Computational Fluid Dynamics Indicators to Improve Cardiovascular Pathologies Diagnosis

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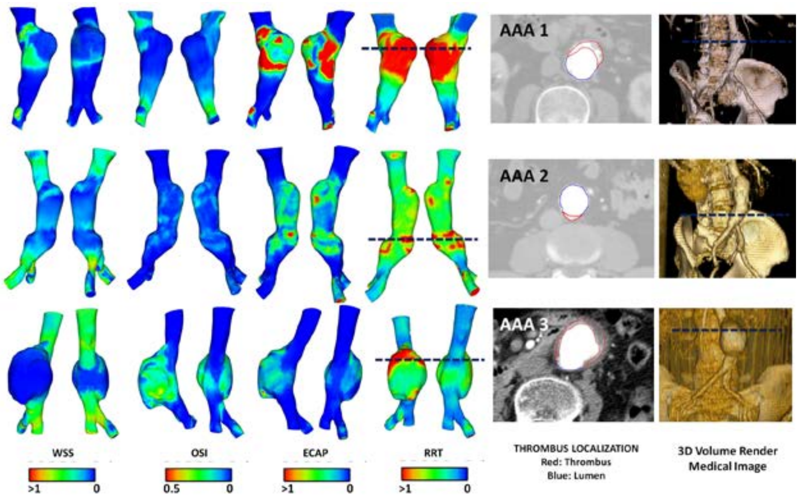

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COMPUTATIONAL FLUID DYNAMICS INDICATORS TO IMPROVE CARDIOVASCULAR PATHOLOGIES DIAGNOSIS
Monograph CIMNE M167

Dedicated to
my father...

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Eduardo Soudah Prieto
Barcelona, 2016

Presentation

The studies included in the monograph belong to the same research line, leading to three papers already published in international journals.

Paper 1.
Title: A Reduced Order Model based on Coupled 1D/3D Finite Element Simulations for an Efficient Analysis of Hemodynamics Problems.
Authors: E.Soudah, R.Rossi, S.Idelsohn, E.Oñate.
Journal: Journal of Computational Mechanics. (2014) 54:1013-1022.
DOI: 10.1007/s00466-014-1040-2

Paper 2.
Title: CFD Modelling of Abdominal Aortic Aneurysm on Hemodynamic Loads using a Realistic Geometry with CT.
Authors: E.Soudah, E.Y.K. Ng, T.H Loong, M.Bordone, P. Uei and N.Sriram.
Journal: Computational and Mathematical Methods in Medicine. Volume 2013 - 472564, 01/06/2013.
DOI: 10.1155/2013/472564

Paper 3.
Title: Mechanical stress in abdominal aortic aneurysms using artificial neural networks.
Authors: Eduardo Soudah, José F. Rodríguez, Roberto López
Journal of Mechanics in Medicine and Biology. Vol. 15, No. 3 (2015) 1550029
DOI: 10.1142/S0219519415500293

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Abstract

In recent years, the study of computational hemodynamics within anatomically complex vascular regions has generated great interest among clinicians. The progress in computational fluid dynamics, image processing and high-performance computing have allowed us to identify the candidate vascular regions for the appearance of cardiovascular diseases and to predict how this disease may evolve. In this monograph we attempt to introduce into medicine the computational predictive paradigm that has been used in engineering for many years. Several groups have tried to create predictive models for cardiovascular pathologies, but they have not yet begun to use them in clinical practice. Our final aim is to go further and obtain predictive variables to be used in the clinical field.

We try to predict the evolution of aortic abdominal aneurysm, aortic coarctation and coronary artery disease in a personalized way for each patient. We propose diagnostic indicators that can improve the diagnosis and predict the evolution of the disease more efficiently than the methods used until now. In particular, a new methodology for computing diagnostic indicators based on computational hemodynamics and medical imaging is proposed. We have worked with data of anonymous patients to create real predictive technology that will allow us to continue advancing in personalized medicine and generate a more sustainable health systems. The objective of this monograph is therefore to develop predictive models for cardiovascular pathologies by merging medical imaging and computational techniques at a clinical level.

It is expected in the near future that larger databases of patient-specific computational models will be available to doctors. These data can be used with predictive models to improve diagnosis and to define personalized therapies and treatments.

Resumen

Durante los últimos años, el estudio de las enfermedades cardiovasculares mediante el uso técnicas computacionales ha generado muchas expectativas en el campo de la medicina. Los avances realizados en técnicas de procesamiento de imágenes, métodos computacionales y el uso de grandes procesadores de cálculo han permitido identificar y correlacionar variables hemodinámicas con los estados incipientes o de desarrollo de patologías cardiovasculares. Hoy en día la medicina se basa en el diagnóstico, pero en esta monografía queremos tratar de introducir el concepto de medicina computacional preventiva. El objetivo principal es desarrollar modelos preventivos basados en indicadores de diagnóstico para patologías cardiovasculares combinando procesamiento de imágenes y técnicas computacionales.

En esta monografía, tratamos de predecir la evolución de aneurismas abdominales, la formación del trombo intraluminal en el interior del saco aneurismático, el estudio de la ateroesclerosis y de la coartación de aorta, así como, posibles problemas derivados de la válvula aórtica de manera personalizada. Para entender cómo una patología cardiovascular evoluciona y cuándo va a convertirse en un riesgo para la salud, es necesario desarrollar una metodología eficiente que permita calcular indicadores de diagnóstico. En esta monografía, hemos propuesto indicadores de diagnóstico basados en técnicas computacionales e imágenes médicas que pueden mejorar el diagnóstico y a la vez predecir la evolución de una patología de manera más eficiente que los métodos utilizados hasta ahora. Sin embargo, el objetivo final es llevar dichos indicadores a la práctica clínica. Actualmente estamos trabajando con datos de pacientes anónimos para crear una gran base de datos que nos permita avanzar en la medicina personalizada y en la generación de sistemas de salud más sostenibles. Es de esperar que en el futuro existan estas bases de datos a disposición de los médicos, y que estos datos sirvan para mejorar el diagnóstico y definir tratamientos personalizados.

Resum

En els últims anys, l'estudi de l'hemodinàmica computacional en regions vasculars anatòmicament complexes ha generat un gran interès entre els clínics. El progrés obtingut en la dinàmica de fluids computacional, en el processament d'imatges i en la computació d'alt rendiment ha permès identificar regions vasculars on poden aparèixer malalties cardiovasculars, així com predir-ne l'evolució. En aquesta tesi s'intenta introduir en la medicina el paradigma computacional predictiu utilitzat des de fa molts anys en l'enginyeria. Diversos grups han tractat de crear models predictius per a les patologies cardiovasculars, però encara no han començat a utilitzar-les en la pràctica clínica. El nostre objectiu és anar més enllà i obtenir variables predictives que es puguin utilitzar de forma pràctica en el camp clínic.

Tractem de predir l'evolució de l'aneurisma d'aorta abdominal, la coartació aòrtica i la malaltia coronària de forma personalitzada per a cada pacient. Per entendre com la patologia cardiovascular evolucionarà i quan suposarà un risc per a la salut, cal desenvolupar noves tecnologies mitjançant la combinació de les imatges mèdiques i la ciència computacional. Proposem uns indicadors que poden millorar el diagnòstic i predir l'evolució de la malaltia de manera més eficient que els mètodes utilitzats fins ara. En particular, es proposa una nova metodologia per al càlcul dels indicadors de diagnòstic basada en l'hemodinàmica computacional i les imatges mèdiques. Hem treballat amb dades de pacients anònims per crear una tecnologia predictiva real que ens permetrà seguir avançant en la medicina personalitzada i generar sistemes de salut més sostenibles. Per tant, l'objectiu d'aquesta tesi és el desenvolupament de models predictius de patologies cardiovasculars mitjançant la fusió d'imatges mèdiques i tècniques computacionals a nivell clínic.

Es pot preveure que en el futur tots els metges disposaran de bases de dades de tota la nostra anatomia, fisiologia i models computacionals. Aquestes dades es poden utilitzar en els models predictius per millorar el diagnòstic i definir teràpies o tractaments personalitzats.

Chapter 1

Introduction

Clinical evidences have always allowed us to identify the candidate vascular regions for the appearance of cardiovascular diseases and to predict how these diseases may evolve. These clinical evidences are usually based on biological markers or anatomical indicators. However, over the last few years, thanks to the progress in computational hemodynamics, imaging processing, geometry reconstruction techniques and the increase in high-performance computing, variables such as, wall shear stress, wall elasticity, vorticity, turbulent kinetic energy, flow patterns or pressure drop, among others, have become new clinical evidences or diagnostic indicators (DIs), especially for cardiovascular diseases (CVD). Previously, patient-specific simulations were typically applied in advanced stages of disease progression, and consequently, from a medical point of view were a diagnosis-costly ineffective. In that sense, computational hemodynamics has emerged as a promising tool to estimate these new DIs and it's playing a key role in the understanding of CVD hemodynamics. The correlation of these new DIs with patient-specific data is needed to predict the development of cardiovascular pathologies and to improve the surgical strategies. In fact, these DIs are increasingly becoming a clinical reference standard for early diagnosis, treatment and prognosis allowing a better stratification of patients with disease stage adapted therapy instead of escalating to the most aggressive and costly therapy. Therefore, the precise knowledge and understanding of computational hemodynamics has become a necessity of the medical community, which includes the cardiovascular physiology, medical imaging and Computational Fluid Dynamics (CFD).

The purpose of this chapter is to give an outline of the most common diagnostic indicators used in cardiovascular diseases, as well as, the objectives and the methodology used in this monograph.

1.1 Biomechanical forces

It is well-known that the interactions of pulsatile blood flow with arterial geometries generate complex biomechanical forces on the vessel wall with spatial and temporal variations [1]. Those biomechanical forces act over the internal layer of the arteries, endothelium. The endothelium produces a wide array of biochemical signals (homeostatic mediators) under physiological conditions [2][3] keeping the artery healthy. A key stimulus to maintain the protective status of the endothelial lining at the inner vessel wall is the tangential force that blood flow exerts on it; this tangential force is known as wall shear stress (WSS) (see figure 1.1). Fluctuations of the wall shear stress provoke changes in the biochemical signals[4], may arise the initiation and progression some cardiovascular diseases. For example, the growth or possibly rupture of the aneurysm wall[5], plaque instability in the carotid bifurcation[6][7] or in the coronaries [8][9], thrombus formation[10][11] or playing an important role in atherogenesis[12][13]. From a clinical stand point, the assessment of hemodynamic forces within the cardiovascular system circulation is still a challenge for the medical community, due to the three dimensional blood flow patterns close to the arterial wall needs to be measured in vivo. For that reason, computational hemodynamics has emerged as important tool for the clinician, allowing to quantify those hemodynamic forces and to correlate with the progression of cardiovascular pathologies.

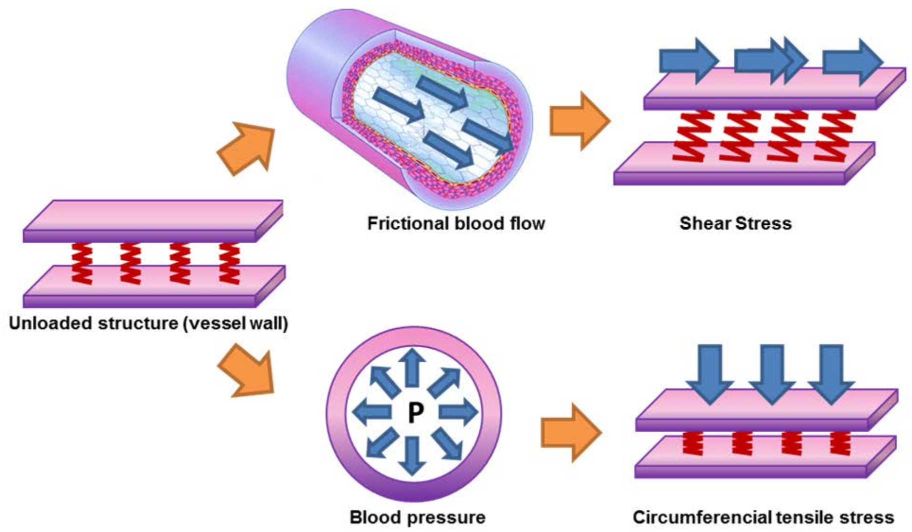

Figure 1.1: Biomechanical forces acting on the arterial wall. Blood pressure and blood flow induce forces in the vascular system that lead the initiation or progression of some cardiovascular diseases. Blood pressure produces a force directed perpendicular to the vessel wall. As a consequence, the cylindrical structure will be stretched circumferentially, resulting in a circumferential stress. In contrast, the force induced by a difference in movement of blood and the non-moving vessel wall leads to stress and strain parallel to the surface of endothelial cells. Due to its shearing deformation, this is called a shear stress. This shear stress exerts its main effects through the activation of mechanosensitive receptors and signalling pathways.

1.2 Diagnostic Indicators

As pointed out, blood flow induces a reaction force F_μ over vessel wall. The reaction force depends of the contact surface, blood-surface interface and velocity gradient between the vessel wall and blood adjacent layers[14]. For a viscous isotropic incompressible fluid, the constitutive relation between τ_{ij} and the strain rate tensor $d_{ij} = 1/2 \cdot (u_{i,j} + u_{j,i})$ is:

$$\tau_{ij} = 2 \cdot \mu \cdot d_{ij} = \mu \left(\frac{\delta u_i}{\delta x_j} + \frac{\delta u_j}{\delta x_i} \right) \tag{1.1}$$

where μ is fluid dynamic viscosity, where $\mathbf{u}$ the fluid velocity, $\delta / x_{i,j}$ is the distance to the vessel wall and τ_{ij} is the wall shear stress. If τ_{ij} is proportional to the deviatoric stress tensor (relation between the shear stress and the strain rate is linear), the fluid is known as Newtonian fluid. And when the relation between the deviatoric shear stress and the strain rate tensor is nonlinear, the fluid is known as Non-Newtonian fluid. Therefore, the relationship between the deviatoric stress tensor and the strain rate tensor models defined the rheological behavior of a fluid. Perktold et al.[14] pointed out how the errors deriving from employing a Newtonian model for blood yield non-essential differences in flow characteristics and wall shear stress distributions. In this monograph, a rigid wall (no slippage is allowed) and blood (see appendix A) as Newtonian fluid are considered, therefore WSS can be defined as:

$$\tau_{ij} = \textbf{WSS} = \mu \cdot \dot{\gamma} = \mu \cdot \frac{\delta u_j}{\delta x_i} \tag{1.2}$$

where $\dot{\gamma}(\sec^{-}1)$ is the shear rate $(\delta u_j / \delta x_i)$, where $\mathbf{u}_j$ is the parallel blood fluid velocity to the wall and x_i the normal distance to the arterial wall. Usually, WSS distributions is normalized by the average parent vessel WSS in the same patient to allow comparison among different patients[15][16]. Figure 1.2 shows the blood flood hemodynamic forces acting on vessel wall.

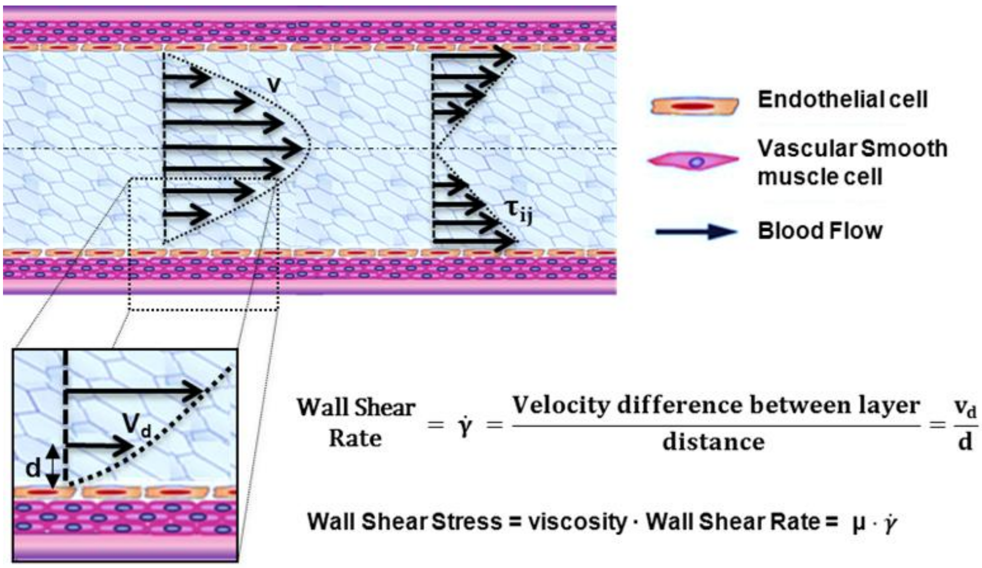

Figure 1.2: Hemodynamic forces that act on blood vessels. Wall shear stress (WSS) is proportional to the product of the blood viscosity (μ) and the spatial gradient of blood velocity at the wall (dv/dy).

When analyzing a cardiac flow (pulsating flow), it may be of interest to quantify the average load at a certain instant of the cardiac cycle, as time averaged WSS (TAWSS).

$$TAWSS = \frac{1}{T} \cdot \left| \int_0^T \mathbf{WSS} \cdot dt \right| \tag{1.3}$$

where WSS is the instantaneous shear stress vector and T is the duration of the cycle. Another parameter related to WSS oscillations is the oscillatory shear index (OSI)[6]:

$$OSI = \frac{1}{2} \left[1 - \frac{\left| \int_0^T \mathbf{WSS} \cdot dt \right|}{\int_0^T |\mathbf{WSS}| \cdot dt} \right] \tag{1.4}$$

Oscillatory shear index is used to identify regions on the vessels wall subjected to highly oscillating WSS values during the cardiac cycle. For example, a purely oscillatory flow with equal forward and backward contributions will produce an OSI of 0.5; however, in unidirectional flows the OSI will be identically zero. High OSI induces region with perturbed endothelial alignment. These regions are usually associated with bifurcations flows and vortex formation that are strictly related to atherosclerotic plaque formation and fibrointimal hyperplasia.

Based on wall shear stress, and its temporal and spatial variations, other indices have been proposed to capture the mechanobiological effects over the endothelium[17], such us, relative residence time(RRT)[18], particle residence time(PRT)[19] or endothelial cell activation potential (ECAP)[11]. Relative Residence Time (RRT) is defined as the state of disturbed flow. The residence time of the blood near the wall is reflected by combination of WSS and OSI. Mathematically, RRT is inversely proportional to the magnitude of the time-averaged WSS vector:

$$RRT = \frac{1}{(1 - 2 \cdot OSI) \cdot TAWSS} \tag{1.5}$$

The particle residence time describes flow stagnation or recirculation, for example in the abdominal aneurysm [11] or cerebral aneurysm [20]. ECAP is defined the endothelial susceptibility, and correlate the TAWSS with the OSI:

$$ECAP = \frac{OSI}{TAWSS} \tag{1.6}$$

The main purpose of this index is to identify local regions of the wall that can be exposed to prothrombotic WSS stimuli. Higher values of the ECAP index will thereby correspond to situations of large OSI and small TAWSS, that is, i.e. in abdominal aneurysm, intraluminal thrombus (ILT) development.

Nowadays, the combination of these WSS based-indicators are employed as promising hemodynamic predictors of the cardiovascular pathologies. Although, computational methods, medical imaging resolution and acquisition speed have increased over the past decades, assessment of

WSS is still challenging in complex flow geometries [21][22][23][24]. For that reason, a good modelization combined with a numerical simulation is still needed (see figure 1.3).

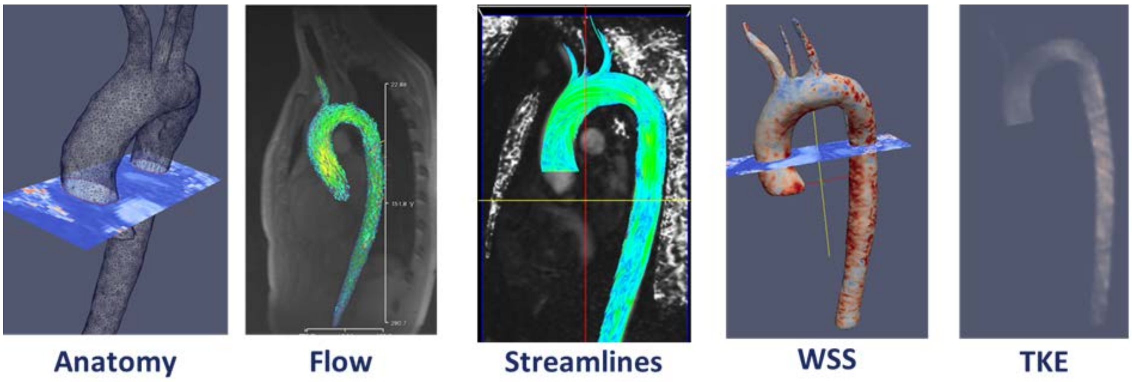

Figure 1.3: Diagnostic Indicators in a patient-specific model

Other importance feature in many cardiovascular diseases is the helical flow patterns and turbulent blood flow, characterized by fast random temporal and spatial velocities fluctuations[25]. These irregular and rapid fluctuations are not present in healthy situations, and play also a key role in some cardiovascular pathologies. The helical flow patterns show a measure(index) of blood flow complexity, and therefore, is an important factor in the development of cardiovascular disease, as shown in figure 1.4. Given the fluid flow velocity vector field **u**, the vorticity vector field **w** is the curl of the velocity field:

$$\mathbf{w} = \nabla \times \mathbf{u} \tag{1.7}$$

Basically, the vorticity vector points along the axis of spin, and the magnitude of the vorticity vector encodes the rate of spin. Given the vorticity vector field, mathematicians introduce several useful additional concepts: vortex lines, vortex sheets and vortex tubes. Technically speaking, vortex lines are the integral curves of the vorticity vector field; this simply means that vortex lines are curves which are tangent to the vorticity field at each point. Vortex sheets, meanwhile, are surfaces which are tangent to the vorticity field at all points. Vortex tubes are three-dimensional regions obtained by taking a 2 dimensional area orthogonal to the vorticity field, and then taking all the vortex lines through that area. Now, the **helicity (h)** is defined as the inner product of the velocity and the vorticity:

$$\mathbf{h} = \mathbf{u}\,\mathbf{w} \tag{1.8}$$

Thus, if the streamlines of the fluid are orthogonal to the vorticity, then the helicity is zero. This is the case with a transverse vortex. In the case of a longitudinal vortex, the helicity is non-zero, and measures how tightly the streamlines corkscrew along a vortex tube. In fact, the helicity of a vortex tube can be defined by integrating the helicity field:

$$\mathbf{H} = \int \mathbf{u} \cdot (\nabla \ x \ \mathbf{u}) \cdot d^3 r \tag{1.9}$$

It is a theorem of inviscid fluid mechanics that the helicity of a vortex tube is preserved over time. However, if a vortex tube is stretched, then its cross sectional area decreases, and the magnitude of the vorticity w increases, lowering the pressure at the center of the vortex. So, from a blood flow dynamics, the stretching of longitudinal vortex tubes could be a indicators of a cardiovascular pathology [26]. These effects are directly correlated with the oscillatory shear index [6].

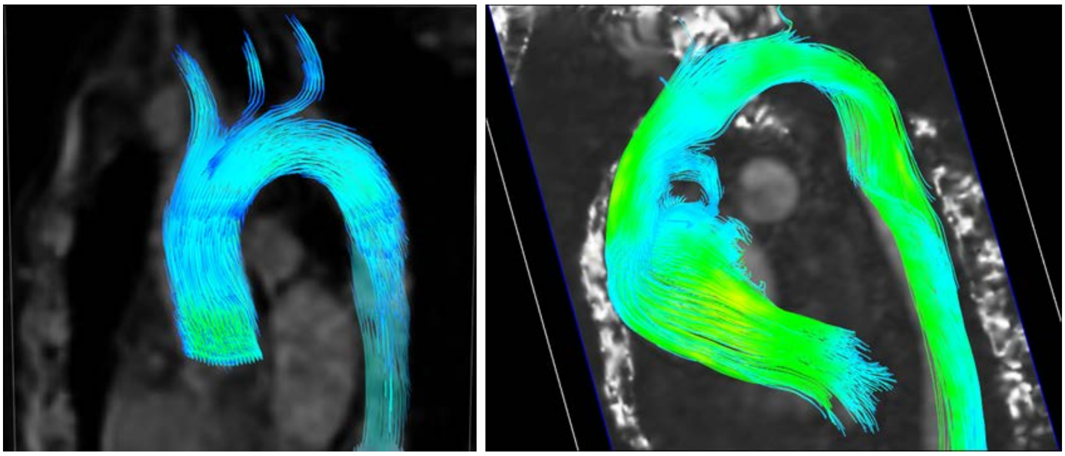

Figure 1.4: Left: Streamlines in a healthy aorta. Right: Streamlines in unhealthy aorta

Another index to evaluate blood complexity is to measure the Turbulent Kinetic Energy (TKE). The velocity and the turbulent kinetic energy combined can give a visualization of disturbed flow. Increased level of TKE indicates more turbulent flow, and it is undesirable for the cardiovascular system. For this reason, analyzing and understanding energy transfer and dissipation in some cardiovascular pathologies is important for the clinician. From mathematical point of view, the turbulent kinetic energy is calculated and defined as half sum of the variance of the velocity fluctuations:

$$TKE = \frac{1}{2} \cdot (\overline{u'^2} + \overline{v'^2} + \overline{w'^2}) \tag{1.10}$$

The pressure is also an important indicator about the arteries status, due to represents the hemodynamic forces within the cardiovascular system circulation. Nowadays, the pressure drop (or gradient) has been evaluated as powerful predictors of epicardial coronary disease or aortic Coarctation. From a clinical standpoint, the assessment of hemodynamic forces within the coronaries circulation (or Aorta) is still difficult, because pressure can be only measured invasively and flow cannot be measured directly with Doppler ultrasound in small deep coronary vessels, as the coronaries.

For that reason, computational hemodynamic becomes a promising tool to estimate the pressure non-invasively. For example, pressure-derived myocardial Fractional Flow Reserve index(FFR) is the standard goal for determining the physiological significance of a coronary stenosis[27]. FFR index is calculated as the ratio of the distal pressure to the stenosis/coartaction by the proximal pressure to the lesion in a non-rest situation (or maximum effort). Furthermore, the clinicians are able to reproduce several patient-conditions modifying the boundary conditions of computational model, based only on a medical image. The clinicians should simulate a non-inducing stress situation to the patient reducing the intervention costs. The capability of computing the pressure drop without pressure-wire has gained wide acceptance in the clinical community in the recent years[28][29].

1.2.1 Clinical practice & Diagnostic Indicators

The purpose of this section is doing a review of how the diagnostic indicators (above mentioned) can be applied into a clinical practice.

1.2.1.1 Atherosclerosis

Atherosclerosis is a disease in which plaque builds up inside your arteries. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries, and in advanced phases of atherosclerosis, plaque becomes vulnerable. This limits the flow of oxygen-rich blood to your organs and other parts of your body and a possible rupture of vulnerable (or unstable) plaque exposes thrombogenic material, such as collagen to the circulation and eventually induces thrombus formation in the lumen. Plaque rupture can occur whenever plaque stress exceeds the plaque strength and thus the prediction of plaque rupture may be augmented by accurate assessment of hemodynamic forces [30]. Atherosclerosis can affect any artery in the body, including arteries in the heart, brain, arms, legs, pelvis, and kidneys, and mainly affects middle and large sized arteries near side branches and at the inner bend of curved segments. At these locations, the average normalized drag force of the flowing blood acting on the vessel wall, the wall shear stress (WSS), is low and/or turbulent leading to endothelial dysfunction and ingress of lipids into the vessel wall, initiating an inflammatory response. Thus in the early phases of the disease WSS can predict locations of plaque initiation and progression[31]. In more advanced stages of disease, when plaque growth results in lumen narrowing, the local WSS patterns will change such that certain plaque regions to mainly located upstream- are exposed to elevated WSS[32]. Evidence is accumulating that the elevated WSS influences plaque composition in such a way that it induces local weakening of the plaque, making plaque regions exposed to high WSS prone to rupture[33][34] [35]. Clinical studies confirmed these findings: plaque rupture, both in coronary arteries and carotid arteries are observed more frequently in the upstream of the plaque[36][37][38]. Shear stress with a low mean or maximum value and varying direction (oscillating shear stress) has been associated with development of plaque vulnerability. As a result, different diseases may develop based on which arteries are affected, for example, acute myocardial infarction is mainly triggered by rupture of so-called vulnerable plaques in the

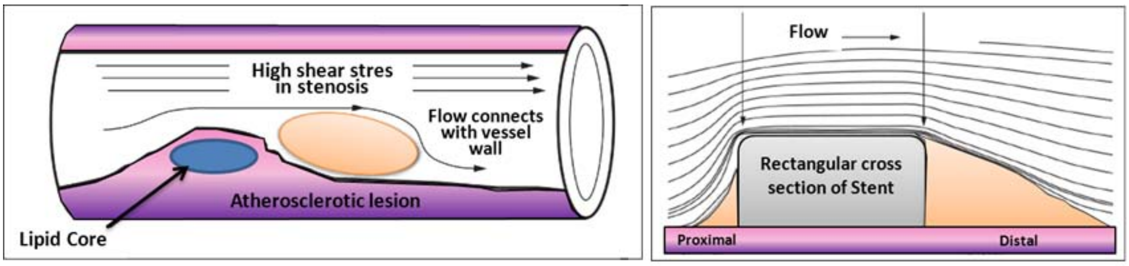

Figure 1.5: Left, Atherosclerosis lesion. Right, Flow around rectangular section of stent

coronary arteries linked with the coronary stenosis. In [39] there is a review comparing the localization of atherosclerotic lesions with the distribution of haemodynamic indicators calculated using computational fluid dynamics.

1.2.1.2 Coronary Artery Disease

Coronary artery disease(CAD) is the most common type of heart disease and cause of heart attacks. CAD is caused by abnormal narrowing of the coronary arteries (coronary stenosis) resulting in reduction of blood flow to the heart. The stenosis impedes to deliver oxygen to the heart muscle, which provoking heart attack. This disease is directly related with the atherosclerosis plaque. When stenosis occurs, the common clinical practice for decision taking related to the need (or not) of implanting a stent in a obstructed coronary artery requires the measurement of the Fractional Flow Reserve (FFR). FFR is derived from measuring the ratio of aortic pressure and pressure beyond a stenosis. Stenting is a specialized treatment for coronary arteries that are narrowed or blocked by plaques. It involves placing a balloon into the narrowed portion of the coronary artery with a surrounding wire mesh (stent). When the balloon is expanded, the stent remains in the vessel keeping the plaque pushed outwards, to let blood flow to the heart pass by.

From the technical point of view, invasive FFR measurement is often flawed by submaximal hyperemia (underestimating the stenosis severity) and by issues related to the guiding catheter[27]. A large guiding catheter may interfere with maximum blood flow and a guiding catheter with side holes may influence proximal coronary pressure and interfere with intracoronary administration of adenosine. Animal studies have suggested that a significant portion of subjects undergoing invasive FFR with adenosine do not achieve maximal hyperemia[40]. This suggests that the physiologic significance of some lesions may be underestimated when using standard current vasodilator doses and that higher, potentially toxic doses, may be needed in order to achieve maximal hyperemia. From clinical point of view, invasive FFR is unable to depict the coronary culprit lesion in cases of serial coronary lesions or in case of lesions in side branches of bifurcations[41][42]. For this reason less than 10% of European patients are subject to an invasive FFR measurement. In recent years, several alternative methods based on Computational Fluid Dynamics (CFD) have been proposed for non-invasive estimation of coronary blood flow circulation [43]. CFD has been applied to coronary computed tomography angiography for computation of FFR. However, accuracy of method[44][45] and diagnostic accuracy remains suboptimal[46]. The main challenges for

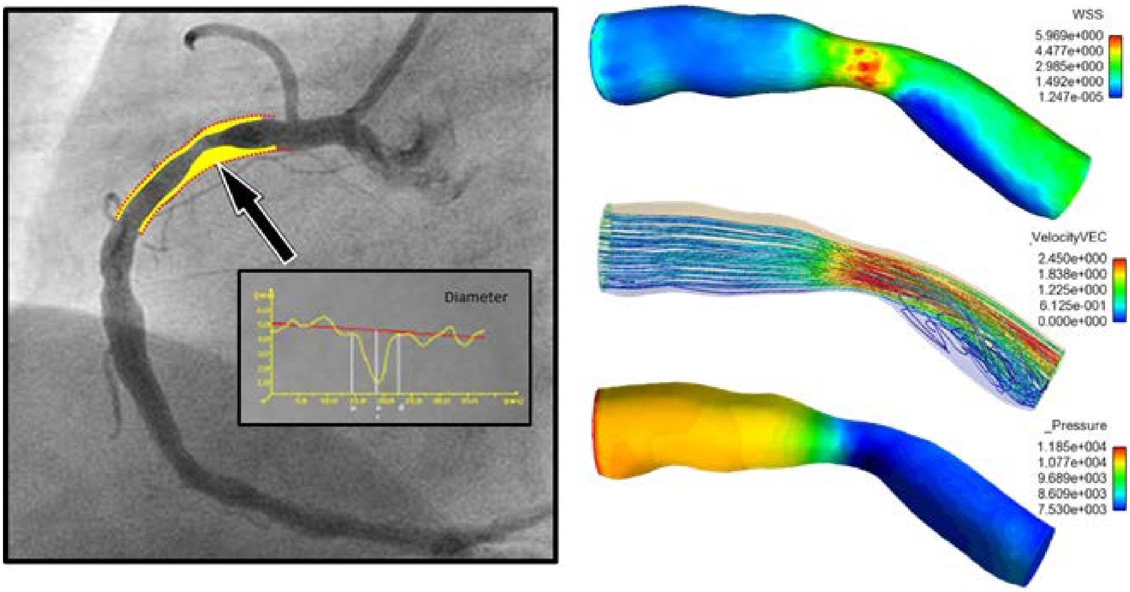

Figure 1.6: Streamline and wall shear stress in a coronary artery

such methods are the lack of patient-specific data including anatomy, patient-specific boundary conditions, the condition of the microvasculature of the myocardium, and the large-scale computational resources required for the complex calculations. In [47] pressure gradients are computed using CFD in which the geometry of the aorta is extracted from MRA. Additional MR Phase contrast imaging is performed to measure the velocity which is used as boundary conditions. In [28] lumped parameter models of the heart, systemic circulation and coronary microcirculation are coupled to a patient specific 3D model of the aortic root and epicardial coronary arteries extracted from CTA. Disadvantages of these approaches are that all calculations are performed exclusively in 3D as well as the fact that the calculations cannot be performed during intervention because of the need for CT. Moreover, one vital piece of information is still missing in CFD, namely the condition of the coronary circulatory auto-regulation, also known as the patients cardiac flow reserve. This results in a method that is of high computational complexity. A recent study applied CFD to three dimensional X-ray angiography for the computation of the FFR incorporating the coronary flow reserve[48]. However, this method requires X-ray angiographic imaging during hyperemia which is a burden to the patient. Placing known side effects of adenosine into perspective; reduced blood flow to the heart which might worsen symptoms in patients with coronary heart diseases or even cause a heart attack, this is clearly an undesired situation especially during diagnostic coronary angiography.

1.2.1.3 Aortic Aneurysms

The aortic dilatation is an asymptomatic disease with complicated and lethal sharp pains that can occur anywhere in the human aorta. By definition, if the aorta diameter at least is 50% greater than the normal size of the aorta produces what is called *aneurysm*. And if this occurs in the thoracic aorta is termed a Thoracic Aortic Aneurysm(TAA), in the abdominal aorta is named Abdominal Aortic Aneurysm(AAA). However, the aneurysm pathogenesis is still unknown. It is thought that

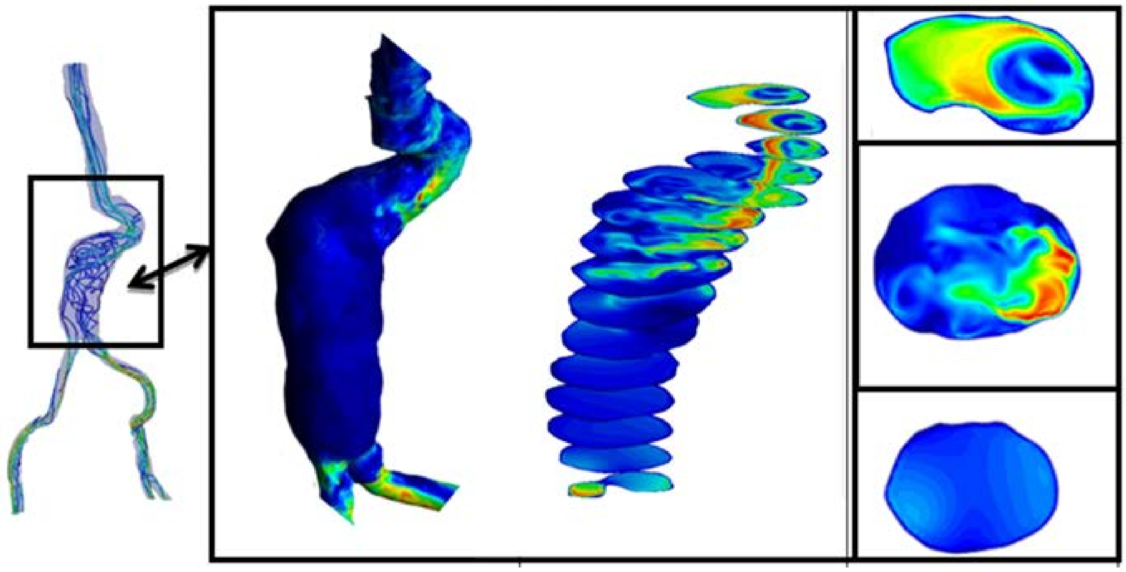

Figure 1.7: Diagnostic Indicators in Aortic Abdominal Aneurysm. Streamlines, wall shear stress and velocity profiles at different sections of the aneurismatic sac.

the initial dilatation is caused partly by degeneration of the medial elastin and smooth muscles in the arterial wall or by the effect of the wall shear stress. Vessel wall remodeling as a result of shear stress alteration is accompanied by synthesis and secretion of *NO*, growth factors and metalloproteins, which contribute to aneurysm pathogenesis. Genetics and risk factors like smoking, hypertension, chronic obstructive pulmonary disease(COPD), inflammation and atherosclerosis play key roles in aneurysms genesis and progression[49]. In this context, there are few predictors of the aorta dilatation available in the clinical practice. Mainly, they are based on the aortic diameter and increasing aortic size. Currently, the accepted values have been changing over time and they are actually being discussed by the groups with experience, for example, [50][51] in TAA patients or [52][53] in AAA patients. There is also a hemodynamic factor of parietal stress in the aortic dilatation, which is currently a little-known factor. Prior works, related TAA, have confirmed the presence of different flux in bicuspid aortic valve without aortic dilation compared to tricuspid aortic valves patterns by using cardiac magnetic resonance imaging (cardiac MRI). Abnormal flow patterns have been also detected in aneurysms located in the ascending aorta which confirms flow jets to the anterolateral wall of the aorta [54]. It is also known that shear stresses play an important role in the initiation, progression and rupture of aneurysms[55][56]. Vorticity inside the aneurysm is connected to aneurysm plaque or thrombus formation [5][11]. Figure 1.7 shows some DI's in an Aortic Abdominal Aneurysm(AAA)[15].

1.2.1.4 Aortic Coarctation

Aortic coarctation(CoA) occurs approximately in 10% of patients with congenital heart defects and represents a narrowing of the descending aorta (see paper 1). Due to the reduction in the aorta descending diameter, high pressure gradients can appear across the CoA, resulting in an increased cardiac workload in the left ventricle during systole [57]. The narrowing of the aorta creates a flow jet with high velocity, inducing a very complex turbulent flow field. Recently, researchers has characterized changes of hemodynamic parameters such as pulse blood pressure, aortic capacitance, and wall shear stress due to the presence of an aortic coarctation [57][58][59]. Hemodynamic changes caused by the coarctation can result in endothelial dysfunction [60], provoking non normal values of TAWSS or elevated OSI for CoA patients.

