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A study of the solid and fluid mechanics of atherosclerotic plaques using numerical simulations

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Abstract

Cardiovascular diseases are closely related to atherosclerosis, a medical condition that consists of a local narrowing of the artery diameter due to the thickening of the artery wall. This narrowing, also known as stenosis, is caused by an accumulation of fatty substances, also known as plaque, in the intima layer of the artery. One of the biggest risks is the rupture of the plaque cap, which may lead to the formation of a blood clot. If this clot moves into the circulation, it can potentially block the blood supply to key organs in the human body, leading to life-threatening conditions. Typical locations where plaque may appear are the carotid arteries in the neck, the coronary arteries in the heart, and renal arteries in the kidneys.

The main objective of this thesis is to shed light on the plaque rupture process using numerical simulations. Specifically, as stated in the title, the goal is to study the fluid and solid mechanics of atherosclerotic plaques using fluid-structure interaction. In order to do this, several models of idealised, atherosclerotic arteries are presented. The blood flow is modelled as steady, incompressible and Newtonian, whereas both linear elastic and hyperelastic behaviours are used to model the artery wall and the plaque.

The results are divided into three main chapters. First, an axisymmetric, thin-wall artery model is analysed. The primary aim is to provide an overview of the main physics that are present in this configuration. Second, a similar

atherosclerotic artery is studied, including the modelling of the plaque. The stress distributions along the geometry are analysed in order to determine how the different parameters affect the stress distributions and, potentially, the location of the rupture. Finally, an eccentric, three-dimensional model is introduced. A subsequent parametric analysis is performed, including the comparison to the previous axisymmetric models. In order to perform the simulations, the commercial software COMSOL Multiphysics has been used.

Among the main conclusions, it should be highlighted that a variation of the stiffness of certain components of the plaque may change the stress distribution significantly. This can have an effect on the location of the stress peaks, hence impacting the potential location of a rupture. Other common features of a plaque, such as positive remodelling, also affect the overall levels of stress, suggesting that certain plaques are more vulnerable than those that do not present remodelling. The comparison of the three-dimensional to the axisymmetric models showed that there are general features that can be observed with the simpler, axisymmetric models. However, some particular traits of the eccentric plaques were only observed in the three-dimensional configurations.

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Chapter 1

Introduction

1.1 Aims and objectives

The objective of this thesis is to shed some light on the initiation of a process called plaque rupture in atherosclerosis. The novelty of the approach exposed here is that the potential axial locations of the rupture are predicted by analysing the stress fields along an atherosclerotic vessel. Specifically, the axial distribution of stress will be investigated in detail by carrying out several parametric analyses, starting with simple, two-dimensional models before introducing more complex geometries. The aim will be to identify how different mechanical features and geometric configurations can impact the location of the rupture. In order to do this, numerical simulations of blood flow through idealised geometries will be performed in the following chapters. Ultimately, identifying which features affect the location of the rupture using idealised models could be a useful tool and help diagnosing patient-specific plaques.

This thesis is organised in three main parts.

First, the introduction to this work is presented in Chapter 1, along with a literature review showing the studies that have been published in the area of

atherosclerosis and plaque rupture. Chapter 2 starts with an introduction to the finite element method, which is the numerical technique used to perform the simulations; alternative methods are mentioned afterwards, followed by a formal presentation of the fluid-structure interaction framework and the governing equations used in the present thesis.

The second part includes the presentation and discussion of the results from the numerical simulations. Specifically, the analysis of a thin, elastic wall with steady flow conditions through an axisymmetric geometry is presented in Chapter 3. A parametric study is performed and several features of the flow and of the solid are analysed. The model is further refined in Chapter 4, with the introduction of the plaque; in particular, the stenotic region of the artery wall includes a lipid core and a fibrous cap to improve the model of an atherosclerotic plaque. The axial distribution of first principal stress along the wall is analysed in order to investigate potential sites of plaque rupture. Finally, Chapter 5 extends the results obtained in Chapter 4 to a three-dimensional space. Specifically, a fully three-dimensional, eccentric plaque model is analysed and compared to the two-dimensional cases studied previously.

The last part, following the results observed in the current simulations, introduces the proposal of the future work. This is presented in Chapter 6, where some research options that may be of interest as a next step are discussed, including the modelling of a more complex geometry and a further analysis of the results. This could be considered as an extension of the work presented in this thesis and a logical next step.

1.2 Literature review

1.2.1 Atherosclerosis and plaque rupture

Atherosclerosis is a disease that occurs when fatty substances, known as *plaque*, build up in the intima layer of an artery [1, 2]. The deposition of macrophage cells in the subendothelial region is one of the early symptoms of the disease, along with an accumulation of extracellular lipids that leads to the formation of a lipid or necrotic core [3, 4]. This provokes a narrowing of the affected vessel, creating a constriction of the artery, as shown in the diagram depicted in figure 1.1. The narrowing of the arterial lumen is called a *stenosis*, a term that derives from the Ancient Greek word *στένωσις*, “narrowing” [5].

The plaque may grow to the point of blocking the blood flow through the artery. However, this is not the most important complication; the worst-case scenario is the rupture of the covering of the plaque, the *fibrous cap* [1]. In this case, the inner components of the plaque may move into circulation creating a blood clot, or thrombus. The clot may eventually block the flow through the artery and stop the blood supply to vital organs [7], such as the heart, the kidneys or the brain. This in turn can result in life-threatening conditions such as coronary artery disease, renal infarction or stroke [8–10], depending on the location of the occlusion.

The focus of this work is to study atherosclerosis in one particular location: the human carotid artery. This vessel is responsible for supplying the head and neck with blood [11]. The human body has two carotid vessels, located on each side of the neck. Each artery bifurcates into the external and the internal carotid arteries. The external branch supplies mainly the face and the neck, while the internal vessel is responsible for supplying the brain

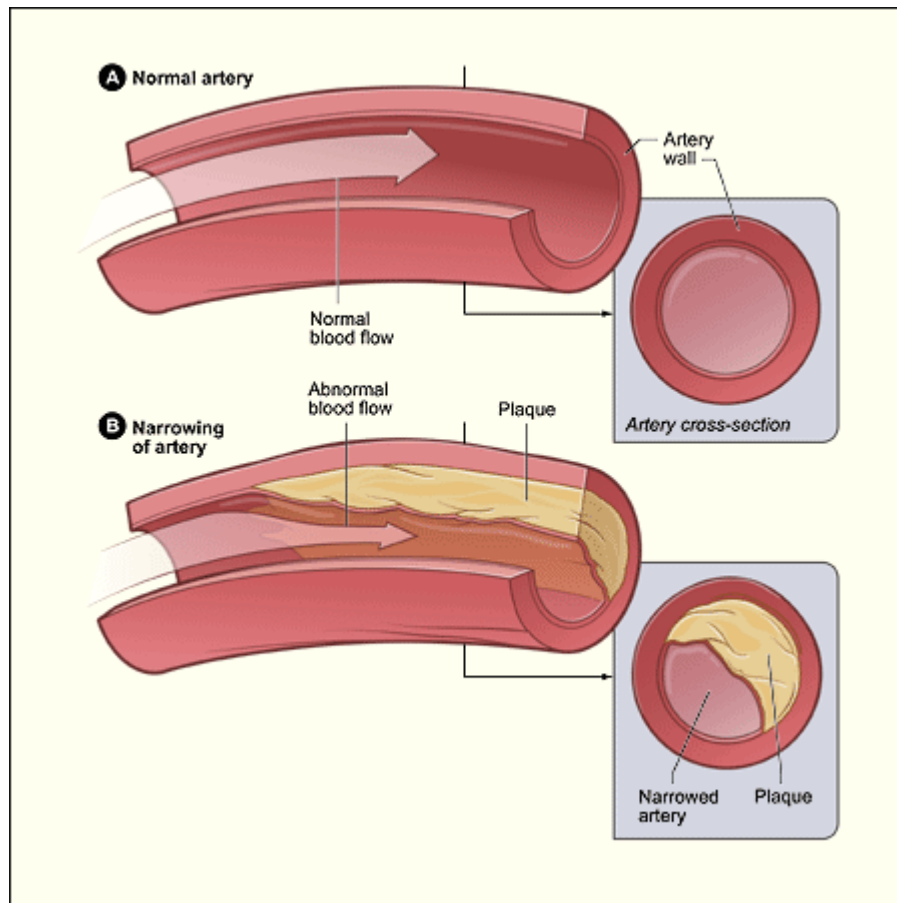


Fig. 1.1: Atherosclerosis diagram. (A) shows a normal artery; (B) shows the narrowing of an artery due to the accumulation of plaque. Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services [6]. The image is in the public domain.

with blood. A graphic representation of the arteries is shown in figure 1.2, which presents one of Gray's drawings [11].

The mechanisms behind disease initiation, progression and rupture are diverse. For example, genetic factors such as elevated levels of lipoproteins, elevated blood pressure, gender or family history play a role in atherosclerosis. Other environmental factors such as diet, lack of exercise or smoking are also associated with this phenomenon [1]. In addition, cellular interactions are important in atherogenesis (disease initiation) as well, especially elements like platelets and macrophages [10], which have higher probability of deposition in stenotic regions [12]. On the other hand, it has been suggested that lipid-rich plaques may more easily detach from the wall [3, 13], so the composition of the plaque is also important when considering the vulnerability. In summary, there are several factors of different nature that affect the apparition of atherosclerosis, and influence the development and possible rupture of the plaque. Some of those are not within the scope of this study, as this work is focused on the mechanical aspects that affect the rupture of the plaque.

Finally, as to why it is relevant to study this problem, it should be noted that atherosclerosis' most common manifestations are cardiovascular diseases [14, 15], which were the leading cause of death in the world in 2015 [16]. According to the same report, compiled by the World Health Organization, cardiovascular diseases accounted for more than a quarter of the 56.4 million deaths globally during that year. In particular, coronary heart disease and stroke were reported as the leading causes of death every year from the year 2000 to 2015.

A similar pattern is observed by looking at the European Union only. Eurostat, the statistical office of the European Union, reported that cardio-

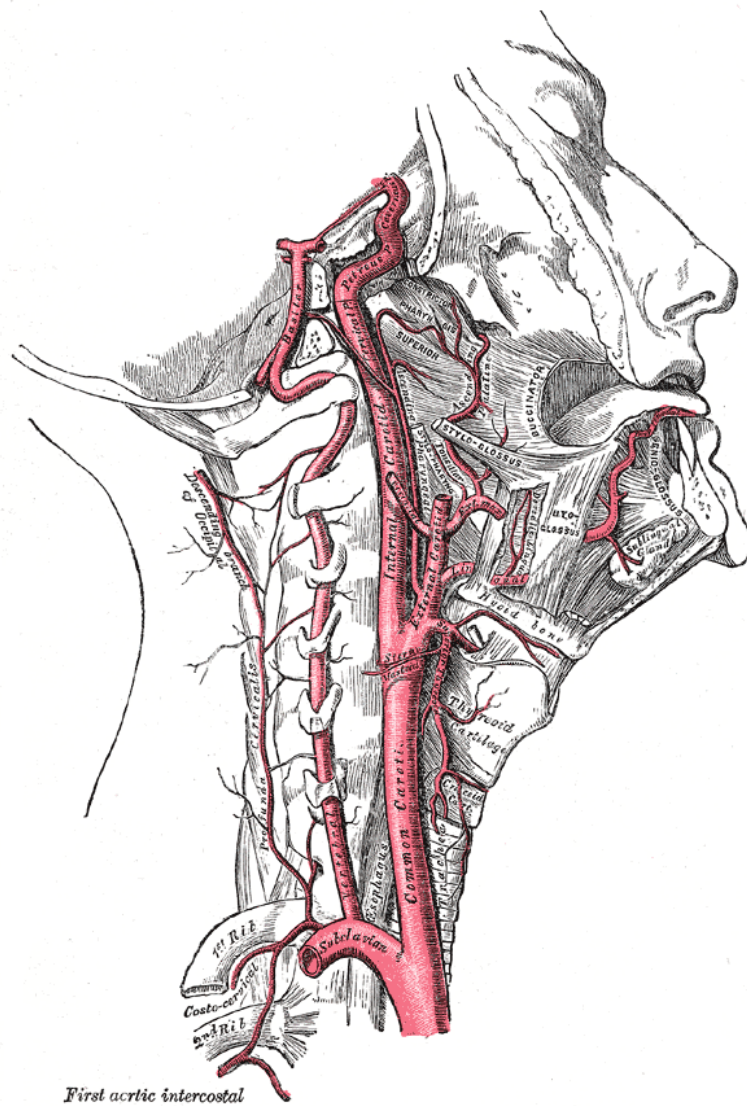


Fig. 1.2: Graphical representation of the right human carotid artery [11]. The image is in the public domain.

vascular diseases were the leading cause of death in 2014 among the twenty-eight EU member states [17], accounting for 1.8 million deaths out of a total of almost five million. Putting that in context, the second largest cause of death was cancer, which accounted for 1.3 million deaths, while the third cause were diseases related to the respiratory system.

In summary, plaque rupture is a process closely related to cardiovascular diseases that still are the most common cause of death. Understanding the mechanisms of plaque rupture could prove to be a very important aspect at the time of diagnosis: some plaques may require surgery, while others may be less prone to rupture and therefore may not pose a risk to the health of the individual.

1.2.2 Fluid dynamics simulations

As it was explained in the previous section, apart from environmental or biochemical factors, the fluid dynamics of the blood flow, also known as hemodynamics, can play an important role in the early stages of a cardiovascular disease. To further investigate this topic, some studies have looked at the local velocity distributions and the shear stresses as important factors to consider in atherosclerosis [18].

The need for blood flow simulations arose as it was difficult to obtain detailed information about the flow patterns using non-invasive techniques, and thus numerical simulations were required. For instance, Ku performed unsteady blood flow simulations in order to study the biological response to unusual flow conditions [19]. Among other results, it was suggested that the local nature of the arterial diseases was caused by local factors, and therefore there was a great interest in studying in detail the local flow distributions. In addition, when analysing the fluid velocity profiles, he considered the use

of the Womersley number, α , which gives an idea of the relationship between the unsteady and the viscous forces within the flow [20]. In particular, $\alpha = (D/2)\sqrt{\omega/\nu}$, where D denotes the artery diameter, ω defines the angular frequency of the unsteady flow, and ν is the kinematic viscosity of the blood.

The study of the blood flow is a broad field, with a wide range of works, from vertebral arteries simulation [21] to control optimisation [22]. In the following, several blood-flow-related works from different backgrounds will be presented in order to summarise some of the existing state of this research area.

As mentioned before, this work is focused on the mechanical factors around the plaque rupture process. In particular, special attention is given to the structural mechanics (e.g. stiffness) of the artery and the plaque itself due to the forces that the blood flow induces around it. From a fluid dynamics point of view, the plaque in the artery can be seen as an obstacle that reduces the cross-sectional area available for the flow, as shown in figure 1.1. As a simplification, the problem can basically be described as a fluid (in this practical case, blood), flowing through a pipe (the artery) that has a constriction at some point (the stenosis). This is usually called a *stenotic flow*, and it is a wide subject that has been extensively studied in the fluid dynamics community [23–29]. The size of the lesion is usually described by the *stenosis severity*, which is a parameter that defines the reduction in cross-sectional area. Other expressions that refer to the same concept are degree of stenosis or area occlusion.

Usually, the geometries were considered axisymmetric and the walls were considered rigid. For instance, in 2005, Sherwin and Blackburn focused on the flow instabilities and transition to turbulence in a three-dimensional stenosis with a 75 % area occlusion [24]. They localised regions of strong turbulence

related to high shear stress gradients, which are believed to play a role in the onset of vascular diseases. The topic of the influence of the wall shear stress on atherosclerosis has been a matter of discussion, as it is also considered that low, oscillatory shear stresses happen at vulnerable locations [23]. Vétel et al. also studied the transition to turbulence using a similar axisymmetric geometry, but from an experimental point of view [30]. In particular, the latter authors reported that the degree of asymmetry of the flow increased when the Reynolds increased, and observed non-stationary effects for Reynolds higher than 400. Others have dealt with optimal boundary perturbations to the steady flow, illustrating that significant transient energy growth is induced when the perturbation was convected downstream by the flow [31]. The stability of the flow was also analysed in similar axisymmetric geometries; for instance, Loh and Blackburn analysed the flow through a corrugated pipe, imposing a sinusoidal variation on the diameter along the axial direction [32]. They found separation when the Reynolds number or the height of the axial corrugation increased.

Varghese et al. also performed three-dimensional fully resolved direct numerical simulations of steady flows through a tube with a 75 % area reduction [25]. They studied a range of Reynolds numbers, from 500 to 1000, introducing a geometric perturbation with the aim of studying the flow transition from a laminar to a turbulent regime. For the axisymmetric configuration, their simulations predicted a laminar flow field downstream the constriction for all Reynolds numbers. On the contrary, the inclusion of a certain degree of eccentricity led to localised transition to turbulence when the Reynolds increased to 1000. A second part of their work focused on pulsatile flow, which introduced time-dependent analyses [26]. Again, the results showed a laminar flow field downstream the stenosis, and a periodic transition to

turbulence when the eccentricity was included.

Other groups have also studied the effects of small asymmetries on the flow configuration, again by means of a stenosis eccentricity. In particular, Griffith et al. compared the differences observed among experimental and numerical studies [28]. They suggested that the presence of asymmetries is inevitable within an experimental setup and therefore steady asymmetric flow is obtained even in axisymmetric geometries (which explained the results observed by Vétel et al. [30]). On the other hand, there are no geometrical imperfections on numerical simulations (provided that the mesh does not introduce any asymmetries), therefore an axisymmetric steady flow was expected when studying axisymmetric geometries for a certain range of Reynolds numbers. A similar numerical study of a stenosis with a steady inflow was performed by Samuelsson et al. a few years later, where the introduction of a perturbation in the geometry lowered the flow critical transition Reynolds number [29]. Specifically, increasing the eccentricity of the stenosis constriction to just a 0.3% of the inlet diameter halved the transition Reynolds number.

Besides the eccentricity, the influence of the shape of the stenosis itself has been considered as well, by varying the geometry of an idealised plaque. A quantitative study on the different geometric aspects of a coronary plaque of multiple patients was performed by Ledru et al. [33]. Among other findings, they reported that the steepness of the outflow stenosis angle as one important factor that predicted later infarctions. Flow separation increased when the outflow angle was more abrupt, suggesting that this could lead to wall vibration. On the other hand, the inlet angles did not affect the results. Lorenzini and Casalena also investigated the flow velocity profiles for different plaque shapes: a triangle, a semi-ellipse and a trapezium [34].

They found the recirculation region to be greatly affected by the slope of the plaque contour in the stenosis region of a rigid artery. They identified the trapezium shape to be the most severe case, being related to higher peak velocities and strains.

Another interesting point was the influence of a smooth or irregular surface. Stroud et al. analysed the effect of the stenosis shape and irregularities on the flow through a rigid stenosis [35]. They found that the degree of stenosis did not fully define the flow, since two arteries with equal stenosis severity but different plaque morphology could lead to different shear stress distributions. They also reported a higher wall shear stress when the surface irregularity was included, and a significant change in the spatial wall shear distribution for cratered vessels that modelled ulceration. Others have varied the height and the width of a smooth, two-dimensional stenosis to study the geometric effect of a plaque [36]. They found that the height of the plaque, i.e. the stenosis severity, was the most important of those two variables, showing higher wall shear stress distributions and gradients, while the wall normal stresses increased only downstream the plaque. On the other hand, the effect of stenosis length and the gap in a double stenosis was analysed by Nandakumar and Anand by performing simulations of a rigid-walled channel at a relatively high Reynolds ($Re = 4000$) [37]. They reported an increase of the wall shear stress peak for larger stenosis lengths, and that this effect had more influence than the gap between stenoses.

As a final note, the biomechanics community has mainly considered more realistic geometries than those mentioned in stenotic flow studies. The reason for this is that the focus of the biomechanical studies is on the features and effects that are directly related to the biological problem (the flow through the artery), rather than analysing the pure nature of the flow as in the fluid

dynamics studies. It is a fairly common practice to consider geometries reconstructed from medical images. For example, Stroud et al. analysed the two-dimensional flow through a carotid bifurcation modelled after a patient-specific geometry [38]. They tested several Reynolds number regimes and reported, among other observations, high wall shear stresses and high shear gradients. Another representative example is the work carried out by Johnston et al. [39]. Instead of focusing on an idealised axisymmetric pipe, numerical simulations were performed for four types of three-dimensional arteries, which had been reconstructed from medical images. Using a pulsatile inflow, they studied the influence of different viscosity models, including non-Newtonian ones. They concluded that the Newtonian model was a good choice overall; the non-Newtonian effects were found to be significant only when the blood flow was slow. The importance of the blood viscosity model used was also analysed in later studies, which considered the time-dependent flow through an axisymmetric artery [40]. In addition, Soulis et al. employed non-Newtonian viscosity models for the blood flowing through a realistic arterial geometry, concluding that the most accurate models were based on the Power Law models [41].

1.2.3 Influence of the elasticity of the wall

Most of the studies mentioned so far focused on the blood flow simulations through rigid artery models. However, it is essential to compute the stresses on the vessel wall when analysing the plaque rupture, and these stresses depend on the vessel elasticity; if the wall is elastic, the stresses on it due to the flow will actually deform the wall. Therefore, the whole situation becomes a *fluid-structure interaction* problem. In the following, the abbreviation FSI will be used to refer to this kind of study.

There are two different approaches to this configuration [42]. The first one is known as one-way coupling, which applies when the solid displacements are relatively small. In this case, the solid is deformed by the stress caused by the flow, but the wall deformation is not considered to modify the flow, which remains unchanged. Therefore, mesh deformation is not taken into account in the flow simulations, if the one-way coupling approach is adopted. The second approach is the two-way coupling, which accounts for larger wall displacements that, at the same time, are allowed to have an effect on the flow. Plaque rupture is by definition a process where relatively large deformation occurs. As the final goal of this research is to shed light on the rupture process, wall deformation needs to be introduced, and thus two-way coupling is considered before making any other assumptions.

There have been a few FSI studies in the literature regarding elastic-walled pipes. One of the first to consider the elasticity of the wall were Luo and Pedley, who studied both steady and unsteady flows through a two-dimensional collapsible channel [43, 44]. Specifically, one of the walls was rigid while the other had a portion made of a finite-length elastic membrane. The membrane was deformed due to the pressure difference between the internal and the external areas. The authors performed numerical simulations based on the finite-element method using three control parameters: the dimensionless flow rate, the pressure difference and the tension in the membrane. By implementing an iterative approach, they solved the flow problem and the wall motion separately, but taking into account the interface boundary condition in every time step. They reported that it was difficult to achieve convergence when the membrane tension was reduced, i.e. when the membrane was more flexible. In addition, they analysed the stability of the flow by imposing some disturbances on the steady solution. It was observed that

the unsteady solution approached the steady one (i.e. the steady solution was stable) for any tension of the membrane when the Reynolds number was under a certain threshold, typically smaller than 100. When the Reynolds increased, the solution remained stable only if the tension was large enough.

A similar configuration was analysed in later studies, but considering a three-dimensional collapsible tube rather than a two-dimensional channel [45, 46]. In particular, Heil and Jensen reviewed the main works in the field, from the one-dimensional approach to a fully three-dimensional problem, where the collapsible tube was modelled using a thin-walled elastic shell, and a linear stress-strain relation [45]. They found some differences between the tubes simulations and the two-dimensional cases, such as the apparition of two flow branches around the most deformed part of the tube near the centre-line, and concluded that there are features that cannot be reproduced with lower-dimensional models.

Tang et al. performed FSI simulations of an axisymmetric stenotic tube with a thin, elastic wall [47]. Among other observations, they reported a negative stress at the throat of the stenosis, which meant that the wall at the maximum constriction section was compressed. Later on, they followed the investigations with three-dimensional simulations and introducing asymmetry, modelling both a thin-wall and a thick-wall stenosis [48, 49]. In the case of the thin-wall model, they reported that the stenosis severity had a great effect on wall stresses, showing a significant increase when the constriction area was smaller [49]. For the thick-wall model, they observed that the flow features were similar to those observed in the thin-wall case [48]. The stenosis severity seemed to affect the deformation and the wall stresses, as the stiffness of the model was affected when varying the area occlusion. This team also observed that the asymmetry of a stenotic model led to an

increase of the compressive stress in the vessel wall [50]. A similar analysis of an idealised stenosis had been performed by Bathe and Kamm as well, who reported an increase of the circumferential wall stress downstream the stenosis during peak flow [51]. Finally, it is worth mentioning another analysis that studied the plaque stress in an axisymmetric stenosis [52]. They found the maximum plaque stress at the inlet and at the outlet sections of the stenosis. However, as they point out in the discussion, the lipid core of the plaque was not included in their model, so the stress field should be analysed with caution.

The influence of an elastic wall on the flow through a stenosis geometry was also considered by Moayeri et al. [53]. They performed time-dependent FSI simulations of an axisymmetric stenosis, analysing the effects of an elastic vessel on the wall displacements and stresses. In particular, they related the deformability of the wall to a decrease of the wall shear stresses, and to an increase of the time-averaged pressure drop. A subsequent study of an elastic renal artery stenosis concluded that the displacements of the wall were driven by the fluid pressure [54]. In addition, the latter authors concluded that the displacement was lower for stenotic geometries than for healthy non-stenotic arteries, due to the differences in stiffness. However, this analysis did not take into account the modelling of the lipid core, which may impact the results. An experimental approach was followed by Usmani and Muralidhar, comparing the flow through a rigid and an elastic model [55]. They found a decrease of the size of the vortex in the recirculation region when the Womersley number increased, that is, when the period of the pulsatile flow was smaller. They also reported lower values of the wall shear stress for the compliant model than for the rigid one, in agreement with previously published results [53].

Another FSI study analysed the effect of surface irregularities in a stenosis

from a mathematical point of view [56]. They compared velocity profiles and wall shear stresses for smooth and irregular geometries, reporting significant differences in magnitude, depending on the location and on the time instant during the period. Although they implemented a viscoelastic model for the solid, they did not analyse the stress inside the wall (other than the shear stress at the wall surface). Liu et al. studied the effect of the location of the narrowest section of the stenosis [57]. For the same severity, they varied the axial position of the section of maximum constriction and analysed the stress and flow fields. They found that the plaque was more vulnerable when the maximum constriction was located proximally (i.e. closer to the upstream end of the stenosis) due to a higher stress value. If the maximum constriction was located distally (i.e. closer to the downstream end of the stenosis), they identified a higher risk of thrombus formation, due to high shear rates and large recirculation regions.

1.2.4 Cross-sectional structural analyses

From a biomechanics perspective, rather than focusing on the flow dynamics, it is important to consider the stresses that the fluid pressure induces on the vessel wall. The main goal is the analysis of the plaque rupture, rather than the initiation or progression of atherosclerosis. Therefore, the first works on this subject were structural analyses.

The first detailed study of the stress distributions and their influence in plaque rupture was performed by Richardson et al. [58], who investigated the rupture locations in coronary arteries. They studied 71 cross-sectional samples, 67 of which had an eccentric lipid pool. They found that 63 % of the eccentric plaques fractured at the junction of the cap with the adjacent layer of the artery, while the rest presented fractures at the middle of the cap. For

the remaining samples the lipid pool was concentric, so no specific rupture location could be indicated. A diagram showing the different rupture locations is shown in figure 1.3. Other authors that investigated this configuration found results consistent with these findings [59–61]. Loree et al. performed two-dimensional finite element simulations of different artery cross-sections, with and without lipid core [59]. They found that the maximum stress on the plaque increased when the fibrous cap thickness decreased. It was suggested as well that the plaque rupture site may be at the same location where the peak stresses were observed. However, other factors such as local variations of the material properties may influence the rupture location as well [60]. In a later study they also reported that stiffer lipid cores decreased the peak stresses on the plaque [62]. These findings were further investigated by Li et al., who carried out a study where the artery geometry was subjected to pulse pressure loading [63]. Apart from the absolute values of stiffness, they noticed that the ratio of the stiffness of the fibrous cap to the stiffness of the lipid core played an important role as well. Specifically, the stress on the plaque increased when the relative stiffness increased.

Summarising, the majority of the ruptures are not always found at the same locations. For example, Virmani et al. found that the rupture took place most often at the central region rather than at the junction of the cap with the adjacent layer of the artery [64]. They refer to this junction as the *plaque shoulders*, a term that is commonly used in the literature [61, 63, 65]. For clarification, a rupture found at the plaque shoulders of a cross-section of an artery would correspond to the location indicated by the red arrow in figure 1.3A.

Among other structural analyses, Huang et al. studied the influence of calcification in plaques, concluding that it did not result in an increase of the

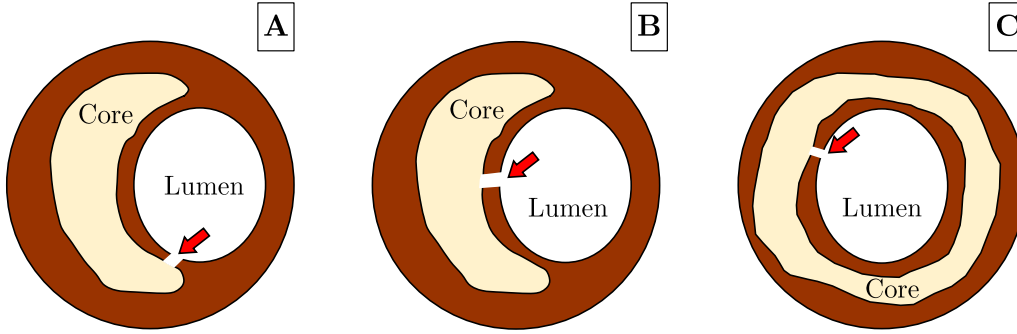


Fig. 1.3: Cross-section diagrams of an atherosclerotic artery. The red arrow denotes the rupture site. (A) Rupture of an eccentric plaque at the junction of the cap with the adjacent layer of the artery; (B) rupture of an eccentric plaque through the centre of the cap; (C) rupture of a concentric plaque.

fibrous cap stresses [66]. They modelled several artery cross-sections based on coronary arteries obtained from 20 patients. They applied a constant internal pressure and found that the stability of the plaque was more dependent on the lipid core rather than on the calcified parts of the plaque. Similarly, in other analyses assessing plaque vulnerability, the lipid-filled plaques were found to more likely to rupture than calcified plaques, which were expected to remain stable [67].

On the other hand, Li et al. identified the differences in stress patterns between symptomatic and asymptomatic plaques [65]. It was reported that symptomatic plaques presented higher stress concentrations, and therefore they may be more vulnerable than asymptomatic plaques. As plaques are subjected to cyclical loading due to the pulsatile nature of the blood flow, other group analysed the crack propagation process in a attempt to predict fatigue life [68]. They found that the main factors affecting fatigue in coronary arteries were the blood pressure and the lipid core stiffness. Finally, Creane et al. used three-dimensional patient-specific geometries and intro-

duced a new index to provide an indication of plaque vulnerability [69]. This index was related to the lumen curvature in the cross-section of the vessel, and it was usually higher at the plaque shoulders.

1.2.5 Plaque stress along the axial direction

The studies reviewed in the previous section are mostly finite element simulations of different artery models subjected to a specific internal pressure. In addition, the usual approach is to investigate the rupture site of plaque in the vessel cross-section [58, 63]. But, what about the axial direction?

Due to the complex nature of the plaque geometry in the axial, or longitudinal, direction, it could be considered that the location of the rupture has not been precisely identified. Back in 1992, Falk stated that the rupture of stenotic plaques could take place upstream, downstream or at the point of the maximum narrowing [3]. For carotid arteries in particular, he reported that some studies found ruptures mostly in the upstream region of the stenosis, while others reported that they took place at the constriction, or minimum lumen section. A few years later, it was suggested that the difference in composition between the upstream and downstream regions of the stenosis could impact the location of the rupture [70]. Specifically, the upstream region was considered to be the most vulnerable part, evidenced by a larger macrophage presence in the region. On the other hand, more smooth muscle cells were found in the downstream part, something that could explain a slow growth of the plaque. Lovett and Rothwell found that the upstream region was also more prone to ulceration [71], i.e. a irregularity on the surface of the arterial lumen that exposes a portion of the plaque to the blood flow [72]. They related this to the higher shear stresses found upstream the stenosis.

A structural-only analysis was performed by Imoto et al., studying an ax-

isymmetric plaque subjected to a uniform internal pressure [73]. The location of the maximum stress was usually found where the thickness of the fibrous cap was smallest, in agreement with previously published observations of two-dimensional models [59]. In addition, they reported that a larger core did not influence the stress should the cap thickness remain constant. However, this last result was further discussed by Ohayon et al. around three years later, who published a two-dimensional study of the influence of the lipid core thickness on the plaque stresses [74]. By modelling several atherosclerotic artery cross-sections, they analysed the stress field for different shapes of the lipid core. They showed that a larger lipid core thickness, i.e. a larger lipid core, led to a significant increase of the stress on the fibrous cap when its thickness remained constant. This result was contrary to the observations reported by Imoto et al. [73]. The explanation for this difference was that the conclusions reported by Imoto et al. for an axisymmetric model were not applicable to the eccentric configurations analysed by Ohayon et al, who indicated that the size of the lipid core is a key factor regarding the vulnerability of plaques [74].

1.2.6 Considerations about the modelling of the artery

When performing the aforementioned studies (either in the cross-sectional or in the longitudinal direction), one important aspect to consider is the modelling of the artery itself. A human vessel like the carotid artery is a soft tissue; hence, its behaviour is more complex to model than that of a metallic structure [75], due to diverse factors. First, two constituents, elastin and collagen, are believed to play a key role in the characterisation of the mechanical behaviour of these materials [76, 77]. Second, soft tissues are non-homogeneous and present anisotropy (i.e. the mechanical properties vary

The Structure of an Artery Wall

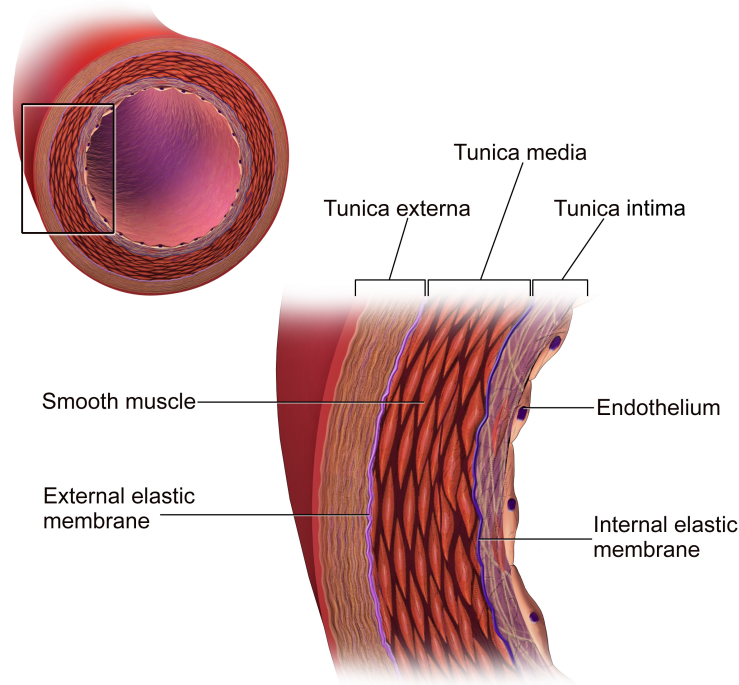


Fig. 1.4: Representation of the micro-structure of an artery showing the three layers: tunica intima, tunica media and tunica adventitia (externa). Image by the Blausen.com staff licensed under CC BY 3.0 [81].

depending on the direction of the stress) due to its fibre-reinforced structure [76]. And finally, the mechanical properties can be affected by a large number of diverse factors, such as age, temperature and pH, among others [76].

The structure of an artery can be described by three concentric layers, or tunicae [11]: the *intima*, which is the innermost layer of the artery; the *media*, which is the thickest; and the *adventitia* (also known as *externa*), which is the outermost layer [78]. These layers present different material properties [79]; in particular, the tunica intima and media have been found to be stiffer than the tunica adventitia [76, 80]. An idealised representation of an artery showing the multi-layer structure is shown in figure 1.4.

Regarding the size, it is worth noting that the carotid arteries in particular vary depending on the individual. For instance, Krejza et al. reported that they are typically smaller in women, even after scaling with the size of the body and the neck [82]. The total thickness can also vary between 0.5 mm and 1.5 mm approximately [83–85].

Some models have been considered to represent the complex micro-structure of the arterial tissues. For instance, the one proposed by Holzapfel et al. characterised an idealised artery by two concentric layers: the media and the adventitia [86]. They did not include the mechanical effect of the intima, as it was the thinnest layer and its mechanical properties were not as relevant as those of the media and adventitia for healthy, young arteries. Still, it should be noted that the intima plays an important role in atherosclerosis, as this is the place where the first signs of atherosclerosis are found, with the accumulation of lipoprotein particles that can eventually develop into a plaque [1]. However, the multi-layer structure and the anisotropic behaviour of the carotid tissue make it difficult to implement a solid model when analysing the blood flow through arteries. Therefore, it is not uncommon to consider some simplifications such as the one presented by Belzacq et al. [87]. By using a modified version of the model proposed by Holzapfel et al., they considered weighted averages in order to combine the material properties of the media and the adventitia. Therefore, the authors effectively ended up with a single-layer model that would make the fluid-structure calculation simpler.

There are still some difficulties present when modelling an artery, such as the correct representation of the layers and the whole tissue. To further simplify the model, one of the approaches commonly used in the literature is the consideration of the vessel as an homogeneous, isotropic material (i.e. the material properties are considered to be the same in all directions) and as

a single-layer structure. This is a strategy widely used in the literature when modelling fluid-structure interaction configurations [52, 88–92], as shown in Section 1.2.7.

