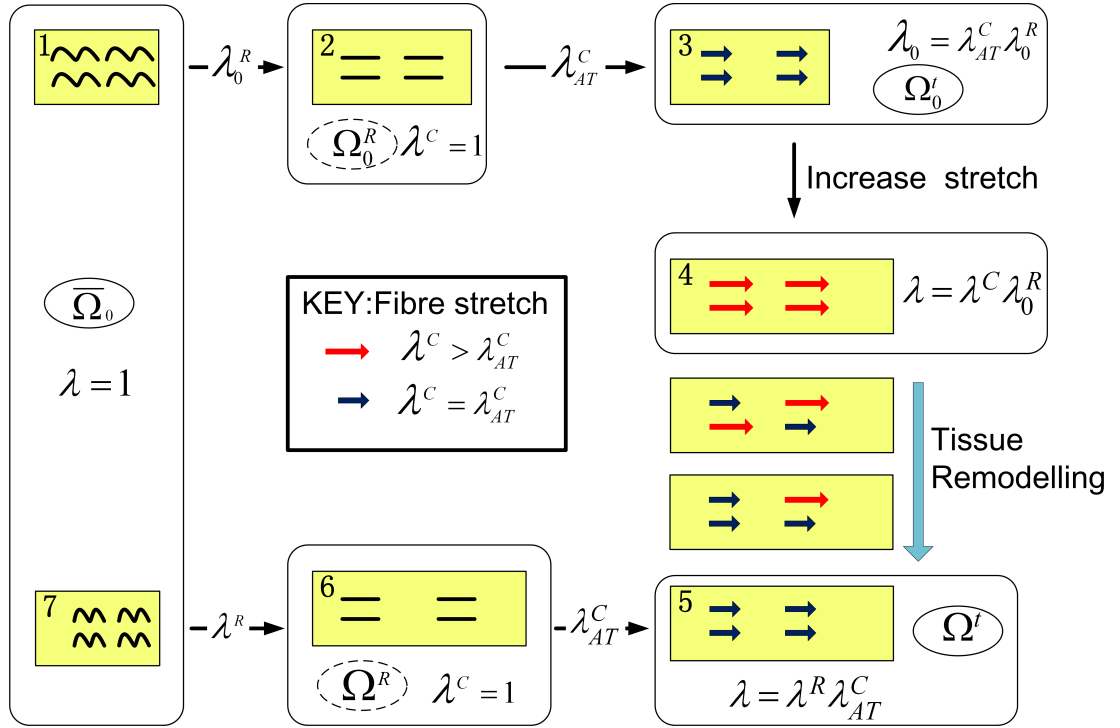


Figure 5.5: Deposition and degradation of the collagen fibres in a tissue that is stretched and held at fixed length. 1. The configuration $\bar{\Omega}_0$ is the undeformed/unloaded reference configuration of the tissue. In this state, the stretch in the tissue is $\lambda = 1$. 2. The initial recruitment configuration Ω_0^R of the collagen fibres. Collagen fibres have straightened out and begin to bear load. 3. The initial loaded configuration Ω_0^t : collagen strain is equal to its equilibrium value λ_{AT}^c . The tissue is currently in homeostasis. New fibres are attached with identical levels of stretch to the tissue as those who decay, thus no change occurs to the gross mechanical properties of the tissue. 4. The tissue is stretched further. The new stretch of the tissue is $\lambda = \lambda^c \lambda_0^R$ where $\lambda^c > \lambda_{AT}^c$. At this state, the collagen fibres are no longer in material equilibrium: subsequent fibre deposition and degradation will result in a change in the configuration of the collagenous tissue. Old fibres are degraded whereas new fibres attach to the tissue with a stretch of λ_{AT}^c , hence the distribution of collagen fibres changes. This process continues to restore the stretches in all the fibres to equilibrium levels. 5. All of the old fibres have been degraded and been replaced by new fibres of stretch λ_{AT}^c . Now the artery reaches a new equilibrium configuration. 6. The new recruitment configuration Ω^R of the collagen fibres following remodelling of the tissue. In this configuration, fibre deposition and degradation continues but no change occurs to the gross mechanical properties of the tissue. 7. If the tissue is presumably contracted back to the reference configuration $\bar{\Omega}_0$, then crimp of the collagen will have increased. Consequently, the factor the tissue must be stretched for the collagens to be recruited to load bearing has increased. Hence the mechanical effects of fibre deposition and degradation in altered configurations can be captured by remodelling the evolution of the recruitment stretch (adapted from Watton and Ventikos (2009)).

functions of time in a half-life model, so that the model itself can correspond to the 1D uni-axial model which is initially in equilibrium and is subject to an increased stretch and held at a new fixed length whilst the collagen remodels to restore its strain by remodelling its recruitment stretch. For more details regarding the determination of this variable see Watton (2002)). Collagen in the healthy arterial wall typically has a half life of 60 days, however turnover rates may increase to 15 days in hypertensive conditions (Nissen et al., 1978) and seem to be typically increased in aneurysmal tissue (Abdul-Hussien et al., 2007; Watton and Ventikos, 2009). In this study, we choose a half-life of one month for the collagens, which corresponds to $\alpha = 0.6 \text{ year}^{-1}$.

As opposed to the common assumption made in the literature where the attachment stretch is constant, in this study we again assume that the collagen attachment stretch distribution can temporally adapt during aneurysm growth. In the normal arteries, the additional adventitial collagen fibres act as a protective sheath, the whole attachment stretch distribution is on the left side of the value of 1, i.e. $\lambda_S^{AT}|^{max} \leq 1$. In the aneurysmal arteries, these collagen fibres are assumed to become the primary load bearer in the artery, hence some newly deposited collagens are borne with stretches greater than unity and we have $\lambda_S^{AT}|^{max} > 1$. This implies the need for an augmenting adaption of the attachment stretch distribution to represent the conversion of the mechanical role of these collagen fibres from a protective sheath to the primary load bearer. Due to the lack of biological information, we analytically prescribe the adaption of the attachment stretch distribution. However, in this study we *only shift the distribution* without any skewing or narrowing. This is done by prescribing the evolution of the maximum attachment stretch $\lambda_S^{AT}|^{max}$. The same approach introduced in Chapter 4.5 is adopted to evolve $\lambda_S^{AT}|^{max}$ based on a simplified Richards' growth function (Richards, 1959). However, a different evolution time is applied:

$$\lambda_S^{AT}|^{max}(t) = \begin{cases} \lambda_S^{AT}|_{t=0}^{max} & t \leq t_1 \\ \lambda_S^{AT}|_{t=0}^{max} + \frac{\lambda_S^{AT}|_{t_2}^{max} - \lambda_S^{AT}|_{t=0}^{max}}{1 + e^{-B(t-t_1-t_2/2)}} & t_1 < t \leq t_2 \\ \lambda_S^{AT}|_{t_2}^{max} & t \geq t_2 \end{cases} \quad (5.36)$$

where t_1 is the time at which the evolution starts and t_2 is the time at which the evolution ends. In this study, we choose $t_1 = 2$ and $t_2 = 4$. B is a parameter which relates to the growth rate of the curve and is numerically determined to be $B = 3$ so that the evolution curve of $\lambda_S^{AT}|^{max}(t)$ is relatively flat near $t = t_1$ and $t = t_2$ while

not too steep in the middle. $\lambda_S^{AT}|_{t_2}^{max}$ is the maximum attachment stretch of the additional adventitial collagens after the entire media layer has been degraded. This variable describes the maximum ability of the fibroblast cells to stretch the newly synthesised collagen fibres and attach them to the extracellular matrix. The value from the 2D model is directly applied to the 3D model, i.e. $\lambda_S^{AT}|_{t_2}^{max} = 1.10$. The minimum and mode attachment stretches $\lambda_S^{AT}|^{min}$ and $\lambda_S^{AT}|^{mod}$ are simply evolved as:

$$\lambda_S^{AT}|^{min}(t) = \lambda_S^{AT}|^{max}(t) - W_S^{AT} \quad (5.37)$$

and

$$\lambda_S^{AT}|^{mod}(t) = \frac{1}{2}[\lambda_S^{AT}|^{min}(t) + \lambda_S^{AT}|^{max}(t)] = \lambda_S^{AT}|^{max}(t) - \frac{W_S^{AT}}{2} \quad (5.38)$$

where W_S^{AT} is the base width of attachment stretch distribution and in this study, we set $W_S^{AT} = 0.1$. The choice of this value is based on the assumption we have made in the study that all new collagen fibres in the aneurysmal tissue are eventually laid down and attached to the extant ECM with stretches. Together the evolution of the three salient variables $\lambda_S^{AT}|^{min}$, $\lambda_S^{AT}|^{max}$ and $\lambda_S^{AT}|^{mod}$ determine the adaption of attachment stretch distribution. Eq. 5.36–5.38 imply a symmetric triangular distribution with constant base width, i.e. the attachment stretch distribution is only shifted without shape change during its evolution. In addition, these equations are not dependent on the orientation of the collagen fibres (the pitch angles), in other words, we consider an isotropic adaption of the additional collagen attachment stretch distribution. However, we note that the adaption of the attachment stretch distribution can be dependent on the Lagrangian coordinates, i.e. it can be *heterogeneous*. More details will be given in Sec. 5.7, where two cases are used to illustrate the differences between a homogeneous adaption (adaption throughout the artery) and a heterogeneous adaption (adaption confined within the aneurysm region).

Above is for the additional adventitial protective collagens. For the normal medial and adventitial collagens, as they have already participated in load bearing in the initial physiological configuration, we simply utilise the existing modelling scheme of Watton and Ventikos (2009): we consider single values of the actual collagen stretch $\lambda_{J_p}^C$, recruitment stretch $\lambda_{J_p}^R$ and attachment stretch λ_{AT}^C instead of distributions. We also assume the attachment stretch λ_{AT}^C is constant during aneurysm

evolution. Under these simplifications, the recruitment stretch is modelled by:

$$\frac{\partial \lambda_{J_p}^R}{\partial t} = \alpha \frac{(E_{J_p}^C - E_{AT}^C)}{E_{AT}^C} \quad (5.39)$$

Finally, we summarise this section here. The growth and remodelling of the arterial tissue during aneurysm evolution has four features within this theoretical framework. Firstly, the degradation of the elastinous constituents is modelled in a specific region to initiate the local inception of an aneurysm and drive its subsequent growth. Secondly, the growth/atrophy of the collagen fibres is simulated by evolving the fibre concentration. Increase of the fibre concentration simulate fibroblasts upregulating collagen synthesis and downregulating enzymes that degrade the collagenous matrix, and vice versa. Thirdly, newly synthesised fibres are assumed to be attached to the ECM in a state of stretch distribution (the attachment stretch distribution) which can vary in altered configurations. Lastly, remodelling the reference configurations in which the collagen fibres are recruited to load bearing by remodelling the recruitment stretch distributions simulates the net effect of fibre deposition and degradation in altered configurations (Watton and Ventikos, 2009).

The sophisticated model is numerically formulated in a finite element method code based on FORTRAN 77. Details about the numerical formation as well as the solutions can be found in Watton (2002) and Watton et al. (2004).

5.7 RESULTS ANALYSIS

We briefly review the framework of this sophisticated 3D model of IA evolution prior to presenting the results. The spatially and temporally dependent SEF for the arterial wall tissue is defined in Eq. 5.15 and 5.16. These functions model the independent reference configurations for the elastins and collagens at each point throughout the domain. The aneurysms develop as the elastins degrade (Eq. 5.27 and 5.28) and the collagens adapt to restore their stretch distributions to the homeostatic distribution (Eq. 5.35a to 5.35c as well as 5.39). In addition, the homeostatic distributions also adapt temporally (Eq. 5.36 to 5.38). The variation of the total potential energy (Eq. 5.9) governs the equilibrium displacement field, and is solved by the finite element method coded in FORTRAN 77.

Four cases of simulations of developing saccular IAs are performed in this study over a time span of 10 years:

1. no additional adventitial protective collagen fibres (i.e. the original model);
2. including the additional protective collagen fibres, but no remodelling of recruitment stretch distribution nor attachment stretch distribution adaption of these fibres;
3. including the additional protective collagen fibres with remodelling of recruitment stretch distribution and adaption of the attachment stretch distribution; adaption of the attachment stretch distribution is throughout the artery;
4. including the additional protective collagen fibres with remodelling of recruitment stretch distribution and adaption of the attachment stretch distribution; adaption of the attachment stretch distribution is confined to the domain of aneurysm growth.

Details about modelling the remodelling of the recruitment stretch distributions and the adaption of the attachment stretch distributions are introduced in Sec. 5.6. We note that in case 1, in order to stabilise the geometry, we increase the value of β in Eq. 5.31 and turn off the value of α in Eq. 5.39 after $t = 9$ years to simulate the upregulation of collagen deposition. Otherwise the aneurysm will continue to enlarge and ultimately the computation will fail to converge. Results including evolutions of the elastin concentration, the elastin GL strains, the collagen GL strains, the collagen concentrations, the remodelled wall thicknesses, as well as the average Cauchy stresses computed based on the remodelled wall thicknesses are illustrated.

Fig. 5.6 illustrates the prescribed degradation of the spatial distribution of the normalised elastin concentration m^E at time $t = 0, 0.5, 1, 1.5, 2$ and 10 years in case 1. The prescribed elastin degradation is identical for the other three cases, hence this figure can be also referred to whilst keeping in mind that the geometry is different. It can be seen that within the aneurysm dome the elastinous constituents have eventually almost completely degraded with only 10% of the original elastinous constituents remain, whilst no degradation has occurred outside the aneurysm dome. A transition region exists where m^E is linearly interpolated between its magnitude in the aneurysm dome to its magnitude in the surrounding tissue.

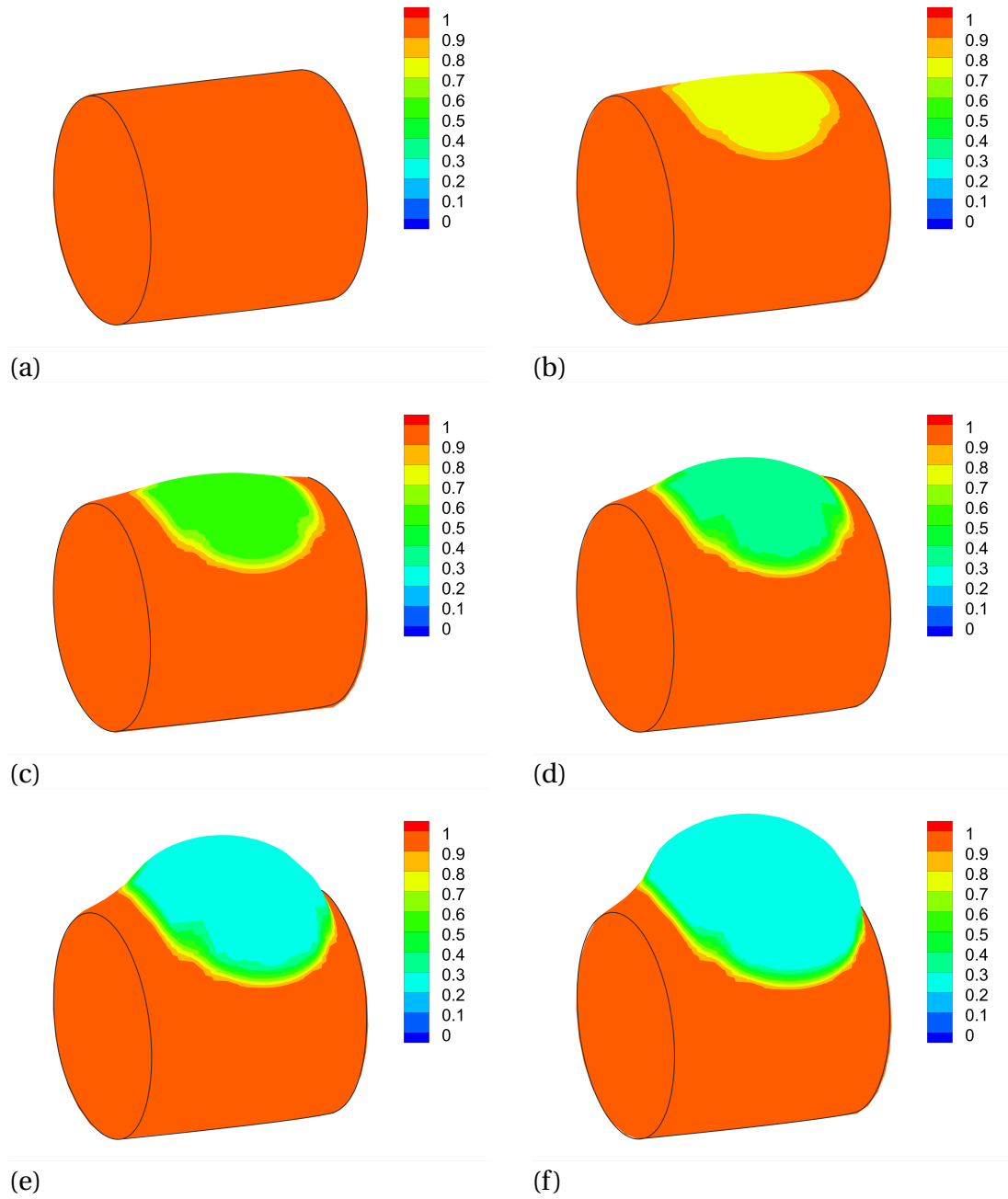


Figure 5.6: The prescribed spatial distribution of the normalised elastin concentration m^E for t values of (a) 0 year, (b) 0.5 year, (c) 1 year, (d) 1.5 years, (e) 2 years and (f) 10 years respectively.

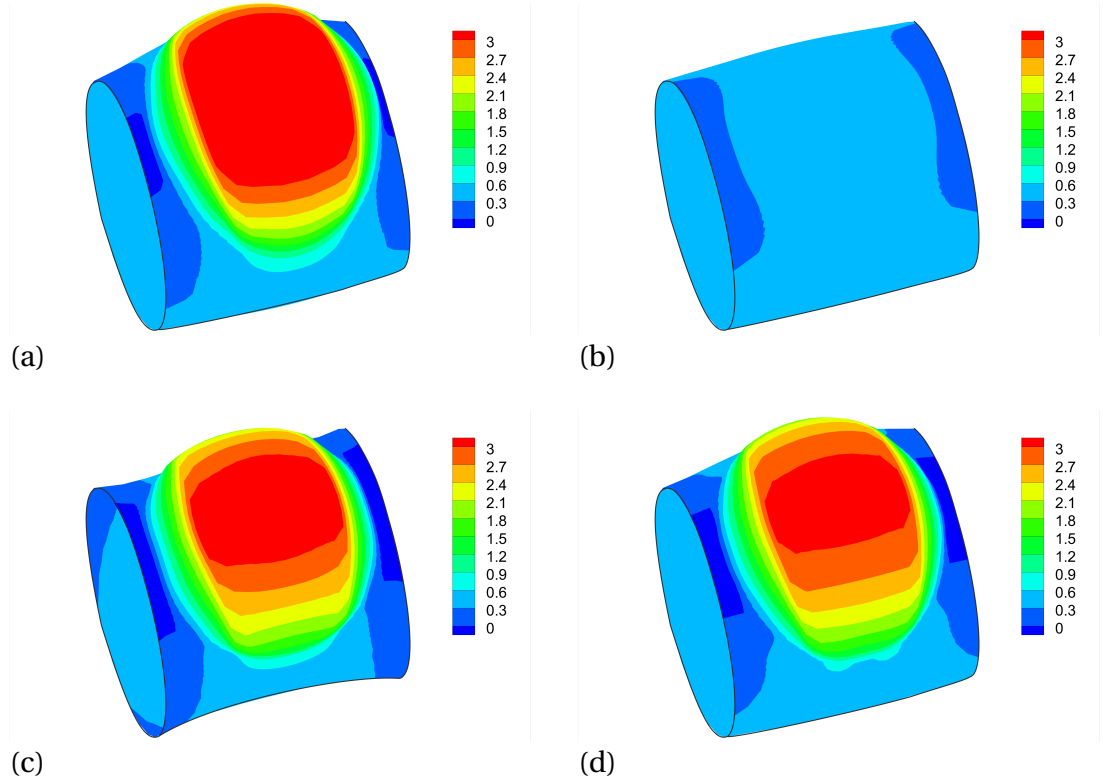


Figure 5.7: The elastin GL strain E_{11} (axial) for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

Fig. 5.7 and 5.8 illustrate the elastin GL strains E_{11} and E_{22} in the four cases at $t = 10$ years. In case 2, only little bulging of the arterial wall is observed, whereas in the other three cases, aneurysms do evolve on the surface of the wall. The size of the aneurysm in case 1 is slightly larger than the ones in case 3 and 4, where the two aneurysms have similar sizes. However, in case 3, shrinking of the artery can be clearly seen. In all of these four cases, maximum values of the GL strains occur at the apexes of the aneurysm domes.

Fig. 5.9 takes case 4 as an example to illustrate the evolution of the GL strains E_{A-}^C of the negatively wound adventitial collagen fibres. Comparing the magnitudes of the collagen GL strains in Fig. 5.9 with elastin GL strains in Fig. 5.7 and 5.8, we notice that whilst there is large deformation of the geometry, the collagen GL strains increase negligibly in comparison with the increase of the elastin strains. This is due to the evolution of the natural reference configurations with respect to which these collagen fibres are recruited to load bearing. Initially, as the aneurysm enlarges, the collagen fibre strains increase throughout the dome with a larger increase around

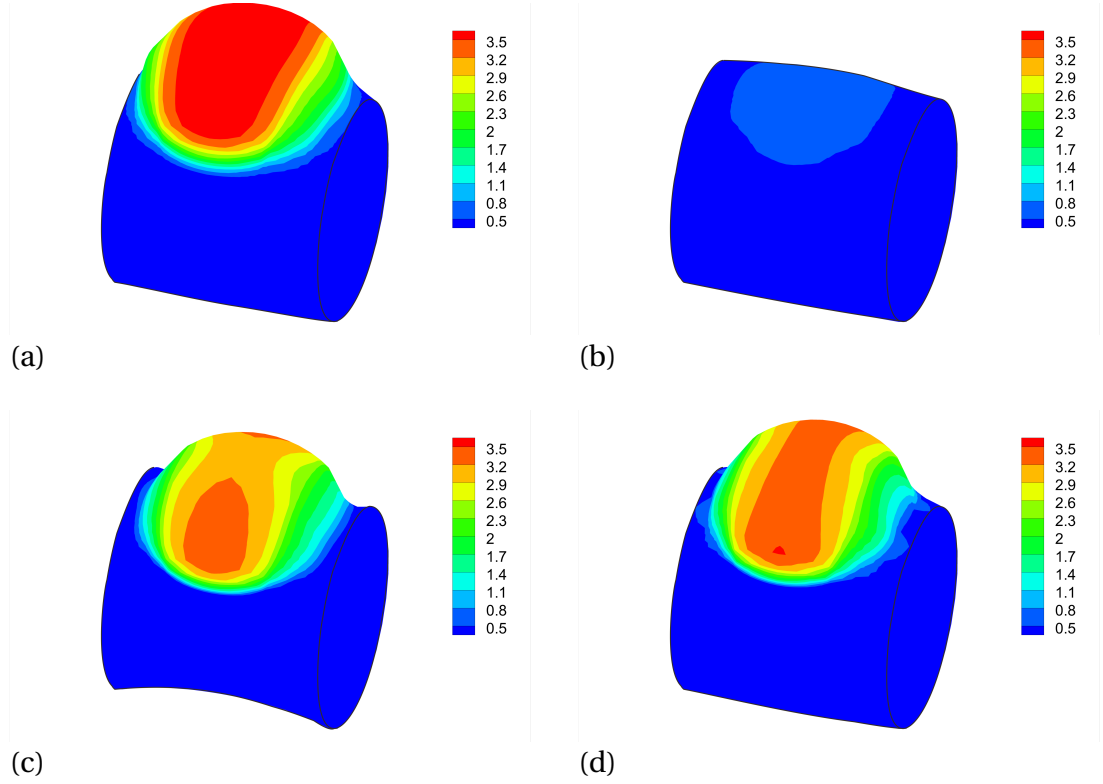


Figure 5.8: The elastin GL strain E_{22} (circumferential) for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

the aneurysm neck. After $t = 7.5$ years, the fibre strains in the dome start to decrease back to the homeostatic levels, i.e. $E_{Ap}^C \rightarrow E_{AT}^C$, indicating a trend for the aneurysm to stabilise in size. However, local maximums still remain at the proximal and distal neck region. The reason why the spatial distribution is asymmetric is because this colourmap depicts the GL strain field of the adventitial collagen fibres which are *negatively wound* relative to the circumferential axis in the unloaded configuration. Similar asymmetric patterns of the spatial distributions can be also observed in Fig. 5.10 and 5.11, in which the collagen fibres are positively wound. Fig. 5.10 and 5.11 illustrate the GL strains E_{M+}^C and E_{A+}^C of the positively wound medial and adventitial collagen fibres in all cases at $t = 10$ years respectively. In both figures, except for case 2 where there is only a slight bulging of the geometry, the collagen GL strains E_{M+}^C and E_{A+}^C appear to be elevated around the neck regions with highest values on the lateral sides. In the aneurysm domes, the values of the GL strains approximate the homeostatic values, indicating the stabilisation of the aneurysms.

Fig. 5.12 illustrates the normalised average collagen fibre concentration m^C for

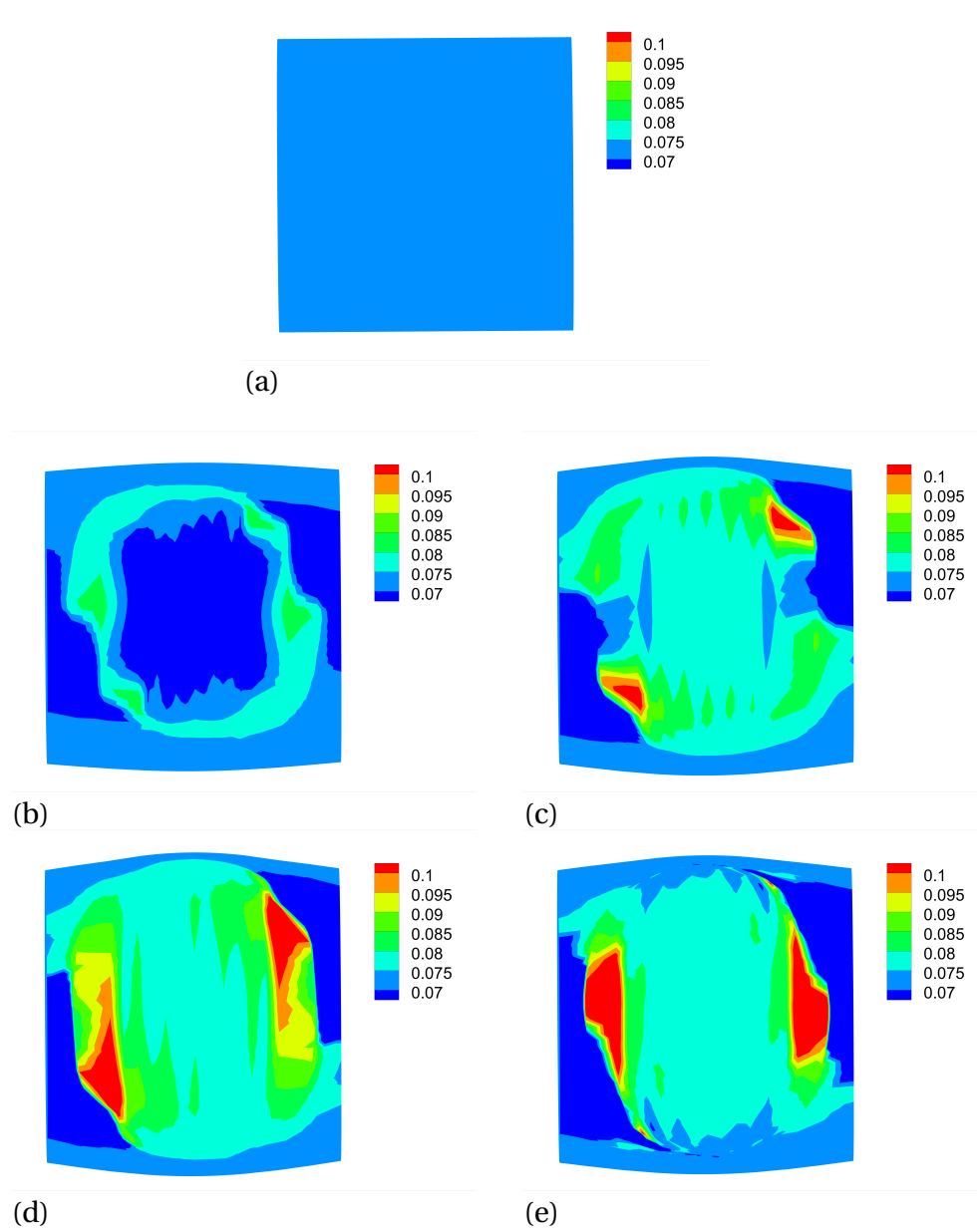


Figure 5.9: The evolution of the negatively wound adventitial collagen fibres' GL strain E_A^C in case 4 for t values of (a) 0 year, (b) 2.5 years, (c) 5 year, (d) 7.5 years and (e) 10 years respectively.