1.3 Objectives

The general objective in this monograph is improving computational hemodynamics to develop patient specific diagnostic indicators for an early identification of cardiovascular pathologies(and its progress). To reach this goal, this monograph attempts to improve the prior mathematical models used for cardiovascular system for a deeper understanding on the response of the cardiovascular system to:

- improve diagnostics and therapeutical procedures for Aorta Coarctation (paper 1 in Chapter 2),
- study the mechanical factors that may be important in triggering the onset of aneurysms (paper 2 in Chapter 3 and paper 3 in Chapter 4),
- combine medical images with computational hemodynamic to estimate DI's (Chapter 5) and
- use medical images data to generate computational model (paper 4 in Chapter 5).

Other applications studied based on the methodology developed in this monograph were, (i) study of new mechanical factor related to the AAA and (ii) studied the effect of vorticity and the eccentricity of the aortic bicuspid valve (in Chapter 6).

From the methodology point of view, a new methodology to compute diagnostic indicators based on computational hemodynamics has been proposed. In order to compute the pressure drop under different patient-specific situations, a reduced-order model has been developed in paper 1. The reduced-order method was implemented as part of the C++ finite element library KRATOS[61]. KRATOS is a multiphysics simulation open source (LGPL licence) framework based on the stabilized Finite Element Method for analysis of the Navier-Stokes equations in viscous flows. Efficient and parallel solvers for 3D fluid problems have been implemented in KRATOS that allow tackling large problems using supercomputers if available. The 1D model developed in this monograph was also implemented as new elements inside KRATOS. Blood was modeled as a Newtonian fluid with constant density and different outlet conditions were implemented. In appendix B a detail description of the implementation is shown.

Additionally, the diagnostic indicators have been correlated with the patient-specific geometry (paper 2). Once a 3D model of a vascular tree is obtained, the geometry is meshed having special attention in the near-wall region(boundary layer) using the tetrahedral (3D) elements. A good boundary layer mesh allows to properly capturing the sharp velocity gradients. The Navier-Stokes equations (see section 1.4.2) were solved with TDYN[62] to model blood flow in the normal and aneurysmatic abdominal aortas. For the 3D model, rigid wall was assumed and no-slip boundary condition was applied at the luminal wall. A volumetric/mass flow rate was applied at the inlet and a pressure wave was applied at the outlets. A python script implemented to compute WSS-based diagnostic indicator is shown in appendix C. A new procedure to segment the aorta using 4D flow Cardiac Magnetic Resonance (CMR) data has been also proposed. Beyond this, 4D flow CMR visualization offer a qualitative and comprehensive descriptions of the flow fields than any other in-vivo imaging technique (in chapter 6). The velocity data provided by 4D flow CMR has been complementary to the higher resolution velocity fields computed by the CFD in order to estimate the WSS. We have also developed an algorithm to compute WSS based on the 4D flow CMR data. To compute vorticity and helicity from a velocity field a Vascular Modeling Toolkit (VMTK)[26] and TDYN[62] were used. In spite of this, a new diagnostic indicator to estimate coronary artery disease based on computational hemodynamics has been also proposed (in chapter 6).

In this monograph, blood has been considered as incompressible and Newtonian fluid, and we will focus on the systemic arterial system and coronary circulation. Further information about cardiovascular physiology can be found in appendix A. In the following, a brief summary of the methods employed to reach the objectives of this monograph is given in the next section. For a complete description of the methodology used in this monograph see papers 1-4 in chapter 2-5, respectively.

1.4 Methodology

1.4.1 Patient-specific modelling

Patient-specific modeling is the development of computational models of human physiology that are individualized to patient-specific data[63]. Imaging data can be stored in the Digital Imaging and Communication in Medicine (DICOM) format [64]. The DICOM format file contains two parts: the header which stores detailed information about the patient such as name, type of scan, ages, dimension of the image and the voxel, image position, and so forth. The second data set contains information of each scanned image. Segmentation of medical image was required to extract the geometry of the region of interest (or analysis). The segmentation process can include several procedures as threshold, region growing, centerline, among others, followed by 3D anatomical reconstruction to obtain a coarse solid model[65] . During threshold, a range of gray scale values are selected such that the region to be selected is of the best contrast. After the regions of interest are extracted, the voxels are labelling together with an identificator to create the 3D geometry.

In previous work[65] an efficient methodology for pre-processing medical images to generate computational meshes for numerical simulation is explained. A schematic flowchart for creating and validating a 3D patient-specific model is shown in figure 5 of [65]. Aneurysm models (patient-specific geometries) of paper 2 were reconstructed from computer tomography-angiography (CTA) scan using the diagnostic software ITK-SNAP[66] and DIPPO[67].

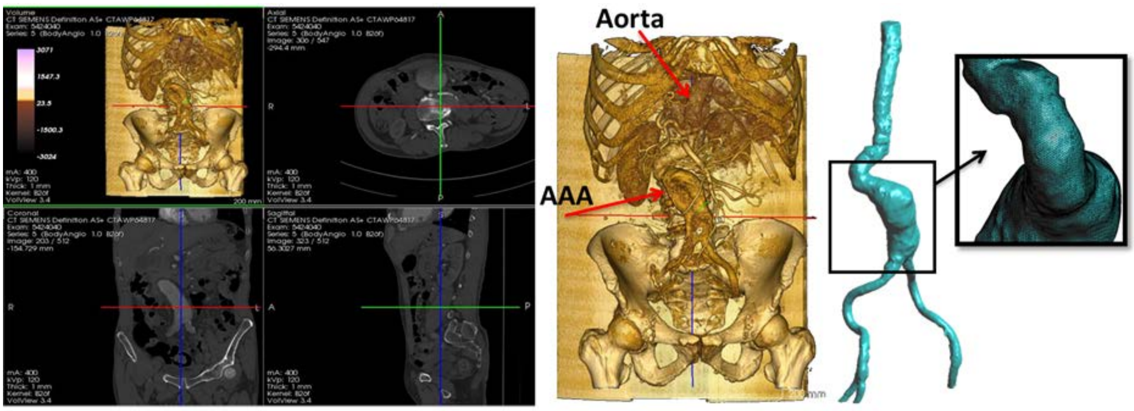

Figure 1.8: Left CT DICOM (sagital, coronal and axial images) of patient with Aortic Abdominal Aneurysm. Center CT volume render of Aortic Abdominal Aneurysm illustrating the Abdominal sac. Right computational patient-specific model and computational mesh

Both image processing programs employ active contour (deformable models) which move under the action of external forces according to the image intensity and first and second spatial image gradients. A schematic diagram depicting the segmentation of medical image at various locations of the abdominal aneurysm is shown in figure 1.8. Coronary models of chapter 6 were reconstructed from X-ray coronary angiography (XA). At the moment, X-ray coronary angiography is the standard technique for anatomical assessment and the diagnosis of coronary arteries. The

3D coronary models reconstructed was based on two bi-dimensional images taken from different perspectives. Then the reconstruction of abdominal aneurysm anatomy or coronary into a computational mesh (computer model) is performed based on the segmentation information. To generate the computational mesh GiD pre and ostprocessor[67] and the open source Vascular Modeling Toolkit (VMTK) [26] were used.

Next, a list of freely available tools for medical image processing and mesh generation using in the appended papers is outlined; VTK[68] is an open-source software toolkit for visualization, computer graphics and image processing with a great online community and numerous examples. VTK is cross platform with implementations for Windows, Mac Os and Linux. Users can code in C++, Java, Phyton or TCL. Knowlegde of VTK means that developers can take advantage of other tools such as ITK or ITK-SNAP, to name a few. ITK[69] is an open-source, cross-platform system that sits on top of VTK. It provides developers with an extensive suite of software tools for image analysis. ITK-SNAP[66] is a freely available tool built on ITK and VTK for image manipulation. The source code for ITK-SNAP is part of ITK Applications, so developers can add their own modifications. DCMTK[70] is a collection of libraries and applications for reading, writing and otherwise manipulating DICOM images. It works with multiple operating systems. VMTK[26] is collection of applications for pre and postprocessing medical images.

1.4.1.1 4D flow cardiovascular magnetic resonance imaging

At present, 4D flow cardiovascular magnetic resonance imaging (4D CMRI) sequences are being a promising tool to visualize and quantify 4D (3D+t) blood flow. From these sequences the raw data can be obtained and conveniently processed, allowing visualization of the blood flow patterns in any segment of the cardiovascular tree[71][72][73]. Nevertheless, the visualization of these images entails an important manual work, becoming a very time-dependent task and then turning out to be not useful in the current clinical practice. Therefore, it is important to improve the technology and the methods of automatic representation of the 4D blood flows, in particular for the WSS analysis. In chapter 5, it is demonstrated that 4D flow CMRI technique is a reliable tool to provide the boundary conditions for the Computational Fluid Dynamics(CFD) in order to estimate the WSS within the entire thoracic aorta in a short computation time. Our image-based CFD methodology exploits the morphological MRI for geometry modelling and 4D flow CMRI for setting the boundary conditions for the fluid dynamics modelling. The aim is to evaluate visualization of well-defined aortic blood flow features and the associated wall shear stress by the combination of both techniques. In that sense, CIMNE has developed a home-made ad-hoc software (Aorta4D) oriented to make progress in this field of work [72][74][73]. Aorta4D will afford analysis and spatially visualization of the registered 3-directional blood flow velocities, and perform a 3D semi-automatic segmentation based on the 4D flow CMRI data.

1.4.2 Computational hemodynamics

In this section we will limit to the essential description of mathematical equations and the most important dimensionless parameters to characterize the blood flow[75]. In this monograph, we consider blood as an homogeneous, incompressible, constant-density (ρ =1050 kg/m^3), Newtonian fluid with constant viscosity (μ =0.0035 Pa.s). and vascular walls are modeled as non-permeable and rigid walls (see appendix A). Under these assumptions, the conservation of mass and momentum in the compact form are described by the following system of partial differential equations (1.11):

$$\begin{aligned} \rho \cdot \left(\frac{\partial \mathbf{u}}{\partial \mathbf{t}} + (\mathbf{u} \cdot \triangledown \mathbf{u}) \right) + \nabla\, p - \nabla \cdot (\mu \bigtriangleup \mathbf{u}) &= \rho \cdot \mathbf{f} \qquad \text{in } \Omega(0,t) \\ \nabla u &= 0 \qquad \text{in } \Omega(0,t) \end{aligned} \tag{1.11}$$

where Ω is a three-dimensional domain, **u** denotes the blood velocity, **p** is the pressure field, ρ density, μ the dynamic viscosity of the fluid and **f** the volumetric acceleration. Volumetric forces($\rho \cdot \mathbf{f}$) and thermal effects are not considered in this monograph. The spatial discretization of the Navier-Stokes equations has been done by means of the finite element method (FEM), while for the time discretization an iterative algorithm that can be considered as an implicit fractional step method has been used [62][61]. Blood flow can be characterized by the Reynolds and Womersley [76] dimensionless number. These numbers correlate the inertial and viscous forces of the previous equation 1.11. The **Womersley** number(α) is a dimensionless parameter that represents the ratio between oscillatory inertial forces and viscous forces. Physically, the Womersley number can be interpret as the ratio of artery diameter to the laminar boundary layer growth over the pulse period (characteristic frequency):

$$\alpha = \frac{D}{2} \cdot \sqrt{\frac{w\rho}{\mu}} \tag{1.12}$$

where *w* the characteristic frequency and *D* is the characteristic diameter. If α is high, the fluid is non-viscous, and if α is low, the viscosity of the fluid is high. Womersley number characterizes the unsteady of the blood flow. The ratio of the inertial force to the viscous forces is the dimensionless parameter called **Reynolds** number:

$$Re = \frac{U^2\rho}{\frac{\mu u}{D}} = \frac{LU\rho}{\mu} \tag{1.13}$$

When we have a large Reynolds number inertial forces are dominant over viscous forces and viceversa. This naturally leads us to the role of Reynolds number as the key parameter which identifies the transition of the flow to turbulence. Usually, Reynolds number suggests that in most arteries of the cardiovascular system the flow is laminar. The exceptions are the flow in severely stenotic vessels, where the flow regime can be become transitional or turbulent. Turbulence blood flow implies fluctuating pressure acting on the arterial wall, and fluctuating, increased shear stress, which can be provoke post-stenotic dilation or atherogenesis. In this monograph, blood flow has being considering laminar. Figure 1.9 shows the full process from the medical image to the numerical simulation: aortic abdominal aneurism imaging, geometry modelling, finite elements meshing and mechanical and hemodynamics numerical simulation.

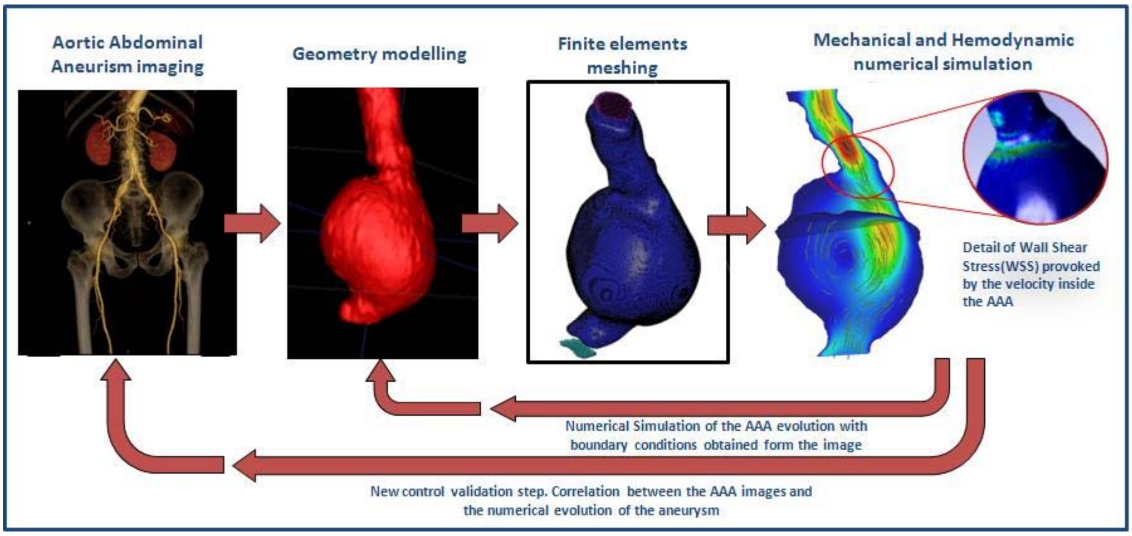

Figure 1.9: From the medical image to the simulation

1.4.2.1 Patient-specific boundary conditions

It is well known that to estimate properly the DI's, the specific patient-specific boundary conditions are needed. Several authors [77][78][79] have noted how inlet velocity profiles and flow waveform shapes play an non-negligible role on wall shear stress or pressure distributions. Nowadays, there are several medical techniques to perform velocity measurements inside large arteries in vivo and non-invasively, as Doppler Ultrasound or phase-contrast magnetic resonance. Using these acquired data into the computational hemodynamical model will provide us enough information to define our simulation. It should be pointed out that the conditions measured depend on physical activity and posture of the patient [80]. In paper 2 and chapter 7 the technique uses to acquire the velocity information for the prescription of patient-specific boundary conditions was phase-contrast magnetic resonance.

Acquisition of boundary conditions by phase-contrast magnetic resonance: At present Cardiac Magnetic Resonance Imaging (CMRI) image is the only non-invasive imaging modality that can measure 3D blood velocity in a 3D representation, and that allows visualization of spatial velocity distribution velocity in a two-dimensional plane (2D). This technique is valuable non-invasively tool for evaluation of the cardiovascular flow patterns owing to its unique possibility to simultaneously acquire sectional imaging without restriction, anatomy (magnitude image) and blood flow velocities(phase image) with a single scan. The majority of the commercial systems offer the bi-dimensional phase-contrast sequence to quantify blood velocity and derivative cardiac flow. These sequences are reliable and precise methods to calculate stroke volume for pulmonary/systemic flow ratios estimation (Qp:Qs) and to calculate volume regurgitation in valvular insufficiencies [81][82]. At present, the phase-contrast sequences are being developed to allow obtaining information of the 4D flow (see 1.4.1.1).

Boundary conditions from multiscale modeling of circulation: Another approach to impose the boundary conditions is to use reduced models, as 1D model or 0D (lumped) models. 1D and 0D models are mathematical models able to reproduce the systemic and pulmonary circulation. Figure 1.10 shows a standard approach to provide realistic local boundary conditions for 3D CFD simulations at the specific arterial domain using 1D models of the entire arterial tree and 0D models at the distal ends[83]. 1D model solves the Navier-Stokes equations under some assumptions (see appendix B) and lumped models (0D models) can be derived from electrical circuit analogies where blood flow is represented by the current and arterial pressure by the voltage. Usually the electrical components of these circuits are resistances, inductances and capacitors. Where resistances represent arterial and peripheral resistance that occur as a result of viscous dissipation inside the vessels, capacitors represent volume compliance of the vessels that allows them to store large amounts of blood, and inductors represent inertia of the blood[75]. The values of these electrical components can be estimated from physical data of the subject [84][85]. This approach is quite used because it is capable to account for the effect of local pathological conditions on the whole circulatory system, providing realistic boundary conditions for the 3D problem [75][79][86].

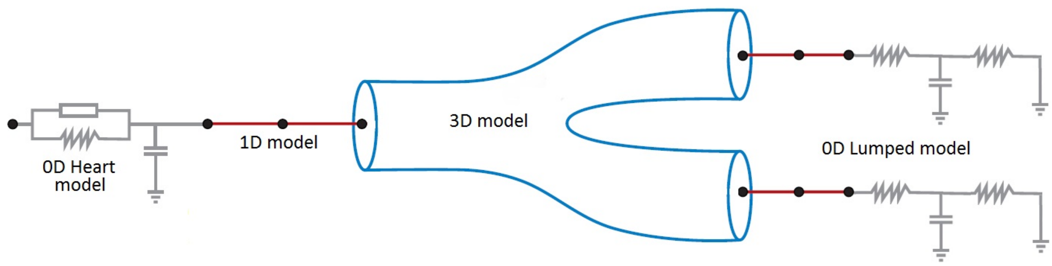

Figure 1.10: Coupling of 0D heart model, with 1D model (Systemic Circulation), 3D model (patient-specific geometry) and 0D lumped models (terminal resistance) to perform a computational analysis

1.4.3 Postprocessing

Output data were imported into GiD for post-processing[67]. A python script to compute WSS-based indicators was performed into EnSight[87] (see appendix C).

Chapter 2

A Reduced Order Model based on Coupled 1D/3D Finite Element Simulations for an Efficient Analysis of Hemodynamics Problems.

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DOI: 10.1007/s00466-014-1040-2

Scientific contribution: Design of a new methodology to estimate the pressure drop in aortic coarctation under different scenarios. The methodology is based on the integration a 1D numerical model (see appendix B) into a reduced order model based on 3D CFD formulation.

Contribution to the paper: The principal author developed and implemented the 1D model and the reduced order model into the KRATOS Multi-Physics software (www.cimne.com/kratos)([61]).

Comput Mech (2014) 54:1013–1022
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ORIGINAL PAPER

A reduced-order model based on the coupled 1D-3D finite element simulations for an efficient analysis of hemodynamics problems

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Abstract A reduced-order model for an efficient analysis of cardiovascular hemodynamics problems using multiscale approach is presented in this work. Starting from a patient-specific computational mesh obtained by medical imaging techniques, an analysis methodology based on a two-step automatic procedure is proposed. First a coupled 1D-3D Finite Element Simulation is performed and the results are used to adjust a reduced-order model of the 3D patient-specific area of interest. Then, this reduced-order model is coupled with the 1D model. In this way, three-dimensional effects are accounted for in the 1D model in a cost effective manner, allowing fast computation under different scenarios. The methodology proposed is validated using a patient-specific aortic coarctation model under rest and non-rest conditions.

Keywords Blood flow · Boundary conditions · Reduced-order models and Aortic coarctation

1 Introduction

The simulation of blood flow problems assumes a large importance in biomechanics due to the many potential fields of application. The use of realistic boundary conditions is essential to guarantee the performance and the accuracy of numerical simulations, especially in cardiovascular problems. In particular, the flow in arteries depends strongly on the outflow boundary conditions which model the downstream domain. The application of constant tractions as outlet boundary conditions for 3D domains represents the simplest possibility. Unfortunately, such conditions are not realistic and cause spurious pressure waves to become in the solution. Such waves travel along the artery network and distort the numerical solution. An efficient technique is thus needed to minimize these effects. Sophisticated outlet boundary conditions [29,30] aimed to minimizing such problem can be found in the literature. Others authors address the problem by applying geometrical multiscale modeling [4,7,9,17,34,36]. These approaches typically consist in the combination of models with different levels of approximation (3D, 1D and 0D models) each aimed at capturing particular features of the solution. 3D models are applied in regions where details of the local flow are needed. This is typically the case when the flow is strongly three dimensional or it tends to be turbulent. 1D models are typically used in the up-downstream domain of the 3D models, so that the whole arterial network can be described efficiently taking into account flow propagation effects. Zero dimensional models (or lumped models) are generally used to describe the lower level of the cardiovascular system or to model the heart. A typical problem that rises at the interface between the 1D and 3D domains is the mapping of the parabolic velocity distribution (assumed in the 1D model) to an "equivalent" distribution on the 3D inlet. Such mapping is not trivial since the discretized 3D model is generally not exactly circular. A proposal to solve the impasse can be found in [2]. In current work we opted for the simpler (but less accurate) option of applying a spatially uniform inlet velocity, with a total flow corresponding to the one of the 1D. This is only acceptable since our aim is not to compute the Wall Shear Stress (WSS) but rather to estimate the dissipation induced by the non-standard topol-

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ogy of the artery or area of interest. We also observe that the method we propose works under the assumption that the 3D inlet and outlet boundaries are approximately perpendicular to the centerline of the artery and positioned at points in which the flow can be reasonably approximated as 1D. It is interesting to remark that, as observed in the extensive review paper [18,31], the reliable computation of WSS, which is often the target of CFD simulations, depends on the availability of a sufficiently fine discretization of the boundary layer and is sensibly affected by the Fluid-Structure Interaction of the flow with the artery boundaries. The idea we leverage in the current work is that the extra dissipation induced by severe variations of the geometry is dominated by the appearance of turbulent effects within the volume. The evaluation of such effect requires a sufficiently fine discretization of the volume but does not put the extra requirements on the boundary layer mesh, and shall not be severely affected by the deformability of the walls, hence allowing the assumptions of considering the walls rigid which greatly simplifies the simulation and reduces the runtime. In [25] an extensive review of the most popular 1D models can be found. Recently, new models have been proposed [1,20,22,28] improving the viscoelastic behavior of the walls. However, the 1D models alone are not capable to capture in an effective way the energy losses due to the 3D geometrical shapes of the arteries, e.g, in stenotic arteries, aneurysms or other cardiovascular pathologies, such as aorta coarctation. Nevertheless, to discretize the whole 3D cardiovascular domain or coupled fluid-structure interaction (FSI) modeling is computational expensive and unfeasible in practical applications due to the numerical challenges involved. Despite its modeling shortcomings, geometrical multiscale models combined with patient-specific geometries remains the predominant approach for vascular blood flow. Such models allow quantifying the hemodynamics variables such as, flow reversal, flow separation and wall shear stress areas over the arterial wall in a non-invasive way useful for clinicians. Notable exceptions include the work of [29,32,33] on cerebral aneurysms.

In this paper, we propose a reduced-order Computational Fluid Dynamics (CFD) model specifically aimed to the estimation of the pressure gradient and the energy losses induced by stenosis in cardiovascular scenarios. The key features of our approach are: (1) a patient-specific anatomy and a computational mesh obtained during a routine clinical imaging session; (2) a coupled multiscale 0D-1D-3D model to approximate the energy losses induced by a narrowing of the artery lumen. The solution of the 3D model is used to train a reduced-order model which is aimed to capturing the pressure drop within two sections located upstream and downstream of the stenosis. Then the reduced-order model is integrated within the 1D model to create a 1D reduced-order model. Such model is able to simulate the energy losses and the flow distribution taking into account the patient-specific anatomy in real time under different scenarios. The ultimate goal is to validate the CFD framework with the energy losses through an aortic coarctation (CoA) under resting and non-resting conditions of the patient. CoA of the aorta occurs approximately in 10 % of patients with congenital heart defects and represents a narrowing of the descending aorta. Due to the reduction in the aorta descending diameter, high pressure gradients can appear across the CoA, resulting in an increased cardiac workload in the left ventricle during systole [14]. Investigation into the hemodynamics and bio-mechanical basis of the morbidity in CoA shows that the pressure gradient is dependent on the aorta area reduction, the flow rate and the physiological state of the patient: during non-rest conditions the pressure gradient can increase considerably and can provoke heart failure [13]. To measure the pressure gradient under these non-rest conditions, that are difficult to replicate in a clinic environment, is a biomedical challenge [3]. For is reason, a procedure that combines patient-specific image data and numerical tools to further understand the hemodynamics alterations, under resting and non-resting situations will allow clinicians to improve the diagnosis and define which should be the CoA treatment for the patient [14,23]. Some authors have used CFD models to study the hemodynamics in the CoA [12,13]. However, different numerical approaches might lead to different pressure predictions. The reduced-order methodology described in this paper has been implemented as part of the C++ finite element library KRATOS (www.cimne.com/kratos) [5]. KRATOS is a multiphysics simulation open source (LGPL licence) framework based on the stabilized Finite Element Method for analysis of the Navier-Stokes equations in viscous flows. Efficient and parallel solvers for 3-D fluid-structure interaction (FSI) [6] problems have been implemented in KRATOS that allow tackling large problems using supercomputers if available.

2 Computational framework

As previously stated, realistic boundary conditions are essential for simulating a appropriately behavior of the blood flow propagation. In this section we define a 1D FSI model coupled to a reduced-order model for cardiovascular analysis. The methodology used consists on a two step process. The first step (training phase) consists in estimating correctly the pressure drop between two sections of a 3D model by solving a geometrical multiscale problem. From the numerical point of view, we embed a 3D domain into a 1D network in order to perform 3D simulations within a consistent hemodynamics conditions provided by a 1D FSI model. A lumped model is used to simulate the peripheral vascular beds of the cardiovascular system. Once the first simulation is completed, the pressure drop predicted by the 3D model is used to train the 1D reduced-order model via a least square fitting procedure.

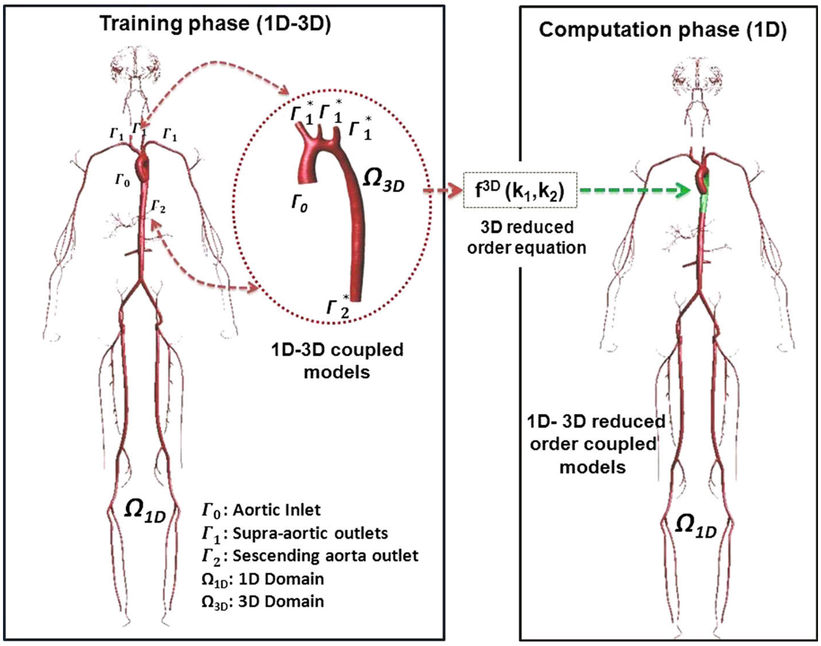


Fig. 1 3D-1D coupled approach schematics. Γ_i are the interface surfaces

The trained model is thus able to estimate the energy losses between the two areas selected in the 3D model. Once the reduced-order model is defined, a coupled 1D FSI-reduced-order model will be capable of estimating the patient-specific pressure drop under different rest or non-rest situations. The second step (computing phase) consists in setting different boundary conditions for the coupled 1D FSI-reduced-order model to estimate the pressure drop (at any point) taking in account the 3D anatomical model. This will enable us to simulate different pathological situations taking into account the energy losses produced by the 3D model. Besides, this reduced-order approach brings down the computational costs significantly. The flow diagram of this scheme is shown in Fig. 1.

2.1 Mathematical model for the 1D reduced-order model

In this section we describe a non-linear 1D formulation and the reduced-order model proposed to account for the 3D effects caused by the patient-specific area of interest. In absence of branching, an artery may be considered as a cylindrical compliant tube which extends from z = 0 to z = L, where L is the the artery length. The artery takes into account the assumptions of axial symmetry, radial displacements, constant pressure on each section, no body forces and dominance of axial velocity. The governing system of equations for an incompressible newtonian fluid are derived by applying conservation of mass and momentum in a 1-D impermeable and deformable tubular control volume. These equations are:

$$\left(\frac{\partial \mathbf{A}}{\partial \mathbf{t}} + \frac{\partial \mathbf{Q}}{\partial \mathbf{z}}\right) = 0 \tag{1a}$$

$$\left(\frac{\partial Q}{\partial t}\right) + \frac{\partial}{\partial z}\left(\alpha \frac{Q^2}{A}\right) + \frac{\mathbf{A}}{\rho}\frac{\partial \mathrm{P}}{\partial z} + \mathbf{K_R}\left(\frac{Q}{A}\right) = 0 \tag{1b}$$

$$P_{ext} + \frac{E h_o \sqrt{\Pi}}{1-\mu^2}\frac{\sqrt{A}-\sqrt{A_o}}{A_o} = P \tag{1c}$$

where A(z,t) is the cross-sectional area of the vessel, Q(z,t) is the mean blood flow, P is the average internal pressure over the cross-section, α is the momentum-flux correction coefficient, z is the axial coordinate along the vessel, t is the time, ρ is the density of the blood taken as 1,050 $\mathrm{Kg/m^3}$ and K_R is the friction force per unit length, which is modeled as $K_R = 2\pi \cdot \nu(\gamma + 2)$ [8], with ν being the viscosity of the blood taken here as 4.5 m·Pa·s. The vessel wall is modeled as a thin, homogeneous and elastic material. Parameters A_0 and h_0 in Eq. 1(c) are the sectional area and the wall thickness, respectively, at the reference state (P_0,U_0), with P_0 and U_0 assumed to be zero, E is the Young modulus and μ is the Poisson's ratio, typically taken as $\mu \approx 0.5$, which implies that the biological tissue is practically incompressible. In absence of detailed of patient-specific data, the wall elasticity and the thickness of the 55 largest arteries are based on data published by Wang and Parker [35]. At each domain decomposition, whether corresponding to a discontinuity in the mechanical or geometrical vessel properties, or to a cardiovascular branching, continuity of flow and of total pressure is enforced as follows:

$$Q_i = \sum_d (Q_j)_d \tag{2}$$

$$P_i + \frac{1}{2}\rho \frac{{Q_i}^2}{{A_i}^2} = (P_j)_d + \frac{1}{2}\rho \frac{({Q_j}^2)_d}{({A_j}^2)_d} + ({f^{3D}}_j(k_1, k_2))_d \tag{3}$$

where indexes i and j denote the parent and the daughter vessels respectively, and d indicates the number of system domains. Function $f^{3D}(k_1, k_2)$ denotes the energy losses of the 3D model, where k_1 and k_2 are obtained by fitting the pressure drop between the two planes defined in the 3D model. k_1 and k_2 are the viscous and turbulent coefficients that should be adjusted according to the pressure drop between the two planes defined in the 3D model. In this work we do not consider the inertial term. The system obtained is solved by a Newton iteration scheme, taking as the starting point the reference section area and flow, i.e:

$${f^{3D}}_j(k_1, k_2) = k_1 Q_j + k_2 \mid Q_j \mid Q_j \tag{4}$$

With simple manipulations of the differential Eq. (1) it is possible to obtain the conservative form for the temporal evolution of the flow and the vessels area and discretize the system obtained using a second order Taylor-Galerkin scheme. This scheme is appropriate for this problem as it can propagate waves of different frequencies without suffering from excessive dispersion and diffusion errors. A derivation of the 1D-FSI models can be found in [8] and [27]. The Taylor-Galerkin scheme requires a time step limitation in order to keep the solution stable. In this work the stabilization technique adopted has been the Courant Friedrichs Lewy condition (CFL condition) [21].

$$\Delta t \leq CFL \min_{0 \leq i \leq N} \left(\frac{h_i}{max(\lambda_{1,i}, \lambda_{1,i+1})} \right) \tag{5}$$

where N is the number of the elements, h_i is the local element size and $\lambda_{1,i}$ indicates the value of the eigenvalue evaluated at the mesh i^{th} node of the matrix of the conservative form obtained from the derivation of the 1D-FSI model [8]. The CFL value adopted is 0.57 [21]. The 3D computational analysis is performed assuming that the arterial wall is rigid. Blood is considered as an homogeneous laminar Newtonian fluid modelled by the incompressible Navier-Stokes equations using the same density and dynamic viscosity as for the 1D model. Although these are important limitations, they make the simulation effort simpler. Furthermore, the knowledge of the patient-specific mechanical properties is quite difficult, consequently the objective of this work is to determine the pressure gradient in the anatomical domain using a reduced-order model based on multiscale modeling. Recent studies [15] use turbulence models to predict the kinetic energy due to the narrowing of the coarctation.

2.2 3D-1D Coupling interfaces

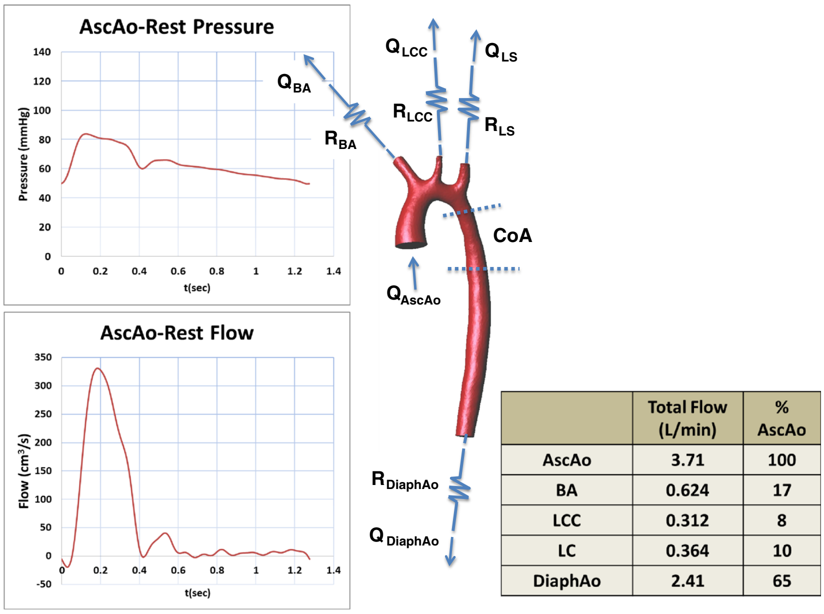
In order to keep the continuity in the area sections between the 3D and the 1D geometrical models, the diameters of the 1D geometrical model were firstly scaled taking into account a proportional diameter factor between the 3D and 1D geometrical models. The properties of the 1D geometrical models were taken from [35]. For the training phase, at each coupling 1D-3D interface we enforce the continuity of the flow and the total pressure (Eqs. 2, 3). This means that at every time step t_n we compute the velocity and the pressure using the 1D approach over the whole domain Ω_{1D}. Then, the variables over the interface sections (Γ_1, Γ_2) of the Ω_{1D}-Ω_{3D} domain are determined (Fig. 1). Following that, the 3D problem is solved in Ω_{3D} using the boundary conditions obtained in the Γ_1, Γ_2 sections from the 1D model. For the next time step ($t_n + 1$) the process is repeated until the final simulation time is reached. This coupling procedure is justified by the fact that the 1D domain can be considered as a passive element which absorbs the flow generated by the 3-D domain. During the training phase, pressure values at Γ_1 and Γ_2 interfaces are stored for each time step with the objective of estimating the coefficients k_1 and k_2 of Eq. 4 by the least squares method. We choose the value of f^{3D} (k_1,k_2) that minimizes the sum of the squared pressure drop from the 1D flow values compared to the 3D values. In Sect. 3.1.3 we show a pressure drop of the 3D computational values versus the predictions of the reduced-order model (Fig. 3). For the computation phase, the coupled 1D coupled FSI—reduced-order model is solved by using the coefficients k_1 and k_2 estimated previously.

3 Study case: aorta coarctation

3.1 Training phase

3.1.1 Model anatomy, geometry and mesh

The physiological and geometrical data used in this work was obtained from [3].The patient was a 71 kg, 177 cm tall, 17-year old male with a mild thoracic aortic coarctation. Image data come from a 1.5-T Phillips scanner using a gadolinium-enhanced MR angiography (MRA) with the patient in the supine position. The 3D model (Fig. 2) includes the ascending aorta, aortic arch, descending aorta, left subclavii, brachiocephalic and finally left common carotid arteries in Stereo Lithography (STL) file format. To generate the 3D volume we used the pre and post-processor GiD [10]. GiD can be efficiently used for mesh generation in CFD analysis. For generating the 3D volume mesh from the STL file, we have used an isosurface stuffing procedure. This algorithm generates tetrahedral element form a small set of precomputed stencils. The boundary mesh is guaranteed to be a geo-



	Total Flow (L/min)	% AscAo
AscAo	3.71	100
BA	0.624	17
LCC	0.312	8
LC	0.364	10
DiaphAo	2.41	65

Fig. 2 Patient-specific anatomical model with a mild thoracic aortic coarctation (CoA). Ascending aortic flow waveforms (in cm^3/s) under rest conditions measured by the (PC)-MRI sequence and ascending aortic pressure (in mmHg) measured with a pressure catheter under rest conditions. The table shows the total flow (in L/min) and percentage of ascending aortic flow through the various branches of the aortic model under rest conditions

metrically and topologically accurate approximation of the isosurface [16]. This technique ensures tetrahedral volume elements with optimal angle and volume for the simulations. Using this method we have obtained smooth elements and an aspect radio for the whole mesh greater than 0.9 (the ideal ratio is one for an equilateral triangle). In this work we dont need a refined boundary layer mesh, due to the we have focused on the energy dissipation induced by the turbulence effects. In [18] other authors propose how to build a patient-specific models from medical images taking into account a fine discretization of the boundary layer in order to capture the WSS and OSI effects over the arterial wall. The result of the isostuffing procedure is a volume mesh of 4,322,556 four-noded tetrahedral elements and 206,880 three-noded triangles with 777,235 nodes. The original surface mesh has 138,532 linear triangles and 69,268 nodes. Figure 2 shows a rendering image of the 3D volume mesh. The 1D computational mesh contains 551 linear two-noded elements and 586 nodes.

3.1.2 Boundary conditions: inlet and outlet conditions at rest

Blood flow information [3] was acquired using a cardiac-gated, 2D, respiratory compensated, phase-contrast (PC) sequence with through-plane velocity encoding. The cardiac output of the patient was 3.71 L/min, the heart rate was 47 beats per minute (cardiac cycle T = 1.277 s). Figure 2 shows the blood flow and pressure waveforms at the ascending aorta (AscAo). The inlet velocity profile is prescribed as uniform and flat at the inlet surface. The quality of the waveforms to the supra-aortic vessels (the Brachiocephalic artery (BA), the left common carotid artery (LCC) and the left subclavian artery (LS) arteries) was deemed too noisy to be used in the computations. Figure 2 and the related table show the total flow through each branch given as a percentage of the ascending aortic flow.