Another issue that arises when modelling an artery is the measure of the values of the mechanical properties. Indeed, there is some disparity in the literature regarding the material properties of the vessels, which may be explained by the difficulty of measuring those values. Some authors have reported that the stiffness of the artery as a whole, described by the Young’s modulus, E , was in the order of the hundreds of kilopascals. For instance, Riley et al. reported a significant increase of the Young’s modulus of the common carotid artery with age for both male and female subjects [93]. The authors found that the average Young’s modulus was 701 kPa for female patients in their forties, whereas said value increased to 965 kPa for women in their sixties. Similar results were observed for male patients, with the Young’s modulus increasing with age from an average of 771 kPa to 983 kPa. In general, the average value was around 850 kPa. In the case of the material properties of animals, the results seemed to be within the same order of magnitude. For example, Bergel reported values of 640 kPa for the left common carotid artery of dogs [94], as did Patel and Janicki, who found a Young’s modulus of 970 kPa [95].

When performing fluid-structure simulations, some groups have used material properties similar to those proposed by Riley et al. For instance, Gao et al. considered a one-layered model of an aorta with a Young’s modulus of 840 kPa [96]. Li et al. on the other hand described the artery by using a softer model for the healthy part of the wall ($E = 400$ kPa) and a stiffer one for the diseased region ($E = 1.6$ MPa) [52]. Higher values of stiffness however were reported by Mortazavinia et al., who defined a Young’s modulus of

4.66 MPa [54]. As a side note, a direct comparison to the works of Holzapfel et al. is not simple as the latter authors defined two set of parameters: one describing the isotropic behaviour of the artery, and other that modelled the anisotropic part [86].

Another way to describe the material properties of a vessel is by defining the bulk modulus, K , which can be easily related to the Young's modulus for homogeneous, isotropic materials. Indeed, $E = 3K(1-2\nu) = 9KG/(3K+G)$, where G denotes the shear modulus and ν is the Poisson ratio. Some works that have used this notation have indirectly defined a different value of the Young's modulus which was significantly larger than the one reported by Riley et al. Among them, Li et al. reported a value of 1600 MPa for K [63, 65]. Assuming a Poisson ratio of 0.49 (a typical value used to describe the material as nearly incompressible [87, 97]), the Young's modulus was 96 MPa. A similar value of 1500 MPa was used for the bulk modulus by Rotman et al. in a experimental study [98]. Kock et al. also reported values in the order of several MPa: specifically, they used $K = 600$ MPa and $G = 6$ MPa [90], therefore the equivalent Young's modulus was around 18 MPa. In summary, there appears to be a significant variability around the elastic material properties of the carotid artery.

In addition, it should be taken into account that the material properties of both the fibrous cap and the lipid core differ from those corresponding to a healthy vessel. In general, the fibrous cap has been reported to be stiffer than the nondiseased artery [99], whereas the lipid core has been consistently considered to be around two orders of magnitude less stiff than the artery wall [62, 89].

1.2.7 Fluid-structure interaction simulations

Once the modelling of the artery has been defined, fluid-structure interaction simulations are usually considered in order to analyse the maximum stresses on the artery wall. The methodology is similar to the one followed by the studies reported in section 1.2.3, though the aim is significantly different. In particular, the main objective of the works reported in section 1.2.3 was the study of the flow field, and the influence of the elasticity of the wall on different flow features. From a biomechanical point of view, however, the main goal is to analyse the stresses exerted on the vessel wall due to the blood flow, rather than the effects on the flow itself. It is, in summary, a way of approaching the same problem from another perspective and focusing on other system features.

Following their initial works on the interaction between the flow and the elastic wall [47–50], Tang et al. group incorporated the modelling of a lipid core within the plaque, with different material properties to those of the artery wall [88]. They considered an idealised, three-dimensional, asymmetric stenosis, where the plaque contained a lipid core that was around one hundred times softer than the vessel wall. The authors varied the size of the lipid core, as well as varying the thickness of the fibrous cap. Since the influence of the cap thickness on the plaque stresses is a key factor [59], it was not straightforward to conclude how the lipid core size affected the stress field. In general, they found that a smaller lipid pool lowered the stresses on the wall, while a thinner fibrous cap increased them. The topic of the fibrous cap thickness was further investigated by Li et al. [100]. They modelled an eccentric stenosis and performed an FSI simulation while varying the thickness of the cap and the stenosis severity. Their results were in agreement with those presented by Tang et al. [88], reporting an increase of the stress

levels when the thickness of the fibrous cap decreased. In addition, they showed that similar levels of stress could be achieved for very different degrees of stenosis, as the influence of the thickness was much more important. They highlighted that the most vulnerable plaques were those that presented a thin cap and a severe stenosis. More recently, Yuan et al. analysed the effects of the material properties on the stress levels of a three-dimensional, idealised model of an eccentric plaque [101]. They reported that a softer media layer of the wall would result in higher stress in the cross-sectional shoulder of the plaque, but highlighted that those findings were largely affected by the thickness of the fibrous cap.

It is also worth mentioning other works that have studied the shape of the stenosis as a main factor affecting the stress field along the vessel. For example, Belzacq et al. found that a short stenosis was more vulnerable than a long one, due to a change of the stress distribution that led to a particular deformation field along the plaque [87]. The same group further investigated the geometry of a stenosis model, including shape irregularities, by modelling evenly-spaced bumps along the vessel wall [102]. They reported an increase of the plaque stresses if the stenosis wall presented those irregularities.

In 2004, Tang et al. introduced the modelling of patient-specific geometries based on magnetic resonance imaging (MRI) [89, 103]. In line with previous results, they found that large lipid cores and thin fibrous caps were signs of high stresses on the plaque [89]. Similar results were observed in a subsequent work, where they also reported an increase of the peak stresses when the stiffness of the lipid core was halved [103]. Kock et al. performed two-dimensional FSI simulations of a geometry based on *in vivo* (“within the living organism” [104]) MRI and found the highest stresses at the inlet and outlet of the stenosis region [90]. On closer inspection, those locations

seemed to be the ones where the fibrous cap was thinnest for that specific geometry. They also stated that the wall shear stresses had been linked to plaque growth rather than rupture, and they were several orders of magnitude lower than the wall principal stresses, which were linked to the plaque rupture. Similar results regarding the influence of the plaque stress (specifically, the maximum principal stress) rather than the flow shear stress were reported later [105]. The link between high wall stresses and thin fibrous caps was also reported in studies that focused on three-dimensional geometries reconstructed from *in vivo* MRI [91]. On the other hand, additional studies reported that in half of the cases the maximum stress was located upstream the stenosis, where the cap was thinnest [106], especially for severe plaques [107].

As a general remark, MRI patient-specific models offer the advantage of showing real plaque configurations, that may allow to predict the exact location and magnitude of the peak stresses. This offers valuable information for the treatment and classification of plaques for each specific case. One shortcoming, however, is the lack of generalisation due to the unique nature of each geometry. In particular, it may be difficult to obtain general conclusions from a complex, patient-specific model, and apply those conclusions to other cases. That is where idealised geometries come into play, where the simpler model may offer more generic results about the flow and structural fields and may help stratifying which plaques are more likely to rupture based on the stress distributions. This kind of model should be considered complementary to the complex geometry simulations, as both offer insights about the plaque rupture process. An idealised model allows a parametric analysis, where the influence of different features can be studied under a user-controlled environment. The conclusions obtained from these simulations may be general

results that could be applied later for patient-specific cases.

The aim of this thesis is to shed some light on the plaque rupture process. The novelty of the work presented here lies on the approach taken to study the problem. In particular, this thesis is focused on finding the potential location of the rupture by considering the axial stress distributions on the vessel. The results obtained in this work could prove to be valuable on later research, as they may help in situations dealing with patient-specific geometries. For instance, based on the results found for analyses of idealised models, some geometrical features observed in a subject-specific plaque could point to a certain vulnerable region, or even help differentiating plaques that need surgical intervention from those which do not.

In order to do this study, works that analysed the stress field along the plaque have been summarised in the present review, as the plaque is expected to rupture at the locations where the wall stresses are high. It is worth pointing out that the relationship between high stresses on the plaque and rupture sites had to be challenged at some point, and that analysis on this was carried out by Tang et al. in 2009 [108]. In that article they showed that plaque ruptures usually took place where the maximum principal stresses were the highest. Therefore, the focus here is on the mechanical factors related to the blood flow and the artery wall, even though there are other elements that could influence the rupture such as biochemical reactions between the blood cells and the vessel wall. The main hypothesis that will be introduced in Chapter 4 is that the lipid core stiffness, along with the geometry, have a great impact on the stress distribution and, hence, on the location of the maximum stresses. The objective of this chapter will be to find potential sites of rupture based on the axial stress distributions, and analyse how those locations vary with regards to the different parameters considered. For the

three-dimensional analysis, the hypothesis will be that the sites of rupture are influenced by the same factors that affected the location of the rupture for two-dimensional plaques. This statement will be tested in Chapter 5, along with the study of the features that only apply to a three-dimensional case, such as the distribution of stresses along the cross-sectional direction of the model.

Chapter 2

Methods

2.1 The finite element method

2.1.1 Introduction

In general, the fluid-structure interaction problem of the blood flow through an elastic stenosis cannot be solved analytically, unless there are many simplifications. Therefore, numerical simulations have become the best approach to analyse this kind of configuration. There are several techniques available for the numerical solution of fluid-structure interaction problems and, among them, solvers based on the so-called finite element method are perhaps the most common. Another approach worth mentioning is the spectral element method [109], which derived from the standard finite element method and is used within the fluid dynamics community.

The finite element method, often abbreviated as FEM, is a numerical technique that is used to find the solution to problems where the physics are described by a system of partial differential equations [110]. In the beginning, the first applications were focused on solving structural mechanics problems

[111]. Later on it has been applied to a broad number of fields, such as electromagnetism [112], fluid dynamics [113] or heat transfer [114].

The general idea behind the method is the division of a continuous domain into several smaller and simpler regions known as *finite elements*. This process is called *discretisation*. The discretisation leads to a matrix-vector formulation of the system of equations, which can then be solved numerically. The solution to the problem is obtained by using polynomial interpolation at some prescribed points within each element, called *nodal points*.

One aspect to consider though is that every discretisation of a continuum problem involves an approximation, which becomes more accurate with an increasing number of elements [115]. In order to overcome this limitation, a numerical method such as FEM offers the flexibility of increasing the number of elements at the user's will, hence minimising the error. However, it should be taken into account that the improved accuracy of the calculation derived from increasing the number of elements involves an increase of the computational cost required to perform the simulation. This is the reason why some kind of grid convergence criteria must be adopted. For instance, one could discretise a fluid domain with the goal of calculating the velocity field. A typical strategy would be to start with large elements and then refine the discretisation by gradually increasing the number of elements, i.e. decreasing the size of each element. A user then may require to run the simulations until the incremental changes of the velocity field after consecutive iterations are smaller than a certain value. The number of elements required to solve the problem would then be imposed by the desired precision.

Performing a finite element method analysis requires some steps that can be outlined as follows [110, 116]:

1. Discretisation of the continuous domain. The first step involves the partition of the continuous domain, Ω , into a finite number N of smaller subdomains (elements), Ω_e . These subdomains conform the finite element *mesh*. The discretisation of a domain may be performed using specific software or the pre-processing module of a finite element analysis package. Depending on the type of elements used, the mesh may be:

- Structured: the elements are regularly arranged and are usually quadrilateral (in two-dimensional domains) or hexaedra (in three-dimensional spaces). These are usually efficient meshes that converge quicker to the solution. However, they are not very flexible and are not appropriate when meshing relatively complex geometries.
- Unstructured: the elements are arbitrarily arranged and may be triangles (in 2-D) and tetrahedra (in 3-D). Contrary to the structured grids, the unstructured ones are not that efficient, but on the other hand they can be used to mesh any kind of irregular surface.

When the modelling requires any level of geometrical complexity, it usually involves the use of an unstructured grid. However, the user may be able to partition the model and separate simpler regions where a regular structured grid may be of use, improving the convergence of the simulation. In addition, the mesh may be refined to improve

the resolution only at some locations. This is known as local mesh refinement, and it is done to improve the efficiency of the simulation.

2. Definition of the element equations. This is at the core of the finite element analysis, since the idea behind the method is to solve the equations by considering the discretised system. This step also includes the definition of the element properties. For instance, when defining the system of equations of a solid structure, the matrix that relates the displacements to the loads depends on the material properties of the structure. In addition, the polynomial interpolation functions need to be defined at the nodal points, by using the so-called shape functions. This will allow to interpolate any field variables over each element.
3. Assembly of the element equations. All the equations defined for each local element must be combined, or assembled, in order to obtain a global system of equations.
4. Solution of the global system. Once the global system of equations has been defined, boundary conditions are usually imposed. In a solid structure, this could take the form of an external force that is applied at a certain boundary; in a flow dynamics problem, it could refer to an imposed pressure profile at any domain location. When the boundary conditions are defined, the system of equations can be solved numerically using direct or iterative methods, for example. Ultimately, a solution for each nodal point is computed. The convergence criteria and the error estimation should be taken into account as well, to make sure that the problem is solved to the desired degree of precision.
5. Post-processing of the solution. The last step involves the calculation of any other quantities or variables that may be of interest. For example,

this could include the calculation of the maximum principal stresses in a loaded structure, right after finding the displacement field solution with the finite element method. Alternatively, in a flow dynamics problem, this step could refer to the calculation of the wall shear stresses.

2.1.2 Formulation example

The following gives a general idea of the formulation required to solve a structural mechanics problem by using the finite element method. This example is relevant as the equations presented here are actually part of the governing equations used in this thesis to model the artery wall, as it will be shown in Section 2.4. The process to solve any other problem using FEM, such as fluid dynamics, would be analogue, but applied to a different set of governing equations. In this case, the physics are described by the following set of equations:

- First, the equilibrium equation, which derives from Newton's second law of motion:

$$\nabla \boldsymbol{\sigma} + \mathbf{f} = \rho_s \partial^2 \boldsymbol{\xi} / \partial t^2. \quad (2.1)$$

In this expression, $\boldsymbol{\sigma}$ denotes the Cauchy stress tensor, $\mathbf{f}$ is the body force vector, ρ_s refers to the density of the solid, $\boldsymbol{\xi}$ denotes the displacement vector and t is the time. In the following, the time-dependent term $\partial^2 \boldsymbol{\xi} / \partial t^2$ will be denoted by $\ddot{\boldsymbol{\xi}}$, for simplicity.

- The second condition is the strain-displacement equation, which is given by

$$\boldsymbol{\epsilon} = \mathbf{D} \boldsymbol{\xi}, \quad (2.2)$$

where $\boldsymbol{\epsilon}$ refers to the deformation of the solid and $\mathbf{D}$ is a tensor that defines the relation between the deformation and the displacements.

For small deformations, this equation may be defined as $\boldsymbol{\epsilon} = \mathbf{D}\boldsymbol{\xi} = (\nabla\boldsymbol{\xi} + \nabla\boldsymbol{\xi}^T)/2$.

- The last equation required is the constitutive equation, which relates the stress tensor with the deformations. In general, this equation takes the form

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}(\boldsymbol{\epsilon}). \quad (2.3)$$

The simplest case would be that of the linear elasticity. In that situation, the constitutive relation would be $\boldsymbol{\sigma} = \mathbf{E}\boldsymbol{\epsilon}$, where $\mathbf{E}$ refers to the elasticity tensor. On the other hand, for more complex, hyperelastic models the relation would take the form $\boldsymbol{\sigma} = \partial W / \partial \boldsymbol{\epsilon}$, where W denotes the strain energy density function.

Once the governing equations are defined, the first step to solve the system would be to divide the spatial domain Ω into smaller, finite elements. Using a notation in the same way as previous works found in the literature [117], this means that the real domain Ω is approximated by a domain defined by the user, $\hat{\Omega}$, which is equal to the sum of all the finite subdomains. The mathematical expression would be

$$\Omega \approx \hat{\Omega} = \sum_{e=1}^N \Omega_e, \quad (2.4)$$

where Ω_e defines the subdomain of each element e and N denotes the total number of elements in which the domain is discretised. The same discretisation is performed for the boundary, Γ , of the domain: $\Gamma \approx \hat{\Gamma} = \sum_{e=1}^N \Gamma_e$.

Similarly, a generic time-dependent displacement field $\boldsymbol{\xi}(\mathbf{x}, t)$ ¹ is approx-

¹ $\mathbf{x}$ denotes the position and t the time.

imated by another vector, $\hat{\boldsymbol{\xi}}$ defined by

$$\boldsymbol{\xi}(\mathbf{x}, t) \approx \hat{\boldsymbol{\xi}} = \mathbf{N}(\mathbf{x})\mathbf{q}(t). \quad (2.5)$$

In the former expression, the approximated displacement field is defined by using interpolation functions at the nodal points. In particular, $\mathbf{N}$ refers to the matrix of shape functions used to approximate the solution, and $\mathbf{q}$ are the time-dependent displacements of the nodal points. The vector $\mathbf{q}$ is the unknown to be determined from the global equation system.

At this moment, the equation 2.2 may be rewritten as

$$\boldsymbol{\epsilon} = D\boldsymbol{\xi} \approx D\mathbf{N}\mathbf{q} = \mathbf{B}\mathbf{q}, \quad (2.6)$$

where the tensor $\mathbf{B} = \mathbf{N}D$ has been introduced and defines the relation between the deformation field and the nodal displacements.

2.1.3 Weak form

Before implementing these expressions, it is important to obtain the *weak form* (also known as variational form) of the equilibrium equation. The weak form is a scalar equation obtained by multiplying the system of equations by an arbitrary function, integrating the resulting expression over the domain and, finally, setting the result to zero [118].

A common weak form in structure mechanics is obtained when the arbitrary function is a virtual displacement, $\delta\boldsymbol{\xi}$. In this case, the weak form is denoted as the virtual work of the system [118]. For an elastic structure as the one modelled in this example, the virtual work is a derivation of the Galerkin expression, G . In this case, considering equation 2.1 and the definition of virtual work, the Galerkin expression is given by

$$G = \int_{\Omega} \delta\boldsymbol{\xi}^T \left(\nabla\boldsymbol{\sigma} + \mathbf{f} - \rho_s\ddot{\boldsymbol{\xi}} \right) d\Omega = 0. \quad (2.7)$$

Taken into account the equations defined previously and using integration by parts as presented in the literature [118], the former equation becomes

$$G = 0 = \int_{\Omega} \delta \boldsymbol{\xi}^T \rho_s \ddot{\boldsymbol{\xi}} d\Omega + \int_{\Omega} \delta (\mathbf{D} \boldsymbol{\xi})^T \boldsymbol{\sigma} d\Omega - \int_{\Omega} \delta \boldsymbol{\xi}^T \mathbf{f} d\Omega - \int_{\Gamma_t} \delta \boldsymbol{\xi}^T \mathbf{t} d\Gamma_t. \quad (2.8)$$

In this expression there is a new term corresponding to the integration along the boundary of the domain where stress conditions are applied, Γ_t , and $\mathbf{t}$ denotes the traction force vector at that boundary.

2.1.4 Reformulation of the equations

As it was the case of the domain or the displacement field, the Galerkin expression may also be approximated by considering the discretisation of the domain. Specifically,

$$G \approx \hat{G} = \sum_{e=1}^n G_e = 0, \quad (2.9)$$

where G_e denotes the approximated Galerkin expression for each element e . Now, by combining equations 2.8 and 2.9 and by making use of the shape functions used to approximate the displacement field, the approximated Galerkin expression $\hat{G}$ is described by

$$\hat{G} = \sum_{e=1}^N \left[\int_{\Omega_e} \delta(\mathbf{N} \mathbf{q})^T \rho_s \mathbf{N} \ddot{\mathbf{q}} d\Omega + \int_{\Omega_e} \delta (\mathbf{D} \mathbf{N} \mathbf{q})^T \boldsymbol{\sigma} d\Omega - \int_{\Omega_e} \delta(\mathbf{N} \mathbf{q})^T \mathbf{f} d\Omega - \int_{\Gamma_{t,e}} \delta(\mathbf{N} \mathbf{q})^T \mathbf{t} d\Gamma_t \right] = 0. \quad (2.10)$$

Rewriting the former:

$$\hat{G} = \delta \mathbf{q}^T \sum_{e=1}^N \left(\int_{\Omega_e} \mathbf{N}^T \rho_s \mathbf{N} d\Omega \ddot{\mathbf{q}} + \int_{\Omega_e} \mathbf{N}^T \mathbf{D}^T \boldsymbol{\sigma} d\Omega - \int_{\Omega_e} \mathbf{N}^T \mathbf{f} d\Omega - \int_{\Gamma_{t,e}} \mathbf{N}^T \mathbf{t} d\Gamma_t \right) = 0. \quad (2.11)$$

Finally, after considering the definition of tensor $\mathbf{B}$ (eq. 2.6), the approximated Galerkin expression is given by

$$\begin{aligned} \hat{G} = \delta \mathbf{q}^T \sum_{e=1}^N \left(\int_{\Omega_e} \mathbf{N}^T \rho_s \mathbf{N} d\Omega \ddot{\mathbf{q}} + \int_{\Omega_e} \mathbf{B}^T \boldsymbol{\sigma} d\Omega \right. \\ \left. - \int_{\Omega_e} \mathbf{N}^T \mathbf{f} d\Omega - \int_{\Gamma_{t,e}} \mathbf{N}^T \mathbf{t} d\Gamma_t \right) = 0. \end{aligned} \quad (2.12)$$

Since the virtual displacements $\delta \mathbf{q}$ are arbitrary, the following system is obtained:

$$\begin{aligned} \overbrace{\left(\sum_{e=1}^N \int_{\Omega_e} \mathbf{N}^T \rho_s \mathbf{N} d\Omega \right)}^{\mathbf{M}} \ddot{\mathbf{q}} + \overbrace{\sum_{e=1}^N \int_{\Omega_e} \mathbf{B}^T \boldsymbol{\sigma} d\Omega}^{\mathbf{P}(\boldsymbol{\sigma})} \\ - \underbrace{\sum_{e=1}^N \left(\int_{\Omega_e} \mathbf{N}^T \mathbf{f} d\Omega + \int_{\Gamma_{t,e}} \mathbf{N}^T \mathbf{t} d\Gamma_t \right)}_{\mathbf{b}} = 0, \end{aligned} \quad (2.13)$$

which may be rewritten in a simpler form by introducing the tensors $\mathbf{M}$, $\mathbf{P}$ and the vector $\mathbf{b}$:

$$\mathbf{M} \ddot{\mathbf{q}} + \mathbf{P}(\boldsymbol{\sigma}) = \mathbf{b}. \quad (2.14)$$

The former is a partial differential equation system where the new tensors are defined as per Zienkiewicz's notation [117].

In order to obtain a clearer picture of the numerical method, let us assume that the constitutive equation is governed by a linear elastic model. In that case, the stresses and the strains are related by the expression $\boldsymbol{\sigma} = \mathbf{E} \boldsymbol{\epsilon}$, where the coefficients of the elasticity matrix $\mathbf{E}$ are constant values that depend on the Lamé parameters. On the other hand, as per equation 2.6 the strain tensor may be approximated by $\boldsymbol{\epsilon} \approx \mathbf{B} \mathbf{q}$. Therefore, the tensor $\mathbf{P} = \mathbf{P}(\boldsymbol{\sigma})$ is

described by:

$$\mathbf{P}(\boldsymbol{\sigma}) = \sum_{e=1}^N \int_{\Omega_e} \mathbf{B}^T \boldsymbol{\sigma} d\Omega = \sum_{e=1}^N \int_{\Omega_e} \mathbf{B}^T \mathbf{E} \boldsymbol{\epsilon} d\Omega \quad (2.15)$$

$$= \underbrace{\sum_{e=1}^N \int_{\Omega_e} \mathbf{B}^T \mathbf{E} \mathbf{B} d\Omega}_{\mathbf{K}} \mathbf{q} = \mathbf{K} \mathbf{q}. \quad (2.16)$$

$\mathbf{K}$ is the linear stiffness matrix, whose components depend on the material properties of the structure. Taking this result into equation 2.14, the system becomes

$$\mathbf{M} \ddot{\mathbf{q}} + \mathbf{K} \mathbf{q} = \mathbf{b}, \quad (2.17)$$

which is partial differential equation system that can be solved numerically by introducing discrete approximations in time. For problems that were not time-dependent, the former is significantly simplified as $\ddot{\mathbf{q}} = \mathbf{0}$. Therefore, the final expression would be

$$\mathbf{K} \mathbf{q} = \mathbf{b}. \quad (2.18)$$

This is a linear system of equations which may be solved numerically by employing different computational techniques, such as LU decomposition or iterative methods.

2.1.5 FEM applied to plaque rupture analysis

In the previous section, a generic structural analysis example has been used to introduce the finite element method. As it has already been mentioned, the FEM is a flexible framework and has been applied to different types of problems, including plaque rupture analysis.

The first simulations involving plaques were two-dimensional structural analyses that considered cross-section models of the artery and calculated

the stress distribution along the vessel when certain pressure was applied to the inner wall (blood pressure). For instance, Loree et al. performed a finite element analysis of the influence of the fibrous cap thickness on the maximum circumferential stresses for ten different artery cross-sections [59]. In order to improve the accuracy of the simulation, they refined the mesh in the expected high-strain regions by considering smaller elements. Regarding their results, as it was outlined in the previous chapter, they found a significant increase of the stress when the cap thickness decreased. They also mentioned that plaques may start to rupture at a threshold of 300 kPa.

Simulations of blood flow through a rigid wall stenosis have also been computed using solvers based on the FEM. In particular, Tu et al. studied the steady and pulsatile flow through a stenotic artery [119]. They used a quadratic interpolation for the flow velocities and a linear one for the pressure field, and then solved the equations using a variable time step. Among other findings, an increase of the pressure drop at the throat of the stenosis was reported when the frequency of the pulsatile flow increased. Milner et al. also used a solver based on the finite element method to study the flow through a carotid bifurcation [120]. They focused their work on the wall shear stresses, reporting differences based on the geometry of each configuration.

Finally, there have been applications to fluid-structure interaction problems as well. A fully coupled analysis was performed by Bathe and Kamm, where they studied the influence of the stenosis severity on the flow and on the stress fields [51]. Another group also used a FEM-based solver to study the flow through an elastic, axisymmetric artery and compared the results to experimental observations, finding a good correlation overall [121]. Li et al. used a commercial finite element software, COMSOL Multiphysics [122], to study the effect of the fibrous cap thickness in an idealised model that de-

picted an elastic plaque interacting with a time-dependent blood flow [100]. The same software was used by Kock et al. to calculate the fluid-structure interaction in a two-dimensional model carotid bifurcation model [90]. Overall, the finite element method is a popular technique that is still being used to model this type of simulations.

2.2 Alternative techniques

2.2.1 FEM-based approaches

In the beginning of this chapter it was mentioned that there is also another method that derives from the FEM: the spectral element method. There are some open-source solvers that are based on this approach and can be quite useful for this kind of simulations, so they will be briefly discussed here for the sake of completion.

The spectral element method (SEM) can be described as another formulation of the finite element method, but using high order interpolation functions instead [109]. The open-source software NEK5000 is a computational fluid dynamics solver that uses this discretisation [123]. The high order of the SEM makes this software quite accurate when tackling fluid dynamics simulations. It has been applied to rigid wall stenotic geometries such as the ones featuring in this thesis, in particular to analyse the transition from steady to unsteady flow [29]. However, fluid-structure interaction was not fully incorporated into the code, so it did not result into the most appropriate choice for the kind of simulations as shown in the following chapters. A similar approach was followed by Cantwell et al. to develop Nektar++ [124]. It is designed to be highly scalable and one of the main applications is the solution of different flow dynamics configurations. Among them, it is

worth mentioning that it has been used to study the wall shear stress distributions caused by the blood flow using a rabbit aorta as the geometric model [125]. Other applications include, for instance, acoustic perturbations or cardiac electrophysiology [126]. Again, fluid-structure interaction was not fully implemented into the code, so it was not finally used for the simulations presented in the coming chapters.

Lastly, it is worth mentioning FreeFem++, which is an open-source finite element solver of partial differential equations [127]. One of the advantages it offers is the opportunity to develop fairly complex systems, given its highly flexible interface. For instance, it is possible to integrate the fluid-structure interaction equations, as all the input must be coded by the user. Specifically, the user is required to write the equations in a variational form. On the other hand, defining the geometry is a fairly complex process: each geometrical boundary should be defined parametrically, with the appropriate boundary conditions specified for them. In particular, the software was tested by simulating the flow through a two-dimensional stenotic elastic channel. This two-dimensional geometry allowed for a quick analysis as it was simpler than a three-dimensional one. The expected results were found: in particular, the flow recirculation regions downstream the constriction of the channel were well defined, as was the pressure drop along the domain. Regarding the solid deformations, they were especially related to the flow pressure. Still, those results were related to a channel geometry rather than to a stenotic pipe geometry that would model an artery better. But implementing complex geometries, especially a three-dimensional one, would be a fairly complicated task, so after considering these factors it was decided to focus on other software packages more suitable for the situation.

2.2.2 Other methods

There are also other approaches that can be used to model the blood flow through the human arteries. They are not the focus of this work, but are still worth mentioning.

One technique created to tackle the fluid-structure interaction of living tissues is the immersed boundary method. First introduced by Peskin in 1972, it was created to study heart valves and the flow around them [128]. It later evolved to a more general approach for fluid-structure interaction problems. In this method, there are two meshes: one is the fixed Cartesian mesh, where the Eulerian variables are defined; the other is a curvilinear mesh, where the Lagrangian variables are defined. This curvilinear mesh can move with no restrictions through the Cartesian mesh [129]. An application of this method was, for example, the solution of complex three-dimensional incompressible flows, with an application solving the flow induced by a human body in walking motion [130]. Fedosov et al. also used the immersed boundary method to perform numerical simulation of blood flow, where the red blood cells were considered as elastic elements within the flow [131]. They found good agreement with previously published results, suggesting that the method could become a viable alternative when the cell interactions needed to be accounted for.

It is also worth mentioning the volume of fluid method, formally presented by Hirt and Nichols in 1981 [132], which was introduced to model the fluid dynamics of free surface configurations. In particular, this technique focused on situations where the Eulerian formulation was preferred, due to the free boundaries experiencing large deformations. One of the shortcomings, however, is that imposing some boundary conditions may be complex. Recently, Rosti and Brandt used a formulation based on the volume of fluid

method, solving one set of equations over the whole domain, to simulate a channel flow with high Reynolds ($Re = 2800$) and a hyperelastic wall [133]. In this work, the authors highlighted the influence of low values of the wall elasticity on the turbulent flow, due to the fluctuations that appeared at the fluid-solid interface.

As a final note, in the recent years, a new kind of blood flow analysis is attracting some interest in the form of multi-scale simulations. It has been reported that blood flow interactions in the human body occur between large arteries (part of the macrovascular network), smaller arteries (part of the mesovascular network) and capillaries (that conform the microvascular network) [134]. The arterial diameter in the macrovascular network is equal to or larger than 0.5 mm, while the in the microvasculature the diameter is a hundred times smaller, being in the order of 5 μm . Therefore, this can be considered a multi-scale system, even more so if cellular and biological processes are also taken into account. A similar point of view was followed in a previous work that studied cerebral aneurysms, which made use of a fluid-structure interaction framework as well [135]. They investigated how cells behave within different types of flows and their implications on cardiovascular diseases, and confirmed their results via experimental comparison.

2.3 Fluid-structure interaction in COMSOL Multiphysics

The results of the numerical simulations presented in this thesis have been performed using the finite element method through the commercial solver COMSOL Multiphysics [122]. Fluid-structure interaction simulations of blood flow through a stenotic artery have been performed, considering the elasticity

of the plaque and the vessel wall. The governing equations have been solved for the fluid and the solid regions in a coupled manner.

Unless otherwise stated, the two-way FSI coupling is used in this work, where the fluid is influenced by the solid deformation. In other words, the blood flow deforms the elastic artery wall, and that leads to a change of the flow domain. The matching conditions in this case are: first, the velocity of the fluid at the wall-flow interface is the same as the velocity of the vessel wall; second, the stress continuity, meaning that the force applied by the fluid on the wall is equal to the negative of the force exerted by the wall on the fluid [122]. When the deformation is small enough so that the effects on the flow field are negligible, one-way coupling is used as well, once it has been checked that the results are the same as those obtained by running the two-way coupling mode.

The COMSOL simulations are based on an arbitrary Lagrangian-Eulerian formulation. The Lagrangian formulation considers that the physical variables of the problem are linked to certain materials, or pieces of matter [136]. In the context of FSI simulations, the solid mechanics follow a Lagrangian description while the flow field is described by an Eulerian formulation. This means that the solid quantities are defined as functions of the time and of the material element of the solid (material coordinate system). On the other hand, the flow quantities are defined as functions of time and position in space as in the Eulerian description (spatial coordinate system).

It is worth noting that COMSOL has been previously used and validated in the context of blood flow simulations [34], as well as in fluid-structure interaction studies of flow through elastic arteries using idealised geometries [87, 100, 137] and patient-specific models [90, 106].

In summary, COMSOL Multiphysics combines the solid mechanics and

the fluid dynamics to model the interaction between the two media. The flow is described by the conservation of mass and conservation of momentum equations, while the solid is governed by the constitutive equation, the strain-displacement equation and the equilibrium equation, as it will be shown in the next section. Finally, boundary conditions for the solid and the fluid must be applied in order to solve the model, along with the matching condition at the interface between the flow and the solid domains.

2.4 Governing equations

The blood is modelled as a Newtonian, incompressible fluid. The equations that describe the flow field are the continuity (conservation of mass) and the Navier-Stokes (conservation of momentum) equations:

$$\nabla \cdot \mathbf{u} = 0, \quad (2.19)$$

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \mu \nabla^2 \mathbf{u}, \quad (2.20)$$

where $\mathbf{u}$ is the fluid velocity vector, t the time, p the pressure, ρ the fluid density and μ the dynamic viscosity.

On the other hand, the artery wall is described by the equilibrium and the constitutive equations, as in the example described in section 2.1.2:

$$\nabla \boldsymbol{\sigma} + \mathbf{f} = \rho_s \frac{\partial^2 \boldsymbol{\xi}}{\partial t^2}, \quad (2.21)$$

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}(\boldsymbol{\epsilon}). \quad (2.22)$$

The variables are defined in the same way as it was described in section 2.1.2: $\boldsymbol{\sigma}$ is the Cauchy stress tensor, $\mathbf{f}$ defines the body force vector, ρ_s denotes the density of the solid, $\boldsymbol{\xi}$ refers to the displacement vector and t is the time. In the second equation $\boldsymbol{\epsilon}$ denotes the deformation tensor, which for

small deformations is described by the following mathematical expression:

$$\boldsymbol{\epsilon} = \boldsymbol{D}\boldsymbol{\xi} = (\nabla\boldsymbol{\xi} + \nabla\boldsymbol{\xi}^T)/2.$$

Equations 2.19 to 2.22 are implemented in COMSOL Multiphysics, and are computed using a built-in FEM-based solver. However, the governing equations would not be complete without the definition of the appropriate boundary conditions: for the blood flow, for the artery wall and for the fluid-structure interface. But since the boundary conditions are dependent of the problem being solved, they are presented in the coming chapters, where the exact configuration of the simulations will be introduced for each case. A similar point should be made regarding the definition of equation 2.22, which defines the solid model used when performing the simulations. In particular, two models will be presented in the following chapters: the linear elastic and the hyperelastic descriptions.

Chapter 3

Thin-wall simulations

3.1 Introduction

As stated in the first chapter of this thesis, the main objective of this work is to analyse the initiation of the rupture of an atherosclerotic plaque from a mechanical point of view. In order to do so, this chapter starts by presenting some results related to the flow through an idealised stenosis geometry with a thin, elastic wall. The main goal of this part is to provide a general overview of the fluid-structure interaction of the problem. The way in which the stiffness of the artery influences the flow will be studied alongside the effect of the flow on the stress values on the wall. In order to do this, a simple, idealised model of an elastic stenosis is used.

In the following, the stiffness, or elasticity of the wall, is analysed by means of the Young's modulus of the vessel. In addition, another parameter will be varied: the Reynolds number, which is an important flow dynamics quantity. Several aspects are analysed, some of them flow-related quantities (such as the length of the recirculation region downstream the constriction, the wall shear stress distribution and the fluid pressure), and some are solid-

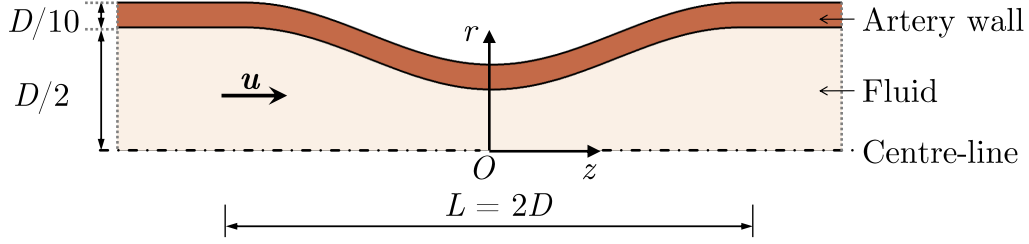


Fig. 3.1: Idealised axisymmetric stenosis geometry showing both the fluid and the solid domains. The origin, O , is located at the centre line of the throat. The thickness of the artery wall is $D/10$, being D the diameter of the fluid domain.

related variables (the radial displacement and the first principal stress at the inner wall of the vessel).

Once the underlying dynamics are clear, the next step will be to proceed with more complex models that will make it possible to further investigate potential plaque rupture sites.

3.2 Geometry

The selected geometry is an idealised, axisymmetric pipe configuration adapted from previous studies [24, 25, 28, 29]. This pipe includes a constriction which simulates the stenosis region, as shown in figure 3.1. In order to further understand the blood flow through a stenotic elastic artery, a good first approach is to focus on an idealised geometry and perform a parametric analysis. One can study patient-specific arteries directly obtained by medical observation, but the use of this model is justified as the aim here is to capture general patterns and distribution changes rather than specific peak values.

In order to properly work with this configuration, a system of coordinates needs to be defined. In this case, the origin, O , is located at the intersection of the section of minimum cross-sectional area with the centre-line of the

artery lumen. Since this problem involves an axisymmetric geometry, only two coordinates are required to define any given position: z in the axial direction and r in the radial direction.