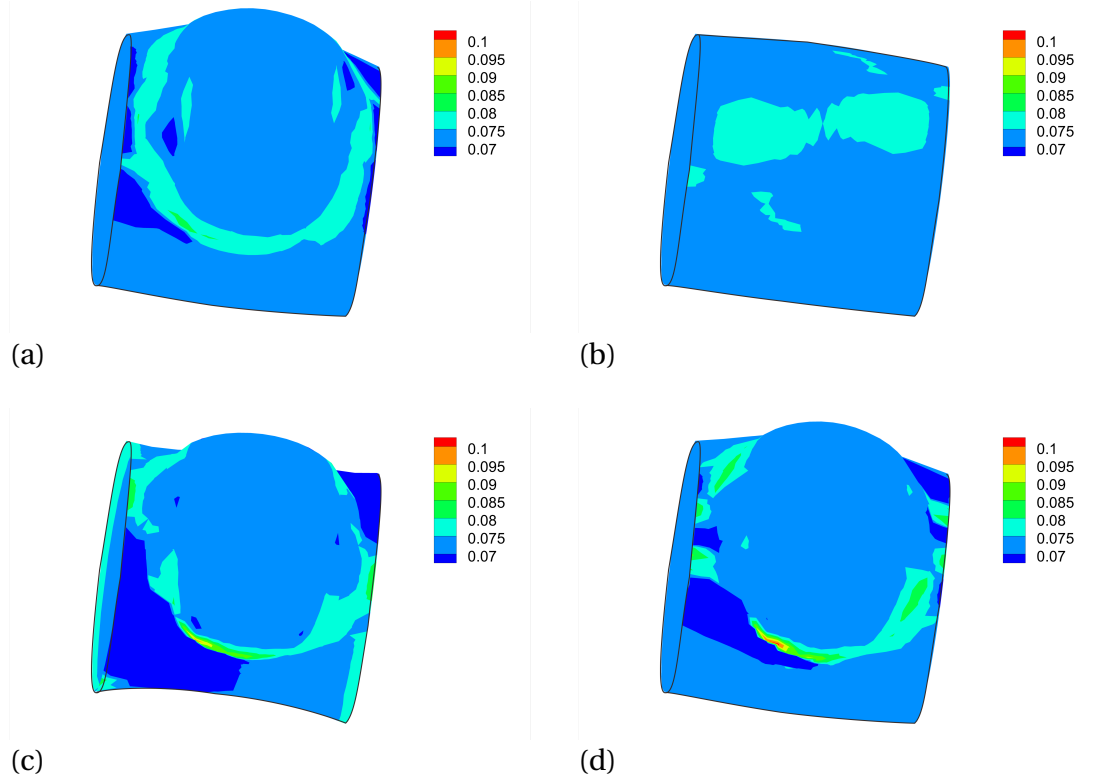


Figure 5.10: The positively wound medial collagen fibres' GL strain E_{M+}^C for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

the four simulated cases at $t = 10$ years respectively. Significant differences are observed: in case 1, the collagen fibre concentration dramatically increases approximately about 20 fold within the aneurysm dome to compensate for the loss of the elastinous constituents and the enlargement of the geometry. In other cases, since the normal collagens are prescribed to degrade, then m^C calculated based on Eq. 5.33 is also decreasing during aneurysm evolution.

Fig. 5.13 illustrates the remodelled arterial wall thickness H_{rem} incorporating the volumetric growth of the tissue (calculated based on the equation proposed in Sec. 4.6 of the 1D model) for the four simulated cases at $t = 10$ years respectively. Similar patterns of spatial distribution to Fig. 5.12 are observed: in case 1, comparing with other regions of the artery, the wall in the aneurysm dome thickens by approximately 2–3 times while the geometry enlarges, whereas in the other three cases, H_{rem} decreases significantly in the aneurysm dome.

Fig. 5.14 and 5.15 illustrate the average Cauchy stresses σ_{11} and σ_{22} based on the

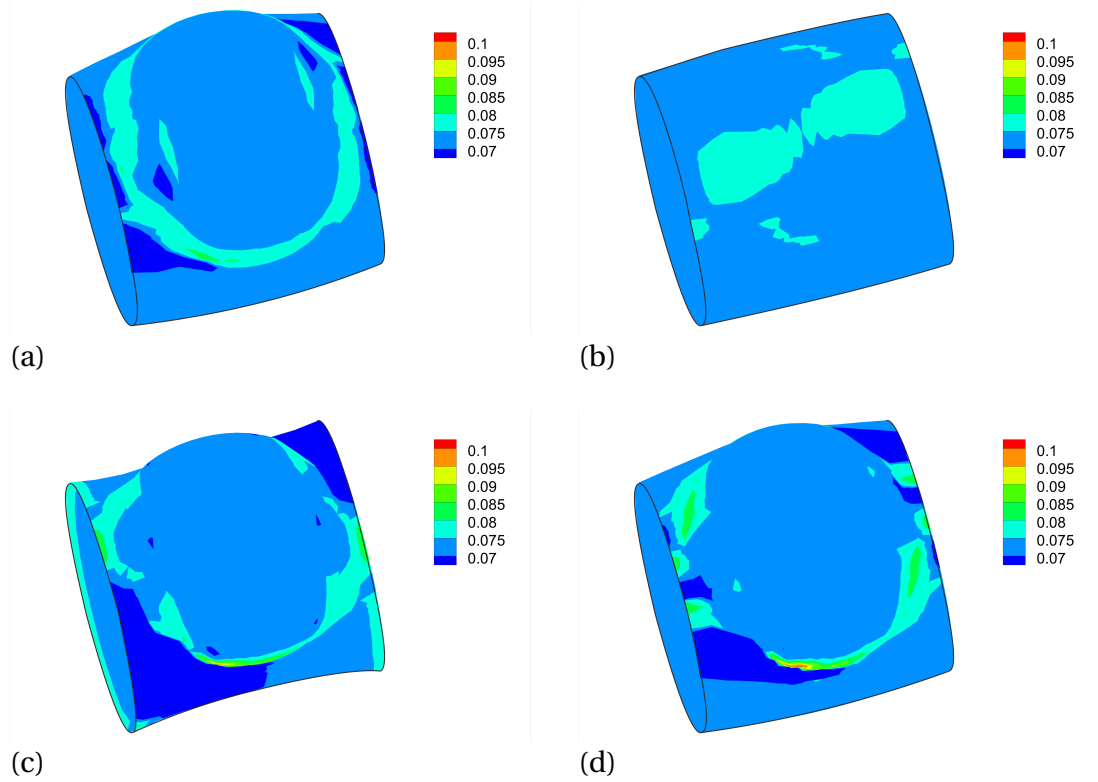


Figure 5.11: The positively wound adventitial collagen fibres' GL strain E_{A+}^C for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

remodelled thickness in the four cases at $t = 10$ years from different views. In case 1, as the aneurysm grows, both σ_{11} and σ_{22} decrease significantly in the dome. Local maximum values of σ_{11} appear on the lateral sides of the neck region, whereas local maximum values of σ_{22} appear on the proximal and distal sides of the neck region. On the contrary, in case 3 and 4, Cauchy stresses σ_{11} and σ_{22} increase dramatically within the aneurysm dome compared with the average level on the parent artery. In case 2, where only little bulging of the arterial wall is observed, the increase of σ_{11} and σ_{22} is much smaller than the increases in case 3 and 4 due to the smaller geometric deformation. Global minimum values of the Cauchy stresses occur at the apex of the aneurysm dome in case 1, whereas global maximum values occur at the apexes in case 2, 3 and 4.

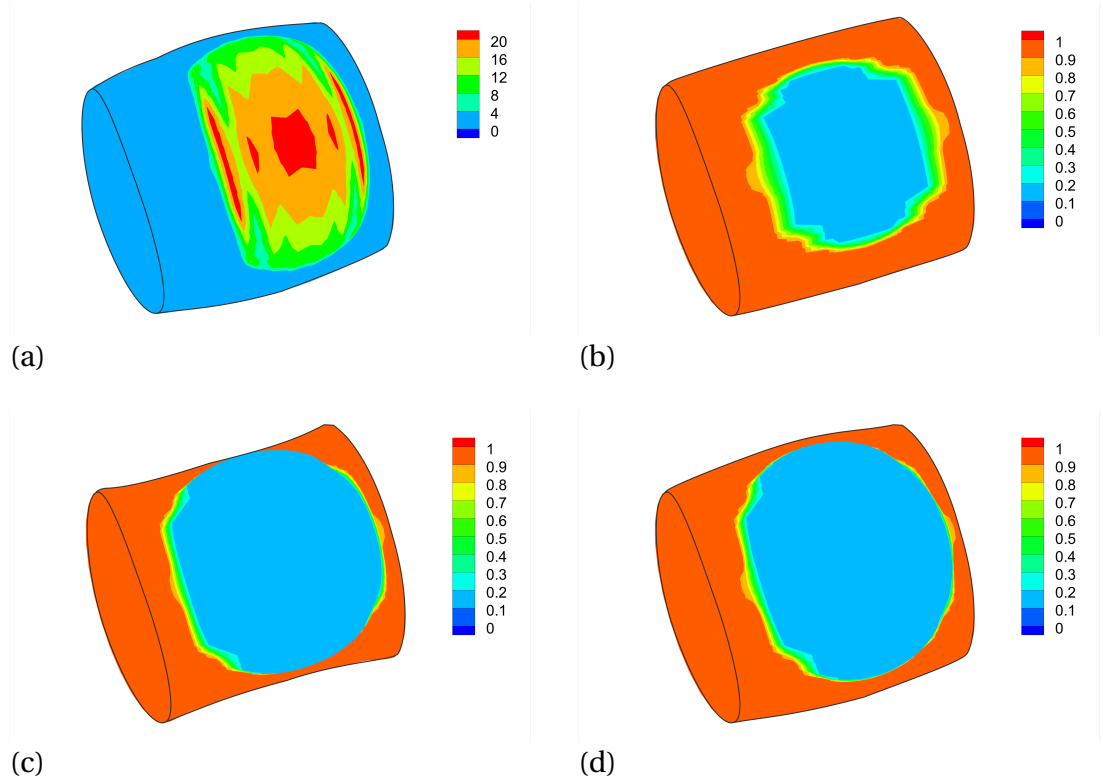


Figure 5.12: The normalised average collagen fibre concentration m^C for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

5.8 DISCUSSION

In this study, in order to model the formation of a 3D saccular IA, the growth & remodelling (G&R) framework proposed by Watton and Ventikos (2009) is successfully sophisticated to incorporate the novel 1D model of collagen microstructural adaptation presented in Chapter 4. A localised degradation of the elastins is prescribed in a circular patch in the centre of the artery. An additional layer of collagen fibres is added onto the adventitia layer to simulate its initial mechanical role as a protective sheath and its conversion into the main load bearing layer during aneurysm evolution. The normal medial and adventitial collagen fibres are degraded to facilitate the additional protective collagens to take the load shifted from elasin degradation, whereas the mass concentrations of the these additional collagen fibres are set to be constant. The natural reference configurations of the collagen fibres are remodelled to simulate the effect of fibre deposition and degradation in the altered configurations. The state of stretch distribution with which new additional collagen fibres are attached to the ECM (i.e. the attachment stretch distribution) is also adapted.

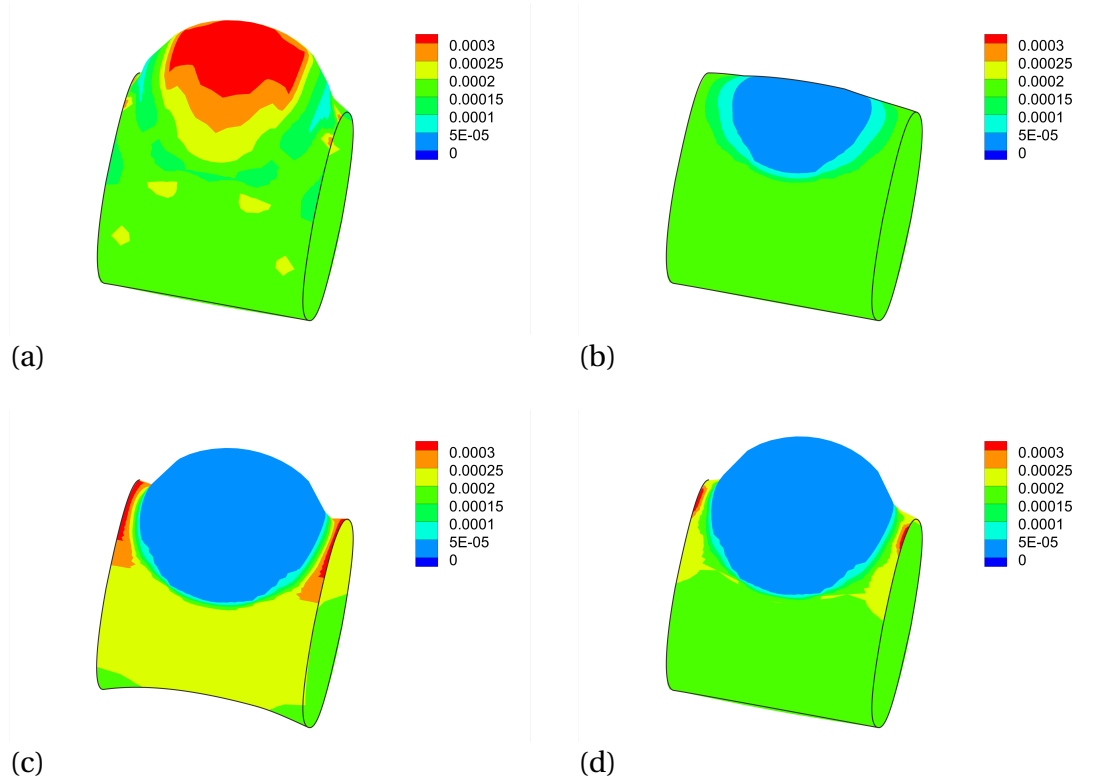


Figure 5.13: The remodelled wall thickness H_{rem} (m) incorporating the volumetric growth of the tissue for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

It is observed that given almost complete loss of elastinous constituents, in all of the four cases the geometries finally stabilise in size. No additional protective collagen layer is added into the model in case 1. This case is a replica of the original model discussed in Watton and Ventikos (2009) and serves as a role with which we want to compare our sophisticated 3D model. The load shifted from the elastin degradation is taken on by the normal collagen fibres in the wall, which is allowed to grow as well as remodel. For the value of the growth parameter β used in this case, the aneurysm enlarges rapidly and does not stabilise. Hence we temporarily increase the value of β to simulate the increased collagen synthesis and/or reduced enzymatic degradation. This yields almost immediate stabilisation. In case 2, neither the remodelling of recruitment stretch distribution nor the adaption of the attachment stretch distribution is modelled. In other words, the natural reference configurations of the additional collagen fibres are assumed to be constant. Hence these fibres always act as a protective sheath which does not remodel. This limits the enlargement of the geometry. Even though the normal collagens have also

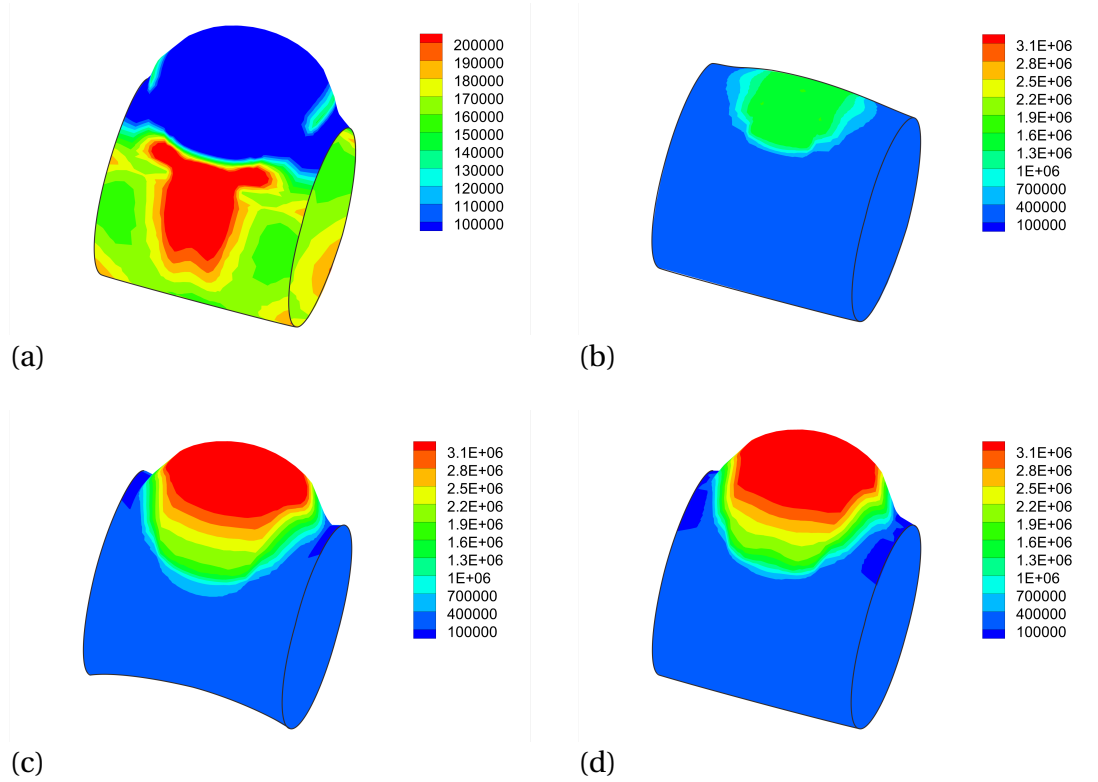


Figure 5.14: The average Cauchy stress σ_{11} (Pa) (axial) in the wall based on the remodelled thickness for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

been degraded, the additional protective collagens bear the load shifted from elastin degradation. As a result only a slight bulge of the arterial wall is observed instead of an obvious aneurysm. This case clearly demonstrates the biomechanical role of the adventitia layer as a protective sheath to prevent over-dilation of the artery. The only difference between case 3 and 4 lies in the initiation of the simulations: in case 3, adaption of the attachment stretch distribution is throughout the artery, whereas in case 4, it is confined in the domain of aneurysm growth. Adaption of the attachment stretch distribution over the whole geometry implies that some of the new additional collagen fibres are also laid down to bear load outside the aneurysm region. As a consequence it can be clearly observed that in case 3 the entire geometry shrinks, which would be impossible in reality. In case 4, where adaption of the attachment stretch distribution is confined in the region of aneurysm growth, no shrinking of the artery is observed. Hence this leads us to propose the following question: how do vascular cells realise the heterogeneous adaption of the attachment stretch distribution? Are these cells dictated to by some specific bio-molecules

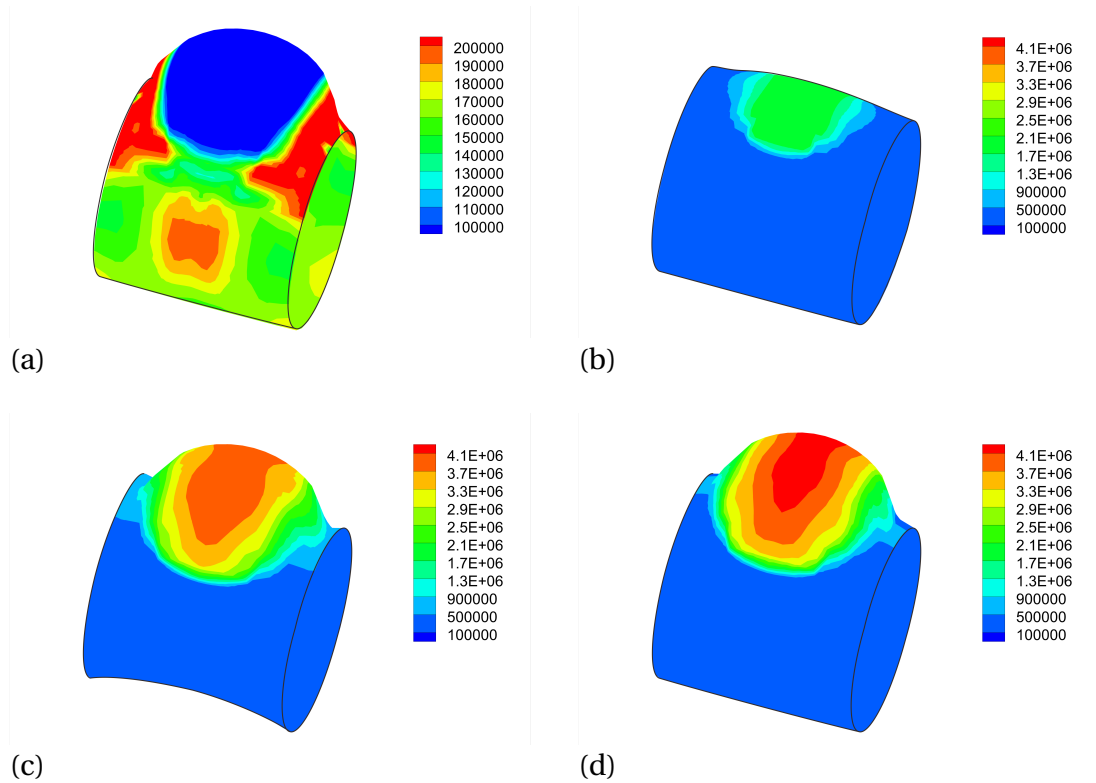


Figure 5.15: The average Cauchy stress σ_{22} (Pa) (circumferential) in the wall based on the remodelled thickness for the four simulated cases at $t = 10$ years respectively. (a) case 1, (b) case 2, (c) case 3, (d) case 4.

within the arterial wall or are they influenced by the extracellular mechanical environment? Is the adaption of the attachment stretch distribution also heterogeneous within the aneurysm region during IA evolution? Or the worst scenario: is our hypothesis on the adaption of the attachment stretch distribution simply incorrect? Currently none of these question could be answered due to the lack in biological understanding of vascular cells. Nowadays, the consensus accepted by most of the people in this field is still that the attachment of the collagen constituents into the ECM by the vascular cells is independent of the current configurations of the cells. To improve this, we must have a better understanding of the biology of the vascular cells, in particular how exactly they interact with the extracellular environment.

It is also observed that the GL strains of the collagen fibres have almost restored to homeostatic levels within the aneurysm dome, indicating the stabilisation of the aneurysms in the four cases. However, small regions of elevation still remain around the necks. Similar patterns are also observed in Watton and Ventikos (2009) and according to the authors, this may merely be an artifact of the model, e.g. implement-

ing hypotheses for fibre reorientation may redress this issue. However, the authors also pointed out that the remaining elevation of the collagen GL strains around the neck may just be an implication of fact that the domes have already stabilised whilst the aneurysms continue to enlarge from the neck region. Given that most of the IAs do stabilise in size (Koffijberg et al., 2008; Wermer et al., 2005), we do need to have a better understanding of the mechanisms which govern the compensatory adaption of the collagen fabrics during aneurysm development (Watton and Ventikos, 2009). This includes the understandings of why/how most aneurysms stabilise and of why subsequent evolution/rupture can still occur.

For the two types of simulations illustrated in Fig. 5.12, it can be seen that the collagen concentration is significantly increased in the case 1 where no additional protective collagen is added into the model. This result is consistent with some of the other studies in the literature, where a large increase in the collagen mass concentration can be seen (Watton et al., 2009a; Watton and Ventikos, 2009). On the contrary, in case 4 where the additional protective collagen fibres are included, the aneurysm can still stabilise even though most of the normal medial and adventitial collagen fibres have been prescribed to degrade by a large amount (only less than 10% of the normal collagens are left in the arterial wall) and the concentration of the additional protective collagen fibres are set to be constant. In other words, in case 1, the complete loss of elastin and the enlargement of the geometry need to be compensated by a large increase in the collagen concentration; whereas in case 4, these are compensated by the change of the mechanical role of the additional protective collagen fibres from merely a protective sheath which do not bear any load initially to the main load bearer after the aneurysm has stabilised. Here we just remind the readers again that this is achieved by adapting the attachment stretch distributions of these additional collagen fibres. Initially the upper bound of the distribution, i.e. the maximum attachment stretch is set to be 1, hence these additional collagens only act as a sheath bearing no load. As other constituents in the wall are degraded during aneurysm growth, the attachment stretch distribution is shifted rightwards so that some of the newly synthesised collagens are borne to be load bearers. From this comparison between case 1 and 4, it can be inferred that although the adaptation of the attachment stretch distribution is merely an assumption proposed in our study so far and clinical evidences are definitely needed to prove its facticity, it is beyond all doubt that adapting the attachment stretch distribution is a very wise way for the collagen fibres to be able to stabilise the enlarged geometry without being

over-synthesised.

The remodelled wall thickness H_{rem} takes the volumetric growth of the tissue into account. The approximate inference of the remodelled thickness is based on the mass concentrations of the constituents and is derived in Appendix B. Consequently similar patterns of remodelled thicknesses can be observed among these cases as the patterns of collagen mass concentrations. In case 1, the remodelled thickness dramatically increases due to the large increase in collagen concentration. Other studies showing a thickened arterial wall during aneurysm evolution can also be found in the literature (Baek et al., 2005, 2006; Kroon and Holzapfel, 2009). Baek et al. (2006) concluded that the ability of the lesion to thicken quickly is critical to arresting the enlargement and thus yielding a stable growth of the aneurysm. However, in many of the histological observations of the aneurysmal tissue, thinning of the lesion wall is usually observed (Kondo et al., 1997), see Fig. 5.16 for graphic illustration. In case 4, on the contrary, it is observed that the remodelled wall thickness actually decreases by a large amount in the aneurysm dome due to the prescribed degradation of the normal collagen fibres in the two layers and the fixed value of the additional collagen concentration. The reduced wall thickness in this case is more consistent with histological observations, and hence is more realistic compared with case 1. This comparison clearly illustrates the advantage of the sophisticated 3D solid model of IA evolution incorporating microstructural adaption of the collagens over the original 3D model: simulation of IAs stabilising at a similar size but with more realistic wall thickness.

The average Cauchy stress σ_{rem} is computed based on the remodelled thickness H_{rem} . In case 1, we observe low Cauchy stress in the aneurysm dome with some local elevations outside the aneurysm neck, whereas in case 4, elevated Cauchy stress is only observed in the aneurysm dome. In general, the strains of the constituents in the aneurysm dome is larger than the strains of the same type of constituents outside the dome on the parent artery. This larger strain field in the dome is compensated by the dramatic increase in wall thickness in case 1, resulting in low a Cauchy stress field in the dome. On the contrary, in case 4, the larger strain field is amplified by the much thinned wall thickness, leading to a huge elevation in the stress field in the dome region. In the literature, there are a few aneurysm studies with which our results can be compared ((Isaksen et al., 2008; Bazilevs et al., 2010a,b; Zhou et al., 2010)). In these studies, the geometries of the aneurysms are reconstructed from

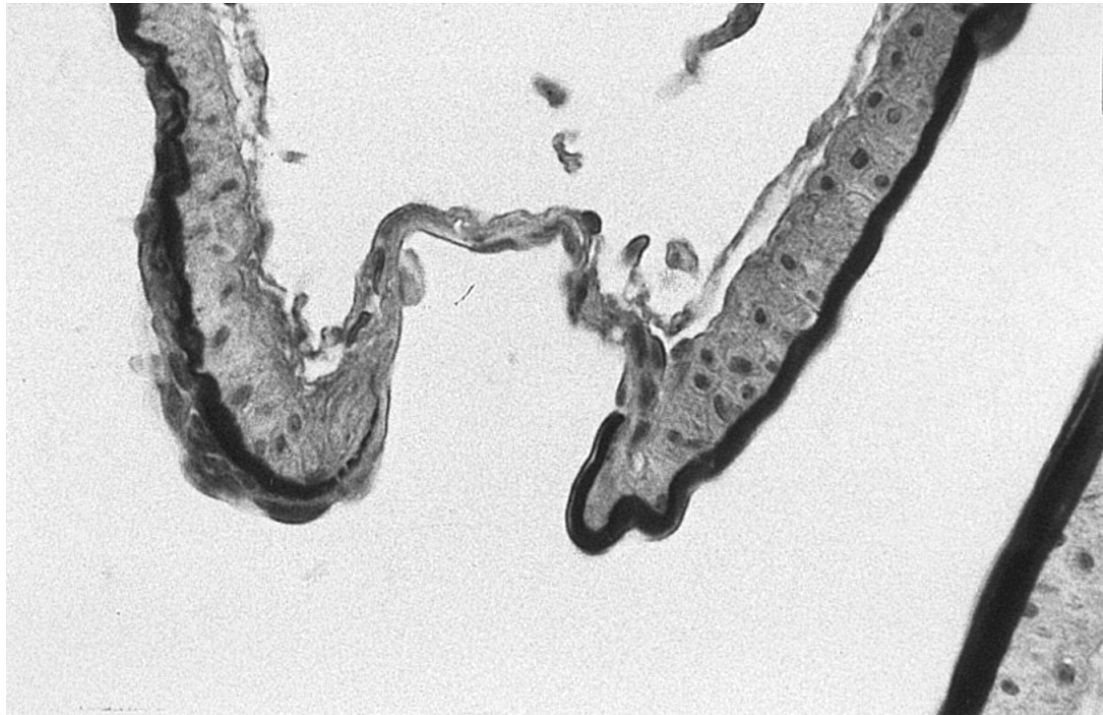


Figure 5.16: Illustration of the thinned arterial wall of a saccular aneurysm growing at the bifurcation of anterior cerebral artery and olfactory artery bifurcation (adapted from Kondo et al. (1997)).

realistic imaging data; the wall stress/tension, which is defined as the principal in-plane stress, is determined either from fluid solid interaction (FSI) simulations (Isaksen et al., 2008; Bazilevs et al., 2010a,b)) or using an inverse approach (Zhou et al., 2010) in which the aneurysms are modelled as nonlinear thin shell structures. One consistency in all these studies is that, compared with the wall stresses on the parent vessels, elevated stresses are clearly present in the aneurysm domes. This is also consistent with the result of case 4 in our study, despite the fact that the maximum stresses may not occur at the tip of aneurysms in their studies due to the geometric irregularity of their aneurysm domes. In reality, although the mechanical properties of aneurysmal tissue may deteriorate compared with those of the healthy tissue in the parent vessel, it is still likely that the stress in the aneurysm dome is higher than that of the surrounding parent artery, given that aneurysms usually bleed and rupture from the dome. Consequently, this comparison demonstrates that the sophisticated 3D aneurysm growth model also provides a more realistic prediction of the wall stress, whereas the old model, which assumes single and constant attachment stretch, unrealistically underestimates the wall stress in

the aneurysm dome.