Invasive pressure wire measurements were acquired in a catheterization laboratory-equipped XMR suite [3]. Pressure was obtained in the ascending aorta (proximal to the coarctation). The proximal systolic, diastolic, and mean pressures were 83.92, 49.68, and 63.35 mmHg, respectively. These values were used to set the parameters for the lumped model. These lumped models are usually composed of a set of resistances and compliances to model the microvascular beds. The compliance influences the transient flow waveform, while the mean value is affected by the resistance only. Due to the assumption that only the mean flow over the cardiac cycle in the BA, LCC , LS and DiaphAo arteries is known, the boundary condition estimation is limited to correctly determining the resistance values at each of these outlets. For estimating the terminal resistance parameter, we use Ohm's law taking into account the flow distribution at the rest state(see the Table in Fig. 2);

$$Q_i * R_i = P_i - P_{out} \tag{6}$$

where Q_i is the flow at the BA, LCC , LS and DiaphAo arteries, P_i is the mean systolic pressure at the aortic root, P_{out} is the venous pressure for the cardiovascular system and R_i is the flow resistance for each branch-domain. Since the circulation system is not closed, a constant venous pressure of 5 mmHg is prescribed at the output of each artery [24]. Solving the set of differential-algebraic equations we obtain the following flow resistance for each branch as: $R_{BA} = 7.48 \cdot 10^{11}\text{Pa} \cdot \text{s/m}^3$, $R_{LCC} = 1.50 \cdot 10^{12}\text{Pa} \cdot \text{s/m}^3$, $R_{LS} = 1.28 \cdot 10^{12}\text{Pa} \cdot \text{s/m}^3$ and $R_{DiaphAo} = 1.94 \cdot 10^{11}\text{Pa} \cdot \text{s/m}^3$. Once the total resistances are estimated at these branches, the next step is to distribute the total resistances to the lumped models for all outlets of the 1D cardiovascular domain. To do that we have used a technique based on scaling laws for estimating the blood resistance. This method assumes that the radii and the lengths can be approximated as $R_1 = \varphi R_0$ and $L_1 = \lambda L_0$, being R_0 and L_0 is the radii and the length of the artery at a further distance and φ and λ are constant scaling factors. Therefore for any artery the radii and the length are $R_n = \varphi R_{n-1}$ and $L_n = \lambda L_{n-1}$, respectively. Under the Poiseuille law and assuming that we have 2^n arteries, then the flow distribution is $Q_0/2^n$, and the resistances in the terminal branches can be estimated as follows:

$$\Delta p_n = Q_n \frac{8_n \mu}{\pi R_n^4} \Rightarrow \Delta p_n = \left\{\frac{\lambda}{2\varphi^4}\right\}^n Q_0 \frac{8 L_0 \mu}{\pi R_0^4} = \left\{\frac{\lambda}{2\varphi^4}\right\}^n \Delta p_0$$

$$\Delta p_T = \sum_{n=1}^{N} \Delta p_n = \Delta p_0 \sum_{n=1}^{N} \left\{\frac{\lambda}{2\varphi^4}\right\}^n \tag{7}$$

where Δp_T is the sum of the pressure gradients after each bifurcation through the network, Δp_n is the starting point from the outlet of the terminal artery and N is the number of bifurcations. Dividing Δp_T by Q_0, the resistance $R_\mu T$ can be estimated as:

$$R_{\mu T} = R_{\mu 0} \sum_{n=1}^{N} \left\{\frac{\lambda}{2\varphi^4}\right\}^n \tag{8}$$

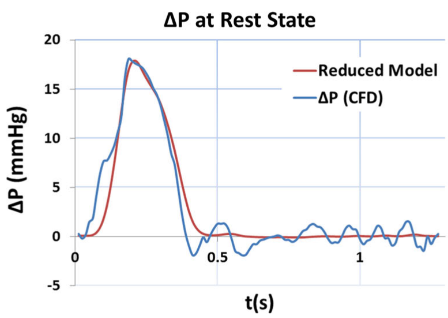
The flow can be approximated using Murray's law [19] as $Q \simeq kr^3$. Therefore $\lambda = \sqrt{0.6}$. Murray's law determines the vessel radius that requires a minimum of energy the vascular system. A relation between φ and λ can be estimated as [26]:

$$\lambda = \frac{N}{N+1}\frac{1}{2\varphi^2} \tag{9}$$

On the other hand, considering the main 55 arteries of the 1D arterial model [35], the R_{BA}, R_{LCC}, R_{LS} and $R_{DiaphAo}$ parameters and taking in account the vessels that arise from BA, LCC, LS and DiaphAo arteries the resistance values for all the terminal branches at the rest condition are finally estimated (see Table 1).

3.1.3 Reduced-order model

In order to settle Eq. 4, we have to define two planes in the 3D geometrical model. The planes chosen were in the ascending aorta (proximal to the coarctation) and in the descending aorta (distal to the coarctation); see Fig. 2. Once these two planes and the inlet and boundary conditions for rest situations are defined, we solve the coupled 3D-1D model. We use an adaptative time step based on the 1D simulation. For each time step, we calculate and store the mean values of the pressure and blood flow for the two planes. These values are then used to estimate the k_1 and k_2 coefficients in (Eq. 4) using a least squares method. The coefficients values found are $k_1 = 3.08 \cdot 10^{-3}$ and $k_2 = 5 \cdot 10^{-4}$, so that function $f^{3D}(k_1,k_2)$ minimizes the sum of the squared pressure drop from the flow values versus the 3D values. Figure 3 (left) shows the pressure drop obtained with the 3D computational values and the reduced-order model. The mean error between the CFD pressure drop and the 3D reduced-order model is 3 %. Figure 3 (right) shows the dependence between the pressure drop and the flow. The area below the hysteresis loop is the energy dissipated. If it is low we can estimate the pressure drop by function $f^{3D}(k_1,k_2)$. Thus, the reduced-order model is capable to capture the energy losses provoked by the geometry of the 3D model. The total computation time for the training phase in a standard PC with Linux environment, 32 bit, 4 GB RAM and dual core 2.83 GHz CPU was about 10 h.



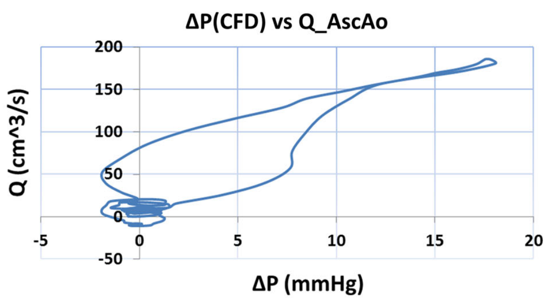
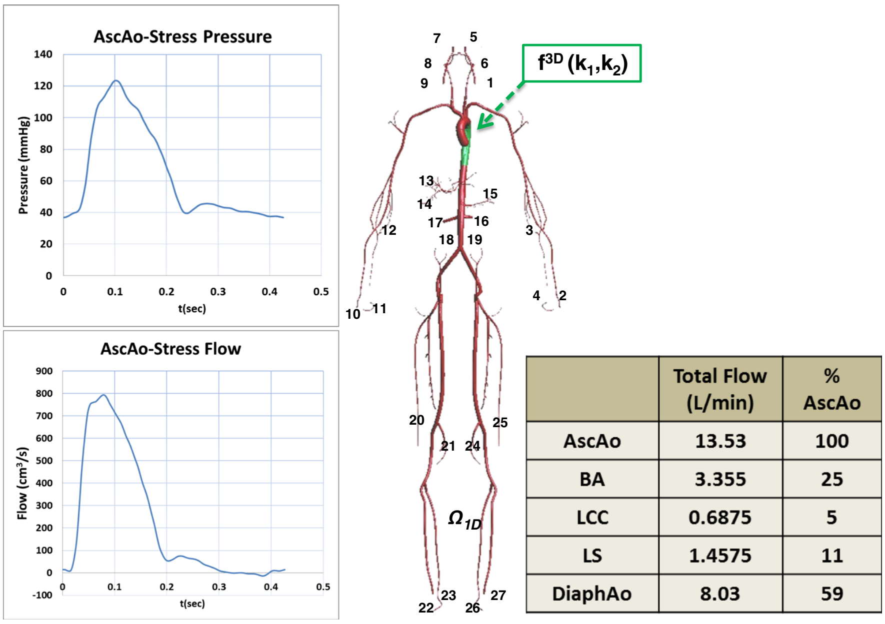


Fig. 3 *Left*: pressure drop between the 3D computational values versus the reduced-order model. *Right*: dependence between the pressure drop and the flow (hysteric loop)



	Total Flow (L/min)	% AscAo
AscAo	13.53	100
BA	3.355	25
LCC	0.6875	5
LS	1.4575	11
DiaphAo	8.03	59

Fig. 4 1D anatomical model based on [35]. Ascending aortic flow waveforms (in cm^3/s) under non-rest conditions as measured by the PC-MRI sequence and ascending aortic pressure (in mmHg) measured with a pressure catheter under non-rest conditions. Table shows the total flow (in L/min) and percentage of ascending aortic flow through the various branches of the aortic model under non-rest conditions. Numbers indicate the terminal branches. Table 1 shows the name and resistance values

3.2 Computation phase

3.2.1 Non-rest situation

Stress (or non-rest) conditions were induced by administering isoprenaline to the patient. Flow and pressure data waveforms were acquired using the same protocol as in rest conditions [3]. The cardiac output of the patient increased to 13.53 L/min and the heart rate to 141 beats per minute (cardiac cycle T = 0.425 s). Figure 4 shows the flow waveform at AscAo. Similar as for a rest situation, the quality of the waveforms at the BA, LCC, and LS arteries was deemed too noisy to be used for the computations. Figure 4 shows the total flow through each branch given as a percentage of the ascending aortic flow. Pressure was obtained in the ascending aorta (proximal to the coarctation). The proximal systolic, diastolic, and mean pressures were 123.35, 36.77, and 64.30 mmHg, respectively (Fig. 4). For estimating the terminal resistance parameters under non-rest situations we have used the same procedure as in rest situations (3.1.2). The results are $R_{BA} = 1.41 \cdot 10^{11}\text{Pa} \cdot \text{s/m}^3$, $R_{LCC} = 6.90 \cdot 10^{11}\text{Pa} \cdot \text{s/m}^3$, $R_{LS} = 3.25 \cdot 10^{11}\text{Pa} \cdot \text{s/m}^3$ and $R_{DiaphAo} = 5.91 \cdot 10^{10}\text{Pa} \cdot \text{s/m}^3$. Table 1 shows the terminal resistance values for the terminal vessels for rest and non-rest situations.

Once the terminal resistances for the non-rest condition are set and the parameters k_1 and k_2 of the 3D reduced-order model are fitted (see Sect. 3.1.3). We are able to estimate the pressure drop under non-rest conditions. For this purpose, we impose the flow profile (Fig. 4) in the ascending aorta of the 1D model. In Fig. 5 the pressure drop under non-rest conditions is shown. The table below shows the mean, systolic and diastolic pressure for the rest and non-rest situations obtained with the reduced-order model. Experimental results are also shown for comparison purposes. The 1D reduced-order model can be also used to simulate other pathological conditions without the necessity to perform the 3D simulation.

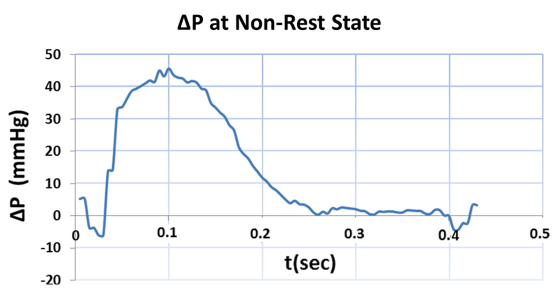
4 Results

From a qualitative point of view, the numerical results shows that the pressure is correctly captured by the reduced-order model (Fig. 3). For the rest situation, the mean (2.83 mmHg) and maximum (18.07 mmHg) pressure drops are estimated using the 3D-1D coupling model. For the non-rest situation, the mean and maximum pressure drops of 13.68 and 44.06 mmHg are estimated using the 1D-reduced-order model. These values are in agreement with previous studies [3,13]. In the rest situation, the reduced model is able to capture the pressure drop with an error under 3 %. Note that the methodology used for parameter estimation can be improved

Table 1 Resistance values for the cardiovascular model in Fig. 4

	Artery name	R_{Rest}	$R_{Non\text{-}rest}$		Artery name	R_{Rest}	$R_{Non\text{-}rest}$
1	Right vertebral	29.6	7.52	15	Intercostals	4.47	1.36
2	Right radius	0.68	0.14	16	Renal	0.68	2.02
3	Right interosseous	4.5	1.14	17	Inferior mesenteric	0.68	2.02
4	Right ulnar	4.5	1.14	18	Superior mesenteric	0.68	2.02
5	Right int. carotid	34.6	15.9	19	Splenic	0.68	2.02
6	Right ext. carotid	34.6	15.9	20	Left ext. iliac	0.10	0.0315
7	Left int. carotid	29.6	7.52	21	Left deep femoral	0.10	0.0315
8	Left ext. carotid	29.6	7.52	22	Left posterior tibial	0.0157	0.00479
9	Left vertebral	17.3	3.27	23	Left anterior tibial	0.0157	0.00479
10	Left radius	0.4	0.075	24	Right ext. iliac	0.10	0.0315
11	Left interosseous	2.63	0.49	25	Right deep femoral	0.0157	0.00479
12	Left ulnar	2.63	0.49	26	Right posterior tibial	0.0157	0.00479
13	Hepatic superior	4.47	1.36	27	Right anterior tibial	0.10	0.0315
14	Gastric	4.47	1.36				

R is the terminal resistance (10^9Pa s/m^3) for the rest and non-rest situations based on the experimental measurements from [35]



	Rest (CFD)	Rest (Exp)	Non-Rest (CFD)	Non-Rest (Exp)
Mean Pressure	60.61	63.35	61	64.30
Max Pressure	97.99	83.917	136.71	123.35
Min Pressure	46.37	49.68	31.59	36.77
Mean ΔP CoA	2.83	-	13.86	-
Max ΔP CoA	18.07	-	45.66	-

Fig. 5 Pressure drop for non-rest situation and CFD results versus experimental results. Pressures are in mmHg. CoA represents the coarctation and ΔP the pressure drop

with the objective of avoiding the oscillatory behavior of the pressure in the descending aorta. Some authors [11,36] use the three-element Windkessel model for improving the fitting of the lumped model. The approach used in this work is however much simpler in the mathematical treatment, while still being able to match the systolic, diastolic and mean pressure values.

5 Conclusion

We have presented a CFD framework which combines patient-specific model and a reduced-order model to estimate the energy losses in cardiovascular problems. The framework has been evaluated with a patient-specific aortic coarctation(CoA) under non-rest and rest situations with satisfactory results. The procedure consists of a two step process. First a reduced-order model is trained using a coupled 1D-3D FEM analysis and then is used together with a 1D solver under different pathological conditions. The reduced-order model is expressed as a sum of the viscous and turbulent terms, and it is capable to capture the energy losses provoked by the anatomy shape. The error of the reduced-order model is acceptable to capture the pressure drop over two sections of the 3D FEM model. We have modified the 1D formulation in order to integrate the reduced-order model into the framework developed. Results demonstrate that the reduced model is robust with respect to changes in the pathological conditions for patient-specific cases. In order to apply the procedure for a new patient, the framework developed requires a patient-specific model and knowledge of the pathological conditions in a rest situation. In terms of clinical diagnosis the most important feature to be captured is the pressure drop which can be estimated under non-rest situations. The main advantage of the proposed framework is that it relies only on measurements acquired during a rest situation. Then, it can be used under non-rest or rest conditions in a small computation time. The most important numerical approximation introduced in this work is that the training of the reduced-order model is performed using the 3D patient-specific anatomical data considering the boundary conditions taken from the 1D model. The advantage is a great reduction of the computational time versus the fully coupled analysis. The numerical results show that the 1D model retrofitted by using the trained reduced model correctly captures the pressure gradient and the energy losses in cardiovascular diseases.

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Chapter 3

CFD Modelling of Abdominal Aortic Aneurysm on Hemodynamic Loads using a Realistic Geometry with CT.

Title: CFD Modelling of Abdominal Aortic Aneurysm on Hemodynamic Loads using a Realistic Geometry with CT.
Authors: E.Soudah, E.Y.K. Ng, T.H Loong, M.Bordone, P. Uei and N.Sriram.
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Scientific contribution: Computational fluid dynamics studies of abdominal aortic aneurysms (AAA) to find a correlation between hemodynamics parameters and geometrical factors.

Contribution to the paper: The principal author developed the segmentation and mesh procedures together with M.Bordone and T.H Loong. He also had a major active part in the interpretation of the results together with E.Y.K. Ng, P. Uei and N.Sriram. This overall work was carried out in collaboration with Tan Tock Seng Hospital and Nanyang Technological University of Singapore under the NTU-NHG Innovation Seed Grant Project no. ISG/11007.

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Research Article

CFD Modelling of Abdominal Aortic Aneurysm on Hemodynamic Loads Using a Realistic Geometry with CT

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The objective of this study is to find a correlation between the abdominal aortic aneurysm (AAA) geometric parameters, wall stress shear (WSS), abdominal flow patterns, intraluminal thrombus (ILT), and AAA arterial wall rupture using computational fluid dynamics (CFD). Real AAA 3D models were created by three-dimensional (3D) reconstruction of in vivo acquired computed tomography (CT) images from 5 patients. Based on 3D AAA models, high quality volume meshes were created using an optimal tetrahedral aspect ratio for the whole domain. In order to quantify the WSS and the recirculation inside the AAA, a 3D CFD using finite elements analysis was used. The CFD computation was performed assuming that the arterial wall is rigid and the blood is considered a homogeneous Newtonian fluid with a density of 1050 kg/m^3 and a kinematic viscosity of 4×10^{-3} Pa·s. Parallelization procedures were used in order to increase the performance of the CFD calculations. A relation between AAA geometric parameters (asymmetry index (β), saccular index (γ), deformation diameter ratio (χ), and tortuosity index (ε)) and hemodynamic loads was observed, and it could be used as a potential predictor of AAA arterial wall rupture and potential ILT formation.

1. Introduction

Most of abdominal aortic aneurysms (AAA) (about 90%) are located below the level of the renal arteries and are known as infrarenal aortic aneurysms. Infrarenal aortic aneurysm is a pathological enlargement of the aorta in the inferior thoracic area taking a fusiform shape and may extend into the iliac arteries. The mortality of this pathology is high (15% for ruptured aneurysms), and the current standard of determining rupture risk is based on the anteroposterior diameter. It is known that smaller AAAs that fall below the threshold of 5.5 cm diameter may also rupture, and yet larger AAAs (diameter > 5.5 cm) may remain stable [1–3]. However, occasionally the AAA diameter is lower than 5 cm and an unexpected ruptured is produced [4], in these cases, other biomechanical factors [5–8], such as Wall Shear Stress (WSS), or geometrical factors [9–12] can play an important role in the rupture of the aneurysm.

To estimate the AAA rupture risk, from a biomechanical point of view (material failure), an aneurysm ruptures when the stresses acting on the arterial wall exceed its failure strength. According to Laplace's law, the wall stress on an ideal cylinder is directly proportional to its radius and intraluminal pressure. Even though an AAA is not an ideal cylinder, Laplace's law still applies and with an increasing aortic diameter, the internal pressure increases, and so does the risk of rupture. The increase in internal pressure against the aortic walls results in progressive growth of the AAA diameter, and, eventually, this pressure may overcome the resistance of the aortic wall resulting in rupture [1, 2]. On the other hand, abnormal flow patterns and recirculation develop in the AAA sac leading to the formation of the intraluminal thrombus (ILT) [6, 13]. This phenomenon can provoke the AAA stabilization and start a vicious circle inside the AAA [14]. It is reflected by the interaction between the arterial wall structural remodeling and the forces generated by blood flow within the AAA [2, 13]. Therefore, it is apparent that Laplace's Law is insufficient when investigating AAA collapsibility. Rather, the aneurysm shape has a strong influence on flow patterns, ILT formation, wall stress distribution (peak values and locations), and consequently its potential rupture [1, 15].

The aim of this study is to analyze and to characterize the effect of wall shear stress and the internal pressure together with the main AAA geometric parameters (maximum diameter (D_{AMAX}), length (L_{AAA}), AAA proximal neck diameter ($d_{\text{proximal\_neck}}$), tortuosity (ε), and asymmetry (β)) in order to assess its potential rupture. Five patient-specific AAA models were created from CT scans. A normal descending aorta was also simulated to provide a comparison.

2. Material and Methods

Five patients with infrarenal aneurysms on followup at Tan Tock Seng Hospital (Singapore) were included in this study. The patients chosen for this study were selected with different sized AAAs, in order to cover the different stages of this pathology. All the patients participated in this trial analysis volunteered and provided written informed consent of the study. This study was reviewed and approved by the Ethics Committee of the Tan Tock Seng Hospital, Singapore. For the medical image acquisition, a computed tomography (CT) Somatom Plus Scanner (*AS*+) (Siemens Medical Solutions) was used with the following parameters: $512 \times 512 \times 110$, pixel spacing: 0.785/0.785 with a resolution of 1.274 pixels per mm and 5 mm slice thickness. CT scanning was conducted while the volunteer was awake in the head first-supine position using an endoleak protocol. The CT covered the entire abdomen and pelvis and was performed after the administration of intravenous Omnipaque 350 as IV contrast medium.

To characterize the structure of the AAA, the main geometrical AAA parameters are measured: aneurysm length (L_{AAA}) and maximum diameter of the aneurysm (D_{AMAX}) (Figure 1(a)). The factor which assesses the length (L_{AAA}) and the diameter (D_{AMAX}) of the AAA sac is known as saccular index (γ) (1) [16]. If the saccular index is close to 1, the aneurysm is saccular (spherical), but if it is close to 0 the aneurysm is more fusiform. The deformation diameter rate (χ) (1) [17] characterizes the nondeformed abdominal aorta diameter ($d_{\text{proximal\_neck}}$) with the maximum diameter of the aneurysm sac, D_{AMAX}. A nonaneurysmal aorta is defined as ($D_{\text{AMAX}} = d_{\text{neck}}$)

$$\begin{aligned}
\beta &= \frac{r}{R}, \\
\gamma &= \frac{D_{\text{AMAX}}}{L_{\text{AAA}}}, \\
\chi &= \frac{D_{\text{AMAX}}}{d_{\text{proximal_neck}}}, \\
\varepsilon &= \frac{L}{\tau} - 1.
\end{aligned} \tag{1}$$

To evaluate the asymmetry (β) [18] of the aneurysm (1), r and R are defined as the radii measured at the midsection of the AAA sac from the longitudinal z-axis to the posterior and anterior walls, respectively, as shown in the inset of Figure 1(b). Thus, $\beta = 1.0$ yields an azimuthal symmetry and $\beta = 0.2$ is an AAA for which only the anterior wall is dilated while the posterior wall is nearly flat. The tortuosity index (ε) (1) [19] is the relation between the actual lengths of the centerline of the AAA with the length of a hypothetical healthy aorta (Figure 1, center).

Based on these indexes and the wide clinical empirical evidence, there are several criteria of the AAA grade. However, at present, there is no clinical consensus to use it. Table 1 shows the main AAA geometrical characteristics for each patient in our study.

To create the computational model, the medical data were sent directly to a personal computer and stored in Digital Imaging and COmmunications in Medicine format (DICOM format). Figure 2 shows the segmentation workflow. The region of interest (ROI) analyzed was segmented using the three-dimensional computer-aided design system DIPPO software [20]. The segmented area for each patient started at the abdominal aorta (approximately in the infra renal arteries) and extended down to the common iliac arteries (Figure 2). The abdominal images were segmented from CT DICOM images combining two different segmentation procedures, thresholding and level set method (based on snakes). Thresholding is a nonlinear operation that converts a gray-scale image into a binary image where the two levels are assigned to pixels that are below or above the specified threshold value. The image snake operation creates or modifies an active contour/snake in a greyscale image. The operation iterates to minimize the snake's energy which consists of multiple components including the length of the snake, its curvature, and image gradient [21].

After AAA segmentation, we get a 3D volume image useful to create a 3D computational model to analyze the blood flow behavior inside the AAA using computational fluid dynamics (CFD). A mesh sensitivity analysis was performed to ensure the accuracy of the simulations using steady test. Depending on the complexity of the AAA model, a 3D mesh consisted of 2.000.000–2.500.000 tetrahedral elements. Using the isosurface stuffing algorithm [22], we have obtained a smooth element and an aspect radio for the whole of the meshes higher than 0.9 (ideal ratio = 1 for an equilateral triangle). For the five acquisitions, the same medical image protocol, image processing, and volume mesh reconstruction were used.

3. Computational Fluid Mechanics Solver

CFD analysis was performed using BioDyn, a friendly user interface based on the commercial software Tdyn [23]. Tdyn is a fluid dynamics and multiphysics simulation environment based on the stabilized finite element method that solved the Navier-Stokes equations. To characterize accurately the blood flow in the AAA, a Reynolds number was calculated for whole cases. Reynolds number is a dimensionless number that determinates the dynamic of the fluid. Reynolds number

Table 1: Patient and AAA geometrical characteristics (L, τ, $d_{\text{proximal\_neck}}$, r, R, D_{AMAX}, and L_{AAA}), and all the measurements are expressed in centimeter. AAA geometrical indexes (β, γ, χ, and ε).

Case	Sex	Thoracic aorta length (L)	Hypothetic thoracic aorta length (τ)	AAA proximal neck ($d_{\text{proximal\_neck}}$)	r	R	AAA max diameter (D_{AMAX})	AAA length (L_{AAA})	χ	β	γ	ε
1	Male	359,94	320,44	2,8	1,49	2,45	3,945	6,7	1,408	0,608	0,588	0,123
2	Male	319,5	310,2	1,7	0,67	1,74	2,416	4,1	1,421	0,388	0,589	0,029
3	Male	216,28	176,8	2,6	1,02	2,03	3,056	8,98	1,176	0,508	0,340	0,223
4	Male	293,55	255,26	2,6	0,95	3,07	4,031	15,6	1,55	0,309	0,258	0,150
5	Male	310,34	296,24	2,5	1,25	1,25	2,5	—	1	1	—	0,047

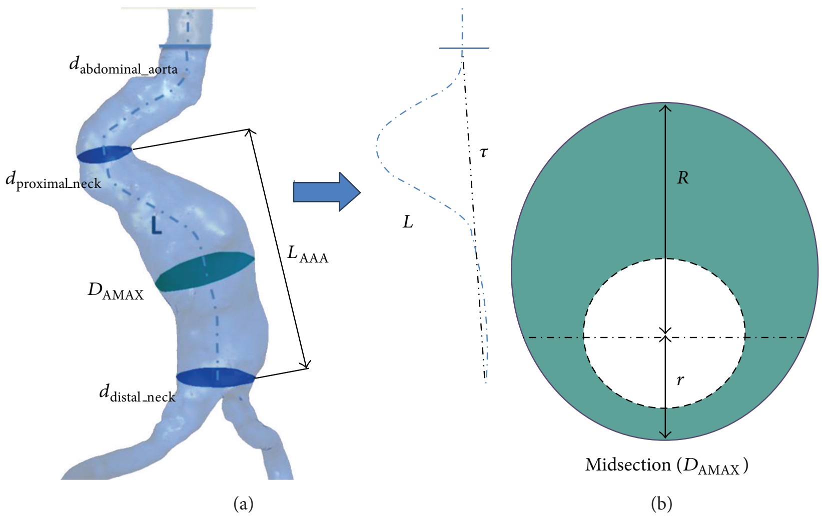

Figure 1: (a) Main geometrical parameters: L_{AAA} aneurysm length, D_{MAX} maximum diameter of the aneurysm $d_{\text{proximal\_neck}}$ beginning of the AAA sac, $d_{\text{distal\_neck}}$ ending of the AAA sac, $d_{\text{abdominal\_aorta}}$ nondeformed abdominal aorta diameter, L is the absolute length of the tortuous vessel, and τ is the imaginary straight line. (b) Schematic visualization of a cross-sectional AAA section, where r and R are defined as the radii measured at the midsection of the AAA sac from the longitudinal z-axis to the posterior and anterior walls.

is defined as $\text{Re} = UD/\nu$, where U is the mean velocity, ν is the kinematic viscosity of air, and D is the characteristic length given as the hydraulic diameter $D = 4A/P$ for the inlet velocity, and here A is the cross-sectional area and P is the perimeter of the aorta. Because the Reynolds number in inlet is low (<1000), we decided to use a CFD solver for laminar flow considering steady, homogeneous, incompressible, adiabatic, and Newtonian fluid. However, three-dimensional flow features such as flow separation and recirculation might trigger a transition to turbulence at lower Reynolds numbers [9]. Based on a preliminary study [6], the effect of the turbulence has been considered to be negligible. Following, we show the Navier-Stokes equations (2)

$$\begin{aligned}\rho\left(\frac{\partial u}{\partial t}+(u\cdot\nabla)u\right)+\nabla p & \\ -\nabla\cdot(\mu\nabla u)=\rho f, \qquad & \text{in } \Omega\times(0,t), \\ \nabla\cdot u=0, \qquad & \text{in } \Omega\times(0,t),\end{aligned} \tag{2}$$

where $u = u(x,t)$ denotes the velocity vector, $p = p(x,t)$ the pressure field, and the density (ρ) is considered constant with a value of 1050 Kg·m^{-3} and dynamic viscosity (ν), fixed at 0.004 Pa·s and f the volumetric acceleration. The spatial discretization of the Navier-Stokes equations has been done by means of the finite element method (FEM), while for the time discretization an iterative algorithm that can be considered as an implicit two steps fractional step method has been used. A new stabilisation method, known as finite increment calculus, has recently been developed [24]. By considering the balance of flux over a finite sized domain, higher order terms naturally appear in the governing equations, which supply the necessary stability for a classical Galerkin finite element discretization to be used with equal order velocity and pressure interpolations. The inlet velocity waveform was taken from the literature [25], and **Figure 3** shows the pulsatile waveforms used. For inlet condition, a transient blood flow was imposed in the descendent abdominal aorta. The velocity U was calculated for each patient in order to obtain a total fluid volumetric flow rate of 500 mL for an entire cardiac cycle. The outlet boundaries were located at the common iliac arteries where the pressure follows pulsatile waveforms as defined

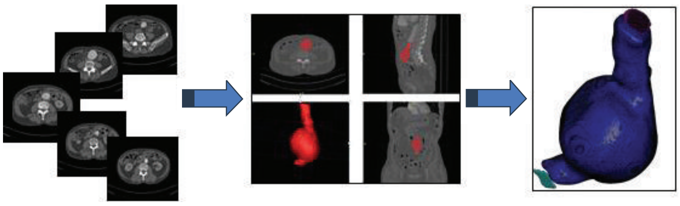

Figure 2: Workflow of the 3D AAA model. Obtaining the CT image of the abdominal aorta, segmentation of the vessel lumen using thresholding and level set method, and 3D model of the AAA.

in Figure 4(b). It is important to remark that these profiles are not patient-specific data (MR velocity mapping was not performed on these subjects), which can be a limitation of this study. In further studies, a patient-specific velocity and pressure profile will be used as boundary conditions.

Mathematically, the boundary conditions can be expressed as in (3a), (3b), and (3c). No-slip condition (vessel rigid wall) was imposed on the surface of the arteries, (3a). This choice is motivated by the fact that the physiological parameters characterizing the arterial mechanical behaviour of the AAA wall are not well determined. This approach, however, reduces the discretization effort considerably, in particular boundary layer gridding and the computational cost although other approaches consider fluid structure interaction (FSI) models [13, 25–28]. The inlet velocity is assumed to fully developed their parabolic profile at the inlet (3b), and time-dependent normal traction due to luminal pressure at the outlet (3c) as

$$V = 0\,\big|_{\text{wall}}, \tag{3a}$$

$$u_z = 2\,(u\,(t))\left(1 - \left(\frac{2r}{d_r}\right)^2\right); \qquad u_r = 0\big|_{z=0}, \tag{3b}$$

$$\tau_{nn} = \hat{n} \cdot p\,(t)\, I \cdot \hat{n}, \tag{3c}$$

where d_r is the inner radius of the abdominal aorta, u_r is the Cartesian component of the velocity vector in the "z" direction, and $u(t)$ and $p(t)$ are the time-dependent velocity and pressure waveforms designated in Figure 3. The pressure boundary conditions are given by (3c), where τ_{nn} is the normal traction designates at the outlet, I is the standard identity matrix, and $\hat{n}$ designates the normal of the respective boundary. Figure 4 shows case 4 of the AAA reconstructed model and the layers in which our domain is divided in order to impose the boundary conditions.

4. Results

Five models of infrarenal aneurysm with patient-specific geometry were analyzed using computational fluid dynamics in order to evaluate the flow patterns, wall shear stress, and pressure over the aneurysm sac. Patients 1 to 4 had infrarenal aneurysms whilst patient 5 is the control case. ILT was not found in any case. The unsteady flow simulations were performed through two pulsatile cycles to eliminate the influence of initial transients. The results of pressure, stress, and flow patterns are shown for the peak systole (0.2 s) of the second cardiac cycle.

Figure 5 shows the flow patterns, velocity streamlines inside the infrarenal aneurysms sac, and three cross-sectional areas of the AAA (proximal, midsection, and distal neck) for the five patients studied. Note that forward flow points downwards and has a negative value in the adopted coordinate system. The direction of the flow is from top to bottom (direction Z negative). We notice that when the AAA has asymmetry, the velocity streamlines correspondingly show an asymmetric flow pattern inside the AAA sac. As shown in [6, 7, 26, 29], the asymmetric flow patterns can provide an insight into the mechanism that promotes the thrombus renewal and possibly enlargement inside the aneurysm. Rapid decrease in the velocity and regions of very high (or low) hemodynamic stresses gradients may all contribute in various ways to the vascular disease, primarily via their effects on the endothelium. For example, platelets trapped in recirculation zones tend to be deposited in areas of low shear stress (stenosis) [14], since this and the presence of vortices cause prolonged contact of the platelets with the surface in the layer of slow fluid motion [6, 19]. This effect can be observed for the pathological cases; however, in case 4 we observe a flow recirculation in the middle section and the asymmetry is low. Consequently, the flow patterns of the aneurysm not only depend of the asymmetry of the aneurysm but also depend of the AAA tortuosity. Details of the flow patterns for the AAAs is shown in Figure 5 (cross-sectional areas column). From the top to the bottom: neck section, midsection (maximum diameter in the aneurysm sac), and distal section. We notice that the tortuosity of the AAA provokes an asymmetric flow patterns in the AAA sac. When ε is high, we observe that in the AAA proximal neck section there is a strong irregular flow, causing also an irregular flow in the AAA sac meanwhile, when ε is low, this effect does not appear. From these findings, the greater the asymmetry and tortuosity of the AAA, the higher the possibility of blood recirculation, ILT formation, and a possible rupture. Thus, the importance of geometry in the hemodynamic behavior of AAAs is supported.

Anterior and posterior wall shear stress views are shown in Figure 6, as well as the pressure on the aneurysm sac at the peak systole. The mean WSS in the aneurysm sac of the 5 patients varied between 0.28 (case 5) and 12.72 Pa (case 4) with a median of 3.52 Pa and mean of 5.74 Pa. The areas with WSS values under the mean value have been classified as low

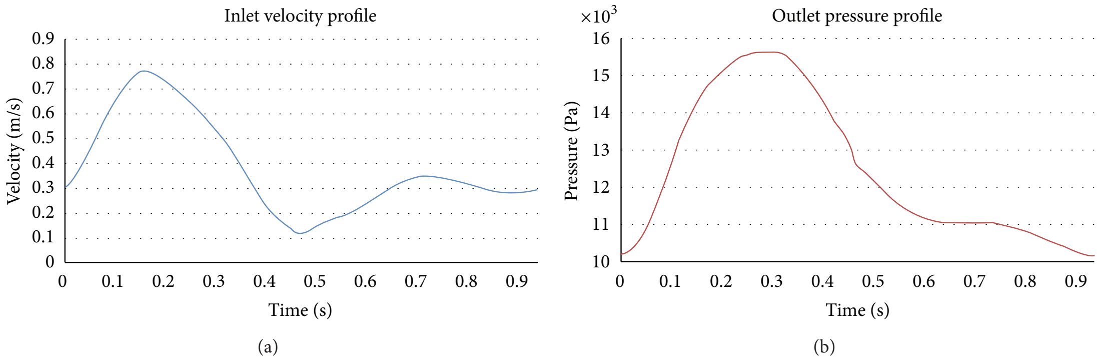

FIGURE 3: Boundary conditions for the hemodynamic simulations, adapted from [11].

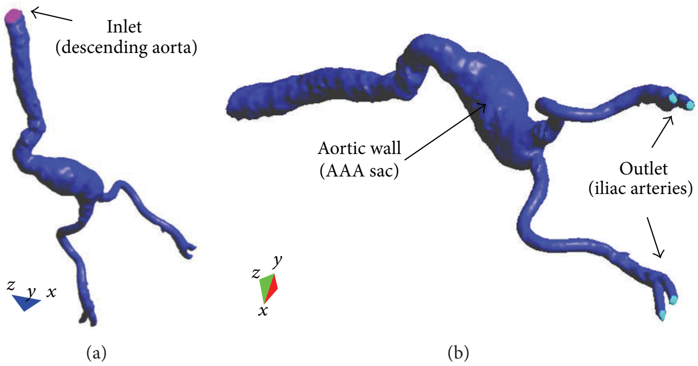

FIGURE 4: Mesh surface: different layers are shown: aortic wall (dark blue) and inlet (purple) and outlet sections (light blue).

WSS areas (blue) and areas with WSS values higher than the mean value as high WSS (red). Analysis of WSS maps for all cases shows that the area of low WSS coincides with the location of the recirculation areas (low velocities), and higher WSS values are found in two regions: in the neck area and in the corresponding area where the blood flow jet has an impact on the aneurismal sac. The blood flow jet has an impact directly on the arterial wall producing higher WSS values. The blood flow jet path is provoked by the proximal neck angle, consequently by the AAA tortuosity (see Figure 5). These WSS peak values do not influence too much in aneurysm growth; however, in these areas a material failure could be produced provoked by blood flow jet. It is interesting to note that shear stress levels in all infrarenal aneurysms models are higher than those in the normal aorta, where ε is low, which has a fairly uniform stress shear spatial distribution. Maximal values are found in the neck region, where ε is high.

Due to the increasing of the internal pressure, against the aortic walls, the AAA diameter grows progressively, and eventually it could be able to overcome the resistance of the aortic wall with its breakup. This internal pressure is directly proportional with the aneurysm diameter; thereby, when the diameter grows, the pressure increases. High deformation diameter rate (χ) index could indicate higher internal pressure however, it should be noticed that the pressure also depends on the tortuosity index (inversely proportional) and the flow characteristics (see Figure 5). For instance, in case 4 even when the section diameter is large, the internal pressure is lower than that in case 2. This is originated by a notably pressure drop as a result of the vorticity and flow recirculation (energy losses) in the cases with a high tortuosity index. This effect also provokes a pressures gradient between the anterior and posterior arterial wall in the interior of the AAA sac. These internal high pressure areas inside the sac may indicate the growth directions of AAA sac.