The reference length unit used in this model is the inlet diameter of the lumen, D . In this case, the diameter is set to $D = 7\text{ mm}$, which is based on the typical dimensions of a human carotid artery [23, 38, 97, 120, 138]. The inlet section is located at $z = -6D$, while the outlet section is located at $z = 16D$. This domain length was proven to be long enough to avoid any perturbations due to the wall boundary condition at the inlet and outlet sections, as further described in the next section. The wall thickness is constant along the axial direction and equal to $D/10$ [139].

In order to allow an easy coupling between the flow dynamics and the structural mechanics, the numerical simulations are performed using this dimensional formulation. The only non-dimensional parameter considered is the Reynolds number, Re , which defines the flow regime and will be introduced in the next section. The results are also presented in a dimensional form, which is a typical representation in the biomechanics field, especially when showing stress or pressure values [40, 87, 90]. The only variables that have been made non-dimensional are the lengths. In particular, any spatial coordinate is presented in terms of the diameter, as it allows for an easier interpretation. Similarly, the wall displacements are given in terms of diameters rather than in absolute magnitudes. The rest of the variables are all expressed in the corresponding dimensional form.

The inner wall radius is constant and equal to $D/2$ for all z , except for the stenotic region. For $-D \leq z \leq D$, the radius is defined as

$$r(z) = \frac{D}{2} \left\{ 1 - \frac{1-\gamma}{2} \left[1 + \cos \left(\frac{2\pi z}{L} \right) \right] \right\}, \quad (3.1)$$

where $L = 2D$ is the length of the stenosis and γ is the ratio of the

minimum diameter to the inlet diameter. For this model, the minimum diameter $D_{\min}$ is $D/2$ and is located at $z = 0$, hence $\gamma = D_{\min}/D = 0.5$. This 50 % reduction in diameter leads to a 75 % area constriction (also known as stenosis severity, S), which is a typical value among previous stenotic flow studies [24, 25, 31]. The 75 % occlusion is also significant from a medical point of view, as it indicates when surgery may be recommended [19].

The radius defined for this geometry is interesting as well because it provides a smooth transition from the non-stenotic region to the constriction. Indeed, the derivative of the expression is given by

$$\frac{dr(z)}{dz} = -\frac{D}{2} \frac{1-\gamma}{2} \left[-\frac{2\pi}{L} \sin\left(\frac{2\pi z}{L}\right) \right], \quad (3.2)$$

so the wall slope becomes zero at the beginning of the stenosis ($z = -L/2$) and at the end of the stenosis ($z = L/2$).

3.3 Models and boundary conditions

3.3.1 Flow field

The study of blood flow through an elastic artery implies that the fluid and solid mechanics are coupled. This means that boundary conditions are not only needed for the flow field but also for the solid. And finally, additional matching conditions at the fluid-structure interface boundary must be defined as well.

The governing equations for the blood flow are the ones described in the previous chapter, section 2.4: the conservation of mass and the conservation of momentum. In this case, the flow parameters used are $\rho = 1000 \text{ kg/m}^3$ and $\mu = 4 \times 10^{-3} \text{ Pa} \cdot \text{s}$, which are based on average values used in previous works [50, 139–141]. In addition, in order to simplify some parameters of the

simulations, the flow is considered Newtonian. The Reynolds number, Re , is defined as the ratio of inertial forces to viscous forces. It is based on the inlet diameter, therefore $Re = \rho U D / \mu$. For the base model, the Reynolds number is set to $Re = 300$, which is a physiologically representative value and used also in previous studies of carotid arteries [12, 97].

The boundary conditions are the standard ones for a pipe flow configuration. First, at the inlet section, a steady, parabolic velocity profile u is defined in the axial direction z , by the expression

$$u = 2U \left[1 - 4 \left(\frac{r}{D} \right)^2 \right], \quad (3.3)$$

where U is the cross-sectional average velocity at the inlet and it is defined by the Reynolds number. On the other hand, a simple pressure outflow condition, p_{out} , is prescribed at the outlet. In this case, $p_{\text{out}} = 100 \text{ mmHg} = 13.33 \text{ kPa}$, which is an average value within the range of those used in previous works [87, 140, 142, 143]. This pressure value is prescribed by means of a normal stress condition: $[-p\mathbf{I} + \mu(\nabla\mathbf{u} + \nabla\mathbf{u}^T)] \cdot \mathbf{n} = -p_{\text{out}}\mathbf{n}$. This expression is the typical stress-free outflow condition applied in fluid dynamics simulations when $p_{\text{out}} = 0$ [24, 29].

3.3.2 Solid field

As mentioned earlier, apart from the flow field, this problem also deals with the solid deformation of the artery wall, so the vessel must be modelled as well by another set of equations.

It was shown in Chapter 1 that the structure of the artery wall is complex and that it presents non-homogeneous, anisotropic behaviour; in addition, it is characterised by three layers with different material properties. Considering these features would increase the complexity of the simulation. Therefore,

since the goal here is to model an idealised, thin-wall artery, the following simplifications will be taken into account. First, the wall is modelled as an homogeneous, isotropic material (that is, it presents the same mechanical properties in all directions). Second, a single-layer structure is considered, which allows for a more straightforward definition and analysis of the model. Finally, the wall is considered as a linear elastic material, which serves as a first simple approximation to the elastic behaviour of the vessel. Therefore, equation 2.22 becomes

$$\boldsymbol{\sigma} = 2G\boldsymbol{\epsilon} + \lambda \text{tr}(\boldsymbol{\epsilon})\boldsymbol{I}, \quad (3.4)$$

where $\boldsymbol{\sigma}$ denotes the stress tensor inside the solid, $\boldsymbol{\epsilon}$ defines the strain tensor, $\text{tr}(\boldsymbol{\epsilon})$ refers to the trace of the strain tensor and $\boldsymbol{I}$ is the identity tensor. The strain tensor is a function of the displacements field, $\boldsymbol{\xi}$. It is defined by the stress-displacement relation:

$$\boldsymbol{\epsilon} = \frac{1}{2} (\nabla \boldsymbol{\xi} + \nabla \boldsymbol{\xi}^T). \quad (3.5)$$

Finally, G and λ are the Lamé parameters, which are defined as a function of other material properties that are usually used to define a material behaviour. In particular, G and λ are dependent on the Young's modulus, E , and the Poisson ratio of the solid, ν . The mathematical relation is defined as

$$\lambda = \frac{E\nu}{(1+\nu)(1-2\nu)}, \quad (3.6)$$

$$G = \frac{E}{2(1+\nu)}. \quad (3.7)$$

In the following, E and ν will be used to characterise the material properties.

As shown in the literature review in Chapter 1, there is some variability regarding the material properties of the vessels. Whereas Riley et al.

reported that the Young's modulus of the artery, E , was in the order of hundreds of kilopascals [93, 96], others have set an equivalent Young's modulus in the order of the megapascals [54, 63]. For this model, a mean value $E = 1$ MPa has been used; in addition, the Poisson ratio is set to $\nu = 0.49$, in order to consider the vessel as a nearly incompressible material. Finally, the density of the solid is considered to be $\rho_s = 900 \text{ kg/m}^3$, as in previous studies [90].

The boundary conditions applied for the solid field are the following: at the inlet ($z = -6D$), the wall is considered to be fixed with all components of the displacement equal to zero ($\boldsymbol{\xi} = \mathbf{0}$), which is equivalent to consider the wall clamped at the inlet. On the other hand, at the outlet ($z = 16D$), only the axial component of the displacement is fixed, while the wall can be deformed in the radial direction. Therefore, it is possible to formulate this condition as $\xi_z = 0$. These conditions provided a good definition of both the inflow and the outflow. In addition, the domain lengths upstream and downstream the stenosis were varied to ensure that the stenosis region was not perturbed by the mechanical constraints imposed at the inlet and at the outlet sections. Specifically, the distributions of first principal stress and wall shear stress along the stenosis region were compared for different domain lengths, and it was observed that they were not affected by the boundary conditions imposed at the inlet and at the outlet.

3.3.3 Matching conditions

In the above, the velocities of both fluid and solid at the wall are unspecified, so two additional conditions are required to close the coupled system. The first condition is the velocity continuity, meaning that velocities of the fluid and the solid at the wall are equal. The velocity of the vessel at the inner wall

can be defined as the partial derivative of the displacements $\boldsymbol{\xi}$ with respect of the time t . On the other hand, as mentioned earlier, the velocity of the blood is denoted by $\mathbf{u}$. Therefore, the kinematic condition at the fluid-solid interface is defined as

$$\mathbf{u} = \frac{\partial \boldsymbol{\xi}}{\partial t}. \quad (3.8)$$

In addition, a second condition regarding the stress continuity is required as well. Indeed, the stresses on the solid and fluid at the artery wall must be equal, but opposite in the outward normal direction. Mathematically,

$$\mathbf{f} = \mathbf{n} \cdot \left[-p\mathbf{I} + \mu (\nabla \mathbf{u} + \nabla \mathbf{u}^T) - \frac{2}{3}\mu (\nabla \cdot \mathbf{u}) \mathbf{I} \right], \quad (3.9)$$

where $\mathbf{f}$ is the body force vector at the solid-fluid boundary and $\mathbf{n}$ denotes the outward normal to the boundary.

3.4 Mesh convergence analysis

A mesh convergence analysis was performed in order to justify the chosen grid discretisation. Several results will be presented in the coming sections. In particular, two main parameters will be analysed in detail: the Reynolds number and the stiffness of the arterial wall, via the Young's modulus.

As explained in section 2.3, the results presented in this thesis have been performed using COMSOL Multiphysics [122]. As stated in the previous chapter, COMSOL has been used in several studies modelling blood flow, including rigid walls [34] and fluid-structure interaction analysis with elastic walls [87, 100, 137].

The mesh considered for this model has also been created in COMSOL, by making use of the available built-in tools. A hybrid approach regarding the type of discretisation was followed in order to mesh the two-dimensional

domain. Specifically, the lumen and the vessel wall along the inlet and outlet pipes, upstream and downstream the stenosis respectively, were discretised using a structured grid made of quadrilateral elements. On the other hand, the stenosis region was discretised using an unstructured grid made of triangular elements, in order to make it easier to accommodate the curved nature of the domain in this area. A second order discretisation was used for the blood velocity field and for the wall displacement field, while the pressure field was solved using a first order interpolation (P2-P2-P1).

A grid convergence analysis was performed by analysing the axial distribution of first principal stress and the wall shear stress distribution along the stenosis region (between $z = -D$ and $z = D$). The results will be shown between $z = -2D$ and $z = 2D$ to take into account any features that may be present just upstream or downstream the stenosis. The simulations were started with a coarse mesh, which was gradually refined. The number of elements and degrees of freedom corresponding to each mesh tested are shown in table 3.1. Specifically, mesh 4 and mesh 5 were particularly refined in the stenosis region, where the changes of the system were most significant.

Mesh	Number of elements	Degrees of freedom
1	8085	36051
2	18167	74326
3	42203	182260
4	137184	471715
5	421436	1300770

Table 3.1: Mesh parameters used for the convergence analysis.

The axial distributions of first principal stress, σ_1 , at the inner wall are shown in figure 3.2. Each line corresponds to a different mesh, as defined in

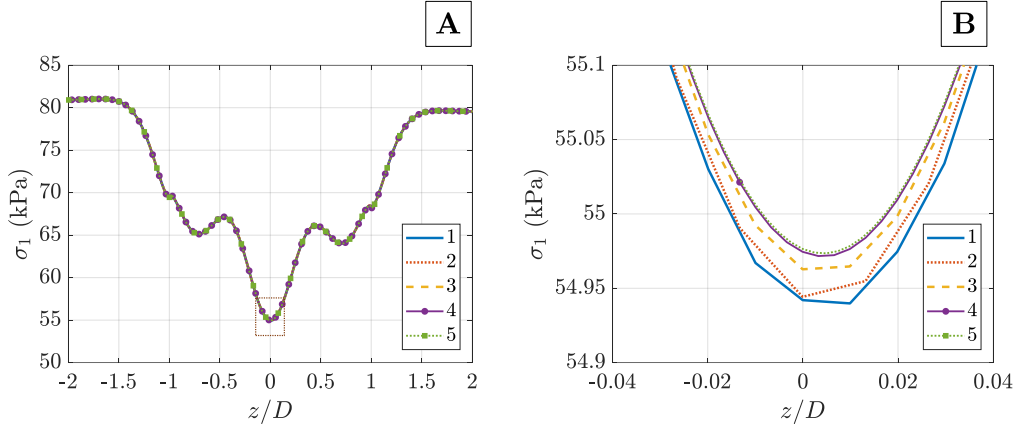


Fig. 3.2: Axial distribution of first principal stress, σ_1 , at the inner wall for each mesh considered in the convergence analysis. (A) General profiles. (B) Zoomed-in section around $z = 0$.

table 3.1. Figure 3.2A shows the general plot, where the red-dotted square denotes the area that is shown with greater detail in figure 3.2B. This second figure represents a zoomed-in section close to the minimum value of σ_1 at $z = 0$. Increasing the number of elements slightly affected the stress distribution, as can be observed in the detail shown in figure 3.2B. In particular, the change observed in the results for mesh 3 compared to the results for meshes 4 and 5 was less than 0.5 %.

Figure 3.3A shows the wall shear stress distribution, WSS, along the axial direction at the interface between the fluid and the wall. The peak immediately prior to the constriction was due to the pressure drop created by the stenosis. Again, the curves were quite similar for all the meshes considered, so a zoomed-in section is shown in figure 3.3B, showing the values around the peak. As in the case of the velocity profiles, the results obtained with mesh number 3 seemed to be accurate: increasing the number of elements up to an order of magnitude only led to a change of around a 0.5 %.

All things considered, the mesh 3 was proven to capture both solid and

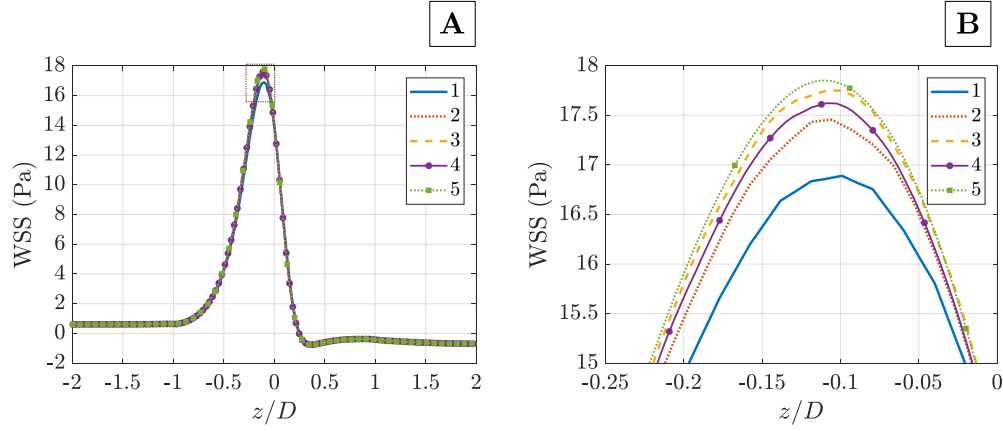


Fig. 3.3: Wall shear stress distributions, WSS, for each mesh considered in the convergence analysis. (A) General profiles. (B) Zoomed-in section close to the peak value upstream the constriction.

flow features of this particular model to the same degree as the meshes 4 and 5. Therefore, mesh 3 was used to perform the parametric analyses. A general picture of the mesh is shown in figure 3.4. Two similar structured grids were used to discretise the inlet and outlet pipes, for a total of 15600 elements. The domain between the coordinates $z = -2D$ and $z = 2D$ (containing the stenosis region, L , and the last/first portion of the inlet/outlet pipes) was discretised by means of an unstructured grid with 26603 elements, with a maximum element size of 1.17×10^{-4} m, equivalent to $D/60$. The fluid-solid interface was further refined (maximum element size of $D/100$) in order to better capture the stress distributions along the inner wall.

3.5 Design of the parameter sensitivity study

This section provides an overview of the parameter sensitivity analyses that have been performed in this chapter. The first result that will be shown is a figure depicting the flow and solid fields, which aims to provide a general

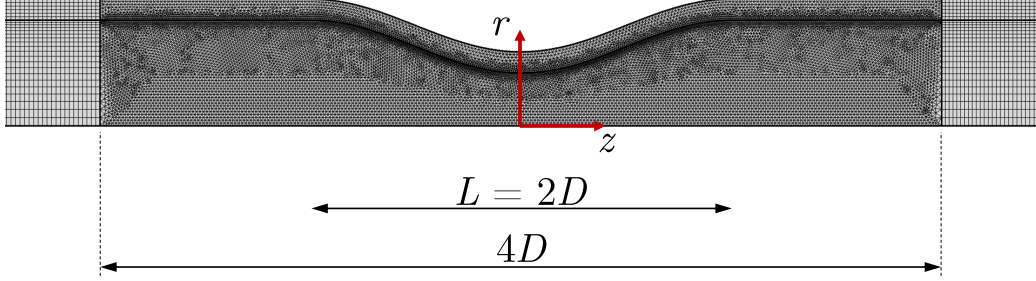


Fig. 3.4: General picture of the mesh, showing part of the inlet and outlet pipes, and the stenosis region.

idea of the present configuration. Next, the results corresponding to the parametric study will be presented: in particular, the analysis of the effect that the Reynolds number of the flow and the Young's modulus of the wall have on different flow and solid parameters. Here, the Reynolds numbers tested are $Re = 200, 300$ and 400 . On the other hand, a larger variation of the Young's modulus was performed, considering $E = 0.5, 1$ and 10 MPa. This way, both ends of the wall modelling were considered: a less stiff material ($E = 0.5$ MPa), and a very stiff one ($E = 10$ MPa) that may behave like a rigid-wall model.

The first parameter considered is the length of the recirculation region. This region refers to the area downstream the stenosis where the flow separates from the wall due to the adverse pressure gradient. The recirculation region is related to the appearance of flow instability and transition to turbulence [29, 144], which could trigger larger perturbations that may affect the stresses on the wall.

The next analysis is focused on the wall shear stress, WSS. This magnitude is described by

$$\text{WSS} = \mu \left. \frac{\partial u_t}{\partial y} \right|_{y=0}, \quad (3.10)$$

where y denotes the distance from the wall, and u_t describes the component of the velocity tangential to the wall (i.e. $u_t = \mathbf{u} \cdot \mathbf{e}_t$, where $\mathbf{e}_t$ denotes the direction tangential to the wall). The wall shear stress has been the object of several discussions regarding its role in plaque formation. In particular, it has been reported that regions where the wall shear stresses are low and oscillatory are prone to plaque development [12, 19, 26]. More recently, a new variant related to this variable has been introduced in the form of the transverse wall shear stress [125]. This magnitude is an average over the cardiac cycle of the wall shear stress components that act in a transverse direction to the mean WSS vector, and it was found to have good correlation with lesion prevalence.

The last flow parameter analysed is the fluid pressure along the centre-line, which can provide valuable information about the flow field. It is also related to the length of the recirculation region, which appears when the pressure gradient is adverse.

Finally, two solid parameters (related to the wall behaviour) are studied as well: first, the wall displacement in the radial direction; and second, the axial distribution of the first principal stress, σ_1 , along the interface boundary.

3.6 Results

3.6.1 Flow and stress fields

Figure 3.5 shows a two-dimensional picture of the whole domain and a detailed view of the stenosis region for the base model ($Re = 300$ and $E = 1$ MPa). In order to allow a more detailed visualisation of this area, subsequent figures will only show the geometry between the axial coordinates $z = -2D$ and $z = 2D$. The variables represented are the axial flow

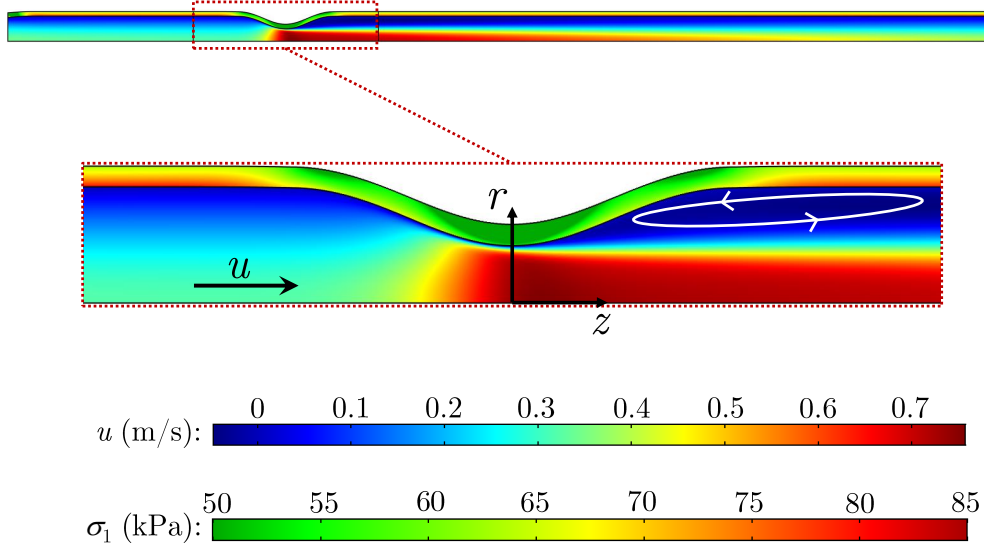


Fig. 3.5: General representation of the axial velocity, u , of the flow field and the first principal stress along the wall, σ_1 .

velocity, u , and the first principal stress along the wall, σ_1 . In this kind of configuration, the stenotic shape of the wall led to a region of high-velocity flow around the constriction, which is shown in dark red colour in the figure. In addition, due to the adverse pressure gradient downstream the throat, the flow separated from the wall and created a recirculation region in the axial direction (highlighted by the white closed line in the figure).

The acceleration of the flow at the stenosis can be explained since the flow must satisfy the mass-conservation equation, as mentioned in section 2.4. The shape of the stenosis was also responsible for the pressure drop around $z = 0$, as represented in figure 3.6.

The stress distribution along the wall was mainly affected by the fluid pressure distribution. For this particular geometry, the maximum stress was located outside the stenosis region. This was due to the pressure being higher upstream ($z < D$) and downstream the stenosis ($z > D$), as the thickness of

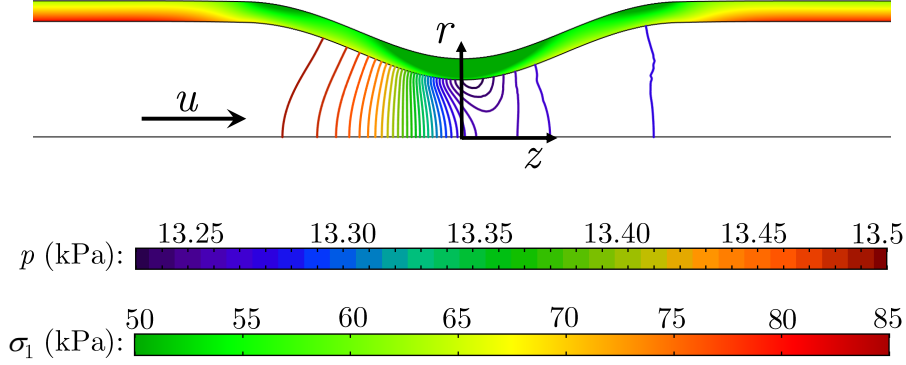


Fig. 3.6: Axisymmetric flow pressure field, p , and first principal stress along the wall, σ_1 .

the wall was constant along the domain. It is worth noting however that the first principal stress in the downstream region was slightly lower than the one upstream the constriction, something that can be attributed to the pressure distribution as well. In particular, just downstream the stenosis the pressure value increased again, but it did not rise to the same level as upstream, and so this was reflected on the stress on the wall.

3.6.2 Effect of Reynolds number and the Young's modulus

Length of recirculation region

The axial length of the recirculation region is denoted by L_{rc} and it was measured from the origin of the system of coordinates at $z = 0$, using D as the reference unit. Results for the different Young's moduli tested are shown in figure 3.7A, for a constant $Re = 300$. The largest recirculation region was $7.6D$ for $E = 0.5$ MPa, and the smallest value was $7.0D$ for $E = 10$ MPa. The relative difference was just of a 8 %, so the variation with the artery stiffness was relatively small, especially considering that E increased by a factor of

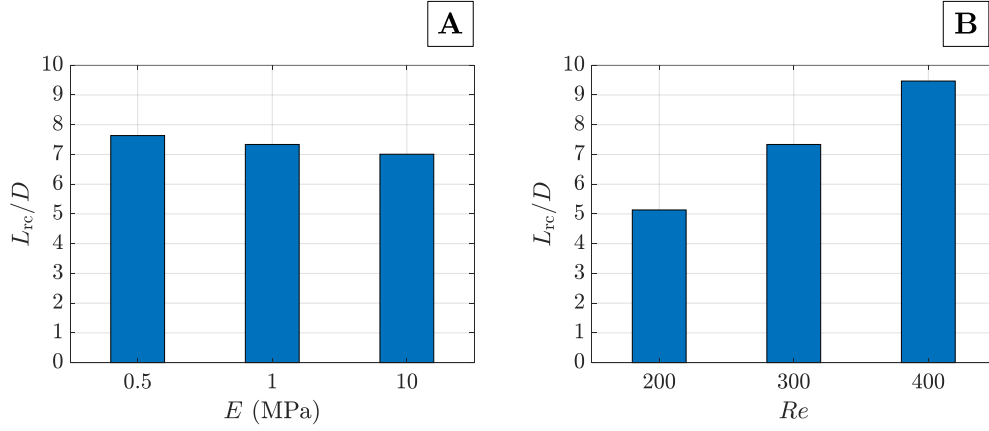


Fig. 3.7: Non-dimensional axial length L_{rc}/D of the recirculation region, measured from $z = 0$: (A) as a function of the Young modulus, with $Re = 300$; (B) as a function of the Reynolds number, with $E = 1$ MPa.

20. The length of the recirculation for each Reynolds number is shown in figure 3.7B, for a fixed value of $E = 1$ MPa. In this case, L_{rc} increased from $5.1D$ for $Re = 200$ to $9.5D$ for $Re = 400$. This variation was practically linear, increasing slightly more than $2D$ for each case. This behaviour may be explained by the basic definition of the Reynolds number, $Re = \rho U D / \mu$. Increasing the Reynolds meant that the ratio of inertial forces to viscous forces increased, and in fact meant an increase of the velocity of the fluid (as ρ , D and μ were fixed values by definition in this model). This had a direct effect on the recirculation region, that increased significantly, in comparison with the Young's modulus analysis.

Wall shear stress

The wall shear stress distribution in the model along the axial direction z is presented in figure 3.8. Again, the three different values of the Young's modulus were tested, as well as the three Reynolds numbers. The situation was similar to the one presented in the previous section: the elasticity of the

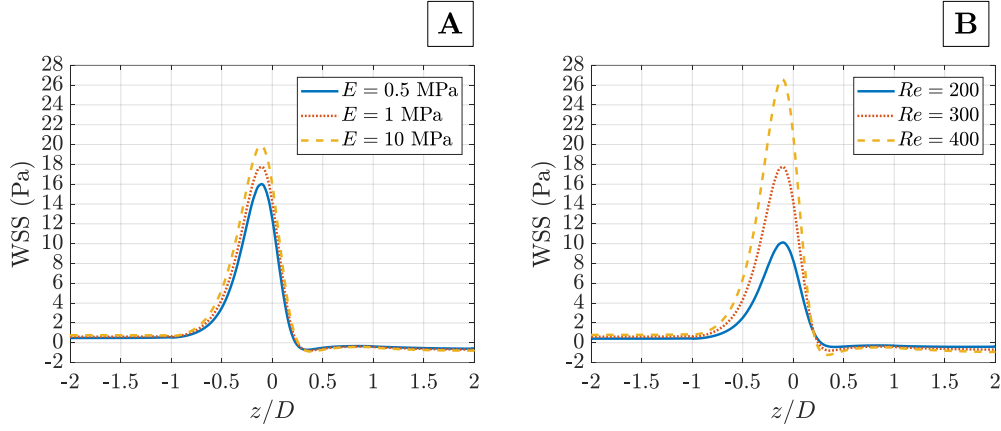


Fig. 3.8: Wall shear stress WSS along the axial direction z : (A) as a function of the Young's modulus, with $Re = 300$; (B) as a function of the Reynolds number, with $E = 1$ MPa.

wall did not greatly affect the WSS values, while the effect of the Re was quite different. Specifically, the WSS outside the stenosis region was practically the same for the three Young's modulus studied (figure 3.8A), staying at around 0.6 Pa. Similarly, the peak did not experience much variation either, increasing from 16 Pa for $E = 0.5$ MPa to 19 Pa for $E = 10$ MPa. This was in agreement with previously published observations, which concluded that decreasing the elasticity of the wall led to an increase of the maximum WSS [53, 97]. It is also worth noting that this peak was located just upstream of the maximum constriction section, not at $z = 0$. The peak-to-upstream ratio of the WSS ranged from 26 to 31. For comparison, it was reported that this ratio was more than 30 for $Re = 500$ in a rigid wall geometry [25], which is in the order of the results presented in this study.

The influence of the Reynolds number was more significant, especially around the WSS peak (figure 3.8B). In particular, the maximum increased by more than a 100%, going from a value of 10 Pa for the lowest Re case, to more than 26 Pa for $Re = 400$. In this case, the peak-to-upstream ratio

ranged approximately from 17 to 34.

The explanation for this peak was the smaller cross-section that the flow faces in the stenosis region. The constriction led to a great change in the fluid velocity, which was accelerated in order to keep fulfilling the conservation of mass equation. This acceleration created a larger variation of the axial velocity along the radial coordinate which, by definition of the WSS, yielded a stress peak.

Fluid pressure

The main characteristic of the fluid pressure field was the drop observed through the stenosis constriction, as previously shown in the two-dimensional picture represented in figure 3.6. The pressure distribution along the centre-line is shown here, which was a simpler way to carry out the parametric analysis.

The effect of the Young's modulus of the wall on the pressure distribution was not very significant, as shown in figure 3.9A. On the other hand, the variation of the Reynolds number showed larger effect on the pressure field (figure 3.9B). In particular, the pressure upstream the stenosis increased when Re increased. Downstream the constriction, the opposite behaviour was observed: the pressure decreased when Re increased. What this meant was that the overall pressure drop along the stenosis was larger for higher Reynolds numbers.

The explanation for the drop around $z = 0$ may be done by looking at the axial variation of the cross-section. The reduction of the cross-sectional area implies that, in order to fulfil the conservation of mass equation, the flow accelerates. The increase of the flow velocity also leads to a drop of the pressure. It is also worth mentioning the adverse pressure gradient down-

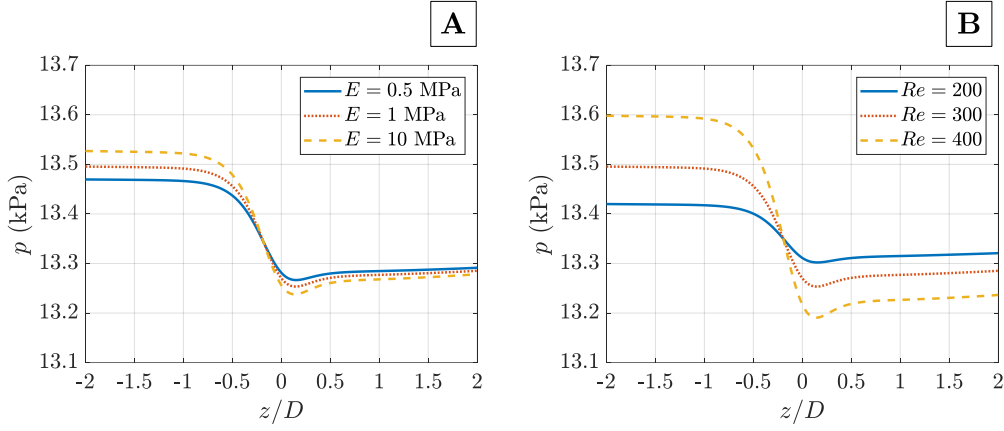


Fig. 3.9: Fluid pressure, p , along the axial direction z : (A) as a function of the Young modulus, with $Re = 300$; (B) as a function of the Reynolds number, with $E = 1$ MPa.

stream the stenosis ($\partial p / \partial z > 0$), that explains the creation of a recirculation region just downstream the constriction.

Wall displacement

Figure 3.10 shows the non-dimensional radial displacement of the wall, ξ_r/D . In particular, figure 3.10A shows the radial displacement along the axial coordinate z for different values of the Young's modulus and a constant $Re = 300$. As can be observed in the plot, the stiffness of the wall greatly affected the magnitude of the radial displacements. Specifically, the relation between the stiffness and the displacements was inverse, as increasing the Young's modulus led to a decrease of the magnitude of the displacements (which is related to equation 3.4). As stated in the beginning, the stiffest case with $E = 10$ MPa was used as a model that resembled the rigid-like wall behaviour. This figure shows that the displacement was not exactly zero, but it stayed close to that level, at around $\xi_r/D \approx 0.003$, an order of magnitude smaller than the other cases.

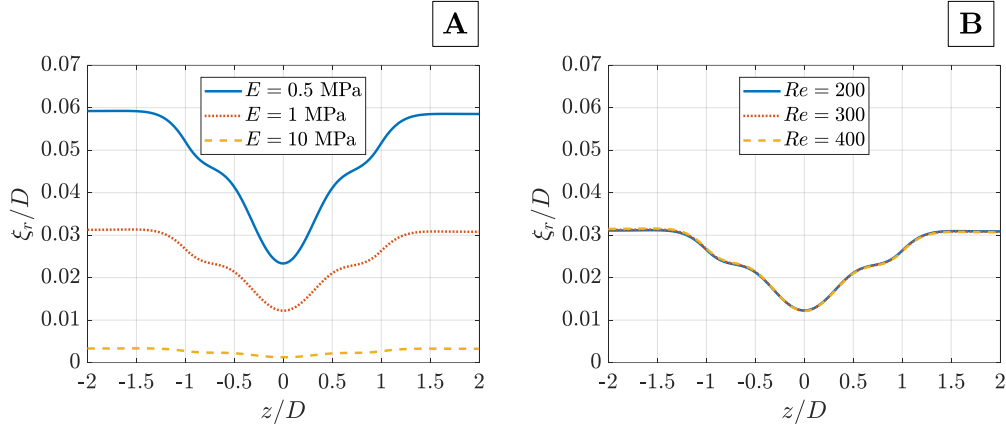


Fig. 3.10: Non-dimensional radial displacement, ξ_r/D , along the axial direction z : (A) as a function of the Young modulus, with $Re = 300$; (B) as a function of the Reynolds number, with $E = 1$ MPa.

On the contrary, figure 3.10B shows that the effect of the Reynolds on the displacements was negligible. The distribution stayed the same for the three Re tested.

First principal stress

The axial distribution of the first principal stress, σ_1 , along the interface boundary is shown in figure 3.11. The first remark is that the Reynolds number variation did not significantly affect the first principal stresses, which behaved similarly to the radial displacements of the wall. That is, the Reynolds number of the flow was not a key factor that contributed to a large variation of stress within the range of Re tested here. On the other hand, the stiffness of the vessel notably influenced the stress levels, showing an increase of σ_1 when the Young's modulus decreased. An interesting point was that at the throat of the stenosis all three curves got closer to the same value, at around 54 kPa. This is where the displacement was always minimum (as shown in figure 3.10A).

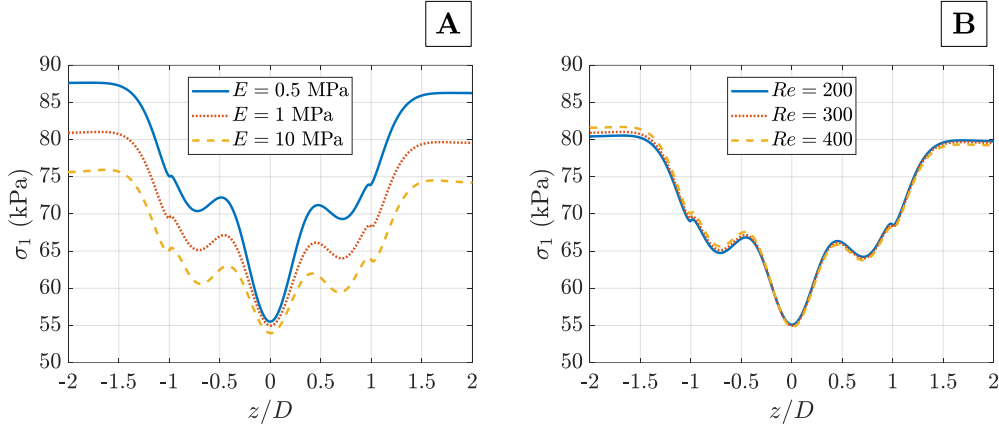


Fig. 3.11: First principal stress, σ_1 , along the axial direction z : (A) as a function of the Young modulus, with $Re = 300$; (B) as a function of the Reynolds number, with $E = 1$ MPa.

The stress levels outside the stenosis region were constant and they approximately corresponded to the circumferential stress of an equivalent thick-wall cylinder loaded with internal pressure. Therefore, the predominant direction of the first principal stress was mainly the circumferential one. On the other hand, the explanation of the shape of the distributions may be related again to the pressure distribution, along with the actual shape of stenosis. In particular, the pressure drop helps explaining why the minimum of σ_1 was located at $z = 0$, and it also explains why the downstream levels were slightly smaller than the upstream stress levels. The stress distribution was also similar in shape to the one shown in figure 3.10 regarding the radial displacements. This behaviour may be explained by the linear elastic model used for this simulation, which defined a linear stress-strain relation.

3.7 Discussion

It has been stated that the pressure may be considered as the driving force behind the displacements in stenotic arteries [54, 88]. In particular, the shape of the displacement curves, which presented a minimum at the throat of the stenosis, may be explained by the distribution of the fluid pressure. This may be interpreted as the flow affecting the displacements (and in subsequent, more complex models, the plaque rupture), mainly through stream-wise pressure variations, as per equation 3.9. It could be noted that the pressure was asymmetric with respect to the throat (figure 3.9), whereas on the other hand the displacements seemed to be symmetric with respect to the coordinate $z = 0$ (figure 3.10). However, this difference may be explained by considering the geometry of the artery, which was also symmetric with regards to the throat, as presented in figure 3.1. In addition, it should be taken into account that the value of the pressure recovered slightly in the downstream part of the stenosis region, thus increasing the radial displacements for $z > 0$. Finally, this situation could be compared to a collapsible tube configuration [45]; however, in the present case the vessel did not collapse due to a relatively high value of the wall stiffness.