In summary, we have illustrated that the sophisticated 3D solid structural model of aneurysm evolution with the 1D collagen microstructural adaption model implemented can be utilised to develop saccular aneurysms with more realistic results on the evolution of the remodelled wall thickness and the average stress in the wall. However, this model would still benefit from further sophistications. An immediate one would be to model the dispersion of the additional protective collagen fibres about a mean orientation and the remodelling of the fibre orientation as well as the dispersion: the orientations of the collagen fibres can be assumed to follow a certain statistic distribution with mean orientations (Rezakhaniha et al., 2012; Schrauwen et al., 2012). Both the mean orientations and the distributions remodel during aneurysm evolution. More details are provided in Chapter 6. Another sophistication would be to model the adaption of the shape of the collagen attachment stretch distribution, for example, apart from being shifted in the model, it can also be skewed or narrowed down (using similar ways introduced in the 1D model of collagen adaption). In addition to this, more realistic analytic functional forms of the attachment stretch distribution directly fitted from experimental data can also be implemented into this model. The implementation of these sophistications will reduce even more the collagen concentration in the wall required to compensate for the loss of other constituents, and hence will result in an even thinner arterial wall and higher stress in the wall. Other sophistications such as more explicit modelling of the vascular cells, development of thick-walled G&R formulation with volumetric adaption of the arterial constituents, as well as development of 3D aneurysm growth models based on arbitrary geometries will be discussed in Chapter 6. Experimental evidences and better understanding of the arterial biology, in particular the biology of the vascular cells are clearly in an urgent need to guide further sophistication of this model.

5.9 IMPLEMENTATION OF 1D COLLAGEN ADAPTION INTO THE 3D FSG MODEL

This section presents the implementation of the 1D collagen microstructural adaption model into the state-of-the-art 3D Fluid-Solid-Growth framework of aneurysm evolution. One illustrative case is provided to show the application of this sophis-

ticated FSG framework to model the evolution of an IA on patient-specific vasculature. The results demonstrate the successful implementation of the collagen adaption model into the FSG framework.

5.9.1 Overview of the sophisticated Fluid-Solid-Growth framework of IA evolution

We would like to begin by generally overviewing this FSG computational framework sophisticated with the 1D collagen microstructural adaption model. In the framework, the sophisticated solid structural model (two-layer, nonlinear elastic cylindrical membrane model with elastins and normal collagens in the media and adventitia as well as the additional adventitial protective collagen) presented in this chapter is integrated into a patient-specific geometry of the vasculature. For each computational cycle, it starts with a finite element quasi-static structural analysis to solve the initial equilibrium deformation fields in the systolic and diastolic configurations for a given blood pressure and boundary conditions (Fig. 5.17(i)). This quantifies mechanical information such as stress/stretch of the vascular cells and components of the ECM as well as the cyclic deformations. Then the systolic geometry of the aneurysm is automatically prepared for a rigid-wall computational fluid dynamics (CFD) analysis (Fig. 5.17(ii)): the geometry file of the structural domain is exported from the structural solver and integrated into a physiological geometrical domain which serves as the parent vessels in a scripted manner using ANSYS ICEM; the volumetric domain is meshed; physiological flow rates and pressures are applied as the boundary conditions and the flow is solved with ANSYS CFX V14. Once the flow has been solved, haemodynamic information evaluated on the surface of the fluid domain (to be specific, the WSS) are obtained and then interpolated onto the nodes of the structural mesh. Now each node of the structural mesh is associated with both local mechanical information from the structural analysis as well as haemodynamic information from the CFD simulation. Subsequently, these informations are fed into the G&R formulations which simulate cell-mediated adaption of tissue (Fig. 5.17(iii)). Following this, the constitutive model of the aneurysmal tissue is updated: degradation of the elastins and normal collagen fibres is linked to the reductions in WSS below the assumed homeostatic threshold; remodelling of the collagen recruitment stretches allow the degradation and deposition of collagen fabrics in altered configurations to be simulated. Temporal adaptations of the attachment stretch distribution of the additional protective collagen fibres are modelled

to simulate their transition from the protective sheath to the main load bearer during IA evolution. Once the constitutive model of the aneurysmal tissue is updated, the computational cycle then begins again and the structural analysis is re-executed to calculate the new systolic and diastolic deformation fields of the updated tissue. The updated geometry is exported again for a new haemodynamic analysis. As the computational cycle repeats, the tissue continuously adapts and the geometry continuously enlarges, i.e. an IA develops (Aparício et al., 2014). Compared with the updated solid structural model, the sophisticated FSG framework enables the growth and remodelling of the arterial tissue to be linked to the physiologically representative spatial distributions of haemodynamic stimuli obtained from the CFD analysis. Key aspects of implementing the 1D collagen microstructural adaption model into the framework are discussed in the following sections.

5.9.2 Structural model of aneurysm evolution

The 3D solid model introduced in this chapter serves as the structural model of the FSG framework. We will not repeat introducing this again here. Instead, we introduce one novel index of interest associated with the cyclic deformation of the arterial wall: the *biaxial stretch index* (BSI) χ^{BSI} . The biological motivation for this index is that, in the initial geometrical configuration, the artery is subject to cyclic stretch that is only in the circumferential direction, i.e. one dimensional. As the aneurysm evolves, regions of the artery experience biaxial stretching. To characterise the evolution of the cyclic stretch environment, we consider a novel Biaxial Stretch Index χ^{BSI} proposed by Watton et al. (2011a), where $0 \leq \chi^{BSI} \leq 1$. This variable quantifies the degree of the biaxial distortion of the tissue during the cardiac cycle and is independent of the magnitude of the GL strains. If $\chi^{BSI} = 0$, the tissue is subject to 1D cyclic stretching whereas if $\chi^{BSI} = 1$, the tissue is subject to equi-biaxial cyclic stretching. If the cyclic (linearised) strain in the direction of the first principal stretch is a factor κ greater than the cyclic (linearised) strain in the direction of the second principal stretch then $\chi^{BSI} = 1/\kappa$.

5.9.3 Haemodynamic modelling

A patient-specific geometry of an IA is utilised to generate the pre-aneurysmal geometry of the vasculature; the general process is illustrated in Fig. 5.18. A 3D surface geometry of the internal carotid artery with a sidewall aneurysm is provided to us

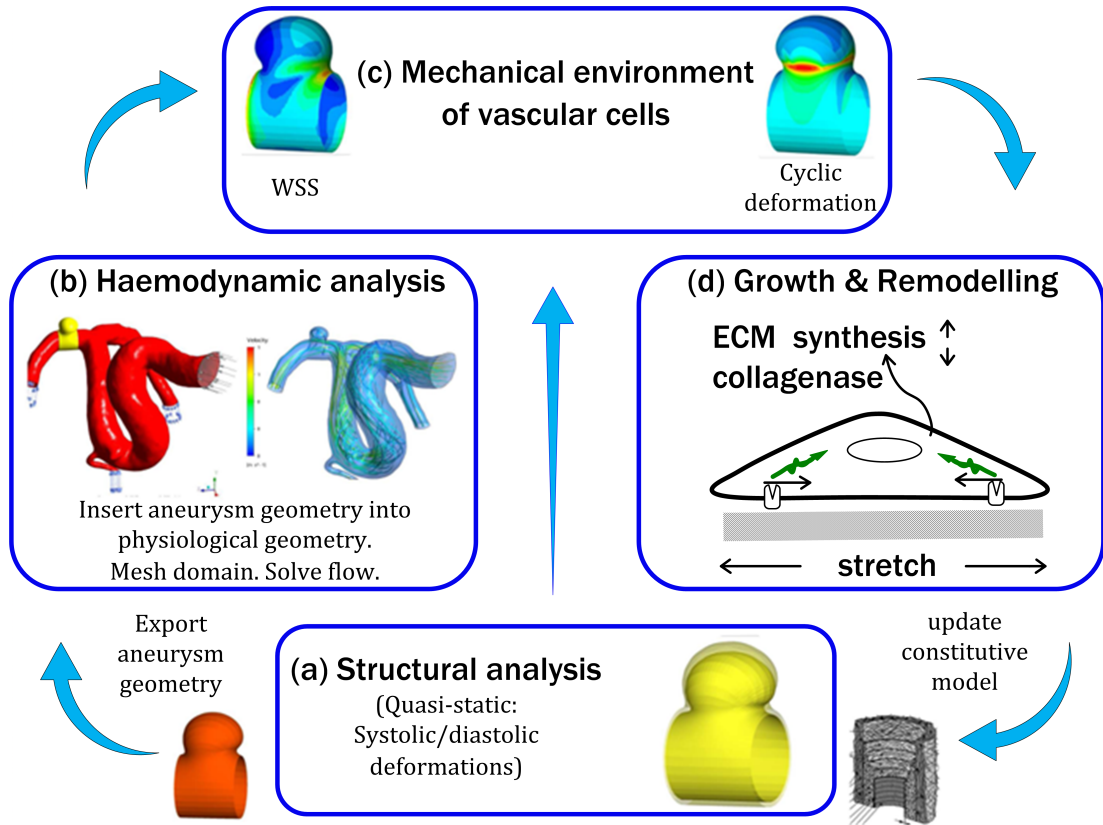


Figure 5.17: Overview of the state-of-the-art Fluid-Solid-Growth computational framework for modelling aneurysm evolution. (a) structural analysis to solve the initial equilibrium deformation fields in the systolic and diastolic configurations; (b) computational fluid dynamics (CFD) analysis to evaluate the haemodynamic information on the surface of the aneurysm domain; (c) local mechanical environment of vascular cells exported from the structural and haemodynamic analysis; (d) Cell-mediated G&R of the arterial tissue (adapted from Watton et al. (2011a)).

which is generated from the segmentation of a DICOM data set of Computed Tomography Angiography (CTA) images depicting the cerebral region. Based on this geometry, the 'pre-aneurysmal' geometry is obtained through the following procedures:

1. upstream and downstream segments were clipped; the aneurysm segment is removed; the skeleton of the artery and a reference anterior point (the neck point) are defined to guide positioning of the cylindrical artery (Fig. 5.18(a));
2. the radius of the cylinder is chosen to be equal to the mean of the average radii of the upstream outlet and downstream inlet, while the length of the cylinder ($\lambda_z L$) is chosen subjectively to be around 80% of the distance between the

two boundaries of the removed aneurysm segment. This is done for smoothly connecting the cylindrical segment to the upstream and downstream geometries;

3. the cylindrical segment is placed in the domain using the information of the neck point and the skeleton (Fig. 5.18(b));
4. two smooth connecting surfaces are generated between the cylindrical segment and the upstream as well as downstream segments respectively using the novel vessel reconstruction method introduced in Chapter 2 (Fig. 5.18(c)).

Fig. 5.19 illustrates the final geometry consisting of the upstream and downstream segments, as well as the cylindrical segment used to simulate aneurysm growth.

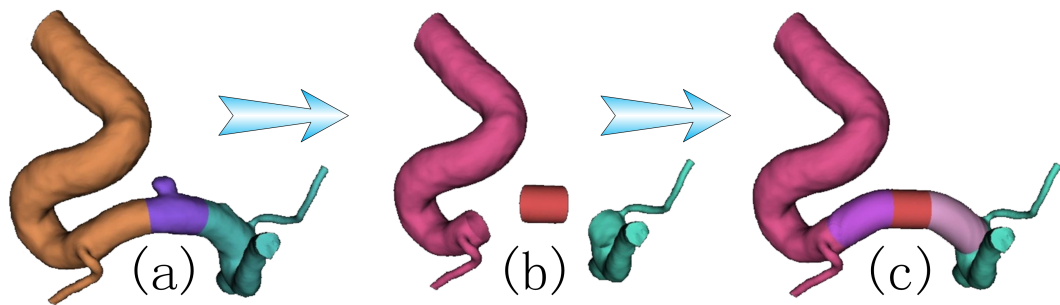


Figure 5.18: Integration of the cylindrical artery into the patient-specific vasculature. (a) Original aneurysmal geometry with aneurysm segment identified; (b) Removal of the aneurysmal segment and placement of the cylindrical artery; (c) connecting the cylindrical artery into the upstream and downstream segments of the parent artery.

The method to solve the haemodynamics as the aneurysm evolves is summarised as follows. The geometry of the aneurysmal section is exported from the structural solver to ANSYS ICEM. ANSYS ICEM then automatically attaches the upstream and downstream boundaries to the parent vessel so that the aneurysmal section is integrated into the physiological geometrical domain. Then an unstructured tetrahedral mesh is automatically generated with three prism layers lining the boundary (See Fig. 3.3). The mean flow and pressure boundary conditions are computed from the software suite @neufuse (Villa-Uriol et al., 2011) based on a 1D model of the arterial tree (Reymond et al., 2009). It solves the 1D form of the Navier-Stokes equation in a distributed model of the human systemic arteries, accounting for the ventricular-vascular interaction and wall viscoelasticity (Aparício et al.,

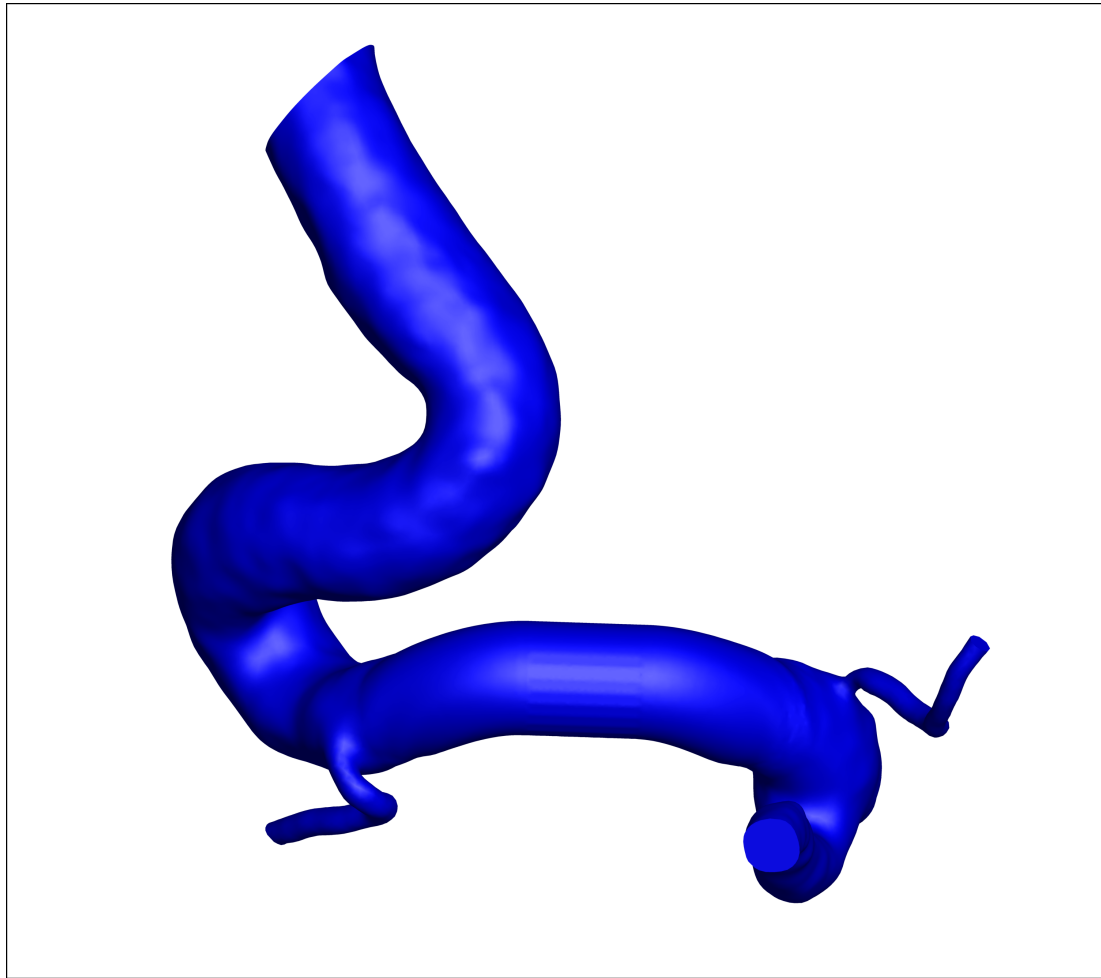


Figure 5.19: The final geometry consisting of the upstream and downstream segments, as well as the cylindrical segment in the FSG model.

2014). This model is recently validated through a comparison with in vivo flow measurements (Reymond et al., 2011). The flow rate boundary condition prescribed at the inlet and the pressure boundary conditions prescribed at each outlet are detailed (see Sec. 3.2 for the initiation of CFD simulation). However, we note that in order to reduce the cost of the simulation in this illustrative FSG study, we actually adopt *steady flow conditions* instead of pulsatile flow. Blood is modelled as a Newtonian fluid with constant density 1069kg/m^3 and a constant viscosity $0.0035\text{Pa}\cdot\text{s}$. No slip, no-flux conditions are applied at the arterial wall boundaries.

Simulations are performed on a 64-bit desktop computer (four-core Intel® Xeon® Processor W3530 @2.80 GHz, 12GB RAM) running windows 7 professional. Flow was solved by ANSYS CFX using two cores with a criterion for maximum resid-

ual of 0.0001. A complete FSG simulation consists of 250 solid steps and the CFD is performed every ten steps. This takes approximately one day. Here we note that, although specific computational tools (ANSYS, Tecplot360 et al.) are used as individual modules of the FSG framework, the overall framework does not depend on the particular implementation of these individual modules. In other words, for example, replacing the CFD solver with any other same type of solvers can still provide the same information such as wall shear stress.

5.9.4 Growth and remodelling of the arterial tissue

The approach of modelling growth and remodelling of the arterial tissue detailed in Sec. 5.6 also serves as the foundation of modelling arterial G&R in the FSG study. However, differences do exist. In this FSG study, we link the G&R of arterial tissue to the haemodynamic environment in the aneurysmal domain. To be more specific, the degradation of elastin and the atrophy of the normal collagens are linked to the low WSS haemodynamic stimuli. Details are given as follows.

5.9.4.1 Elastin Degradation

As reviewed in Sec. 1.5.2, low WSS may result in inflammatory cell infiltration, which is the main factor that drives the successive growth of IAs (Shojima et al., 2004). Thus the spatial and temporal changes in the WSS distribution could influence the degradation of elastin and thus the rate at which an IA enlarges.

In the FSG study, the degradation of elastin is linked to the low WSS that acts on the vascular wall and is modelled in two distinct stages. First, a degradation of elastin is prescribed to create a small AAA (as introduced in Sec. 5.6.1). The only difference is that in this study, the parameter T in Eq. 5.28 is set as $T = 5$ so that elastin degradation is only prescribed in the initial $t \leq 5$ year. This creates a perturbation to the geometry and the haemodynamic environment so that the WSS distribution is perturbed from its original distribution. The initial prescribed small out-pouching of the wall is made to stabilise ($4 < t \leq 5$) by increasing the growth rate parameter β by a factor of 100 for $4 < t < 5$ and reset to its default value for $t \geq 5$. Doing this allows the stretch of the collagen fabric to restore to the homeostatic values throughout the domain. This is to prevent further enlargement of the aneurysm which may be a consequence of the collagen fabric not being initially in homeostasis (Aparício et al., 2014). Subsequently from $t = 5$ years, the FSG coupling starts and the degra-

dation of elastin is linked to the deviations in WSS from homeostatic values, which needs to be defined. The concentration of elastin m^E evolves according to:

$$\frac{\partial m^E}{\partial t} = -\mathcal{F}_D D_{max} m^E \quad (5.40)$$

where D_{max} specifies the maximum rate of elastin degradation and this illustrative study, $D_{max} = 0.5$ is chosen. $\mathcal{F}_D(\theta_1, \theta_2, t)$: $0 \leq \mathcal{F}_D \leq 1$ is a spatially dependent function that describes the relation between the local WSS and the degree of the degradation of elastin. If $\mathcal{F}_D = 1$, elastin degrades at a maximum rate whilst if $\mathcal{F}_D = 0$, no degradation occurs. In this study, we assume that low WSS drives elastin degradation and that there exists a homeostatic WSS threshold τ_h . If the maximum value of the WSS is greater than τ_h , then no degradation of elastin occurs. Additionally, we also assume that there exists a value of WSS τ_X : $0 \leq \tau_X < \tau_h$, at which the maximum rate of elastin degradation occurs. To simplify the modelling, we set $\tau_X = 0\text{Pa}$ and assume a simple quadratic functional form for the degradation function $\mathcal{F}_D$:

$$\mathcal{F}_D[\tau(\theta_1, \theta_2, t)] = \begin{cases} 0 & \tau \geq \tau_h \\ (\frac{\tau_h(\mathbf{X}, t) - \tau(\mathbf{X}, t)}{\tau_h(\mathbf{X}, t) - \tau_X(\mathbf{X}, t)})^2 & \tau_X < \tau < \tau_h \\ 1 & \tau \leq \tau_X \end{cases} \quad (5.41)$$

Now the homeostatic WSS threshold $\tau_h(\mathbf{X}, t)$ needs to be defined. In this illustrative study, we simply choose a homogeneous and constant value as the homeostatic WSS threshold: i.e. $\tau_h = 5\text{Pa}$. However, we note that considering the fact that the phenotypic response of ECs to WSS is a complex process which may be modulated by some genes expressions sensitive to local haemodynamic environment, the latest FSG framework allows this threshold to be spatially heterogeneous and temporally adaptive. More details about the definition and selection of spatially heterogeneous and temporally adaptive homeostatic WSS threshold can be found in Aparício et al. (2014).

5.9.4.2 Collagen growth and remodelling

Growth/atrophy of the collagen fabric In this FSG study, in order to realise the adaption of the role of the additional protective collagens from a protective sheath to the main load bearer, we still assume the atrophy of the normal fibres instead of growth so that they are not able to bear much load. The method of modelling atrophy of these collagens is identical to the method of modelling elastin degradation

as introduced in Sec. 5.9.4.1 and will not be repeated again. However, we note that, if modelling collagen growth is needed, then the approach proposed by Aparício et al. (2014) can be utilised, which is an update of the current approach utilised in our 3D solid model: the phenomenological growth parameter β is explicitly linked to the magnitude of the differential cyclic areal stretch A^{CS} , which is defined as the ratio of the area metrics in the systolic and diastolic configurations. A specific functional form for β is also suggested, for details, refer to Aparício et al. (2014).

As for the additional protective adventitial collagen, again, their mass concentrations are constantly set to 1.

Collagen remodelling To model collagen remodelling, the following equations are utilised:

$$\frac{\partial \lambda_{J_p}^R}{\partial t} = \alpha \frac{[E_{J_p}^C]_{max} - E_{AT}^C}{E_{AT}^C} \quad (5.42)$$

for normal medial and adventitial collagen fibres, where

$$[E_{J_p}^C]_{max} = \max([E_{J_p}^C]_{sys}, [E_{J_p}^C]_{dias}) \quad (5.43)$$

and

$$\frac{\partial \lambda_{S_p}^R|^{min}}{\partial t} = \alpha \left(\frac{[\lambda_{S_p}^C|^{max}]_{max} - \lambda_S^{AT}|^{max}}{\lambda_S^{AT}|^{max}} \right) \quad (5.44a)$$

$$\frac{\partial \lambda_{S_p}^R|^{max}}{\partial t} = \alpha \left(\frac{[\lambda_{S_p}^C|^{min}]_{max} - \lambda_S^{AT}|^{min}}{\lambda_S^{AT}|^{min}} \right) \quad (5.44b)$$

$$\frac{\partial \lambda_{S_p}^R|^{mod}}{\partial t} = \alpha \left(\frac{[\lambda_{S_p}^C|^{mod}]_{max} - \lambda_S^{AT}|^{mod}}{\lambda_S^{AT}|^{mod}} \right) \quad (5.44c)$$

for adventitial protective collagen fibres, where

$$[\lambda_{S_p}^C|^{max}]_{max} = \max([\lambda_{S_p}^C|^{max}]_{sys}, [\lambda_{S_p}^C|^{max}]_{dias}) \quad (5.45a)$$

$$[\lambda_{S_p}^C|^{min}]_{max} = \max([\lambda_{S_p}^C|^{min}]_{sys}, [\lambda_{S_p}^C|^{min}]_{dias}) \quad (5.45b)$$

$$[\lambda_{S_p}^C|^{mod}]_{max} = \max([\lambda_{S_p}^C|^{mod}]_{sys}, [\lambda_{S_p}^C|^{mod}]_{dias}) \quad (5.45c)$$

$[E_{J_p}^C]_{sys}$ and $[E_{J_p}^C]_{dias}$ denote the magnitudes of the strains of the normal collagen strains in the J layer evaluated in the systolic and diastolic configurations respectively. $[\lambda_{S_p}^C|^{max}]_{sys}$, $[\lambda_{S_p}^C|^{min}]_{sys}$ and $[\lambda_{S_p}^C|^{mod}]_{sys}$ are the magnitudes of the maximum, minimum and mode actual stretches of the additional protective collagen evaluated in the systolic configuration respectively, and $[\lambda_{S_p}^C|^{max}]_{dias}$, $[\lambda_{S_p}^C|^{min}]_{dias}$

and $[\lambda_{Sp}^C]^{mod}_{dias}$ are the magnitudes of the maximum, minimum and mode actual stretches of the additional protective collagen evaluated in the diastolic configuration. The motivation for updating the remodelling equations from the ones in the 3D solid structural model to Eq. 5.42 to 5.45c is that, as the geometry becomes more complex, the temporal largest deformations during one cardiac cycle may not be achieved in the systolic configuration. In this study we assume that they occur in either the systolic or diastolic configuration. However, we note that due to the geometric complexity, for some positions on the geometry, the temporal largest deformations are very likely to be achieved at some specific configurations between the systolic and diastolic ones.

Mostly importantly in this FSG model, we consider the adaption of the collagen microstructure, i.e. the adaption of the attachment stretch distribution for the additional protective collagen fibres. The modelling approach is identical to that used in the 3D solid model hence will not be repeated here. For details, refer to Sec. 5.6.3.

5.9.5 Results analysis

We present one illustrative example of an enlarging IA in a patient-specific arterial geometry. Before presenting the results, we briefly review the implementation of the 1D collagen adaption model into the state-of-the-art 3D FSG framework. Initially ($t < 5$ years), the elastin degradation is prescribed to create a small IA on the wall surface. This aneurysm is numerically stabilised so that the collagen fabric is initially in homeostasis (i.e. the actual stretch distribution of the additional protective collagens is identical to its attachment stretch distribution). For $t > 5$ years, evolution of the aneurysm is driven by the atrophy of the elastin and normal collagen fibres in the wall linked to deviations of WSS from homeostatic levels. The homeostatic WSS level is considered to be a spatially homogeneous and temporally constant. Degradation of the elastin and normal collagen fibres leads to a transfer of load onto the additional protective collagens and the stretches of these collagens increase (i.e. the actual stretch distribution moves rightwards). Subsequent collagen G&R, as well as collagen microstructural adaption, attempt to restore these collagens to homeostasis (restoring the actual stretch distribution to the adapted attachment stretch distribution).

Streamlines in the whole artery are first illustrated to give the reader a first impression of the CFD simulation. Results of the GL strains of the elastin, the GL strain

of the medial collagen fibres, the evolutions of WSS, the elastin concentration, as well as the biaxial stretch index are also illustrated.

Fig. 5.20 shows the streamlines within the entire geometry including the growth of a small IA. Initial prescription of the degradation of elastins and normal collagen fibres localise the IA at the desired region. Further bulge of the geometry is a consequence of the continuous G&R of the arterial constituents. The region where the IA grew is zoomed in. It can be observed that the local out-pouching of the geometry complicates the flow condition within that region.

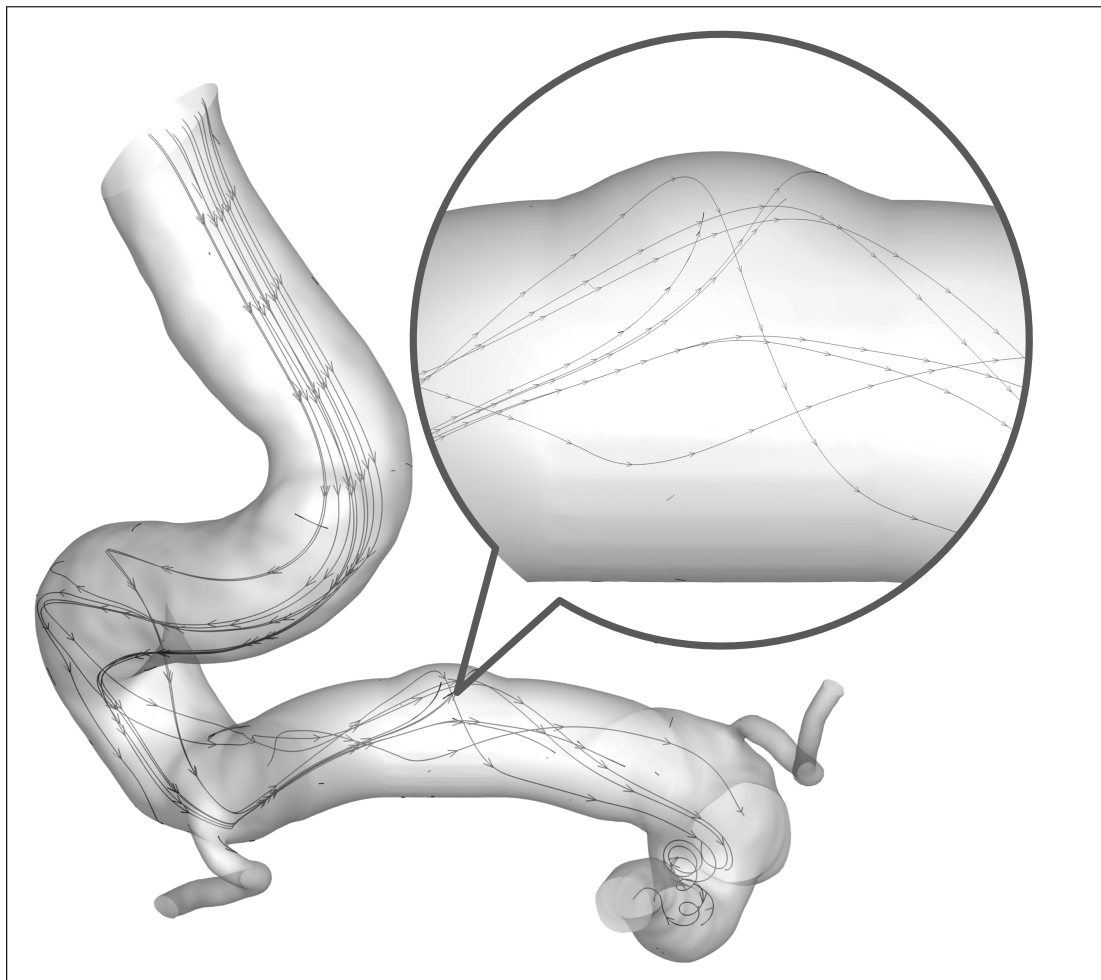


Figure 5.20: Streamlines within the entire geometry including the growth of a IA. The aneurysm region is zoomed in. The flow condition becomes more complicated in the aneurysm region where the geometry bulges out locally.