5. Discussions

The objective of this study is to use patient-specific AAA models for correlating the geometric indices of the aneurysm with the hemodynamic loads and, eventually, with the potential risk of AAA rupture. From a mechanical point of view, AAA ruptures when a maximum stress value over the wall is exceeded. The stress peak refers to the mechanical load sustained by the AAA wall, during maximal systolic pressurization. In addition, it is known that wall stress alone does not completely govern failure as an AAA will usually rupture when the wall stress exceeds the wall strength. Its value depends on arterial systolic pressure, the mechanical properties, and the geometric configuration of the material

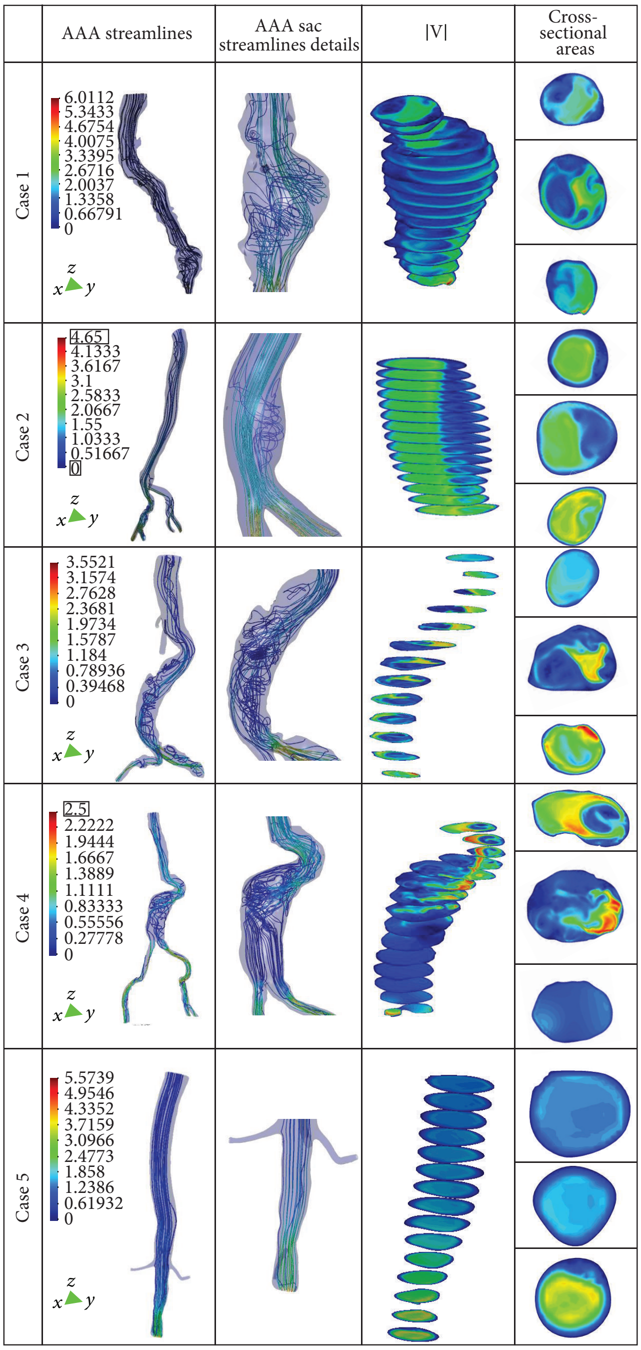

Figure 5: Streamlines, details of AAA sac streamline, blood flow velocity, and three cross-sectional areas (from the top to the bottom: proximal AAA neck and midsection and distal AAA neck) for the five patient studied.

under study. However, the mechanism of arterial wall failure due to (1) the AAA shape or (2) the pressure distribution is physically different. The first is because of a punctual force over a wall point, and the second is because a consequence of a pressure distribution over the AAA wall. Based on the AAA shape, several authors have proposed different criteria for the AAA collapsibility; if the AAA diameter is higher than 5.5 cm [4], the AAA may rupture or if the asymmetry index

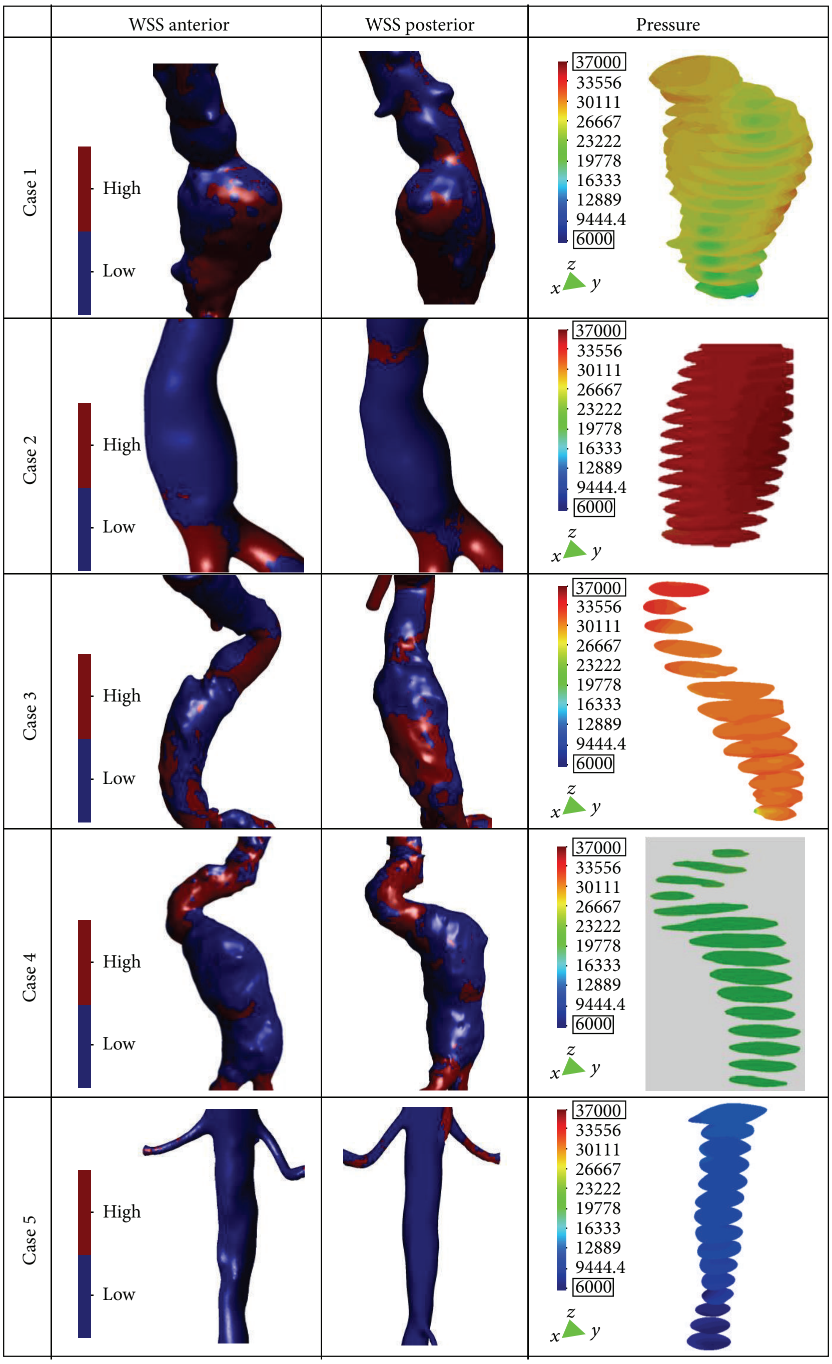

FIGURE 6: Anterior and posterior wall shear stress views (high WSS in red, and low WSS in blue) and normalized pressure on the aneurysm sac at the peak systole for the five patients.

factor (β) is $\beta < 0.4$, the AAA rupture is high [8]. In [10] the AAA collapses when the deformation diameter ratio is $\chi > 3.3$ or if the saccular index is <0.6 [11]. But depending on the index that is analysed, the surgical criteria are different. More recently, the proposed AAA rupture risk is related with the presence of intraluminal thrombus (ILT) [6, 26]. The intraluminal thrombus plays an important role in expansion and rupture of advanced aneurysms through direct mechanical as well as indirect chemomechanical effects [6]. Therefore, the AAA dilatation (and a potential rupture) is dependent on the correlation between the geometrical factor and the hemodynamic load. Consequently, alternative methods of AAA rupture assessment are needed.

The majority of these new approaches involve the numerical analysis of AAAs using computational fluid dynamics (CFD) to determine the wall shear stress (WSS) distributions and flow patterns in the aneurysm sac [5, 12, 13, 15, 16, 30]. In our study, we did not evaluate the patient-specific wall strength or the effect of intraluminal thrombus. Nevertheless, the AAA cases analyzed provide useful information to understanding how hemodynamic loads can affect aneurysm growth and possible rupture. The pathological cases (cases 1 to 4) always present irregular flow in the aneurysm sac, no uniform distribution of WSSs and great WSS values in the curvatures of the aortic vessel. These anomalies are proportional to the shape of the aneurysm and the angles of twist that the aorta has. Asymmetric flow is always correlated to the modified curvature of the vessel or when some enlargement in the aneurysm is present (high saccular index (γ) and tortuosity (ε) index). The AAA tortuosity could initiate ILT formation and at the same time could provoke arterial wall failure. In a situation where the tortuosity is high and the saccular index is low, the WSS has more effects than the pressure distribution in a possible AAA failure. However, where the AAA is not twisted and the saccular index is high, the pressure effect takes priority. In Figure 6, the highest shear stress values are dependent especially on the tortuosity of the AAA. The neck angle substantially impacts flow fields, causing strong irregular flow patterns in the AAA sac (Figure 5) significantly influencing wall stress distribution (Figure 6). The relationship between these indexes can provide an insight into the mechanism that promotes the thrombus renewal and possibly enlargement inside the aneurysm.

6. Conclusions

To conclude, in this work, the wall shear stress, internal pressure, and flow patterns of five patients-specific aortas have been analyzed using a finite element method, and the results have been correlated with the geometrical features. Results from the patient-specific infrarenal aneurysm models (cases 1–4) were compared with those of a normal aorta (case 5) and it has been found that the normal aorta has a uniform distribution of the velocity streamlines, wall shear stress, and pressure compared to that in the pathological cases. Maximum wall shear stresses in all infrarenal aneurysm models are higher than those in the normal aorta and these values are not directly related to the maximum aneurysm diameter, providing evidence that a patient-specific aorta shape analysis is necessary for a more reliable assessment of the rupture risk of aortic aneurysms. Therefore, based on one or two simple indexes alone, to determine the risk of rupture accurately is insufficient. AAA rupture is a complex situation, depending on the maximum diameter, internal pressure, wall stress, asymmetry, saccular index, intraluminal thrombus, and tortuosity, among others. Our results demonstrate how the hemodynamic loads as simulated by computational fluid dynamics (CFD) are influenced by the geometrical factors of the aneurysm.

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Chapter 4

Mechanical Stress in Abdominal Aneuryms using Artificial Neural networks.

Title: Mechanical stress in abdominal aortic aneurysms using artificial neural networks.
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Scientific contribution: Combination of artificial neural networks with computational mechanics procedures to estimate the principal stresses in the aneurismatical sac in idealized AAA geometries.

Contribution to the paper: Pres and post processing tools for mesh generation for numerical simulations. Development, implementation and application of the artificial neural model together with José F. Rodríguez and Roberto López. This overall work was carried out in collaboration with Group of Applied Mechanics and Bioengineering from University of Zaragoza.

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MECHANICAL STRESS IN ABDOMINAL AORTIC ANEURYSMS USING ARTIFICIAL NEURAL NETWORKS

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Combination of numerical modeling and artificial intelligence (AI) in bioengineering processes are a promising pathway for the further development of bioengineering sciences. The objective of this work is to use Artificial Neural Networks (ANN) to reduce the long computational times needed in the analysis of shear stress in the Abdominal Aortic Aneurysm (AAA) by finite element methods (FEM). For that purpose two different neural networks are created. The first neural network (Mesh Neural Network, MNN) creates the aneurysm geometry in terms of four geometrical factors (asymmetry factor, aneurism diameter, aneurism thickness, aneurism length). The second neural network (Tension Neural Network, TNN) combines the results of the first neural network with the arterial pressure (new factor) to obtain the maximum stress distribution (output variable) in the aneurysm wall. The use of FEM for the analysis and design of bioengineering processes often requires high computational costs, but if this technique is combined with artificial intelligence, such as neural networks, the simulation time is significantly reduced. The shear stress obtained by the artificial neural models developed in this work achieved 95% of accuracy respect to the wall stress obtained by the FEM. On the other hand, the computational time is significantly reduced compared to the FEM.

Keywords: Artificial neural network; AAA; real time.

1. Introduction

About 90% of Abdominal Aorta Aneurysms (AAA) are located below the level of the renal arteries. This pathology is known as infrarenal aneurysm, and involves the

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enlargement of the aorta in the inferior thoracic area. It takes a fusiform shape and might extend into the iliac arteries. The mortality by infrarenal aneurysms is high (15% for ruptured aneurysms), and the current standard of determining rupture risk is based on the maximum diameter. One of these AAA rupture criteria are based on the aortic size (diameter) and the rate of growth.[1] This criterion is based on Laplace law for hollow cylinders, which establishes that maximum stress in the artery increases with the radius. Other authors[2–5] based on the AAA shape as its asymmetry or tortuosity have proposed different criteria for the AAA collapsibility, if the AAA diameter is higher than 5.5 cm the AAA may rupture[2]; if the asymmetry index factor, $\beta < 0.4$ the AAA rupture risk is high[3]; if the deformation diameter ratio is $\chi > 3.3$ the AAA might collapse[4]; if the saccular index is < 0.6 the rupture risk is high.[5] But depending on the index that is analyzed the surgical criteria is different. All above studies suggest that not only size but also the shape of the aneurysm appears to be important factors in determining the risk of rupture of a given aneurysm. Therefore, alternative approach of AAA rupture assessment and other biomechanical variables are needed. The majority of these new approaches involve the numerical analysis using finite element methods (FEM) to determine new biomechanical variables inside the AAA.[6–9]

In this line, during the last period, some authors suggest that peak wall stress correlated with the AAA geometrical factors is the more reliable parameter for the assessment of the rupture risk of aortic aneurysms.[10–14] Filinger *et al.*[14] found that peak wall stress in aneurysms has a higher sensitivity (patients that went under rupture) and specificity (patients which did not undergo rupture) than maximum diameter. These findings appear to be supported by the results obtained by Ref. 8, who analyzed 27 aneurysms (15 nonruptured and 12 ruptured) using the finite element method. In their study, the peak wall stress in the ruptured aneurysms was found to be about 60% higher than for the nonruptured aneurysms. Also, the rupture location matched the area of maximum stress.[15,16] However, the use of finite element methods for the analysis of AAA often requires long computational times. For that reason, the purpose of this work is to develop an artificial neural network to compute the peak stress in real time over the aneurysm wall. To achieve our goal we combine, in a multidisciplinary framework, numerical analysis (finite element) and artificial neural networks (ANN) for the simulation of an aneurysms rupture. To study the peak stress over the AAA wall, a hyperplastic isotropic model without considering the fiber orientation has been implemented using FEM. Based on this arterial model, 243 idealized AAA were generated and simulated. Using the results obtained using the finite element technique, two different neural networks were developed and trained, a Mesh Neural Network (MNN) and a Tension Neural Network (TNN). The first one (MNN) creates an aneurysm mesh in terms of four geometrical factors (asymmetry factor, aneurysm diameter, aneurysm thickness, aneurysm length). And the second neural network (TNN) is coupled with the MNN to calculate the peak wall shear stress on every node of that mesh for a given arterial pressure.

2. Geometrical and Material Model

The shape of an aneurysm can be defined by a "parabolic-exponential shape" function proposed by Elger *et al.*,[4] see Fig. 1.

The mathematical function of this geometry is given by:

$$R(z) = R_a + \left(R_{\text{an}} - R_a - c_3 \frac{Z^2}{R_a^2}\right) \cdot e^{-(c_1 \cdot |\frac{Z}{R_a}|^{c2})}, \tag{1}$$

where R_a is the radius of the un-diseased artery, R_{an} is the maximum radius of the aneurysm. On the other hand, c_1 is a constant to be taken as 5.0, c_2 and c_3 are dimensionless geometrical parameters depending on the geometry of the aneurysm according to:

$$c_2 = \frac{4.605}{(0.5L_{\text{an}}R_a)^{c_1}}, \tag{2}$$

$$c_3 = \frac{R_{\text{an}} - R_a}{R_a \cdot (\frac{0.8L_{\text{an}}}{R_a})^2}, \tag{3}$$

where L_{an} defines the length of the aneurysm and e is the eccentricity between the aneurysm and the nonpathological arterial vessel.

In order to study the effect of the AAA geometry on the distribution of the wall stresses we introduce three (dimensionless) geometrical parameters:

$$F_R = \frac{R_{\text{an}}}{R_a}, \tag{4a}$$

$$F_L = \frac{L_{\text{an}}}{R_{\text{an}}}, \tag{4b}$$

$$F_E = \frac{e}{R_a \cdot (F_R - 1)}, \tag{4c}$$

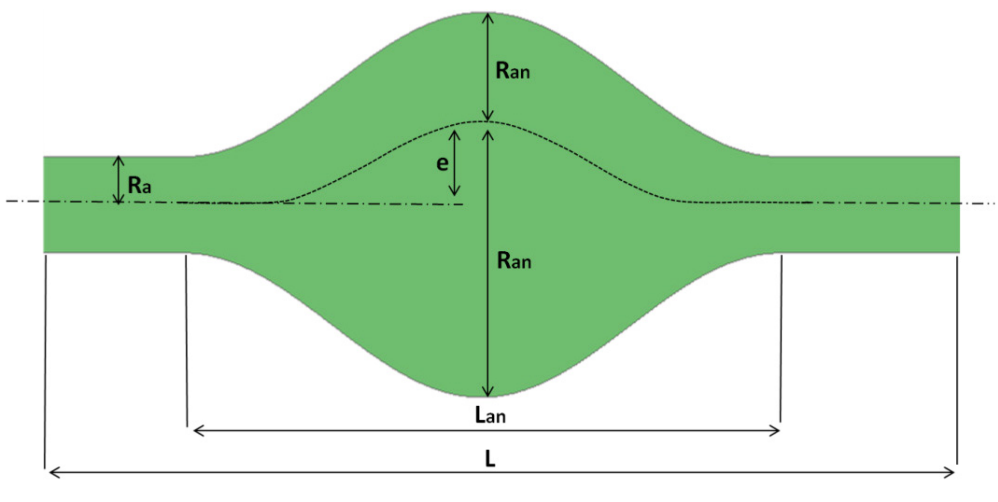


Fig. 1. Idealized geometric model of an AAA with "parabolic-exponential shape".

Table 1. Range of the values F_R, F_L, F_T and β.

Parameter	Description	Range
B	Asymmetry factor	0–1
F_R	Radius factor	2–2.75
F_L	Length factor	1.5–3
F_T	Thickness factor	0.6–1

where $F_R \geq 1$ defines the ratio between the maximum AAA radius and the undiseased arterial radius, F_L defines the ratio between the length of the aneurysm and the maximum AAA radius, and $F_E \in [0, 1]$ is a measure of the aneurismal eccentricity, with e as indicated in Fig. 1 (e is the actual eccentricity between the center of the nonpathological arterial vessel and the center of the section where the maximum aneurismal diameter is located).

The extreme cases are symmetric $F_E = 0$ (with $e = 0$), intermediate eccentric $F_E = 0.5$ and extreme eccentric $F_E = 1$ (with $e = R_{\text{an}} - R_a$). The range of the values F_R and F_L given in Table 1 is in good agreement with values used in previous parametric studies[2] as well as with clinical investigations [4, 10, 11, 19], where F_R ranges from 2.0 to 2.75 and F_L from 1.5 to 3.0. The wall thickness is assumed to be uniform, with 1.5 mm,[7] and the arterial radius is considered to be $R_a = 10.1$ mm. The constant wall thickness assumption has been used in a number of previous studies.[2,6,7,15] In this work random combinations of these parameters were used to create different AAA geometries using GiD.[17] All parametric solid models were meshed with 16896 hexahedral incompressible elements and 25536 nodes using GiD.[17] Figure 2 illustrates six different AAA configurations for different parameters.

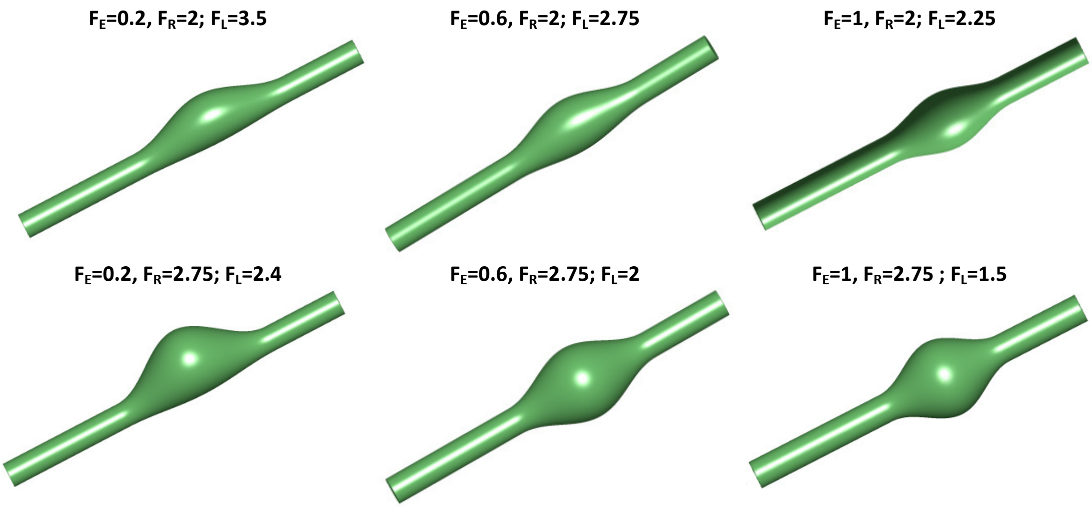


Fig. 2. Geometric models of AAA for three values of aneurismal eccentricity (0.2, 0.6, 1) and for the extreme values for F_R (2–2.75) and F_L (1.5–3).

On the other hand, experimental studies of mechanical properties of the AAA show that high peak wall stress can provoke damage over the arterial wall, and its value can be used as predictor of arterial failure.[18] Therefore, the material model should be able to accurately draw a relation between geometric factors and peak wall shear stress.[19] Based on the knowledge that the AAA wall is incompressible and most likely undergoes large deformations,[18] we can employ the multiplicative decomposition of the deformation gradient F into a volumetric part $J^{-1/3}I$, and an isochoric part $\bar{F}$, with the volume ratio $J = \det F > 0$ and $\det \bar{F} = 1$. By using an additive decomposition of W, we can write[20]:

$$\Psi(C) = U(J) + \bar{\Psi}(\bar{I}_1 \bar{I}_2 \bar{I}_4, \ldots, \bar{I}_8), \tag{5}$$

where $\bar{C} = \overline{F^T} \cdot \bar{F}$ is the right Cauchy Green tensor, and the volumetric elastic response U and the isochoric elastic response Ψ of the material are given scalar-valued objective functions of J and the invariants $\bar{I}_1, \bar{I}_2, \bar{I}_4, \ldots, \bar{I}_8$, respectively.

On assumption that the behavior of the AAA wall is hyperplastic isotropic, and without considering the fiber orientation, the strain energy density W for this material can be written as:

$$W = U(J) + c_{10}(\bar{I}_1 - 3) + c_{20}(\bar{I}_1 - 3)^2, \tag{6}$$

where I_1 is the first invariant, $\bar{I}_1 = \mathrm{tr}(\bar{C})$, of the deviatoric right Cauchy Green tensor $\bar{C}$ is the deviatoric deformation gradient tensor and C_{10} and C_{20} are the model parameters indicative of the mechanical properties of the AAA wall ($C_{10} = 174\,\mathrm{kPa}$, $C_{20} = 1880\,\mathrm{kPa}$).[7]

A range of pressure between 12.3–15.7 kPa was applied to simulate the end systolic conditions, since this pressure represents the stage of the cardiac cycle in which the AAA experiences the largest wall stress. The longitudinal constraining at the proximal and distal parts of the aneurysm due to the renal and iliac arteries was simulated by constraining the displacements to be zero at both ends.[7,15]

After developing the geometrical and computational model, 243 AAA were simulated as a random combination of the geometrical factor (see Table 1) and the internal pressure (12.3–15.7 kPa).

3. Artificial Neural Networks

During the last few years, ANN have found a wide range of applications. One of the most popular learning tasks here is function regression, also called data modeling. The function regression problem can be regarded as the problem of approximating a function from data. These applications always involve a data set, a neural network, a performance functional and a training strategy. The learning problem is then formulated as to find a neural network which optimizes a performance functional by means of a training strategy.[21]

The data set contains the information for creating the model. It comprises a matrix in which columns represent variables and rows instances. Variables in a data set can be of two types: The inputs will be the independent variables, and the targets will be the dependent variables. On the other hand, instances can be: Training instances, which are used to construct the model; generalization instances, which are used for selecting the complexity and testing instances, which are used to validate the functioning of the model.

The neural network defines a function which represents the model. The neural network used here is based on a multilayer perceptron (MLP) with a sigmoid hidden layer and a linear output layer, which is a class of universal approximator.[21] That neural network is also extended with scaling and unscaling layers.

The performance functional plays an important role in the use of neural networks, since it defines the task that the neural network is required to accomplish. The mean squared error is the performance functional used in this work. It measures the difference between the outputs from the neural network and the targets in the data set.[23] The procedure used to carry out the learning process is called training strategy. The training strategy is applied to the neural network in order to obtain the best possible performance. The type of training is determined by the way in which the adjustment of the parameters in the neural network takes place. The quasi-Newton method is the training strategy used here.[23]

In this work, we have designed, trained and validated two artificial neural networks: a MNN to create the computational mesh of the AAA based on the geometrical factors, and a TNN to compute the peak wall shear stress over the AAA wall. The open neural networks library OpenNN[24] has been used for that purpose.

3.1. *Mesh neural networks*

The aim of the MNNs is to create the computational mesh of the AAA in a precise and fast mode. Here, a vector of neural networks with size the number of nodes in the mesh will be created. The number of nodes for all the computational mesh is the same, 25,536 nodes. The inputs to the MNN are the aneurism geometry factors (F_L, F_R, F_T) and the asymmetric factor (β) defined previously. The outputs from the MNN are the corresponding node coordinates (X, Y and Z). While the numbers of inputs and outputs are constrained by the problem, the complexity of the model, defined by the number of hidden neurons in the network, is a design variable. A model order selection analysis showed that 12 neurons in the hidden layer is the optimal architecture for this problem. Figure 3 is a graphical representation of this network architecture.

Defined the input–output variables of the MNN, a data set must be generated for training. In this work an iso-topological hexahedral mesh is considered (Fig. 4). That means that the number and arrangement of nodes and elements is always the same, only the node coordinates can change. All parametric solid models were meshed using the commercial software GiD with 16,896 hexahedral incompressible

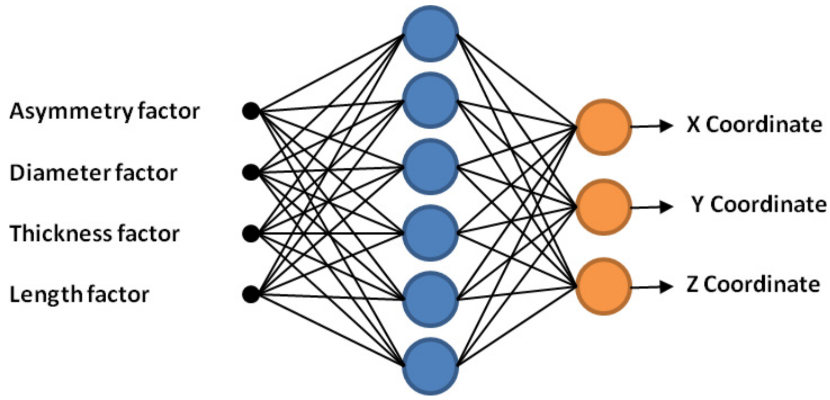


Fig. 3. Neural network architecture for the mesh multilayer perceptron, with 4 inputs, 12 neurons in the hidden layer and 3 output neurons.

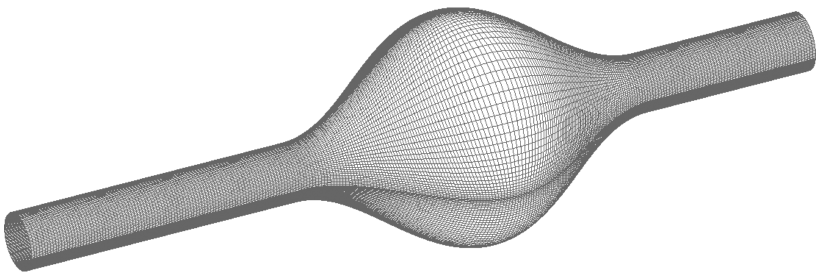


Fig. 4. Hexahedral finite element mesh used for the analysis.

elements and 25,536 nodes. In this way, a vector of data sets has been created, where the number of elements in the vector is equal to the number of nodes, that is, 25,536. Therefore, each element of the MNN will predict the coordinates of the corresponding node.

The number of samples in the data set is a design variable in the problem. In this work, we have used an input target data set with 243 samples for training. The ranges of the input variables are shown Table 1.

Figure 5 shows two examples of the MNN. Table 2 illustrates the data set for a given node.

As nodes positions are not smoothly distributed, the mesh obtained by the MNN gives us noisy results. However, results for meshes already seen by the neural network are not that noisy, and therefore we can use a nearest neighbor approach to solve this problem.

3.2. *Tension neural network*

The aim of the TNN is to calculate the peak wall shear stress over each node of the computational mesh generated by the MNN in a precise and fast mode. The first step for creating the TNN was to choose the network architecture to represent the main shear stress components T_x, T_y, T_z on the mesh generated previously by the

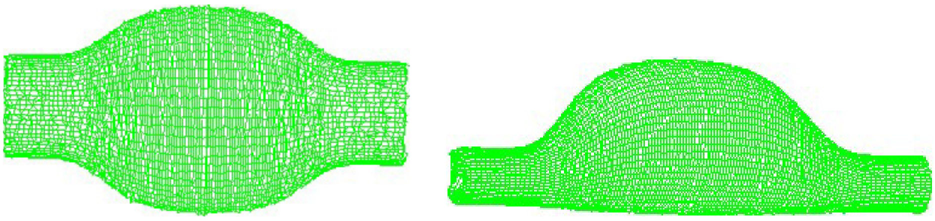


Fig. 5. MNN for $\beta = 0$, $F_R = 2$, $F_T = 0.6$ and $F_L = 1.5$ (a), neural network mesh for $\beta = 1$, $F_R = 2.75$, $F_T = 1$ and $F_L = 2.5$ (b).

MNN. In this way, a vector of neural networks has been created, where the number of elements in the vector is equal to the number of nodes (25,536 in this case).

As before, a MLP with a sigmoid hidden layer and a linear output layer was used. The number of hidden neurons used in the TNN was 10, as it proved good generalization capabilities in this problem. The inputs to the neural network must characterize the X, Y, Z coordinate obtained in the MNN plus the pressure on that artery (P). We include the arterial pressure as an input variable to the neural network (range of pressure between 12.3–15.7 kPa) as inlet conditions for the numerical simulations. The outputs from each neural network are the main shear stress components on the artery, main shear stress x (T_x), main shear stress y (T_y) and main shear stress z (T_z). Figure 6 is a graphical representation of that network architecture.

Defined the input–output variables of the TNN, the second step was to generate the input-target data set. As previously, we have used an input target data set with 243 samples for training. For each sample a numerical simulation was done in a dual-core 2.83 GHz CP, Microsoft Windows XP 32-bit PC with 4 GB-RAM, with a total computation time of approximately five hours. Each simulation provides the shear stress state for each node (T_x, T_y and T_z), and the number of elements in the vector is equal to the number of nodes, that is, 25,536. Each input-target data set will be used for training the TNN.

The number of input variables in the data set must be equal to the number of input variables in the neural network, that is, 4. Similarly, the number of target variables in the data set must be equal to the number of output variables in the

Table 2. Data set for the MNN, with 243 samples, 4 input variables and 3 target variables.

Input variables				Output variables		
β	F_R	F_T	F_L	X coordinate	Y coordinate	Z coordinate
0.0	2.0	0.6	1.5	10.198	0.000	−39.395
0.5	2.75	0.6	1.5	15.154	10.541	−54.169
…	…	…	…	…	…	…
1.0	2.75	1.0	2.5	26.687	25.142	1.255

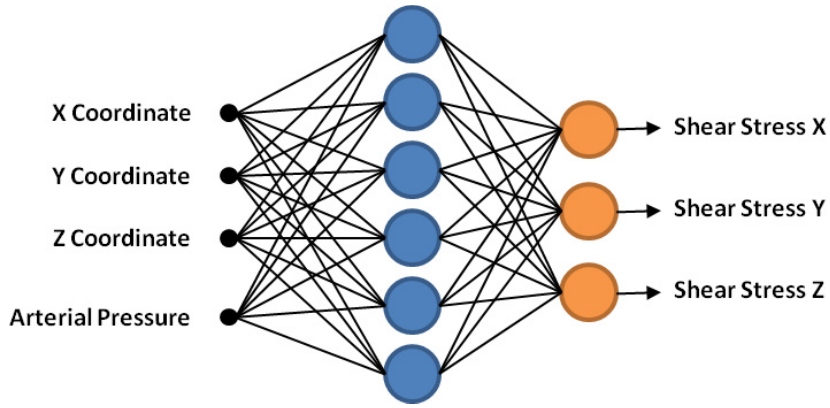


Fig. 6. Network architecture for the TNN.

neural network, that is, 3. Table 3 is a graphical representation of that input target data set.

The third step was to choose a suitable objective functional in order to formulate the function regression problem. Here we use the mean squared error between the outputs from the network and the targets in the data set. And the last step was to choose a training algorithm for solving the reduced function optimization problem. As before a quasi-Newton method with BGFS train direction and Brent optimal train rate is used.[23] The training algorithm is set to stop after 250 iterations. Once the TNN has been created it is ready for use. Figure 7 shows the results, main stresses, for three different cases based on aneurism geometry factors defined previously F_L, F_R, F_T, asymmetric factor (β) and an internal pressure (P).

4. Final ANN and Validation

Figure 8 shows the final neural network developed, where four dimensionless parametric factors: (1) AAA asymmetric factor, (2) AAA diameter factor, (3) AAA thickness factor and (4) AAA length factor are used together with hemodynamic arterial pressure factor to obtain the maximum peak stress over each node of the computational mesh.

Table 3. Data set for the MNN, with 243 samples, 4 input variables and 3 target variables.

Input variables				Output variables		
X coordinate	Y coordinate	Z coordinate	P	T_X	T_Y	T_Z
10.198	0.000	−39.395	12.3	10.198	0.000	−39.395
15.154	10.541	−54.169	12.3	15.154	10.541	−54.169
...	...	...		...	...	...
26.687	25.142	1.255	15.7	26.687	25.142	1.255

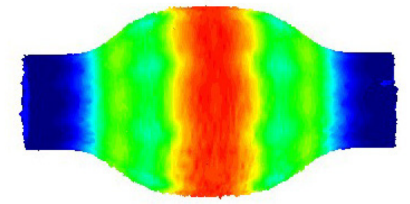
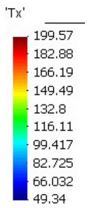
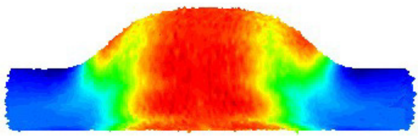
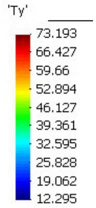
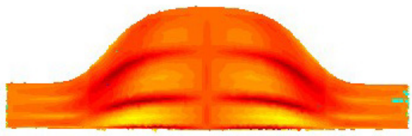
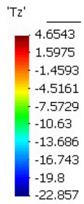
Parameters		Main Stresses	
MNN	TNN	Main Tension T_x for:	
β=0 F_L = 1.5 F_R=2 F_E=0.6	$[X]_i$ $[Y]_i$ $[Z]_i$ P=12.3 Pa		
MNN	TNN	Main Tension T_y for:	
β=0.5 F_L = 1.75 F_R=2.5 F_E=1.5	$[X]_i$ $[Y]_i$ $[Z]_i$ P=13.5 Pa		
MNN	TNN	Main Tension T_z for:	
β=1 F_L = 2.5 F_R=2.75 F_E=1	$[X]_i$ $[Y]_i$ $[Z]_i$ P=15.07 Pa		

Fig. 7. Main shear stress components T_x, T_y and T_z calculations using the TNN for 3 different cases. $[X]$, $[Y]$, $[Z]$ represent the i-node coordiantes created using the aneurism factor (F_L, F_R, and F_T and the asymmetric factor (β)).

To validate the final network developed, the aneurismal principal stresses predicted by the AAA were compared with results obtained from finite element calculations for an aneurismal internal pressure for 27 random cases. The prediction of the error for each principal stress has been quantified according to:

$$\mathbf{error} = \frac{|\mathbf{S} - \mathbf{S}^{\mathbf{TNN}}|_\infty}{|\mathbf{S}|_\infty},$$

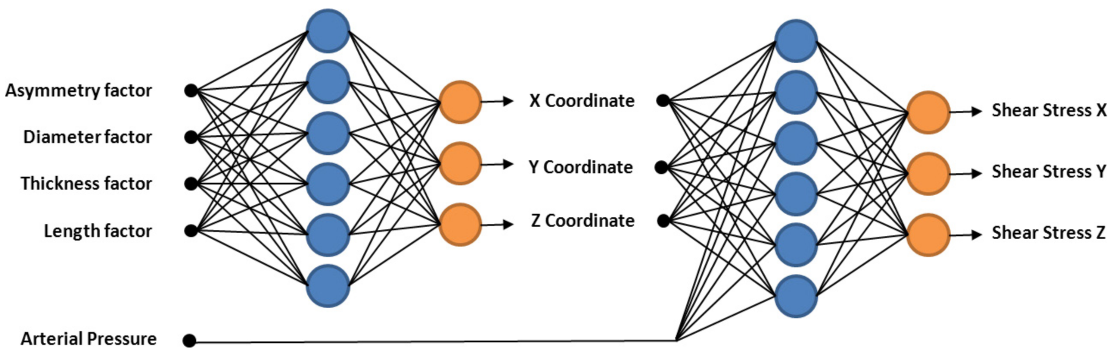


Fig. 8. Final artificial neural network developed. Input variables (F_R, F_L, F_T, β, pressure) and output variables (shear stress X, shear stress Y, shear stress Z).

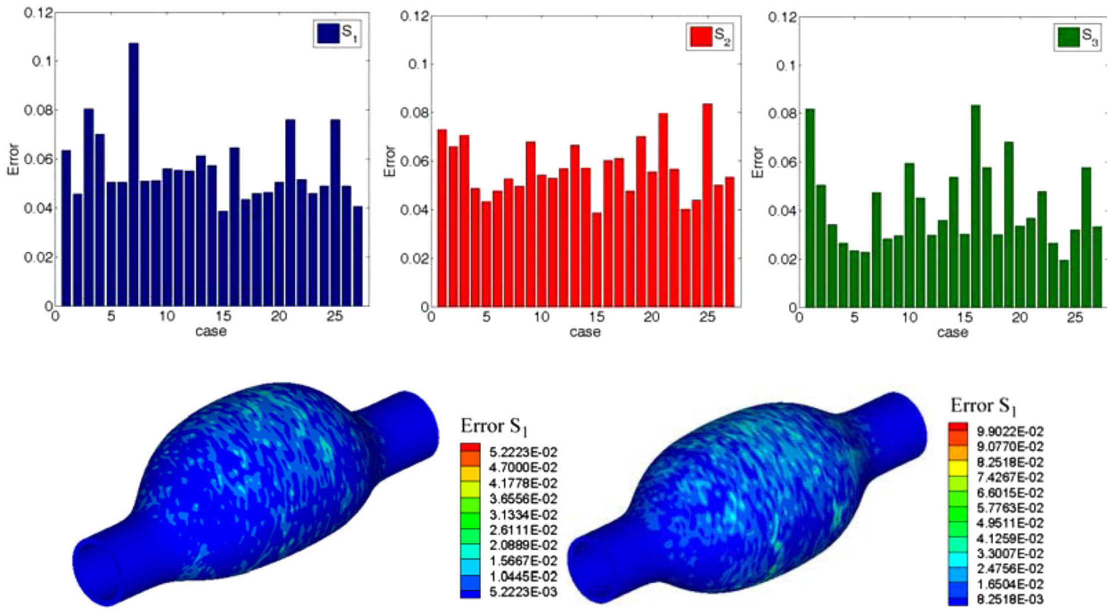


Fig. 9. Shown the error in the maximum principal stress for 27 cases analyzed (top). Shown the error S between the ANN against FEM for two different geometries (bottom).

where S is the vector of the principal stress at each node obtained using FE and S^{TNN} is the vector of principal stress at each node obtained by the TNN. According to Fig. 9, the results obtained in these 27 cases analyzed, the error for the principal stresses between the final network and the FE is negligible, less than 10%, and moreover the time is reduced in more than 95%.