It is also worth mentioning the relation of the wall shear stresses with the displacement distribution. As shown in figure 3.8, the WSS presented a peak just prior to the constriction but, as it can be observed in figure 3.10, this peak had no effect on the radial displacement field. This is a conclusive argument that the WSS was not the driving force behind the radial displacements. It should be noted that the overall level of the first principal stress was in the order of the tens of kilopascals, while the wall shear stresses were much lower in magnitude, in the order of the tens of pascals. In addition, it has been reported that the flow shear stresses are not a meaningful way to locate a

possible site of plaque rupture [105]. It should also be taken into account here that the present study was carried out considering a steady, laminar flow through an axisymmetric configuration.

Overall, the Reynolds number seemed to greatly influence the length of the recirculation region (figure 3.7), the wall shear stress distribution (figure 3.8) and, to a lesser degree, the pressure drop along the stenosis (figure 3.9). These variables have been related to the onset of atherosclerosis; especially the wall shear stress, which has been the object of several research studies [12, 23, 27, 145]. However, less evidence was found of the relation between the Reynolds number and other variables that might be more closely related to a possible plaque rupture: the displacement of the wall and the stress distribution on the artery.

The stiffness of the vessel, by means of the Young's modulus, showed the opposite behaviour: it did not influence any flow-related variables, but it did have a significant effect on the radial displacements and on the distribution of the first principal stress. It should be noted however that for this influence to be significant, the variation of the Young's modulus had to be relatively large. In this case, three values were tested: the baseline Young's modulus ($E = 1$ MPa), half its value (less stiff case, $E = 0.5$ MPa) and an order of magnitude larger (rigid-like wall, $E = 10$ MPa). In addition, the impact of the Young's modulus seemed to be more important on the displacements than on the stress levels. Although studies on the influence of the stiffness of the artery have been carried out using more complex models (containing a lipid core and a fibrous cap), they reported a similar result: a general decrease of the stress levels when the stiffness of the wall increased [101].

3.8 Conclusions and further developments

In this chapter, numerical simulations have been performed to model the blood flow through an axisymmetric stenosis with a thin, elastic wall. The influence of several variables related to the flow and solid fields has been studied by performing a parametric analysis.

In summary, some conclusions can be obtained from this first, idealised model. One, that a flow-related variable like the Reynolds number mainly influenced the flow field and had a limited effect on the solid field. Other, that the material properties of the wall may have a significant impact on the stress distributions and, potentially, in possible sites of rupture, as plaques may rupture where the structural stress is high [108, 146].

As stated in the Introduction to this chapter, one of the main goals of this first model was to understand the basic dynamics of the fluid-structure interaction in an idealised, stenotic geometry. In the next chapter, results will be presented for a more complex geometry. In particular, a better modelling of the stenosis region is introduced by including a lipid core and a fibrous cap, rather than keeping a constant thickness along the domain. It is expected that the new geometry will modify the current stress distributions, which may be of interest when analysing plaque rupture. In addition, a hyperelastic model is used rather than a linear elastic model. The linear elastic one was a logical first step that helps to give a general idea of the simulations and the kind of results and deformation fields that may be expected, but the introduction of a hyperelastic model is recommended when studying a more complex geometry.

Chapter 4

Two-dimensional plaque stress analysis¹

4.1 Introduction

The previous model, described in Chapter 3, considered a thin, elastic wall since the main goal was to understand the basic fluid-structure interaction of the problem. It was found that the wall displacements were mainly affected by the flow pressure distribution rather than the viscous shear forces. In addition, it was also observed that the material properties of the artery could impact the stress distributions, so appropriate modelling of the solid part is required.

This chapter introduces new features to the model by including an idealised, atherosclerotic plaque where not only the artery wall, but also a lipid

¹The contents of this chapter are based on a journal article accepted for publication: Alegre Martínez C., Choi K.-S., Tammisola O., McNally D. On the axial distribution of plaque stress: influence of stenosis severity, lipid core stiffness, lipid core length and fibrous cap stiffness. *Medical Engineering and Physics* **68**, 76-84. ISSN: 1350-4533. (2019)

core and a fibrous cap are modelled. The inclusion of the lipid core, which presents mechanical properties that are significantly different to those of the rest of the wall, means that a redistribution of the mechanical stress along the vessel may be observed. This stress distribution will be investigated in order to analyse what it means with regards to potential sites of plaque rupture. Indeed, some studies have reported a link between sites of plaque rupture and high plaque stresses in carotid arteries [105, 108, 141], as well as in coronary arteries [146, 147]. The hypothesis here is that the most likely axial location of plaque rupture in a carotid artery, indicated by the location of maximum stress, is strongly influenced by changes of the lipid core stiffness and the geometry. In order to do this, a fluid-structure interaction model is used to perform a systematic variation of the following features: stenosis severity, Young’s modulus of the lipid core of the plaque, positive remodelling, lipid core length, and fibrous cap stiffness. The blood is considered as incompressible and Newtonian, while the artery wall and the lipid core of the plaque are modelled as hyperelastic and linear elastic materials respectively. This simplified configuration makes it possible to identify the critical parameters affecting the plaque rupture.

4.2 Geometry

The geometry of the model considered in this chapter is similar to the one used in the previous set of simulations. In particular, the flow domain or lumen shares the same specification. However, the modelling of the vessel wall presents several differences with regards to the thin-wall model. In particular, a *lipid core* is now included, and it is considered to be several times less stiff than the surrounding artery wall. The introduction of this

material model completely changes the behaviour of the wall, as it will be shown in the stress distributions.

The chosen lumen geometry is the same as the one presented in Chapter 3, “Thin-wall simulations”; an idealised, axisymmetric stenosis that has been used in several works [24, 25, 28, 29]. The justification of this model is that the main goal is to capture general changes in the distributions rather than specific peak values, and this geometry is better suited for a parametric analysis. The origin of the coordinate system, O , is located at the same place; the intersection of the centre-line of the lumen with the cross-section at the throat. The two coordinates are the same as in Chapter 3: z in the axial direction and r in the radial direction.

The novelty here is the introduction of the modelling of the plaque, which is located in the constriction, as shown in figure 4.1. In particular, the lipid core and the fibrous cap are included in the model. The contour of the lipid core follows the shape of the stenotic lumen. The part of artery that lies between the lipid core and the flow domain is called the fibrous cap. In this case, the thickness of the fibrous cap, t_{fc} , is considered to be constant along the axial direction and equal to $100\mu\text{m}$, which is a typical value of plaques with thin fibrous caps [100, 148, 149].

As in the previous chapter, the reference length unit is the diameter, D . The same value is used, $D = 7\text{mm}$, which was based on the typical dimensions of a human carotid artery [23, 38, 97, 120, 138]. Therefore, the fibrous cap thickness may also be expressed as $t_{fc} = 0.014D$. The inlet and outlet sections are located at $z = -4D$ and $z = 10D$ respectively. The wall thickness is constant and equal to $D/10$ for the part of the domain that falls outside the stenosis region. This value is in the order of the range of those reported by Pedley for the carotid artery [139].

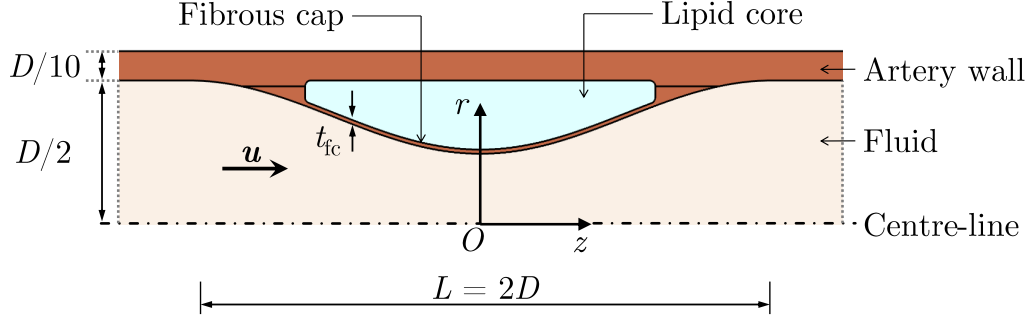


Fig. 4.1: Idealised axisymmetric stenosis geometry showing both the fluid and the solid domains. The origin, O , is located at the centre line of the throat. The thickness of the artery wall is $D/10$, being D the diameter of the fluid domain.

The lumen radius, $r(z)$, defines the stenotic geometry between $z = -D$ and $z = D$ via the following expression

$$r(z) = \frac{D}{2} \left\{ 1 - \frac{1-\gamma}{2} \left[1 + \cos \left(\frac{2\pi z}{L} \right) \right] \right\}, \quad (4.1)$$

while it is equal to $D/2$ outside the stenosis region. In the former, $L = 2D$ denotes the length of the stenosis and $\gamma = D_{\min}/D$ is the diameter ratio. As in the previous chapter, $\gamma = 0.5$ and therefore this leads to a stenosis severity, S , that is equal to 75 %, which has been studied in several works [19, 24, 25, 31].

In addition to this model, the apparition of positive remodelling of the artery will also be considered. Positive remodelling is a biological reaction of the vessel where there is an atherosclerotic lesion, or plaque, that manifests by an expansion of the vessel wall in the outward direction, hence *positive* [150]. Therefore, the external diameter of the artery increases [4]. It is important to take this effect into account, as non-stenotic plaques with positive remodelling also present thin fibrous caps that may rupture at some point [151]. Therefore, two variants of the base model are included with a smaller severity and positive remodelling. In particular, simulations are performed

for a non-stenotic case and a 25 %-stenotic model. In both cases, the thickness of the artery wall around the lipid core is kept constant and equal to the nominal wall thickness, $D/10$. On the other hand, the positive remodelling is assumed to keep the same shape as the stenosis, but in the outward normal direction. This means that the equation that describes the outer wall radius, r_{ow} , is

$$r_{\text{ow}}(z) = \frac{D}{10} + \frac{D}{2} \left\{ 1 + \frac{1-\gamma}{2} \left[1 + \cos \left(\frac{2\pi z}{L} \right) \right] \right\}. \quad (4.2)$$

The geometry of the positive remodelling cases is shown along the base model in figure 4.2. It should be noted that, due to the previous assumptions, the size of the lipid core for the 25 %-stenotic case (defined by its thickness, t_1 , in the figure 4.2C) is larger than the other two (defined by the thickness t_0 , figures 4.2A and 4.2B).

4.3 Models and boundary conditions

4.3.1 Flow field

The modelling of the blood flow is the same as in the simulations of Chapter 3. For the sake of clarity, those conditions are enumerated here as well.

First of all, the governing equations are the conservation of mass and conservation of momentum, as shown in section 2.4. The flow parameters considered are: density $\rho = 1000 \text{ kg/m}^3$, dynamic viscosity $\mu = 4 \times 10^{-3} \text{ Pa} \cdot \text{s}$, based on previous works [50, 139–141], and Reynolds number $Re = \rho U D / \mu = 300$, a physiologically representative magnitude [12, 97]. In addition, the blood is modelled as a Newtonian fluid. This is considered to be an appropriate choice as the non-Newtonian effects are only significant in some specific situations that are not found in this configuration (specifically, when the flow is very slow [39]).

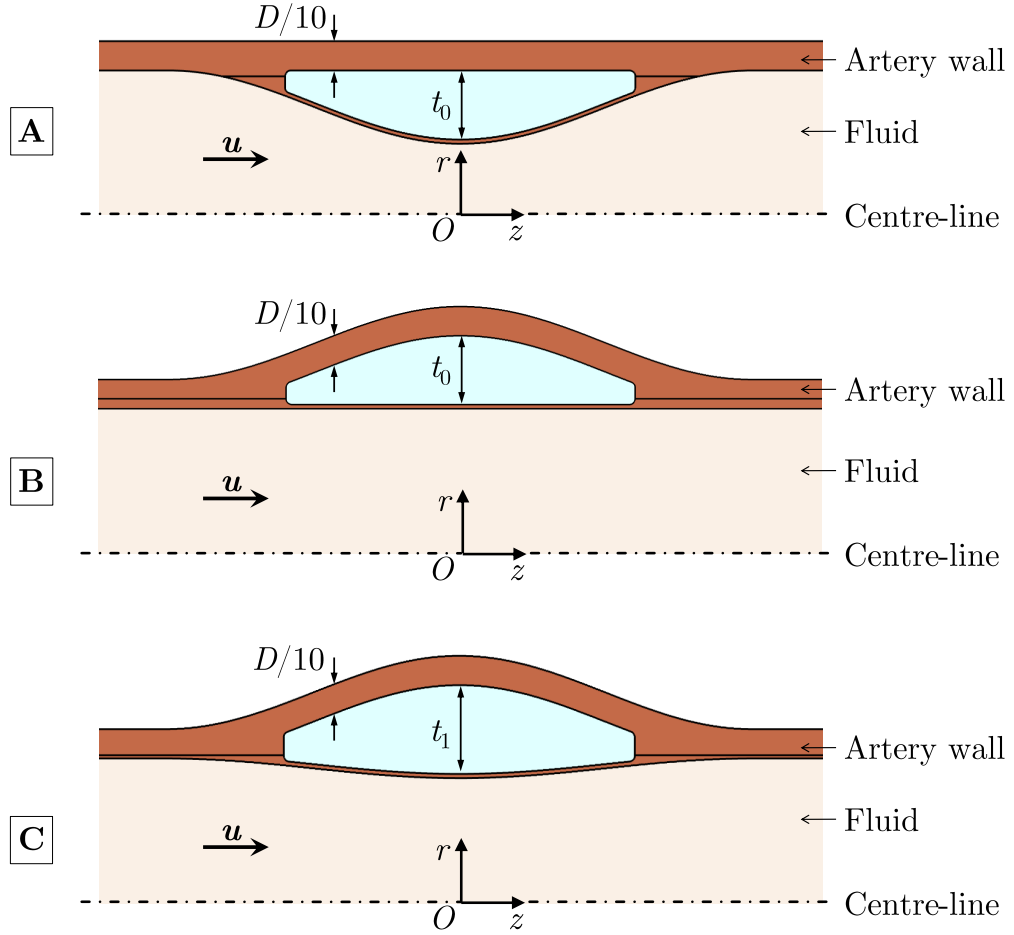


Fig. 4.2: Geometry of the cases in the positive remodelling analysis. (A) 75 %-stenotic base model; (B) non-stenotic case with positive remodelling; (C) 25 %-stenotic case with positive remodelling. The outer wall thickness is equal to $D/10$ in all cases. t_0 and t_1 denote the thickness of the lipid core at $z = 0$.

Regarding the boundary conditions, a steady, parabolic velocity profile u is imposed at the inlet section in the axial direction:

$$u = 2U \left[1 - 4 \left(\frac{r}{D} \right)^2 \right], \quad (4.3)$$

where U denotes the cross-sectional mean velocity (bulk velocity) at the inlet section and is given by the *Re*. At the outlet, a specific pressure p_{out} value is imposed. The outlet pressure is set to $p_{\text{out}} = 160 \text{ mmHg} = 21.33 \text{ kPa}$, which is a rather high value of blood pressure that would correspond to the systole. This is used here as it matches the literature [90], and also to account for any adverse pressure conditions that may make the plaque more vulnerable. Again, this value is imposed by means of a normal stress condition at the outlet: $[-p\mathbf{I} + \mu(\nabla\mathbf{u} + \nabla\mathbf{u}^T)] \cdot \mathbf{n} = -p_{\text{out}}\mathbf{n}$.

4.3.2 Artery wall and lipid core

In this chapter, the artery wall is no longer considered as a uniform material. Now, the introduction of the plaque modelling means that different mechanical properties should be considered for the vessel wall and for the lipid core of the plaque.

As discussed in Chapter 1, the artery wall is a non-homogeneous, soft tissue made up of three layers that present anisotropic behaviour. However, since the objective in this chapter is to model an idealised segment of a carotid artery, the following simplifications are introduced: first, the vessel is modelled as a homogeneous, isotropic material; and second, a mono-layer structure is considered, rather than a multi-layer one.

The next consideration is the material modelling. Specifically, the linear elastic model implemented in the previous chapter does not adequately represent the behaviour of an atherosclerotic artery. Instead, the most common

approach is to represent the vessel as a non-linear, hyperelastic solid. This kind of modelling has been used several times in the past when simulating living tissues [90, 100, 108, 141, 149]. Previous works in the field have considered different types of hyperelastic models: for example, Tang et al. used the modified Mooney-Rivlin model [89, 108]; Li et al. made use of the model proposed by Ogden [100]; and others have included the anisotropic nature of the tissue by means of the Holzapfel-Gasser-Ogden model [87]. In the present work, the vessel is modelled as an isotropic, nearly incompressible neo-Hookean solid. The reason for this choice is that this model has been reported to be valid for small deformations [90] and it has also been used in previous studies [67, 148].

The constitutive equation of a hyperelastic model takes the form

$$\boldsymbol{\sigma} = \frac{\partial W}{\partial \boldsymbol{\epsilon}}, \quad (4.4)$$

where $\boldsymbol{\sigma}$ denotes the Cauchy stress tensor, $\boldsymbol{\epsilon}$ is the deformation of the solid and W refers to the strain energy density function. In the case of the neo-Hookean model, W is given by

$$W = \frac{1}{2} [G (I_1 - 3) + K (J_{\text{el}} - 1)^2], \quad (4.5)$$

where G denotes the shear modulus, I_1 is the first invariant of the isochoric part of the elastic right Cauchy-Green deformation tensor, K refers to the bulk modulus and J_{el} denotes the elastic volume ratio. It was shown in section 1.2.6 that the material properties of an artery show some disparity. In this case, the values used to define the properties are within the range of those reported in the literature review of Chapter 1, and are taken from a previous study from Kock et al. [90]: in particular, the shear modulus is set to $G = 6$ MPa and the bulk modulus is set to $K = 600$ MPa. The density of the wall is set to $\rho_w = 900$ kg/m³.

The fibrous cap, which is the part of the wall that lies between the lipid core and the blood flow (figure 4.1) presents the same mechanical properties as the wall, except for one exception. Specifically, the bulk modulus of the cap, K_{fc} , is set to $K_{fc} = 2K = 1200 \text{ MPa}$, as it has been reported that the wall is stiffer around the atherosclerotic lesion [99].

The lipid core, on the other hand, is described as an isotropic linear elastic material. The variables used to characterise the core are then the Young's modulus, E_c , and the Poisson's ratio, ν_c . It has been reported that the stiffness of the lipid core is around a hundred times smaller than the equivalent Young's modulus of the wall or less [62, 89]. Since the wall was modelled as an isotropic material, the Young's modulus of the vessel is $E = 9KG/(3K + G) \approx 18 \text{ MPa}$. The corresponding Young's modulus of the lipid core would then be in the order of $E_c \sim 18 \text{ MPa}/100 = 180 \text{ kPa}$. In order to consider a value previously used in the literature [90] that is around the same order as that one, $E_c = 100 \text{ kPa}$ is chosen. The density is $\rho_c = 900 \text{ kg/m}^3$, whereas the Poisson's ratio is $\nu_c = 0.49$, which corresponds to a nearly incompressible material [60, 73].

Regarding the boundary conditions, they are the same as in Chapter 3: specifically, the displacement $\boldsymbol{\xi}$ of the artery is constrained at the inlet ($\boldsymbol{\xi} = \mathbf{0}$), and no axial displacement is allowed at the outlet ($\xi_z = 0$). Of the different conditions tested, these were the ones which provided the most well-defined inflow and outflow. In addition, the domain lengths were varied to ensure that the stresses in the stenosis were not affected by the proximity to inflow and outflow boundaries.

4.3.3 Matching conditions

The same matching conditions as those presented in the previous chapter apply here. These are required at the interface between the artery wall and the blood flow, in order to close the coupled system. The first condition is the velocity continuity, which imposes a flow velocity, $\mathbf{u}$, equal to the artery wall velocity, $\partial\xi/\partial t$. Mathematically,

$$\mathbf{u} = \frac{\partial\xi}{\partial t}. \quad (4.6)$$

On the other hand, the stress continuity is required as well. This effectively means that the stresses on the vessel and on the fluid along the interface are equal, but opposite in the outward normal direction. This is given by

$$\mathbf{f} = \mathbf{n} \cdot \left[-p\mathbf{I} + \mu (\nabla\mathbf{u} + \nabla\mathbf{u}^T) - \frac{2}{3}\mu (\nabla\cdot\mathbf{u}) \mathbf{I} \right], \quad (4.7)$$

where $\mathbf{n}$ denotes the outward normal to the boundary.

4.4 Mesh convergence analysis

A mesh convergence analysis was carried out to ensure that the grid discretisation was optimal. The process is similar to the one followed in Chapter 3.

The mesh considered for this model has also been created in COMSOL by making use of the available built-in tools. A hybrid approach regarding the type of discretisation was followed in order to mesh the two-dimensional domain. The lumen and the vessel wall along the inlet and outlet pipes, upstream and downstream the stenosis respectively, were discretised using a structured grid made of quadrilateral elements. On the other hand, the stenosis region, including the artery wall and the lipid core, was discretised

using an unstructured grid made of triangular elements. This was due to make it easier to accommodate the curved nature of the domains in this area. A second order discretisation was used for the blood velocity field and for the solid displacement field, while the pressure field was solved using a first order interpolation (P2-P2-P1).

A grid convergence analysis was performed by analysing the axial distribution of first principal stress and the radial displacements of the inner wall along the stenosis region (between $z = -D$ and $z = D$). The results will be shown between $z = -2D$ and $z = 2D$ to take into account any features that may be present just upstream or downstream the stenosis. The simulations were started with a coarse mesh, which was gradually refined. The number of elements and degrees of freedom corresponding to each mesh tested are shown in table 4.1.

Mesh	Number of elements	Degrees of freedom
1	14408	203861
2	26713	288742
3	42871	391286
4	133384	940016

Table 4.1: Mesh parameters used for the convergence analysis.

Figure 4.3 shows the axial distribution of first principal stress, σ_1 , for the four meshes considered. A general plot is shown in figure 4.3A, whereas a zoomed-in section around the secondary peak (highlighted by the red-dotted square) is shown in figure 4.3B. The shape of the distribution will be further explained in the next section 4.6. The results show that increasing the number of elements had some impact that can be better appreciated on the local stress peak. In particular, there is a 2% difference of the local

stress peak between mesh number 2 and mesh number 4. Mesh 3 and mesh 4 showed less than a 0.5 % difference, even though the time required to run a case for mesh 4 was up to two times larger than for mesh 3. Therefore, this analysis suggested that mesh 3 seemed to be an optimal grid discretisation.

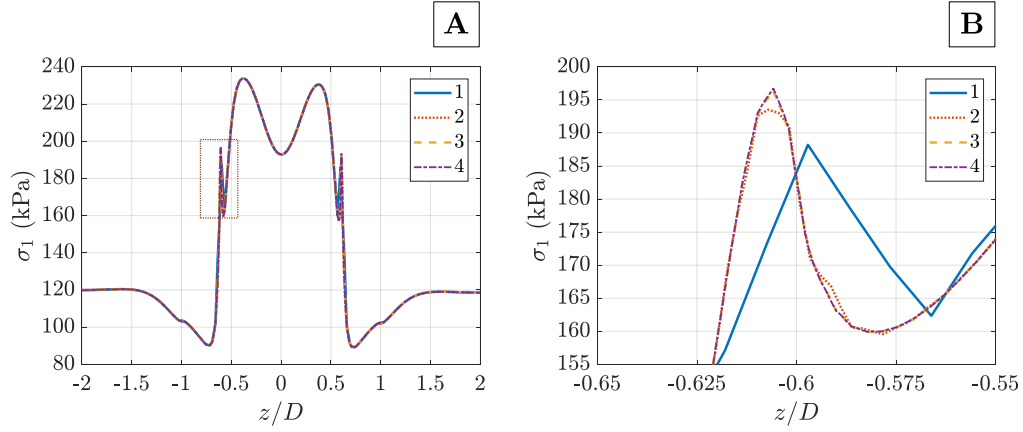


Fig. 4.3: Axial distribution of first principal stress, σ_1 , at the inner wall for each mesh considered in the convergence analysis. (A) General distribution. (B) Zoomed-in section around the secondary peak.

In order to confirm this first result, the variation of the non-dimensional radial displacements of the inner wall, ξ_r/D , was also analysed for each mesh. Results are shown in figure 4.4. As in the previous case, the curves are quite similar for all the cases considered, and the small differences can only be appreciated if zooming in to a specific area. In this case, looking closely at the location of minimum displacements (figure 4.4B), it is clear that except for the less refined mesh 1, the rest of them share the same shape of the curves. In particular, the relative error among them is less than a 0.5 %. Therefore, the results obtained in the previous analysis of the first principal stress seem to be confirmed with this subsequent study. All cases considered, mesh 3 was chosen as a good grid discretisation since increasing the number of elements did not yield a significant precision improvement.

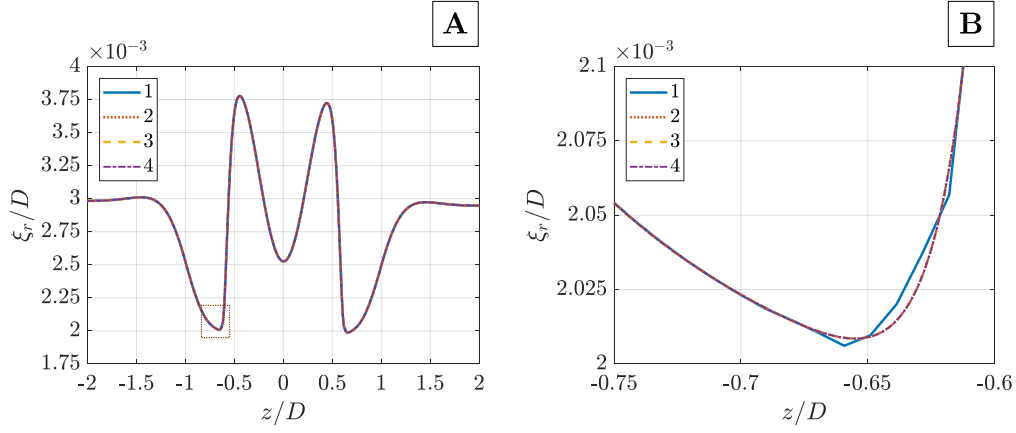


Fig. 4.4: Axial distribution of the non-dimensional radial displacements of the inner wall, ξ_r/D , for each mesh considered in the convergence analysis. (A) General distribution. (B) Zoomed-in section around the location of minimum displacements.

Figure 4.5 shows a general picture of the mesh used for the base model. The structure of the mesh is hybrid: the inlet and outlet pipes are discretised by using structured grids totalling 11040 elements. On the other hand, an unstructured grid is used to mesh the region delimited by the coordinates $z = -1.25D$ and $z = 1.25D$. The number of elements used in this part of the domain was 31831, which was mainly influenced by the element size at the fluid-solid interface. In this case, this size was set to a maximum of $D/240$. This was necessary in order to create a finer mesh along the fibrous cap, which is the area where the solid stresses are analysed in the parametric analysis. The final grid is made up of 42871 elements and 391286 degrees of freedom.

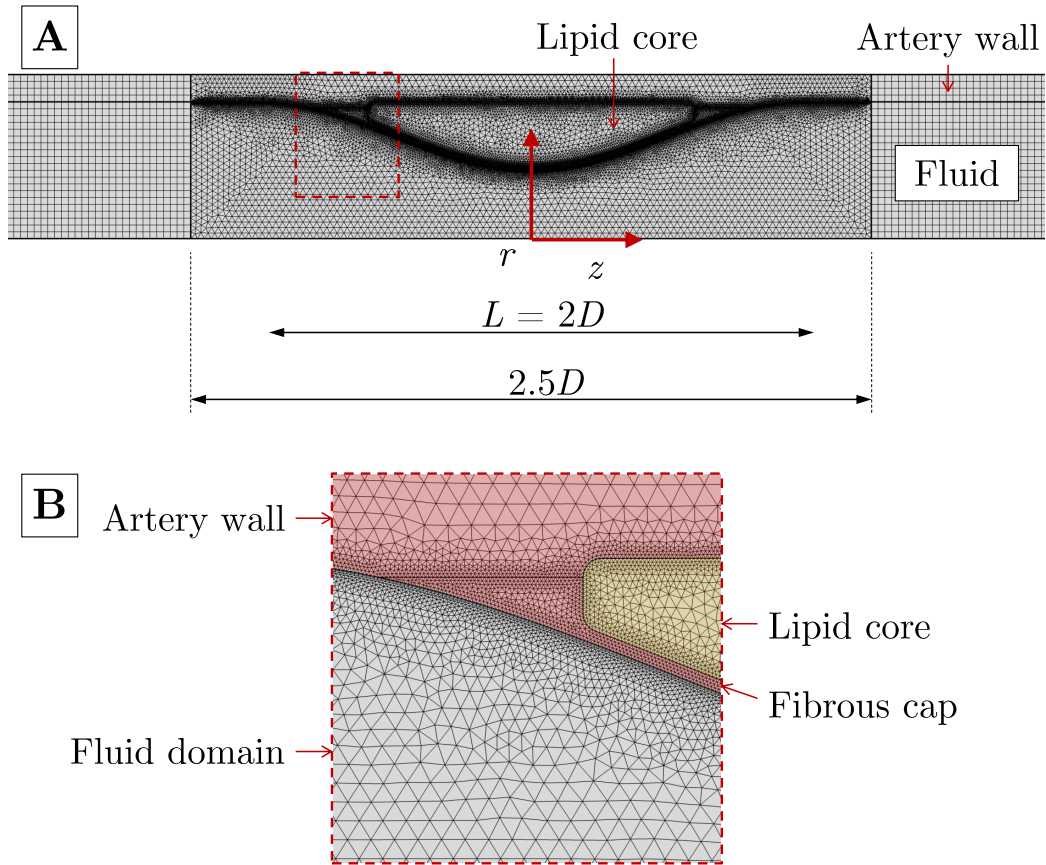


Fig. 4.5: (A) General picture of the mesh, showing part of the inlet and outlet pipes, and the stenosis region. (B) Zoomed-in section showing the mesh refinement around the fibrous cap.

4.5 Design of the parameter sensitivity study

The results of the simulations performed in this chapter will be shown in the next section. First, a general picture of the flow and solid fields is provided. This is followed by a parametric study, with the aim of investigating potential plaque rupture sites, as stated in section 4.1. For each parameter considered, the axial distribution of the first principal stress and the non-dimensional radial displacement of the wall are shown.

The first analysis is focused on the effect of the stenosis severity and the plaque stiffness. In order to simplify the modelling of the different plaque compositions, the elasticity of the lipid core is varied by means of the Young's modulus, E_c . As shown in section 4.3.2, the lipid core is modelled as a linear elastic material with a Young's modulus that is around 100 times smaller than the equivalent Young's modulus of the artery wall [89]. For the base model, this value is set to $E_c = 100$ kPa. A less stiff core that would model a completely lipid-filled plaque is also considered, with $E_c = 50$ kPa. On the other hand, calcified plaques are modelled by increasing the Young's modulus of the lipid core (up to 1000 kPa). Regarding the severity, S , both mild (50 % area occlusion) and severe (75 % area occlusion) cases are considered. Table 4.2 summarises the six different configurations analysed. In particular, the case $E_c = 100$ kPa and $S = 75$ % defines the base model. Due to the significant distributions obtained in this analysis, additional investigations were performed. Specifically, the axial distributions of the non-zero components of the stress tensor as well as the axial and radial displacements were analysed in detail.

The second study is the effect of the positive remodelling on the axial distributions of stress and radial displacement. Therefore, a small variation of the stenotic geometry is introduced by considering two models with positive

Case	Stenosis severity, S	Young's modulus of lipid core, E_c
A	50 %	50 kPa
B	50 %	100 kPa
C	50 %	1000 kPa
D	75 %	50 kPa
E	75 %	100 kPa
F	75 %	1000 kPa

Table 4.2: Stenosis severity and Young's modulus of the lipid core, E_c , for each case considered. Case E corresponds to the base model.

remodelling of the artery wall in addition to the base model, as shown in figure 4.2.

The next parameter considered is the length of the lipid core. In Chapter 3, it was found that the stress distribution along the artery wall was mainly dependent on the material properties of the artery (the Young's modulus), and on the pressure distribution of the flow. In this case, a constant value for the mechanical properties of the wall is considered, $K = 600$ MPa, but the inclusion of the lipid core, which is made of a different material than that of the wall, means that the overall mechanical properties of the solid may change if the shape of the lipid core changes. Therefore, the length of the lipid core, L_c , is varied to analyse its influence on the stress distribution. Three cases are considered: a shorter lipid core, with $L_c = 0.5L$; the normal, base model, $L_c = 0.6L$; and a longer core, $L_c = 0.7L$. The variation of the lipid length is carried out keeping constant the stenosis length, L , the fibrous cap and outer wall thickness, as well as the fillet radius of the core, in order to perform a uniform parametric analysis with other variables unchanged. Specifically, even though the shape of the core changes, the geometry of the

flow domain is the same for all models. The three cases are represented in figure 4.6.

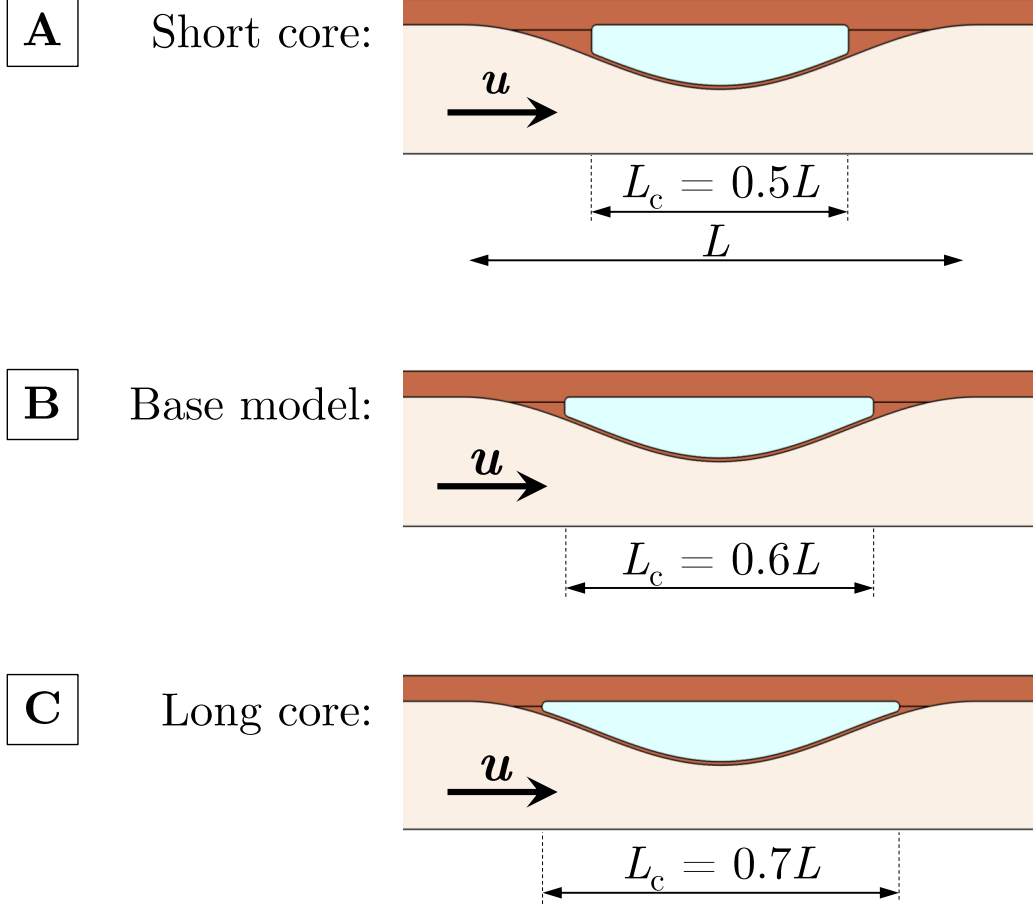


Fig. 4.6: Three configurations considered to analyse the influence of the lipid core length: (A) Short core, $L_c = 0.5L$; (B) base model, $L_c = 0.6L$; (C) Long core, $L_c = 0.7L$.

The last analysis takes into account three different values for the bulk modulus of the fibrous cap, K_{fc} : the same as the wall, $K_{fc} = K$; twice the value of the wall, corresponding to the base model, $K_{fc} = 2K$; and finally an order of magnitude stiffer, $K_{fc} = 10K$.

Finally, a justification for the use of a steady model throughout this chap-

ter is presented in Section 4.6.5; in particular, the axial distribution of first principal stress for the steady case is compared to the pulsatile configuration at four different instants during the period.

4.6 Results

4.6.1 Effect of severity and core stiffness

As in the previous chapter, a general picture of the flow solution and stresses obtained from the simulation is shown first in figure 4.7A. This gives a broad idea of the flow and stress configuration in the model. The colours of the fluid domain denote the axial component of the blood velocity, u , and the colours of the solid domain refer to the first principal stress, σ_1 , on the artery wall and the fibrous cap. On the other hand, the fluid pressure field is shown in figure 4.7B, which presents a pressure drop just downstream the constriction, as it was the case of the previous chapter.

The analysis starts by comparing the axial stress distribution along the interface of the artery wall and the flow domain for the cases considered in table 4.2. The results are shown in figure 4.8A. In all cases, the stress outside the stenosis region was at the same level, at around 120 kPa. This value effectively corresponds to the circumferential stress at the inner wall of a equivalent thick-walled cylinder loaded by internal pressure. Near $z = \pm D$, due to the intimal thickening of the artery at the beginning and at the end of the plaque (as shown in fig. 4.1), the stress decreased reaching a minimum shortly afterwards. Then, the largest differences in the stress distribution were observed due to the lipid core, which was delimited to the region $-0.6D < z < 0.6D$.