Fig. 5.21 and Fig. 5.22 quantify the enlargement of the geometry by showing the evolution of the GL strain component E_{11} (axial direction) and E_{22} (circumferen-

tial direction) of the elastins. These strains increase from between 0.3 and 0.4 (E_{11}) and between 0.2 and 0.3 (E_{22}) in the healthy artery, to between 0.6 and 0.7 (E_{11}) and higher than 1 (E_{22}) in the aneurysm dome at $t = 7.5$. It can also be seen that the axial strains outside both the proximal and distal necks regions of the aneurysm decrease as the aneurysm enlarges. This is a consequence of the axial retraction of the proximal and distal regions in the aneurysm segment. Due to the axial pre-stretch of the healthy artery and remodelling of collagen, this retraction actually assists the axial expansion of the aneurysm. A similar pattern of decreased E_{22} is also observed on the lateral sides of the IA, which also help the circumferential expansion of the aneurysm.

The evolution of the GL strains of the normal collagen fibres differs substantially from that of the elastin strains. This is due to the evolution of the reference configurations that the fibres are recruited to load bearing, as we have discussed throughout the whole chapter. Fig. 5.23 and Fig. 5.24 depict the evolution of the GL strains E_{M-}^C and E_{A+}^C of the normal medial negatively pitched and advential positively pitched collagen fibres, respectively. At $t = 0$ year, the collagen strains are constant throughout the domain, with the magnitudes equal to the attachment strain $E_{AT}^C = 0.073$. As the geometries enlarges ($t > 0$), there is an apparent increase in the magnitudes of the collagen strains in the aneurysm domain. However, due to the continuous evolution of the fibre recruitment stretch and the turnover of the fibres, the increases of collagen strains are negligible compared with the increases of elastin stretch. Interestingly, it can be seen that from time $t = 6$ years, the collagen strains start to decrease again as they tend to restore back to homeostatic levels, even though the aneurysm is still enlarging. However, in Fig. 5.24, both small regions of locally elevated and decreased collagen strains E_{A+}^C are observed outside the proximal and distal neck region of the aneurysm. This might be related to the positive pitch of these fibres which have a preferential axial orientation.

Fig. 5.25, and Fig. 5.26 show the evolutions of the WSS spatial distribution and the evolution of elastin concentration during the aneurysm growth respectively. Initially, a prescribed degradation of the elastin results in a local out-pouching of the geometry, which leads to a localised decrease in WSS within the aneurysm domain (Fig. 5.25 (a)-(d) and Fig. 5.26 (a)-(d)). As the aneurysm enlarges, the proximal regions (left) experience a lower WSS than the distal region (right). Regions of elevated WSS are also observed outside the proximal and distal neck region. From $t = 5$ years,

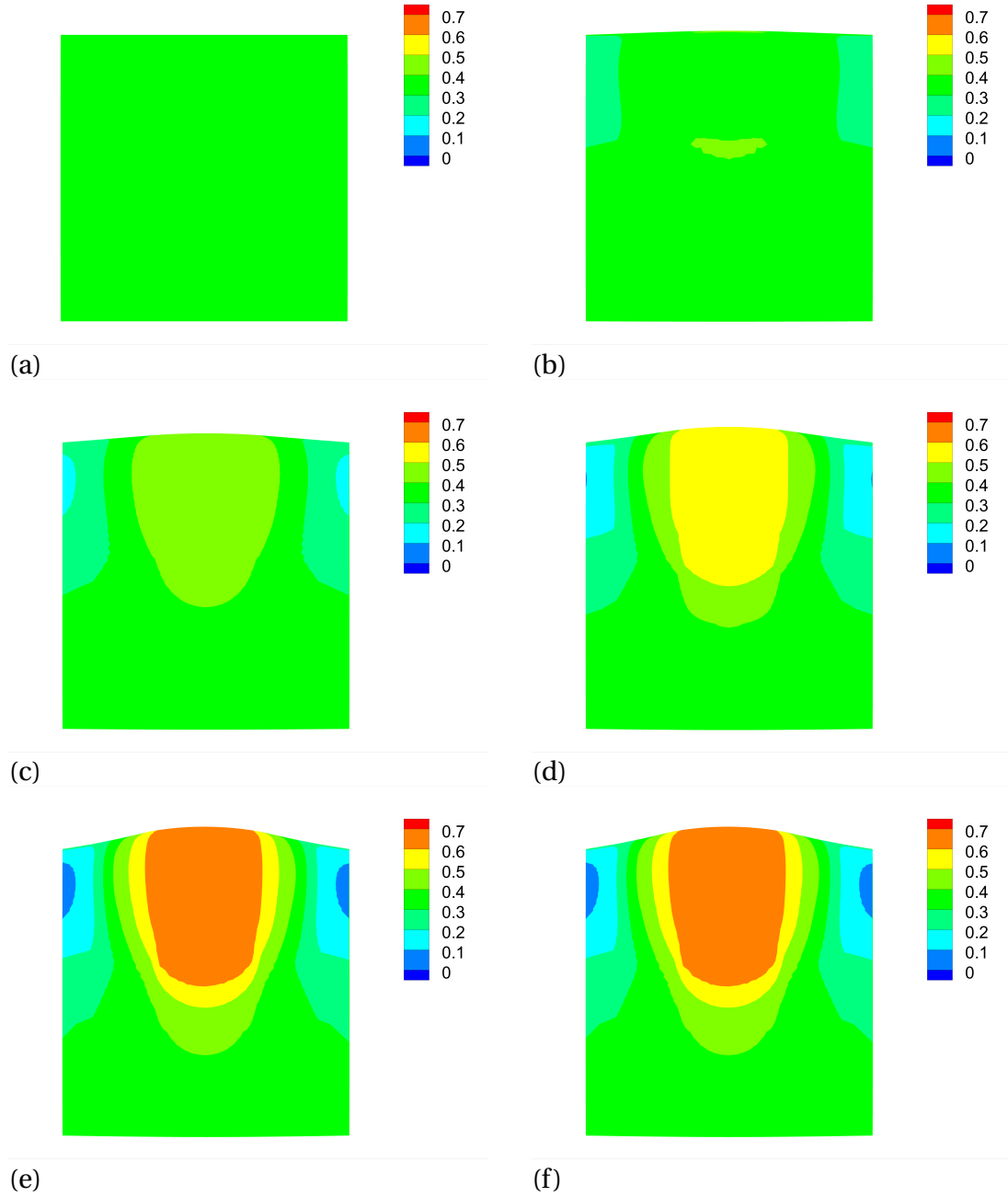


Figure 5.21: Evolution of the GL strain component E_{11} of the elastins for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively.

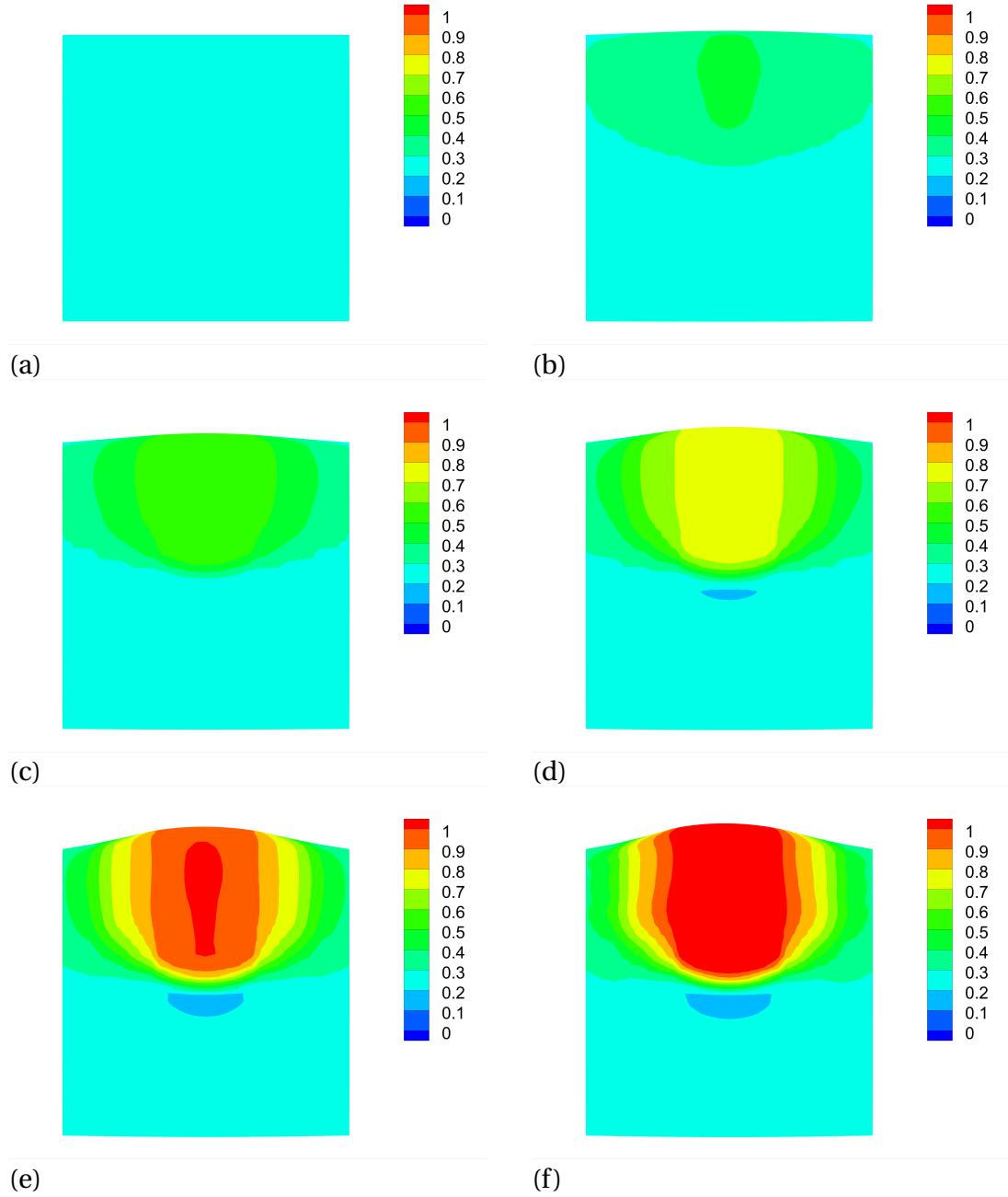


Figure 5.22: Evolution of the GL strain component E_{22} of the elastins for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively.

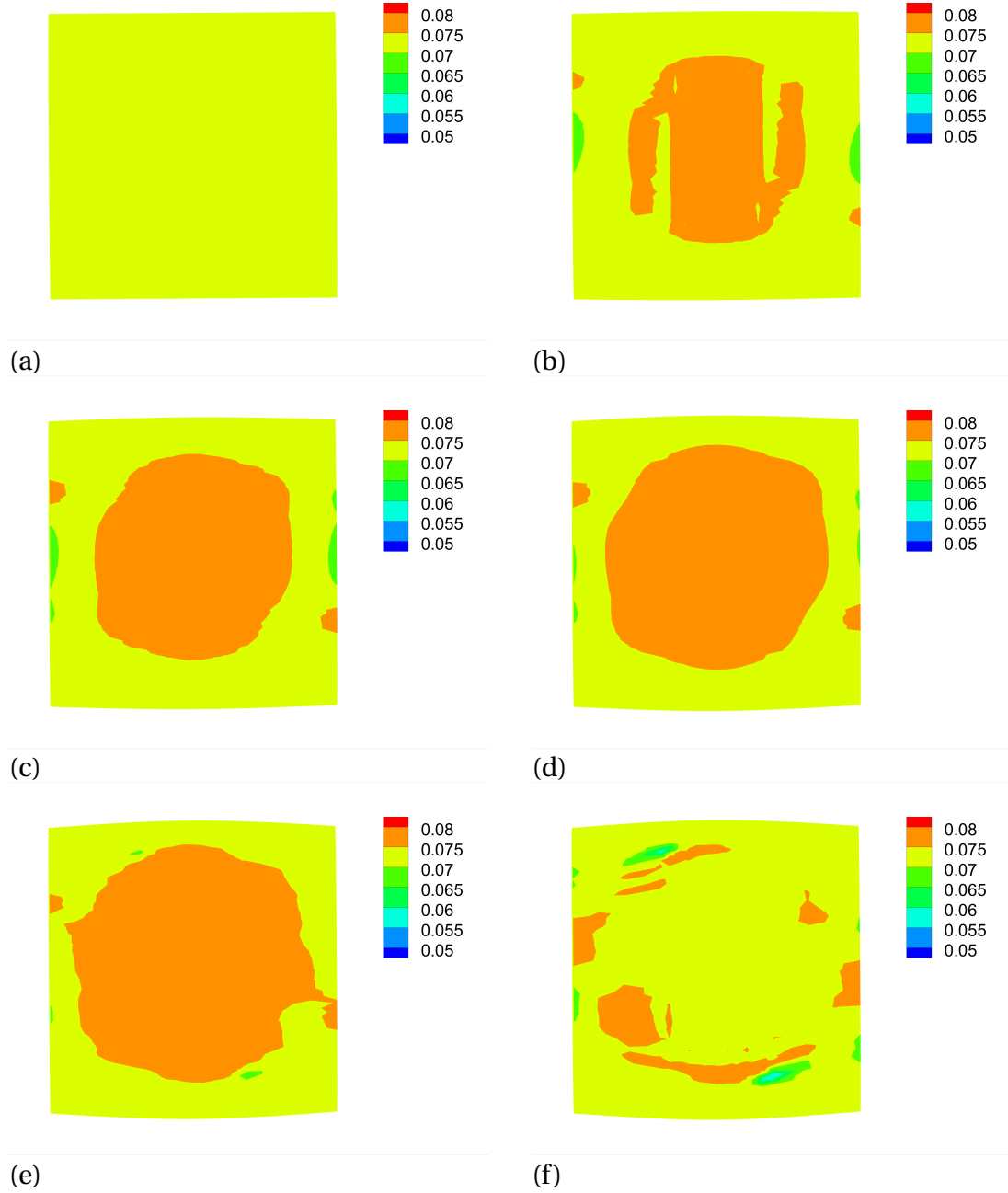


Figure 5.23: Evolution of the GL strains E_{M-}^C of the normal medial negatively pitched collagen fibres for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively.

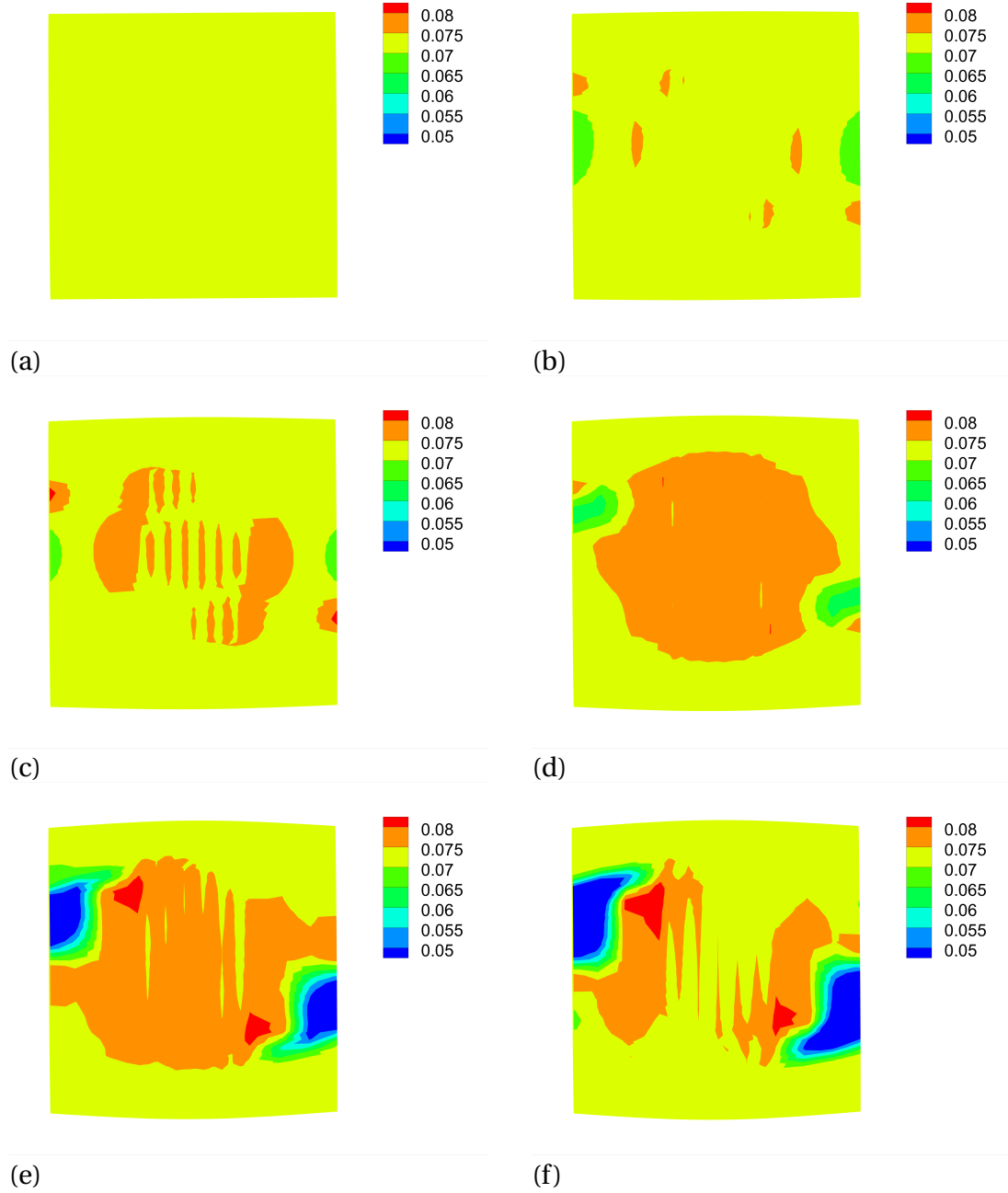


Figure 5.24: Evolution of the GL strain $E_{A_+}^C$ of the normal adventitial positively pitched collagen fibres for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively.

at some locations in the aneurysm domain, the level of WSS had reduced to less than the homeostatic WSS threshold (5Pa), hence the degradation of the elastins starts to be linked to the haemodynamics and is influenced by the further reduction in WSS magnitude. The evolution of the elastin concentration becomes spatially complex as a consequence of the evolving WSS pattern. Notice the similar patterns of distributions between Fig. 5.25 (f) and Fig. 5.26 (f): regions of lower WSS results in faster degradation of the elastin. This complex pattern of elastin degradation further influences the shape of the aneurysm, which in turn, affects the evolving pattern of the WSS.

Lastly, we consider the evolution of the cyclic deformation environment of the vascular wall. Fig. 5.27 illustrates the evolution of the recently proposed biaxial stretch index (BSI) χ^{BSI} . The healthy artery model is only subject to 1D cyclic circumferential stretching, hence $\chi^{BSI} = 0$ throughout the domain. As the aneurysm develops, the distribution of χ^{BSI} becomes more complex. Maximum values of $\chi^{BSI} = 1$ are achieved both in the centre of the aneurysm dome as well as in the regions surrounding the aneurysm neck; these locations are subject to equi-biaxial cyclic stretching.

5.9.6 Discussion

In this section, we present the implementation of the 1D collagen microstructural adaption model into a novel Fluid-Solid-Growth (FSG) computational framework for modelling aneurysm evolution. The 3D solid structural model of IA evolution introduced previously is integrated into a patient-specific geometry of the vasculature. This enables the growth and remodelling of the arterial tissue to be linked to the physiological haemodynamic environment obtained from a rigid-wall CFD analysis. To be more specific, the degradation of the elastinous constituents and the growth/atrophy of the normal collagen fibres are linked to deviations of WSS below its homeostatic level. Then remodelling of the collagen fibres is explicitly linked to the deformation of the arterial wall obtained from the quasi-static structural analysis. Evolution of the microstructure of the additional protective collagen fibres is achieved by adapting the attachment stretch distributions so that they gradually become the main load bearer in the arterial wall during IA evolution. We also use a patient-specific illustrative example to show the successful implementation of 1D collagen microstructural adaption model into the 3D FSG framework: a real-

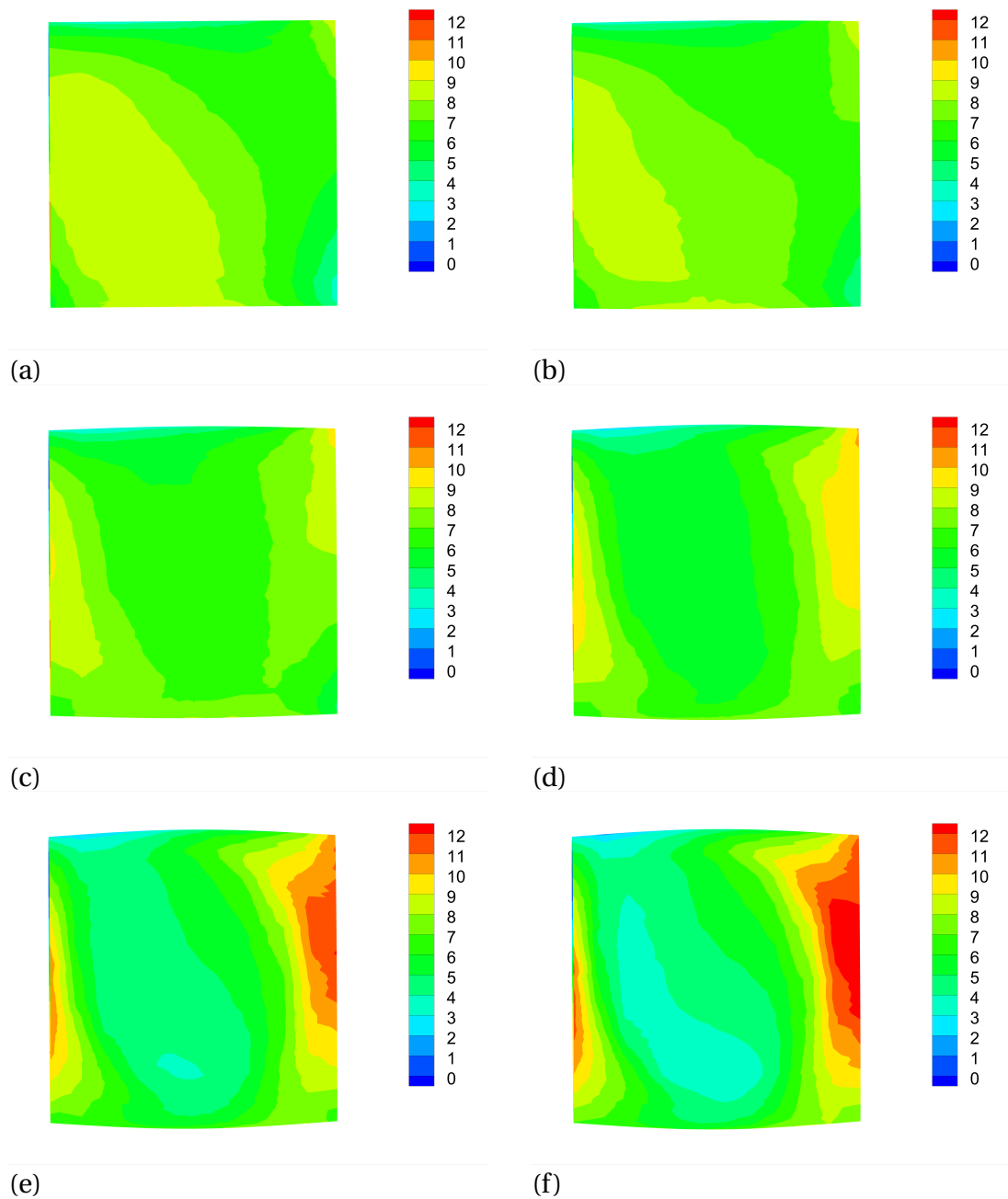


Figure 5.25: Evolution of the WSS on the arterial wall in aneurysm domain for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively. From $t = 5$ years, at some locations in the aneurysm dome, the magnitude of WSS has reduced to be lower than the homeostatic WSS threshold, which is assumed to be 5pa in this study. This is the beginning of linking elastin degradation to the haemodynamics.

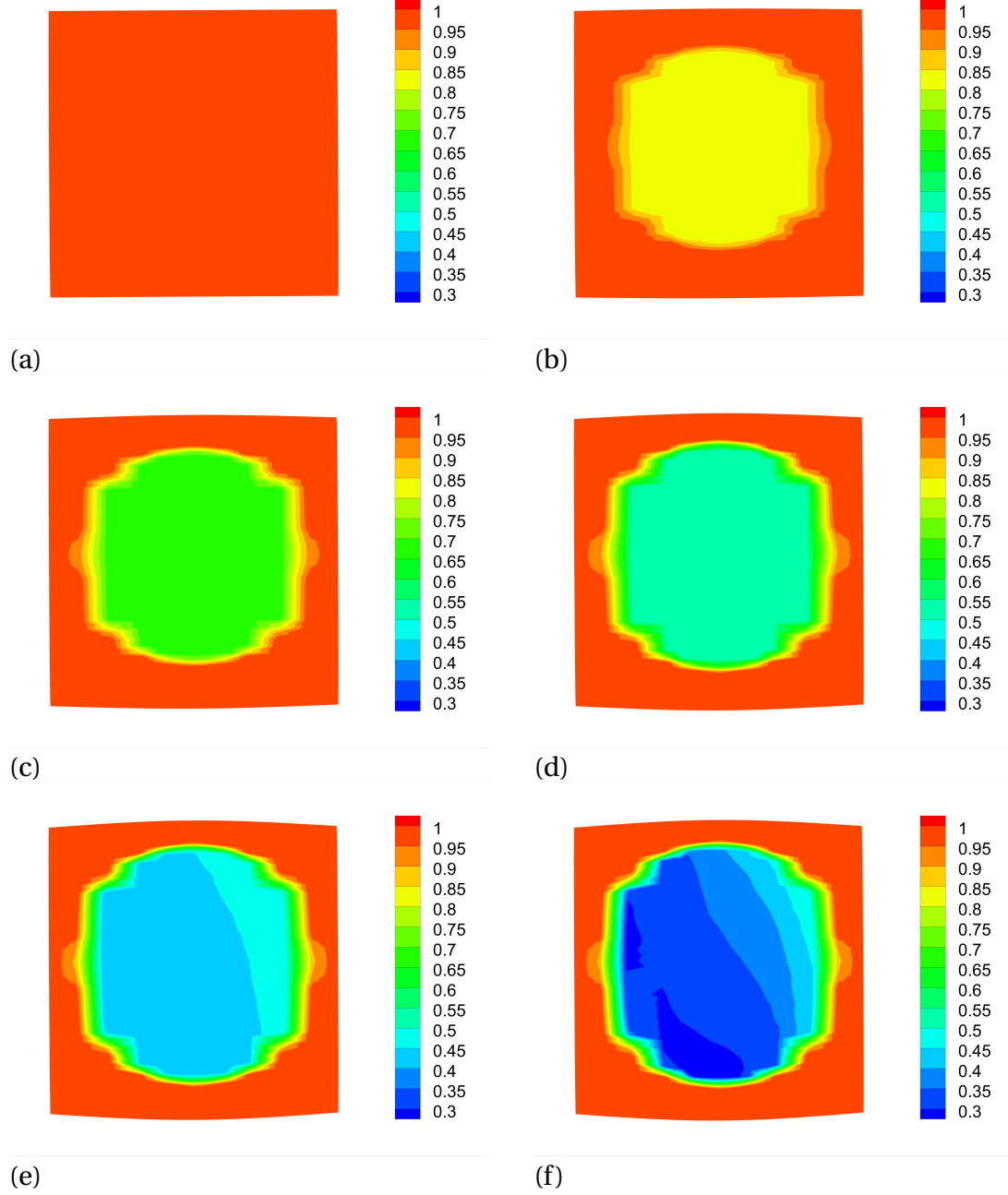


Figure 5.26: Evolution of the elastin concentration m^E during aneurysm growth for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively. (a)-(b) are prescribed evolution, where (e) and (f) are linked to the level of WSS.