5. Conclusions

The overall goal of this paper is to propose a comprehensive computational methodology based on structural analysis and ANN to predict the main stresses in the aneurysm wall in real time. A key feature of the proposed methodology is that the ANN are capable to reproduce the abdominal geometry and approximate the results of the FEM analysis up to a high degree of accuracy. In order to achieve the objective of this work, two different neural networks were created, a MNN to approximate the computational mesh and a TNN to approximate the shear stress components in the AAA. The main stresses obtained by the TNN compared with the FE are negligible as we have shown in Fig. 9. We recognize that the computational model used to simulate the AAA (hyperplastic isotropic and without considering the fiber orientation) is not the most accurate to reproduce the mechanical behavior of the wall. However the methodology suggested in this work could be used to predict the evolution or rupture of the AAA based only on geometrical factors and internal pressure in a real time. A full AAA structural analysis to obtain the main stresses over the wall requires 5 h in a desktop computer (aneurism model CAD, volume mesh generation and a structural analysis), whereas the framework proposed in this work requires less than 2 min. The only parameters needed are the F_L, F_R, F_T, β and an internal pressure (P). Since this work was not based on patient-specific geometry, the geometrical parameters can be easily obtained using image processing techniques and pressure can be measured using a pressure cuff. Note that we have used a constant wall thickness, which is an assumption, the thickness distribution along the AAA changes.

To conclude, it is important to emphasize that computational modeling techniques combined with artificial intelligence procedures can provide an insight into the patient-specific conditions for AAA evolution or rupture in real time. Also, the methodology proposed allows to understanding the geometrical factors governing the maximum stresses in the aneurysm wall. Future studies, an improved material model (anisotropic model) will be developed, as well as, other geometrical factors as the tortuosity of the AAA. In addition, further studies are required to include the effect of the intraluminal thrombus.

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Chapter 5

Estimation of Wall Shear Stress using 4D flow Cardiovascular MRI and Computational Fluid Dynamics.

Title: Estimation of Wall Shear Stress using 4D flow Cardiovascular MRI and Computational Fluid Dynamics (article in preparation)

Scientific contribution: Designed new methodology to estimate the Wall Shear Stress(WSS) using 4D flow cardiovascular MR data and computational fluid dynamics. The methodology proposed is based on interpolate the data acquired from the 4D flow CMR sequence into a patient-specific refined-mesh computational mesh. This paper is a proof-of-concept to validate WSS using CFD data.

Contribution to the paper: This work is being carried out in collaboration with the E.T.S. d'Enginyeries Industrial i Aeronáutica de Terrassa (ETSEIAT), UPC and the Unidad de Imagen Cardiaca, Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau. The simulation in the OPENFOAM software([88]) was performed during the final career project of Jordi Casacuberta in the ETSEIAT. The author of this monograph has developed the algorithm and the methodology for the calculation of the WSS using 4D flow CMR data in collaboration with Jorge S.Pérez (CIMNE). The author of this monograph has also contributed in the segmentation and the analysis of results.

Estimation of Wall Shear Stress using 4D flow Cardiovascular MRI and Computational Fluid Dynamics

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Abstract

In the last years, wall shear stress has arisen as a new diagnostic indicator in patients with arterial disease. There is substantial evidence that the wall shear stress plays a significant role, together with hemodynamic indicators, in initiation and progression of the vascular diseases. Estimation of wall shear stress values, therefore, may be of clinical significance and the methods employed for its measurement are crucial for clinical community. Recently, four-dimensional flow cardiovascular magnetic resonance has been widely used in a number of applications for visualization and quantification of blood flow, and although the sensitivity to blood flow measurement has increased, it is not yet able to provide an accurate three-dimensional wall shear stress distribution. The aim of this work is to evaluate the aortic blood flow features and the associated wall shear stress by the combination of 4D flow cardiovascular magnetic resonance and computational fluid dynamics technique. In particular in this work, we used the 4D flow cardiovascular magnetic resonance to obtain the spatial domain and the boundary conditions needed to estimate the wall shear stress within the entire thoracic aorta using computational fluid dynamics. Similar wall shear stress distributions were found for cases simulated. A sensitivity analysis was done to check the accuracy of the method. 4D flow cardiovascular magnetic resonance begins to be a reliable tool to estimate the wall shear stress within the entire thoracic aorta using computational fluid dynamics. The combination of both techniques may provide the ideal tool to help tackle these and other problems related to wall shear estimation.

Keywords: Phase-contrast MRI, velocity mapping, blood flow patterns, wall shear stress, computational fluid dynamics

1 Introduction

The endothelium is the first-line defense against atherogenesis. A key stimulus to maintain the protective status of the endothelial lining at the inner vessel wall is the wall shear stress (WSS). WSS is the tangential force that blood flow exerts on the endothelium. To quantify WSS, three dimensional blood flow patterns need to be measured in vivo, which has been a challenge in medical imaging for many years(17)(22)(13)(24)(12). Although recent preclinical data of 3D ultrasound studies for general flow visualizations in the left ventricle are promising, at present Magnetic Resonance Imaging (MRI) is the only non-invasive imaging modality that can measure 3D blood velocity in 3D in a standardized fashion. Although MR imaging resolution and acquisition speed has increased over the past decades, assessment of WSS is still challenging in complex flow geometries. The cardiac magnetic resonance imaging allows visualization of spatial distribution of velocity in a two-dimensional plane (2D). This technique is valuable non-invasively tool for evaluation of the cardiovascular flow patterns owing to its unique possibility to simultaneously acquire sectional imaging without restriction, anatomy and blood flow velocities with a single scan. The majority of the commercial systems offer the bi-dimensional phase-contrast sequence to quantify blood velocity and derivative cardiac flow. These sequences are reliable and precise methods to calculate stroke volume for pulmonary/systemic flow ratios estimation (Qp:Qs) and to calculate volume regurgitation in valvular insufficiencies (6)(27). At present, 4D flow cardiovascular magnetic resonance imaging (4D CMRI) sequences are being processed to allow obtaining information of the 4D flow as well as the software to visualize and quantify 4D images. There are several research groups working on these techniques, allowing visualization of the blood flow patterns in any segment of the cardiovascular system (9)(10)(11)(23). Nevertheless, the visualization of these images entails an important manual work, becoming a very time-consuming task and then turning out to be not useful in the current clinical practice. Therefore, it is important to improve the methods of automatic representation of the 4D flows, and to do so it is crucial to have a powerful visualization tool able to analyze the DICOM information from the medical image. In that sense, the International Centre for Numerical Methods in Engineering (CIMNE) has developed a home-made ad-hoc software (Aorta4D) oriented to make progress in this field of work (3)(1)(5)(27)(20). Aorta4D will afford analysis and spatially visualization of the registered 3-directional blood flow velocities, and perform a 3D semi-automatic segmentation based on the 4D flow CMRI data. The purpose of this study is to demonstrate that 4D flow CMRI technique is a reliable tool to provide the boundary conditions for the Computational Fluid Dynamics(CFD) in order to estimate the WSS within the entire thoracic aorta in a short computation time. Our image-based CFD methodology exploits the morphological MRI for geometry modelling and 4D flow CMRI for setting the boundary conditions for the fluid dynamics modelling. The aim is to evaluate visualization of well-defined aortic blood flow features and the associated wall shear stress by the combination of both techniques.

2 Material and Methods

2.1 Medical Image processing

Measurements were carried out using a 3 T MR system (Magnetom TRIO; Siemens, Erlangen, Germany) time-resolved, 3-dimensional MR velocity mapping based on an RF-spoiled, gradient-echo sequence with interleaved 3-directional velocity encoding (predefined fixed velocity sensitivity = 150 cm/s for all measurements). Data were acquired in a sagittal-oblique, 3-dimensional volume that included the entire thoracic aorta and the proximal parts of the supra aortic branches. Each 3-dimensional volume was carefully planned and adapted to the individual anatomy (spatial resolution, $1.78 \times 1.78 \times 2$ mm). In the in vivo situation, measurements may be compromised by the active cyclic motion of the heart (cardiac contraction and dilation) and the passive motion of the heart due to respiration. These motion components may lead to image artifacts and uncertainties about the exact measurement site in the aorta. Only if the breathing state was within a predefined window data was accepted for the geometrical reconstruction. To resolve the temporal evolution of vascular geometry and blood flow, measurements were synchronized with the cardiac cycle. The velocity data was recorder in intervals of Temporal Resolution (TeR) throughout the cardiac starting after the R-wave of the ECG. The initial delay after R-wave detection was required for execution of the navigator pulse and processing of the navigator signal. Two-fold acquisition (k-space segmentation factor = 2) of reference and 3-directional velocity sensitive scans for each cine time frame resulted in a temporal resolution of 8 repetition time = 45 to 49 milliseconds. To minimize breathing artifacts and image blurring, respiration control was performed based on combined adaptive k-space reordering and navigator gating. Further imaging parameters were as follows: rectangular field of view = 400x(267-300) mm2, flip angle = 15 degrees, time to echo = 3.5 to 3.7 milliseconds, repetition time = 5.6 to 6.1 milliseconds, and bandwidth = 480 to 650 Hz per pixel. Velocity measurements a voluntary healthy, male subject underwent MR examinations; written informed consent was obtained from the subject.

2.1.1 Segmentation based on 4D CMRI data

In order to explain how the computational domain was obtained a brief description of the segmentation process is explained. Firstly, we select the time step where velocities are higher (t=0.27 s). For that time step, we have four different set of images (Vx, Vy, Vz and Magnitude), and for each pixel of those images the following equations are evaluated:

$$A(v_{x,y,z}) = X_{max} - \sigma(M_x) \tag{1}$$

$$B(v_{x,y,z}) = \sigma(v_x, v_x, v_x) \tag{2}$$

$$C(v_{x,y,z}) = max(\sigma(T_{vx}), \sigma(T_{vy}), \sigma(T_{vz})) \tag{3}$$

$$D(v_{x,y,z}) = 1/S(v_{x,y,z}) \tag{4}$$

Equation 1 is used to remove air from the images. X_{max} is the maximum value of the v_x component in all the vector pixels in the image. M_x is the collection containing all the v_x components of radius 1 voxel neighborhood of $v_{x,y,z}$. Basically, Ec.1 tries to give higher values to points where the signal-to-noise ratio is higher, i.e., non air pixels. Equation 2 tries to gives higher values to pixels in which the vector direction is stronger in one horizontal or vertical direction, since blood in aorta travels vertically (ascending an descending aorta) or horizontally (aortic arch). In Ec.2, v_x, v_y, v_z are the velocity component values for each pixel$v_{x,y,z}$. Equation 3 makes uses of the fact that blood pumped out from the heart has strong changes of velocity at the highest and lowest peak over time. Ec.3 gives the higher pixel values to pixels where that change occurs. T_{mag} is the collection of magnitude values of a voxel $v_{x,y,z}$ over time. T_{vx}, T_{vz} and T_{vy} means the velocity vector components over time. Equation 4 tries to penalize voxels where the behavior of velocity is irregular. Blood in the aorta has smooth behavior of gaining and loosing speed from diastole to systole and then back. $S(v_{x,y,z})$is a measure of the smoothness of the value changes of a given pixel over time. Each function is encapsulated as ITK filter(30). Therefore, the segmentation pipeline process is:

- Eliminate air class using a mask obtained from the Ec.1. Another practical solution may be using an associated magnitude image and apply a threshold to eliminate lower intensities values.
- Apply Ec2, Ec3, Ec4 (a scalar value is assigned to each pixel).
- Define a threshold in which most aorta pixels lies.
- Binarize the image where (p=1 $\rightarrow if \in aorta$, p=0 $\rightarrow otherwise$)
- Apply morphological filters binary erosion and dilation. This will remove small voxels that can be separated from the aorta.
- The aorta remains as the largest connected component. Select the largest connected component.

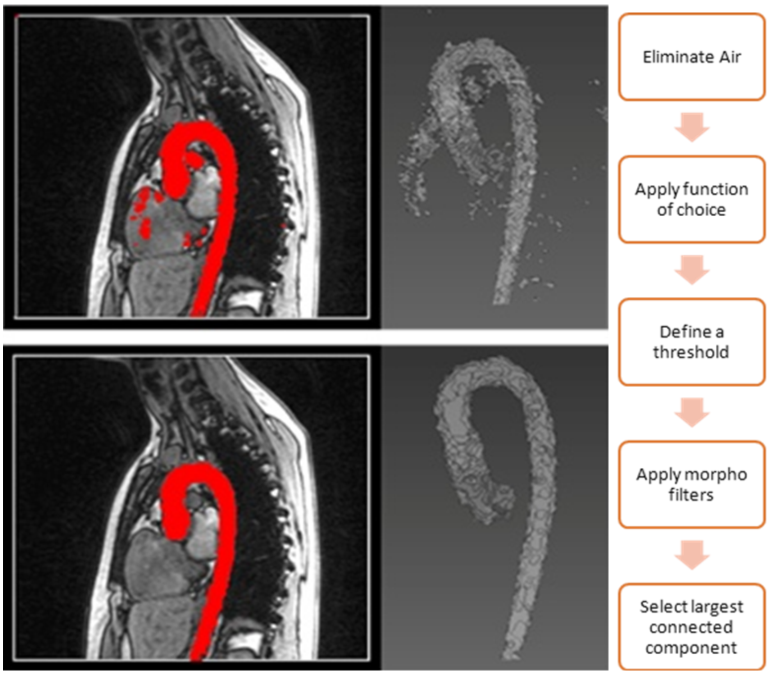

Figure 1: Segmentation workflow

- Smooth the resulting image from step 6 and binarize again to achieve a binary mask.

The only requirement is to set interactively the threshold parameters of the aorta. Once the aorta is segmented, a center line must be defined for visualization and quantification purposes. The skeletonizing process is described in (15). The centerline will allow identifying the inlet and outlet surface to define the boundary conditions needed for the CFD. The segmentation is then used as a mask for the velocity image and is superimposed on a slice of the scalar data. Figure 2 shows respectively the longitudinal cross section of the Aorta, a surface mesh obtained and streamlines inside the aorta. Once we have finished, we use this mask as initial conditions for the other time steps. For an expert user, total time for the segmentation process is less than 5 minutes.

2.1.2 Aorta Meshing

The surface of the aorta segmented is irregular and rough as a consequence of the complexity of the segmentation process. If it were directly meshed, these flaws might lead to misleading conclusions regarding the wall shear stress. Therefore, a Laplacian smoother was applied to the initial aorta segmented, with the aim of smoothing the main irregularities (see figure 2 (center)). The mesh used for the simulations was based on hexahedral cells and was divided into three main parts: an internal uniform core with cells whose size were 0.938 mm x 0.938 mm x 0.969 mm, layers of cells at the aorta wall whose volumes were eight times lower than the central core, and an intermediate region of cells separating the previous regions (see figure 3). In particular, two layers of cells have been added (first layer, 40% thicker than the 6-level cells and second layer 50% thicker than the first layer). The distance between the wall and the first node is of the order of micrometers (10^{-6} m).

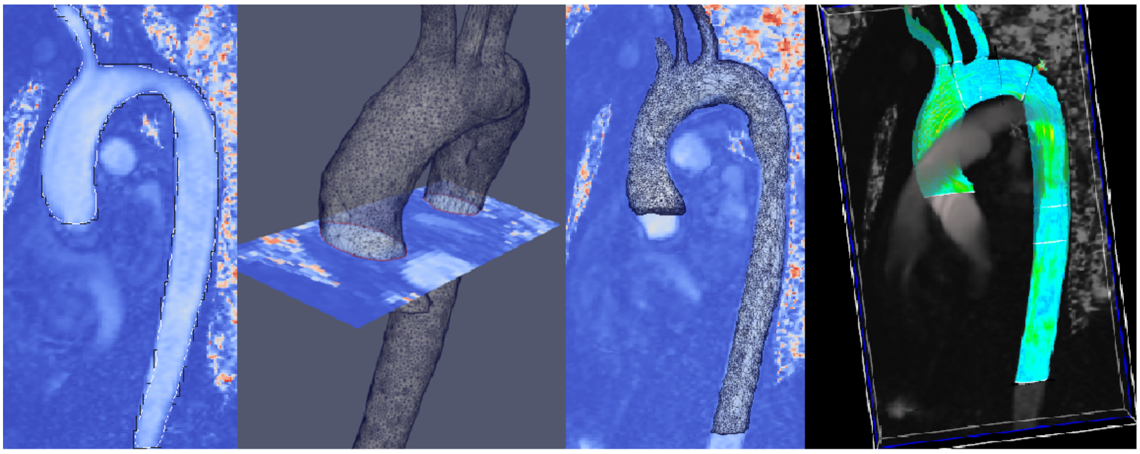

Figure 2: Aorta longitudinal cross section (left), black line in the Aorta longitudinal cross section (left) shows the voxels chosen during the segmentation process, while the white line shows the smoothing approach based on the voxelization process. The two images on the center of the figure show the 3D surface mesh obtained during the smoothing process. A Velocity streamlines(right) obtained using directly the volume mesh at the peak systole.

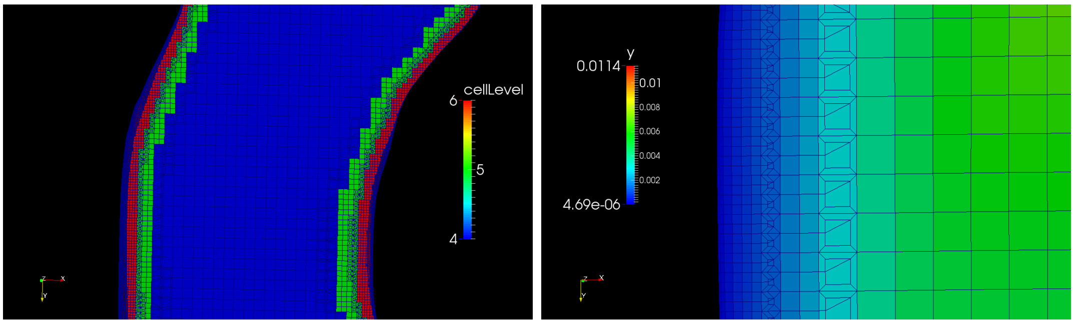

Figure 3: Detail of the cell refinement at the walls of the aorta with the magnitude of the distance between the wall and the nodes. Cellevel represents the number of the cell generated close to the wall. y^+ is the wall coordinate (distance y to the wall).

A very accurate discretization of the arterial wall is needed because one of the objectives of the work is to compute WSS by combining CFD and 4D CMRI data. To achieve this purpose, three computational mesh were created (see figure 5) with different wall refinement. The mesh was highly refined at the walls of the aorta in order to be able to solve the boundary layer correctly (the distances for the first nodes of the original mesh were the order of millimeters, and for the last mesh was the order of micrometers)(2). All the pre-processing was performed using OpenFOAM software package(18).

2.1.3 Computational Fluid Dynamics

The use of CFD techniques in simulating blood patterns and modelling cardiovascular systems has become widespread within bioengineering and medical research in the past few decades. However, the increasing reliance on CFD for hemodynamic simulations requires a close look at the various assumptions required by the modelling activity, and in particular, to assess the sensitivity to assumptions regarding boundary conditions (25)(29). Nowadays, thanks the new advances in 4D flow CMR imaging, we can obtain highly resolved blood flow patterns in anatomically realistic models. Consequently, these realistic blood flow patterns can be used as boundary conditions of the CFD models. Therefore, coupling medical imaging and CFD allows to calculate new hemodynamics indicators, as WSS. An important aspect to compute the distribution of the WSS is the anatomical domain. Local arterial geometry components as curvature and smoothness will highly influence the WSS results(24). Computationally, WSS can be defined in terms of the surface traction vector t whose components are given as:

$$t_i = (-p * \delta_{ij} + \tau_{ij}) * n_j \tag{5}$$

p denoting the pressure, τ_{ij} are the components of the viscous stress tensor and n_j are the components of the normal n to the surface. The WSS is then defined, on each point on the surface, as

$$t_w = |t_w| = |t - (t * n) * n| \tag{6}$$

that is, the magnitude of the traction vectors component in a plane tangential to the surface.

In order to perform a realistic simulation, it is recommended to prescribe outflow boundary conditions based on in vivo accurate measurements. Depending on its location and type, the inlet velocity profile seems to influence both bulk flow and wall shear stress distribution(24). For all case studied in this work, instead of using standard boundary conditions based on lumped models (25)(29), we have fixed the flow rate waveform at the supra-aortic vessels based on the 4D flow CMRI data. The inlet flow profile was measured with 4D CMRI and prescribed in the ascending aorta. The velocity profile at the outlet, simulations were performed without direct constraints on the shape of the outlet velocity profiles, but prescribing zero normal gradient for all flow variables with the exception of pressure. Velocity contours in the descending aorta were found to be in very good agreement with 4D CMRI measurements, with prediction of flow reversal on the inner side in the descending aorta (5). The average peak Reynolds number was higher in the ascending (≈4500) and descending aorta (≈4200) than in the aortic arch (≈3400). The supercritical Reynolds number, indicating flow instabilities, is significantly correlated with body weight, aortic diameter and cardiac output. While the findings might suggest the presence of flow instabilities in the healthy aorta at rest, this does not involve fully turbulent flow(28). In this study, we focus on the WSS distribution at the systolic peak, therefore it is not necessary consider elastic wall. Arterial walls were assumed to rigid, and no-slip condition was imposed. The CFD code used to solve the WSS was the open source code OpenFoam(18). The OpenFoam library solves differential partial equations with the Finite Volume Method. The solver used in the present work is for steady-state flow with the SIMPLE (Semi-Implicit Method for Pressure Linked Equations) algorithm for solving the velocity-pressure coupling(19).

2.1.4 Hypotheses and boundary conditions

The main hypotheses assumed for the aorta simulation are incompressible and laminar flow, Newtonian fluid, rigid wall and uniform inlet velocity profile. Right and left coronaries and intercostal arteries are not included in this study. As one of the main goals of the study was to determine wall shear stress that blood causes in order to prevent medical diseases, the most critical conditions were simulated for the thoracic aorta. As a consequence, the simulations were carried out at the peak systolic time (t=0.27 s). At this time step, blood velocities pulsing through the aorta are high and subsequently the wall shear will be higher. Realistic boundary conditions were applied to the computational model, thanks to the information provided by the 4D flow CMR images. Since the pressure in each outlet is different and difficult to obtain from the 4D CMRI data, we use the velocities and flow rates at each boundary conditions. The uniform inlet velocity profile was applied parallel to the inlet faces normal vector, and its module was computed considering the flow rate and the surface of the inlet face. On the other hand, at the supra-aortic vessels, outlet flow rates were imposed, since the direction of the outlet velocities are not relevant. At the outlet of the descending aorta, null pressure was applied and taken as the reference value. The outlet flow rates used at the supra-aortic branches were the following:

- Brachiocephalic artery: 27.13 ml/s
- Left common carotid artery: 10.15 ml/s
- Left subclavian artery: 18.00 ml/s

For the computation of the inlet velocity vector, the following steps were followed. By considering the real measures obtained from the 4D CMRI, the inlet volumetric flow rate for that aorta was 259.14 ml/s. As the velocity boundary condition needs to be a vector and a standard model was considered, its direction was set parallel to the normal vector of the inlet patch.The area vector of patch inlet was computed $\left|\overline{A}\right| = 4.31163 \times 10^{-4} m^2$. The module of the main inlet velocity was computed considering the inlet area and the volumetric flow rate is: $U_{mean} = k_c \Delta Q_{inlet} / \left|\overline{A}\right|$. Where k_c is a constant that needs to be included because the inlet patch is not completely bidimensional: k_c=flux required/flux of a 3D inlet. This constant was necessary because when the simulation was carried out with an inlet velocity according to U_{mean} without k_c, the inlet flow rate computed after the simulation was higher than expected. It was concluded that this was because of the fact that the inlet patch was not completely two-dimensional. Constant k_c then expresses the relation between the flow rate that was erroneously obtained and the required volumetric flow rate (259.14 ml/s). The area vector of patch inlet was normalized. A comparison between the outlet flow rates at the outlets can be observed in Table 1.

Artery	4D CMRI data	Estimated
Brachiocephalic	10.47 %	13.73 %
Left common carotid	3.92 %	4.20 %
Left subclavian	6.85 %	6.56 %
Descending Aorta	72.86 %	75.51 %

In order to limit the study, the intercostal arteries and left and right coronaries arteries are left out (aprox. 6% of the total flow (16)). It can provide and approximate idea of the error committed.

3 Results

Based on WSS indicators, it has been demonstrated that WSS play an important role in the development and progression of vessel wall pathologies (4). As it is explained in section 3, wall shear computation is based on the velocity gradient close to the wall. For that reason, firstly we have compared the 4D flow CMRI velocities against the CFD velocities obtained. The assumptions taken during the CFD simulation were: flat inlet velocity profile, outlet velocity profiles as boundary conditions and laminar Newtonian flow; and WSS computation will be perform only for the peak systolic instant time, therefore we assume rigid and static aorta walls. Next figure 4 shows the velocity profile obtained using the OpenFOAM software against the 4D flow CMRI velocity distribution at different sections along the entire aorta. Evaluating quantitatively the results, we can observe that the CFD results are capable to capture the vorticity and the flow distribution along of the aorta. However, we can also notice some differences in the ascending aorta due to the assumption of flat inlet velocity profile, as also is reported on (14). For this analysis we do not consider the eccentricity of the aortic valve(7).

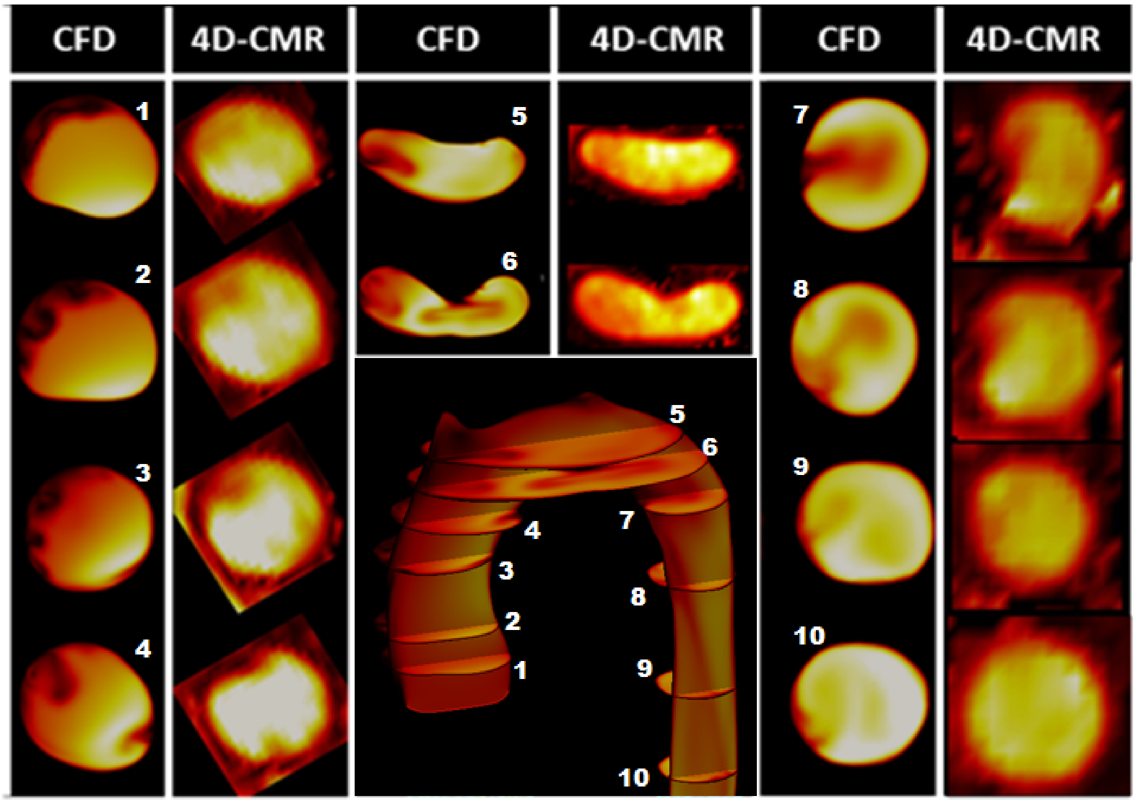

Figure 4: Velocity distribution (CFD versus 4D flow CMRI) through different cross-sectional planes along the aorta (ascending aorta (planes 1-4), aortic arch (planes(5-6), descending aorta(planes 7-10)).

Following table shows the differences between the flow_{4DCMR} and flow_{CFD} for the different cross-sectional planes at the ascending and descending aorta. We observe the flow differences provoked by coronaries arteries in the ascending aorta and by the intercostal arteries in the descending aorta. Another source of error could be the segmentation process.

Cross-sectional Plane	flow_{4DCMR}	flow_{CFD}	Error
Ascending Aorta Plane 1	259.14 ml/s	259.14 ml/s	0%
Ascending Aorta Plane 2	248.7 ml/s	259.14 ml/s	4.1%
Ascending Aorta Plane 3	248.5 ml/s	259.14 ml/s	4.1%
Ascending Aorta Plane 4	248.2 ml/s	259.14 ml/s	4.2%
Descending Aorta Plane 7	196 ml/s	195.67 ml/s	0.16%
Descending Aorta Plane 8	193.30 ml/s	195.67 ml/s	1.21%
Descending Aorta Plane 9	191.47 ml/s	195.67 ml/s	2.14%
Descending Aorta Plane 10	190.95 ml/s	195.67 ml/s	2.41%

Once mass conservation is satisfied, we obtain the WSS *(WSS_{CFD})*. To check the accuracy of the WSS_{CFD}, a sensitivity analysis was carried out to assure grid independence: three meshes were created, with a number of cells ranging from 10^4 to 1.5 X10^6 (figure 5).

- 4D CMR Model: 4D flow CMR data. Original 4D flow CMRI data. Voxels size: 1.78 $\times$ 1.78 $\times$ 2 mm.

- Mesh Model 1: computational mesh using same spatial discretization as 4D CMR Model.
- Mesh Model 2: Refined of Mesh Model 1 (2.1.2).
- Mesh Model 3: Refined of Mesh Model 2 (see figure 3)(2.1.2).

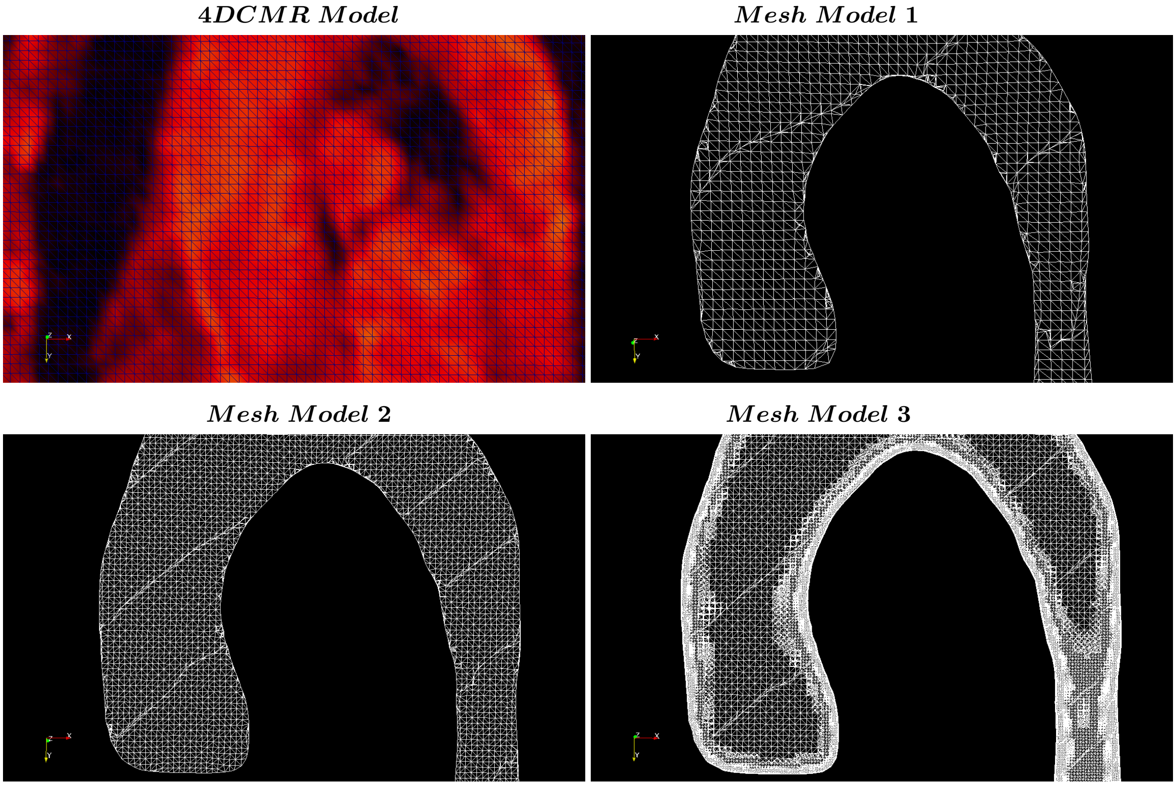

Figure 5: Different computational meshes used to compute the wall shear stress

Next, we have computed the WSS (WSS_{4DCMR}) based on the 4D flow CMR data. To compute the WSS_{4DCMR}, firstly we have calculate the Δvelocity and the Δdistance map function for the aorta binary mask image as a convolution with the derivative of gaussian kernel, after that, the WSS_{4DCMR} is calculated as the directional derivative of the velocity in the direction of the normal to the vessel wall $\mu\Delta\delta\mathrm{V}/\delta\mathbf{n}$. Where μ is the viscosity of the blood.

Figure 6 shows wall shear stress distribution for each case (4D CMR Model, Mesh Model 1, Mesh Model 2 and Mesh Model 3). In order to compare the results, WSS_{4DCMR} and WSS_{CFD} are normalising with their corresponding peak value. The main reason to normalize the WSS_{CFD} is due to artificially high WSS at the vessel boundaries, furthermore in the MRI velocity data (due to image resolution) this end effects are not present. The grid sensitivity study on the aorta model under steady flow conditions (peak systole), demonstrated that there are differences in the maximum WSS scalars. Therefore, it must be noted in this context that the boundary layer plays an important role in the WSS values. Computational time was (Model 1: 64 *sec*, Model 2: 101 *sec* and Model 3: 3534 *sec*). artificially high WSS at then vessel boundaries

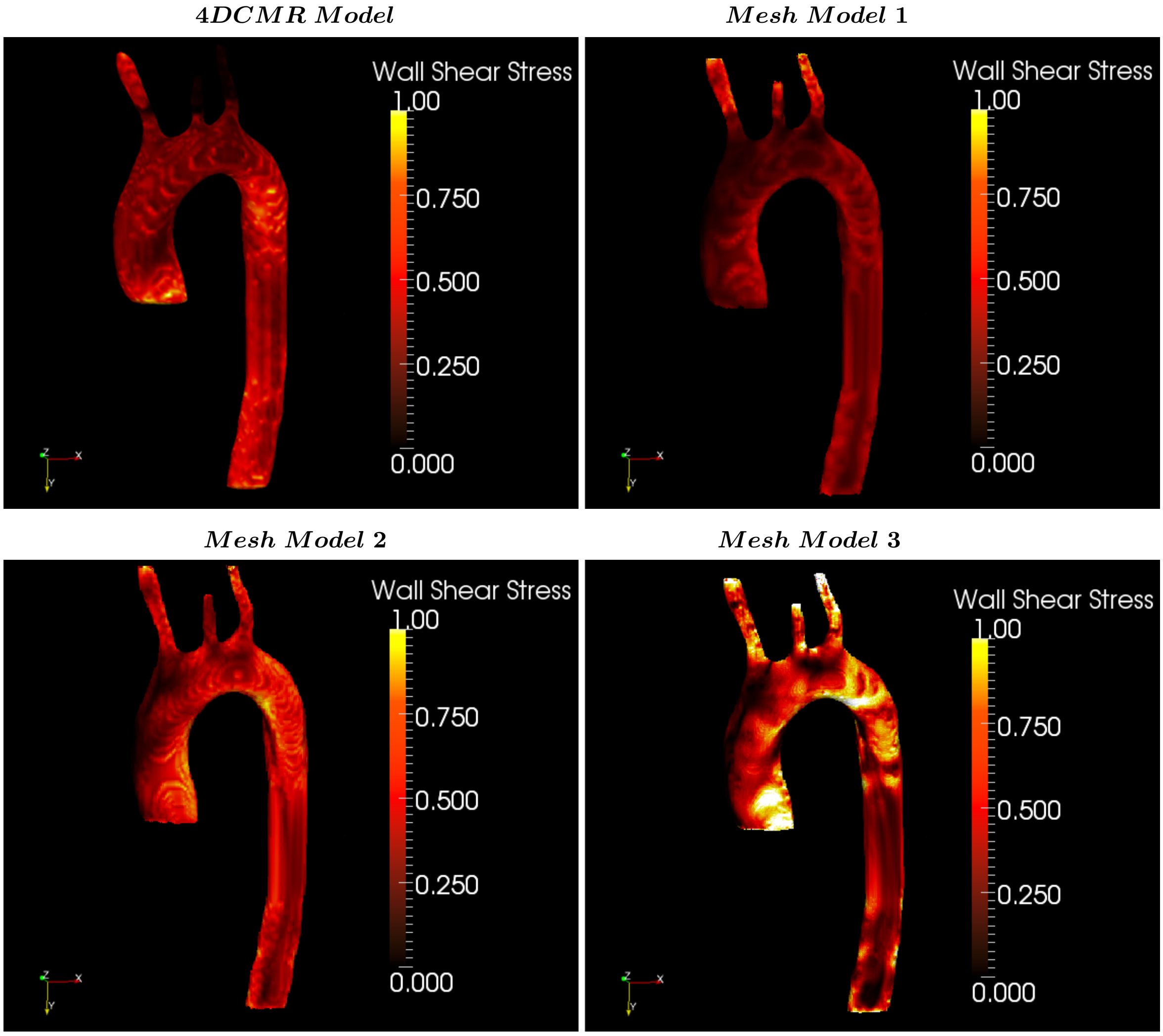

Figure 6: Wall shear stress for the different computational meshes

Due to the lack of 4D flow CMR resolution, for the 4D CMR model, WSS_{4DCMR} at the supra-aortic arteries cannot be estimated. To compute the WSS_{4DCMR}, we based on the directional derivative of the velocity in the direction of the normal to the vessel wall, at least a minimum number of voxels are needed. If we need to estimate WSS_{4DCMR} in small arteries, 4D flow CMR resolution should be increased. For the CFD computation, maximum velocities are reached at the supra-aortic arteries provoking WSS_{CFD} peak values. We have not removed those peak WSS_{CFD} in the outlet arteries because of we are interested to WSS patterns in the ascending and descending aorta. For the cases analysis, we observe that WSS follows the same pattern, and there are two aortic areas when the WSS values are higher, one in the ascending aorta (close to the aortic valve) and other in the internal part of the descending aorta just behind the aortic arch. We can see these aortic areas in other works as (5). When we increase the computational mesh resolution, we notice that the WSS areas and the peak values begin to improve. After that, we have interpolated the 4D velocity CMR data into the Mesh Model 3 (high resolution) with the objective to compare the $\text{WSS}_{4DCMR->MeshModel3}$ against $\text{WSS}_{CFD->MeshModel3}$ and the WSS_{4DCMR}.