The results can be divided into two groups: first, the mild stenosis with

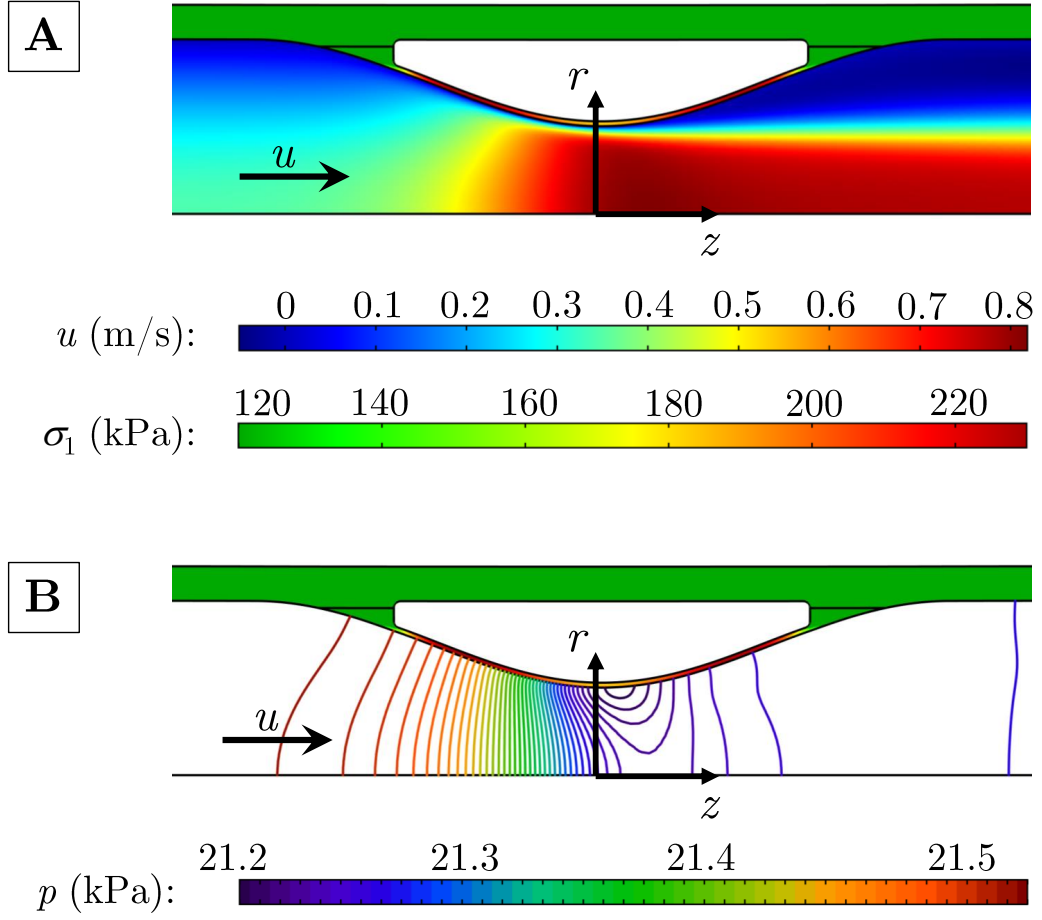


Fig. 4.7: (a) Flow velocity field, u , and first principal stress, σ_1 , distribution on the artery wall for a steady state simulation in the region around the stenosis. (b) Flow pressure field, p , and first principal stress, σ_1 .

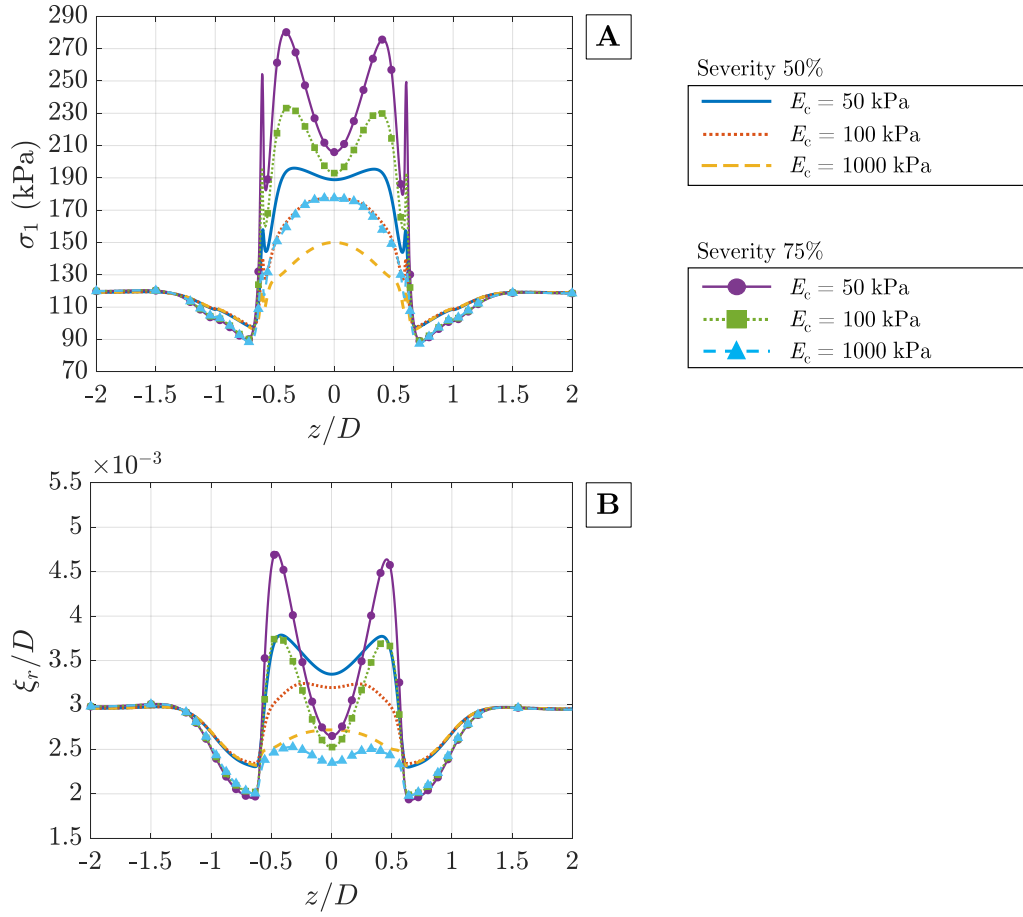


Fig. 4.8: Influence of stenosis severity and plaque composition on the axial distribution of (A) first principal stress, σ_1 , and (B) non-dimensional radial displacements, ξ_r/D . The variables were measured at the interface boundary between the flow field and the wall. Results are shown for all the cases presented in table 4.2.

the calcified core ($E_c = 100\text{-}1000\text{ kPa}$) along with the severe stenosis with the calcified core ($E_c = 1000\text{ kPa}$). Second, the mild stenosis with the lipid-filled core ($E_c = 50\text{ kPa}$) and the severe stenosis with the lipid-filled core ($E_c = 50\text{-}100\text{ kPa}$). For the first group, the stress distribution was relatively flat, with the maximum located in the middle region of the stenosis, at the section of maximum constriction, $z = 0$. For the second group, the first difference observed was that the stress level increased. The distribution also changed and was presented as two peaks, located in the middle of the upstream and downstream regions of the stenosis. The maximum stress for the base model ($S = 75\%$, $E_c = 100\text{ kPa}$) was 30 % higher than the maximum for the calcified plaque model. The variation was significant but it is important to note that the variation of the lipid core material properties was larger, since the Young's modulus decreased by an order of magnitude. For the softest core considered ($E_c = 50\text{ kPa}$) in the severe stenosis, the maximum stress was 280 kPa. This value got closer to the 300 kPa rupture threshold that has been usually mentioned in the literature [60].

The differences in stresses were reflected as well in the radial displacement distribution (figure 4.8B). Indeed, the two-peak distribution characteristic of the base case and the mild and lipid-filled plaque was present. On the other hand, the cases with stiffer (calcified) plaques showed a flatter curve.

In addition to the first principal stress, the shear stress was also examined to check if it was a limiting factor in the plaque rupture process. A graph showing all the non-zero components of the stress tensor for the base model is given in figure 4.9. In general, the circumferential stress, σ_ϕ , was the same as the first principal stress, σ_1 (that is, the first principal direction was mainly the circumferential one). The reader is referred to the Discussion section for a further analysis of this graph.

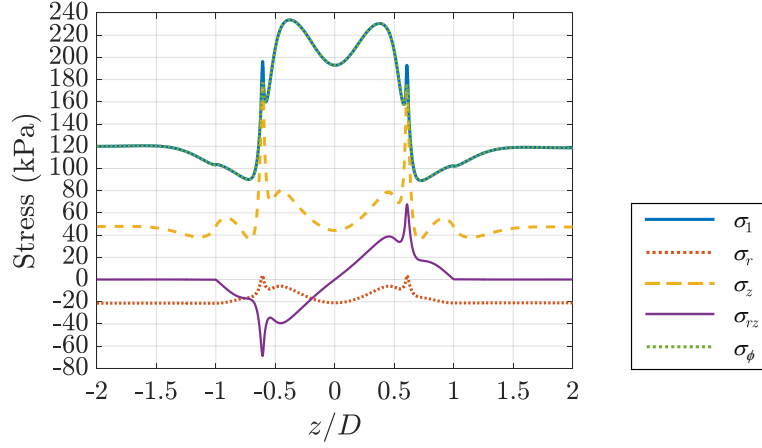


Fig. 4.9: Axial distribution of the components of the stress tensor for the base model (75 % stenosis, $E_c = 100$ kPa). σ_r , σ_ϕ and σ_z denote the radial, circumferential and axial components respectively; σ_{rz} the shear stress component; and σ_1 the first principal stress.

It was interesting also to analyse the axial displacements of the wall, ξ_z , in relation to the radial displacements, ξ_r , as they are expected to be influenced by the fluid pressure as well, but in a different way. This was tested by comparing the curves of the non-dimensional displacements for the base model, and it was found that the axial component was relatively small compared to the radial one, as shown in figure 4.10A. In particular, the maximum of the radial displacement was around 2.6 times larger than the axial one. The shape of the axial displacements curve is due to the deformation created by the fluid pressure on the wall [87], which leads to a positive peak upstream and a negative one downstream the constriction. On the other hand, the wall shear stresses did not seem to impact the displacement field; as shown in Chapter 3, the wall shear stresses were around three orders of magnitude smaller than the pressure field. In addition, the maximum radial and axial displacements are found at the same location. This kind of deformation also

showed a good agreement with the experimental results reported by Choi et al. [152], who studied a pulsatile flow condition. It should be noted as well that these values are relatively small for the material properties considered in this model, with a maximum axial displacement just shy of $1.5 \times 10^{-3}D$. For an clearer representation of the wall displacements, both the deformed and undeformed geometries of the interface wall along the stenosis are shown in figure 4.10B; in this case, the axial component has been scaled in order to make it visible in the figure.

In summary, three different locations were identified in the axial direction that could become sites of rupture. For the most vulnerable plaques ($S = 50\%$, $E_c = 50$ kPa, and $S = 75\%$, $E_c = 50$ -100 kPa), the stress peaks were located approximately at the middle of the upstream and downstream regions of the stenosis respectively. For the other plaques ($S = 50\%$, $E_c = 100$ -1000 kPa, and $S = 75\%$, $E_c = 1000$ kPa), the maximum of the stress peak was close to the minimum lumen section. Finally, all cases presented a local maximum at the beginning of the lipid core region, which will be discussed further in the Discussion section. Hence, depending on the lipid composition and the stenosis severity, the rupture site could be located at three different positions.

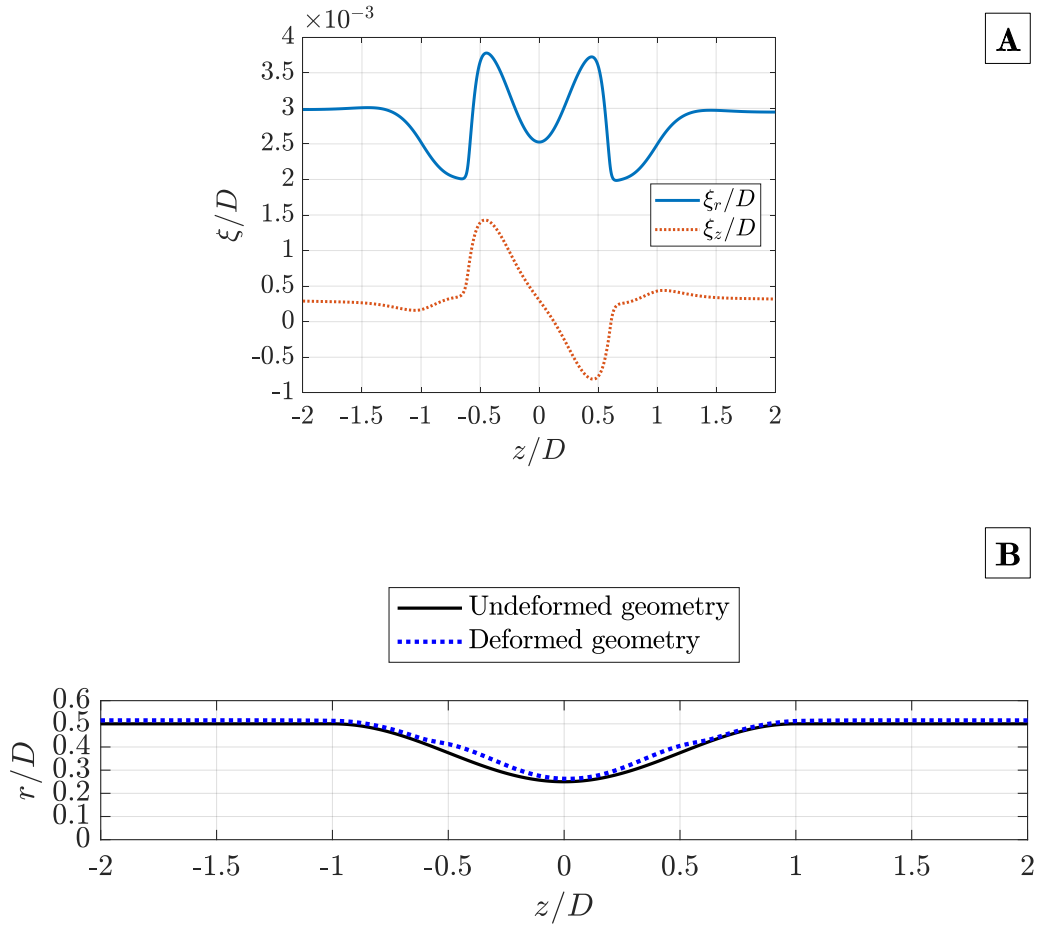


Fig. 4.10: (A) Non-dimensional form of the axial, ξ_z/D , and radial, ξ_r/D , displacements of the wall for the baseline case. (B) Deformed and undeformed shapes of the inner wall along the stenosis region.

4.6.2 Effect of the positive remodelling

Two models with positive remodelling, along with the base model, were compared by studying the axial distribution of the first principal stress, which is presented in figure 4.11A. The first thing to note is a 15 % increment of the maximum stress in the fibrous cap for the 25 %-stenotic case compared to the non-stenotic one. On the other hand, the non-stenotic case presented similar stress levels in relation to the base model. Hence, the only effect of the stenosis severity seemed to be the change of the stress distribution, i.e. presenting the two peaks rather than a flat curve.

The radial displacements showed similar results (figure 4.11B). The two curves of the positive remodelling cases kept the same shape, showing a constant deformation along the fibrous cap. On the contrary, the base model reflected the shape of the stenosis, and the radial displacements presented a distribution similar to that of the first principal stress.

4.6.3 Effect of the lipid core length

Three different lengths of the lipid core were considered. As shown in figure 4.12A, the axial stress distributions were relatively different for each case. Due to the length of the lipid core, the peak stresses were located closer to the centre ($z = 0$) in the shorter core case. In addition, a shorter lipid core increased both the local and the absolute peaks, while also affecting the gradients. These results suggest that shorter lipid cores could be more dangerous than plaques with longer cores, for the same thickness of the fibrous cap. This is also interesting because it may seem counter-intuitive: one may expect that a plaque with a larger, longer lipid core might be more vulnerable than a plaque with a shorter core. However, it was observed that a shorter

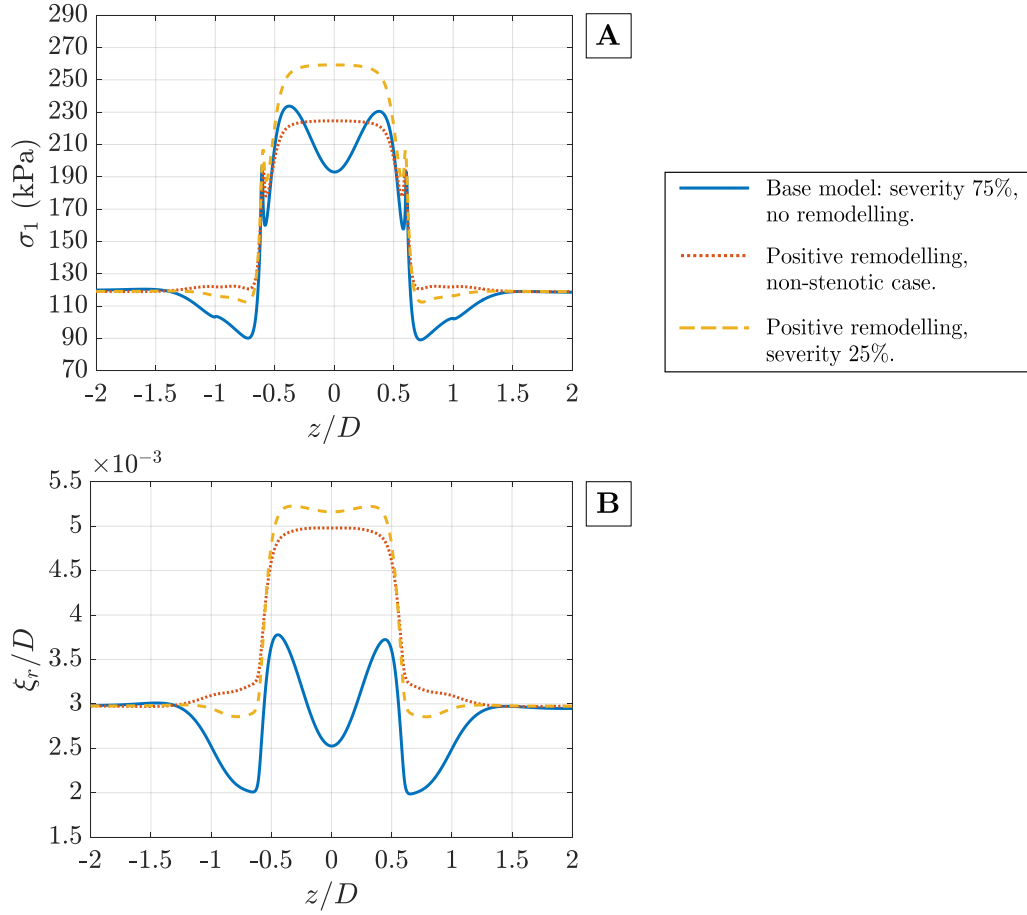


Fig. 4.11: Influence of the positive remodelling on the axial distribution of (A) first principal stress, σ_1 , and (B) non-dimensional radial displacements, ξ_r/D . The variables were measured at the interface boundary between the flow field and the wall.

core with a significant change of wall thickness (larger than the equivalent for longer lipid cores) may present larger levels of stress, and thus the plaque might present a higher risk of rupture.

The radial displacements, as shown in figure 4.12B, presented a similar behaviour. Both the minima and maxima of the curves increased for the shortest lipid core.

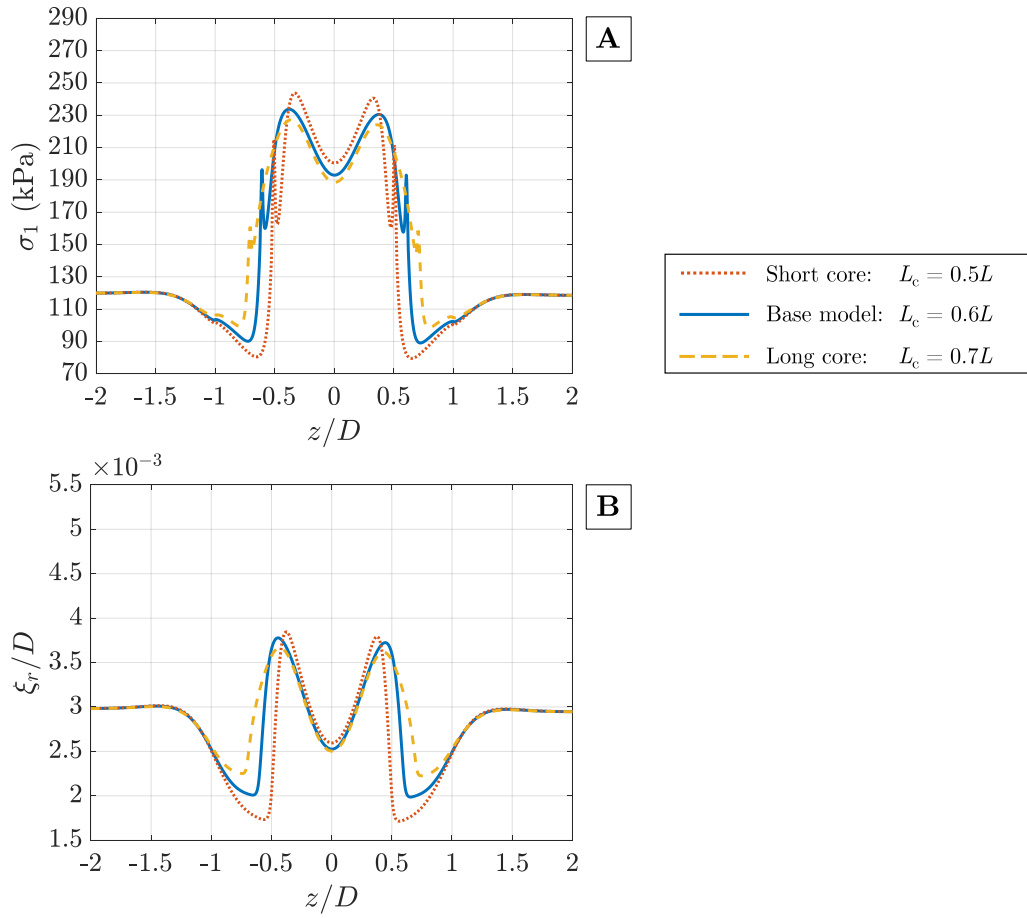


Fig. 4.12: Influence of the lipid core length on the axial distribution of (a) first principal stress and (b) radial displacements. Magnitudes measured at the interface boundary between the flow field and the wall.

4.6.4 Effect of the cap stiffening

The axial stress distribution for the different values of cap stiffness considered is shown in figure 4.13. As it can be seen in the figure, decreasing the cap stiffness to half the base value, or increasing it to 10 times the stiffness of the artery wall had negligible effect on the stress. The same result was observed regarding the radial displacement along the plaque.

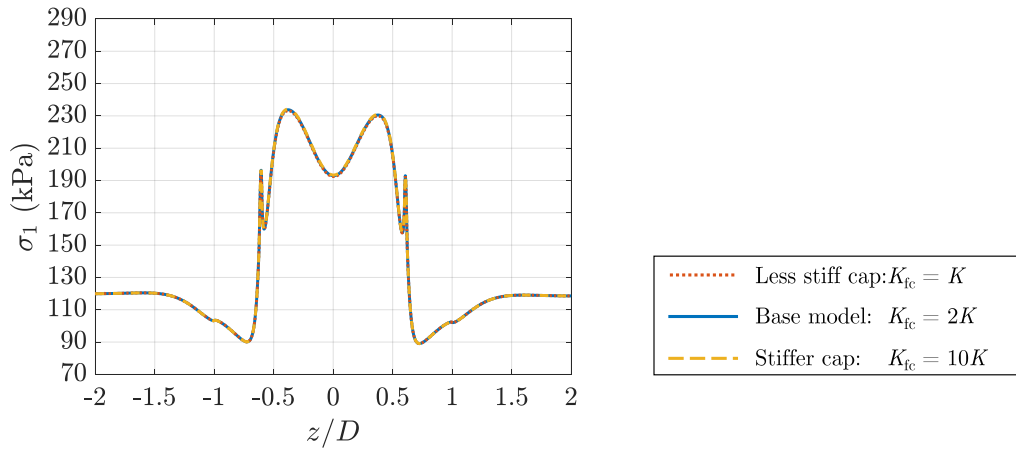


Fig. 4.13: Influence of the cap stiffening on the axial distribution of first principal stresses. Magnitudes measured at the interface boundary between the flow field and the wall.

In summary, each parametric analysis showed different effects on the stress distribution. Over physiologically relevant ranges, the plaque composition and the positive remodelling of the artery were found to be the most important parameters, as they had the largest effect on the absolute peak values, while also changing the axial distribution along the fibrous cap. Specifically, a decrease of the stiffness of the core increased the peak stress by a 20 % with respect to the baseline case, whereas the mild stenotic model with positive remodelling gave rise to an 11 % increase. On the other hand, the length of the lipid core had a smaller impact on the maximum stresses,

but it significantly affected the local maxima. In particular, the local stress peaks increased by a 10 % when the core length decreased. Finally, the stiffening of the fibrous cap did not impact the stress distribution by more than a 1 % for the range of values considered in this work.

4.6.5 Justification of the steady model

Before proceeding with the discussion of the results, a justification for the use of a steady flow instead of a pulsatile one is presented. When the heart beats, the contraction during the systole creates a pressure wave that travels along the arterial tree. The velocity of propagation of these pressure waves is the pulse wave velocity [153]. According to Pereira et al., the pulse wave velocity in the carotid artery is in the range of 3 to 12 m/s. Therefore, considering that the heart typically beats once a second, the minimum wavelength is 3 m, or approximately $428D$. On the other hand, the domain length is $14D$. Since the pressure wavelength is more than 30 times larger than the domain length, the local non-stationary effects on the wall could be neglected.

This assumption was tested by performing a test simulation of a pulsatile inflow case, with a 1-second period. One limitation however was that no turbulence model was considered, even though some unstable effects may appear due to the higher Reynolds at certain times during the period [24]. Still, the main goal of this test was to focus on the effect of the instantaneous hydrostatic pressure on the stress distributions. Specifically, the significant changes of the pressure values during the period (up to a 50 % from the average values) led to similar changes of the stress levels, but the distribution was essentially the same. This is shown in the axial stress distribution for different times during the period T depicted in figure 4.14A.

In addition, the pulsatile case was compared to the steady case at the

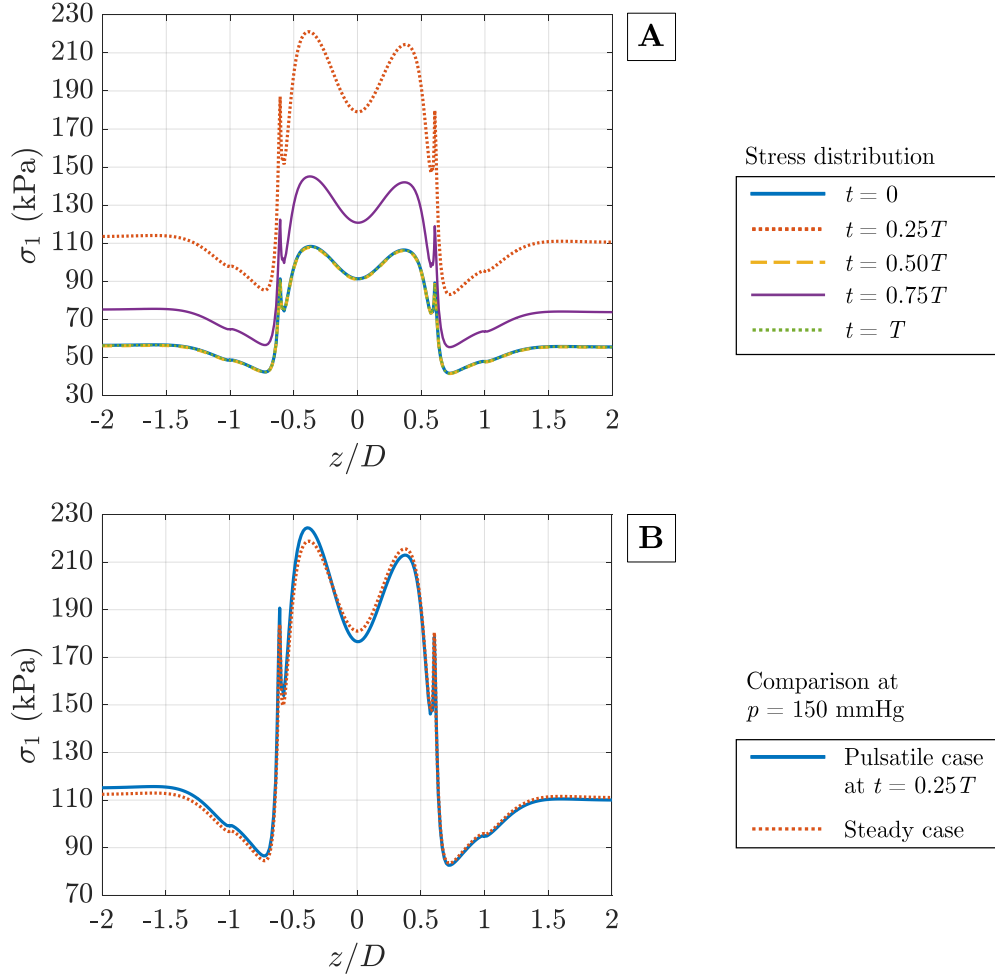


Fig. 4.14: (A) Axial distribution of the first principal stress, σ_1 for different times during the period T for the pulsatile simulation; $t = 0.25T$ corresponds to the systole (highest pressure). (B) Comparison between the steady case and the pulsatile case at $t = 0.25T$, which corresponds to the same pressure value, 150 mmHg

same pressure level. Specifically, the steady case was run by setting the outlet pressure value to 150 mmHg (approx. 20 kPa), which corresponded to the maximum pressure for the pulsatile case, at $t = 0.25T$. The axial distribution of the first principal stress for both models is shown in 4.14B. It was observed that the distribution of the pulsatile case presented some asymmetry with respect to the coordinate $z = 0$; in particular, the upstream maximum increased and the downstream one decreased with regards to the stress maxima of the steady case. However, the overall shape of the curve was very similar, showing the local peaks at the ends of the lipid core, and the two global stress maxima at the midpoints of the upstream and downstream regions of the stenosis.

This pattern repeated over the following periods. Indeed, the peak value of the stress distributions at the same time for different periods did not change significantly; it stayed constant and varied less than a 0.01 %. Therefore, a steady inflow with a high systolic pressure value was used in order to model the most critical conditions during the period. As stated in Section 4.3.1, $p_{\text{out}} = 160 \text{ mmHg}$ was used, taken into account any potential adverse conditions due to high blood pressure, which has been associated with atherosclerosis [1].

4.7 Discussion

The combined analysis of the stenosis severity and plaque composition shows that both effects should be considered simultaneously. Significant differences in the stress levels are observed for both severe and mild stenoses, depending on the stiffness of the lipid core. Indeed, plaque rupture is considered to be more dependent on the plaque composition rather than stenosis severity

[3], as the stress along the fibrous cap increases when the lipid stiffness is lowered.

As expected, the stress distribution of this model is significantly different to the one observed for the thin-wall simulations (Chapter 3), due mainly to the new solid geometry that now includes the lipid core and the fibrous cap. In order to explain this new stress distribution, the fluid pressure along the axial direction should be taken into account, as the pressure is the main contributor to the loading of the wall. This was something that was already observed in the previous chapter regarding the thin-wall simulations. In particular, the pressure was barely affected by large variations of the material properties of the wall. The same applies to the material of the lipid core, especially since the stiffness of the wall and the stiffness of the fibrous cap were kept constant. Therefore, the pressure did not depend on the lipid core elasticity and it was only affected by the stenosis severity. Indeed, a pressure drop of ~ 300 Pa (equivalent to a 1.4 % of the total pressure) was found for the 75 % occlusion, while that value decreased to around 80 Pa for the 50 % severity stenosis. Taking a closer look at the stress plot in figure 4.8A, there was a slight difference in the peak stress before and after the minimum lumen section for the severe stenosis cases. This small change was approximately of 1.5 %, which could be associated with this pressure drop along the plaque, as shown in figure 4.7B.

The novelty of this work is related to the effect of stenosis severity and lipid core stiffness on the stress curve, which varies from a flat shape to a two-peak distribution. A similar change was reported by Belzacq et al. [87], when varying the plaque length (rather than the lipid composition), so they reported it as a ‘pinching effect’. Since a constant plaque length was used, the change in the stress distribution is related to the lipid core

stiffness, which was kept constant in their study. This result implies that the change of the lipid composition may impact the stress values significantly, but only when the change of stiffness is large enough. Small increases of the Young's modulus of the lipid core do not produce a noticeable effect on the stress peaks, which is in agreement with previously published results [78, 89], but changing the Young's modulus by an order of magnitude has noticeable effects on the stress.

It is worth mentioning about the local peaks of stress at the beginning and at the end of the lipid core region ($z \simeq \pm 0.6D$, figure 4.8A). These peaks are largely influenced by the chosen shape of the lipid core ends. This was found by considering a different shape of the lipid core, that showed no concentration of stress when the ends were sharper (figure 4.15). The sudden change of thickness of the wall sustaining the loading (from the thickened wall to the fibrous cap with a lipid core), leads to this local change of the stress. It has been suggested that sometimes the rupture occurs at points of local stress concentrations, but not at the absolute maximum stress location [154]. These local maxima could indicate one of those plaque rupture sites. The local maxima occur at the ends of the plaque while the global maxima occur closer to the middle. This could also help to explain, from a mechanical point of view, why the axial rupture location has not been precisely defined, as reported by Falk [3].

Several points should be noted regarding figure 4.9, which shows the first principal stress alongside the components of the stress tensor: (1) the shear components of the stress tensor $\sigma_{r\phi}$ and $\sigma_{\phi z}$ were equal to zero (due to the axisymmetry). (2) The remaining component σ_{rz} was zero outside the stenosis region, but it presented two peaks of 70 kPa at $z = \pm 0.6D$, corresponding to the ends of the lipid core. (3) The circumferential component, σ_ϕ , matched

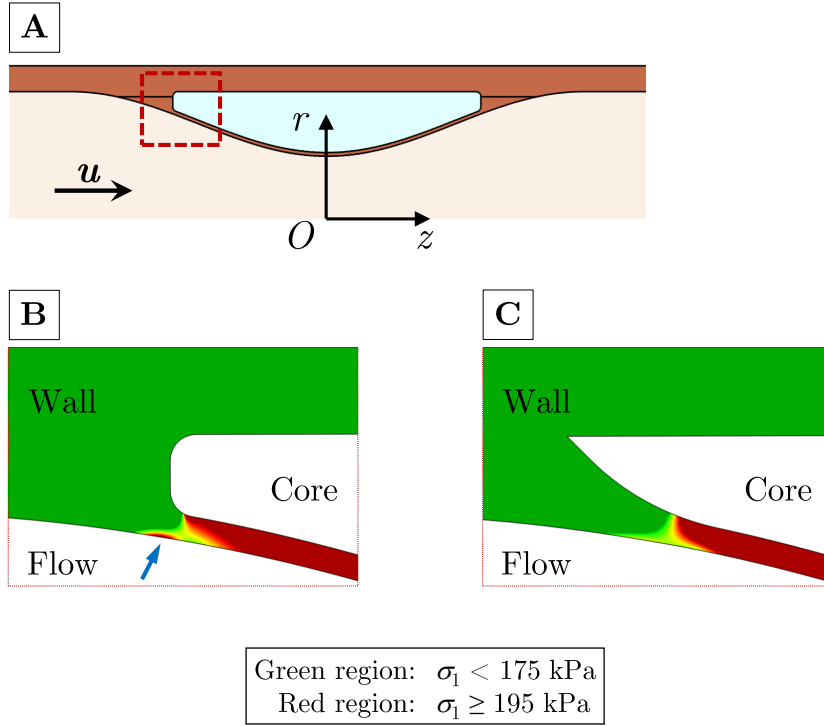


Fig. 4.15: (A) General picture showing the location of the zoomed-in sections. (B) First principal stress along the wall for a lipid core with rounded ends; the arrow points to the location of the local maximum. (C) First principal stress along the wall for a lipid core with sharp ends; the local maximum is not present.

the first principal stress distribution, σ_1 , almost perfectly, except at the lipid core ends ($z = \pm 0.6D$). At these locations, the axial component, σ_z , seemed to be as important as the circumferential component stress. (4) According to the Tresca criterion, the shear strength of an isotropic material is half the tensile yield strength. The results show that the shear stress magnitude was always smaller than half the first principal stress. It was concluded that, although significant at $z = \pm 0.6D$, the shear stress seemed to not be the main contributor to the plaque rupture process.

The positive remodelling study showed some interesting results. As shown in figure 4.11, the average stress levels in the stenosis region are similar between the base model and the non-stenotic positive remodelling case. There is, however, a change in the stress distribution, which could eventually lead to different rupture sites. This change in stress distribution is attributed to the difference in the fluid pressure distribution. Indeed, the stenotic case presents a sudden pressure drop due to the constriction, which affects the stress distribution accordingly. A combination of a positive remodelling effect and a mild stenosis (the 25 % case in the same analysis) has a great effect on the overall stress in the fibrous cap. The peak stress increases by 11 % in the mild stenotic case compared to the base model, reaching a maximum of 259 kPa. This magnitude is also closer to the 300 kPa rupture threshold [60], something that is related as well to the larger lipid core of the mild stenosis case, which can significantly affect the peak stress [74].