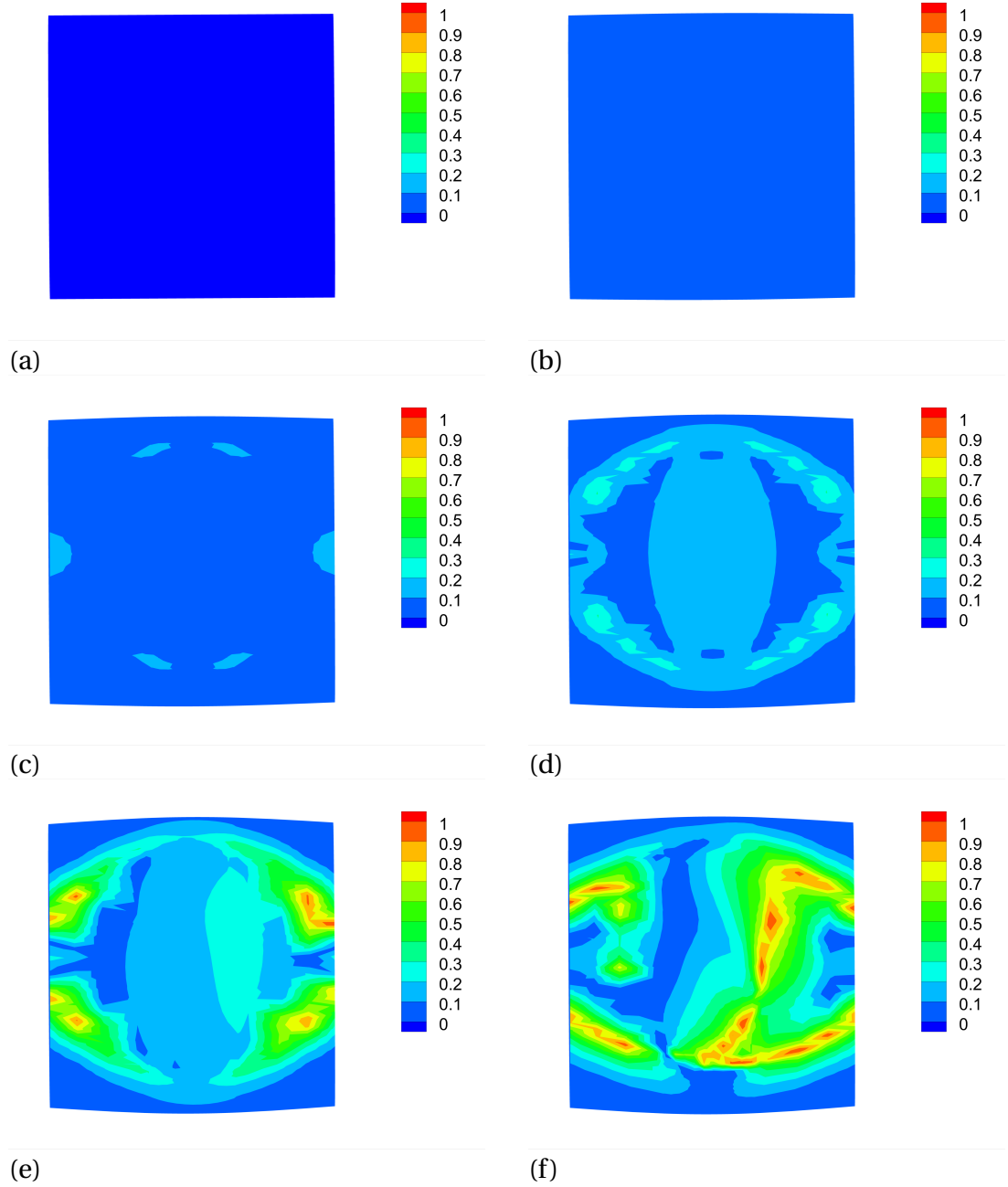


Figure 5.27: Evolution of the biaxial stretch index χ^{BSI} of the arterial wall in aneurysm domain for t values of (a) 0 year, (b) 1.5 years, (c) 3 years, (d) 4.5 years, (e) 6 years and (f) 7.5 years respectively.

istic small aneurysm grows on the surface of the arterial wall under the impact of haemodynamics.

One interesting problem which needs to be addressed is that in this FSG study, the size of the simulated aneurysm is obviously smaller than the aneurysm evolved in case 4 in the 3D solid model. A possible explanation for this is that the elastin and normal collagen degradation rate in the FSG model is significantly slower than that rate in the solid model: in the solid model, most of these constituent has already been degraded by $t = 2$ years (only 10% remains), whereas in the structural model, more than half of these constituents still remain in the arterial wall by $t = 5$ years before their degradation is linked to the haemodynamics. The enlargement of the geometry is a result of the degradation of the constituents. This indicates that at $t = 2$ years, the geometry in the structural model has already bulged by a large amount whereas the geometry in the FSG model only has a slight out-pouching. In addition, in both models, the adaption of the attachment stretch distribution is analytically prescribed between $t = 2$ years and $t = 4$ years. In other words, from $t = 2$ years, the additional protective collagen fibres start to adapt their microstructure and to bear the load shifted from the degradation of other constituents. The attendance of these collagen fibres in load bearing slow down the growth rates of the aneurysms. At $t = 4$ years, the attachment stretch distribution reaches the upper bound and the adaption stops. From this time point, new additional protective collagens are always configured into the ECM with the adapted attachment stretch distribution. These collagen fibres prevent the aneurysm from further enlarging. However, in the FSG model at $t = 4$ years, there are still more than 60% of the other arterial constituents remaining in the wall. Even though they are further degraded as their concentrations are linked to the haemodynamics, these additional protective collagens tightly wrap around the artery so that further enlargement of the geometry is restrained. As a result, only a small aneurysm is observed on the arterial wall. In the FSG model, if we allow the adaption of the attachment stretch distribution to start after most of the constituents have been degraded, we believe an aneurysm of similar size as the one in case 4 of the solid model can be achieved. This problem clearly demonstrates the need for a more realistic adaption of attachment stretch distribution rather than being analytically prescribed. Better understanding of the biological process of how collagens are configured into the matrix by the cell to bear load will be helpful.

In Fig. 5.24(c) and Fig. 5.24(f) as well as a few result figures presented in Sec. 5.7

(such as Fig. 5.12(a)), banded contours of the plotted variables can be clearly seen. We consider this problem to be likely caused by the interpolation artefact during the numerical computation. In both the 3D solid structural model as well as the FSG framework, we use *structured quadrilateral mesh* to discretise the arterial surface for its high space efficiency. The mesh is refined in the aneurysmal segment with fixed smaller node width, but no remeshing of the surface is conducted during the simulations. As the IA grows, the geometry bulges out and becomes more complex. At certain areas of the geometry where the gradients of the field whose solution is sought is high, the accuracy of the solutions will be reduced and sudden changes of values of the variables at the local nodes can be usually encountered. As a result, the values interpolated within each element may also change rapidly (i.e. have large gradients). Therefore as shown in our results, when the contours of these fields are plotted, if no enough levels of the colour maps are set to capture these values with big gradients, then these contours may appear as banded pattern. Improving the mesh quality and using finer unstructured mesh in the regions where the surface tend to bulge out for more accurate solutions might eliminate this problem.

The FSG we adopted in this study includes several modifications compared with Aparício et al. (2014):

- In this study, the homeostatic WSS threshold we used is spatially and temporally homogeneous. However, in Aparício et al. (2014), the homeostatic threshold is allowed to be spatially and temporally heterogeneous and three distinct definitions are considered: 1. constant threshold (which is exactly the definition adopted in our study); 2. spatially heterogeneous threshold; 3. spatially heterogeneous and temporally adaptive. It is observed that different choices of definitions of the thresholds will result in different spatial variations in tissue G&R and distinct predicted geometries of the evolved aneurysms (Aparício et al., 2014). Consequently, in future sophistication, it may actually be necessary to consider the spatial and temporal heterogeneity of endothelial homeostasis. However, the understanding of endothelial homeostasis is still far from enough. Undoubtedly, better representation of the ECs in mathematical modelling (especially on how WSS is sensed by the ECs and influences their functionality, and on the communication between them and other vascular cells), numerical parameter studies may be helpful in gaining this understanding (Aparício et al., 2014).

- In this study, we actually model the atrophy of the normal collagen fibres so that the additional protective collagen fibres can take the role of the main load bearer when the aneurysm grows. In Aparício et al. (2014), where no additional protective collagen is present, collagen growth is modelled and linked to the *cyclic deformation* of the vascular cells (an update on Eq. 5.31.) According to our simulation results, the loading condition in the arterial wall changes from 1D cyclic circumferential stretching in the initial healthy geometry to bi-axial cyclic stretching in the aneurysmal geometry. The vascular cells (particularly the fibroblasts) embedded in the arterial wall may actually be able to ‘feel’ this change and adapt accordingly. This may possibly affect its production of matrix substance. Hence incorporating the effect of cyclic deformation in modelling arterial G&R seems to be more biologically reasonable. However, we must notice that this is still a guess. Experimental guidance is definitely necessary in deepening the understanding of fibroblast mechanobiology.
- In this study, we consider the microstructural adaption of the collagens, i.e. the concept of probability distribution is utilised to more realistically represent the recruitment configurations of the fibres and their attachment to the ECM. In addition, we consider that the state of stretch distribution at which newly synthesised fibres are attached to the ECM is *variable*, which may depend on the extracellular mechanical environment of the cells. On the contrary, in Aparício et al. (2014), the concept of hypothetical fibres are utilised to represent the gross mechanical response of a bundle of fibres. Under this concept, single values of attachment, recruitment and actual stretches are used instead of distributions. More importantly, it is assumed that collagen fibres are configured into the ECM in *fixed* state of stretch, which is independent of the extracellular environment. This is a universal assumption in the literature of modelling arterial G&R. Another study that adopts this FSG to simulate the evolution of IAs is Watton et al. (2011a), in which the attachment stretch is also considered to be constant. Although their study is also about the simulation of IA evolution on cylindrical arteries, due to the huge difference in aneurysm size between their study and ours, it will not be very meaningful to compare our results with theirs. However, it is reasonable to deduce that, given the large increase in the collagen mass density in Watton et al. (2011a), the arterial wall will still be over-thickened, whereas in our study, the remodelled wall thickness could be significantly reduced due to the prescribed atrophy of the

arterial constituents. On this aspect, implementation of the 1D collagen adaption model into the 3D FSG model predict more realistic results than the FSG model itself due to the consideration of collagen microstructural adaption.

5.10 CONCLUSION

In this chapter, we present the successful implementation of the 1D collagen microstructural adaption model introduced in Chapter 4 into two 3D IA evolution models: a solid structural model and a state-of-the-art Fluid-Solid-Growth (FSG) framework. In both models, the arterial segments where IAs form are modelled as two-layer, nonlinear elastic cylindrical membrane subject to internal pressure and physiological axial pre-stretch. Both the media and the adventitia layers are modelled as composites of elastinous and normal collagenous fibres. Additional protective collagen fibres are added to the adventitia layer, which are assumed to bear no load in the normal physiological regime and act as a protective sheath to prevent the artery from over-dilation. IAs develop as a consequence of arterial growth and remodelling. For the sophisticated solid structural model, in order to localise the IA, degradation of the elastins and normal collagens is prescribed within a circular patch. Remodelling of the collagen recruitment stretches allow the degradation and deposition of collagen fabrics in altered configurations to be simulated. Temporal adaptations of the attachment stretch distribution of the additional protective collagen fibres are incorporated to model their transition from the protective sheath to the main load bearer during IA evolution. For the sophisticated FSG framework, the updated solid structural model is integrated into a patient-specific geometry of the vasculature, enabling arterial growth and remodelling (G&R) to be linked to the physiologically representative spatial distributions of haemodynamic stimuli obtained from a rigid-wall computational fluid dynamics (CFD) analysis. In addition, elastin degradation is first prescribed and then linked to the reductions in wall shear stress (WSS) below the assumed homeostatic threshold. IAs realistic in size are observed to develop in both two models. The sophisticated solid structural model demonstrates that incorporation of the collagen microstructural adaption into the previous solid structural model can predict stabilised IAs with more realistic evolving wall thicknesses and stresses, whereas the sophisticated FSG framework exhibits the successful implementation of the collagen adaption model into the previous FSG framework.

In the next chapter, we overview our studies again, summarise the main findings, identify the major limitations and suggest the future research directions.



CONCLUSIONS AND RECOMMENDATIONS FOR MODEL DEVELOPMENT

The focus of this entire thesis is to develop novel methods to model the inception of intracranial aneurysm (IA) disease, as well as the microstructural adaption of the collagen fabrics during IA development. Broadly speaking, the entire study has two aims:

- to examine the hypotheses regarding the influence of different proposed haemodynamic indices on the inception of IAs;
- to identify one of the limitations of current aneurysm growth models: over-thickened wall thickness and under-estimated stresses in the wall, which are caused by unrealistic assumptions in the model formation. And on this basis, to develop new models with more realistic assumptions and exam the results to see improvements;

Bearing in mind these two objectives, we can generally divide this thesis into two big parts:

Modelling aneurysm inception: a novel numerical method is developed to reconstruct the ‘pre-aneurysmal’ geometry of the vasculature from the diseased

one. Subsequently, the method is applied to study the influence of patient-specific haemodynamic environment on IA inception in 22 clinical cases.

Modelling aneurysm growth: a novel 1D mathematical model of the adaption of the microstructure of the collagen fibres during aneurysm evolution is developed. This model is integrated into two models: a 3D solid aneurysm growth model to simulate IA evolution on 3D geometries, as well as a state-of-the-art Fluid-Solid-Growth (FSG) framework to simulate IA evolution on patient-specific geometries where the arterial growth and remodelling is linked to the local haemodynamic environment in the aneurysm domain.

In this chapter, we summarise the key findings and identify limitations of our studies. We also make recommendations for further developments and refinements to the current modelling framework.

6.1 SUMMARIES OF THE STUDY

In this section, we overview our study again and summarise the main findings.

Novel vessel reconstruction method. A novel automated numerical method is developed to reconstruct the hypothetical ‘pre-aneurysmal’ geometry of the healthy vasculature based on medical images depicting IAs. In this novel approach, the aneurysmal segment is reskeletonised and a Frenet frame is computed along the new skeletonisation; upstream and downstream boundaries of the aneurysmal segment are expressed in terms of the local Frenet frame basis vectors; finally a closed curve is propagated along the skeletonisation using the local Frenet frames vectors to smoothly morph the upstream boundary into the downstream boundary. This novel method takes into account the tortuosity of the arterial vasculature and requires minimal user subjectivity.

Investigation of haemodynamics on IA inception. The novel vessel reconstruction method is applied in 22 clinical sidewall IAs to prepare the hypothetical ‘pre-diseased’ geometries; computational fluid dynamic simulations are performed on those geometries; an objective definition of ‘a positive correlation’ is proposed; correlations are analysed between five clearly defined haemodynamic indices (WSS, WSSG, OSI, AFI and GON) and *known* locations of aneurysm formations. It is observed that locally elevated WSS and

GON are highly correlated with regions susceptible to sidewall IA formation, whilst haemodynamic indices associated with the oscillation of the WSS vectors have much lower correlations.

Novel 1D model of collagen microstructure adaption. A novel 1D mathematical model for the microstructural adaption of the collagen fabric during aneurysm evolution is proposed. It is the first collagen microstructural adaption model in the literature that explicitly defines the functional forms for the attachment stretch distribution and considers its temporal adaption. In this model, new collagen fibres are assumed to be configured into the extracellular matrix (ECM) in a state of *stretch distribution* (the attachment stretch distribution) which is temporally *adaptive*. Different means of adapting the collagen attachment stretch distributions are examined in a 1D conceptual model of aneurysm evolution, including different combinations of shifting, skewing and narrowing of the distribution. The aneurysm evolves as a consequence of the degradation of the elastinous constituents and the growth and remodelling of the collagenous constituents. It is observed that in general if larger proportions of collagen fibres are configured into the matrix with bigger attachment stretches, then less collagen fibres are required to stabilise the aneurysm, leading to a much reduced thickness evolution of the arterial wall. It is concluded that in order to achieve a thinned wall during aneurysm evolution, collagen fibres are very likely to be configured into the ECM in a way that their attachment stretch distribution is continuously shifted positively before reaching an upper limit, with the possible presences of narrowing and skewing of the distribution.

Integration of the 1D collagen adaption model into 3D models of IA evolution.

The novel 1D collagen adaption model is successfully implemented into two 3D models of IA evolution: a solid structural model and a Fluid-Solid-Growth (FSG) model. In the sophisticated solid model, the nonlinear membrane formulation is adopted. The arterial wall is modelled as a two-layer, fibre-reinforced composite with the elastinous and collagenous constituents embedded in each layer. Additional protective collagen fibres are added to the adventitia and are assumed to bear no load in the initial physiological configuration. An IA develops as a consequence of the G&R of the arterial constituents: degradation of the elastin and normal collagens is prescribed within a circular patch; collagen recruitment stretch distributions are re-

modelled to simulate the evolution of their natural reference configurations; collagen attachment stretch distribution is also adapted heterogeneously within the artery. It is observed that the IA stabilised in size with more realistic thickness and stress evolution. A question is proposed: how do vascular cells realise the heterogeneous adaption of the attachment stretch distribution in the wall? In the sophisticated FSG model, an illustrative case of IA evolution is utilised to explain the model and demonstrate its implementation: the updated solid structural model is integrated into a patient-specific geometry of the vasculature. This enables the G&R of the arterial tissue to be linked to the physiologically representative spatial distributions of haemodynamic stimuli obtained from a rigid-wall CFD analysis. Degradation of the constituents are initially prescribed and subsequently linked to the reductions in WSS below the homeostatic threshold when the WSS drops below a spatially homogeneous level. Collagen remodelling also accounts for the stretches of the vascular cells in the diastolic configuration. Adaption of the microstructure of the additional collagen fibres is incorporated. It is observed that a small size IA evolves on a patient-specific vasculature.

6.2 LIMITATIONS OF THE STUDY

In this section, we identify some major limitations of the studies.

Difference between the reconstructed geometry and the pre-aneurysmal healthy one.

To investigate the real haemodynamic environment prior to the formation of an IA through CFD simulations, we need the healthy arterial geometry, which is barely available since most clinical collections of aneurysm data do not contain the pre-aneurysmal healthy blood vessel images, as it is impractical, costly and ethically dubious to routinely capture images of subjects without the presence of due clinical concern. Hence numerical methods have been developed to reconstruct this ‘healthy’ geometry from the diseased ones. One key question is to what extent can the reconstructed hypothetical ‘healthy’ geometry reflect the real healthy geometry? In order to reconstruct the aneurysm region, our vessel reconstruction method (in fact all the vessel reconstruction methods in the literature) use local geometric information in the vicinity of the aneurysm region. However, as an IA grows, the local

geometry of the vessel may be distorted, particularly for large aneurysms. In other words, this local geometric information of diseased artery after IA development may already be different from the corresponding information of the real healthy artery. This difference may be even amplified by the errors between in vivo arterial geometries and the computer constructed 3D geometries which rely on the accuracy of the imaging techniques as well as the stability of the patient. As a result, the difference between the ‘healthy’ geometries reconstructed from the numerical methods and in vivo healthy arterial geometries may not even be measurable, which could be possibly significant. However, what we really should be concerned about is whether this difference is acceptable, i.e. whether it will affect the spatial distributions of the haemodynamic indices computed from the CFD analysis, and thereby affect the conclusion of the study. Nevertheless, despite of this limitation, we believe our study still has the potential to examine the hypotheses of the influence of haemodynamics on IA inception.

Vessel reconstruction method not working on bifurcating aneurysms. Another limitation of our vessel reconstruction method is that it cannot be applied to bifurcating aneurysms. Given that 90% of the IAs grows at bifurcations, it would be beneficial to develop an automated vessel reconstruction method that can be applied to bifurcating aneurysms. Some preliminary advancements have been made in developing such a method. More details will be provided in Sec. 6.3.1.

Need of better understanding of endothelial cell homeostasis. Similar to many other computational studies in this field, our study in Chapter 3 is a CFD study with the aim of investigating if there are any correlations between local haemodynamic patterns and the locations where aneurysms are observed to form. There is an obvious lack of the understanding of how exactly haemodynamics interact with the biology of the ECs, and hence how it influences the formation of IAs. It is well known that haemodynamic forces can modulate the structure and function of ECs in blood vessels to maintain a homeostasis within the cell. Under normal conditions, when the pressure and flow change, ECs will adapt accordingly to optimise their functional performance (Chien, 2007). We also reviewed in Sec. 1.4 and 1.5 that previous studies have shown that ECs will have different shapes, alignments, phenotypes and even gene expressions under different types of mechanical environment (such as

high WSS, high WSSG etc). However, the understanding of exact interactions between ECs and different flow environments is still very limited. Questions such as what the exact the definition of EC homeostasis is, whether it is heterogeneous on the lumen surface, whether it is temporally adaptive (Aparício et al., 2014), and more importantly, how exactly it is maintained in the face of external perturbations still cannot be answered. These questions may actually be quite difficult to answer in the near future merely based on experimental observation of ECs. This is also the reason why mathematical models of ECs and their interaction with the mechanical environment is needed: to test different hypotheses. Integration of these two types of research (biological and mathematical modelling) will further help our understanding of the mechanobiology of ECs. With better improved understanding of the mechanisms, CFD will contribute even more to studies of IA inception. This is also one of the reasons why a Fluid-Solid-Growth model is preferable when studying IA evolution.

Modelling of collagen orientation distribution and orientation remodelling. In the IA evolution models in our study, we assume a distribution of collagen attachment stretches based on the consideration of a distribution of collagen waviness in the unloaded configuration. Experimental results show that the spatial orientations of the fibres also follow certain statistical distributions (Rezakhaniha et al., 2012; Schrauwen et al., 2012). However, this fibre property of orientation distribution with respect to a mean direction is not accounted for. Models of arterial tissue G&R incorporating the concept of collagen orientation distribution can be seen in the literature (Hill et al., 2012; Martufi and Gasser, 2012). Ideally this would also be considered in the future. In addition, in our modelling approach, collagen orientations are fixed with respect to the unloaded reference configuration of the artery. Their orientation with respect to the loaded (in vivo) configuration changes over time due to the body-fitted coordinate system that we adapt and to the deformation of the arterial geometry from being a cylinder. New fibres are assumed to be laid down in the direction of the existing fibres in the loaded configuration. Aparício et al. (2014) pointed out the biological justification for this assumption: in order to deposit new fibres, fibroblast cells need to attach themselves to the existing fibres and move in the direction along these fibres. Thus when modelling this effect, it is thought that the orientation of the newly synthesised fibres is

dependent on the orientation of the existing fibres along which the fibroblast cells crawl (Aparício et al., 2014). The net effect of this is that all collagen fibres reorient towards the directions of increasing principal stretch in the loaded configuration as the aneurysm evolves (Aparício et al., 2014). However, studies can also be seen in the literature with different assumptions. For example, Driessen et al., 2005, 2008 assume that new fibres are laid down in the direction of the principal stretches in the loaded configuration. More experimental guidance is needed to examine which assumption has the best consistency with reality. Given that the additional protective collagen fibres in our models take over most of the load during IA evolution, more accurate modelling of how the collagen structure adapts can be of very great significance. Further sophisticating the collagen microstructural adaption model to incorporate orientation distributions of the fibres, as well as the remodeling of this orientation distribution with experimental guidance may prove of great value in this respect.

Need of the understanding of vascular cell mechanobiology. Our lack of understanding of the mechanobiology of the fibroblasts also currently limits the development of our models. It is not known to us what exactly drives the fibroblasts to adapt the attachment stretch distribution of the collagen fibres, not to mention how exactly they achieve a spatially heterogeneous adaption. We have shown in all of our 1D, 3D solid as well as the FSG models that this adaption of the attachment stretch distribution plays an extremely important role in IA evolution, as it controls the mass concentration evolution, thickness evolution, stress evolution, and even the size of the evolved aneurysm. Hence a better understanding of how fibroblasts biomechanically and biochemically interact with the environment is of great necessity. In addition, given the facts that VSMCs deposit the connective tissue and matrix degrading enzymes, and that their apoptosis is associated with the formation of IAs (Watton and Ventikos, 2009), these cells also play a critical role in the development of IAs. Consequently, it would be of interest and value to improve the representation of the mechanobiology of these cells by modelling the signalling pathways relating the mechanical stimuli acting on these cells to the biochemical substances that they produce, as well as enzymes and the production of connective tissues. Moreover, explicit representation of the active and passive responses of the VSMCs under different phenotypes using a proper constitutive

model, and relating their mechanical response to the chemical environment such as calcium concentration (Zulliger et al., 2004; Murtada et al., 2010; Hill et al., 2001) may also be valuable (Watton and Ventikos, 2009).

6.3 FINAL REMARKS AND FUTURE RECOMMENDATIONS

6.3.1 An arterial bifurcation vessel reconstruction method

One limitation of our vessel reconstruction method is that, whilst this method works well for the sidewall saccular aneurysms, it cannot be applied to remove terminal aneurysms at arterial bifurcations (see Fig. 6.1). Given that 90% of cerebral aneurysms are occurring at arterial bifurcations, there is a need for a more advanced automated vessel reconstruction method that works on arterial bifurcations. Inspired by the method of modelling tree branching introduced by (Bloomenthal, 1985), some preliminary work has been conducted and a new vessel reconstruction method is under development. Being different from the vessel reconstruction method presented in this thesis, the new method directly interpolates splines between the upstream boundary and the two downstream boundaries, as well as between the two downstream boundaries (see Fig. 6.2). In Fig. 6.2, two splines are constructed first (yellow and red). Together with the three boundaries, they form the skeleton of the bifurcation. Subsequently, splines are constructed directly to connect the upstream boundary to the two downstream boundaries. To connect the two downstream boundaries smoothly, splines are interpolated with the guidance of the red spline.

One problem encountered so far in the development of this method is the spatial overlapping between the splines on the surfaces of the non-bifurcation regions and of the bifurcation regions (see Fig. 6.3). A numerical algorithm has recently been developed to detect the spatial overlapping points and re-interpolate splines through those points (Dandapani, 2014). Fig. 6.4 shows the general process of this method. Conceptual geometry of the arterial bifurcation has also been reconstructed after the spline overlapping problem was solved.

However, further development of this method is needed:

- The spline overlapping detection algorithm works if there is only one pair of splines that overlap. More splines may overlap if we need a finer reconstruction.

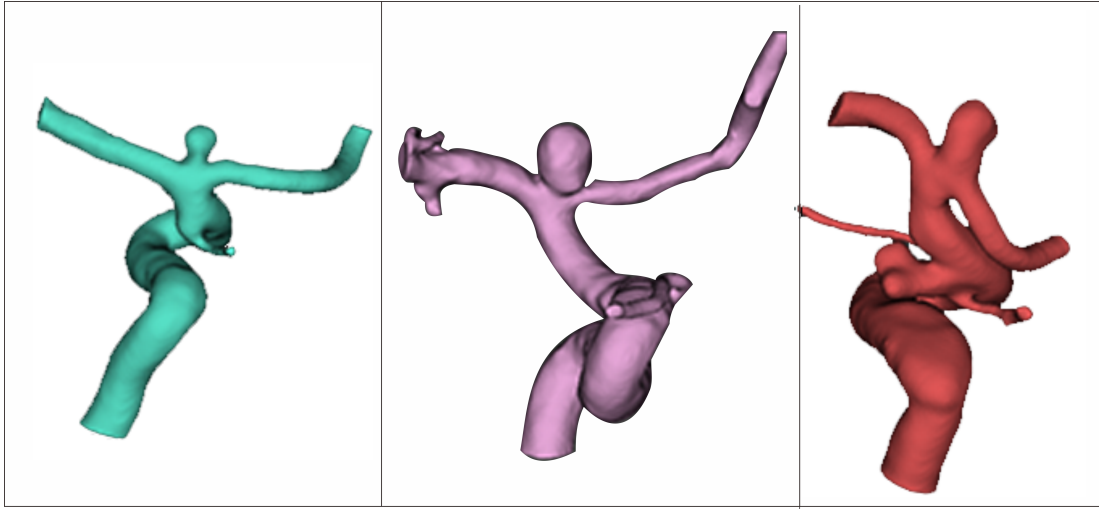


Figure 6.1: Three examples showing IAs growing at bifurcations. The novel vessel reconstruction method proposed within this thesis cannot be applied to these types of geometries.

tion of the geometry. Hence this algorithm needs to be improved so that it also works on detecting the overlapping of multiple splines;

- The entire arterial bifurcation reconstruction method needs to be fully automated;
- This method also needs to be refined so that it also works perfectly on physiological geometries.

Once a fully automated bifurcation reconstruction method is developed to work perfectly on physiological geometries, it can be applied to remove bifurcating aneurysms and reconstruct the geometries. CFD simulations will be carried out on those geometries to investigate the haemodynamic environment at arterial bifurcations and its influence on IA inception.