In order to do this, we use a B-Spline approximation in order to evaluate at any point the 4D velocity CMR over the Mesh Model 3 taking into account null velocity over the wall. Afterward, we compute the WSS based on the directional derivative of the velocity ($WSS_{4DCMR->MeshModel3}$), figure 7. We notice that the WSS areas for the three cases are similar but the peak values are different for each model. The main differences between WSS_{4DCMR} and $WSS_{4DCMR->MeshModel3}$ are related with the mesh or spatial resolution. The fact that use a velocity B-Spline approximation over Mesh Model 3 makes a more realistic velocities close to the wall and subsequently the WSS. The differences between the $WSS_{4DCMR->MeshModel3}$ and $WSS_{CFD->MeshModel3}$ are related with the flow distribution inside the aorta, as we have explained previously, in Mesh Model 3 we are not taking into account the coronary arteries and the intercostal arteries, and the effects provoked by these arteries. Due to the fact we are using a cubic B-Spline interpolation function to interpolate the velocity, the $WSS_{4DCMR->MeshModel3}$ obtained are smoother. In view of the foregoing that results, the interpolation of 4D flow CMR data over a high resolution mesh can be another option to estimate properly the wall shear stress values.

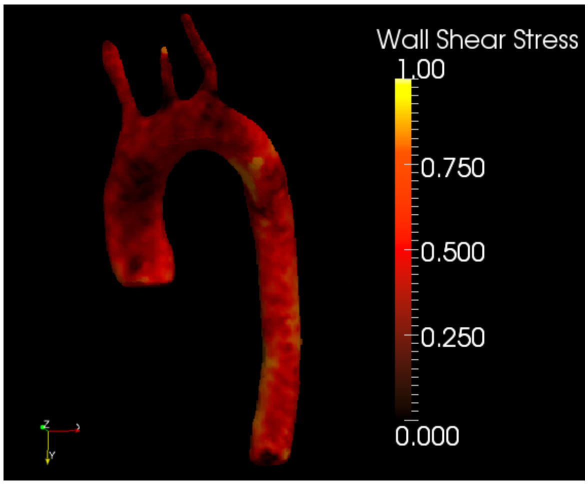

Figure 7: $WSS_{4DCMR->MeshModel3}$ estimated using 4D velocity CMR data into the Mesh Model 3.

4 Discussion

This study has investigated the WSS in a 4D CMRI based subject specific human aorta, using both CFD and 4D flow CMRI models. The methodology proposed can be considered a starting point to compute physiological WSS starting from blood flow measures acquired by 4DMRI in an effective and efficient manner. In fact, 4D flow CMR technique is able to provide us a 3D domain and velocity distribution for any cross-sectional plane of the domain through non-invasive measurements. With the aim to demonstrate that the methodology proposed is possible, wall shear stress distribution was computed for different computational meshes from a healthy patient-specific human aorta. The different computational meshes resolution show differences between the numerical results. However, wall shear distribution along the aorta follows same pattern for the different computational meshes and the areas with low and high WSS may be differentiated. To correctly evaluate the WSS values, a high resolution mesh is in fact necessary with a reasonable computational time. We notice that for the 4D flow CMRI model the image resolution is not enough compared to the CFD analysis. The CFD analysis show similar results compared to the literature (5)(21). Also it is important to remark that, as we are able to compute the flow profile at the outlets of our domain, we do not need to use a multiscale modelling to estimate the boundary conditions of the CFD problem. In (5) the authors notice that there were large differences for the instantaneous WSS between the elastic and rigid wall models. This methodology also avoids to perform CFD Fluid Structure Interaction(FSI) analysis, eluding the difficulties related to setting the patient-specific mechanical properties of the arterial wall. In order to avoid a CFD-FSI problems, the computational mesh and flow measures at the inlet and outlets can be obtained using the 4D flow CMR data for each time step, and for each one we perform a steady-state CFD analysis. Thanks to that, other hemodynamic parameters as the time-averaged WSS (TAWSS), the oscillating shear index (OSI) and the relative residence time (RRT) can be estimated taking the displacement of the aorta into consideration. Where OSI describes the cyclic departure of the WSS vector from its predominant the axial alignment (8), the TAWSS is used to evaluate the total WSS on the wall throughout a cardiac cycle, and it is calculated by integrating each nodal WSS vector magnitude at the wall over the cardiac cycle (14), and the RRT is inversely proportional to the magnitude of the time-averaged WSS vector and it indicates the average amount of time that a particle (molecule) spends at the endothelium. These hemodynamic parameters are emerging as new diagnostic indicators for cardiovascular diseases, such as, atherosclerosis localization (20) or abdominal aortic aneurysm rupture risk prediction (26). In a future study, based on these preliminary results, these hemodynamic parameters will be explored. In this work, we only focus on the computation of the WSS at peak systole.

The main limitation of this study might be represented by the fact that it was carried out considering only one image-based healthy aorta and at the peak systole, but the strategy used to compute the WSS using the 4D flow CMRI data shows promising results. There might be small errors in the segmentation process compared to the real geometry because of the limited 4D flow CMRI resolution during the diastolic phase due to the low velocities at the aorta during this period. This aspect could affect the WSS, but, as the simulations are based on at peak velocity time, and as the main goal is to investigate the differences between the resolution of the models (computational mesh) taking into account the same geometry, a good estimate of WSS can be obtained. It is worth also to take into account that in this study the outflow conditions were all exposed to the same waveform shape at the inlet section of the ascending aorta, and modelling blood as a Newtonian fluid. In our opinion, this does not entail a loss of generality in our study, which aims at investigating a single aspect, i.e., the methodology used to compute faster the WSS distributions combining 4D flow CMRI data and CFD. Due to the lack of 4D flow CMRI resolution, the induced effects of the intercostal arteries and coronaries arteries cannot be captured in our study.

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Chapter 6

Related Work

Thanks to the scientific contributions of paper 1, paper 2, paper 3 and paper 4, in this chapter the following applications have been studied:

- Qualitative evaluation of flow patterns in the Ascending Aorta with 4D phase contrast sequences.
- Study new mechanical factors related to the Abdominal Aortic Aneurysm.

6.1 Qualitative evaluation of flow patterns in the Ascending aorta with 4D phase contrast sequences

4D Phase Contrast Cardiac Magnetic Resonance(4D-PC-CMR) sequences allow to obtain three-dimensional flow images (see section 1.4.1.1) and to analyze of the patient-specific characteristics of intravascular flows under normal and pathological conditions. In clinical practice, these sequences allow to advance the understanding of the pathophysiology of vascular diseases through the interaction between flow and anatomy. Besides of this, it also help to understand the origin of diagnostic errors of 2D flow PC sequences. The aim of this study is to describe and characterize qualitatively different patterns of systolic flow in the Ascending Aorta(AoAsc) against to its aortic diameter with different degrees of root dilatation and against the different aortic valve pathologies using 4D PC Cardio MR sequences. All the patients (31 patients) who participated in this trial were volunteered and provided written consent to be part of this study. This study was reviewed and approved by the Ethics Committee of the Hospital Sant Pau i Creu Blanca, Barcelona, Spain. The 31 patients have different aortic problems, 12 patients suffer cardiomyopathy, 6 patients have a dilated aorta, 4 patients have aortic valve disease, 1 patient has a mitral valve disease, 1 patient has an atrial fibrillation and another suffers syncope, as well as 5 were healthy volunteers. For each patient an anatomy/flow cross-sectional of AoAsc was done. The flow pattern studied was: (i) at the Valsalva sinus (SV), where the flow adopts a uniformity velocity with a peak in the middle of the aorta (see figure 6.1.A and 6.1.B) or an eccetric flow jet with a maximun speed located at the periphery (see figure 6.1.C and 6.1.D), and (ii) at the AoAsc level, where the flow keep constast along the systole phase (see figure 6.1.A and 6.1.B) or the Systolic Turbulent Flow (FTS) can be

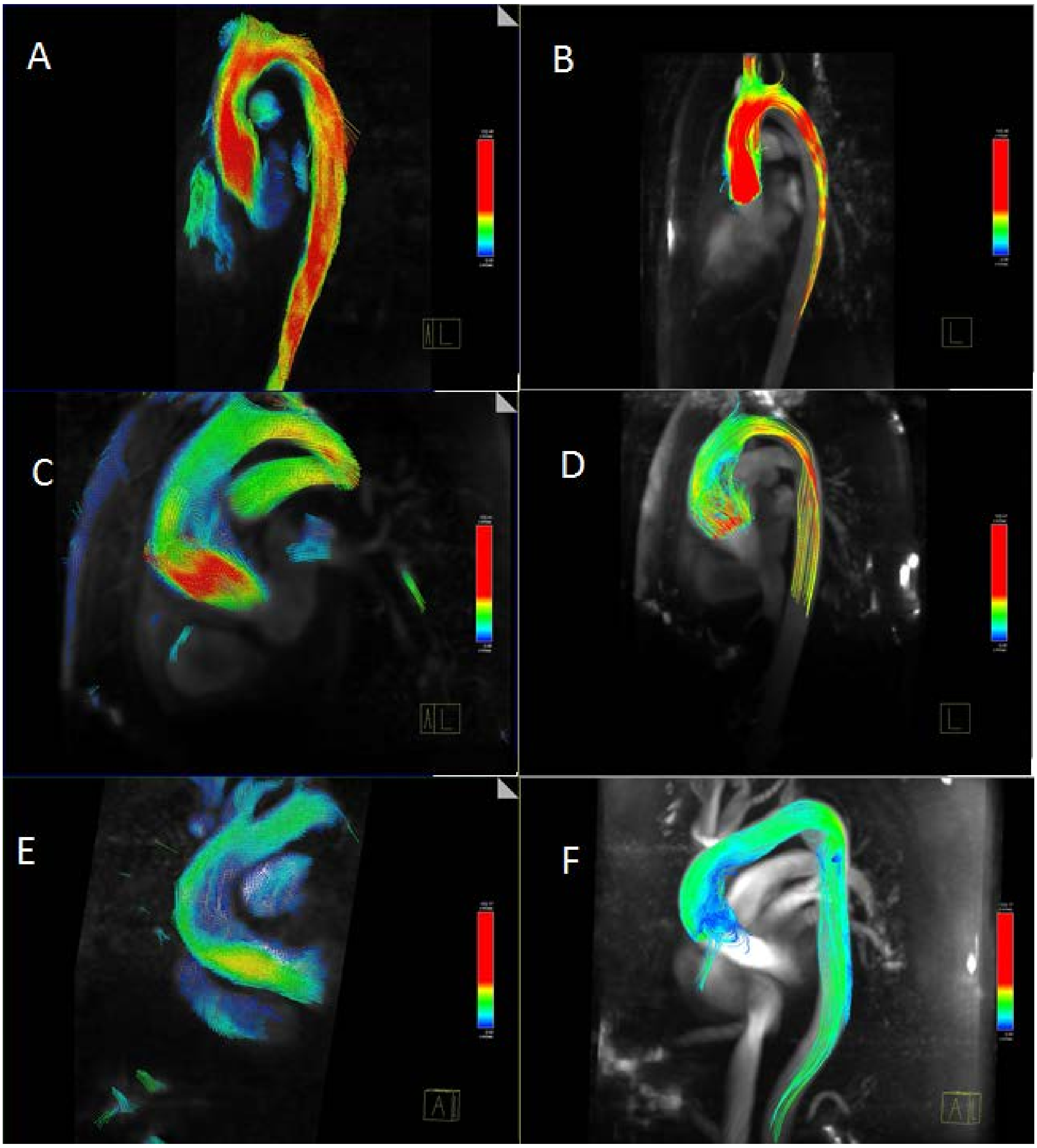

Figure 6.1: Blood flow patterns in ascending aorta, left (velocity vector), right (streamlines). A and B show a laminar flow with maximum speed in the center of the aortic flow. C and D show a turbulent flow into the dilation of the aorta with an eccentric jet. D and E show a turbulent flow into the elongation of the aorta with an eccentric jet.

defined as vortices or circular paths in opposite direction to the normal aortic systolic flow (see figure 6.1.D and 6.1.E). The AoAsc diameter was measured to the level of the bifurcation of the pulmonary artery, and the elongation of the aorta was defined as the maximum distance from the front wall of the AoAsc to the rear wall of the descending aorta at the level also to the bifurcation of the pulmonary artery. Jet's direction is defined as maximum velocity in the streamline related to the perpendicular plane at the aortic root.

In 29 patients (93.5%) the left ventricular ejection fraction was normal. The aortic valve was bicuspid in 4 patients and 3 of them show a dilated AoAsc.The average diameter of the AoAsc was 16.80±4.41mm. The mean aortic elongation diameter was 5.15±0.99cm. From the 4D sequences, 15 patients have a central jet at the Valsalva sinus (48.4%) and 16 patients have an eccentric jet (51.6%). 10 patients have laminar flow at the AoAsc level (32%), 13 patients show a vortex during the systolic phase(42%) and 8 patient during the protosystolic phase(26%) (see figure 6.1). Statistical correlation between FTS against the AoAsc diameter and elongation of the aorta was done 6.2. The analysis shows that the diameter of the AoAsc has a significant linear relationship with the flow pattern in aortic systolic, which indicates higher prevalence of turbulence flow (proto-systolic vs systolic) for a higher aortic diameter (figure 6.2). The flow characteristics in the AoAsc were analyzed by two independent clinicians getting a good concordance. The jet eccentricity in the SV indicates a trend (p = 0.06) for the FTS origin in AoAsc. The presence of a bicuspid valve is also associated with the formation of vortices (p = 0.047), although when it is adjusted by the AoAsc's diameter, statistical significance (P = 0.48) decreases.

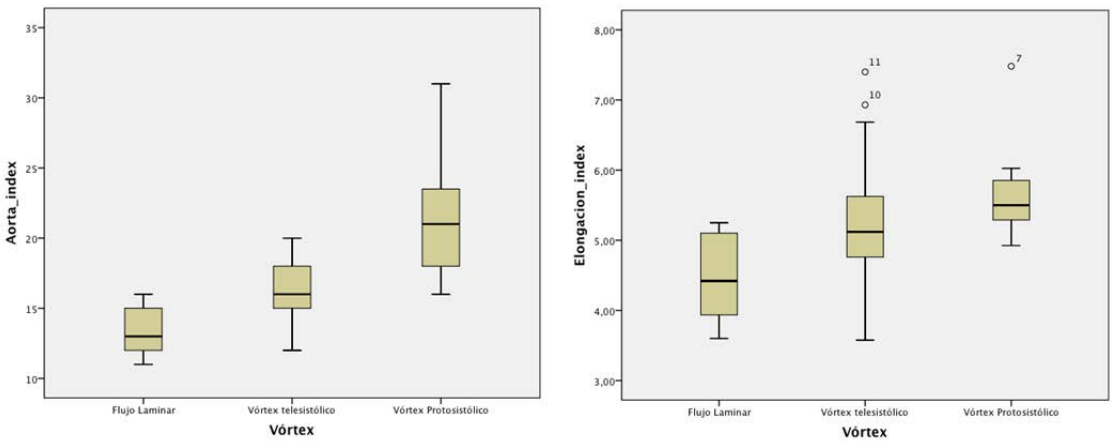

Figure 6.2: Left, Aortic index versus flow characteristics. Right, Aortic elongation versus flow characteristics.

6.1.1 Conclusions

The flow pattern during systolic phase in the ascending aorta changes progressively from laminar flow with directional jet in not-dilated aortas to turbulent flow with eccentricity jet in dilated aortas. Other factors, such as bicuspid aortic valve can increase the turbulence effect but there are not essential to provoke it. This study was done in collaboration with Dr.Francecs Carreras, Dr.Chi-Hion Pedro Li and Dr.Xavier Alomar from Hospital Sant Pau i Creu Blanca and Clinica Creu

Blanca, Barcelona, Spain, respectively. The equipment used was a Magnetom Verio 3T Siemens, Erlangen, Germany.

6.2 Study new mechanical factor related to the Abdominal Aortic Aneurysm

The primary goal of this further work was to motivate a new phenomenological approach for identifying regions of possible formation of Intra Luminal Thrombus (ILT) on an intact but susceptible endothelium within AAAs. Following the idea of paper 2, *"CFD Modelling of Abdominal Aortic Aneurysm on Hemodynamic Loads using a Realistic Geometry with CT"*, thirteen new patients with infrarenal aneurysms from Clinical Hospital of Valladolid (Spain) have been studied. The patients chosen for this study were selected during the first stages of the AAA's development. All the patients who participated in this trial analysis volunteered and provide written consent to be part of the study. This study was reviewed and approved by the Ethics Committee of the Clinical Hospital of Valladolid (Spain). To characterize the AAA shape and size, the main geometrical AAA parameters were determined using the lumen center line [66][26] of the segmented images. Twelve indices were defined and computed for the thirteen AAA patient-specific models. Figure 6.3 shows the seven geometrical parameters defined (AAA morphometry).

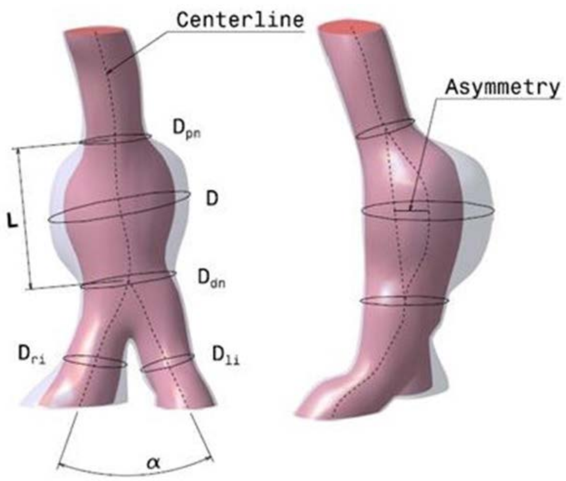

Figure 6.3: Abdominal Aneuryms 1D geometrical parameters. D: maximum transverse diameter, D_{pn}: neck proximal diameter(smallest diameter of the infrarenal artery, just before the AAA), D_{dn}: neck distal diameter (smallest diameter of the aorta, just after the AAA), L: aneurismal length (length between proximal and distal necks), D_{li}: left iliac diameter (left iliac diameter), D_{ri}: right iliac diameter (right iliac diameter) and α is the angle between the right and left iliac arteries.

Another four geometrical indices[15] were defined: γ(saccular index) assesses the length of the AAA region, this region will be affected by the formation and further development of the ILT, χ (deformation rate) characterizes the deformation of the aorta, relation between D_{pn} and D, ϵ (tortuosity index) is the ratio of the length of the curve to the distance between the proximal and distal neck and β (symmetry index) is the result of the non-symmetry expansion of the aneurysm sac. Next table 6.1 shows the parameters for the 13 new cases analyzed.

The hemodynamic variables for the thirteen abdominal aneurysms were obtained using image-

n	V_{AAA} (mm^3)	D (mm)	D_{pm} (mm)	D_{dn} (mm)	L (mm)	D_{li} (mm)	D_{ri} (mm)	γ	χ	ϵ	β	α
1	49223,2	30,34	19,77	23,36	80,42	14,74	12,50	0,377	1,533	0,0389	0,460	56,70
2	43623,0	33,07	26,91	29,70	82,71	15,73	17,62	0,399	1,22	0,022	0,60	57,20
3	51862,0	42,96	20,90	17,82	102,19	12,22	11,85	0,420	2,056	0,140	0,769	50,62
4	55935,0	41,39	24,53	33,56	94,23	18,27	12,32	0,439	1,687	0,0308	0,529	66,27
5	44386,1	34,80	20,88	30,35	109,71	20,23	15,16	0,317	1,667	0,0660	0,490	61,87
6	32740,0	33,51	20,53	23,92	114,88	15,50	13,01	0,29	1,632	0,0147	0,380	64,33
7	40608,0	40,05	32,18	34,86	104,16	23,43	15,67	0,384	1,245	0,0383	0,430	54,67
8	83186,0	50,99	24,23	39,33	105,47	14,81	21,45	0,483	2,104	0,0445	0,748	43,01
9	46676,0	37,28	23,45	24,28	89,19	11,44	11,45	0,417	1,590	0,0645	0,573	38,67
10	45780,0	40,88	25,60	25,90	80,38	9,90	11,18	0,508	1,597	0,0817	0,642	25,56
11	43130,0	42,23	22,02	30,15	85,50	21,63	19,94	0,493	1,918	0,0409	0,709	48,96
12	30538,0	29,81	20,71	19,00	92,39	15,70	11,88	0,322	1,439	0,0655	0,505	43,77
13	51388,0	37,52	33,39	21,66	99,12	12,20	14,80	0,378	1,124	0,0343	0,755	40,58

Table 6.1: Geometrical parameters of the 13 AAA cases analyzed

based CFD under realistic flow conditions. The AAA simulations were performed for three cardiac cycles, and the results from the last cardiac cycle were used to compute the WSS-based diagnostic indicators (WSS(eq.1.2), OSI(eq.1.4), ECAP(eq.1.6) and RRT(eq.1.5)). Depending on the complexity of the AAA model, a 3D mesh consisted of 1.000.000 $\pm 15\%$ tetrahedral elements. A boundary layer was created to capture properly the velocities close to the wall. Next image shows the WSS, OSI, ECAP and RRT values for three different AAAs.

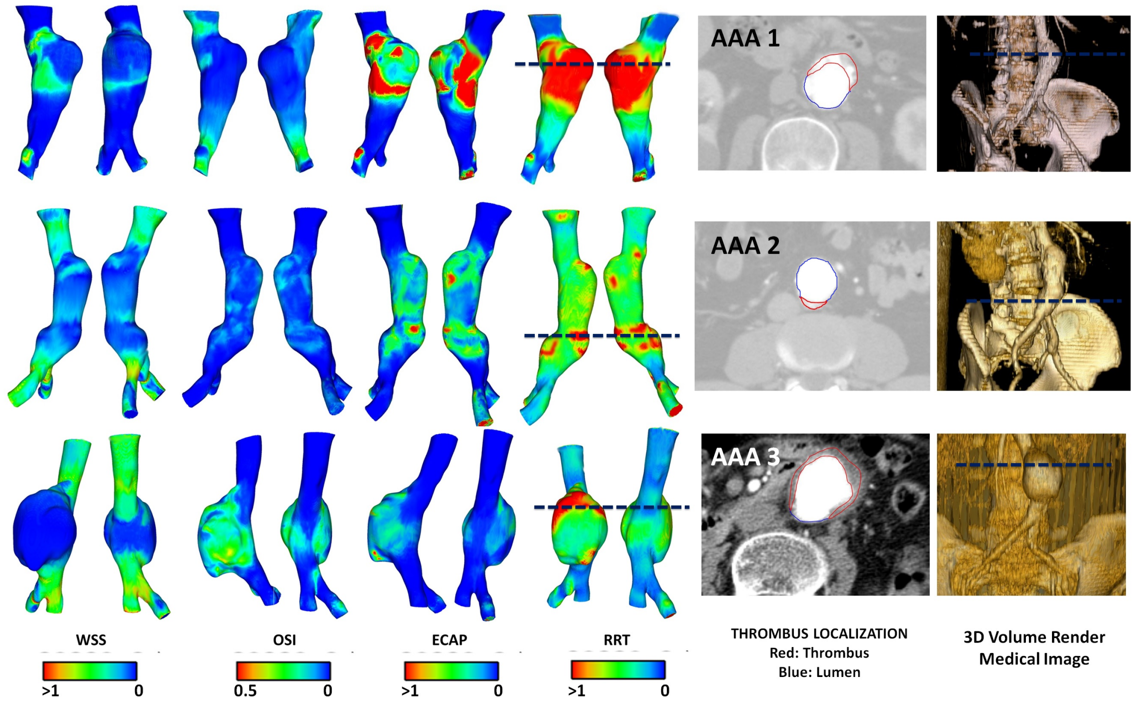

Figure 6.4: Spatial distribution of WSS, OSI, ECAP and RRT in three abdominal aortic aneurysm. For each AAA, anterior and posterior views of the lesions. On the right, 3D volume render and a CT slice showing the localization of the incipient thrombus (red line: thrombus, blue line: lumen). Dark Blue line represents the localization of the CT slice.

6.2.1 Conclusions

The computed WSS-based diagnostic indicators combined with the geometrical factors may provide more information about ILT development for a complex AAA geometries. The results show that aneurysmal wall regions with increased flow and high tortuosity index may be prone to thrombus deposition, and consequently, ILT formation. Higher values of the RRT and ECAP indices correspond to the areas with ILT, as is shown in figure 6.4. A preliminary analysis of the thirteen AAA confirmed that the length, asymmetry and saccular index significantly influence in the WSS-based diagnostic indicators, which highlight the weight of these variables on the ILT development and the rupture-prone AAA areas. No correlations between maximum diameter and WSS-based diagnostic indicators were obtained, as might be expected. This finding is in agreement with the strategy adopted in the research, all the AAAs considered have a diameter around 40 mm, and therefore the rupture risk is not significant. The study shows that WSS-based diagnostic indicators may provide important additional information on aneurysm progression on a patient-specific basis. Based on this preliminary study, it is possible to hypothesize that the characterization of AAA morphometry and its influence on the regional and temporal distribution of the hemodynamical variables would be necessary for patient-specific assessment of rupture risk and ILT development. To improve the reliability of the results, would be needed to expand the number of cases in the study. The methodology here developed could be an indicative that other indices like, asymmetry, deformation rate, AAA length, saccular index, are important and could also be readily incorporated into surgeon's decision making, instead of the classical maximum diameter criterion.

Chapter 7

Conclusions and Future work

7.1 Conclusions

The increasing availability and efficiency of computational tools for patient-specific simulations provides useful data to understand the psychopathology of cardiovascular diseases. The rationale for this monograph is to reinforce the clinical utility of computational hemodynamics, contributing to its translation into clinical practice through the diagnostic indicators. The results of this monograph will provide useful quantitative data for proof-of-concept studies. Hopefully, this will enable clinicians to gain insights, develop intuitions, and provide constructive feedback and guidance for the development of more representative models. Moreover, the increasing sophistication of therapeutic solutions for cardiovascular pathologies require the development of tools for quantitative patient-specific simulations to aid therapeutic planning through the assessment of pre-operative scenarios and the prediction of therapeutic intervention outcomes. The integration of technical developments into prototypes will allow the clinicians to become acquainted with the newly developed technology underpinning exploitation in new products. It should be noted that part of the development performed during this monograph is being integrated into clinical prototypes. Another general objective of this monograph is to generate and share a common technology infrastructure, resources and knowledge across/between clinical practice, physics and bio-engineering. The key findings of the four papers and related work are summarized below.

In this monograph we have developed a geometrical multiscale framework for simulation cardiovascular diseases under different physiological and pathological conditions. The cardiovascular diseases studied under this multiscale framework were the Aorta Coartaction and Coronary Disease, but, the technology underlying is applicable to other common cardiovascular conditions, including peripheral, cerebrovascular, and reno-vascular disease, and may be used to determine whether vascular stenosis are hemodynamically significant as well as the relative benefit of therapeutic interventions. In this line, we have also proposed a new coronary indicator to evaluate the stenosis without hyperemia condition (under evaluation). At the same time, we have developed and validated a 1D numerical model coupled with the reduced order model. A 1D-reduced order model validation for other groups of people or patients could also be useful for research and clinical outcome analysis. The 1D model is able to describe the pulse wave dynamics and the interaction between the heart and the circulatory system. We have also studied the hemodynamics factors that may be important in triggering the onset of aneurysms correlated with the patient-specific anatomy. The hemodynamics factor and the geometry are directly related with the ILT formation. More AAA cases are needed to define a direct correlation between the hemodynamics factors and AAA development. Quantification of WSS, as well as other WSS-based indicators, are of crucial importance for the understanding of the development of cardiovascular pathologies as, aneurysm or arteriosclerosis. In this way, the feasibility of CFD as a predictive tool to use for treatment planning of cardiovascular diseases has been demonstrated. A methodology to obtain computational meshes from medical image has been defined. A new procedure to segment the aorta using 4D flow CMR data has also been proposed. Beyond this, 4D flow CMR visualization offers a more qualitative and comprehensive description of the flow fields than any other in-vivo imaging technique. The velocity data provided by 4D flow CMR has been complementary to the higher resolution velocity fields computed by the CFD in order to estimate the WSS. We have also developed an algorithm to compute WSS based on the 4D flow CMR data. Based on that approach other diagnostic indicators could be estimated, as pulse wave velocity(PWV)[89], turbulent kinetic energy[90], relative pressure fields[91] or volume and kinetic energy of ventricular flow compartments[92]. For full details refer to the *"Results"* sections of papers.

7.2 Limitations and Future work

The diagnostic indicators obtained in this monograph need to be validated and reproducible if they are to be useful for clinical workflows. Multicenter studies are necessary to establish the repeatability of various aspects of the technique used in the papers across centers. Widespread clinical usage would be facilitated by further integration into the standard clinical environment. The methodology developed in this monograph makes the process more robust and transparent, in the way that the models can be incorporated into clinical workflows. This means to develop interfaces and put them in a clinical context (in connection with imaging and clinical data accessed directly from the hospital's computer system) where physicians can use it. Several improvements and further possibilities are offered on the basis on the present papers.

The presented techniques are currently employed for patient-specific modeling of aorta and coronary arteries acquired from different modalities, both from geometric and fluid-dynamics points of view. A study (still to be published) on 20 coronary models reconstructed at Pie Medical Imaging (PMI), Maastricht, Netherlands has further demonstrated the validity of the computation method proposed. The coronary index for all 20 models will be computed in 1 hour with full automation and acceptable results. Further work will consist on reduce the computational time to be useful in a clinical routine and setting properly the hyperemia conditions of the patients. Another study (still to be published) on 23 Abdominal aneurysm model reconstructed at the International Center of numerical Methods in Engineering (CIMNE), Barcelona, Spain and Mechanical Engineering Division, CARTIF Technological, Valladolid, Spain has the objective to correlate the Intra Luminal Thrombus (ILT) with the hemodynamics parameters and the geometrical factor, in the sense of predicting the ILT evolution based only on the geometrical factor. Another indices can be estimated, for example, the flow-induced platelet activation (TFP) proposed by [11]. The main purpose of this index is to identify local regions of the wall that at the same time were exposed to prothrombotic WSS stimuli and a flow rich in activated platelets. TFP is defined as:

$$TFP = ECAP \cdot PLAP = \frac{OSI \cdot PLAP}{TAWSS} \tag{7.1}$$

where PLAP is the PLatelet Activation Potential recently proposed [93]. TFP index combines the ECAP-based on WSS and the fluid shear history-based PLAP obtained by particle tracking. Briefly, the PLAP is a non-dimensional scalar index that represents the magnitude of shear rates that a fluid particle accumulates while travelling throughout the fluid domain.

$$PLAP(x,t) = \int_{t-2T}^{t} |D(x(\tau),\tau)| d\tau \tag{7.2}$$

where |D(x(τ),τ)| is the Frobenius norm of the symmetric part of the spatial gradient of velocity tensor, t is the time of injection of the particle and 2T indicates how long the particle has been tracked. Collecting particle information for multiple cardiac cycles allows one to capture flow stagnation events that might be of importance in thrombogenesis [93].

Two new collaborations with the Hospital Sant Pau i Creu Blanca, Barcelona, Spain are now beginning. Both are related with the 4D flow CMR acquisition, Aortic Dissection and Portal pressure. Related to the Aortic Dissection, the objective is to improve the clinical intervention procedure, we are going to combine 4D flow CMR sequences with CFD to estimate the relative pressure in the true and false lumen. And related to the Portal pressure, the goal is to use 4D flow CMR sequence to estimate the flow and pressure in the Portal system with the objective of check the liver function. Besides of the clinical applications, a prototype of the software (AORTA4D) to visualize and quantify 4D flow CMR data is currently being developed in collaboration with GiD Department of CIMNE.

Several improvements and further technological possibilities are offered on the basis on the present papers. In the current papers there are a number of limitations to obtain the hemodynamics parameters that can be gradually removed. For instance, the autoregulation phenomenon, in response to hemodynamic stimuli, which is an important issue in coronary blood flow mechanisms, was not considered in the related work and it could be included in the future. For the 1D model used in the Paper 1, small distal vessels such as arterioles, capillaries, venules and veins were not modeled directly and may need to be investigated in detail. In that line, a more robust methodology to estimate the lumped parameters in patient-specific models would be needed. Addition of the pulmonary circulation could also close the circulation loop and make an even more useful model. For paper 2, the interaction between arterial blood flow and intraluminal thrombus was not taken into account, and it could play an important role in the development of some abdominal aneurysms, as well as, it would be needed to increase the number of the cases to get more evidences with the hemodynamics parameters obtained. For paper 4, the constitutive arterial model used for the AAA did not take into account the fiber distributions and the model used were geometrical model.

About 4D flow CMR technologies there are still some uncertainties related to the clinical use, chapter 6 and chapter 7. Derived flow parameters, need further development or validation for clinical use, to include measurements of WSS, pressure difference, TKE or intracardiac flow components. The accuracy on the acquisition parameters measured is quite dependent of the clinical sequence (image-protocol) used. In our particular case, the WSS is quite dependent of the spatial resolution, therefore an accurate segmentation is needed. We are working on new segmentation algorithm (see figure 7.1). Additionally, a validation protocol using a phantom model would be needed.

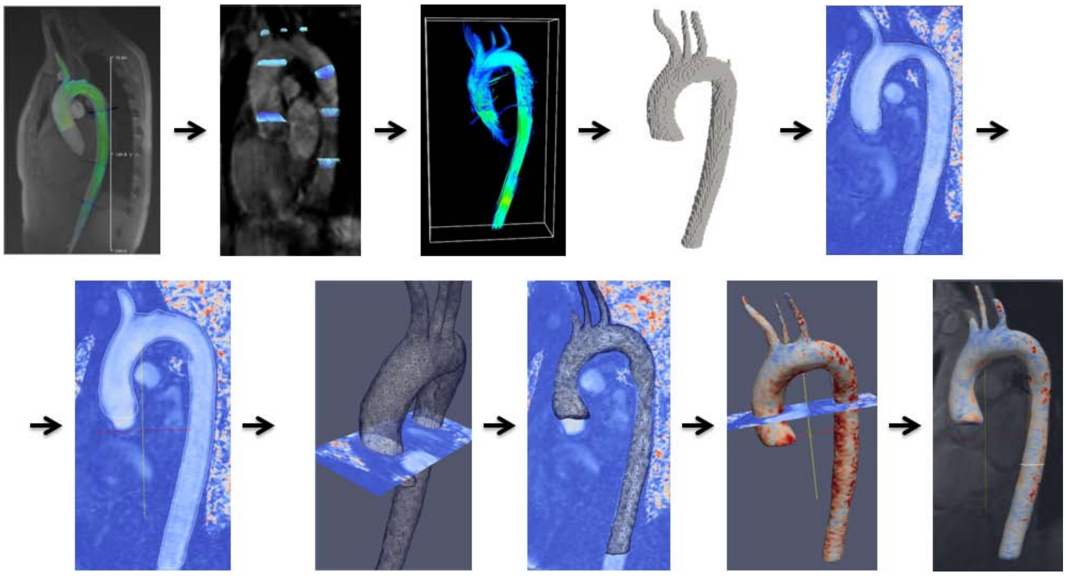

Figure 7.1: Preliminary concept of automatic segmentation of the Aorta based on 4D MRI data

Appendix A

Cardiovascular physiology

The purpose of this appendix is to introduce which are the basics of the cardiovascular physiology. This brief overview of the cardiovascular physiology is only included for the purpose of providing essential information to scientists without a background in medicine. In this appendix the macroscopic and microscopic structure of arterial walls, blood modeling and cardiovascular system is briefly explained. For a more detailed exposition of the different mechanical/rheological characteristics of cardiovascular system and the overall functioning of the blood vessel see Tortora et al.[94].

A Cardiovascular physiology

Cardiovascular physiology is the study of the cardiovascular system, specifically addressing the physiology of the heart (cardiac physiology) and blood vessels (circulatory physiologic) (see figure A1[95]). The cardiovascular system is a pressurized closed system responsible for transporting nutrients, hormones, and cellular waste throughout the body. From a physical point of view, there are three independent circuits:

- Systemic Circulation: The former brings oxygenated blood from the heart, thought arteries and capillaries, to the various organs (systemic arterial system) and then brings it back to heart (systemic venous system). The systemic arterial system is an extensive high-pressure system; hence the structure of its blood vessels reflects the high pressures to which they are subjected. The systemic venous system acts as a collecting system, returning blood from the capillary networks to the heart passively down a pressure gradient.
- Pulmonary circulation: The latter pumps the venous blood into the pulmonary artery where it enters the pulmonary system, through the pulmonary veins, get oxygenated and is finally received by the heart, ready to be sent to the systemic circulation (where the blood is pumped through the aortic valve into the aorta).
- The coronary circulation arises from the aorta and provides a blood supply to the myocardium, the heart muscle

This monograph will focus on systemic arterial system and coronary circulation.

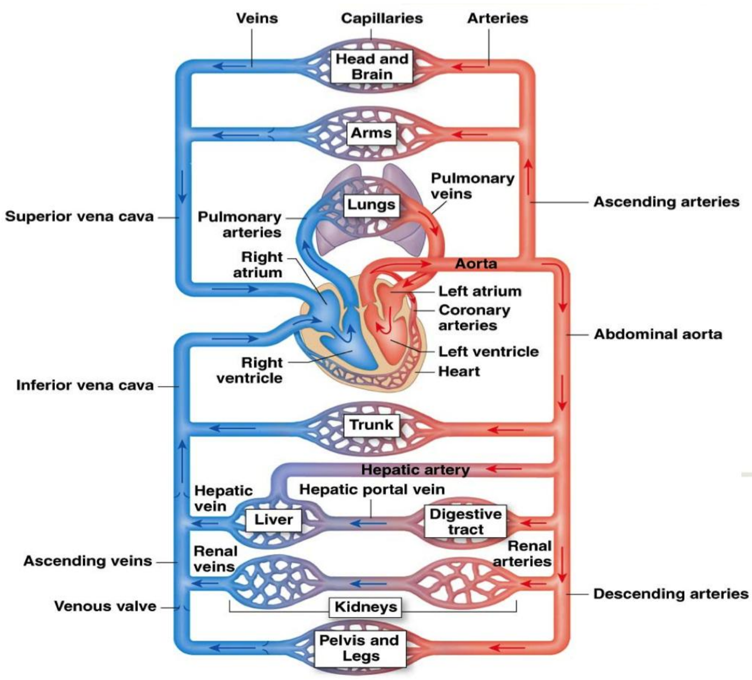

Figure A1: The cardiovascular system is a close loop. The heart is a pump that circulates blood through the system. Arteries take blood away from the heart (systemic circulation) and veins (pulmonary circulation) carry blood back to the heart.

A.1 Blood Vessels

The blood vessels are the part of the circulatory system that transport blood throughout the body. The vascular system is composed of arteries, arterioles, capillaries, venules and veins (see figure A2[96]). The three main types of blood vessels are:

1. Arteries, which carry blood away from the heart at relatively high pressure,

2. Veins, which carry blood back to the heart at relatively low pressure and

3. Capillaries, which provide the link between the arterial and venous blood vessels.

Regarding the small vessels mention that arterioles are the smallest branches of the arterial network. Arterioles vary in diameter ranging from 0.3 mm to 0.4 mm. Any artery with a diameter smaller than 0.5 mm is considered to be an arteriole. Capillaries are specialized for diffusion of substances across their wall. Capillaries are the smallest vessels of the blood circulatory system and form a complex inter linking network. Pressure is essentially lost in the capillaries. As the capillaries begin to thicken and merge, they become venules. Venules eventually become veins and head back to the heart.