It should be noted that although the 75 %-stenotic case and the non-stenotic model with positive remodelling share similar stress levels (with a different distribution), their radial displacement values are different (fig. 4.11B). Two factors could explain this result: first, due to the larger constriction at $z = 0$, the fluid pressure for the 75 %-stenotic case is lower than the

models with positive remodelling, therefore affecting the radial displacement; second, the severe stenotic geometry may be less prone to radial deformation. In particular, the 75 %-stenotic case is deformed in both the radial and axial directions due to the shape of the wall, while the positive remodelling cases are mainly deformed in the radial direction only.

The results from the analysis of the lipid core length showed that, interestingly, the highest stress peaks are found for the shortest core (figure 4.12). Since the lipid length was varied at constant thickness of the fibrous cap and outer wall, the shortest plaque case is subjected to the minimum stress outside the lipid region, where the wall is thickest. This thickness change at the beginning of the fibrous cap creates a sudden increase of the stress levels, and thus the local maxima are also remarkably higher than in the other cases (17-31 %). Interestingly, even though the lipid core thickness at $z = 0$ is the same for the three cases, the stress is not. Therefore, not only the thickness of the lipid core is important to the stress levels (something already reported by Ohayon et al. [74]), but also the axial shape.

The axial distribution of stress resembles that of the plaque composition analysis as shown in figure 4.8. Two peaks appear at the middle of the upstream and downstream regions of the stenosis, and smaller, local peaks at the beginning and end of the lipid core region. Two possible sites of rupture are identified: the first one related to the global maxima in the stress distribution, and others at the beginning and end of the lipid region. The latter should be especially important in longitudinally short plaques presenting a significant change of wall thickness.

The influence of the lipid core size was studied by Tang et al. [88], but a direct comparison cannot be made as in their study the fibrous cap thickness was variable and that has a great impact on the stress values. Indeed, the

stress levels decreased for a smaller lipid pool, but the cap thickness was larger than their baseline model. On the other hand, it is interesting to compare the current results to the ones obtained by Cilla et al. [149]. They performed a parametric variation of the lipid core length, and analysed the peak stress at the minimum lumen section, where the cap thickness was constant. They reported that the stress remained approximately constant (varying less than 10 kPa). In the current simulations, a significant variation of stress distribution was found when varying the lipid core length, but at $z = 0$ (minimum lumen section) the value stayed relatively constant for the three cases considered, within the 10 kPa range (figure 4.12). Hence, the results here are in agreement with those by Cilla et al. [149] at $z = 0$. However, the whole axial distribution has been analysed here, and it was observed that the stress maxima and distributions vary significantly with the core length.

It should be noted that the effect of the lipid length is less than that due to the change of lipid stiffness and stenosis severity. Indeed, when varying the lipid stiffness, a 20 % increase of the maximum stress value was observed with respect to the base model. When analysing the effect of the lipid length, the maximum stress increases only by a 4.3 %. On the other hand, the local maxima are more affected by the lipid core length: the shortest lipid presents a local peak that is 34 % larger than the longest one.

No significant differences in the stress distribution were observed when varying the fibrous cap stiffness. Some authors have reported that the fibrous cap stiffness is 2-5 times larger than that of the healthy artery wall [99]. The current results imply that, for the material properties and geometry considered in this analysis, the stiffening of the fibrous cap does not influence the stress distribution noticeably. This behaviour could be explained by

comparing the current geometry with a thin-walled pressurised tube. In that case, the circumferential stress does not depend on the material properties of the wall, so that could explain why the change of stiffness of the fibrous cap does not change the stress levels. Therefore, the effect of the plaque composition along with the stenosis severity as well as the lipid core length are considered more crucial factors when analysing possible sites of rupture.

4.8 Conclusions and further developments

Numerical simulations of incompressible, steady flow through an axisymmetric stenosed artery have been performed to systematically vary the mechanical parameters in the plaque and analyse the effects of the axial distribution of stresses. This follows the thin-wall simulations presented in the previous chapter, but introducing new features such as the modelling of the lipid core and the fibrous cap. In particular, the following parameters were investigated: the stenosis severity, the lipid core stiffness, the positive remodelling of the artery, the lipid core length and the fibrous cap stiffness. The goal was to analyse the importance of these parameters on the axial distributions of stress, and to identify possible rupture locations in the axial direction.

It was found that the degree of stenosis and the lipid core stiffness, along with the positive remodelling, had the largest effect on the peak values. The stress distribution also changed significantly, especially with the lipid core stiffness, from a one-peak curve (for calcified cores) to a two-peak curve (for lipid-filled plaques). In addition, shorter lipid cores with a significant change of wall thickness (larger than the equivalent for longer lipid cores) resulted in higher maximum stresses, both absolute and local. On the contrary, varying the stiffness of the fibrous cap did not influence the axial distributions.

From these results, potential sites of plaque rupture were identified for each case: the midpoints of the upstream and downstream regions of the stenosis (for severe, lipid-filled plaques), the ends of the lipid core (for longitudinally short cores), and the middle of the stenosis (for mild stenoses with positive remodelling).

As a logical next step, three-dimensional simulations would allow to incorporate the effects of multi-directional flow and eccentric plaques. They would also make it possible to compare the current two-dimensional results to the three-dimensional cases, and then evaluate how useful these first two-dimensional models are when modelling more complex geometries.

Chapter 5

Three-dimensional plaque simulations

5.1 Introduction

So far, potential sites of plaque rupture have been investigated by following an axisymmetric approach. In particular, a stenotic geometry with a thin, elastic wall was studied first (Chapter 3), and was later refined with the introduction of the plaque modelling (Chapter 4). The severity of the stenosis, the stiffness of the lipid core, the presence of positive remodelling and the axial length of the core were factors that could significantly affect the stress distributions on the plaque.

The next step presented here is the three-dimensional model of the geometry, considering that the plaque may not be axisymmetric. Richardson et al. observed that the majority of the plaques they studied presented some kind of eccentricity [58], i.e. the lipid core was located just around one part of the artery, not covering the whole lumen. In order to visualise this, it is useful to recover a figure from Chapter 1. It is shown again here for sim-

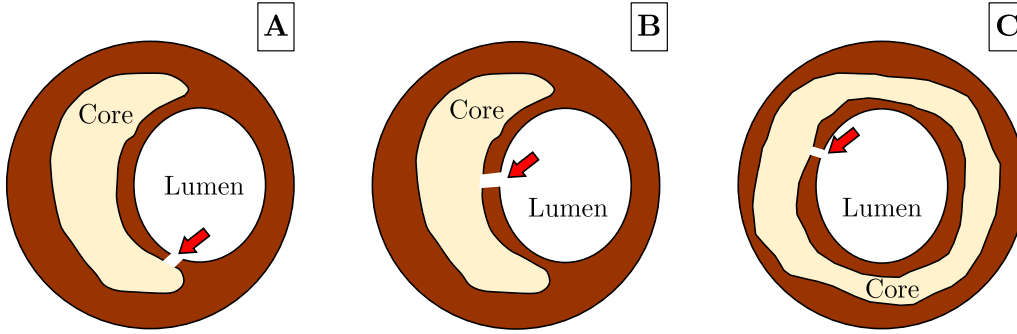


Fig. 5.1: Cross-section diagrams of an atherosclerotic artery. The red arrow denotes the rupture site. (A) Rupture of an eccentric plaque at the junction of the cap with the adjacent layer of the artery; (B) rupture of an eccentric plaque through the centre of the cap; (C) rupture of a concentric plaque.

plicity, in figure 5.1. The model presented in this chapter corresponds to the idealisation of the plaques shown in figures 5.1A and B.

Therefore, the main objective is to shed some light on the axial location of plaque rupture in a three-dimensional, asymmetric geometry. Another goal is to provide some insights that may explain why it is not easy to predict the position of a rupture (which might happen upstream the stenosis [70, 71], but also downstream or at the maximum constriction section [3]), and what can be studied in order to identify plaques that could be vulnerable. The following hypothesis will be tested: the most likely axial location of plaque rupture in an idealised carotid artery is affected by similar features to those that affect the axisymmetric models. These features were presented in Chapter 4: the positive remodelling, the length of the core and the lipid core stiffness. In order to investigate this, the results corresponding to the eccentric plaque will be compared with those of the axisymmetric case.

Following the study performed in Chapter 4, a fluid-structure interaction model is constructed, and the geometric and physical parameters of this

model are varied. The study is focused on the effect of different features on the stress distributions that are related to plaque rupture. As in the case of the previous chapter, it is worth mentioning that previously published results linked high plaque stresses with sites of plaque rupture in carotid arteries [105, 108, 141], and in coronary arteries [146, 147].

In particular, three different eccentric geometries are compared, along with two axisymmetric stenosis models. The effects of the stiffness and the length of the lipid core are also analysed, similarly to the study performed in the previous chapter. Again, the artery wall is modelled as a hyperelastic solid, while the lipid core is considered as a linear elastic material. On the other hand, the blood flow is considered as a Newtonian, incompressible fluid and it is described by the continuity and the Navier-Stokes equations. This simplified configuration makes it easier to identify critical parameters that affect the location of plaque rupture by studying the stress distributions. The findings in this geometry are easier to generalise and, therefore, this could potentially be useful in order to assess the rupture process in more complex, patient-specific cases.

5.2 Geometry

The geometry considered in this chapter is a three-dimensional eccentric carotid stenosis with circular cross-sections for the lumen and the artery wall. The origin of the coordinate system, O , is located at the intersection of the centre-line of the inlet flow with the cross-section at the throat. The coordinates x and y define the position in the cross-section, while z denotes the axial direction. $y = 0$ is considered as a plane of symmetry, and is represented in figure 5.2A.

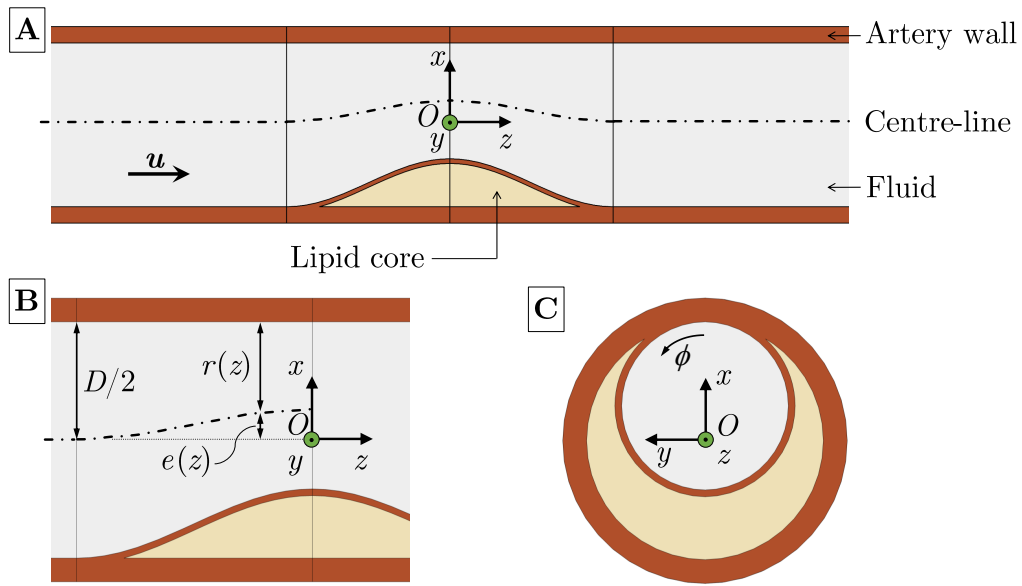


Fig. 5.2: (A) Representation of the geometry at the plane of symmetry $y = 0$. (B) Detail of the stenosis region at the plane of symmetry: $r(z)$ denotes the lumen radius, while $e(z)$ defines the centre-line of the flow domain. (C) Cross-sectional shape of the lipid core at $z = 0$. The origin of the coordinate system, O , is located at the maximum constriction section.

The contour of the lipid core follows the shape of the lumen along the stenosis. The portion of the artery that lies between the lipid core and the lumen is the fibrous cap. The thickness of this cap, t_{fc} , is modelled as constant along the plaque and equal to 200 μm , which is in the typical range of thickness for thin fibrous caps [100]. A cross-sectional representation of the shape of the core is shown in figure 5.2C.

The inlet diameter D is used as the reference length unit, and it is set to $D = 7\text{ mm}$, based on averaged values of a human carotid artery [23, 38, 97, 120, 138]. In terms of this variable, the aforementioned thickness of the fibrous cap is then $t_{fc} = 0.028D$. Outside the stenosis region, the geometry of the model is the same as in the axisymmetric case studied in the previous chapter, where the wall thickness is constant along the axial direction and equal to $D/10$. The positions of the inlet and outlet sections are $z = -4D$ and $z = 4D$ respectively.

The lumen radius, $r(z)$, is defined in the same way as in the previous chapters. Specifically, $r(z) = D/2$ outside the stenosis region, whereas for $-D \leq z \leq D$ the lumen radius is described by

$$r(z) = \frac{D}{2} \left\{ 1 - \frac{1-\gamma}{2} \left[1 + \cos \left(\frac{2\pi z}{L} \right) \right] \right\}, \quad (5.1)$$

where $L = 2D$ is the length of the stenosis and $\gamma = D_{\min}/D$ is the diameter ratio. The stenosis severity, S , is defined as

$$S = \frac{\text{Inlet area} - \text{min. area}}{\text{Inlet area}} = 1 - \left(\frac{D_{\min}}{D} \right)^2 = 1 - \gamma^2, \quad (5.2)$$

and in this case $S = 50\% = 0.5$ in order to facilitate the comparison to the axisymmetric models, as it will be explained later. Therefore, the diameter ratio is set to $\gamma = 1/\sqrt{2} \simeq 0.7071$.

Similarly to the work performed by Samulesson et al. [29], the eccentricity e of the stenosis is defined by introducing an offset of the geometry of the

artery wall in the vertical direction x . Alternatively, the function e describes the centre-line of the fluid domain, as shown in figure 5.2B. Therefore, the expression that defines the x and y coordinates of the lumen may be rewritten in terms of the lumen radius, r , and the eccentricity, e :

$$x(z) = r \cos \phi + e, \quad (5.3)$$

$$y(z) = r \sin \phi, \quad (5.4)$$

where r is given by the expression 5.1 and $\phi = \arctan[y/(x - e)]$ denotes the angle in the circumferential direction. The eccentricity is $e = 0$ outside the stenosis region. For $-D \leq z \leq D$, it is described by a sinusoidal function such as

$$e(z) = \frac{D}{2} e_0 \left[1 + \cos \left(\frac{2\pi z}{L} \right) \right]. \quad (5.5)$$

The value e_0 is set to $e_0 = (1 - \gamma)/2$, so the top edge of the geometry at the plane of symmetry ($y = \phi = 0$) remains undeformed, and only the bottom edge ($y = 0, \phi = \pi$) defines the stenosis shape. Therefore, the equations that describe those edges are:

$$x(\phi = 0) = x_{\text{top}}(z) = D/2, \quad (5.6)$$

$$x(\phi = \pi) = x_{\text{bot}}(z) = -r + e. \quad (5.7)$$

Some variants of this geometry are considered as well and included in a parametric analysis. In particular, three additional models are studied: (1) a three-dimensional, eccentric geometry similar to the original one, but with a modification that introduces a small chamfer (of size similar to that of the fibrous cap) at the ends of the lipid core in the axial and in the cross-sectional directions; (2) another three-dimensional, eccentric model that includes the positive remodelling of the artery, and thus a larger lipid core; (3) a two-dimensional, axisymmetric stenosis with a concentric lipid core. This last

model serves as a base comparison to validate the results against a simpler geometry.

Considering the same severity as in the three-dimensional cases (50 % in area occlusion), the wall shape of the axisymmetric model is slightly different. In particular, the plaque is smoother. For this reason, a higher stenosis value (75 %) is also considered, in order to impose the same shape of the wall as in the eccentric models. The geometries at the planes of symmetry for all five models considered in the analysis are shown in figure 5.3, along with the corresponding cross-sections.

5.3 Models and boundary conditions

5.3.1 Flow field

The same model for the blood flow as the one presented in Chapters 3 and 4 is used here. A summary is given in the following.

The governing equations are the ones shown in section 2.4. In particular, the conservation of mass and the conservation of momentum for Newtonian, incompressible fluids:

$$\nabla \cdot \mathbf{u} = 0, \quad (5.8)$$

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \mu \nabla^2 \mathbf{u}. \quad (5.9)$$

The flow parameters are unchanged from the previous chapter: density $\rho = 1000 \text{ kg/m}^3$, dynamic viscosity $\mu = 4 \times 10^{-3} \text{ Pa} \cdot \text{s}$, based on previous works [50, 139–141], and Reynolds number $Re = \rho U D / \mu = 300$, a physiologically representative magnitude [12, 97]. In addition, the flow is considered to be Newtonian.

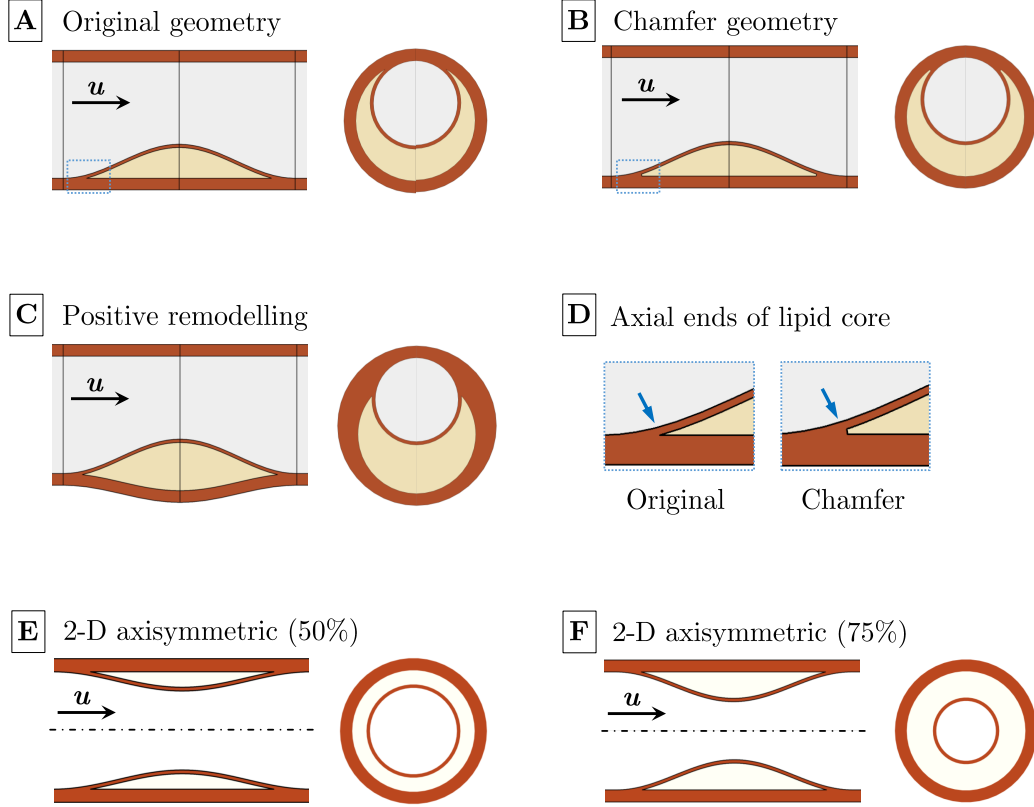


Fig. 5.3: Geometry at the plane of symmetry and cross-section at $z = 0$ for the models considered: (A) Original eccentric geometry; (B) eccentric geometry with chamfer at the ends of the lipid core; (C) eccentric geometry with positive remodelling of the artery wall; (D) comparison between the axial ends of the lipid core for the original and chamfer geometries (zoomed-in section); (E) two-dimensional axisymmetric model (50 % stenosis); (F) two-dimensional axisymmetric model (75 % stenosis); the severity is higher in this last case, but the shape of the wall is the same as the bottom edge of the eccentric models.

The boundary condition at the inlet cross-section of the flow domain is the same as in Chapter 4, but applied now in a three-dimensional setting. Specifically, a parabolic velocity profile in the axial direction, $\mathbf{u}_{\text{in}} = (0, 0, w_{\text{in}})$, is prescribed at the inlet:

$$w_{\text{in}}(x, y) = 2U \left[1 - 4 \left(\frac{\sqrt{x^2 + y^2}}{D} \right)^2 \right], \quad (5.10)$$

where U denotes the cross-sectional mean velocity at the inlet section and is given by the *Re*. The justification for the use of a steady flow rather a pulsatile one is the same as the one explained at the beginning of Section 4.7, Chapter 4 (the local, non-stationary effects on the wall could be neglected since the pressure wavelength is more than 30 times larger than the domain length). Again, as in Chapter 4, the outflow pressure condition is imposed at the outlet by setting $p_{\text{out}} = 160 \text{ mmHg} = 21.33 \text{ kPa}$, using the same values as in former studies [90].

5.3.2 Artery wall and lipid core

The artery wall and lipid core models of this chapter are the same as those used in the previous axisymmetric analysis. Therefore, a neo-Hookean, non-linear, hyperelastic model is chosen to describe the artery wall. The strain-energy density function, W , corresponding to the vessel is then:

$$W = \frac{1}{2} [G (I_1 - 3) + K (J_{\text{el}} - 1)^2], \quad (5.11)$$

where G denotes the shear modulus, I_1 is the first invariant of the isochoric part of the elastic right Cauchy-Green deformation tensor, K refers to the bulk modulus and J_{el} denotes the elastic volume ratio. The mechanical properties are $G = 6 \text{ MPa}$ and $K = 600 \text{ MPa}$, in accordance with previous works [90]. The density is set to $\rho_w = 900 \text{ kg/m}^3$.

The lipid core, on the other hand, is modelled as an isotropic, linear elastic material that is less stiff than the artery wall. The Young's modulus of the base model is set to $E_c = 100$ kPa, in order to keep it around a hundred times smaller than the equivalent Young's modulus of the wall [89]. The Poisson's ratio is set to $\nu_c = 0.49$, corresponding to a nearly incompressible material [60, 73], and the density is $\rho_c = 900$ kg/m³.

The boundary conditions are also the same as the ones used in the two-dimensional models. Specifically, the displacement of the artery wall, $\boldsymbol{\xi}$, is constrained at the inlet ($\boldsymbol{\xi} = \mathbf{0}$). On the contrary, at the outlet, only the axial displacement is constrained ($\xi_z = 0$). It should be noted that the domain lengths were varied to ensure that the boundary conditions did not affect the stress distributions along the stenosis region.

5.3.3 Matching conditions

In order to close the coupled system (flow and solid fields), matching conditions are required at the interface between the solid and the fluid. First, the velocity continuity, which means that the flow velocity must be equal to the velocity of the vessel wall:

$$\mathbf{u} = \frac{\partial \boldsymbol{\xi}}{\partial t}, \quad (5.12)$$

and then the stress continuity, so that the stresses on the wall are equal to those of the fluid along the interface, but opposite in the outward normal direction:

$$\mathbf{f} = \mathbf{n} \cdot \left[-p\mathbf{I} + \mu (\nabla \mathbf{u} + \nabla \mathbf{u}^T) - \frac{2}{3}\mu (\nabla \cdot \mathbf{u}) \mathbf{I} \right], \quad (5.13)$$

where $\mathbf{n}$ denotes the outward normal to the boundary.

5.4 Mesh convergence analysis

Following the methodology employed in previous chapters, a mesh convergence analysis was performed in order to ensure that the discretisation of the domain was adequate. The process is analogue to the one carried out in Chapter 4.

The mesh considered for this model has also been created in COMSOL by making use of the available built-in tools. A hybrid approach regarding the type of discretisation was followed in order to mesh the three-dimensional domain. The vessel wall along the inlet and outlet pipes, upstream and downstream of the stenosis respectively, was discretised using a structured grid made of hexahedral elements. This choice was based on the shape of the pipes, which made it possible to use a regular grid. The lumen domain mesh presented some differences with regards to the two-dimensional model. In particular, the cross-section of the flow domain was discretised using an unstructured grid of triangular elements in order to better accommodate for the semi-circular shape. Those elements were swept in the axial direction leading to triangular prisms in the three-dimensional space for $z < D$ and $z > D$.

On the other hand, in the stenosis region, all the corresponding domains (flow, vessel and lipid core) were discretised using an unstructured grid made of tetrahedral elements. This choice was justified given the more complex geometry within this region. A second order discretisation was used for the blood velocity field and for the solid displacement field, while the pressure field was solved using a first order interpolation (P2-P2-P1), as previously reported in the literature [102].

The convergence analysis was carried out by studying several features of the flow and of the solid in the most interesting region, which is the

stenosis. In particular, the following features were analysed: the velocity profiles downstream the stenosis (at $y = 0, z = L/2$); the axial distribution of the first principal stress along the bottom edge at the plane of symmetry ($x = x_{\text{bot}}, y = 0$); and the cross-sectional distribution of the first principal stress along the fibrous cap at the section of maximum constriction ($z = 0$). The simulations were started with a coarse mesh, which was gradually refined (first, the flow domain and, secondly, the solid regions). The number of elements, the degrees of freedom and the approximate solution time corresponding to each mesh tested are shown in table 5.1.

Mesh	Number of elements	Degrees of freedom	Solution time (hh:mm)
1	64048	511110	00:20
2	128132	1030905	01:15
3	294376	2053409	03:00
4	315650	2162312	04:00

Table 5.1: Mesh parameters used for the convergence analysis.

The process started by refining the flow domain, so the velocity profiles were analysed at $y = 0, z = L/2$ in order to assess the quality of the mesh. The results for each grid are shown in figure 5.4A, along with a zoomed in detail in figure 5.4B. It was visible that all meshes other than the first one provided a good definition of the velocity profile.

In order to assess the mesh refinement in the solid domains, the axial distribution of first principal stress along the bottom edge ($x = x_{\text{bot}}, y = 0$) is shown in figure 5.5. The shape of the distribution resembles the one observed in the axisymmetric simulations of Chapter 4, as it will be discussed further. The detail presented in figure 5.5B better shows the discrepancies by zooming in on the local peak at the beginning of the stenosis. Indeed, mesh 1 and

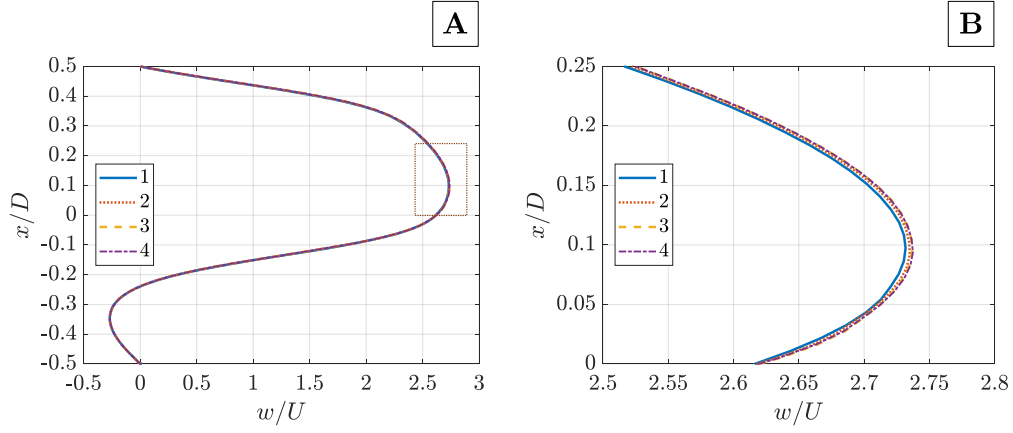


Fig. 5.4: (A) Velocity profiles at $z = L/2$ measured at the plane of symmetry for each mesh considered in the convergence analysis. (B) Zoomed-in section.

mesh 2, which contained the lowest number of elements, did not represent the local maximum well. On the other hand, mesh 3 and mesh 4 showed similar results, with a relative difference that was less than a 0.5%. After this analysis, mesh 3 apparently seemed to be an adequate discretisation. However, a further check was performed in order to take into account the three-dimensional nature of the configuration. Specifically, the first principal stress distribution along the cross-section was analysed at the throat of the stenosis ($z = 0$). The arc coordinate varies along the cross-section from $\phi = 0$ (top edge) to $\phi = \pi$ (bottom edge). Results are shown in figure 5.6A. Again, the observations reported for the axial distributions still hold here: mesh 3 presented values that were notably close to those shown by mesh 4. In addition, as shown in table 5.1, increasing the degrees of freedom by a 5% for mesh 4 (with relation to mesh 3), gave rise to a 30% increase in the overall solution time, due to RAM limitations. Therefore, mesh 3 was chosen as the appropriate mesh that will be used as the base to perform the calculations in the next section. On the other hand, the mesh corresponding to the axisymmetric geometries is the same as the one used in Chapter 4.

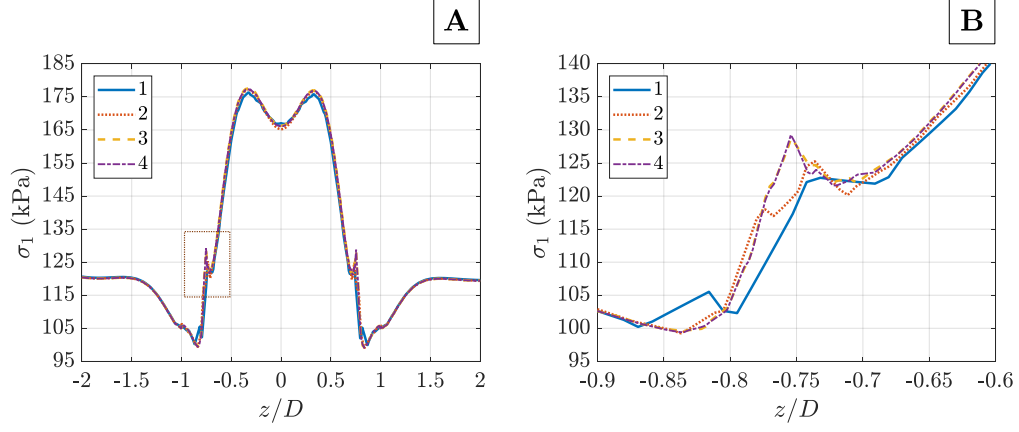


Fig. 5.5: (A) Axial distribution of first principal stress, σ_1 , at the plaque edge along the plane of symmetry for each mesh considered in the convergence analysis. (B) Zoomed-in section.

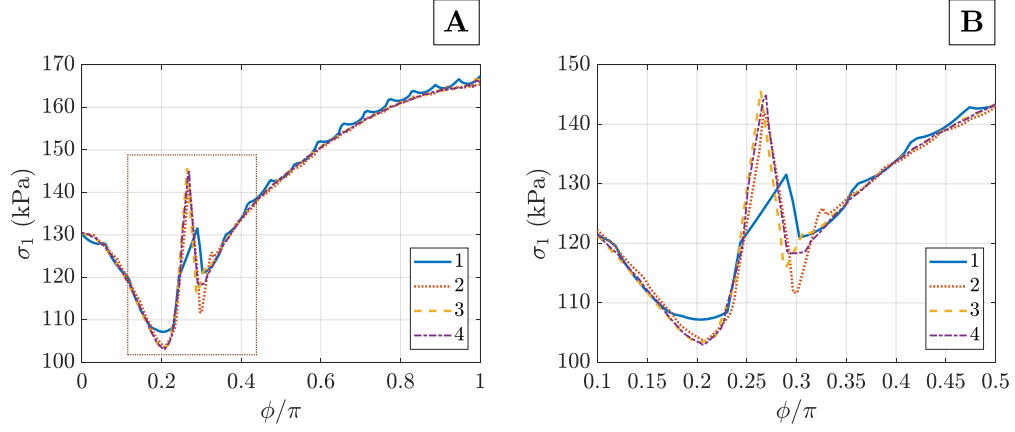


Fig. 5.6: (A) Cross-sectional distribution of first principal stress, σ_1 , at the minimum lumen section for each mesh considered in the convergence analysis. (B) Zoomed-in section.

It is worth mentioning that a further validation of the mesh was performed by comparing the flow solution to the one obtained by using an open-source solver, NEK5000 [123]. The results corresponding to this study are presented in Appendix A (“Validation of the flow solution”).

The final three-dimensional mesh is shown in figure 5.7. Hexahedra and triangular prism element types are used for the discretisation of the inlet and outlet pipes. The mesh around the stenosis is made of tetrahedra and pyramid element types, which are smaller than the ones used for the inlet and outlet pipes in order to better capture interesting flow and solid features. The final grid used for the base model is made up of 294376 elements and 2053409 degrees of freedom. The mesh at the plane of symmetry is represented in figure 5.7A; the inlet cross-section is shown in fig. 5.7B; and finally a three-dimensional detail of the inner wall is shown in fig. 5.7C.

5.5 Design of the parameter sensitivity study

Similarly to Chapter 4, an overview of the parameter sensitivity analysis is provided here before showing the results of the three-dimensional simulations.

First, the Results start with an introduction figure of the general flow and stress fields. A parametric study is performed in the following sections, following a methodology similar to that of Chapters 3 and 4. Again, for each parameter considered, the axial distribution of first principal stress is analysed.

This study starts by considering the effect of the different geometries depicted in figure 5.3. Specifically, the first principal stress is plotted along selected edges of the geometry. The distributions can then be compared using two-dimensional graphs. In particular, the stresses are analysed along the

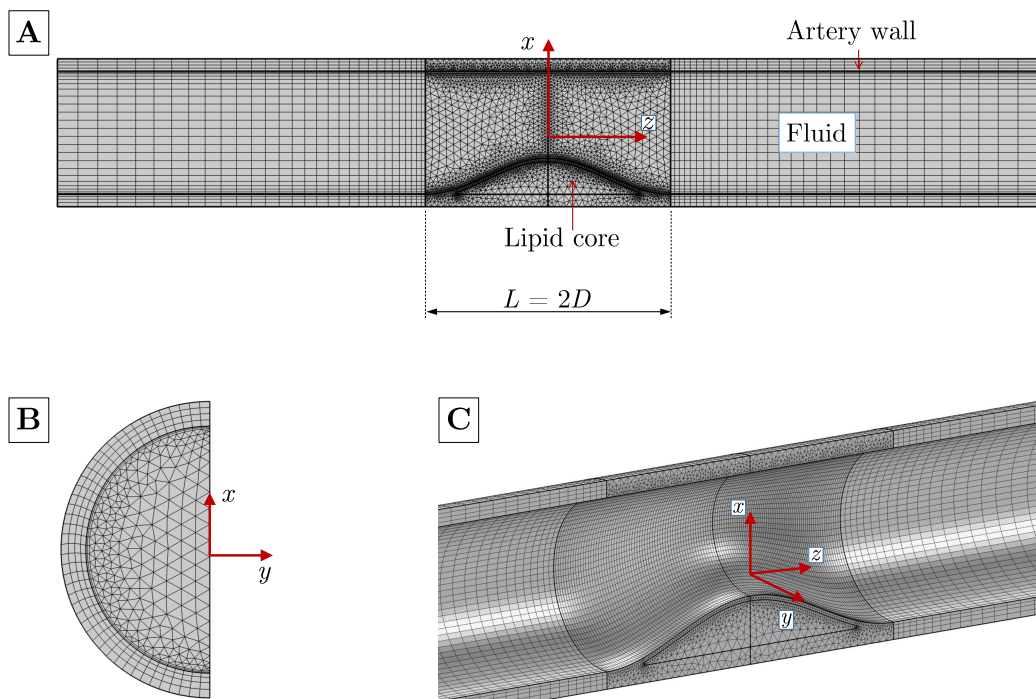


Fig. 5.7: Representation of the mesh. (A) Plane of symmetry $y = 0$; (B) Cross-section at the inlet; (C) Detail in 3-D of the artery wall in the stenosis region.

top edge ($x = x_{\text{top}}, y = 0$) and the bottom edge ($x = x_{\text{bot}}, y = 0$), which are located at the plane of symmetry. In addition, the cross-sectional distribution of the stress is also considered at the minimum constriction section, $z = 0$. The last part of this study also includes the analysis of the flow velocity profiles for each of the geometry models considered. Specifically, the non-dimensional axial velocity profiles are compared at two different sections ($y = 0, z = 0$ and $y = 0, z = L/2$).

The next analysis is the influence of the lipid core stiffness on the stress distributions. To perform this study, the Young's modulus of the lipid core, E_c , is varied. Three different values are tested: $E_c = 50$ kPa (as a simplified lipid-filled core model), $E_c = 100$ kPa (another lipid-filled model but with double the stiffness, which is the baseline case), and $E_c = 1000$ kPa (increasing the stiffness one order of magnitude, to model calcified cores). The distributions of first principal stress along the bottom edge are shown for each value of E_c .

The last study considers the effect of the lipid core length on the stress distributions. Two models are compared, the base line core and a new, short core model. For the short core case, the shape of the stenosis is the same as in the other models, so the lumen of the artery remains unchanged. The thickness of the fibrous cap and the outer part of the wall are kept constant as well.

5.6 Results

5.6.1 Introduction

A general picture of the flow solution and stress field obtained from the simulation is presented in figure 5.8. The colours of the solid domain (fig.

5.8A) refer to the first principal stress, σ_1 , on the artery wall, whereas the colours of the fluid domain (fig. 5.8B) denote the axial component of the non-dimensional blood velocity, w/U . In addition, the secondary flow is represented in figure 5.8C, which shows the non-dimensional velocity in the x direction, u/U , at different cross-sections. Red and blue colours denote high and low values respectively of stress/velocity. The lipid core stiffness was set to the lowest value, 50 kPa. The highest stresses were located in the stenosis region, particularly along the fibrous cap area. The maximum values were located at the upstream and downstream parts of the cap. Outside the stenosis, the stress stayed uniformly constant at around 120 kPa. It should be noted that the stress maxima present at the inlet section were due to the boundary condition of the solid; in particular, since the artery is constrained at the inlet ($\xi = \mathbf{0}$), the reaction creates a stress peak. Taking this into account, the domain length was varied to ensure that the stresses in the stenosis were not affected by the proximity to the inflow and the outflow boundaries. In other words, the chosen length was investigated so it did not affect the stress distribution along the stenosis.