6.3.2 Modelling IA evolution on arbitrary geometries

The sophisticated 3D solid structural model of IA evolution that we present in this thesis simulates the growth of an aneurysm on an idealised cylindrical vessel. Modelling the artery as a cylinder implies that the structure of the collagen and spatial distributions of G&R variables are initially homogeneous and can be analytically determined (Aparício et al., 2014). For aneurysms growing on short segments of

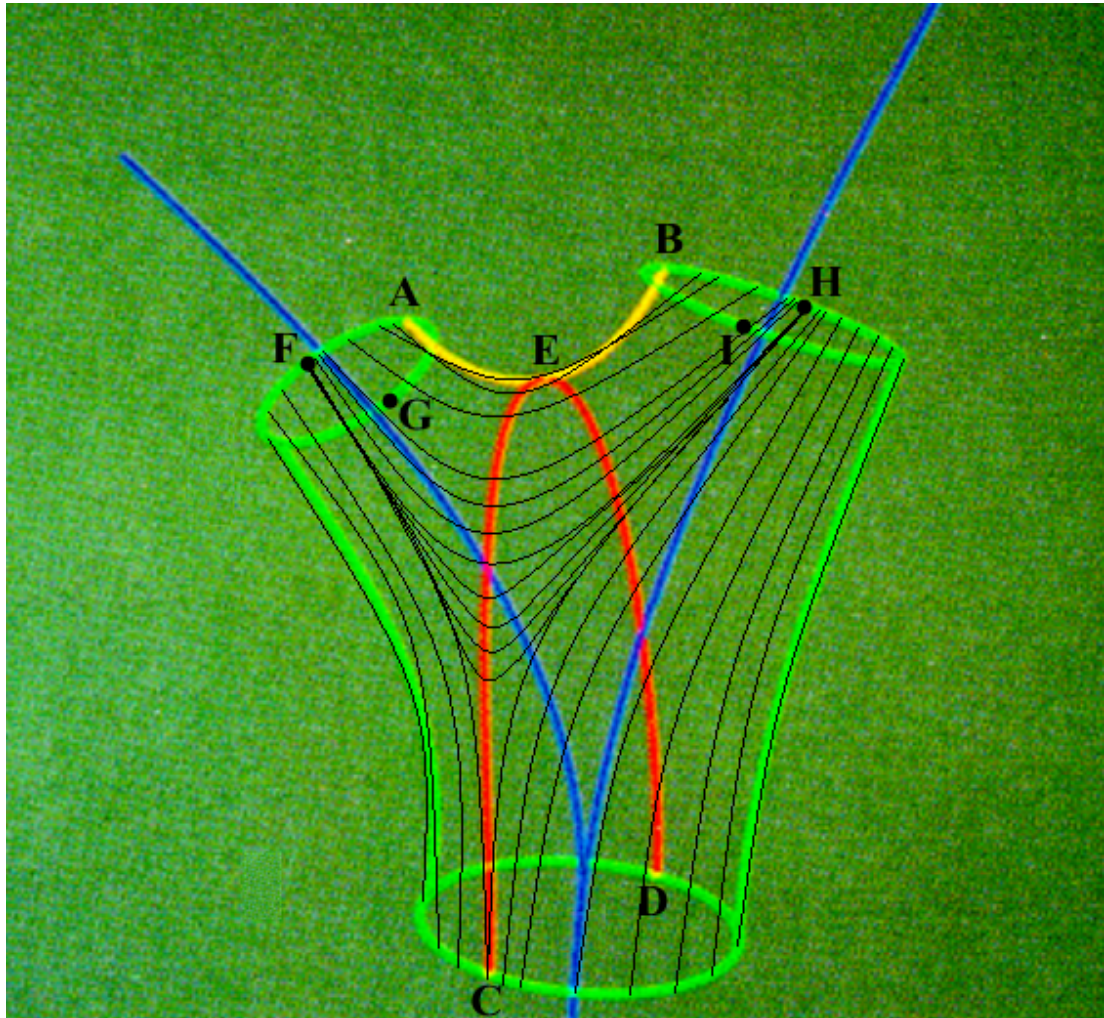


Figure 6.2: A developing automated numerical method to reconstruct the arterial geometry at bifurcations (adapted from Bloomenthal (1985)).

cerebral arteries, we consider a cylinder to be a good approximation of the physiological arterial geometry. This sophisticated 3D solid model is also integrated into a patient-specific geometry in the FSG modelling framework so that the G&R of the arterial tissue benefits from the real physiological haemodynamic stimuli. However, the haemodynamic environment in the idealised cylindrical arterial segment may still be different from that of the physiological healthy artery. This triggers the need to further sophisticate the FSG framework so that the development of IAs can be simulated on a patient-specific physiological arterial geometry directly. Additionally, it would also be of interest and value to model the evolution of bifurcation IAs. Hence modelling IA evolution on arbitrary geometries draws our attention.

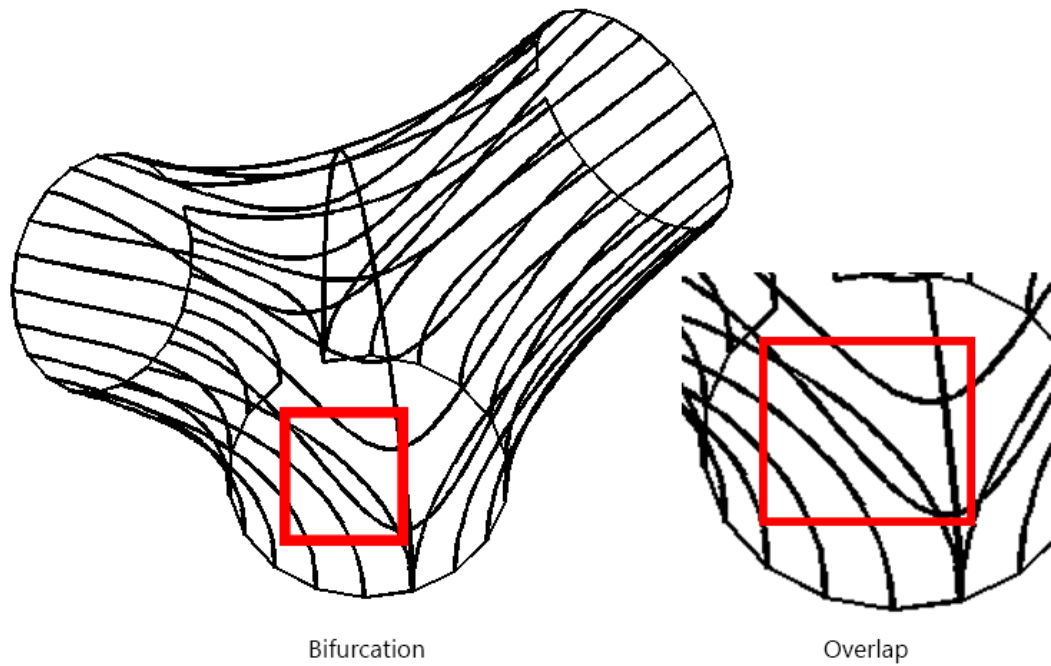


Figure 6.3: Spatial overlapping between the splines on the surfaces at the non-bifurcation sites and at the bifurcation site.

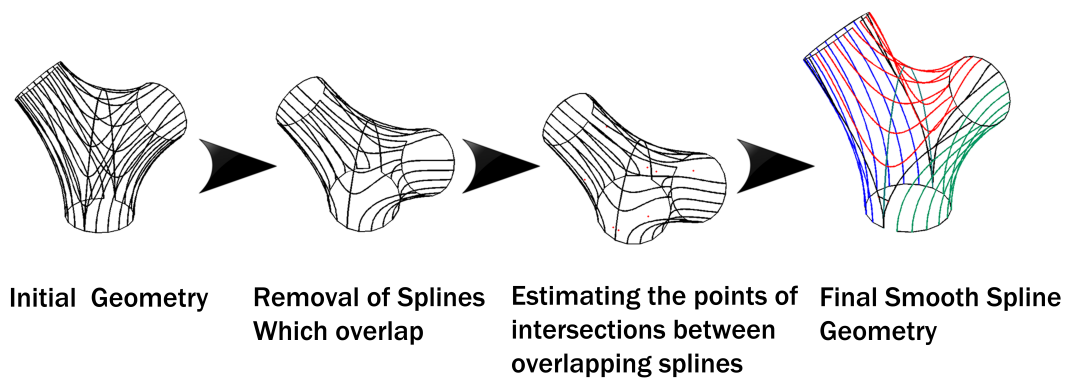


Figure 6.4: The general process to solve the spline overlapping problem. The red points denote the identified spatial overlapping points between these splines. New splines are interpolated through these points (adapted from Dandapani (2014)).

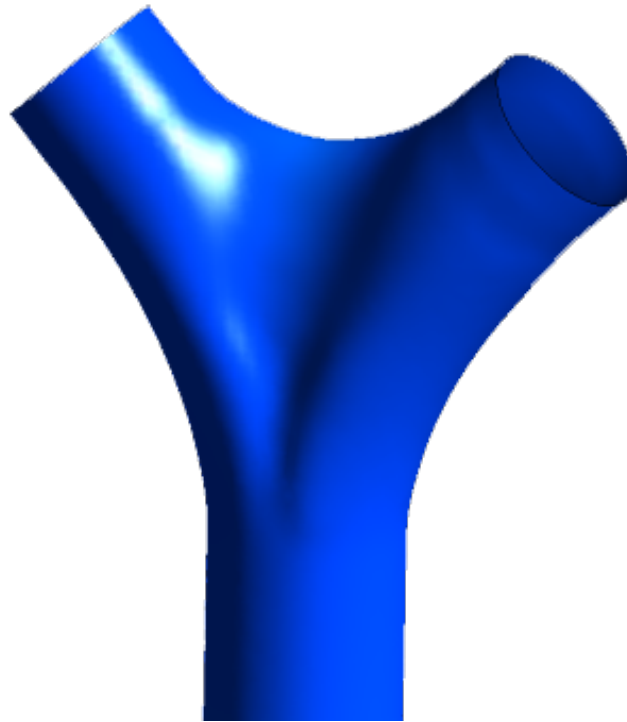


Figure 6.5: A reconstructed conceptual geometry of artery bifurcation after the spline overlapping problem is solved.

In order to achieve this, the current structure solver which only works on cylindrical geometries needs to be replaced by new structure solver. This poses several challenges:

- Clinical imaging data only depicts the loaded configuration. For accurate structural analysis, the geometry in the unloaded reference configuration needs to be obtained. A new structural code that can be accessed to, FEANOR, which has this functionality, will be utilised (see Fig. 6.6). However, to simulate growth and remodelling of arterial tissue, the unloaded reference configurations for each constituent need to be determined, which means a more sophisticated algorithm needs to be developed to determine the unloaded reference configurations of the collagens fibres;
- Collagen fibres are distributed with a range of orientations in vascular tissue. For a cylindrical artery, it is straightforward to define the fibre orientations with respect to the unloaded configuration. However, for more complex geometries, especially arterial bifurcations, an algorithm needs to be developed

to map fibre orientations on to the surface of the geometries;

- To simulate the evolution of an IA, the updated structural solver also needs to be incorporated into the arterial G&R framework.

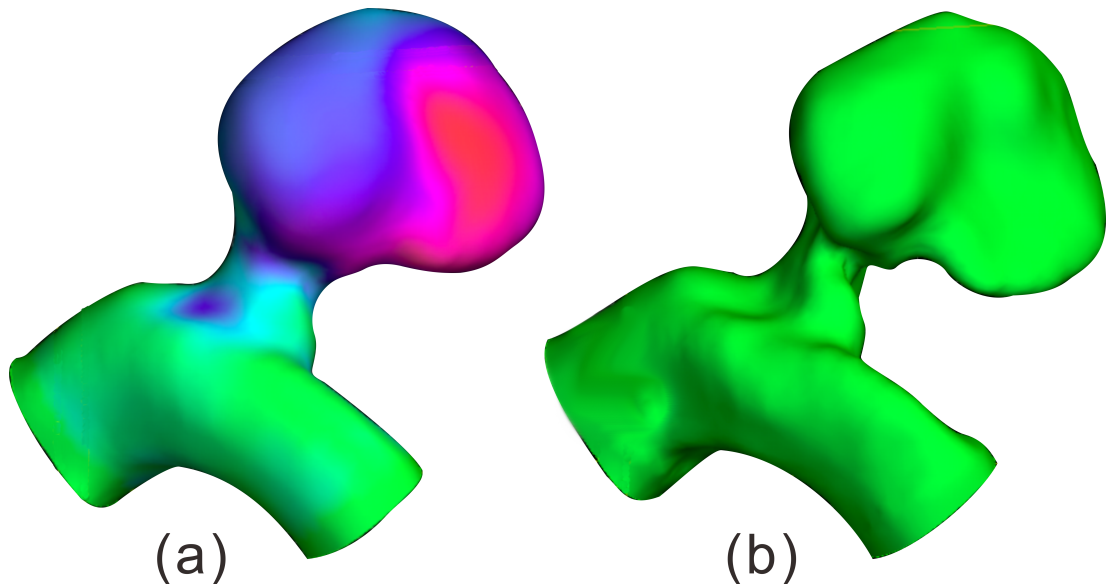


Figure 6.6: Calculation of the unloaded reference configuration of the geometry from the loaded one. (a) Loaded reference configuration for the structural constituents; (b) unloaded reference configuration for structural constituents solved from a structural analysis of (a) (using FEANOR code developed by Dr. Jens Georg Schmidt (Department for Mathematics and Technology, University of Applied Sciences Koblenz/RheinAhrCampus)).

Once this model is developed, given any arbitrary IA geometry (sidewall or bifurcation), we can use the vessel reconstruction methods either introduced in Chapter 2 or Sec. 6.3.1 to remove the aneurysm and reconstruct the ‘pre-aneurysmal healthy’ geometry. Then IA evolution can be simulated on these hypothetical ‘healthy’ arteries using the new model. The simulated aneurysms will be compared with the original aneurysms that grow on these geometries. This allow us to examine different hypotheses proposed in arterial G&R during aneurysm evolution.

6.3.3 Application of the Fluid-Solid-Growth framework to experimental rabbit model

One key question associated with FSG modelling would be how to validate the framework, and especially how to assess whether the theoretical modelling hy-

potheses utilised in the FSG framework on modelling G&R of the arterial tissue during aneurysm evolution is correct.

Recently, the FSG framework has been applied to model experimental rabbit models of elastase induced aneurysms (See Fig. 6.7). The general procedure of the ongoing work can be summarised as follows: the rabbit ‘pre-aneurysmal healthy’ geometries are reconstructed using our novel vessel reconstruction method based on 3D images of the rabbit aneurysm geometries; CFD simulations are initiated with boundary conditions measured directly from the experiment model; other variables used in the model (e.g. collagen recruitment stretch distribution, orientation, concentration and elastin degradation) are determined directly from the quantitative data associated with the constituents in the arterial wall (e.g. collagen waviness, orientations, densities and internal elastic lamina damage) from the experiments using multi-photon microscopy/mechanical testing techniques; FSG simulations of aneurysm evolution is performed for the given rabbit geometry.

Application of the FSG framework to experimental models of rabbit aneurysms directly enable the FSG framework to benefit from the following advantages:

- the use of quantitative information of the arterial constituents measured directly from the experiment using techniques such as mechanical testing/multi-photon microscopy imaging;
- the use of temporal data from the rabbit aneurysm experiments, which is usually unavailable for human aneurysms;
- the testing of the adopted hypotheses of arterial G&R during aneurysm evolution.

Ultimately, the direct validation of the FSG framework from the rabbit models will improve our understanding of the role of arterial mechanobiology during aneurysm evolution.

6.3.4 Sophistication of the FSG model to a thick-walled model

In the all of the three models we presented in this thesis, the arterial wall is modelled as a nonlinear incompressible elastic membrane structure. There are two motivations for doing this: firstly, the arterial wall is relatively thin; secondly, the residual

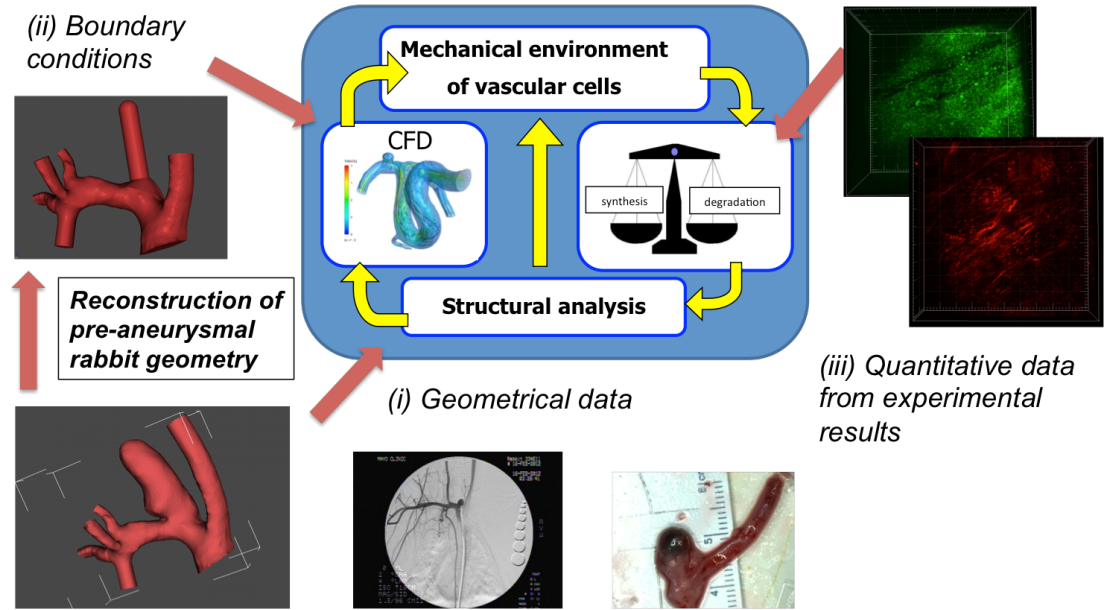


Figure 6.7: Application of the FSG modelling framework to experimental rabbit models of elastase induced cerebral aneurysms. Information that can be utilised from the experimental model and integrated into the FSG modelling framework: (i) geometrical data of the rabbit arterial geometries; a 3D image of the rabbit aneurysm geometry will be used to computationally reconstruct the ‘pre-aneurysmal healthy’ rabbit geometry; (ii) boundary conditions for the CFD simulations can be directly measured from the experimental models; (iii) quantitative data such as collagen waviness, fibre orientations and densities can be obtained directly from the experimental measurement (e.g. using multi-photon microscopy). These can be used to inform the initial conditions and the G&R hypotheses in the FSG framework.

strain that is present in the unloaded reference configuration of the artery gives rise to an approximately uniform strain field through the thickness of the arterial wall at physiological pressures (Aparício et al., 2014). For modelling purposes, we believe that a membrane model of the arterial wall is adequate. However, one key limitation associated with the membrane model is that it is impossible to accurately predict volumetric change of the arterial wall. In Appendix B, we show the derivation of the remodelled wall thickness considering the tissue volumetric growth in our model. However, the volumetric growth of the wall is inferred from the mass growth of the wall constituents, i.e. the volumetric change is assumed to be proportional to the mass change of the wall constituents based on the incompressibility assumption made in the membrane formation. More accurate prediction of the volumetric change of the arterial wall is needed so that the thickness evolution and stress evo-

lution can be also predicted more accurately.

Recently, Eriksson et al. (2014) proposed a novel finite element framework for modelling the G&R of a fibre-reinforced artery incorporating volumetric change of the wall. Two underlying assumptions for modelling G&R including constant individual density (CID) and adaptive individual density (AID) are examined. They also suggest a novel combination approach to describe the collagen growth using CID, and model elastin atrophy using AID to simulate volumetric G&R. In the future, it is suggested that our novel collagen microstructural adaption model could be integrated into their thick wall framework. The integrated model will predict more realistic volumetric changes within the wall, which can be further integrated into other models such as the FSG framework in order to obtain better predictions of thickness evolution and stress evolution of the arterial wall during arterial disease evolution.

6.4 CONCLUSION

In this thesis, a novel automated method is proposed to numerically remove the intracranial aneurysms and reconstruct the hypothetical ‘pre-diseased healthy’ arterial vasculature. This method is then applied to 22 clinical cases depicting sidewall IAs to prepare the geometries prior to IA formation. Computational fluid dynamics simulations are conducted on these geometries and investigations are performed on the influence of haemodynamic indices on IA inception. Results show that locally elevated wall shear stress and gradient oscillatory number are highly correlated with regions susceptible to sidewall IA formation. A novel 1D model of microstructural adaption of the collagen fabrics during aneurysm evolution is proposed. This is the first ever model in the literature to explicitly define the functional forms of collagen fibre *attachment stretch distribution* and more importantly, considers its *temporal adaption*. This 1D model is successfully implemented into two 3D models of aneurysm evolution: a solid structural model, as well as a Fluid-Solid-Growth model. Results show that in order to achieve an aneurysm stabilised in size with physiologically realistic evolution of the wall thickness and stress, adaption of the attachment stretch distribution is necessary. However, what drives the vascular cells to adapt the collagen attachment stretch distribution and how a heterogeneous adaption is achieved is worth more investigation. As a computational study of modelling IA disease, our study examines the hypotheses proposed in this field regarding

IA inception and growth. However, more understanding of the biology, especially of how vascular cells respond to external mechanical stimuli, is urgently needed. This will help to develop more sophisticated models of aneurysm inception, growth and rupture, which hopefully can guide clinical decision making for the interventional treatment of the disease.

REFERENCES

- ABDUL-HUSSEIN, H., SOEKHOE, R. G. V., WEBER, E., VON DER THÜSEN, J. H., KLEEMANN, R., MULDER, A., VAN BOCKEL, J. H., HANEMAAIJER, R., AND LINDEMAN, J. H. N. Collagen degradation in the abdominal aneurysm: a conspiracy of matrix metalloproteinase and cysteine collagenases. *The American journal of pathology*, 170(3):809–817, 2007.
- AFFELD, K., GOUBERGRIJS, L., WATANABE, N., AND KERTZSCHER, U. Numerical and experimental evaluation of platelet deposition to collagen coated surface at low shear rates. *Journal of Biomechanics*, 46(2):430–436, 2013.
- AIRD, W. C. Spatial and temporal dynamics of the endothelium. *Journal of thrombosis and haemostasis*, 3(7):1392–1406, 2005.
- AKPEK, S., ARAT, A., MORSI, H., KLUCZNICK, R. P., STROTHER, C. M., AND MAWAD, M. E. Self-expandable stent-assisted coiling of wide-necked intracranial aneurysms: a single-center experience. *AJNR. American journal of neuroradiology*, 26(5):1223–1231, 2005.
- ALBERTS, B., JOHNSON, A., LEWIS, J., RAFF, M., ROBERTS, K., AND WALTER, P. *Molecular Biology of the Cell Fifth Edition*. Garland Science, 2008.
- ALBINSSON, S., NORDSTRÖM, I., AND HELLSTRAND, P. Stretch of the vascular wall induces smooth muscle differentiation by promoting actin polymerization. *Journal of Biological Chemistry*, 279(33):34849–34855, 2004.
- ALDERAZI, Y. J., SHASTRI, D., KASS-HOUT, T., PRESTIGIACOMO, C. J., AND GANDHI, C. D. Flow diverters for intracranial aneurysms. *Stroke Research and Treatment*, 2014, 2014.
- ANTIGA, L., PICCINELLI, M., BOTTI, L., ENÉ-IOORDACHE, B., REMUZZI, A., AND STEINMAN, D. A. An image-based modeling framework for patient-specific computational hemodynamics. *Medical & Biological Engineering & Computing*, 46(11):1097–1112, 2008.
- AOKI, T. AND NISHIMURA, M. Molecular mechanism of cerebral aneurysm formation focusing on nf- κ b as a key mediator of inflammation. *Journal of Biorheology*, 24(1):16–21, 2010.
- APARÍCIO, P., MANDALTSI, A., BOAMAH, J., CHEN, H., SELIMOVIC, A., BRATBY, M., UBEROI, R., VENTIKOS, Y., AND WATTON, P. N. Modelling the influence of endothelial heterogeneity on the progression of arterial disease: application to abdominal aortic aneurysm evolution. *International Journal of Numerical Methods in Biomedical Engineering*, 2014.
- AUGST, A. D., ARIFF, B., MCG THOM, S. A. G., XU, X. Y., AND HUGHES, A. D. Analysis of complex flow and the relationship between blood pressure, wall shear stress, and intima-media thickness in the human carotid artery. *American journal of physiology Heart and circulatory physiology*, 293:H1031–H1037, 2007.
- BAAIJENS, F., BOUTEN, C., AND DRIESSEN, N. Modeling collagen remodeling. *Journal of Biomechanics*, 43(1):166–175, 2010.
- BAEK, H., JAYARAMAN, M. V., AND KARNIADAKIS, G. E. Wall shear stress and pressure distribution on aneurysms and infundibulae in the posterior communicating artery bifurcation. *Annals of Biomedical Engineering*, 37:2469–2487, 2009.
- BAEK, S., RAJAGOPAL, K. R., AND HUMPHREY, J. D. Competition between radial expansion and thickening in the enlargement of an intracranial saccular aneurysms. *Journal of Elasticity*, 80(1–3):13–31, 2005.
- BAEK, S., RAJAGOPAL, K. R., AND HUMPHREY, J. D. A theoretical model of enlarging intracranial

- fusiform aneurysms. *Journal of biomechanical engineering*, 128(1):142–149, 2006.
- BARSKY, B. A. AND BEATTY, J. C. Local control of bias and tension in beta-splines. *ACM Transactions on Graphics*, 2(2):109–134, 1983.
- BAZILEVS, Y., HSU, M. C., ZHANG, Y., WANG, W., KVAMSDAL, T., HENTSCHEL, S., AND ISAKSEN, J. G. Computational vascular fluid-structure interaction: Methodology and application to cerebral aneurysms. *Biomechanics and Modeling in Mechanobiology*, 9(4):481–498, 2010a.
- BAZILEVS, Y., HSU, M. C., ZHANG, Y., WANG, W., LIANG, X., KVAMSDAL, T., BREKKEN, R., AND ISAKSEN, J. G. A fully-coupled fluid-structure interaction simulation of cerebral aneurysms. *Computational Mechanics*, 46(1):3–16, 2010b.
- BERGE, J., BIONDI, A., MACHI, P., BRUNEL, H., PIEROT, L., GABRILLARGUES, J., K. KADZIOŁKA, BARREAU, X., DOUSSET, V., AND BONAFÉ, A. Flow-diverter silk stent for the treatment of intracranial aneurysms: 1-year follow-up in a multicenter study. *AJNR. American journal of neuroradiology*, 33(6):1150–1155, 2012.
- BIRUKOV, K. G., SHIRINSKY, V. P., STEPANOVA, O. V., TKACHUK, V. A., HAHN, A. W., RESINK, T. J., AND SMIRNOV, V. N. Stretch affects phenotype and proliferation of vascular smooth muscle cells. *Molecular and cellular biochemistry*, 144(2):131–139, 1995.
- BLACHER, J., GUERIN, A. P., PANNIER, B., MARCHAIS, S. J., AND LONDON, G. M. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension*, 38(4):938–942, 2001.
- BLACK, S. M., BEKKER, J. M., JOHENGEN, M. J., PARRY, A. J., SOIFER, S. J., AND FINEMAN, J. R. Altered regulation of the et-1 cascade in lambs with increased pulmonary blood flow and pulmonary hypertension. *Pediatric research*, 47(1):97–106, 2000.
- BLOOMENTHAL, J. Modeling the mighty maple. In *SIGGRAPH 85 Proceedings of the 12th annual conference on Computer graphics and interactive techniques*, volume 19, pages 305–311, 1985.
- BLOOMENTHAL, J. Calculation of reference frames along a space curve. In *Graphics gems*, pages 567–571. Academic Press Professional, Inc, San Diego, CA, USA, 1990.
- BOUSSEL, L., RAYZ, V., MCCULLOCH, C., MARTIN, A., ACEVEDO-BOLTON, G., LAWTON, M., HIGASHIDA, R., SMITH, W. S., YOUNG, W. L., AND SALONER, D. Aneurysm growth occurs at region of low wall shear stress: Patient-specific correlation of hemodynamics and growth in a longitudinal study. *Stroke*, 39:2997–3002, 2008.
- BOWER, A. F. *Applied Mechanics of Solids*. CRC Press, 2010.
- BRANDES, R. P., FLEMING, I., AND BUSSE, R. Endothelial aging. *Cardiovascular Research*, 66(2):286–294, 2005.
- BRISMAN, J. L., SONG, J. K., AND NEWELL, D. W. Cerebral aneurysms. *The new England Journal of Medicine*, 355:928–939, 2006.
- CANHAM, P. B., FINLAY, H. M., DIXON, J. G., AND FERGUSON, S. E. Layered collagen fabric of cerebral aneurysms quantitatively assessed by the universal stage and polarized light microscopy. *The Anatomical record*, 231(4):579–592, 1991.
- CASTRO, M. A. Understanding the role of hemodynamics in the initiation, progression, rupture, and treatment outcome of cerebral aneurysm from medical image-based computational studies. *ISRN radiology*, 2013:602707, 2013.
- CASTRO, M. A., PUTMAN, C. M., AND CEBRAL, J. R. Computational study of anterior communicating artery hemodynamics before aneurysm formation. In *Proc. SPIE 8317, Medical Imaging 2012*, 2012.
- CEBRAL, J. R., CASTRO, M. A., SOTO, O., LÖHNER, R., AND ALPERIN, N. Blood-flow models of the circle of willis from magnetic resonance data. *Journal of Engineering Mathematics*, 47:369–386, 2003.
- CEBRAL, J. R. AND MENG, H. Counterpoint: realizing the clinical utility of computational fluid dynamics - closing the gap. *AJNR. American journal of neuroradiology*, 33(3):396–398, 2012.
- CEBRAL, J. R., SHERIDAN, M., AND PUTMAN, C. M. Hemodynamics and bleb formation in intracranial aneurysms. *AJNR. American journal of neuroradiology*, 31(2):304–310, 2010.
- CHALOUHI, N., ALI, M. S., JABBOUR, P. M., TJOUMAKARIS, S. I., GONZALEZ, L. F., ROSENWASSER, R. H., KOCH, W. J., AND DUMONT, A. S. Biology of intracranial aneurysms: role of inflammation. *Journal of Cerebral Blood Flow & Metabolism*, 32(9):1659–1676, 2012.