In general, arteries are roughly subdivided into two types: elastic (or large arteries) and muscular (or small arteries). Elastic arteries have relatively large diameters and are located close to the heart (for example, the aorta, the carotid and iliac arteries), while muscular arteries are located at the periphery (for example, femoral, celiac, cerebral arteries). The walls of all the blood vessels, except the capillaries which are only one cell thick, have the same basic components but the proportion of the components varies with function. Therefore, the structure of the vessels in the different parts of the circulatory or vascular system varies and the differences relate directly to the function of each type of vessel (see table A1). Arteries are not just tubes through which the blood flows.

Table A1: Vessel Type

Vessels	Diameter of lumen (mm)	Wall thickness (mm)	Mean pressure (kPa)
Aorta	25	2	12.5
Large arteries	1-10	1	12
Small arteries	0.5-1	1	12
Arteriole	0.01-0.5	0.03	7
Capillary	0.006-0.01	0.001	3
Venule	0.01-0.5	0.003	1.5
Vein	0.5-15	0.5	1
Vein cava	30	1.5	0.5

All blood vessels, except capillaries, are composed of three distinct layers (tunica intima, tunica media and tunica externa or adventicia) surrounding a central blood carrying canal (known as the lumen). The constituents of arterial walls from the mechanical perspective are important to researchers interested in constitutive issues.

- Tunica intima. The tunica intima is the innermost layer of the artery. It composed of a lining layer of highly specialized multi-functional flattened epithelial cells termed endothelium. This sits on a basal lamina; beneath this is a very thin layer of fibro-collagenous support tissue.

- Tunica media. The tunica media is the middle layer in a blood vessel wall and is a complex three-dimensional network of smooth muscle cells reinforced by organized layers of elastic tissue which form elastic laminae. The tunica media is particularly prominent in arteries, being relatively indistinct in veins and virtually non-existent in very small vessels. From the mechanical perspective, the media is the most significant layer in a healthy artery.

- Tunica Adventicia. The tunica adventitia or externa is the outermost layer of blood vessels. It is composed largely of collagen, but smooth muscle cells may be present, particularly in veins. The tunica adventitia is often the most prominent layer in the walls of veins. Within the tunica adventitia of vessels with thick walls (such as large arteries and veins) are small blood vessels which send penetrating branches into the media to supply it with blood.

Veins do not have as many elastic fibers as arteries. Veins do have valves, which keep the blood from pooling and flowing back to the legs under the influence of gravity. When these valves break down, as often happens in older or inactive people, the blood does flow back and pool in the legs. The result is varicose veins, which often appear as large purplish tubes in the lower legs.

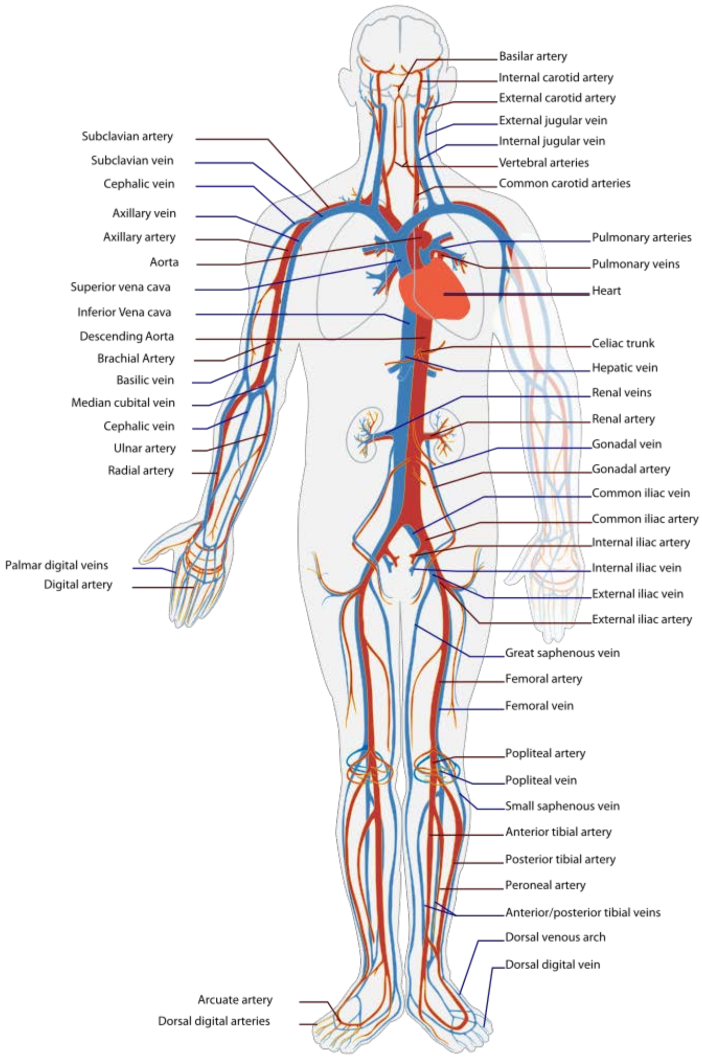

Figure A2: The human circulatory system (simplified). Red indicates oxygenated blood (arterial system), blue indicates deoxygenated (venous system).

A.2 Blood Modelling

Blood is a suspension of cells into a fluid called plasma. It delivers oxygen and nutrients to the cells and remove CO_2 and waste products. Blood also enables hormones and other substances to be transported between tissues and organs. The blood makes up about 7% of the weight of a human body, with a volume of about 5 litters in an average adult. Understanding blood physiology depends on understanding the components of blood. Blood is made up of plasma (about 55%) and cellular elements (about 45%). These cellular elements include red blood cells (also called RBCs or erythrocytes), white blood cells (also called leukocytes) and platelets (also called thrombocyte) suspended in a plasma. Plasma is essentially a blood aqueous solution containing 92% water, 8% blood plasma proteins, and trace amounts of other materials (i.e albumin or globulin). Plasma has many functions as involving colloid, osmotic effects, transport, signaling, immunity and clotting.

- $5{*}10^{12}$ erythrocytes or red cells (45.0% of blood volume)in a woman 4.800.000 and in a men 5.400.400 erythrocytes per mm^3 (or microliter) Size: disc biconcave 7 or 7.5 μm of diameter. Erythrocytes are responsible for the exchange of oxygen and CO_2 with the cells.
- $9{*}10^{9}$ leukocytes or white cells(1.0% of blood volume) 4.500 y 11.500 per mm^3 (or microliter) in the blood. Size: between 8 and 20 μm. Leukocytes play a major role in the human immune system.
- $3{*}10^{11}$ thrombocytes (>1.0% of blood volume): Platelets are responsible for blood clotting (coagulation).

Blood viscosity is a measure of the resistance of blood to flow. The blood viscosity increases as the percentage of cells in the blood increases: more cells mean more friction, which means a greater viscosity. The percentage of the blood volume occupied by red blood cells is called the haematocrit. With a normal haematocrit of about 40 (that is, approximately 40% of the blood volume is red blood cells and the remainder plasma), the viscosity of whole blood (cells plus plasma) is about 3 times that the viscosity of the water. Other factors influencing blood viscosity include temperature, where an increase in temperature results in a decrease in viscosity. This is particularly important in hypothermia, where an increase in blood viscosity will provoke problems with blood circulation.

Blood compressibility is the relation between all of its components and their volume fraction or a measure of the relative volume change of a fluid as a response to a pressure change. The 92% of the blood is water, and how the water has a high relation of compressibility, blood can be consider an incompressible fluid. Mathematically, it is mean that the mass is conserved within the domain.

Usually, for small arteries (less than 1mm in diameter) blood is consider as Non-Newtonian fluid, however in medium/large arteries blood may be considered as Newtonian fluid. To explain this behaviour it is necessary to explain which the Fahraeus-Lindqvist effect is. Fahraeus-Lindqvist effect is characterized by a decrease in the apparent blood viscosity as the arteries diameter decreases below 500 mm. The minimum apparent viscosity is reached when the tube diameter is higher than 8 mm, upon further decreases in tube diameter, the apparent viscosity increases very rapidly. The physical reason behind the Fahraeus-Lindqvist effect is the formation of a cells-free layer near the wall of the tube[14]. The layer is devoid of RBCs and has a reduced local viscosity.

The extent of the cell-free layer, which depends on the vessel size and haematocrit, is a major factor that determinate the apparent viscosity of the blood. The core of the tube, on the contrary, is rich with RBCs and has a higher local viscosity. However, in large arteries with internal diameter > 500 mm, although the blood density depends on the red cells concentration, the blood may be considered a homogeneous fluid with standard behavior (Newtonian fluid)[14]. The viscosity μ of the fluid is proportional to τ_{ij}. Therefore, the rheological properties of blood depends on the vessels size, for instance, when the vessel diameter reduces to size comparable with the one of the red cells (below 12μm), blood cannot be considered as continuum any longer, therefore, blood is a complex fluid whose flow properties are significantly affected by the arrangement, orientation and deformability of red blood cells.

Appendix B

Numerical Model

One-Dimensional (1D) models of blood flow have been extensively used to study wave propagation phenomena in arteries. These models allow us to investigate physical mechanisms underlying changes in pressure and flow pulse waveforms that are produced by cardiovascular disease, however these models do not taken into account the effects provoked by the 3D geometry. In this appendix, the 1D mathematical formulation and the reduced model used in paper 1 (*"A Reduced Order Model based on Coupled 1D/3D Finite Element Simulations for an Efficient Analysis of Hemodynamics Problems."*) are briefly explained.

B 1D Mathematical Model

A preliminary basic knowledge about the cardiovascular system was given in appendix A. We introduce an one-dimensional mathematical model to describe the flow motion in arteries and its interaction with the wall displacement in order to provide a better understanding of the hemodynamics in large vessels. In absence of branching, a short of an artery may be considered as a cylindrical compliant tube, and it can be described by using a curvilinear cylindrical coordinate system $(\mathrm{r}, \Theta, \mathrm{z})$ with the corresponding base unit vector $(\mathrm{e_r}, \mathrm{e_\Theta}, \mathrm{e_z})$ radial, circumferential and axil unit vector, respectively, as show in figure B1. The vessel extends from $\mathrm{z} = 0$ to $\mathrm{z} = \mathrm{L}$ and this length L is constant with time, therefore, the spatial domain Ω_c in cylindrical coordinate is defined as follows:

$$\Omega_c = \{(\mathrm{r}, \Theta, \mathrm{z}) : 0 \leqslant \mathrm{r} \leqslant \mathrm{R}(\mathrm{z}, \mathrm{t}); \Theta\epsilon[0, 2\Pi); \mathrm{z}\epsilon(0, L); \Delta t > 0\} \tag{B.1}$$

Defined our domain, the following assumptions must be taken into account in order to deduce the one-dimensional mathematical model:

- Radial displacements. The wall displaces along the radial direction solely, thus at each point on the tube surface we may write $\eta = \eta \mathrm{e_r}$, where $\eta = \mathrm{R_z} - \mathrm{R_0}$ is the displacement with respect to a reference radius $\mathrm{R_0}$.

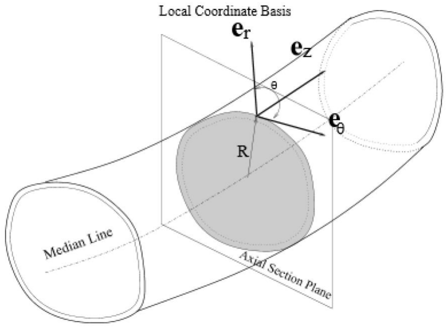

Figure B1: Section of an artery with the principal geometrical parameters

- Axial symmetry. All quantities are independent from the angular coordinate Θ. As a consequence, every axial section, $\mathrm{z} = \mathrm{constant}$, remains circular during the wall motion. The arteries radius R is a function of z and t. A generic axial section will be indicated by $\mathrm{S} = \mathrm{S}(\mathrm{z}, \mathrm{t})$ where,

$$S(z,t) = \{(r, \Theta, z) : 0 \leqslant r \leqslant R(z,t); \Theta \epsilon [0, 2\Pi); \Delta t > 0\} \tag{B.2}$$

and, its measure A is given by

$$A(z,t) = \int_S d\sigma = \pi R^2(z,t) = \pi \left[R_0(z) + \eta(z,t)\right]^2 \tag{B.3}$$

- Dominance axial velocity, the velocity components orthogonal to the z axis are negligible compared to the component along z. The latter is indicated by $\mathrm{u_z}$ and its expression in cylindrical coordinates reads:

$$u_z(r,z,t) = \overline{u}(z,t) s \left[\frac{r}{R(z,t)}\right] \tag{B.4}$$

where $\overline{\mathrm{u}}$ is the mean velocity in each axial section and s is a velocity profile.

$$\overline{u}(z,t) = \frac{1}{A} \int_S u_z \, d\sigma \tag{B.5}$$

- Constant pressure, we assume that the pressure P is constant on each axial section S, so that it depends only on z and t.

$$\overline{p}(z,t) = \int_S p_z \, d\sigma \tag{B.6}$$

- No body forces. We neglect body forces.

The resulting state variables are

$$
\begin{aligned}
\overline{Q}(z,t) &= \int_{S}(z,t)u_z\, d\sigma = A(z,t)\overline{u} \\
A(z,t) &= \int_{\mathcal{S}(z,t)} d\sigma = \pi R^2(z,t)
\end{aligned}
\tag{B.7}
$$

where A is the cross-sectional area and Q is the volumetric flow rate.

Therefore, we have three independent variables $(\mathrm{A}, \mathrm{u}, \mathrm{p})$, or equivalently $(\mathrm{A}, \mathrm{Q}, \mathrm{p})$. Thus, we require three independent equations to get a solution. These three equations will be provided by equations of conservations of mass and momentum and an algebraic law that link the pressure and area of the artery.

B.1 Conservation equations

The conservation equations reflect a certain physical amount of a continuous medium that must always be satisfied and which are not limited in their application to the material. By applying the conservation equations in the domain Ω the body β leads to an integral relationship. Since the integral relationship must hold for any sub-domain of the body, then the conservation equations can be expressed as partial differential equations. Before continuing with the conservation equations, the material time derivative of an integral relationship to any property space is defined by

$$
\frac{d}{dt}\int_{\Omega}(\bullet) = \int_{\Omega}(\frac{d(\bullet)}{dt} + \nabla(\bullet)\cdot\mathbf{v})d\Omega \tag{B.8}
$$

which is the Reynold's transport theorem.

B.2 Conservation of the mass

A fundamental law of Newtonian mechanics is the conservation of the mass, also called continuity equation, contained in a material volume. Considering the vessel shown in figure B1 as our control volume, the principle of mass conservation requires that the rate of change of mass within the domain Ω_t plus the net mass flux out of the control volume is zero.

Denoting the vessel volume as

$$
V(t) = \int_0^L Adz, \tag{B.9}
$$

where L is the length of the vessel and assuming there are no infiltration through the side walls, the mass conservation can be written as

$$
\rho\frac{dV(t)}{dt} + \rho Q(L,t) - \rho Q(0,t) = 0 \tag{B.10}
$$

where ρ is the blood density. If infiltration does occur we must add a source term to this equation [97]. To determine the one-dimensional equation of mass conservation, we insert the volume into equation B.10 and, note that

$$Q(L,t) - Q(0,t) = \int_0^L \frac{\partial Q}{\partial z} dz,$$

we obtain

$$\rho \frac{d}{dt} \int_0^L A(z,t) dz + \rho \int_0^L \frac{\partial Q}{\partial z} dz = 0.$$

If we assume L is independent of time we can take the time derivative inside the integral to arrive at

$$\rho \int_0^L \left\{ \frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} \right\} dz = 0$$

Since we have not specified the length L, the control volume is arbitrary and so the above equation must be true for any value of L and so in general we require that the integrand is zero. We therefore obtain the differential one-dimensional mass conservation equation:

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} = \frac{\partial A}{\partial t} + \frac{\partial (uA)}{\partial z} = 0 \tag{B.11}$$

B.3 Conservation of the momentum

The momentum equation, also called the equation of motion, is a relation equating the rate of change of momentum of a selected portion of the body and the some of all forces acting on that portion. Again we consider the vessel as our control volume and assume that there is no flux through the side walls in the z-direction. In this case, it states that the rate of change of momentum within the integration domain Ω_t plus the net flux of the momentum out of the domain itself is equal to the applied forces on the domain and can be expressed over an arbitrary length L as

$$\frac{\partial}{\partial t} \int_0^L \rho Q dz + (\alpha \rho Q u)_L - (\alpha \rho Q u)_0 = F \tag{B.12}$$

where F is defined as the applied forces in the z-direction acting on the domain. The equation B.12 includes the *momentum-flux correction coefficient* α, also called *Coriolis coefficient*, which accounts for the fact that the momentum flux calculated with averaged quantities ($\bar{u}$) does not consider non-linearity of sectional integration of flux momentum. So we may assume

$$\frac{\partial}{\partial t} \int_S \rho \tilde{u}^2 A \equiv \alpha \rho \tilde{u}^2 A = \alpha \rho Q \tilde{u} \quad \Rightarrow \quad \alpha(z,t) = \frac{\int_S \tilde{u}^2 d\sigma}{A \tilde{u}^2} = \frac{\int_S \tilde{s}^2 d\sigma}{A} \tag{B.13}$$

In general, the coefficient α vary in time and space, yet in our model it is taken constant as a consequence of B.5 It is immediate to verify that $\alpha \geq 1$.

The axial velocity profile *s(y)* is chosen a priori through the power-law relation

$$s(y) = \gamma^{-1}(\gamma + 2)(1 - y^{\gamma}) \tag{B.14}$$

where y is the radial coordinate and γ is a proper coefficient. Commonly accepted approximation are $\gamma = 2$ ($\alpha = 4/3$), which corresponds to the Poiseuille solution (parabolic velocity profile), while $\gamma = 9$ ($\alpha = 1.1$) leads to a more physiological flat profile, following the Womersley theory. The blood profile trend with these values are shown in figure B2.

We will see that the choice of $\alpha = 1$, which indicates a completely flat velocity profile, would lead to certain simplification in our analysis.

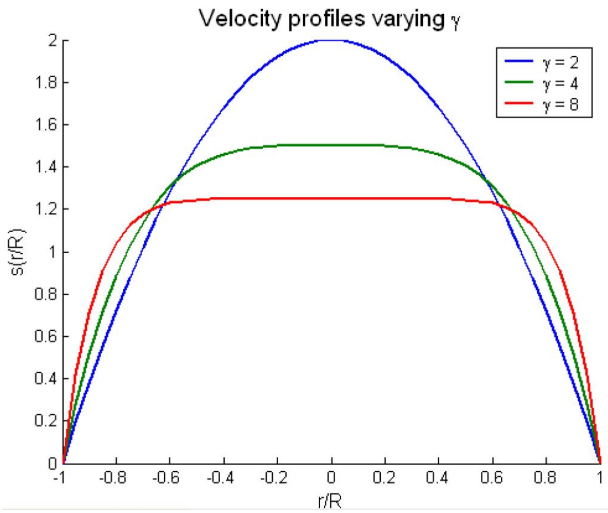

Figure B2: Blood flow profile adopting different values of γ.

To complete the equation B.12 we need to define the applied forces **F** which typically involve a pressure and a viscous force contribution,

$$F = (PA)_0 - (PA)_L + \int_0^L \int_{\partial S} \hat{P} n_z ds dz + \int_0^L f dz \tag{B.15}$$

where ∂S represents the boundary of the section S, n_z is the z-component of the surface normal and f stands for the friction force per unit of length. The pressure force acting on the side walls, given by the double integral, can be simplified since we assumed both constant sectional pressure and axial symmetry of the vessel; so we have

$$\int_0^L \int_{\partial S} \hat{P} n_z ds dz = \int_0^L P \frac{\partial A}{\partial z} dz \tag{B.16}$$

If we finally combine equations B.12,B.15 and B.16 we obtain the momentum conservation for the computation domain expressed as

$$\frac{d}{dt} \int_0^L PQ dz + (\alpha \rho Q u)_L - (\alpha \rho Q u)_0 = (PA)_0 - (PA)_L + \int_0^L P \frac{\partial A}{\partial z} dz + \int_0^L f dz \tag{B.17}$$

To obtain the one-dimensional differential equation for the momentum we note that

$$(\alpha\rho Qu)_L - (\alpha\rho Qu)_0 = \int_0^L \frac{\partial(\alpha\rho Qu)}{\partial z}dz$$
$$(PA)_0 - (PA)_L = -\int_0^L \frac{\partial(PA)}{\partial z}dz$$

which inserted into B.17, taking L independent of time and ρ constant, gives

$$\rho\int_0^L \left\{ \frac{\partial Q}{\partial t} + \frac{\partial(\alpha Qu)}{\partial z} \right\} dz = \int_0^L \left\{ -\frac{\partial(PA)}{\partial z} + P\frac{\partial A}{\partial z} + f \right\} dz$$

Once again this relationship is satisfied for an arbitrary length L and therefore can only be true when the integrands are equal. So the one-dimensional equation for the momentum conservation becomes

$$\frac{\partial Q}{\partial t} + \alpha\frac{\partial}{\partial z}\left(\frac{Q^2}{A}\right) = -\frac{A}{\rho}\frac{\partial P}{\partial z} + \frac{f}{\rho} \tag{B.18}$$

The viscous term in the equation B.15 can be taken proportional to the averaged velocity $\bar{u}$, thus we write

$$\frac{f}{\rho} = K_R\frac{Q}{A}$$

Therefore we finally obtain the equation of the momentum continuity

$$\frac{\partial Q}{\partial t} + \alpha\frac{\partial}{\partial z}\left(\frac{Q^2}{A}\right) = -\frac{A}{\rho}\frac{\partial P}{\partial z} + K_r\bar{u} \tag{B.19}$$

where K_R is a strictly positive quantity that represents the viscous resistance of the flow per unit length of tube. It depends on the kinematic viscosity $\nu = \frac{\mu}{\rho}$ of the fluid and the velocity profile s chosen. For a power law profile $s(y)$, we have $K_R = 2\pi\nu(\gamma + 2)$. In particular, for a parabolic profile $K_R = 8\pi\nu$, while for a flat profile we obtain $K_R = 22\pi\nu$.

B.4 Vessel wall constitutive model

Once we obtained the two governing equations B.11 and B.19, it is possible to write the one-dimensional system as

$$\begin{cases} \dfrac{\partial A}{\partial t} + \dfrac{\partial Q}{\partial z} = 0 \\ \dfrac{\partial Q}{\partial t} + \dfrac{\partial}{\partial z}(\alpha\dfrac{Q^2}{A}) + \dfrac{A}{\rho}\dfrac{\partial P}{\partial z} + K_R\dfrac{Q}{A} = 0 \end{cases} \tag{B.20}$$

for all $z \in (0, L)$ and $t > 0$, where the unknown variables are A, Q and P. The system of equations B.20 may be also expressed alternatively in terms of the variables $(A, \bar{u})$ instead (A, Q).

$$\begin{cases} \dfrac{\partial A}{\partial t} + \dfrac{\partial A\bar{u}}{\partial z} = 0 \\ \dfrac{\partial \bar{u}}{\partial t} + \bar{u}\dfrac{\partial \bar{u}}{\partial z} + \dfrac{1}{\rho}\dfrac{\partial P}{\partial z} + K_R\bar{u} = 0 \end{cases} \tag{B.21}$$

As we can notice the number of unknown variables is greater than the number of equations (three against two); therefore we must provide another equation in order to close the system. A possibility is to introduce an algebraic relation linking the area of the vessel and pressure to the wall deformation. For the paper 1 we have considered the *Generalised string model* [98], which is written in the following form

$$\rho_w h_0 \frac{\partial^2 \eta}{\partial t^2} - \tilde{\gamma}\frac{\partial \eta}{\partial t} - \tilde{a}\frac{\partial^2 \eta}{\partial z^2} - \tilde{c}\frac{\partial^3 \eta}{\partial t \partial z^2} + \tilde{b}\eta = (P - P_{ext}), \qquad z \in (0, L), t > 0 \tag{B.22}$$

We may identify the physical significance of the various terms:

- *Inertia term:* $\rho_w h_0 \frac{\partial^2 \eta}{\partial t^2}$, proportional to the wall acceleration
- *Voigt viscoelastic term:* $\tilde{\gamma}\frac{\partial \eta}{\partial t}$, viscoelastic term, proportional to the radial displacement velocity
- *Longitudinal pre-stress state of the vessel:* $\tilde{a}\frac{\partial^2 \eta}{\partial z^2}$,
- *Viscoelastic term:* $\tilde{c}\frac{\partial^3 \eta}{\partial t \partial z^2}$,
- *Elastic term:* $\tilde{b}\eta$.

Besides ρ_w is the vessel density, h_0 is the wall thickness, $\tilde{a}$, $\tilde{b}$ and $\tilde{c}$ are three positive coefficients. We can develop the last term of B.22 being

$$\eta = R - R_0 \qquad \Rightarrow \qquad \eta = \frac{\sqrt{A} - \sqrt{A_0}}{\sqrt{\pi}}, \qquad A_0 = \pi R_0^2$$

Elastic model

The elastic response is the dominating effect, while the other terms are less important. Consequently, a first model is obtained by neglecting all derivatives in B.22. Pressure and area will then be related by the following algebraic law

$$\tilde{b} = \frac{E h_0}{k R_0^2} = \frac{\pi E h_0}{k A_0}, \qquad k = 1 - \nu^2$$

where E is the Young modulus of elasticity and ν represents the Poisson ratio, typically taken to be $\nu = 0.5$ (then $k = 0.75$) since biological tissue is practically incompressible. We have taken $k = 1$.

$$P - P_{ext} = \tilde{b}\eta = \beta\frac{\sqrt{A} - \sqrt{A_0}}{A_0} \tag{B.23}$$

where

$$\beta = E h_0 \sqrt{\pi}$$

is in general a function of z trough the Young modulus E. In a more general setting, the algebraic relationship may be expressed as

$$P = P_{ext} + \psi(A; A_0, \beta) \tag{B.24}$$

where we outlined that the pressure will depend not only on A, but also on A_0 and on a set of coefficients $\beta = \beta_1, \beta_2, \ldots, \beta_n$ which accounts for the physical and mechanical characteristics of the arterial vessel. Both A_0 and β are given functions of z, but they do not vary in time. It is required that ψ be at least a C^1 function of its arguments and be defined for each positive value of A and A_0. In addition we must have, for all the allowable values of A, A_0 and β that

$$\frac{\partial \psi}{\partial A} > 0, \qquad \psi(A_0; A_0, \beta) = 0$$

There are several examples of algebraic pressure-area relationship for one-dimensional models of arterial flow [**? ?**]; here we assumed the relationship B.23, where $\beta = \beta_1$ and, for the sake of simplicity, $P_{ext} = 0$. The function ψ can be written as

$$\psi(A; A_0, \beta_1) = \beta_1 \frac{\sqrt{A} - \sqrt{A_0}}{A_0} \tag{B.25}$$

It is useful introduce the Moens-Korteweg velocity

$$c_1(A; A_0, \beta) = \sqrt{\frac{A}{\rho} \frac{\partial \psi}{\partial A}}$$

which represents the propagation speed of waves along the cylindrical vessels. In our case may be readily computes as

$$c_1 = \sqrt{\frac{\beta}{2\rho A_0}} A^{\frac{1}{4}} \tag{B.26}$$

Taking into account B.23 the system B.20 can be written in the conservation form

$$\frac{\partial \mathbf{U}}{\partial t} + \frac{\partial \mathbf{F}(\mathbf{U})}{\partial z} = \mathbf{S}(\mathbf{U}), \quad z \in (0, L), \quad t > 0 \tag{B.27}$$

where

$$\mathbf{U} = \begin{bmatrix} A \\ Q \end{bmatrix} \tag{B.28}$$

are the conservative variables,

$$\mathbf{F}(\mathbf{U}) = \begin{bmatrix} Q \\ \alpha \dfrac{Q^2}{A} + C_1 \end{bmatrix}$$

the corresponding fluxes, and

$$\mathbf{S}(\mathbf{U}) = \begin{bmatrix} 0 \\ -K_R \dfrac{Q}{A} + \dfrac{\partial C_1}{\partial A_0}\dfrac{dA_0}{dz} + \dfrac{\partial C_1}{\partial \beta}\dfrac{d\beta}{dz} \end{bmatrix}$$

a source term of the system. In our modelling, A_0 and β_1 are taken constant along the axial direction z because we assume that both the initial area A_0 and the Young modulus E do not vary in space; so the expression of $\mathbf{S}$ accounts only for the friction term depending on K_R.

C_1 is a primitive of the wave speed c_1, given by

$$C_1(A; A_0, \beta) = \int_{A_0}^{A} c_1^2(\tau; A_0, \beta) d\tau$$

Applying the relationship B.26 and B.4, we obtain

$$c_1 = \sqrt{\frac{\beta_1}{2\rho A_0}} A^{\frac{1}{4}} \quad \Rightarrow \quad C_1 = \frac{\beta_1}{3\rho A_0} A^{\frac{3}{2}} \tag{B.29}$$

B.5 Characteristic analysis

One of the methods for solving non-linear hyperbolic system of partial differential equations, like the one-dimensional elastic model B.27 , is the *characteristic analysis* [78]. After some simple manipulations the system B.27 may be written in the *quasi-linear* form:

$$\frac{\partial \mathbf{U}}{\partial t} + \mathbf{H}(\mathbf{U}) \frac{\partial \mathbf{U}}{\partial z} = \mathbf{B}(\mathbf{U}), \qquad z \in (0, L), t > 0 \tag{B.30}$$

where

$$\mathbf{H}(\mathbf{U}) = \begin{bmatrix} 0 & 1 \\ \dfrac{A}{\rho} \dfrac{\partial \psi}{\partial A} - \alpha \bar{u}^2 & 2\alpha \bar{u} \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ c_1^2 - \alpha \left(\dfrac{Q}{A} \right)^2 & 2\alpha \dfrac{Q}{A} \end{bmatrix}$$

is the Jacobian matrix. If A_0 and β are constant $\mathbf{B} = -\mathbf{S}$. Considering B.30, we can calculate the eigenvalues for the matrix $\mathbf{H}(\mathbf{U})$

$$\lambda_{1,2} = \alpha \frac{Q}{A} \pm c_\alpha \tag{B.31}$$

where

$$c_\alpha = \sqrt{c_1^2 + \alpha(\alpha - 1) \frac{Q^2}{A^2}}$$

Since the Coriolis coefficient $\alpha \geq 1$ (we considered, for simplicity, $\alpha = 1$), c_α is a real number; besides, under the assumption that $A > 0$, indeed a necessary condition to have physical relevant solution, $c_1 > 0$; therefore we have $c_\alpha > 0$ which means $\mathbf{H}$ has two real distinct eigenvalues and so, by definition, the system B.30 is *strictly hyperbolic*. For typical values of velocity, vessel section and mechanical parameter β_1 encountered in main arteries under physiologically conditions, we find that $\lambda_1 > 0$ and $\lambda_2 < 0$, i.e., the flow is *sub-critical* everywhere. Furthermore, it may be shown [99] that the flow is smooth. Discontinuities, which would normally appear when treating a non -linear hyperbolic system, do not have the time to form on out context because of the pulsatility of the boundary conditions. Afterwards this considerations, from now on we will assume sub-critical regime and smooth solutions.

Let $(\mathbf{l}_1, \mathbf{l}_2)$ and $(\mathbf{r_1}, \mathbf{r_2})$ be two couples of left and right eigenvectors of $\mathbf{H}$. The matrices $\mathbf{R}$, $\mathbf{L}$ and $\mathbf{\Lambda}$ are defined as

$$\mathbf{L} = \begin{bmatrix} \mathbf{l}_1^T \\ \mathbf{l}_2^T \end{bmatrix}, \quad \mathbf{R} = \begin{bmatrix} \mathbf{r}_1 & \mathbf{r}_2 \end{bmatrix}, \quad \mathbf{\Lambda} = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} \tag{B.32}$$

Since left and right eigenvalues are mutually orthogonal, we choose them so that $\mathbf{LR} = \mathbf{I}$, being $\mathbf{I}$ the identity matrix. Matrix $\mathbf{H}$ may then be decomposed as

$$\mathbf{H} = \mathbf{R\Lambda L}$$

and the system B.30 takes the equivalent form

$$\mathbf{L}\frac{\partial \mathbf{U}}{\partial t} + \mathbf{\Lambda L}\frac{\partial \mathbf{U}}{\partial z} + \mathbf{LB}(\mathbf{U}) = 0 \tag{B.33}$$

If there exist two quantities W_1 and W_2 which satisfy

$$\frac{\partial W_1}{\partial \mathbf{U}} = \mathbf{l_1}, \quad \frac{\partial W_2}{\partial \mathbf{U}} = \mathbf{l_2} \tag{B.34}$$

we will call them *characteristic variables* of the hyperbolic system. By setting $\mathbf{W} = [W_1, W_2]^T$ the system B.33 may be elaborated into

$$\frac{\partial \mathbf{W}}{\partial t} + \mathbf{\Lambda}\frac{\partial \mathbf{W}}{\partial z} + \mathbf{G} = 0 \tag{B.35}$$

where

$$\mathbf{G} = \mathbf{LB} - \frac{\partial \mathbf{W}}{\partial A_0}\frac{dA_0}{dz} - \frac{\partial \mathbf{W}}{\partial \beta}\frac{d\beta}{dz}$$

Under the assumption that A_0 and β_1 are constant in space and taking $\mathbf{B}$ negligible, the equation B.35 becomes

$$\frac{\partial \mathbf{W}}{\partial t} + \mathbf{\Lambda}\frac{\partial \mathbf{W}}{\partial z} = 0$$

which is a system of decoupled scalar equation written as

$$\frac{\partial W_i}{\partial t} + \lambda_\mathbf{i}\frac{\partial W_i}{\partial z} = 0 \tag{B.36}$$

From B.36 we have W_1 and W_2 are constant along two *characteristics curves* in the (z,t) plane B3 described by the differential equations

$$\frac{dz}{dt} = \lambda_1 \quad , \quad \frac{dz}{dt} = \lambda_2$$

The expression for the left eigenvectors $\mathbf{l}_1$ and $\mathbf{l}_2$ is given by

$$\mathbf{l}_1 = \xi \begin{bmatrix} c_\alpha - \alpha\bar{u} \\ 1 \end{bmatrix}, \quad \mathbf{l}_2 = \xi \begin{bmatrix} -c_\alpha - \alpha\bar{u} \\ 1 \end{bmatrix}, \tag{B.37}$$

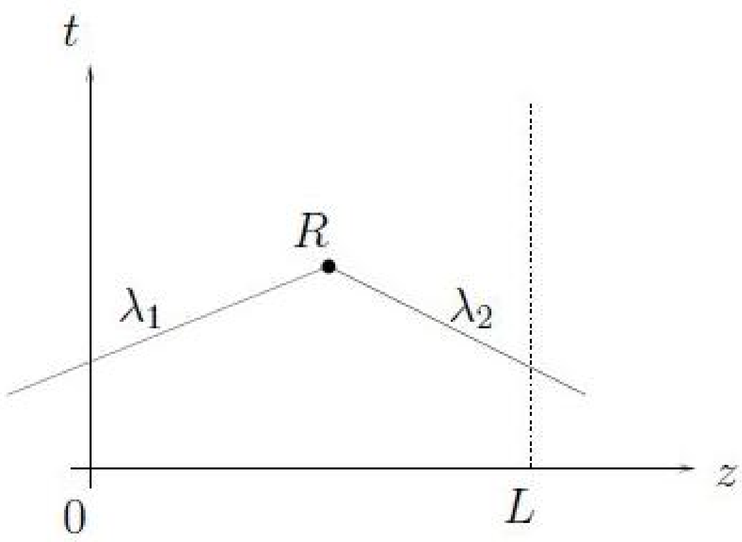

Figure B3: Diagram of characteristics in the (z,t) plane. The solution on the point R is obtained by the superimposition of the two characteristics W_1 and W_2.

where $\xi = \xi(A, \bar{u})$ is any arbitrary smooth function of its arguments with $\xi > 0$. Here we have expressed $\mathbf{l}_1$ and $\mathbf{l}_2$ as functions of $(A, \bar{u})$ instead of (A, Q) in order to simplify the next developments.

For an hyperbolic system of two equations is always possible to find the characteristic variables (or, equivalently, the Riemann invariants) locally, that is in a small neighbourhood of any point $\mathbf{U}$ [100], yet the existence of global characteristic is not in general guaranteed. However, assuming $\alpha = 1$ the relationship B.37 take the much simpler form

$$\frac{\partial W_1}{\partial A} = \xi c_1, \qquad \frac{\partial W_1}{\partial \bar{u}} = \xi A \tag{B.38}$$

$$\frac{\partial W_2}{\partial A} = -\xi c_1, \qquad \frac{\partial W_2}{\partial \bar{u}} = \xi A \tag{B.39}$$

We now show that a set of global characteristic variables do exist for the problem at hand. Since we note, from B.38, that $W_{1,2}$ are exact differentials being

$$\frac{\partial^2 W_i}{\partial A \partial \bar{u}} = \frac{\partial^2 W_i}{\partial \bar{u} \partial A}$$

for any values of A and $\bar{u}$, we also have that c_1 does not depend on $\bar{u}$ and then, from above relationship we obtain

$$c_1 \frac{\partial \xi}{\partial \bar{u}} = \xi + A \frac{\partial \xi}{\partial A}$$

In order to satisfy this relation we have to choose $g = g(A)$ such that $g = -A\dfrac{\partial g}{\partial A}$. To do this we can take $g = A^{-1}$. As a consequence we can write

$$\partial W_1 = \frac{c_1}{A} \partial A + \partial \bar{u}, \quad \partial W_2 = -\frac{c_1}{A} \partial A + \partial \bar{u} \tag{B.40}$$

Taking $(A_0, 0)$ as a reference state for our variables $(A_0, \bar{u})$ we can integrate the above relationships obtaining

$$W_1 = \bar{u} + \int_{A_0}^{A} \frac{c_1(\epsilon)}{\epsilon} d\epsilon, \qquad W_2 = \bar{u} - \int_{A_0}^{A} \frac{c_1(\epsilon)}{\epsilon} d\epsilon \tag{B.41}$$

Introducing the expression B.4 for c_1 we have

$$W_{1,2} = \frac{Q}{A} \pm 4\left(\sqrt{\frac{\beta_1}{2\rho A_0}} A^{\frac{1}{4}} - c_0\right) \tag{B.42}$$

with c_0 is the wave speed related to the reference state. We finally can write the variables (A, Q) in terms of the characteristic ones,

$$A = \left(\frac{2\rho A_0}{\beta_1}\right)^2 \left(\frac{W_1 - W_2}{8}\right)^4, \qquad Q = A\frac{W_1 + W_2}{2} \tag{B.43}$$

allowing in particular, the implementation of boundary and compatibility conditions, that we will discuss in the next section.

B.6 Boundary conditions

By the characteristic analysis of the one-dimensional model we pointed out the hyperbolic nature of the one-dimensional system of blood flow in arteries; consequently the solution is given by the superimposition of two waves whose eigenvalues $\lambda_{1,2}$ represent the propagation speeds of such waves. As we have seen previously, they always have opposite sign and so blood flow is *subcritical*; under this condition, we need an initial condition along all the spatial domain and two boundary conditions to close the governing system: one at the inlet section $z = 0$ and the other at the outlet $z = L$ (see figure B4).