On the other hand, the flow field presented the typical features of an eccentric, stenotic flow, with a region of accelerated fluid at the constriction due to the pressure drop, and a recirculation region (negative axial velocity) downstream the throat. Figure 5.8C shows that the stenosis created a secondary flow, especially at the throat of the stenosis, where the velocity in the x direction was maximum. This was due to the change of the lumen shape, from a straight wall upstream the stenosis to the plaque slope for $-D \leq z \leq D$. Still, it is worth noting that the maximum axial velocity was more than ten times larger than the maximum cross-sectional velocity.

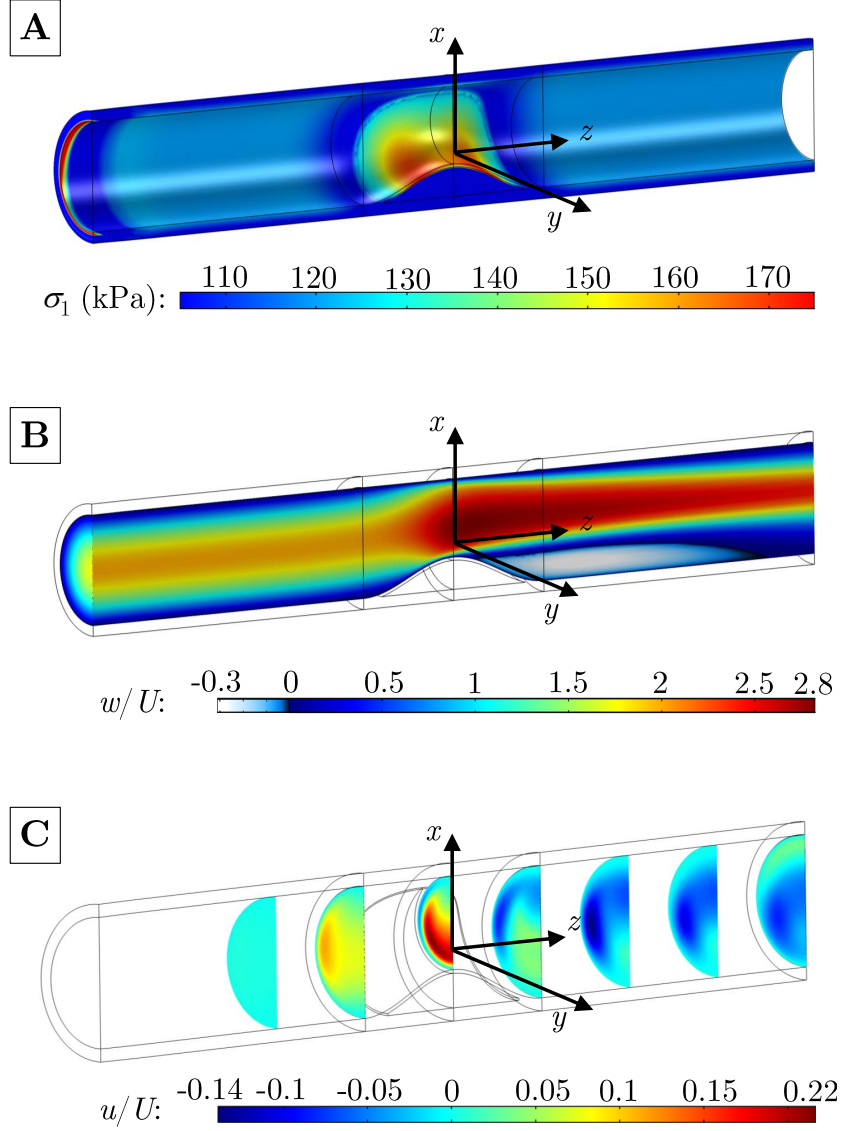


Fig. 5.8: (A) Three-dimensional representation of the first principal stress, σ_1 , distribution along the artery wall. (B) Non-dimensional axial flow velocity, w/U . (C) Non-dimensional flow velocity in the x direction, u/U , at selected cross-sections. The case considered is the original geometry, the Young's modulus of the lipid core is set to 50 kPa and the Reynolds number is $Re = 300$.

5.6.2 Effect of the different geometries

Figure 5.9A shows the axial stress distribution along the bottom edge for the five different geometries considered. The largest stress values of around 200 kPa corresponded to the positive remodelling case, while the lowest ones corresponded to the axisymmetric case with a 50 % stenosis. The rest of the models presented similar stress levels (varying less than a 4 %), especially the original geometry and the one with the chamfer ends. These results indicated that the plaque end shape did not significantly influence the overall stress level. Finally, although the maximum stress of the axisymmetric geometry with a 75 % stenosis was close to the one of the original model, the distribution varied significantly at the maximum constriction section. At $z = 0$, the minimum stress was 15 % smaller than the stress for the original case. On the other hand, the artery modulation (positive remodelling) increased the overall stress level in a similar way to the increase due to the 25 % change in severity in the axisymmetric models.

The axial distribution of stress along the top, undeformed edge is shown in figure 5.9B. In this case, the stress level was noticeable smaller than the one along the bottom edge, mainly due to the constant thickness of the wall, which is the same for the three eccentric models. The original geometry presented a maximum of $\sigma_1 = 135$ kPa at $z = 0$, which was still smaller than the minimum stress observed at the bottom edge. Therefore, the fibrous cap region was subjected to the main stress, whereas in the top edge the load was notably lower. It should be noted that the axisymmetric cases are not present in this plot due to the absence of an undeformed edge.

Finally, figure 5.10A shows the stress distribution along the cross-section $z = 0$. Both the maximum and the minimum values corresponded to the positive remodelling model. It should be noted the presence of small, sec-

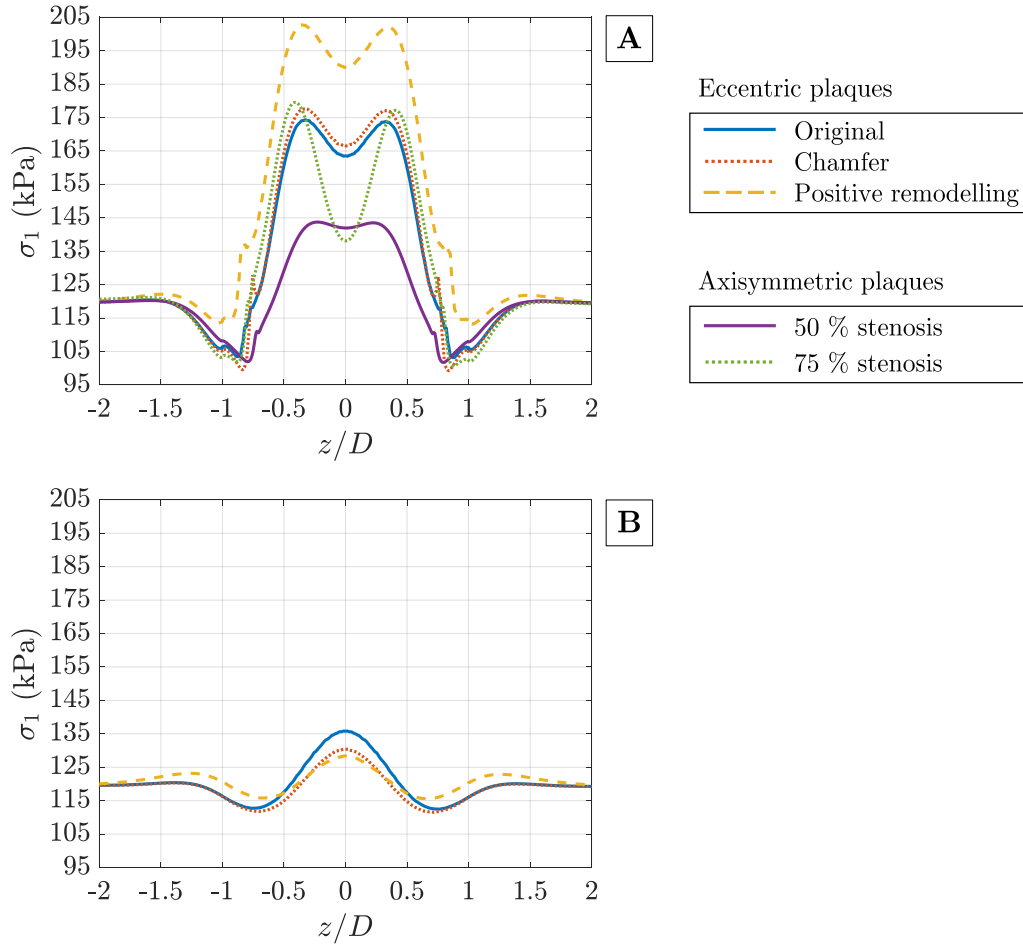


Fig. 5.9: Axial distribution of the first principal stress, σ_1 for the five different geometry models considered: (A) distribution along the bottom edge ($x = x_{\text{bot}}, y = 0$); (B) distribution along the top, undeformed, edge ($x = x_{\text{top}}, y = 0$).

ondary peaks, which were located at the ends of the lipid core. Finally, the two-dimensional cases were represented by the horizontal lines, as the stress was constant due to the axisymmetry. It was apparent from the plot that the thickness distribution of the wall notably influenced the stresses; in particular, the fibrous cap region presented the highest stress levels. This would correspond to the region located between the positions (2) and (3) as shown in figures 5.10B and 5.10C. The reader is referred to the Discussion section for further analysis of the stress distributions.

The axial velocity profiles of the flow, w , were investigated at the maximum constriction section ($z = 0$) and downstream the stenosis ($z = L/2$). The profiles are shown in figure 5.11 and are given in a non-dimensional form, using the bulk velocity U as the reference. Both graphs showed that the eccentric cases shared the same shape of the velocity profiles, which were qualitatively similar to the axisymmetric case with 50 % stenosis. On the other hand, the axisymmetric model with 75 % stenosis presented significantly higher axial velocities. At $z = 0$ (fig. 5.11A), the maximum velocity for the axisymmetric model with 75 % stenosis was $w = 4.67U$, which was 68 % larger than the maximum for the three-dimensional geometries. This difference was due to the larger severity of the axisymmetric model: as mentioned in section 5.2, the occlusion in this axisymmetric case is larger than in the 3-D one in order to keep the same shape of the wall and make a direct comparison of the stress distributions. In addition, it is worth mentioning that the profile of the 75 % stenosis model was flatter due to a larger acceleration at the stenosis. On the other hand, the maximum velocity of the axisymmetric case with 50 % stenosis ($w = 2.70U$) was very similar to the maximum of the eccentric models ($w = 2.77U$). Similar results were observed downstream the constriction at $z = L/2$ (fig. 5.11B): the maximum of the

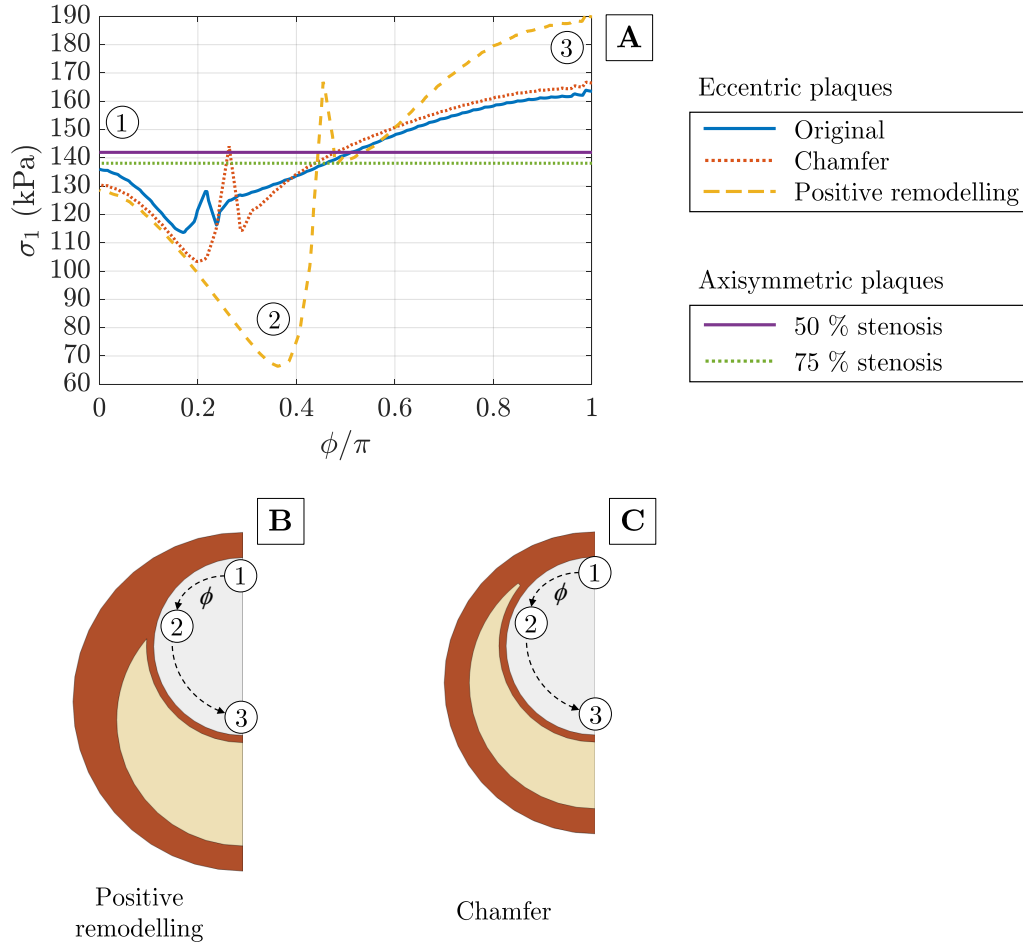


Fig. 5.10: (A) Distribution of the first principal stress, σ_1 , along the cross-section $z = 0$. Results are shown for the five different geometry models considered. (B) Half cross-section of the positive remodelling model. (C) Half cross-section of the chamfer model. The arrows denote the direction of the arc length coordinate.

75 % axisymmetric model was 67 % larger than the corresponding value of the three-dimensional models, while the maximum of the 50 % axisymmetric model ($w = 2.59U$) was again closer to the maximum of the eccentric geometries ($w = 2.74U$). It should be noted at this stage the presence of flow recirculation regions, exposed by the negative axial velocity values of the profiles. In particular, the 75 % stenosis profile showed a greater recirculation, caused by a larger deceleration near the wall that promoted flow separation. In conclusion, the 50 % axisymmetric case presented a qualitative approximation of the expected three-dimensional profiles, due to the same severity as in the three-dimensional models. On the other hand, the 75 % axisymmetric case presented higher velocity levels, even though the shape of the plaque was the same as in the 3-D models.

In summary, the highest stress values were observed for the positive remodelling case, both in the axial and in the cross-sectional directions. In particular, the thickness distribution of the wall and the lipid core seemed to influence significantly the first principal stresses along the vessel. In addition, the comparison of the different models showed that the 50 % axisymmetric case resembled better the behaviour of the three-dimensional eccentric models with regards to the flow field. On the other hand, the 75 % axisymmetric case offered a closer representation of the stress distribution along the wall, mainly because of the same shape of the plaque.

5.6.3 Effect of the lipid core stiffness and length

The results corresponding to the influence of the lipid core stiffness are shown in figure 5.12A for the original geometry, and in figure 5.12B for the positive remodelling case. Overall, it was observed that the stress at the cap decreased when the stiffness of the lipid core increased. Lowering E_c from 1000 kPa to

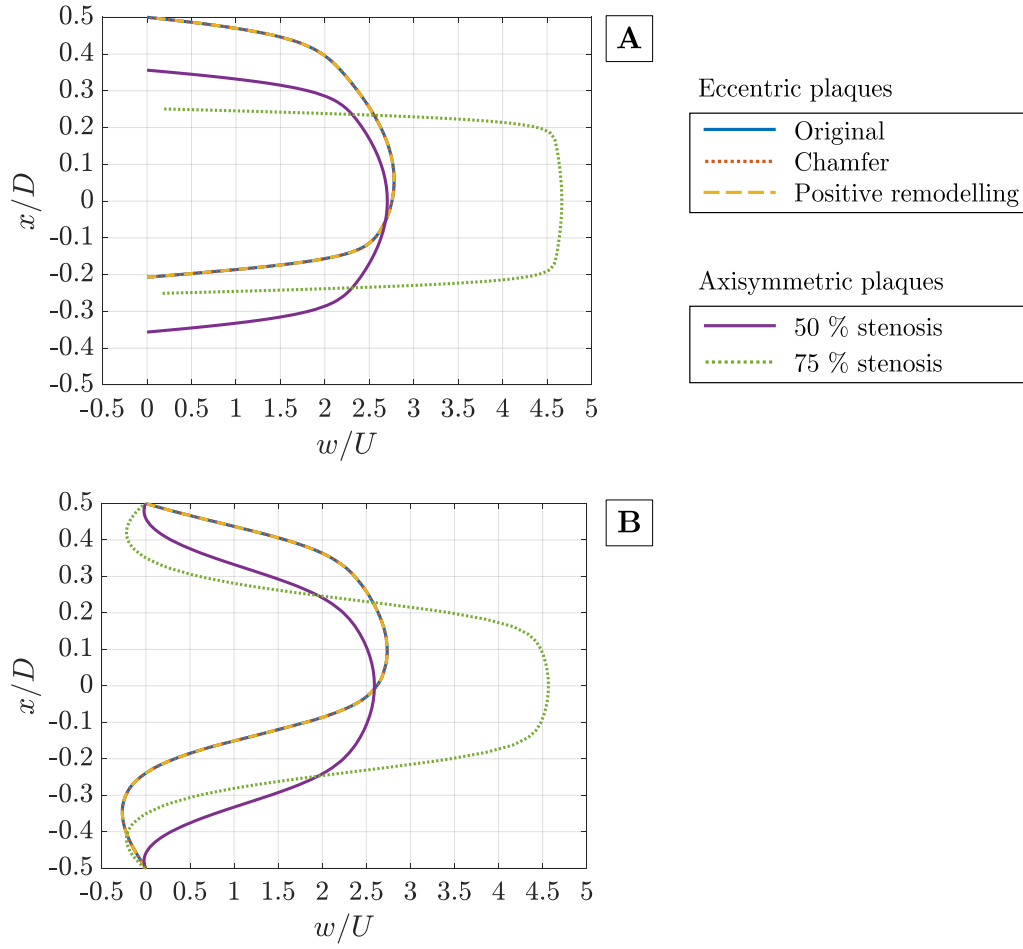


Fig. 5.11: (A) Non-dimensional axial velocity profiles, w/U , at the throat of the stenosis ($y = 0, z = 0$). (B) Non-dimensional axial velocity profiles, w/U , downstream the stenosis ($y = 0, z = L/2$).

50 kPa gave rise to a 26 % increase of stress for the original geometry, and to a 32 % increase for the positive remodelling case. In addition, the distribution changed: for lower values of E_c , there were two stress peaks that were located upstream and downstream the stenosis, while there was only one peak (at $z = 0$) for $E_c = 1000$ kPa.

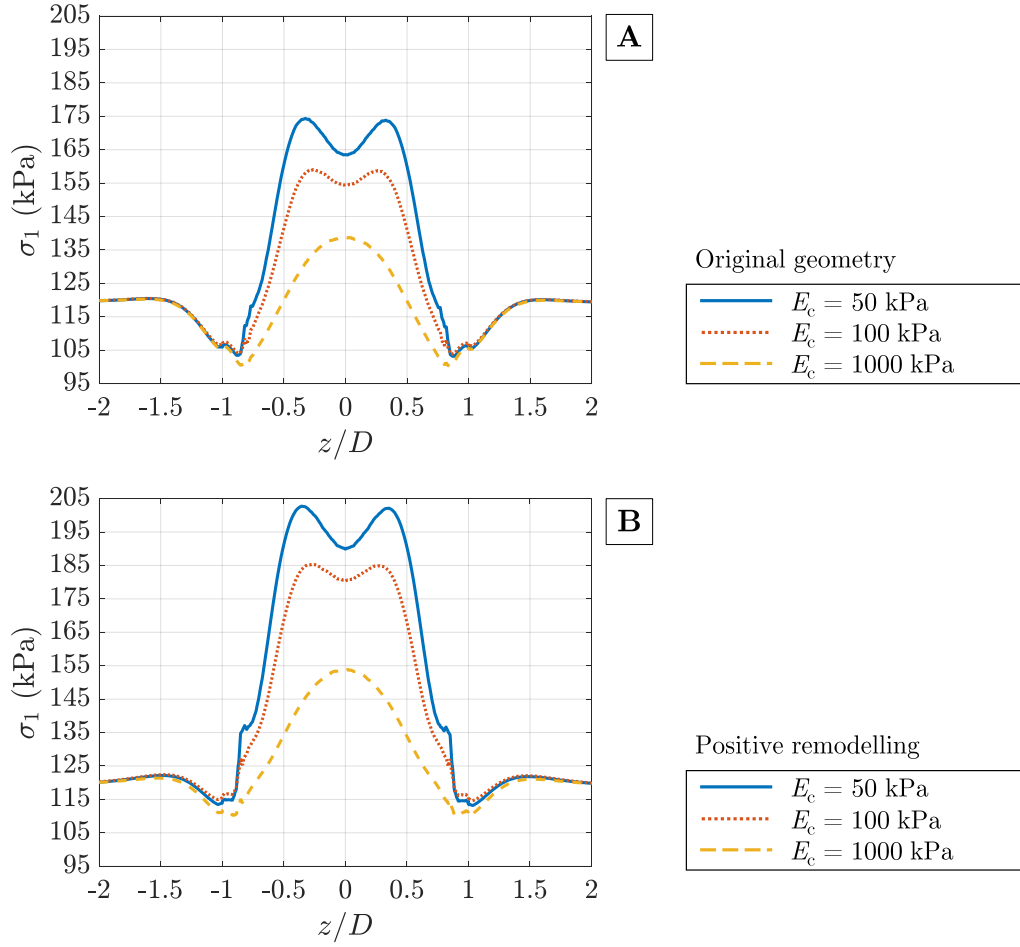


Fig. 5.12: Axial distribution of first principal stress, σ_1 , for the three different values of the Young's modulus of the lipid core considered in the study: (A) original geometry; (B) positive remodelling case.

Finally, the length of the lipid core was considered as well by comparing the base line core length with a shorter one, as shown in figure 5.13A. The

results presented in figure 5.13B showed that the stress level in the stenosis region increased for the shorter core model, as well as the gradients of the distribution. In addition, the local peaks at the ends of the core increased substantially for the shorter core from 128 kPa to 145 kPa, due to the abrupt change in the wall thickness at the ends of the core.

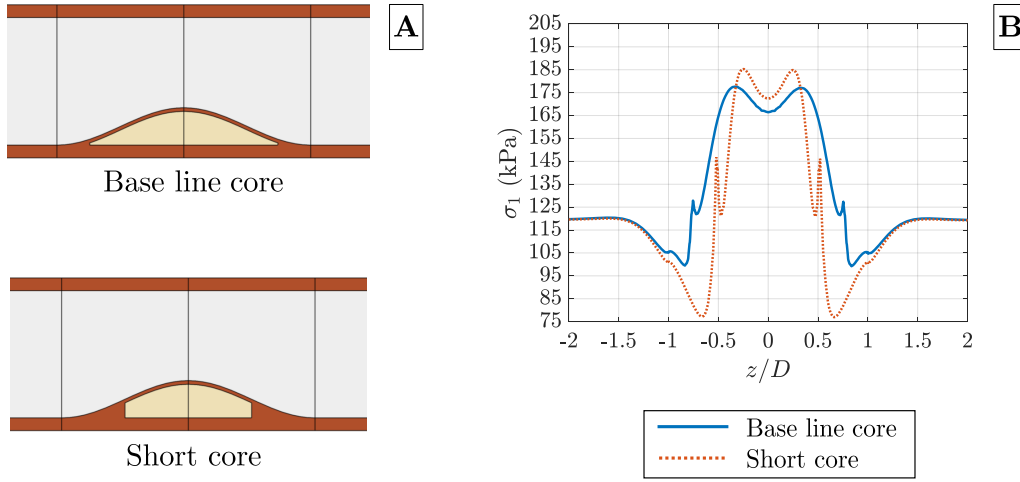


Fig. 5.13: (A) Geometric representation of the short core model, compared to the normal sized one. (B) Axial distribution of the first principal stress, σ_1 , along the bottom edge for the normal and short-core models.

5.7 Discussion

Figure 5.8 gives a general idea of the stress distributions expected at the inner wall of the artery. Outside the stenosis, at the straight inlet and outlet pipes, the stress stays more or less constant, at 120 kPa. This value is consistent with the circumferential stress at the inner wall of an equivalent thick-walled cylinder loaded by internal pressure. Higher stress levels are present at the stenosis, due to the smaller thickness of the fibrous cap and the low stiffness of the lipid core compared to that of the wall. Considering the axial direction,

two main regions of high stress are observed, approximately at the middle of the upstream and downstream zones of the stenosis. On the other hand, looking at the cross-sectional direction, the highest stresses are found close to the plane of symmetry $y = 0$. This means that the peak stresses are found near the middle of the cap rather than the shoulders. The term *shoulders* refers here to the junctions of the cap with the adjacent layer of the artery in the cross-sectional direction (see diagram A in fig. 5.1). Several studies have reported that the highest stresses usually appear at the cross-sectional shoulders of the plaque [58–60], and hence pointed that it is the most probable location of plaque rupture. However, it has been observed that in around a third of the cases the rupture takes place in the middle region of the cap [58], which is in agreement with the results found in the present simulations, based on the location of the peak stresses. The fact that the peak stresses are not seen at the shoulders of the cap can be attributed to the geometry of the model itself. The model investigated here is an idealised stenosis with constant wall and cap thickness, so the irregularities that may be present in patient-specific geometries and that could lead to stress concentrations at the ends of the core are not taken into account. In addition, the cross-section of the core is modelled in such way that the sharp ends create a smooth change of the wall thickness at the transition at the shoulders (as shown in figure 5.2C), therefore minimising any potential stress concentration except for the short lipid core case, which will be discussed shortly.

The study of the axial distribution of the first principal stress is carried out by focusing on the top and bottom edges of the geometry. Figure 5.9A shows mostly similar curves for both the original and chamfer geometries, suggesting that small changes of the ends of the lipid core do not affect the stress distributions. The only significant difference are the local maxima that

appear at $z = \pm 0.75D$ for the chamfer geometry, where there is a sudden change of thickness due to the blunter ends. These local peaks are small compared to the absolute maxima, so it would be expected to find the rupture locations closer to the mid points of the upstream and downstream regions of the stenosis, rather than at the ends of the core. However, blunter ends of the core can lead to higher local maxima, so the rupture location could move to that region. This was also suggested by previous studies that linked the location of the rupture with the location of local stress concentrations [154]; therefore, it could be important to consider the shape of the ends of the core with regards to the axial location of a rupture.

The positive remodelling gives rise to an overall increase of the stress levels, which are significantly higher. In a two-dimensional structural analysis, Ohayon et al. [74] showed that a larger lipid core thickness led to a significant increase of the cap stress for a constant fibrous cap thickness, as in this case. Therefore, the higher stress levels of the positive remodelling case can be attributed to the larger thickness of the core (fig. 5.3). On the other hand, it is worth noting that the axial distribution was similar to the one corresponding to the original geometry.

Finally, the curves corresponding to the axisymmetric cases serve as a reference point and also facilitate the comparison to the model used in Chapter 4. However, there are significant differences depending on the severity of the axisymmetric case considered. The 50% axisymmetric model does not provide a useful picture of the stress levels, even though the severity of the stenosis is the same as in the eccentric geometries. This is due to the different shape of the wall for the axisymmetric case, since the slope in the stenosis region is smaller than for the eccentric model. On the other hand, the stress levels in the 75%-stenotic case are similar to the original and chamfer ge-

ometries, which is reasonable since the shape of the wall is the same for the deformed part of the eccentric stenosis cases. The axisymmetric study performed in Chapter 4 may be considered then as a qualitative first analysis of a 3-D geometry. The difference among the 75%-axisymmetric model and the eccentric cases at $z = 0$ may be explained by the severity of the stenosis only, which creates a larger pressure drop at the throat. This decreases the stress at the wall near the constriction, hence the minimum value is 15% smaller than the equivalent stress for the original geometry.

A lower level of overall stress was observed at the top, undeformed, edge of the geometry than for the bottom one, as shown in figure 5.9B. In this case, the peak values are located at the constriction and the maximum value corresponds to the original geometry, whereas it is the lowest stress for the bottom edge. On the other hand, the distribution of the chamfer and the original models are very similar. The positive remodelling presents a slightly different distribution, which is influenced by the different shape of its core. Some authors have reported that the location of the maximum stress in a stenosis was in the healthy part of the artery wall [88], but in those cases the thickness of the fibrous cap was larger than in the present geometry, and therefore the stress distribution was different. If there is a lipid pool and the thickness of the cap is small compared to the thickness of the wall, then the peak stresses are usually found in the cap region [58, 59], as in this study.

The analysis of the stress distributions along the cross-section at the throat of the stenosis (figure 5.10A) showed that the maximum stress levels were always observed at the middle of the cap ($\phi = \pi$) rather than at the shoulders. In order to explain the differences observed in the stress distribution for each model, it is useful to look at the geometry of each case (figures 5.10B and 5.10C). Several features have been marked with numbers,

which are explained as follows: (1) At the top edge of the plane of symmetry ($\phi = 0$), all cases present similar stress levels, which is explained by the fact that the artery wall at that point is the same for all models. (2) At the shoulder of the core, there is a local peak due to the abrupt thickness change. In addition, at around $\phi = 0.4\pi$ the positive remodelling case presents the lowest stress value, due to the thicker wall at that point. (3) Finally, at the middle of the fibrous cap ($\phi = \pi$), the positive remodelling presents the highest stress, due to the larger core-to-wall thickness ratio at that section. Overall, the thickness distributions of the vessel and the lipid core seem to influence the stress distribution more than the axial geometry of the lipid core or the flow. Indeed, the secondary flow depicted in figure 5.8C showed some acceleration in the cross-sectional direction, but the thickness distribution seems to be the main factor with regards to the first principal stress.

It is important to note that the curves of the axisymmetric cases stay constant at $\sigma_1 = 142.0$ kPa (50 % stenosis) and $\sigma_1 = 138.1$ kPa (75 % stenosis) due to the axisymmetry. Qualitatively, these values can be viewed as a stress average of the more complex, eccentric geometries. Indeed, the average stress for the original geometry case is 137.7 kPa, which is close to the axisymmetric stress levels. A similar situation applies to the positive remodelling model, where the average is 127.5 kPa. The difference in this case with the axisymmetric stress levels is larger, due to the fact that the change of the lipid core geometry is more substantial. Still, the axisymmetric simulations provide a good first picture of the stress levels that can be expected at the cross-section, at a much lower computational cost than running a full three-dimensional model. This is especially applicable to the 75 % severity case, which also presents an axial stress distribution that is very similar to

the eccentric ones. Therefore, the use of a simple, axisymmetric model such as the one investigated in Chapter 4 can be a good first approximation, as it gives a general idea of the stress levels that may be present in more complex, eccentric models.

The flow velocity fields show that the shape of the core does not affect the velocity profiles at $z = 0$, as shown in figure 5.11A. The only differences are observed between the eccentric and the axisymmetric flows. In particular, the 75 % axisymmetric geometry presents higher velocity levels at both sections, due to the greater severity. On the contrary, the velocity profile corresponding to the 50 %-stenotic, axisymmetric case is very similar to the one observed for the eccentric models. Hence, the velocity difference can be attributed to the larger pressure drop at the constriction. On the other hand, the shape of the curve is similar for all cases; in particular, the axisymmetric velocity profile looks as an average of the eccentric geometries. Therefore, the axisymmetric model serves again as a simpler approximation of the more complex, three-dimensional ones. The latter simulations capture precise details of the flow and stress distributions, but some of the general features of the flow and stress fields are captured in the axisymmetric model. This is also in agreement with previous works in the literature which have used axisymmetric [73, 87] or two-dimensional [90] models to study the mechanics of a stenosis. A similar behaviour is observed at $z = L/2$ (fig. 5.11B). The main feature of this plot is the recirculation regions, which are denoted by the portions of negative axial velocity. For the axisymmetric case, the recirculation region is axisymmetric as well, whereas for the eccentric ones, the recirculation is present only at the bottom part of the domain, that is, downstream the part where the plaque is located. The width of these regions is also comparable: $2 \times 0.15D = 0.30D$ for the axisymmetric model with

75 % severity, and around $0.26D$ for the eccentric ones. It is worth noting that these profiles are comparable to those reported by Choi et al. [152]. As a final note, it should be pointed out that the smaller negative axial velocities for the 50 % axisymmetric case are due to the smaller slope of the wall, since this smoother transition through the stenosis region does not create a recirculation similar to the ones observed in the remaining cases.

The effect of the core stiffness on the original and on the positive remodelling geometries is similar (fig. 5.12). In both cases, the results show that the overall stress level increases when the stiffness of the core decreases. In order to explain this, it should be taken into account that a stiffer core is capable of sustaining more load, thus decreasing the loading on to the cap region. At the same time, the distribution changes as well. In particular, for calcified cores, $E_c = 1000$ kPa, the results show a stress peak at $z = 0$, which means that the most probable location of the plaque rupture would be the maximum constriction section. However, for lipid-filled cores, $E_c = 50$ kPa, the shape of the curves changes and two peaks appear upstream and downstream the constriction. So depending on the stiffness of the core, the expected rupture locations can move along the axial direction of the stenosis. This behaviour was also observed in the axisymmetric analysis presented in Chapter 4. Therefore, the change of the stress distribution for lipid-filled and calcified plaques can be considered as a stable feature which does not depend on the geometry of the model (2-D or 3-D), or on the shape of the lipid core ends. It should be noted that the change of stiffness has to be large enough: in this case, the Young's modulus increased by an order of magnitude. A small increase of the Young's modulus would not lead to a particularly different distribution, which is in agreement with former studies [78, 89]. In addition, the change of distribution is similar to the one reported

by Belzacq et al. [87]. However, they observed this result when varying the overall length of the stenosis (the parameter L in this thesis) rather than the core stiffness, which was kept constant.

In addition, it is also worth noting that the upstream maximum is marginally higher than the downstream one (around 0.3 % larger). This could explain why a majority of the ruptures have been observed upstream rather than downstream the stenosis [70, 71]. Finally, as it was mentioned previously, the positive remodelling case presents higher levels of the first principal stress while keeping the same shape of the stress distributions. The larger values are due to the different geometry of the core, increasing the core-to-wall thickness ratio and the loading of the cap. Therefore, the positive remodelling can be associated with a higher risk of rupture.

The results obtained for the short core case (fig. 5.13B) present several differences compared to the baseline core model. The first difference is the change of the location of the stress peaks due to the different geometry of the lipid core. Indeed, both the absolute maxima and the local maxima are closer to the centre of the stenosis at $z = 0$, and the same applies to the stress minima. In particular, these minimum stress values upstream and downstream the core are significantly smaller (22 %) than in the original case. This difference can be explained by considering the vessel portion close to the core, which is thicker in the short core model, as shown in figure 5.13A. The thickness change at the beginning of the fibrous cap creates an abrupt increase of the stress levels for the short core model, and thus the local maxima are also remarkably higher than in the normal case, increasing from 127.9 kPa to 145.0 kPa. Considering this result, apart from the previous rupture site related to the global maxima, another possible site of rupture is identified at the axial ends of the lipid core region. Finally, the absolute

maxima also increase for the shorter core case, possibly due to the higher stress concentration created by the shorter cap region. Specifically, the peak value experiences a 4.3 % increase, but it should be noted that this change is not as significant as the one observed at the local peaks (13.4 % increase, three times larger variation). In addition, the relatively small change observed at $z = 0$ is in agreement with previously reported results [149]. However, the variation of the whole stress distribution, and especially the change at the local peaks, were not reported in that study, since it was focused on the stress at the central cross-section of the artery. Again, it is worth noting that these findings are consistent with the results reported in Chapter 4, where only axisymmetric models were investigated. The hypothesis stated in the Introduction section seems to be confirmed, as the variations of the axial stress distributions in the three-dimensional models are mainly affected by the same features as in the axisymmetric cases.

Previous studies analysed the effect of the core size on the wall stress, but it is difficult to make a comparison to those cases where the cap thickness was variable [73, 88]. Still, since the focus here is on the wall stress distributions rather than on the actual values, the change due to the length of the core is significant. It should be noted, however, that the effect of the lipid core length (fig. 5.13) is less than that due to the change of lipid core stiffness (fig. 5.12). In general, the latter has a larger impact on the stress levels and the stress distributions. The length of the core is still an important parameter due to the effect on the local maxima at the axial ends of the core, which could lead to another site of rupture.

In summary, it was observed that an axisymmetric model of the artery can provide results that are qualitatively similar to the ones that can be expected in a three-dimensional model. If considered as a first approach, it gives a

general idea of the stress distribution that can be expected in more complex geometries at a much lower computational cost, provided that the severity is adjusted so the shape of the plaque resembles the 3-D geometry. On the other hand, an axisymmetric model with the same severity of the stenosis provides information about the expected flow velocity field. There were also some differences among the axisymmetric and the three-dimensional models that should be taken into account. For example, the first principal stress along the bottom edge is significantly lower for the axisymmetric cases at $z = 0$. On the other hand, there are features of the stress distributions along the cross-section $z = 0$ for the 3-D models that are not captured by the axisymmetric models, such as the local stress peaks.

In addition, relatively small changes in geometry may impact the stress distributions significantly. In particular, the positive remodelling of the artery (with a thicker lipid core) has the largest influence on the stress levels, compared to other changes made to the axial geometry of the core. On the other hand, the stiffness of the lipid core plays an important role on the axial location of plaque rupture, as it changes the location and the magnitude of the peak values. Finally, it was found that a shorter lipid core with a significant change in wall thickness leads to a change in the stress distribution as well as in the overall values, so both the length of the lipid core and the changes in wall thickness should be considered as important geometric features, regardless of the length of the stenosis.

5.8 Conclusions

Numerical simulations of steady blood flow through a three-dimensional stenotic artery were performed in order to study the stress distributions along

the wall. This chapter presented the next step to the axisymmetric models investigated in Chapter 4 by introducing the eccentricity of the plaque. Several features were investigated: the shape of the axial ends of the core, the positive remodelling of the artery, the lipid core stiffness and the lipid core length. The findings have been compared to a simpler axisymmetric model such as the one analysed in Chapter 4.