- CHEN, H., SELIMOVIC, A., THOMPSON, H., CHIARINI, A., PENROSE, J., VENTIKOS, Y., AND WATTON, P. N. Investigating the influence of haemodynamic stimuli on intracranial aneurysm inception. *Annals of biomedical engineering*, 41(7):1492–1504, 2013.
- CHENG, C. P., PARKER, D., AND TAYLOR, C. A. Quantification of wall shear stress in large blood vessels using lagrangian interpolation functions with cine phase-contrast magnetic resonance imaging. *Annals of Biomedical Engineering*, 30(8):1020–1032, 2002.
- CHIEN, S. Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell. *American journal of physiology. Heart and circulatory physiology*, 292(3):H1209–H1224, 2007.
- CHIQUET, M., GELMAN, L., LUTZ, R., AND MAIER, S. From mechanotransduction to extracellular matrix gene expression in fibroblasts. *Biochimica et Biophysica Acta - Molecular Cell Research*, 1793(5): 911–920, 2009.
- CHIQUET, M., RENEDO, A. S., HUBER, F., AND FLÜCK, M. How do fibroblasts translate mechanical signals into changes in extracellular matrix production? *Matrix Biology*, 22:73–80, 2003.
- CHIU, J. J. AND CHIEN, S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. *Physiological Reviews*, 91(1):327–387, 2011.
- COHEN, J. E., GOMORI, J. M., AND LEKER, R. R. Thrombosis of non-giant unruptured aneurysms causing ischemic stroke. *Neurological research*, 32(9):971–974, 2010.
- CUNNINGHAM, J. J., LINDERMAN, J. J., AND MOONEY, D. J. Externally applied cyclic strain regulates localization of focal contact components in cultured smooth muscle cells. *Annals of Biomedical Engineering*, 30(7):927–935, 2002.
- DANDAPANI, S. Reconstruction of arterial bifurcation prior to cerebral aneurysm formation: a novel approach. Master's thesis, University of Sheffield, 2014.
- DEPAOLA, N., GIMBRONE, M. A., DAVIES, P. F., AND DEWEY, C. F. Vascular endothelium responds to fluid shear stress gradients. *Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association*, 12(11):1254–1257, 1992.
- DOENITZ, C., SCHEBESCH, K. M., ZOEPHEL, R., AND BRAWANSKI, A. A mechanism for rapid development of intracranial aneurysms: A case study. *Neurosurgery*, 67:1213–1221, 2010.
- DOLAN, J. M., KOLEGA, J., AND MENG, H. High wall shear stress and spatial gradients in vascular pathology: A review. *Annals of Biomedical Engineering*, 41(7):1141–1427, 2013.
- DOLAN, J. M., MENG, H., SINGH, S., PALUCH, R., AND KOLEGA, J. High fluid shear stress and spatial shear stress gradients affect endothelial proliferation, survival, and alignment. *Annals of Biomedical Engineering*, 39:1620–1631, 2011.
- DRIESSEN, N. J. B., BOUTEN, C. V. C., AND BAAIJENS, F. P. T. A structural constitutive model for collagenous cardiovascular tissues incorporating the angular fiber distribution. *Journal of biomechanical engineering*, 127(3):494–503, 2005.
- DRIESSEN, N. J. B., COX, M. A. J., BOUTEN, C. V. C., AND BAAIJENS, F. P. T. Remodelling of the angular collagen fiber distribution in cardiovascular tissues. *Biomechanics and Modeling in Mechanobiology*, 7(2):93–103, 2008.
- EASTWOOD, M., MCGROUTHER, D. A., AND BROWN, R. A. Fibroblast responses to mechanical forces. *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of engineering in medicine*, 212(2):85–92, 1998.
- EFREMOV, V., KILLARD, A. J., BYRNE, B., AND LAKSHMANAN, R. S. The modelling of blood coagulation using the quartz crystal microbalance. *Journal of Biomechanics*, 46(3):437–442, 2013.
- ENGLER, A., BACAKOVA, L., NEWMAN, C., HATEGAN, A., GRIFFIN, M., AND DISCHER, D. Substrate compliance versus ligand density in cell on gel responses. *Biophysical journal*, 86(1 Pt 1):617–628, 2004.
- ERIKSSON, T., KROON, M., AND HOLZAPFEL, G. A. Influence of medial collagen organization and axial in situ stretch on saccular cerebral aneurysm growth. *Journal of biomechanical engineering*, 131(10):101010, 2009.
- ERIKSSON, T., WATTON, P., LUO, X., AND VENTIKOS, Y. Modelling volumetric growth in a thick walled fibre reinforced artery. *Journal of the Mechanics and Physics of Solids*, 2014.

- EROSCHENKO, V. P. AND MARIANO, S. H. D. F. *Di-Fiore's Atlas of Histology with Functional Correlations*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013.
- FIGUEROA, C. A., BAEK, S., TAYLOR, C. A., AND HUMPHREY, J. D. A computational framework for fluid-solid-growth modeling in cardiovascular simulations. *The British Journal of Radiology*, 82:55–61, 2009.
- FLAMM, M. H. AND DIAMOND, S. L. Multiscale systems biology and physics of thrombosis under flow. *Annals of Biomedical Engineering*, 40(11): 2355–2364, 2012.
- FORD, M. D., HOI, Y., PICCINELLI, M., ANTIGA, L., AND STEINMAN, D. A. An objective approach to digital removal of saccular aneurysms: technique and applications. *The British Journal of Radiology*, 82:55–61, 2009.
- FORSTING, M. AND WANKE, I. *Intracranial Vascular Malformations and Aneurysms: From Diagnostic Work-Up to Endovascular Therapy*. Springer, 2008.
- FRANKLIN, S. S. Hypertension in older people: part 1. *Journal of clinical hypertension*, 8(6):444–449, 2006.
- FREESE, A. *Principles of Molecular Neurosurgery*. Basel: Karger, 2005.
- FRÖSEN, J., TULAMO, R., PAETAU, A., LAAKSAMO, E., KORJA, M., LAAKSO, A., NIEMELÄ, M., AND HERNESNIEMI, J. Saccular intracranial aneurysm: Pathology and mechanisms. *Acta Neuropathologica*, 123:773–786, 2012.
- GASSER, T. C., OGDEN, R. W., AND HOLZAPFEL, G. A. Hyperelastic modelling of arterial layers with distributed collagen fibre orientations. *Journal of the Royal Society, Interface*, 3(6):15–35, 2006.
- GERBER, S., DORMONT, D., SAHEL, M., GROB, R., FONCIN, J. E., AND MARSAULT, C. Complete spontaneous thrombosis of a giant intracranial aneurysm. *Neuroradiology*, 36(4):316–317, 1994.
- GLASSER, S. P., SELWYN, A. P., AND GANZ, P. Atherosclerosis: risk factors and the vascular endothelium. *American heart journal*, 131(2):379–384, 1996.
- GLEASON, R. L. AND HUMPHREY, J. D. A 2d constrained mixture model for arterial adaptations to large changes in flow, pressure and axial stretch. *Mathematical medicine and biology*, 22(4):347–369, 2005.
- GLEASON, R. L., TABER, L. A., AND HUMPHREY, J. D. A 2-d model of flow-induced alterations in the geometry, structure, and properties of carotid arteries. *Journal of biomechanical engineering*, 126(3): 371–381, 2004.
- GLOR, F. P., ARIFF, B., HUGHES, A. D., CROWE, L. A., VERDONCK, P. R., C, B. D., MCG THOM, S. A., FIRMIN, D. N., AND XU, X. Y. Image-based carotid flow reconstruction: a comparison between mri and ultrasound. *Physiological Measurement*, 25: 1495–1509, 2004.
- GLOR, F. P., LONG, Q., HUGHES, A. D., AUGST, A. D., ARIFF, B., THOM, S. A., VERDONCK, P. R., AND XU, X. Y. Reproducibility study of magnetic resonance image-based computational fluid dynamics prediction of carotid bifurcation flow. *Annals of Biomedical Engineering*, 31:142–151, 2003.
- GRINNELL, F. AND PETROLL, W. M. Cell motility and mechanics in three-dimensional collagen matrices. *Annual review of cell and developmental biology*, 26:335–361, 2010.
- GUPTA, V. AND GRANDE-ALLEN, K. J. Effects of static and cyclic loading in regulating extracellular matrix synthesis by cardiovascular cells. *Cardiovascular Research*, 72(3):375–383, 2006.
- HAGA, J. H., LI, Y. S. J., AND CHIEN, S. Molecular basis of the effects of mechanical stretch on vascular smooth muscle cells. *Journal of biomechanics*, 40 (5):947–960, 2007.
- HAHN, C. AND SCHWARTZ, M. A. The role of cellular adaptation to mechanical forces in atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 28:2101–2107, 2008.
- HANSEN, F., MANGELL, P., SONESSON, B., AND LÄNNE, T. Diameter and compliance in the human common carotid artery—variations with age and sex. *Ultrasound in medicine & biology*, 21(1):1–9, 1995.
- HANSSON, G. K. Inflammation, atherosclerosis, and coronary artery disease. *The New England journal of medicine*, 352(16):1685–1695, 2005.
- HARITON, I., DEBOTTON, G., GASSER, T. C., AND HOLZAPFEL, G. A. Stress-driven collagen fiber remodeling in arterial walls. *Biomechanics and Modeling in Mechanobiology*, 6(3):163–175, 2007.
- HASHIMOTO, T., MENG, H., AND YOUNG, W. L. Intracranial aneurysms: links among inflammation, hemodynamics and vascular remodeling. *Neurological research*, 28(4):372–380, 2006.

- HAYAKAWA, K., SATO, N., AND OGINATA, T. Dynamic reorientation of cultured cells and stress fibers under mechanical stress from periodic stretching. *Experimental cell research*, 268(1):104–114, 2001.
- HE, X. AND KU, D. N. Pulsatile flow in the human left coronary artery bifurcation: average conditions. *Journal of Biomechanical Engineering*, 118(1):74–82, 1996.
- HEIL, M. The stability of cylindrical shells conveying viscous flow. *Journal of Fluids and Structures*, 10: 173–196, 1996.
- HILL, M. A., ZOU, H., POTOCNIK, S. J., MEININGER, G. A., AND DAVIS, M. J. Invited review: arterio-lar smooth muscle mechanotransduction: Ca(2+) signaling pathways underlying myogenic reactivity. *Journal of applied physiology*, 91(2):973–983, 2001.
- HILL, M. R., DUAN, X., GIBSON, G. A., WATKINS, S., AND ROBERTSON, A. M. A theoretical and non-destructive experimental approach for direct inclusion of measured collagen orientation and recruitment into mechanical models of the artery wall. *Journal of Biomechanics*, 45(5):762–771, 2012.
- HOFFMAN, B. D., GRASHOFF, C., AND SCHWARTZ, M. A. Dynamic molecular processes mediate cellular mechanotransduction. *Nature*, 475(7356):316–323, 2011.
- HOI, Y., MENG, H., WOODWARD, S. H., BENDOK, B. R., HANEL, R. A., GUTERMAN, L. R., AND HOPKINS, L. N. Effects of arterial geometry on aneurysm growth: three-dimensional computational fluid dynamics study. *Journal of neurosurgery*, 101(4):676–81, 2004.
- HOLZAPFEL, G. A. *Nonlinear Solid Mechanics. A Continuum Approach for Engineering*. John Wiley & Sons, Chichester, 2000.
- HOLZAPFEL, G. A., GASSER, T. C., AND OGDEN, R. W. A new constitutive framework for arterial wall mechanics and a comparative study of material models. *Journal of elasticity*, 61(1–3):1–48, 2000.
- HOSAKA, K. AND HOH, B. L. Inflammation and cerebral aneurysms. *Translational Stroke Research*, 5(2):190–198, 2014.
- HUMPHREY, J. D. Remodeling of a collagenous tissue at fixed lengths. *Journal of biomechanical engineering*, 121(6):591–597, 1999.
- HUMPHREY, J. D. Mechanisms of arterial remodeling in hypertension: Coupled roles of wall shear and intramural stress. *Hypertension*, 52(2):195–200, 2008.
- HUMPHREY, J. D. Coupling haemodynamics with vascular wall mechanics and mechanobiology to understand intracranial aneurysms. *International Journal of Computational Fluid Dynamics*, 23(8): 569–581, 2009.
- HUMPHREY, J. D. AND RAJAGOPAL, K. R. A constrained maxiture model for growth and remodeling of soft tissues. *Mathematical Models and Methods in Applied Sciences*, 12(3):407–430, 2002.
- HUMPHREY, J. D. AND TAYLOR, C. A. Intracranial and abdominal aortic aneurysms: Similarities, differences, and need for a new class of computational models. *Annual Review of Biomedical Engineering*, 10:221–246, 2008.
- ISAKSEN, J. G., BAZILEVS, Y., KVAMSDAL, T., ZHANG, Y., KASPERSEN, J. H., WATERLOO, K., ROMNER, B., AND INGEBRIGTSEN, T. Determination of wall tension in cerebral artery aneurysms by numerical simulation. *Stroke*, 39(12):3172–3178, 2008.
- JOU, L. D. AND MAWAD, M. E. Hemodynamic effect of neuroform stent on intimal hyperplasia and thrombus formation in a carotid aneurysm. *Medical and Biological Engineering and Computing*, 33: 573–580, 2011a.
- JOU, L. D. AND MAWAD, M. E. Timing and size of flow impingement in a giant intracranial aneurysm at the internal carotid artery. *Medical and Biological Engineering and Computing*, 49:891–899, 2011b.
- JOU, L. D., WONG, G., DISPENSA, B., LAWTON, M. T., HIGASHIDA, R. T., YOUNG, W. L., AND SALONER, D. Correlation between luminal geometry changes and hemodynamics in fusiform intracranial aneurysms. *American Journal of Neuroradiology*, 26(9):2357–2363, 2005.
- JUVELA, S. Treatment options of unruptured intracranial aneurysms. *Stroke*, 35:372–374, 2004.
- KANEMATSU, Y., KANEMATSU, M., KURIHARA, C., TADA, Y., TSOU, T., VAN ROOIJEN, N., LAWTON, M. T., YOUNG, L. W., LIANG, E. I., NUKI, Y., AND HASHIMOTO, T. Critical roles of macrophages in the formation of intracranial aneurysm. *Stroke; a journal of cerebral circulation*, 42(1):173–178, 2011.

- KARMONIK, C., ARAT, A., BENNDORF, G., AKPEK, S., KLUCZNIK, R., MAWAD, M. E., AND STROTHER, C. M. A technique for improved quantitative characterization of intracranial aneurysms. *American Journal of Neuroradiology*, 25:1158–1161, 2004.
- KARŠAJ, I. AND HUMPHREY, J. D. A multilayered wall model of arterial growth and remodeling. *Mechanics of Materials*, 44:110–119, 2012.
- KILLER-OBERPFALZER, M., AICHHOLZER, M., WEIS, S., RICHLING, B., JONES, R., VIRMANI, R., AND CRUISE, G. M. Histological analysis of clipped human intracranial aneurysms and parent arteries with short-term follow-up. *Cardiovascular Pathology*, 21(4):299–306, 2012.
- KOCHANÉK, D. H. U. AND BARTELS, R. H. Interpolating splines with local tension, continuity, and bias control. *ACM SIGGRAPH Computer Graphics*, 18(3):33–41, 1984.
- KOFFIJBERG, H., BUSKENS, E., ALGRA, A., WERMER, M. J. H., AND RINKEL, G. J. E. Growth rates of intracranial aneurysms: exploring constancy. *Journal of neurosurgery*, 109(2):176–185, 2008.
- KOLAH, K. AND MOFRAD, M. R. K. Mechanotransduction: A major regulator of homeostasis and development. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 2(6):625–639, 2010.
- KOLEGA, J., GAO, L., MANDELBAUM, M., MOCCO, J., SIDDIQUI, A. H., NATARAJAN, S. K., AND MENG, H. Cellular and molecular responses of the basilar terminus to hemodynamics during intracranial aneurysm initiation in a rabbit model. *Journal of Vascular Research*, 48(5):429–442, 2011.
- KONDO, S., HASHIMOTO, N., KIKUCHI, H., HAZAMA, E., NAGATA, I., AND KATAOKA, H. Cerebral aneurysms arising at nonbranching sites. an experimental study. *Stroke; a journal of cerebral circulation*, 28(2):398–403, 1997.
- KONDO, S., HASHIMOTO, N., KIKUCHI, H., HAZAMA, E., NAGATA, I., AND KATAOKA, H. Apoptosis of medial smooth muscle cells in the development of saccular cerebral aneurysms in rats. *Stroke; a journal of cerebral circulation*, 29(1):181–189, 1998.
- KOSIERKIEWICZ, T. A., FACTOR, S. M., AND DICKSON, D. W. Immunocytochemical studies of atherosclerotic lesions of cerebral berry aneurysms. *Journal of neuropathology and experimental neurology*, 53(4):399–406, 1994.
- KROON, M. AND HOLZAPFEL, G. A. A model for saccular cerebral aneurysm growth by collagen fibre remodelling. *Journal of Theoretical Biology*, 247(4):775–787, 2007.
- KROON, M. AND HOLZAPFEL, G. A. Modeling of saccular aneurysm growth in a human middle cerebral artery. *Journal of biomechanical engineering*, 130(5):051012, 2008.
- KROON, M. AND HOLZAPFEL, G. A. A theoretical model for fibroblast-controlled growth of saccular cerebral aneurysms. *Journal of Theoretical Biology*, 257(1):73–83, 2009.
- KU, D. N., GIDDENS, D. P., ZARINS, C. K., AND GLAGOV, S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. positive correlation between plaque location and low oscillating shear stress. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 5(3):293–302, 1985.
- KULCSÁR, Z., HOUDART, E., BONAFÉ, A., PARKER, G., MILLAR, J., GODDARD, A. J. P., RENOWDEN, S., GÁL, G., TUROWSKI, B., MITCHELL, K., GRAY, F., RODRIGUEZ, M., VAN DEN BERG, R., GRUBER, A., DESAL, H., WANKE, I., AND RUFENACHT, D. A. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow-diversion treatment. *American Journal of Neuroradiology*, 32(1):20–25, 2011a.
- KULCSÁR, Z., UGRON, A., MAROSFOI, M., BERENTEI, Z., PAÁL, G., AND SZIKORA, I. Hemodynamics of cerebral aneurysm initiation: the role of wall shear stress and spatial wall shear stress gradient. *American Journal of Neuroradiology*, 32:587–594, 2011b.
- LAMACK, J. A. AND FRIEDMAN, M. H. Individual and combined effects of shear stress magnitude and spatial gradient on endothelial cell gene expression. *American journal of physiology. Heart and circulatory physiology*, 293(5):2853–2859, 2007.
- LAMACK, J. A., HIMBURG, H. A., LI, X. M., AND FRIEDMAN, M. H. Interaction of wall shear stress magnitude and gradient in the prediction of arterial macromolecular permeability. *Annals of Biomedical Engineering*, 33(4):457–464, 2005.
- LANGILLE, B. L. Remodeling of developing and mature arteries: endothelium, smooth muscle, and matrix. *Journal of cardiovascular pharmacology*, 21:11–17, 1993.

- LANGILLE, B. L. AND ADAMSON, S. L. Relationship between blood flow direction and endothelial cell orientation at arterial branch sites in rabbits and mice. *Circulation research*, 48(4):481–488, 1981.
- LASHERAS, J. C. The biomechanics of arterial aneurysms. *Annual Review of Fluid Mechanics*, 39(1):293–319, 2007.
- LASHERAS, J. C. Haemodynamic stresses and the onset and progression of vascular diseases. *Journal of Fluid Mechanics*, 664:1–4, 2010.
- LE, W., ZHU, Y., LI, M., YAN, L., TAN, H., XIAO, S., AND CHENG, Y. New method for retrospective study of hemodynamic changes before and after aneurysm formation in patients with ruptured or unruptured aneurysms. *BMC neurology*, 13(1):166, 2013.
- LEE, H. Y. AND OH, B. H. Aging and arterial stiffness. *Circulation journal : official journal of the Japanese Circulation Society*, 74(11):2257–2262, 2010.
- LEE, R. T., YAMAMOTO, C., FENG, Y., POTTER-PERIGO, S., BRIGGS, W. H., LANDSCHULZ, K. T., TURI, T. G., THOMPSON, J. F., LIBBY, P., AND WIGHT, T. N. Mechanical strain induces specific changes in the synthesis and organization of proteoglycans by vascular smooth muscle cells. *Journal of Biological Chemistry*, 276(17):13847–13851, 2001.
- LI, C. AND XU, Q. Mechanical stress-initiated signal transduction in vascular smooth muscle cells in vitro and in vivo. *Cellular Signalling*, 19(5):881–891, 2007.
- LONDON, G. M., PANNIER, B., AND MARCHAIS, S. J. Vascular calcifications, arterial aging and arterial remodeling in esrd. *Blood Purification*, 35:16–21, 2013.
- MACHYSHYN, I. M., BOVENDEERD, P. H. M., VAN DE VEN, A. A. F., RONGEN, P. M. J., AND VAN DE VOSSE, F. N. A model for arterial adaptation combining microstructural collagen remodeling and 3d tissue growth. *Biomechanics and modeling in mechanobiology*, 9(6):671–687, 2010.
- MALEK, A. M., ALPER, S. L., AND IZUMO, S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA : the journal of the American Medical Association*, 282(21):2035–2042, 1999.
- MANNING, J. R. Continuity conditions for spline curves. *The Computer Journal*, 17:181 – 186, 1974.
- MANATHA, A., KARMONIK, C., BENNDORF, G., STROTHER, C., AND METCALFE, R. Hemodynamics in a cerebral artery before and after the formation of an aneurysm. *American Journal of Neuroradiology*, 27:1113 – 1118, 2006.
- MARTUFI, G. AND GASSER, T. C. Turnover of fibrillar collagen in soft biological tissue with application to the expansion of abdominal aortic aneurysms. *Journal of The Royal Society Interface*, 9(77):3366 – 3377, 2012.
- MARTYN, C. N. AND GREENWALD, S. E. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet*, 350(9082):953–955, 1997.
- MASSEY, F. J. J. The kolmogorov-smirnov test of goodness of fit. *Journal of the American Statistical Association*, 46:68–78, 1951.
- MENG, H., METAXA, E., GAO, L., LIAW, N., NATARAJAN, S. K., SWARTZ, D. D., SIDDIQUI, A. H., KOLEGA, J., AND MOCCO, J. Progressive aneurysm development following hemodynamic insult. *Journal of Neurosurgery*, 114(4):1095–1103, 2011.
- MENG, H., SWART, D. D., WANG, Z., HOI, Y., KOLEGA, J., METAXA, E., AND SZYMANSKI, M. P. A model system for mapping vascular responses to complex hemodynamics at arterial bifurcations in vivo. *Neurosurgery*, 59(5):1094 – 1100, 2006.
- MENG, H., TUTINO, V. M., XIANG, J., AND SIDDIQUI, A. High wss or low wss? complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: Toward a unifying hypothesis. *American Journal of Neuroradiology*, 35(7):1254–1262, 2014.
- MENG, H., WANG, Z., HOI, Y., GAO, L., METAXA, E., SWART, D. D., AND KOLEGA, J. Complex hemodynamics at the apex of an arterial bifurcation induces vascular remodeling resembling cerebral aneurysm initiation. *Stroke*, 38:1924–1931, 2007.
- MESHEL, A. S., WEI, Q., ADELSTEIN, R. S., AND SHEETZ, M. P. Basic mechanism of three-dimensional collagen fibre transport by fibroblasts. *Nature cell biology*, 7(2):157–164, 2005.
- METAXA, E., MENG, H., KALUVALA, S. R., SZYMANSKI, M. P., PALUCH, R. A., AND KOLEGA, J. Nitric oxide-dependent stimulation of endothelial cell proliferation by sustained high flow. *American journal of physiology. Heart and circulatory physiology*, 295(2):736–742, 2008.

- METAXA, E., TREMMEL, M., NATARAJAN, S. K., XIANG, J., PALUCH, R. A., MANDELBAUM, M., AND SIDDIQUI, A. H. Characterization of critical hemodynamics contributing to aneurysmal remodeling at the basilar terminus in a rabbit model. *Stroke*, 41(8):1774–1782, 2010.
- MOISEYEV, G. AND BAR-YOSEPH, P. Z. Computational modeling of thrombosis as a tool in the design and optimization of vascular implants. *Journal of Biomechanics*, 46(2):248–252, 2013.
- MOISEYEV, G., GIVLI, S., AND BAR-YOSEPH, P. Z. Fibrin polymerization in blood coagulation—a statistical model. *Journal of Biomechanics*, 46(1):26–30, 2013.
- MONSON, K. L., GOLDSMITH, W., BARBARO, N. M., AND MANLEY, G. T. Axial mechanical properties of fresh human cerebral blood vessels. *Journal of biomechanical engineering*, 125(2):288–294, 2003.
- MOORE, J. E., BURKI, E., SUCIU, A., ZHAO, S., BURNIER, M., BRUNNER, H. R., AND MEISTER, J. J. A device for subjecting vascular endothelial cells to both fluid shear stress and circumferential cyclic stretch. *Annals of Biomedical Engineering*, 22(4):416–422, 1994.
- MORTENSON, M. E. *Geometric Modeling*. New York: Industrial Press Inc., 2006.
- MURAYAMA, Y., NIEN, Y. L., DUCKWILER, G., GOBIN, Y. P., JAHAN, R., FRAZEE, J., MARTIN, N., AND VIÑUELA, F. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years’ experience. *Journal of neurosurgery*, 98(5):959–966, 2003.
- MURTADA, S. I., KROON, M., AND HOLZAPFEL, G. A. A calcium-driven mechanochemical model for prediction of force generation in smooth muscle. *Biomechanics and Modeling in Mechanobiology*, 9(6):749–762, 2010.
- NA, S., MEININGER, G. A., AND HUMPHREY, J. D. A theoretical model for f-actin remodeling in vascular smooth muscle cells subjected to cyclic stretch. *Journal of Theoretical Biology*, 246(1):87–99, 2007.
- NAGATA, I., KIKUCHI, H., YAMAGATA, S., MIYAMOTO, S., KANEKO, T., AND ASATO, R. Intraluminal thrombosis and growth-mechanism of giant intracranial aneurysms. *Neurological Surgery*, 18(12):1115–1120, 1990.
- NAGEL, T. AND KELLY, D. J. Remodelling of collagen fibre transition stretch and angular distribution in soft biological tissues and cell-seeded hydrogels. *Biomechanics and Modeling in Mechanobiology*, 11(3–4):325–339, 2012.
- NGUYEN, H. T., ADAM, R. M., BRIDE, S. H., PARK, J. M., PETERS, C. A., AND FREEMAN, M. R. Cyclic stretch activates p38 sapk2-, erbb2-, and at1-dependent signaling in bladder smooth muscle cells. *American journal of physiology: Cell physiology*, 279(4):1155–1167, 2000.
- NISSEN, R., CARDINALE, G. J., AND UDENFRIEND, S. Increased turnover of arterial collagen in hypertensive rats. *Proceedings of the National Academy of Sciences of the United States of America*, 75(1):451–453, 1978.
- NIXON, A. M., GUNEL, M., AND SUMPIO, B. E. The critical role of hemodynamics in the development of cerebral vascular disease. *Journal of neurosurgery*, 112(6):1240–1253, 2010.
- OHASHI, T. AND SATO, M. Remodeling of vascular endothelial cells exposed to fluid shear stress: Experimental and numerical approach. *Fluid Dynamics Research*, 37(1–2):40–59, 2005.
- OKADA, M., MATSUMORI, A., ONO, K., FURUKAWA, Y., SHIOI, T., IWASAKI, A., MATSUSHIMA, K., AND SASAYAMA, S. Cyclic stretch upregulates production of interleukin-8 and monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 in human endothelial cells. *Arteriosclerosis, thrombosis, and vascular biology*, 18(6):894–901, 1998.
- OPITZ, F., SCHENKE-LAYLAND, K., COHNERT, T. U., AND STOCK, U. A. Phenotypical plasticity of vascular smooth muscle cells—effect of in vitro and in vivo shear stress for tissue engineering of blood vessels. *Tissue engineering*, 13(10):2505–2514, 2007.
- OSTROWSKI, M. A., HUANG, N. F., WALKER, T. W., VERWIJLEN, T., POPLAWSKI, C., KHOO, A. S., COOKE, J. P., FULLER, G. G., AND DUNN, A. R. Microvascular endothelial cells migrate upstream and align against the shear stress field created by impinging flow. *Biophysical Journal*, 106(2):366–374, 2014.
- OWATVEROT, T. B., OSWALD, S. J., CHEN, Y., WILLE, J. J., AND YIN, F. C. P. Effect of combined cyclic stretch and fluid shear stress on endothelial cell morphological responses. *Journal of biomechanical engineering*, 127(3):374–382, 2005.

- PALLISTER, C. J. AND WATSON, M. S. *Haematology, second edition*. Scion Publishing Ltd., 2010.
- PASZKOWIAK, J. J. AND DARDIK, A. Arterial wall shear stress: observations from the bench to the bedside. *Vascular and endovascular surgery*, 37(1):47–57, 2003.
- PERKTOLD, K., GRUBER, K., KENNER, T., AND FLORIAN, H. Calculation of pulsatile flow and particle paths in an aneurysm-model. *Basic Research in Cardiology*, 79(3):253–261, 1984.
- QIU, J., ZHENG, Y., HU, J., LIAO, D., GREGERSEN, H., DENG, X., FAN, Y., AND WANG, G. Biomechanical regulation of vascular smooth muscle cell functions: from in vitro to in vivo understanding. *Journal of the Royal Society, Interface*, 11(90):20130852, 2014.
- RAYZ, V. L., BOUSSEL, L., GE, L., LEACH, J. R., MARTIN, A. J., LAWTON, M. T., MCCULLOCH, C., AND SALONER, D. Flow residence time and regions of intraluminal thrombus deposition in intracranial aneurysms. *Annals of Biomedical Engineering*, 38(10):3058–3069, 2010.
- RAYZ, V. L., BOUSSEL, L., LAWTON, M. T., ACEVEDO-BOLTON, G., GE, L., YOUNG, W. L., HIGASHIDA, R. T., AND SALONER, D. Numerical modeling of the flow in intracranial aneurysms: Prediction of regions prone to thrombus formation. *Annals of Biomedical Engineering*, 36(11):1793–1804, 2008.
- REASOR, D. A., MEHRABADI, M., KU, D. N., AND AIDUN, C. K. Determination of critical parameters in platelet margination. *Annals of Biomedical Engineering*, 41(2):238–249, 2013.
- REGAN, E. R. AND AIRD, W. C. Dynamical systems approach to endothelial heterogeneity. *Circulation research*, 111(1):110–130, 2012.
- RESNICK, N., YAHAV, H., SHAY-SALIT, A., SHUSHY, M., SCHUBERT, S., ZILBERMAN, L. C. M., AND WOFOVITZ, E. Fluid shear stress and the vascular endothelium: For better and for worse. *Progress in Biophysics and Molecular Biology*, 81(3):177–199, 2003.
- REYMOND, P., BOHRAUS, Y., PERREN, F., LAZEYRAS, F., AND STERGIOPULOS, N. Validation of a patient-specific one-dimensional model of the systemic arterial tree. *AJP: Heart and Circulatory Physiology*, 301:1173–1182, 2011.
- REYMOND, P., MERENDA, F., PERREN, F., RÜFENACHT, D., AND STERGIOPULOS, N. Validation of a one-dimensional model of the systemic arterial tree. *AJP: Heart and Circulatory Physiology*, 297:208 – 222, 2009.
- REZAKHANIHA, R., AGIANNIOTIS, A., SCHRAUWEN, J. T. C., GRIFFA, A., SAGE, D., BOUTEN, C. V. C., AND VOSSE, F. N. V. D. Experimental investigation of collagen waviness and orientation in the arterial adventitia using confocal laser scanning microscopy. *Biomechanics and Modeling in Mechanobiology*, 11(3–4):461–473, 2012.
- RICHARDS, F. J. A flexible growth function for empirical use. *Journal of Experimental Botany*, 10(2):290–301, 1959.
- RINKEL, G. J., DJIBUTI, M., ALGRA, A., AND VAN. GIJN, J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke; a journal of cerebral circulation*, 29(1):251–256, 1998.
- ROBERTSON, A. M. AND WATTON, P. N. Computational fluid dynamics in aneurysm research: critical reflections, future directions. *American journal of neuroradiology*, 33(6):992–995, 2012.
- ROSSITTI, S. Shear stress in cerebral arteries carrying saccular aneurysms. a preliminary study. *Acta radiologica*, 39(6):711–717, 1998.
- RUBBENS, M. P., DRIESSEN-MOL, A., BOERBOOM, R. A., KOPPERT, M. M. J., ASSEN, H. C. V., ROMENY, B. M. T., BAAIJENS, F. P. T., AND BOUTEN, C. V. C. Quantification of the temporal evolution of collagen orientation in mechanically conditioned engineered cardiovascular tissues. *Annals of Biomedical Engineering*, 37(7):1263–1272, 2009.
- SAKAMOTO, N., SAITO, N., HAN, X., OHASHI, T., AND SATO, M. Effect of spatial gradient in fluid shear stress on morphological changes in endothelial cells in response to flow. *Biochemical and biophysical research communications*, 395(2):264–269, 2010.
- SALAMEH, A. AND DHEIN, S. Effects of mechanical forces and stretch on intercellular gap junction coupling. *Biochimica et Biophysica Acta - Biomembranes*, 1828(1):147–156, 2013.
- SCHRAUWEN, J. T. C., VILANOYA, A., REZAKHANIHA, R., STERGIOPULOS, N., VAN DE VOSSE, F. N., AND BOVENDEERD, P. H. M. A method for the quantification of the pressure dependent 3d collagen configuration in the arterial adventitia. *Journal of Structural Biology*, 180:335–342, 2012.

- SCHRIEFL, A. J., ZEINDLINGER, G., PIERCE, D. M., REGITNIG, P., AND HOLZAPFEL, G. A. Determination of the layer-specific distributed collagen fibre orientations in human thoracic and abdominal aortas and common iliac arteries. *Journal of The Royal Society Interface*, 9(71):1275–1286, 2012.
- SELIMOVIC, A. *Patient-specific models of cerebral aneurysm evolution*. Ph.d. thesis, Department of Engineering Science, University of Oxford, Oxford, 2013.
- SFORZA, D. M., PUTMAN, C. M., TATESHIMA, S., VIÑUELA, F., AND CEBRAL, J. R. Effects of perianeurysmal environment during the growth of cerebral aneurysms: A case study. *American Journal of Neuroradiology*, 33(6):1115–1120, 2012.
- SHADDEN, S. C. AND SAHAR, H. Potential fluid mechanic pathways of platelet activation. *Biomechanics and Modeling in Mechanobiology*, 12(3):467–474, 2013.
- SHADWICK, R. E. Mechanical design in arteries. *The Journal of experimental biology*, 202(23):3305–3313, 1999.
- SHIMOGONYA, Y., ISHIKAWA, T., IMAI, Y., MATSUKI, N., AND YAMAGUCHI, T. Can temporal fluctuation in spatial wall shear stress gradient initiate a cerebral aneurysm? A proposed novel hemodynamic index, the gradient oscillatory number (GON). *Journal of Biomechanics*, 42:550–554, 2009a.
- SHIMOGONYA, Y., ISHIKAWA, T., IMAI, Y., MATSUKI, N., AND YAMAGUCHI, T. A realistic simulation of saccular cerebral aneurysm formation: focussing on a novel haemodynamic index, the gradient oscillatory number. *International Journal of Computational Fluid Dynamics*, 23(8):583–593, 2009b.
- SHIMOGONYA, Y., KUMAMARU, H., AND ITOH, K. Sensitivity of the gradient oscillatory number to flow input waveform shapes. *Journal of Biomechanics*, 45(6):985–989, 2012.
- SHIN, H. Y., GERRITSEN, M. E., AND BIZIOS, R. Regulation of endothelial cell proliferation and apoptosis by cyclic pressure. *Annals of Biomedical Engineering*, 30(3):297–304, 2002.
- SHOJIMA, M., OSHIMA, M., TAKAGI, K., TORII, R., HAYAKAWA, M., KATADA, K., MORITA, A., AND KIRINO, T. Magnitude and role of wall shear stress on cerebral aneurysm: computational fluid dynamic study of 20 middle cerebral artery aneurysms. *Stroke; a journal of cerebral circulation*, 35:2500–2505, 2004.
- SINGH, P. K., MARZO, A., HOWARD, B., RUFENACHT, D. A., BIJLENGA, P., FRANGI, A. F., LAWFORDE, P. V., COLEY, S. C., HOSE, D. R., AND PATEL, U. J. Effects of smoking and hypertension on wall shear stress and oscillatory shear index at the site of intracranial aneurysm formation. *Clinical Neurology and Neurosurgery*, 112(4):306–313, 2010.
- SOMMER, G. *Mechanical properties of healthy and diseased human arteries and related material modeling*. Ph.d. thesis, Institute of Biomechanics, Graz University of Technology, Graz, 2008.
- SOTOUDEH, M., JALALI, S., USAMI, S., SHYY, J. Y. J., AND CHIEN, S. A strain device imposing dynamic and uniform equi-biaxial strain to cultured cells. *Annals of Biomedical Engineering*, 26(2):181–189, 1998.
- STANDLEY, P. R., CAMMARATA, A., NOLAN, B. P., PURGASON, C. T., AND STANLEY, M. A. Cyclic stretch induces vascular smooth muscle cell alignment via no signaling. *American journal of physiology. Heart and circulatory physiology*, 283(5):1907–1914, 2002.
- SUGIYAMA, S. I., MENG, H., FUNAMOTO, K., INOUE, T., FUJIMURA, M., NAKAYAMA, T., OMODAKA, S., SHIMIZU, H., TAKAHASHI, A., AND TOMINAGA, T. Hemodynamic analysis of growing intracranial aneurysms arising from a posterior inferior cerebellar artery. *World Neurosurgery*, 78:462–468, 2012.
- SUGIYAMA, S. I., NIIZUMA, K., NAKAYAMA, T., SHIMIZU, H., ENDO, H., INOUE, T., FUJIMURA, M., OHTA, M., TAKAHASHI, A., AND TOMINAGA, T. Relative residence time prolongation in intracranial aneurysms: A possible association with atherosclerosis. *Neurosurgery*, 73(5):767–776, 2013.
- SZYMANSKI, M. P., METAXA, E., MENG, H., AND KOLEGA, J. Endothelial cell layer subjected to impinging flow mimicking the apex of an arterial bifurcation. *Annals of Biomedical Engineering*, 36(10):1681–1689, 2008.
- TANOUE, T., TATESHIMA, S., VILLABLANCA, J. P., VIÑUELA, F., AND TANISHITA, K. Wall shear stress distribution inside growing cerebral aneurysm. *AJNR. American journal of neuroradiology*, 32(9):1732–1737, 2011.
- TATESHIMA, S., TANISHIMA, K., OMURA, H., VILLABLANCA, J. P., AND VIÑUELA, F. Intra-aneurysmal hemodynamics during the growth of an unruptured aneurysm: In vitro study using longitudinal ct angiogram database. *AJNR. American journal of neuroradiology*, 28(4):622–627, 2007.

- TREMME, M., XIANG, J., HOI, Y., KOLEGA, J., SIDDIQUI, A. H., MOCCO, J., AND MENG, H. Mapping vascular response to in vivo hemodynamics: application to increased flow at the basilar terminus. *Biomechanics and Modeling in Mechanobiology*, 9: 421–434, 2010.
- VALENTÍN, A. AND HUMPHREY, J. D. Evaluation of fundamental hypotheses underlying constrained mixture models of arterial growth and remodelling. *Philosophical transactions. Series A, Mathematical, physical, and engineering sciences*, 367(1902):3585–3606, 2009a.
- VALENTÍN, A. AND HUMPHREY, J. D. Parameter sensitivity study of a constrained mixture model of arterial growth and remodeling. *Journal of biomechanical engineering*, 131(10):101006–1, 2009b.
- VENTIKOS, Y., BOWKER, T. J., WATTON, P. N., KAKALIS, N. M. P., AND BYRNE, J. V. Risk evaluation and interventional planning for cerebral aneurysms: computational models for growth, coiling and thrombosis. *International Journal of Computational Fluid Dynamics*, 23(8):595–607, 2009.
- VILLA-URIOL, M. C., BERTI, G., HOSE, D. R., MARZO, A., CHIARINI, A., PENROSE, J., POZO, J., SCHMIDT, J. G., SINGH, P., LYCETT, R., LARRABIDE, I., AND FRANGI, A. F. @neurist complex information processing toolchain for the integrated management of cerebral aneurysms. *Interface Focus*, 1:308–319, 2011.
- VIÑUELA, F., DUCKWILER, G., AND MAWAD, M. Guglielmi detachable coil embolization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. *Journal of neurosurgery*, 86(3):475–482, 1997.
- VLAK, M. H., ALGRA, A., BRANDENBURG, R., AND RINKEL, G. J. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *The Lancet Neurology*, 10(7):626–636, 2011.
- WAN, W., HANSEN, L., AND GLEASON, R. L. A 3-d constrained mixture model for mechanically mediated vascular growth and remodeling. *Biomechanics and modeling in mechanobiology*, 9(4):403–419, 2010.
- WANG, J. H. C. AND THAMPATTY, B. P. An introductory review of cell mechanobiology. *Biomechanics and Modeling in Mechanobiology*, 5(1):1–16, 2006.
- WANG, W., JÜTTLER, B., ZHENG, D., AND LIU, Y. Computation of rotation minimizing frames. *ACM Transactions on Graphics*, 27(1):1–18, 2008.
- WANG, W. AND KING, M. R. Multiscale modeling of platelet adhesion and thrombus growth. *Annals of Biomedical Engineering*, 40(11):2345–2354, 2012.
- WANG, X. AND LI, X. Biomechanical behaviour of cerebral aneurysm and its relation with the formation of intraluminal thrombus: a patient-specific modelling study. *Computer Methods in Biomechanics and Biomedical Engineering*, 16(11):1127–1134, 2013.
- WANG, Z., KOLEGA, J., HOI, Y., GAO, L., SWARTZ, D. D., LEVY, E. I., MOCCO, J., AND MENG, H. Molecular alterations associated with aneurysmal remodeling are localized in the high hemodynamic stress region of a created carotid bifurcation. *Neurosurgery*, 65(1):169–177, 2009.
- WATTON, P. N. *Mathematical modelling of the abdominal aortic aneurysm*. Ph.d. thesis, Department of Applied Mathematics, University of Leeds, Leeds, 2002.
- WATTON, P. N. AND HILL, N. A. Evolving mechanical properties of a model of abdominal aortic aneurysm. *Biomechanics and modeling in mechanobiology*, 8(1):25–42, 2009.
- WATTON, P. N., HILL, N. A., AND HEIL, M. A mathematical model for the growth of the abdominal aortic aneurysm. *Biomechanics and modeling in mechanobiology*, 3(2):98–113, 2004.
- WATTON, P. N., HOLZAPFEL, N. B., HOLZAPFEL, G. A., AND VENTIKOS, Y. Coupling the hemodynamic environment to the evolution of cerebral aneurysms: computational framework and numerical examples. *Journal of biomechanical engineering*, 131(10):101003, 2009a.
- WATTON, P. N., HUANG, H., AND VENTIKOS, Y. Multi-scale modelling of vascular disease: Abdominal aortic aneurysm evolution. In GERIS, L., editor, *Computational Modeling in Tissue Engineering*, volume 10 of *Studies in Mechanobiology, Tissue Engineering and Biomaterials*, pages 309–339. Springer Berlin Heidelberg, 2013.
- WATTON, P. N., SELIMOVIC, A., RABERGER, N. B., HAUNG, P., HOLZAPFEL, G. A., AND VENTIKOS, Y. Modelling evolution and the evolving mechanical environment of saccular cerebral aneurysms. *Biomechanics and Modeling in Mechanobiology*, 10(1):109–132, 2011a.

- WATTON, P. N. AND VENTIKOS, Y. Modelling evolution of saccular cerebral aneurysms. *The Journal of Strain Analysis for Engineering Design*, 44(5):375–389, 2009.
- WATTON, P. N., VENTIKOS, Y., AND HOLZAPFEL, G. A. Modelling the growth and stabilization of cerebral aneurysms. *Mathematical medicine and biology*, 26(2):133 – 164, 2009b.
- WATTON, P. N., VENTIKOS, Y., AND HOLZAPFEL, G. A. Modelling the mechanical response of elastin for arterial tissue. *Journal of Biomechanics*, 42(9):1320–1325, 2009c.
- WATTON, P. N., VENTIKOS, Y., AND HOLZAPFEL, G. A. Modelling cerebral aneurysm evolution. In MCGLOUGHLIN, T., editor, *Biomechanics and Mechanobiology of Aneurysms*, volume 7 of *Studies in Mechanobiology, Tissue Engineering and Biomaterials*, chapter 12, pages 307–322. Springer-Verlag, Heidelberg, 2011.
- WERMER, M. J. H., SCHAAF, I. C. V. D., VELTHUIS, B. K., ALGRA, A., BUSKENS, E., AND RINKEL, G. J. E. Follow-up screening after subarachnoid haemorrhage: Frequency and determinants of new aneurysms and enlargement of existing aneurysms. *Brain*, 128(10):2421–2429, 2005.
- WOLFE, S. Q., BASKAYA, M. K., HEROS, R. C., AND TUMMALA, R. P. Cerebral aneurysms: learning from the past and looking toward the future. *Clinical neurosurgery*, 53:157–178, 2006.
- WORKMAN, M. J., CLOFT, H. J., TONG, F. C., DION, J. E., JENSEN, M. E., MARX, W. F., AND KALLMES, D. F. Thrombus formation at the neck of cerebral aneurysms during treatment with guglielmi detachable coils. *American Journal of Neuroradiology*, 23(9):1568–1576, 2002.
- XIANG, J., TREMMEL, M., KOLEGA, J., LEVY, E. I., NATARAJAN, S. K., AND MENG, H. Newtonian viscosity model could overestimate wall shear stress in intracranial aneurysm domes and underestimate rupture risk. *Journal of NeuroInterventional Surgery*, 4(5):351–357, 2012.
- YILDIZ, O. Vascular smooth muscle and endothelial functions in aging. *Annals of the New York Academy of Sciences*, 1100:353–360, 2007.
- ZENG, Z., KALLMES, D. F., DURKA, M. J., DING, Y., LEWIS, D. A., KADIRVEL, R., AND ROBERTSON, A. M. Hemodynamics and anatomy of elastase-induced rabbit aneurysm models—similarity to human cerebral aneurysms? *American journal of neuroradiology*, 32:595–601, 2011.
- ZHAO, S., SUCIU, A., ZIEGLER, T., MOORE, J. E., B'URKI, E., MEISTER, J. J., AND BRUNNER, H. R. Synergistic effects of fluid shear stress and cyclic circumferential stretch on vascular endothelial cell morphology and cytoskeleton. *Arteriosclerosis, thrombosis, and vascular biology*, 15(10):1781–1786, 1995.
- ZHOU, X., RAGHAVAN, M. L., HARBAUGH, R. E., AND LU, J. Patient-specific wall stress analysis in cerebral aneurysms using inverse shell model. *Annals of Biomedical Engineering*, 38(2):478–489, 2010.
- ZULLIGER, M. A., RACHEV, A., AND STERGIOPOULOS, N. A constitutive formulation of arterial mechanics including vascular smooth muscle tone. *American journal of physiology. Heart and circulatory physiology*, 287(3):H1335–H1343, 2004.



DERIVATION OF THE ACTUAL FUNCTIONAL FORM OF $f_{\Lambda_R}(\lambda_R)$ BASED ON $f_{\Lambda_{AT}}(\lambda_{AT})$ AT INITIAL HOMEOSTASIS

We want to determine the PDF $f_{\Lambda_R}(\lambda_R)$ of the recruitment stretch distribution $Pr(\Lambda_R)$ based on the attachment stretch distribution $Pr(\Lambda_{AT})$ when the tissue is in initial homeostasis. First we have the following relationship (repeating Eq. 4.4):

$$\lambda_{AT}^{min} \cdot \lambda_R^{max} = \lambda_{AT}^{max} \cdot \lambda_R^{min} = \lambda_{AT}^{mod} \cdot \lambda_R^{mod} = \Lambda_{AT} \cdot \Lambda_R = \lambda \quad (\text{A.1})$$

We use $F_{\Lambda_R}(\lambda_R)$ to denote the cumulative distribution function (CDF) associated with $Pr(\Lambda_R)$. Utilising the equation above, $F_{\Lambda_R}(\lambda_R)$ can be computed by:

$$F_{\Lambda_R}(\lambda_R) = Pr(\Lambda_R \leq \lambda_R) = Pr\left(\frac{\lambda}{\Lambda_{AT}} \leq \lambda_R\right) = Pr\left(\Lambda_{AT} \geq \frac{\lambda}{\lambda_R}\right) \quad (\text{A.2})$$

Note that $Pr\left(\Lambda_{AT} \geq \frac{\lambda}{\lambda_R}\right)$ represents the proportion of collagen fibres whose attachment stretch is bigger than the value of $\frac{\lambda}{\lambda_R}$, hence it can be computed by:

$$Pr\left(\Lambda_{AT} \geq \frac{\lambda}{\lambda_R}\right) = 1 - Pr\left(\Lambda_{AT} \leq \frac{\lambda}{\lambda_R}\right) = 1 - \int_{\lambda_{AT}^{min}}^{\frac{\lambda}{\lambda_R}} f_{\Lambda_{AT}}(\lambda_{AT}) d\lambda_{AT} \quad (\text{A.3})$$

Now $f_{\Lambda_R}(\lambda_R)$ can be obtained by differentiating $F_{\Lambda_R}(\lambda_R)$ with respect to λ_R :

$$f_{\Lambda_R}(\lambda_R) = \frac{d}{d\lambda_R} F_{\Lambda_R}(\lambda_R) = -\frac{d}{d\lambda_R} \int_{\lambda_{AT}^{min}}^{\frac{\lambda}{\lambda_R}} f_{\Lambda_{AT}}(\lambda_{AT}) d\lambda_{AT} \quad (\text{A.4})$$

As $f_{\Lambda_{AT}}(\lambda_{AT})$ is a piecewise triangular function described by (repeating Eq. 4.3):

$$f_{\Lambda_{AT}}(\lambda_{AT}) = \begin{cases} 0 & \lambda_{AT} < \lambda_{AT}^{min} \\ \frac{2(\lambda_{AT} - \lambda_{AT}^{min})}{(\lambda_{AT}^{max} - \lambda_{AT}^{min})(\lambda_{AT}^{mod} - \lambda_{AT}^{min})} & \lambda_{AT}^{min} \leq \lambda_{AT} \leq \lambda_{AT}^{mod} \\ \frac{2(\lambda_{AT}^{max} - \lambda_{AT})}{(\lambda_{AT}^{max} - \lambda_{AT}^{min})(\lambda_{AT}^{max} - \lambda_{AT}^{mod})} & \lambda_{AT}^{mod} < \lambda_{AT} \leq \lambda_{AT}^{max} \\ 0 & \lambda_{AT} > \lambda_{AT}^{max} \end{cases} \quad (A.5)$$

$f_{\Lambda_R}(\lambda_R)$ is also a piecewise function. Utilising Eq. A.1, the explicit functional form of $f_{\Lambda_R}(\lambda_R)$ can be written as:

$$f_{\Lambda_R}(\lambda_R) = \begin{cases} 0 & \lambda_R < a \\ \frac{2(\lambda_R - a)}{(b - a)(c - a)} \cdot \frac{abc}{\lambda_R^3} & a \leq \lambda_R < c \\ \frac{2(b - \lambda_R)}{(b - a)(b - c)} \cdot \frac{abc}{\lambda_R^3} & c \leq \lambda_R < b \\ 0 & \lambda_R \geq b \end{cases} \quad (A.6)$$

where a , b and c are used to denote λ_R^{min} , λ_R^{max} and λ_R^{mod} respectively for convenience.



DERIVATION OF THE REMODELLED THICKNESS h_{rem} OF THE ARTERIAL WALL CONSIDERING THE VOLUMETRIC GROWTH OF THE WALL CONSTITUENTS

At the beginning we note that variables such as $\lambda(t)$, $h(t)$ and $r(t)$ are used to represent the values calculated from our model (as introduced in Chapter 4), whereas variables such as $\lambda_{rem}(t)$, $h_{rem}(t)$ and $r_{rem}(t)$ are used to represent the corresponding values of the arterial geometry considering volumetric growth of the wall constituents. First, consider a segment of the 1D cylindrical unloaded artery of unit length, whereby the volume of the arterial wall is V_n . Then this artery segment is pressurised by blood pressure p as well as stretch axially by λ_Z to simulate the physiological condition. Due to the incompressibility of the wall, the loaded wall volume, denoted as $V(0)$, is the same as the unloaded volume, i.e. $V_n = V(0)$. Now we use $\kappa_{rem}(t)$ to denote the volumetric growth of the wall constituents during aneurysm growth:

$$V_{rem}(t) = \kappa_{rem}(t) \cdot V(0) \quad (\text{B.1})$$

where $V_{rem}(t)$ is the volume of the remodelled wall of the same artery at time t . For a 1D cylindrical artery subject to blood pressure p and constant axial stretch λ_Z , the remodelled geometry is still a cylinder. The thin membrane formulation of the arterial wall assumes that the area elements of the upper and lower surfaces are ap-

proximated to be equal to those of the midplane. Hence Eq. B.1 can be alternatively written as:

$$r_{rem}(t) \cdot h_{rem}(t) = \kappa_{rem}(t) \cdot r(0)h(0) \quad (B.2)$$

where $r_{rem}(t)$ and $h_{rem}(t)$ are the remodelled radius and wall thickness of the artery, and $r(0)$ and $h(0)$ are the initial radius and thickness in the loaded configuration at time $t = 0$. Applying the incompressibility condition, we can calculate $r(0)$ and $h(0)$ based on the radius R and thickness H of the artery in the unloaded configuration, i.e.:

$$r(0) = R\lambda(0) \quad \text{and} \quad h(0) = \frac{H}{\lambda(0)\lambda_Z} \quad (B.3)$$

where $\lambda(0)$ is the initial circumferential stretch of the tissue at time $t = 0$. In addition, we also have $r_{rem}(t) = R\lambda_{rem}(t)$, where $\lambda_{rem}(t)$ is the remodelled circumferential stretch. Substituting this relationship as well as Eq. B.3 into Eq. B.2, we have:

$$h_{rem}(t) = \kappa_{rem}(t) \cdot \frac{H}{\lambda_{rem}(t) \cdot \lambda_Z} \quad (B.4)$$

Now, we assume the circumferential stretch $\lambda(t)$ calculated from the our model can represent the actual circumferential stretch $\lambda_{rem}(t)$ of the remodelled geometry, i.e. $\lambda(t) \approx \lambda_{rem}(t)$. Substituting this equation into Eq. B.4 eventually yields the equation that is used to infer the remodelled wall thickness:

$$h_{rem}(t) \approx \kappa_{rem}(t) \cdot \frac{H}{\lambda(t) \lambda_Z} \quad (B.5)$$

where $\kappa_{rem}(t)$ accounts for the wall thickness change due to volumetric growth and the second term after the dot is the thickness only considering the incompressibility condition of the arterial wall.

In addition, the dimensionless variable χ which is defined as the ratio of remodelled thickness to remodelled radius, can be calculated by:

$$\chi(t) = \frac{h_{rem}(t)}{r_{rem}(t)} = \frac{h_{rem}(t)}{R\lambda_{rem}(t)} \quad (B.6)$$

Utilising the relationship $\lambda(t) \approx \lambda_{rem}(t)$ as well as Eq. B.5, we have:

$$\chi(t) \approx \frac{H}{R\lambda_Z} \frac{\kappa_{rem}(t)}{[\lambda(t)]^2} \quad (B.7)$$

In order to calculate $\kappa_{rem}(t)$, we assume that the volumetric growth of the tissue is proportional to the mass growth of the constituents. Ignoring the intima layer, we can infer $\kappa_{rem}(t)$ by:

$$\kappa_{rem}(t) = \frac{M_{rem}(t)}{M(0)} = \frac{M_{rem|E_M}(t) + M_{rem|C_M}(t) + M_{rem|C_A}(t) + M_{rem|GW}(t)}{M_{E_M}(0) + M_{C_M}(0) + M_{C_A}(0) + M_{GW}(0)} \quad (B.8)$$

where $M_{rem}(t)$ is the mass of the same arterial wall considering volumetric growth of the wall constituents at time t , whereas $M(0)$ is the corresponding initial mass at time $t = 0$. $M_{rem|EM}(t)$, $M_{rem|CM}(t)$, $M_{rem|CA}(t)$ and $M_{rem|GW}(t)$ are the masses of medial elastin, medial collagen, adventitial collagen as well as other ground substance and water respectively, whereas $M_{EM}(0)$, $M_{CM}(0)$, $M_{CA}(0)$ and $M_{GW}(0)$ are the corresponding masses in the initial configuration at time $t = 0$. We assume the total mass of other ground substance and water is constant during aneurysm growth, i.e. $M_{rem|GW}(t) = M_{GW}(0)$, and represent this term by a constant G . We also assume that the remodelled masses of the constituents can be calculated based on the current mass densities computed from the model and the initial volumes of the arterial layers, i.e. $M_{rem|JL}(t) = m_{JL}(t)\rho_{JL}V_L(0)$, where $m_{JL}(t)$ is the normalised mass density of the J constituent in the L layer, ρ_{JL} is its mass density at time $t = 0$, and $V_L(0)$ is the initial volume of L layer so that $V_M(0) + V_A(0) = V(0)$. Now, expressing the masses in terms of the mass densities and volumes, we have:

$$\kappa_{rem}(t) = \frac{[m_{EM}(t)\rho_{EM} + m_{CM}(t)\rho_{CM}]V_M(0) + m_{CA}(t)\rho_{CA}V_A(0) + G}{[m_{EM}(0)\rho_{EM} + m_{CM}(0)\rho_{CM}]V_M(0) + m_{CA}(0)\rho_{CA}V_A(0) + G} \quad (B.9)$$

We let $\omega_1 = \rho_{EM}/\rho_{CA}$ and $\omega_2 = \rho_{CM}/\rho_{CA}$. Considering $m_{EM}(0) = m_{CM}(0) = m_{CA}(0) = 1$, we can further reduce the preceding equation into:

$$\kappa_{rem}(t) = \frac{[\omega_1 m_{EM}(t) + \omega_2 m_{CM}(t)]V_M(0) + m_{CA}(t)V_A(0) + \frac{G}{\rho_{CA}}}{(\omega_1 + \omega_2)V_M(0) + V_A(0) + \frac{G}{\rho_{CA}}} \quad (B.10)$$

Now utilising the relationship $V_M(0) = 2V_A(0)$ (thin membrane), Eq. B.10 can be reduced to:

$$\kappa_{rem}(t) = \frac{2[\omega_1 m_{EM}(t) + \omega_2 m_{CM}(t)] + m_{CA}(t) + \frac{G}{\rho_{CA}V_A(0)}}{2(\omega_1 + \omega_2) + 1 + \frac{G}{\rho_{CA}V_A(0)}} \quad (B.11)$$

The term $\frac{G}{\rho_{CA}V_A(0)} = \frac{M_{GW}(0)}{M_{CA}(0)}$, i.e. it represents the ratio of total mass of other ground substances and water to the mass of adventitial collagen fibres in the initial configuration. This ratio is generally unknown. However, if we assume it is relatively small compared with the sum of other terms in the numerator and denominator in the preceding equation, then this makes $\kappa_{rem}(t)$ calculable by simply taking off the term $\frac{G}{\rho_{CA}V_A(0)}$. Then $\kappa_{rem}(t)$ can be approximated by:

$$\kappa_{rem}(t) \approx \frac{2[\omega_1 m_{EM}(t) + \omega_2 m_{CM}(t)] + m_{CA}(t)}{2(\omega_1 + \omega_2) + 1} \quad (B.12)$$

Due to the lack of biological information, in this study we assume that the initial mass densities of elastins and collagens are all identical, i.e. $\omega_1 = \omega_2 = 1$. Eventually

we have:

$$\kappa_{rem}(t) \approx \frac{2m_{EM}(t) + 2m_{CM}(t) + m_{CA}(t)}{5} \quad (\text{B.13})$$

Note we have $\kappa_{rem}(0) = 1$ satisfying the initial condition.