Overall, the study showed that some differences observed in the axial stress distributions remained stable regardless of the axisymmetric or three-dimensional model used: the positive remodelling increased the stress levels compared to models that presented no remodelling; a decrease of the lipid core stiffness gave rise to an increase of the stress levels, while also changing the distribution; and the effect of the length of the lipid core affected the axial location of the peak stresses and, potentially, the plaque rupture sites. In addition, the peak stresses were usually located at the midpoints of the upstream and downstream regions of the stenosis, except when the stiffness of the core was increased substantially. On the other hand, the flow field was not affected by changes of the geometry of the core, and only showed a different profile for the axisymmetric cases.

The analysis of the cross-section of the artery was useful in order to explain the stress distribution in the circumferential direction, which was mainly influenced by the thickness of the vessel, the lipid core and the fibrous cap. In particular, it is worth mentioning that the maximum stresses were found at the middle of the cap rather than at the shoulders, further justifying the use of axisymmetric models.

The results presented here have been explained taking the geometry and other parameters such as the stiffness of the core into consideration. In the future, it would be interesting to apply these findings to more complex,

patient-specific geometries, and compare the results to the already completed analysis using idealised geometries.

Chapter 6

Future work and overall conclusions

6.1 Introduction

The work presented in this thesis involves the use of idealised geometries. In particular, a thin-wall, axisymmetric model was analysed in Chapter 3; another axisymmetric case, which included the plaque, was studied in Chapter 4; and finally, a fully three-dimensional geometry with an eccentric plaque was investigated in Chapter 5. A logical next step to this series, and also an appropriate future direction, is the implementation of patient-specific cases.

Therefore, in this chapter, the differences between a subject-specific model and the previous idealised models will be highlighted. In addition, it will be discussed to what extent the conclusions from the idealised cases could be applied to the more complex geometries. This could be helpful when diagnosing a patient with a carotid plaque. In particular, the information obtained from the idealised cases would give a general idea of the expected stress distributions, depending on some features such as the geometrical parameters

of the lesion or on the mechanical properties of the vessel. From another point of view, a cost-efficient simulation could also provide a reasonable approximation to the flow and solid fields.

In order to keep a structure similar to the one followed in the previous chapters, the matters discussed here will be organised in a similar way: first, several aspects regarding the reconstruction of the geometry are discussed. This is followed by some comments about the models and the boundary conditions, as well as a mention to the required mesh convergence analysis. Finally, the results and discussion bring up different points that could be interesting in this case. Overall, the main point of this chapter is the comparison to the work done with the idealised geometries.

6.2 Geometrical considerations for patient-specific configurations

The main difference between the proposed future work and the findings presented in this thesis is the geometry of the model itself. In particular, the work studied in the previous chapters focused on idealised models. The word *idealised* refers to the adaptation carried out to model realistic geometries by using simpler configurations. For example, the inner radius of the vessel along the stenotic region, r , was described in Chapter 3 as a sinusoidal function such as

$$r(z) = \frac{D}{2} \left\{ 1 - \frac{1 - \gamma}{2} \left[1 + \cos \left(\frac{2\pi z}{L} \right) \right] \right\}. \quad (6.1)$$

This mathematical expression depicts a smooth stenosis, symmetric with regards to the throat at $z = 0$. It is unlikely that a patient-specific plaque presents exactly this shape; however, the main goal was to model the axial

variation of the lumen, which in the end was the main factor behind the pressure field (figure 4.7B) and ultimately, the stress distribution.

Other simplifications were the use of a constant value of the wall thickness and the straight pipes that modelled the inlet and outlet regions outside the stenosis. These simplifications did not exactly reflect a realistic geometry, but they made it possible to perform several parametric analyses. Usually, it will be difficult to model a patient-specific geometry using an analytic expression, since many irregularities may be present on the surface of the vessel. In addition, every plaque may be unique, so a mathematical expression is not useful for every case, as it would only apply to a specific subject.

Therefore, if an analytic expression is not the best way to model the geometry of a patient-specific plaque, then other methods should be used. Tang et al. were among the first to study the fluid-structure interaction of carotid plaques using a subject-specific model [89]. The geometries were reconstructed from images obtained by magnetic resonance imaging (referred to as “MRI” onwards). As mentioned in the same work, MRI was intended to “quantify noninvasively plaque size, shape, and plaque constituents” [89].

There are several steps involved in the reconstruction of a geometry from MRI-based scans. The first stage is obtaining the MRI data sets. There are some limiting factors at this point, such as the resolution of the scan [155]. The second stage is the segmentation, i.e. the identification of the anatomical structures. In the specific case of carotid plaques, the segmentation phase involves the definition of the features that are present in the plaque: the non-diseased and the atherosclerotic regions of the vessel, the lipid core and the fibrous cap, along with the identification of the lumen region. The resolution of the scan is a particularly important factor: the dimension of the fibrous cap of a carotid plaque may be as thin as 50-100 μm [59, 100], whereas the

in-plane resolution of the scan may be in the order of $390\text{ }\mu\text{m} \times 390\text{ }\mu\text{m}$ [107] or $310\text{ }\mu\text{m} \times 310\text{ }\mu\text{m}$ [108]. This can give rise to partial-volume effects that would need to be dealt with.

The concept of partial-volume effects refers to the loss of definition when identifying the different components due to the finite spatial resolution of the scan [156]. The contours of the plaque will not match the resolution of the scan; this leads to pixels (in two-dimensions) or voxels (in three-dimensions) that may show blurry areas, and therefore the contour of the lumen, the fibrous cap or the lipid core can not be clearly defined. A diagram, which has been adapted from the literature [156], shows this phenomenon in figure 6.1. On the left hand side of figure 6.1A, the real geometry (an idealised lumen in this case, represented by a circle) is plotted over the grid that represents the resolution of the imaging system. On the right hand side, the image measured by the scan is represented: the black pixels show the highest signal intensity, indicating that those areas lie in the lumen section; the white pixels on the other hand denote areas that do not represent the lumen; and finally, the different grey pixels denote some areas containing part of the geometry and part of the outside domain. In a real application, the geometry has to be reconstructed using the information provided by this last image after doing the scan. This small example illustrates the difficulties that may appear in the segmentation process, as correctly identifying the different parts of the plaque could prove to be a complicated task. More complex geometries might make the segmentation process more difficult, as shown in figure 6.1B. Overall, the limitation in resolution can be very important, since the spatial dimensions of the different parts of the plaque have a great impact on the stress distributions, as shown in Chapters 4 and 5. Recently, Chai et al. have been able to provide a method that can accurately quantify the lipid core

region in a carotid plaque by using a specific MRI technique known as T_2 mapping [157].

The last step of the process is the three-dimensional reconstruction of the geometry using the two-dimensional images. By following this method, several published articles showed that MRI makes it possible to characterise complex geometries at different locations. For instance, it has been applied to model carotid plaques [89], including the carotid bifurcation [158] and the coronary arteries [154].

It is worth noting that a patient-specific model may be obtained using other methods. For example, another non-invasive technique is angiography, in which a radio opaque dye is inserted in the artery so it can be visualised using an x-ray. This technique became the reference standard for characterising cardiovascular diseases [159], being in use since 1924 [160]. One important shortcoming is that the visualisation of the artery is two-dimensional, since the quantification of the stenosis is performed with respect to the diameter of the lumen [159]. Therefore, some spatial information is missing and should be reconstructed either by approximation or by employing other techniques. On the other hand, the comparison with the idealised models would be easier. Improved techniques based on angiography were developed later, such as computed tomography angiography, which enabled the use of three-dimensional scans [160]. Another method available to obtain the geometry of the plaque of a specific subject is intravascular ultrasonography [161]. This technique consists of the generation of several cross-sectional scans such that the geometry of the wall and the plaque can be reconstructed. The axial resolution is around $150\mu\text{m}$, so an accurate modelling in this direction is possible.

In summary, there are several methods available that could be used to

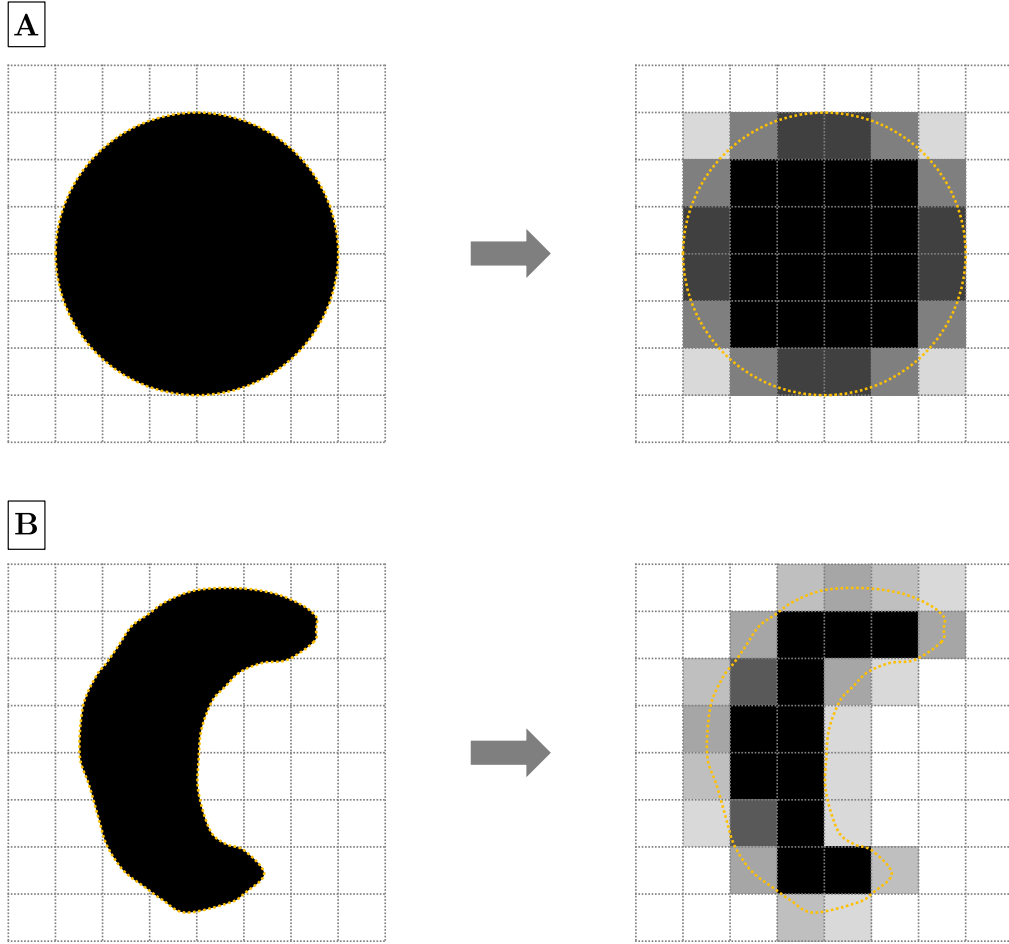


Fig. 6.1: Diagram showing the partial-volume effects that may appear in an MRI process. Left hand side: actual geometry represented over the grid of the scan. Right hand side: Measured intensities in grey scale. Black pixels denote the highest intensity (all the areas belong to the measured geometry), whereas the grey pixels represent sections that belong to both the geometry and the outside domain. (A) Idealised lumen geometry. (B) Partial-volume effects with more complex shapes.

model a more complex geometry. Although there are some limitations, analysing the differences among idealised and patient-specific models would certainly be of interest.

6.3 Modelling aspects for patient-specific geometries

In principle, the governing equations would not change; in particular, the equations presented in Section 2.4 still apply. Indeed, even though the geometry is more complex, the basic fluid-structure interaction physics are the same. However, some ideas may be implemented later to improve the flow and solid models.

6.3.1 Considerations about the flow field

For the first test involving the new geometry, the fluid could still be considered as Newtonian and incompressible. In addition, the boundary conditions could be kept as outlined in the previous chapters of this thesis (as shown in Section 5.3), i.e. a steady flow profile can be prescribed at the inlet section.

An extra, optional step could be the implementation of a pulsatile flow profile, in addition to the patient-specific geometry. The use of steady flow conditions was justified at the beginning of Section 4.7: using data from a study published by Pereira et al. [153], it was shown that the pressure wavelength was more than thirty times larger than the domain length of the current model, and therefore the non-stationary effects on the wall could be neglected. However, the use of a pulsatile profile also makes sense in case that the data can be obtained from the patient. In particular, it may be possible

to measure the flow rate through the carotid artery by doing a vascular ultrasound scan [19], so that a more realistic profile could be prescribed at the inlet of the model. Then, the results at a specific time during the period could be compared to the already reported observations at steady flow.

If a pulsatile profile is prescribed, then it would also be appropriate to consider the blood as a fluid with non-Newtonian viscosity. The reason is that some non-Newtonian effects have been observed when using a non-stationary inflow [39]. In particular, some differences in wall shear stress using Newtonian and non-Newtonian formulations were reported at certain times during the period (when the flow was slower). An interesting analysis would then be the study of the influence of a non-Newtonian model on the stress distributions along the artery wall.

It should be taken into account that in the non-Newtonian formulation the viscosity depends on the shear rate, $\dot{\beta}$. It is worth mentioning now two non-Newtonian models that have been used in the past when simulating the blood rheology.

First, the Carreau-Yasuda model, which has been used in several works dealing with blood flow [40, 41, 57, 162]. In this case, the flow viscosity is described by

$$\mu = \mu_{\infty} + (\mu_0 - \mu_{\infty}) \left[1 + \left(\lambda \dot{\beta} \right)^b \right]^{(p-1)/b}. \quad (6.2)$$

In this expression, μ_0 and μ_{∞} are the zero and infinite shear-rate viscosity, respectively; λ is a time constant; b denotes the Yasuda exponent and p refers to the power law index.

On the other hand, the Power Law model, which according to Soulis et al. provided the most accurate representation of the blood rheology [41], is given by the following expression:

$$\mu = \mu_0 \left(\dot{\beta} \right)^{q-1}, \quad (6.3)$$

where q denotes another constant. It is worth noting as well that the implementation of the variable viscosity would have an effect on the computational cost, compared to a simpler Newtonian model where the value is constant. Therefore, it would be important to analyse whether the non-Newtonian effects are significant.

6.3.2 Considerations about the artery wall and the lipid core

In addition to patient-specific geometries, another issue here would be the need to consider also subject-specific solid models. As shown in Chapters 4 and 5, one option is to consider the vessel and the lipid core as hyperelastic and linear elastic materials respectively. However, since subject-specific models are considered, it is expected that the material properties of the arterial tissue vary among different groups. For instance, as reported by Riley et al., the mean Young's modulus of the carotid artery seems to increase with age for both male and female patients [93]. Additional distinctions could be introduced considering the clinic history of the individual. In summary, the generalisation of the material properties is a complex subject and, if subjects-specific models are introduced, the same should apply to the choice of mechanical properties.

On the other hand, the material properties used in this thesis modelled the behaviour of the artery wall when it was subjected to a certain stress distribution. However, a proper failure model was not implemented. Therefore, fatigue and fracture mechanics are proposed as suitable options that would enrich the simulation. As to why it would be interesting to consider fatigue effects, it is worth noting that the vessel is subjected to more than 31 million stress cycles every year for a typical resting heart rate of 60 beats

per minute.

One of the most common models used to calculate the fatigue life of a structure is the Paris' law, which relates the crack growth with the range of stress intensity factor [163, 164]. Mathematically, this is usually described as

$$\frac{da}{dN} = C\Delta K^m. \quad (6.4)$$

On the left hand side of this expression, a denotes the length of the crack and N refers to the number of loading cycles. Therefore, da/dN describes the crack growth rate. On the other side, $\Delta K = K_{\max} - K_{\min}$ defines the range of the stress intensity factors, whereas C and m are constants. Taking this into account, it would be interesting to apply this failure model to the simulations.

However, it is worth noting that even though the fatigue analysis can lead to some interesting findings, it is important to consider one important difference between the mechanics of a diseased artery and a metallic structure: the artery is a *living* tissue. This means that the artery behaves differently due to its capacity to remodel [165], and so it can partly overcome the effects of fatigue that would affect other materials or structures. Therefore, this should be considered when implementing a failure model, for instance by taking into account some modifications that model the growth of biological structures [166], rather than a general fatigue model.

This way, the work proposed here would be an extension to the study presented by Versluis et al., who investigated the fatigue effects on plaque rupture in coronary arteries [68]. They reported that an increase in the stiffness of the lipid core, a thicker fibrous cap and a lower internal pressure led to an increase of the fatigue life. The novelty here would be the implementation of the fatigue calculation considering a three-dimensional domain, rather than the two-dimensional analysis of idealised cross-sections performed in the

study by Versluis et al. In addition, since one of the main factors they identified was the stiffness of the lipid core, it would be useful to relate that with the results reported in Chapters 4 and 5 of this thesis, where the stiffness of the lipid core was found to significantly affect the stress distributions along the artery wall (and, ultimately, the potential location of the rupture). A later study also identified some geometrical features, such as the thickness of the fibrous cap and the lipid core volume, as important factors that could have an effect on the fatigue life of the vessel [167].

6.4 Patient-specific mesh and convergence analysis

Once the patient-specific geometry has been obtained and reconstructed with the appropriate software, a mesh is required in order to perform the numerical simulations. This process would be analogue to the one outlined in Chapters 3, 4 and 5. It is expected that the patient-specific model would be more complex to mesh compared to the previous, idealised cases. Therefore, a specific pre-processing software may be required. However, the process of optimising the mesh would be the same, i.e. a mesh convergence analysis is needed in order to find an optimal compromise between accuracy and computational cost.

In Chapter 5, the model used to characterise a three-dimensional, eccentric plaque presented a plane of symmetry (shown in figure 5.2A). However, due to the irregular nature of a real plaque, the use of any symmetries that would simplify the subject-specific modelling is unlikely. Finding an optimal mesh discretisation is thus quite important and could prove to be challenging.

6.5 Results and discussion

Once the simulations are performed, it is important to choose the main goals of the analysis. Given that the work presented in this thesis focuses on the spatial distributions of the stress along the plaque, it would make sense to further investigate these distributions in a patient-specific geometry. This would also be a way of differentiating this work from previously published studies. Generally, the investigations of patient-specific models have focused on the peak stress values at a given instant during the period; some examples are the studies performed by Tang et al. [89, 103, 108]. However, the conclusions usually are only applicable to the specific geometry being analysed.

One immediate shortcoming arises from the nature of the model, as it is not straightforward to choose a suitable *edge* (such as the top and bottom edges studied in Chapter 5, for instance), in order to measure and compare the stress distributions. Gao and Long overcame this problem by analysing the peak stress values at different points along the vessel for subject-specific geometries [158]. On a subsequent study, they compared the wall stress for four patients, showing the whole stress field along the vessel for each case [91]. It was difficult however to make a proper comparison among the models, as the four plaques considered were quite different. They reported higher stress values when the lipid core volume increased and the cap thickness decreased, and also that considering more case studies would be desirable. An alternative way of making use of those results is proposed here: a comparison of the new data with the idealised models such as the ones investigated in this thesis. Therefore, an appropriate first stage would be to analyse the three-dimensional stress field on the inner wall of the vessel, and then focus on the axial planes that may provide the most significant comparison to a two-dimensional analysis. This process may become fairly difficult, depend-

ing on the complexity of the geometry. In addition, it would be important to ensure that no relevant information is left out of the study. Therefore, several planes should be considered. It is also worth mentioning Kock et al. approach, as they generated a two-dimensional model by sectioning the three-dimensional geometry obtained using MRI [90]. On the contrary, the analysis proposed in this chapter involves first a fully three-dimensional calculation in order to account for out-of-plane effects (which will inherently increase the computational cost), and then the sectioning of the model (to facilitate the comparison to the idealised cases).

Once the planes of analysis have been chosen, the first part of the study should be similar to those performed in Chapters 3, 4 and 5. Several differences are expected due to the irregular geometry, for example: the thickness of the fibrous cap may not be constant along the axial direction, hence impacting the stress distributions accordingly; the inner radius may present an irregular, axial variation as well, affecting the flow field; and an irregular shape of the lipid core may create a stenosis that is not symmetric with respect to the throat. Therefore, these new factors would likely play a role in a patient-specific geometry, and so they must be taken into account. Afterwards, a comparison with the idealised geometries should be possible.

It would be interesting to check which flow and solid features change with respect to the idealised models. Or, the other way around, to study what features that were identified before are still applicable in a patient-specific setting. The stress levels, for instance, should be similar or in the same order of magnitude, as the parameters used in the previous chapters were based on clinical observations from the literature. On the other hand, the shape of the curve that depicts the stress distribution along the plaque is expected to change. However, it would be interesting to check if the maxima

are located at the same positions, or if there are any other features from the idealised models that can be applied to the more complex case. For example, the local peaks at the ends of the core, as reported in Chapters 4 and 5, might be present in a subject-specific model as well. Ideally, this comparison between the idealised and the patient-specific configurations may help stratifying which plaques are more vulnerable and, consequently, more likely to rupture.

Another focus of the analysis can be the flow field. In particular, stationary, laminar conditions were investigated in this thesis. Nonetheless, given the irregular geometry of a more realistic plaque, the flow may present several disturbances due to the surface roughness. It should be interesting to consider the pressure distribution, as it was the driving force behind the wall displacements and the stress distributions (as shown in Chapter 3). If the pressure is not significantly affected by the irregularities of the geometry, then the conclusions found for the idealised models may be similar to those of the patient-specific case. Another issue would be the addition of the pulsatile flow. In particular, it would be interesting to analyse the flow field at the instant during the period when the pressure is maximum, in order to consider the most critical conditions. The oscillatory nature of the stresses due to the pulsatile flow could also lead to fatigue-related effects [68, 91], so this should be taken into account as well. If any failure models, as proposed in section 6.3.2, are considered, the analysis of the crack initiation and fatigue mechanics may be interesting as well.

As shown in Section 5.6.2, the stress distributions along the cross-section at the throat of the stenosis were mainly influenced by the thickness of the different components. This conclusion could be applied to a patient-specific case even prior to performing any simulations, once the geometry is known.

Among other features, some important parameters that would need to be investigated are: the shoulders of the plaque, the minimum thickness of the fibrous cap and the size and stiffness of the lipid core.

In Chapters 4 and 5, several factors that increase the overall stress levels and, therefore, increase the risk of rupture, have been highlighted: the positive remodelling of the artery, a low value of the stiffness of the lipid core, a shorter lipid core with an abrupt change of wall thickness and a thin fibrous cap. All these features could be studied in patient-specific cases and may help achieving the ultimate goal of identifying, from a mechanical point of view, which plaques are more likely to rupture.

6.6 Overall conclusions

At this point, it is worth summarising the conclusions that have been reported so far in this thesis.

In Chapter 3, numerical simulations were performed to model the flow through an axisymmetric stenosis. The wall was considered as linear elastic and with constant thickness. Two main parameters were studied: the Reynolds number of the flow and the stiffness of the wall.

It was reported that the Reynolds number primarily influenced the flow field. In particular, the length of the recirculation region downstream the stenosis, the wall shear stress distribution and the pressure drop along the stenosis were greatly impacted. On the contrary, the Reynolds variation showed little effect on the solid field.

On the other hand, the stiffness of the artery wall significantly affected the vessel-related variables. Indeed, the radial displacements and the stress distribution along the wall were largely influenced by the Young's modulus of

the artery. In particular, the stress levels increased when the stiffness of the vessel decreased. The sites of plaque rupture have been related to high stress values [108], so it was concluded that the material properties could affect the location of the rupture. In addition, the wall shear stresses were around three orders of magnitude smaller than the first principal stresses along the wall. Therefore, the key takeaway was that the material properties of the vessel were found to have a greater impact on the stress distributions along the artery (and, indicatively, the potential locations of rupture).

Overall, this chapter provided a general idea of the flow field and of the main parameters involved, while also showing the stress distributions that may be expected in this kind of geometries.

The next step was the two-dimensional modelling of the blood flow through an axisymmetric plaque, as introduced in Chapter 4. This model included a lipid core and a thin fibrous cap in the plaque region. The solid models were also refined and a hyperelastic formulation was used for the vessel, whereas the lipid core was still considered as a linear elastic material. The stiffness of the lipid core was considered to be around a hundred times smaller than that of the artery, as previously reported in the literature [62, 89].

A parametric analysis was performed and the following parameters were studied: the stenosis severity, the lipid core stiffness, the positive remodelling of the artery, the lipid core length and the fibrous cap stiffness. In general, it was found that whereas the flow field was relatively similar to the one observed for the thin-wall simulations, the stress distribution along the fibrous cap was significantly different due to the inclusion of the lipid core.

The degree of stenosis combined with the lipid core stiffness affected the most the maximum stress values. The positive remodelling also had a similar effect. A change of the stress distribution was reported depending on the

stiffness of the lipid core, which may influence the location of a rupture. The study of the length of the lipid core showed that a plaque with a short core (in the axial direction) and with an abrupt change of wall thickness was more vulnerable than a plaque with a long lipid core. In particular, the local stress peaks at the axial ends of the lipid core increased substantially, suggesting another potential location of a rupture. Finally, the stiffness of the fibrous cap did not affect the stress distributions for the range of values considered in this analysis.

Overall, the most interesting outcome was the variation of the axial stress distributions depending on the value of the different parameters considered. Based on this findings, three potential locations of plaque rupture were identified: the middle of the upstream and downstream regions of the stenosis (especially for lipid-filled plaques with significant area occlusion), the axial ends of the lipid core (for short cores rather than long ones), and also the middle of the stenosis (when the artery presented positive remodelling).

The final analysis introduced in Chapter 5 was the three-dimensional modelling of the plaque. In particular, an idealised, eccentric plaque was studied and compared to the results obtained in Chapters 3 and 4. The methodology was similar to the previous chapters: a parametric analysis in order to measure the influence of several variables reported to be significant in Chapter 4. The following features were investigated in detail: the shape of the axial ends of the lipid core, the positive remodelling of the artery, the lipid core stiffness and the lipid core length. In order to perform the study, five different geometries were considered. Among them, two two-dimensional models, such as the one analysed in Chapter 4, were included.

The main result was that several features observed for the two-dimensional geometries were still applicable to a three-dimensional setting. In particular,

the stress levels increased when the artery presented positive remodelling; they also increased when the lipid core stiffness decreased; and finally, the length of the core also showed a similar effect to the two-dimensional cases, since shorter lipid cores presented higher stress peaks. The midpoints of the upstream and downstream regions of the stenosis were the locations of the maximum stress values in several cases, indicating the location of a potential rupture. However, when the lipid core stiffness increased, the maximum was located at the throat of the stenosis. Due to the eccentricity, the stress distribution was also investigated in the cross-sectional direction. Again, the fibrous cap seemed to be the most vulnerable location, since the maximum was located always at the middle of the fibrous cap of the plaque. In addition, the different features of the cross-sectional distribution did not seem to be affected by the secondary flow and were explained by considering the thicknesses of the model in that direction.

Another part of the analysis focused on the flow field. It was shown that the axisymmetric model could provide a general picture of the expected flow behaviour. In addition, the only parameter affecting the flow was the shape of the stenosis, at least for the range of stenosis severity considered in the study (50-75 % area occlusion).

After performing the simulations proposed in this chapter, the past conclusions would be extended by new ones. As explained in the previous sections, a methodology similar to the one followed in Chapters 4 and 5 could be applied, so that the results could be compared. It would be interesting to check to what extent the conclusions still apply to a subject-specific model. This would mean that, given a certain plaque geometry, simple observations could be made depending on the features of the model considered (such as the shape of the lipid core). For instance, based on the conclusions obtained in

the idealised analyses, a short lipid core with an abrupt change of wall thickness in a patient-specific situation could indicate that the risk of rupture is greater at the ends of the core, before making any other studies. Another example would be the presence of positive remodelling: this would mean that the plaque is more vulnerable, as it was found that the overall stress levels increased compared to plaques with no remodelling. Supplemental information could be provided as well by analysing some measured values; for instance, the stiffness of the lipid core could provide valuable information.

Another comparison could be made regarding the flow profiles. The simulations performed in Chapters 3, 4 and 5 considered steady flow conditions. If a pulsatile profile is included in the patient-specific analysis, it would be useful to run a steady simulation as well. This would make it possible to evaluate whether the steady flow conditions are also a good approximation in a real plaque, especially in combination with the fatigue analysis proposed in this chapter.

In the previous chapters, idealised models were considered in order to simulate the flow through an atherosclerotic plaque. This made it possible to perform parametric analyses that highlighted how the idealised cases can be of interest. The work proposed in this final chapter would extend and complement that knowledge. Ideally, it would also improve the capabilities of those idealised cases in order to better understand the initiation of the plaque rupture process.

Appendix A

Validation of the flow solution

From a numerical point of view, due to the three-dimensional nature of the model presented in Chapter 5, the case is significantly more complex than those shown in Chapters 3 and 4. Due to the eccentricity of the geometry, the domain is no longer axisymmetric, and thus secondary flows appear in the cross-sectional planes. In order to confirm that the flow solution obtained with COMSOL was accurate, the code was validated against another computational fluid dynamics solver. The choice for this comparison was NEK5000 [123], which was introduced in Chapter 2.

This open-source solver is based on the spectral element method, and uses a high-order interpolation. In this case, a polynomial order of 8 was chosen, compared to the usual second order of the finite element method solvers. In addition, this software was a sensible choice as it has already been used to model similar stenotic geometries [29].

A direct numerical simulation (DNS) of a rigid-wall model was performed using the same flow parameters as those presented in Section 5.3.1. The simulation was started at lower Reynolds ($Re = 10$) in order to facilitate the numerical process. The flow solution was used as the initial condition for a

subsequent simulation at $Re = 100$. Again, the solution for this configuration was used as a initial condition for the simulation at $Re = 300$, which is the Reynolds number used in the present cases. The DNS was run until it reached a steady state and the flow variables did not experience further variations over time. Non-stationary flow was not observed in this simulation for $Re = 300$, which may be explained by considering the relatively low value of the stenosis severity (50 %), along with the smooth geometry of the lumen.

In order to compare the solutions obtained with both codes, the general flow field is presented in figure A.1, which shows the non-dimensional axial velocity, w/U , at the plane of symmetry, $y = 0$. Figure A.1A depicts the solution obtained with NEK5000, while figure A.1B shows the solution obtained with COMSOL. The scale of the velocity was the same in both cases and the flow fields resembled each other. The differences observed in the picture are mainly due to the different colour scheme used by each code.

The secondary flow was also compared by analysing the velocity in the x direction (u/U) at the throat of the stenosis. The solution obtained with NEK5000 is shown in figure A.2A, while the flow field predicted by COMSOL is presented in figure A.2B. Both cases showed again a closely matched flow field.

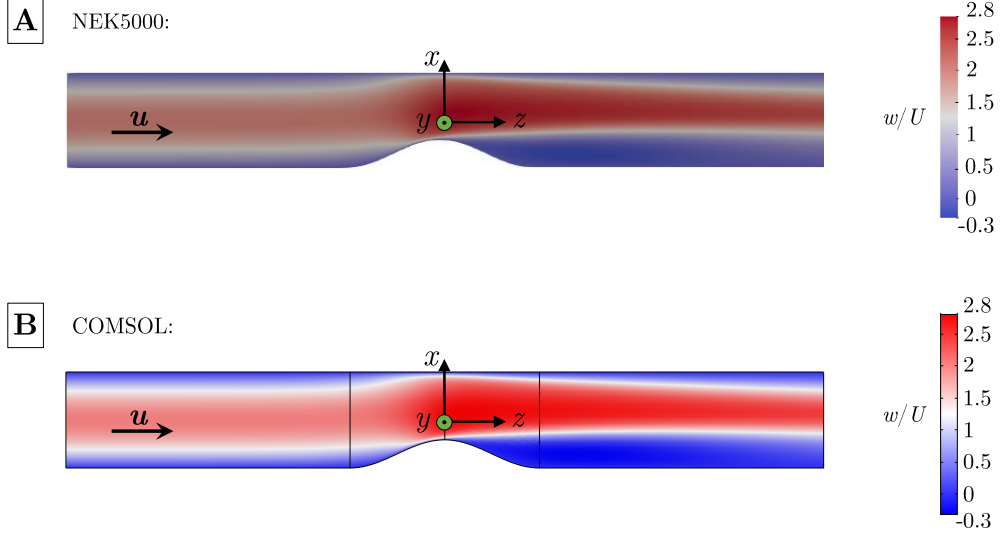


Fig. A.1: Representation of the flow field at the plane of symmetry, $y = 0$. (A) Non-dimensional axial velocity field, w/U , obtained with NEK5000. (B) Non-dimensional axial velocity field, w/U , obtained with COMSOL.

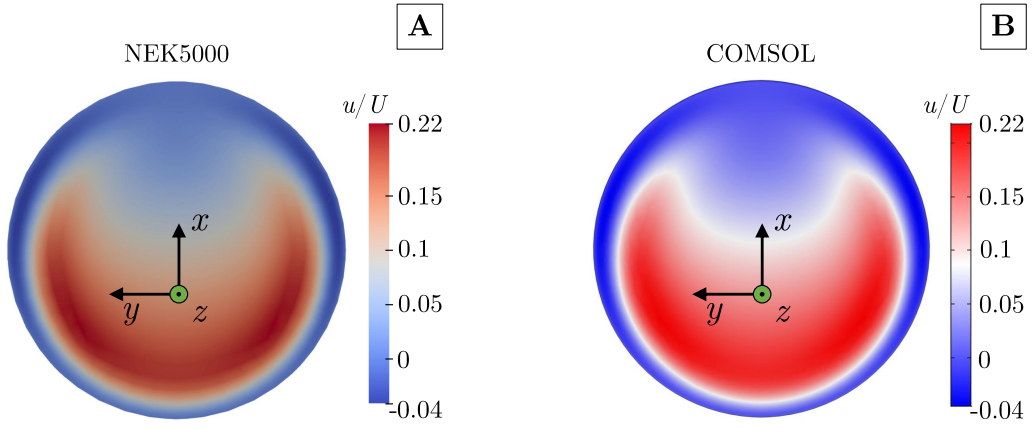


Fig. A.2: Representation of the flow field at the cross-section $z = 0$. (A) Non-dimensional velocity field, u/U , obtained with NEK5000. (B) Non-dimensional velocity field, u/U , obtained with COMSOL.

Finally, in order to provide a more accurate comparison of the two flow fields, the velocity profiles at two specific sections of the plane of symmetry were studied: figure A.3 shows the velocity profiles at the throat of the stenosis ($y = 0, z = 0$), while figure A.4 shows the velocity profiles at the downstream end of the stenosis ($y = 0, z = L/2$). As it can be seen in the figures, the curves in both cases matched each other well, as the relative error stayed below 0.5 %.

In summary, the 3-D simulations presented in Chapter 5, which were performed using COMSOL, have been validated against a high-order computational fluid dynamics solver. In addition, these results also suggest that the full two-way coupling simulation may not be required, as no significant effect of the wall deformation on the flow field was observed for the material properties considered in this case.

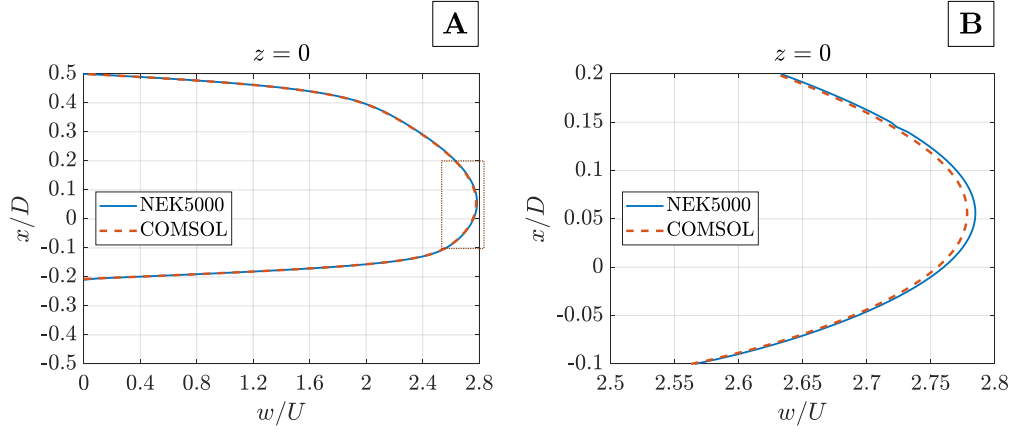


Fig. A.3: (A) Non-dimensional velocity profiles obtained with COMSOL and with NEK5000 at $y = 0, z = 0$. (B) Zoomed-in section.

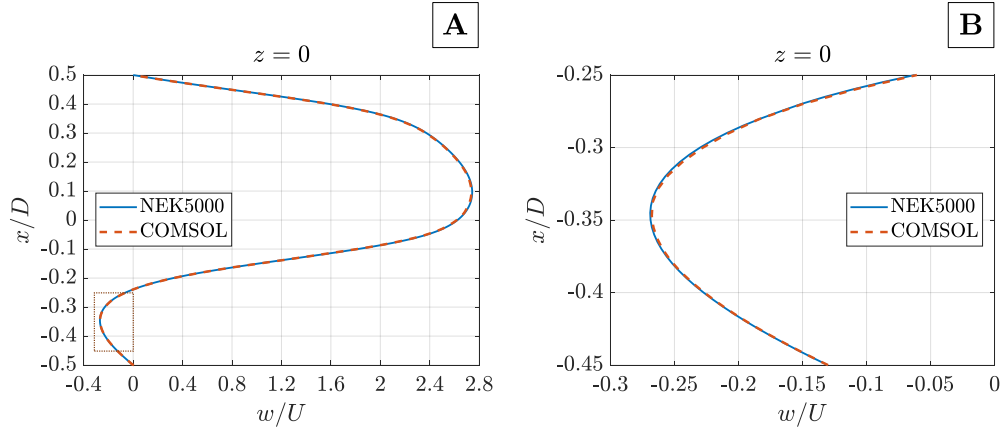


Fig. A.4: (A) Non-dimensional velocity profiles obtained with COMSOL and with NEK5000 at $y = 0, z = L/2$. (B) Zoomed-in section.

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