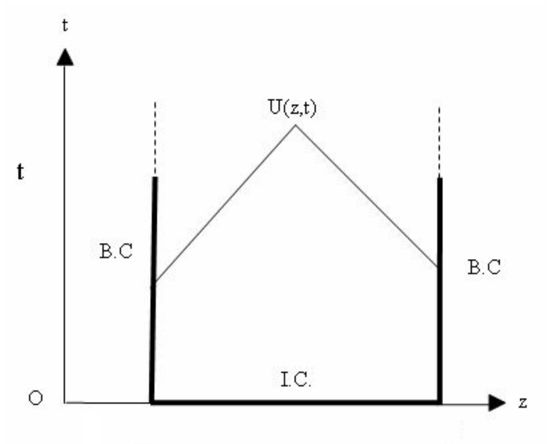

Figure B4: Boundary and initial conditions of the hyperbolic system.

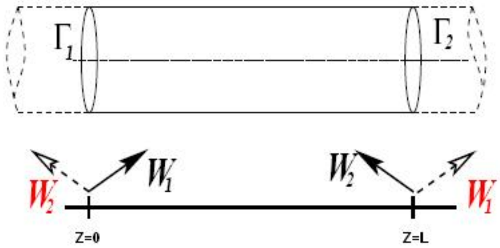

Figure B5: One-dimensional model with absorbing conditions.

Different type of boundary conditions can be imposed. An important class of boundary conditions is represented by the so-called *non-reflecting* or *absorbing* boundary conditions [101], which allows the simple wave associated with the characteristics to enter or leave the domain without spurious reflections (see Figure B5). Absorbing boundary conditions can be imposed by defining values for the wave entering the domain; in our case we have $\lambda_1 > 0$ and $\lambda_2 < 0$ so W_1 is the entering characteristic in $z = 0$ and W_2 the inlet characteristic in $Z = L$. In Hedstrom [102], non-reflecting boundary conditions for an hyperbolic problem are written as

$$\mathbf{l}_1 \cdot \left[\frac{\partial \mathbf{U}}{\partial t} - \mathbf{B}(\mathbf{U})\right]_{x=0} = 0, \quad \mathbf{l}_2 \cdot \left[\frac{\partial \mathbf{U}}{\partial t} - \mathbf{B}(\mathbf{U})\right]_{x=L} = 0$$

When there is an explicit formulation of the characteristic variables, it is possible impose the boundary conditions directly in terms of incoming characteristics, for example

$$W_1(t) = g_1(t), \qquad \text{in} \quad z = 0, t > 0$$

being $g_1(t)$ a given function. However, the problem rarely have boundary data in terms of variable characteristics, they are normally expressed in terms of physical variables.

In addition to absorbing boundary conditions based on characteristic variables, it may impose a function that describes the temporal trend on the edge of one of the unknown functions of the problem, then the flux flow Q (or the speed u) or the area A. Conditions of this type are typically used on the proximal node $z = 0$ and can be expressed as follows:

$$\begin{aligned} Q(0,t) &= g_q(t), \quad t > 0 \\ A(0,t) &= g_a(t), \quad t > 0 \end{aligned}$$

The boundary conditions imposed by the knowledge of the physical variables are *reflective*. Therefore, if we impose such a condition in the proximal node, the incoming characteristic variable, that we denoted by W_2, will be partially reflected in the computational domain. This is a real physical phenomenon.

The *initial conditions* are the conditions to be imposed by defining the value of $A(z,t)$ and $Q(z,t)$ along the spatial domain $z \in (0, L)$ at the initial time $t = 0$. For instance if we require the area at the initial time, the initial condition is expressed as

$$A(z,t) = A_0(z), \quad z \in (0, L)$$

B.6.1 Terminals lumped parameter

The assumptions made for the 1-D model become less appropriate with decreasing the size of the arteries; for example, the blood flow in the larger arteries is pulsatile and is dominated by inertia while in the capillaries is almost stable and dominant by the viscosity. Consequently, the 1-D model should be limited until at the distal section of the domain ($z = L$). We have seen a first approach which imposes not reflective boundary conditions in the vessels terminals B.6, but this solution is not adherent to reality. We then introduce the lumped parameter models (0-D) who consider the fact that the pressure waves are physically in part reflected and partly absorbed. These models coupled with the one-dimensional constitutive equation B.27 leads to a multiscale framework 1-D/0-D. Therefore, the hemodynamic effects of the blood vessels after the distal section limit are generally simulated using a lumped parameter model governed by ordinary differential equations that relate the pressure with the flow at the outlet of the 1-D model [103].

Expressing the system B.30 in terms of (A, P, Q) with $Q = A\bar{u}$ and linearising around the state of reference $(A_0, 0, 0)$, with β an A_0 be constant along z, is obtained.

$$\begin{cases} C_{1D}\dfrac{\partial p}{\partial t} + \dfrac{\partial q}{\partial z} = 0 \\ L_{1D}\dfrac{\partial q}{\partial t} + \dfrac{\partial p}{\partial z} = -R_{1D}q \\ p = \dfrac{a}{C_{1D}} \end{cases} \tag{B.44}$$

where a,p and q are the perturbation variables for area, pressure and volume flux, respectively $(A_0 + a, p, q)$ and

$$R_{1D} = \frac{\rho c_0}{A_0}, \qquad C_{1D} = \frac{A_0}{\rho c_0^2}, \qquad L_{1D} = \frac{\rho}{A_0} \tag{B.45}$$

are the viscous resistance to flow, wall compliance and blood inertia, respectively, per unit of length of vessel l. Integrating system B.44 over the length l yields the lumped parameter model, where the variables are $R_{0D} = R_{1D}l$, $C_{0D} = C_{1D}l$, $L_{0D} = L_{1D}l$ and $\hat{p} = \frac{1}{l}\int_0^l p dz$, $\hat{q} = \frac{1}{l}\int_0^l q dz$ are the mean pressure and flow over the whole domain. In physiological conditions pulsatile waves travel at a speed greater compared to that of the blood, then $\hat{p} = p_{in}$ and $\hat{q} = q_{out}$. Therefore, the final 0-D model is the following:

$$\begin{cases} C_{0D}\dfrac{\partial p_{in}}{\partial t} + q_{out} - q_{in} = 0 \\ L_{0D}\dfrac{\partial q_{out}}{\partial t} + R_{0D}q_{out} + p_{out} - p_{in} = 0 \end{cases} \tag{B.46}$$

where $q_{in} = q(0, t)$, $q_{out} = q(L, t)$, $p_{in} = p(0, t)$ and $p_{out} = p(L, t)$ are the flows and pressures at the inlet and outlet of the 0-D domain. As it is represented in Figure B6, the system B.46 is analogous to an electric circuit, in which the role of the flow and pressure are played by the current and potential, R_{0D} corresponds to an electric resistance, C_{0D} to a capacitance and L_{0D} to an inductance [104].

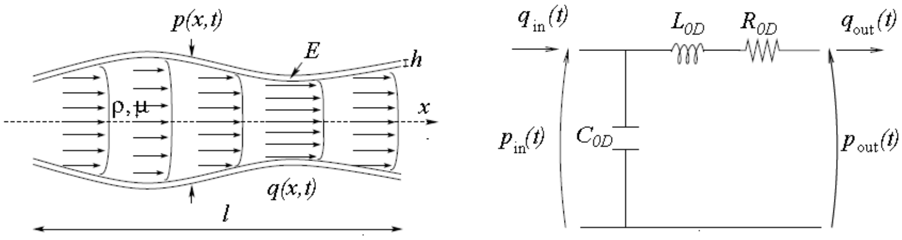

Figure B6: 1-D arterial vessel domain (left) and the equivalent 0-D system discretises at first order in space (right).

Hydraulic	Physiological variables	Electric
Pressure $P[Pa]$	Blood pressure $[mmHg]$	Voltage V
Flow rate $Q[m^3/s]$	Blood flow rate $[L/s]$	Current I
Volume $V[m^3]$	Blood volume $[L]$	Charge $q[C]$
Viscosity η	Blood viscosity $\mu[Pa \cdot s]$	Electrical resistance R
Elastic coefficient	Vessel's wall compliance	Capacitance C
Inertance	Blood inertia	Inductance L

Table B1: Analogy between hydraulic and electrical network.

B.7 Implementation

The nonlinear hyperbolic system B.27 has been discretized using a Taylor-Galerkin scheme [105], which is the finite element equivalent of Lax-Wendroff (based on the expansion in Taylor series) stabilisation for the finite difference method. This method may result in short computational times, and is second order accurate in both time and space.

Considering the equation B.27 and having $\mathbf{H} = \dfrac{\partial \mathbf{F}}{\partial \mathbf{U}}$ we may write

$$\begin{aligned}\frac{\partial \mathbf{U}}{\partial t} &= \mathbf{S} - \frac{\partial \mathbf{F}}{\partial z} \\ \frac{\partial^2 \mathbf{U}}{\partial t^2} &= \frac{\partial \mathbf{S}}{\partial \mathbf{U}}\frac{\partial \mathbf{U}}{\partial t} - \frac{\partial}{\partial z}\left(\mathbf{H}\frac{\partial \mathbf{U}}{\partial t}\right) \\ &= \frac{\partial \mathbf{S}}{\partial \mathbf{U}}\left(\mathbf{S} - \frac{\partial \mathbf{F}}{\partial z}\right) - \frac{\partial \mathbf{HB}}{\partial z} + \frac{\partial}{\partial z}\left(\mathbf{H}\frac{\partial \mathbf{F}}{\partial z}\right)\end{aligned} \tag{B.47}$$

For simplicity the dependence of $\mathbf{S}$ and $\mathbf{F}$ from $\mathbf{U}$ is dropped. Starting from the above equations, we now consider the time intervals (t^n, t^{n+1}), for $n = 0, 1, \ldots, T$; then we discretize the equation in time using a Taylor series which includes first and second order derivatives if $\mathbf{U}$. Therefore we obtain the following *semi-discrete* schemes for the approximation $\mathbf{U}^{n+1}$ of $\mathbf{U}(t^{n+1})$:

- **Taylor-Galerkin scheme:**

$$\mathbf{u}^{n+1} = \mathbf{u}^n + \Delta t \mathbf{u}_t^n + \frac{\Delta t^2}{2}\mathbf{u}_{tt}^n \tag{B.48}$$

$$\begin{aligned}\mathbf{U}^{n+1} =& \mathbf{U}^n - \Delta t \frac{\partial}{\partial z}\left(\mathbf{F}^n + \frac{\Delta t}{2}\mathbf{H}^n\mathbf{S}^n\right) + \frac{\Delta t^2}{2}\left[\mathbf{S}_{\mathbf{U}}^n\frac{\partial \mathbf{F}^n}{\partial z} - \frac{\partial}{\partial z}\left(\mathbf{H}^n\frac{\partial \mathbf{F}^n}{\partial z}\right)\right] \\ &+ \Delta t\left(\mathbf{S}^n + \frac{\Delta t}{2}\mathbf{S}_{\mathbf{U}}^n\mathbf{S}^n\right), \qquad n = 0, 1, \ldots\end{aligned} \tag{B.49}$$

where $\mathbf{S}_{\mathbf{U}}^n = \dfrac{\partial \mathbf{S}^n}{\partial \mathbf{U}}$ and $\mathbf{F}^n$, stands for $\mathbf{F}(\mathbf{U^n})$, just as $\mathbf{H}^n$, $\mathbf{S}^n$ and $\mathbf{S}_{\mathbf{U}}^n$; the value $\mathbf{U}^0$ is given by the initial conditions.

For each time interval (t^n, t^{n+1}) we apply a spatial discretization carried out using the Galerkin finite element method. To this purpose we subdivide the domain $\Omega = \{z : z \in (0, L)\}$, which is the 1-D counterpart of the 3-D domain Ω_t, into a finite number N_{el} of linear elements length l (Figure B7).

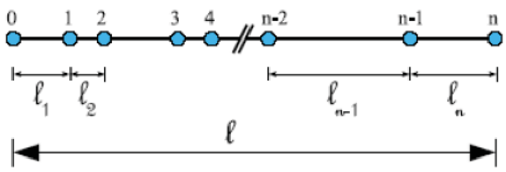

Figure B7: One-dimensional mesh representing a vessel.

Moreover we introduce a trial function space, $\mathcal{T}$, and a weighting function space, $\mathcal{W}$. These spaces are both defined to consist of all suitably smooth functions and to be such that

$$\mathcal{T} = \Big\{\mathbf{U}(z,t)|\mathbf{U}(z,0) = \mathbf{U}^0(z) \text{ on } \Omega_t \quad \text{at} \quad t = t^0\Big\}, \qquad \mathcal{W} = \Big\{\mathcal{W}(\mathbf{z})\Big\}$$

Considering the scheme, we multiply the equation B.49 for the weight function $\mathbf{W}$ and we integrate it over the domain Ω_t obtaining, for $\forall t > 0 t^0$

$$\begin{aligned}\int_\Omega \left(\mathbf{U}^{n+1} - \mathbf{U}^n\right) d\Omega =& -\Delta t\left[\int_\Omega \frac{\partial \mathbf{W}}{\partial z}\mathbf{F}_{LW}^n d\Omega - \int_\Omega \mathbf{S}_{LW}^n \mathbf{W} d\Omega\right] - \\ &- \frac{\Delta t^2}{2}\left[\int_\Omega \frac{\partial \mathbf{W}}{\partial z}\mathbf{S_U}^n\mathbf{F}^n - \int_\Omega \frac{\partial \mathbf{W}}{\partial z}\frac{\partial \mathbf{F}^n}{\partial z}\mathbf{H}^n\right] - \\ &- \Delta t\left[N_i \bar{\mathbf{F}}_r^n|_{z=L} - N_i \bar{\mathbf{F}}_l^n|_{z=0}\right]\end{aligned} \tag{B.50}$$

where we have assumed

$$\mathbf{F}^n_{LW}(\mathbf{U}_j) = \mathbf{F}^n + \frac{\Delta t}{2}\mathbf{H}^n\mathbf{S}^n$$

and

$$\mathbf{S}^n_{LW}(\mathbf{U}_j) = \mathbf{S}^n + \frac{\Delta t}{2}\mathbf{S_U}^n\mathbf{S}^n$$

Starting from the weak form of the problem B.50 we build the subspaces $\mathcal{T}^h$ and $\mathcal{W}^h$ for the trial and weighting function spaces $\mathcal{T}$ and $\mathcal{W}$ defining them as

$$\begin{aligned} \mathcal{T}^h &= \left\{ \hat{\mathbf{U}}(z,t)|\hat{\mathbf{U}}(z,t) = \sum_{j=1}^{N} \mathbf{U}_j(t)N_j(z); \quad \mathbf{U}(t^0) = \bar{\mathbf{U}}(z_j) = \mathbf{U}^0_j \right\} \\ \mathcal{W}^h &= \left\{ \mathcal{W}(z,t)|\mathcal{W}(z) = \sum_{j=1}^{N} W_j(t)N_j(z) \right\} \end{aligned} \tag{B.51}$$

where N_j is the standard linear finite element shape function (Figure B8) associated to the $j-th$ node, located at $z = z_j$, and $\mathbf{U}_j$ and $\hat{\mathbf{U}}$ at the node j. Since we are using the Galerkin method, the base shape functions defined above are used as weighting. Adopting the following notation

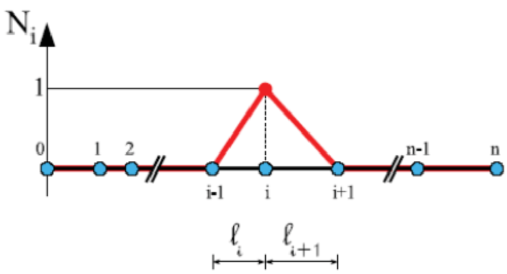

Figure B8: Sketch of a 1D linear shape function.

$$(W,U)_{\Omega_e} = \int_{\Omega_e} W \cdot U d\Omega,$$

and considering the sum of each element contribution

$$\int_{\Omega} \cdots = \sum_{el} \int_{\Omega_e} \cdots ,$$

the equation B.50 becomes

$$\begin{aligned}\sum_{el}(N_i,N_j)_{\Omega_e}(\mathbf{U}_j^{n+1}-\mathbf{U}_j^n) = \Delta t\sum_{el}[(N_{i,z},N_j)_{\Omega_e}\mathbf{F}_{LW}^n(\mathbf{U}_j) + N_i,N_j)_{\Omega_e}\mathbf{S}_{LW}^n(\mathbf{U}_j)]-\\ -\frac{\Delta t^2}{2}\sum_{el}\left((N_i,N_j)_{\Omega_e}\mathbf{S_U}^n(\mathbf{U}_j)\frac{\partial\mathbf{F}_j^n}{\partial z}\right)-\\ -\frac{\Delta t^2}{2}\sum_{el}\left((N_{i,z},N_j)_{\Omega_e}\mathbf{H}_j^n(\mathbf{U}_j)\frac{\partial\mathbf{F}_j^n}{\partial z}\right)-\\ -\Delta t\left[N_i\bar{\mathbf{F}}_r^n|_{z=L}-N_i\bar{\mathbf{F}}_l^n|_{z=0}\right]\end{aligned} \tag{B.52}$$

For what concerns the border nodes, we have to consider the boundaries condition. Starting from the equation B.52, we have the term of boundary conditions represented by

$$\Delta t\left[N_i\bar{\mathbf{F}}_r^n|_{z=L}-N_i\bar{\mathbf{F}}_l^n|_{z=0}\right], \qquad i=1,2$$

which implies the knowledge of the flux terms depending from the values of A and Q at inlet and outlet sections of the domain. To extract them from the characteristic information $W_1(0,t)$ and $W_2(L,t)$ we need an additional expression for the other characteristic variables $W_2(0,t)$ and $W_1(L,t)$ to recover $\mathbf{U}(A,Q)$ using the equation B.43. To this purpose we adopted a technique based on the extrapolation of the outgoing characteristics. Having the friction parameter K_r small with respect to the other equation terms in B.27, we assume that at the boundary points $z=0$ and $z=L$ the flow is generated by the characteristic system B.36. At a generic time step n we have $\mathbf{U}^n$ known and we linearise the eigenvalues $\lambda_{1,2}$ of B.27 by taking their values at respective boundary for $t=t^n$. The solution corresponding to this linearised problem at time t^{n+1} gives

$$\begin{aligned}W_2^{n+1}(0) = W_2^n(-\lambda_2^n(0)\Delta t)\\ W_1^{n+1}(L) = W_1^n(-\lambda_1^n(L)\Delta t)\end{aligned}$$

which is a first-order approximation of the outgoing characteristic variables from the previous step. By using these information together with the values of $W_1^{n+1}(0)$ and $W_2^{n+1}(L)$, we are able to compute, through B.43, the required boundary data.

We choose to use, for time integration, both a second and fourth order explicit Runge-Kutta scheme; such methods are diffused in computational fluid dynamics, and show good properties, e.g ease of programming, simple treatment of boundary conditions and good stability. Regarding the stability, the second order Taylor-Galerkin scheme entails a time step limitations. A linear stability analysis [106] indicates that the following Courant-Friedrichs-Lewy condition should be satisfied

$$\Delta t \leq \frac{\sqrt{3}}{3}\min_{0\leq i\leq N}\left[\frac{h_i}{\max(\lambda_{1,i},\lambda_{1,i+1})}\right] \tag{B.53}$$

where $\lambda_{1,i}$ here indicates the value of λ_1 at mesh node z_i. This condition, which is necessary to obtain the stability of a method explicitly imposes a constraint on the choice of the discretization time and space of the method used; it corresponds to a CFL number of $\frac{\sqrt{3}}{3}$.

B.7.1 Branching

The vascular system is characterized by the presence of branching. The flow in a bifurcation is intrinsically 3-D, however may be still described by means of a 1-D model. In order to manage a branching zone, when using a 1-D formulation, we follow a technique called *domain decomposition* [107]. The numerical solver accounts for the treatment of two types of bifurcation: the bifurcation 2-1 typical of the arterial system and the bifurcation 1-1 which represents two vessel linked together with different mechanical properties.

B.7.2 Bifurcation 1-2

The bifurcation 1-2 represents the typical branching of the arterial system. As we have introduced we have used the domain decomposition method to solve this problem. We divide the domain Ω into three partitions Ω_1,Ω_2 and Ω_3 as is showed at Figure B9; doing this we have 3 sub-problems which must be coupled imposing adequate boundary conditions. Then we have to evaluate 6 variables, (A_i, Q_i) with $i = 1, 2, 3$, corresponding to the problem unknowns, area and flow rate for each one of the vessels composing the branching. From the decomposition of the governing

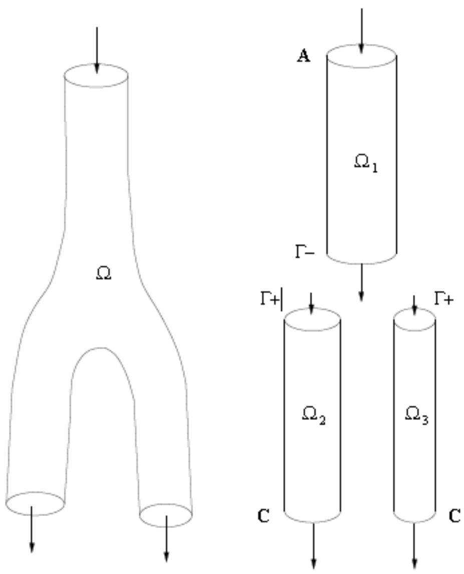

Figure B9: Domain decomposition of a bifurcation 1-2.

system into characteristic variables we know that the system can be interpreted in terms of a forward and backward travelling waves. Considering the model of a splitting bifurcation shown in

Figure B9, we denote the parent vessel by an index 1 and its two daughter vessels by the indices 2 and 3, respectively. The simplest condition we can impose to require the mass conservation through the bifurcation and therefore the flow rate balance can be written

$$Q_1 = Q_2 + Q_3$$

remembering that the flow moves from the sub-domain Ω_1 to the sub-domain Ω_2 and Ω_3. Other two assumptions can be obtained from the requirement of continuity of the momentum flux at the bifurcation. This lead to consider the *total pressure* term continuous at the boundary. So we may write

$$P_1 + \frac{1}{2}\rho\left(\frac{Q_1}{A_1}\right)^2 = P_2 + \frac{1}{2}\rho\left(\frac{Q_2}{A_2}\right)^2$$

$$P_1 + \frac{1}{2}\rho\left(\frac{Q_1}{A_1}\right)^2 = P_3 + \frac{1}{2}\rho\left(\frac{Q_3}{A_3}\right)^2$$

The remaining three relationship can be derived using the characteristic variables. The parent vessel can only reach the junction by a forward travelling wave. This wave is denoted as W_1^1, where the superscript is the vessel number while the subscript stands for the forward direction. Similarly, the characteristics variables of daughter vessels, which can reach the bifurcation only by backwards travelling wave, are represent by W_2^2 and W_2^3.

$$\begin{aligned}
W_1^1 &= \frac{Q_1}{A_1} + 4\sqrt{\frac{\beta_1}{2\rho A_{01}}}A_1^{1/4} = u_1 + 4(c_1 - c_0^1) \\
W_2^1 &= \frac{Q_2}{A_2} - 4\sqrt{\frac{\beta_2}{2\rho A_{02}}}A_2^{1/4} = u_2 + 4(c_2 - c_0^2) \\
W_2^2 &= \frac{Q_3}{A_3} - 4\sqrt{\frac{\beta_3}{2\rho A_{03}}}A_3^{1/4} = u_3 + 4(c_3 - c_0^3)
\end{aligned}$$

where c_0^1,$c_0^2$and c_0^3 are the values of the wave speed evaluated using the area A_0 in the vessels 1,2 and 3. In summary, the resulting system which determines the values (A_1, Q_1),(A_2, Q_2) and

(A_3, Q_3) at the bifurcation is the following

$$\begin{cases} W_1^1 = \dfrac{Q_1}{A_1} + 4\sqrt{\dfrac{\beta_1}{2\rho A_{01}}} A_1^{1/4} \\ W_2^1 = \dfrac{Q_2}{A_2} - 4\sqrt{\dfrac{\beta_2}{2\rho A_{02}}} A_2^{1/4} \\ W_2^2 = \dfrac{Q_3}{A_3} - 4\sqrt{\dfrac{\beta_3}{2\rho A_{03}}} A_3^{1/4} \\ Q_1 = Q_2 + Q_3 \\ P_1 + \dfrac{1}{2}\rho\left(\dfrac{Q_1}{A_1}\right)^2 = P_2 + \dfrac{1}{2}\rho\left(\dfrac{Q_2}{A_2}\right)^2 \\ P_1 + \dfrac{1}{2}\rho\left(\dfrac{Q_1}{A_1}\right)^2 = P_3 + \dfrac{1}{2}\rho\left(\dfrac{Q_3}{A_3}\right)^2 \end{cases} \tag{B.54}$$

We can solve it through the Newton-Raphson technique for differential systems of non-linear equations.This type of modelling does not consider the geometry of the junctions. For instance, the angle between the various vessels are not take into account.

B.7.3 Bifurcation 1-1

The discontinuity at the interface between arteries with different materials(mechanical behaviour) or geometrical properties is solved with a similar process used in the treatment of the bifurcations 2-1. Following the domain decomposition method adopted before, we proceed by splitting the problem in two sub-domains Ω_1 and Ω_2, and solving the following non-linear system for the interface variables, namely

$$\begin{cases} W_1 = \dfrac{Q_1}{A_1} + 4\sqrt{\dfrac{\beta_1}{2\rho A_{01}}} A_1^{1/4} \\ W_2 = \dfrac{Q_2}{A_2} - 4\sqrt{\dfrac{\beta_2}{2\rho A_{02}}} A_2^{1/4} \\ Q_1 = Q_2 \\ P_1 + \dfrac{1}{2}\rho\left(\dfrac{Q_1}{A_1}\right)^2 = P_2 + \dfrac{1}{2}\rho\left(\dfrac{Q_2}{A_2}\right)^2 \end{cases} \tag{B.55}$$

Again, We solve the non-linear system obtained through the Newton-Raphson method. In both systems B.54 and B.55, it has been verified that the determinant of the Jacobian is different from zero for all allowable values of the parameters, thus guaranteeing that the Newton iteration is well-posed [108].

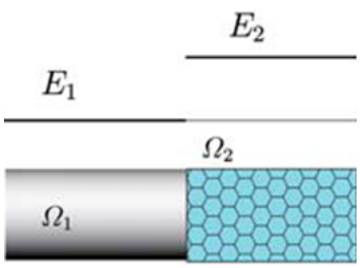

Figure B10: Domain decomposition of a bifurcation 1-1.

B.7.4 Coupling 1-D and 3D-reduced model

In order to consider into the 1D model an external pressure drop, we need to modify the total pressure term (B.55) adding the function $f^{3D}(k_1,k_2)$:

$$P_i + \frac{1}{2}\rho\frac{Q_i{}^2}{A_i{}^2} = P_j + \frac{1}{2}\rho\frac{Q_j{}^2}{A_j{}^2} + f^{3D}{}_j(k_1, k_2) \tag{B.56}$$

where indexes *i* and *j* denote the parent and the daughter vessels respectively and the function $f^{3D}(k_1,k_2)$ denotes the external pressure drop (or energy losses). In our case f^{3D} is the pressure drop of the 3D model.

$$f^{3D}{}_j(k_1, k_2) = k_1 Q_j + k_2 \mid Q_j \mid Q_j \tag{B.57}$$

k_1 and k_2 are the viscous and turbulent coefficients that should be adjusted according to the pressure drop between the inlet/outlet planes defined in the 3D model.

B.7.4.1 Personalized 3D reduced order model In our particular case, firstly we need to solve the 3D problem (real case). To estimate the coefficients k1 and k2 of the equation (B.57), at each time step t_n, we calculate and store the mean values of the flow and the pressure at the inlet and the outlet of our 3D domain. Using these values we choose k_1 and k_2 that minimizes the sum of squared pressure drop by least squares method. In this way we are able to capture the energy losses provoked by the geometry of our 3D model, and take into account in the 1D model.

B.8 Coupling 1-D and 0-D models

The existence and uniqueness of the solution of a coupled problem between the 0-D model system B.46 and the hyperbolic 1-D system B.35, has been proven by Formaggia [109] for a sufficiently small time so that the characteristic curve leaving the 1-D/0-D interface does not intersect with incoming characteristic curves. Numerically, the coupling problem between a 1-D domain and a 0-D model is established through the solution of a Riemann problem at the interface (Figure B11). An intermediate state (A^*, U^*) originates at time $t + \Delta t$ from the states (A_L, U_L) and (A_R, U_R) at time t. The state (A_L, U_L) corresponds to the end point of the 1-D domain, and (A_R, U_R) is a virtual state selected so that (A^*, U^*) satisfies the relation between A^* and U^* dictated by system B.46. The 1-D and 0-D variables at the interface are related through $q_{in} = A^*U^*$ and

$p_{in} = \frac{\beta}{A_0}(\sqrt{A^*} - \sqrt{A_0})$, and p_{out} is prescribed as a constant parameter that represents the pressure at which flow to the venous system ceases.

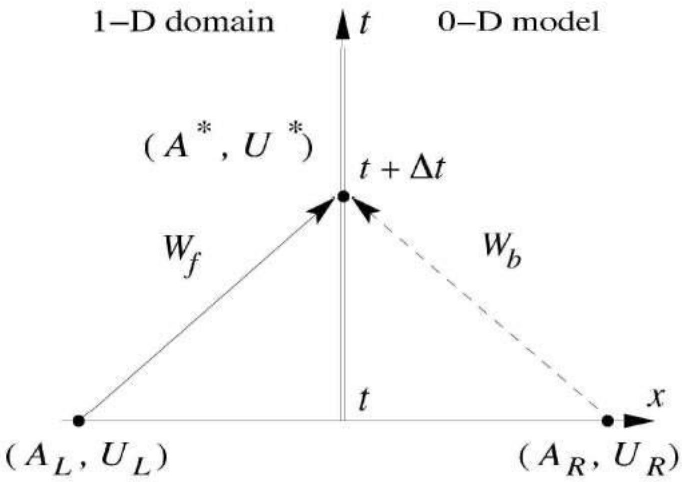

Figure B11: Coupling 1-D/0-D model.

According to the method of characteristics, if $G = 0$ equation B.35 leads to

$$W_1(A^*, U^*) = W_1(A_L, U_L) \tag{B.58}$$

$$W_2(A^*, U^*) = W_2(A_R, U_R) \tag{B.59}$$

Solving B.58 for A^* and U^* yields

$$A^* = \left[\sqrt{\frac{2\rho A_0}{\beta}} \frac{W_1(A_L, U_L) - W_2(A_R, U_R)}{8} + A_0^{\frac{1}{4}} \right]^4 \tag{B.60}$$

$$U^* = \frac{W_1(A_L, U_L) + W_2(A_R, U_R)}{2} \tag{B.61}$$

The 1-D outflow boundary condition is imposed by enforcing that either $U_R = U_L$, which reduces Eq. B.60 to

$$A_R = \left[2(A^*)^{\frac{1}{4}} - (A_L)^{\frac{1}{4}} \right]^4 \tag{B.62}$$

or $A_R = A_L$, which reduces Eq. B.61 to

$$U_R = 2U^* - U_L \tag{B.63}$$

B.8.1 Terminal resistance (R) model

This model simulates the peripheral circulation as a purely resistive load Rp, (R_{0D}=Rp, L_{0D}=0, C_{0D}= 0) (Figure B6) and in which the state (A^*, U^*) satisfies

$$A^*U^* = \frac{P(A^*) - p_{out}}{R_p} \tag{B.64}$$

Combining with B.46 we leads to a non-linear equation

$$\mathcal{F}(A^*) = R_p\left[\Big[U_L + 4c(A_L)\Big]A^* - 4c(A^*)A^*\right] - \frac{\beta}{A_0}\left(\sqrt{A^*} - \sqrt{A_0}\right) + p_{out} = 0 \tag{B.65}$$

which is solved using Newton-Raphson method, with the initial value of $A^* = A_L$. Once A^* has been obtained, U^* is calculated from Eq. B.61. If we consider both C and L equal to zero, we lead to the single terminal resistance model.

B.8.2 Three-element (RCR) Windkessel model

This model accounts for the resistance and the compliance of the peripheral vessels using the RCR Windkessel model, which accounts for the cumulative effects of all distal vessels (small arteries, arterioles and capillaries). The three-element Windkessel model consists of two resistances R_1 and R_2 and a capacitor C. According to Section B.8.1, we consider R_1 to let any incoming wave reach the CR_2 system without being reflected. Waves are reflected by the CR_2 system, which is governed by

$$C\frac{dP_c}{dt} = A^*U^* - \frac{p_c - p_{out}}{R_2} \tag{B.66}$$

The first resistance, R_1, is introduced in order to absorb the incoming waves and reduces artificial wave reflections. It satisfies

$$A^*U^* = \frac{P(A^*) - (p_c)^n}{R_1} \tag{B.67}$$

where $(p_C)^n$ is the pressure at C at the time step n. It is determining by solving at every time step n the first-order time discretisation of the Eq. B.66

$$p_C^n = p_C^{n-1} - \frac{\Delta t}{C}A^*U^* \tag{B.68}$$

The coupling is solved as for the R terminal resistance model, but with $p_{out} = p_c$ and $R_1 = R_p$

$$\mathcal{F}(A^*) = R_1\left[\Big[U_L + 4c(A_L)\Big]A^* - 4c(A^*)A^*\right] - \frac{\beta}{A_0}\left(\sqrt{A^*} - \sqrt{A_0}\right) + p_c = 0 \tag{B.69}$$

Again, once A^* is obtained by Netwon-Rapshon, we can proceed to calculated U^*, int his case from B.67.

B.9 Validation

A validation against in-vivo data is very difficult because some of the geometrical and elastic properties of the biological system are very complicated to measure. This is the reason because experimental replicas of the cardiovascular system to assess numerical tool are commonly used. To validate the 1D formulation implemented, the experimental model developed by Matthys et al. has been used [103] (1:1 silicone human arterial network). The silicone network is connected proximal to a pulsatile pump providing for a periodic input flow with the following settings: 70 bpm and a stroke volume of 70 ml, creating a mean pressure of approximately 100 $mmHg$ at the aortic root, these are typical values of a normal healthy person. Outflow boundary conditions were set of terminal resistance tubes connected to overflow reservoirs, creating a closed loop hydraulic system which induces a back pressure of 3.2 $mmHg$. A 65$-$35$\%$ water$-$glycerol mixture, with density ρ = 1050 $kg \cdot m^3$ and viscosity μ =5 $mPa \cdot s$, was used to simulate the blood. The elastic wall properties of the silicone sample have a constant Young's modulus of 1.2 MPa. The properties of the silicone network are summarize in table B2[103], as we can see the measurement report an interval of confidence, which unfortunately will affect the comparison between the experimental data and our results. For the simulations we have used the mean values show in the table B2.

Although the experimental set-up is only an approximation to the human systemic circulation, it is able to reproduce pulse waveforms with significant physiological features in the aortic vessels. Figure B13 shows some of the main physiological features of pulse pressure, velocity and flow rate described previously. We observe that the numerical solver is able to describe the peaking and steepening pulse pressure as we move away from the heart, and a reduction in amplitude of the flow with the distance from the heart.

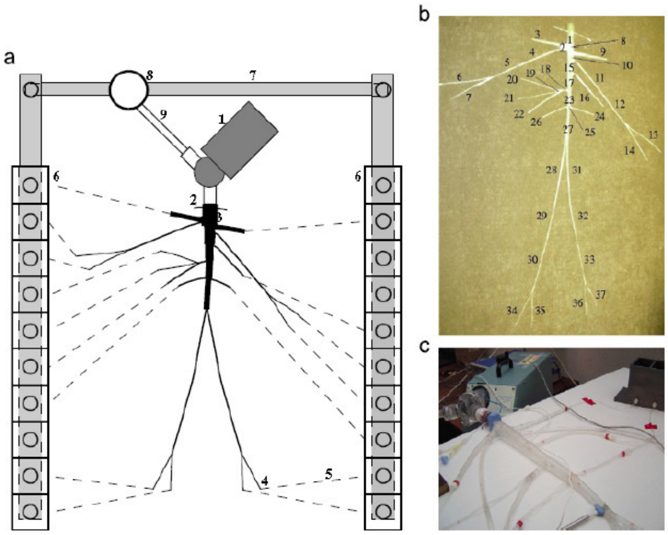

Figure B12: a) Plan view schematic of the hydraulic model. 1: Pump (left heart); 2: catheter access; 3: aortic valve; 4: peripheral resistance tube; 5: stiff plastic tubing (veins); 6: venous overflow; 7: venous return conduit; 8: buffering reservoir; 9: pulmonary veins. (b) Topology and references labels of the arteries simulated, whose properties are given in table B2. (c) Detail of the pump and the aorta.

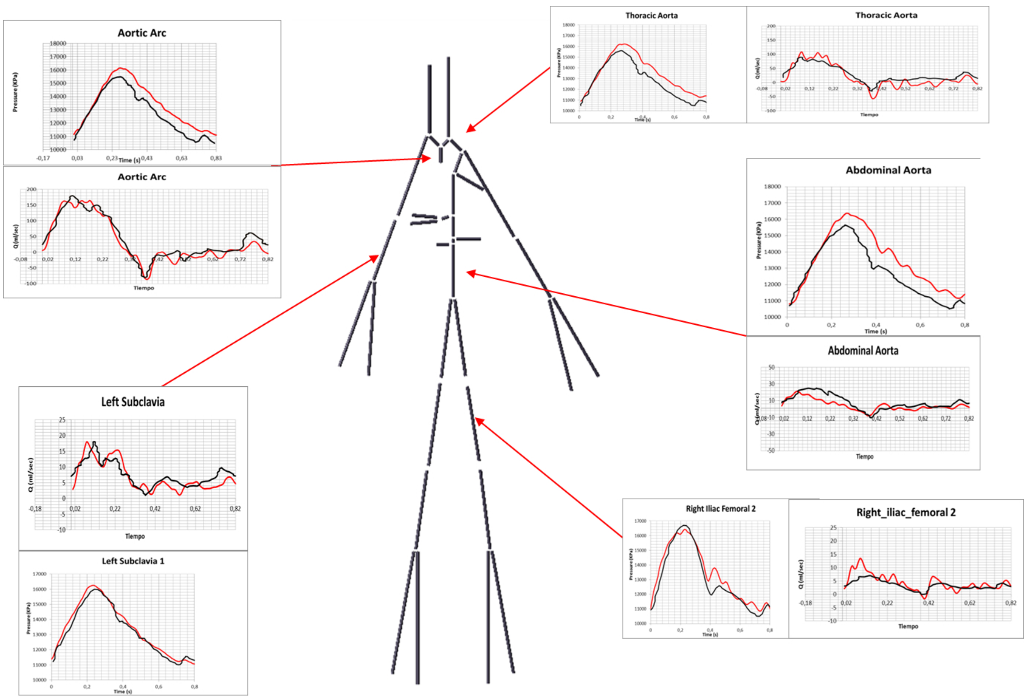

Figure B13: Simulated physiological(blank line) versus numerical results(red line) features of pressure and flow rate in difference section of the cardiovascular system.

n	Arterial segment	l [cm] ± 2.0%	r [cm] ± 3.5%	h [mm] ± 2.5%	c[ms^{-1}]	$R_p[GPa \cdot s \cdot m^{-3}]$
1.	Ascending Aorta	3.6	1.440	0.51	5.21	-
2.	Innonimate	2.8	1.100	0.35	4.89	-
3.	R. Carotid	14.5	0.537	0.28	6.35	2.67
4.	R. Subclavian I	21.8	0.436	0.27	6.87	-
5.	R. Subclavian II	16.5	0.334	0.16	6.00	-
6.	R. radial	23.5	0.207	0.15	6.78	3.92
7.	R. ulnar	17.7	0.210	0.21	8.81	3.24
8.	Aortic arch I	2.1	1.300	0.50	5.41	-
9.	L. Carotid	17.8	0.558	0.31	6.55	3.11
10.	Aortic arch II	2.9	1.250	0.41	4.98	-
11.	L. Subclavian I	22.7	0.442	0.22	6.21	-
12.	L. Subclavian II	17.5	0.339	0.17	6.26	-
13.	L. radial	24.5	0.207	0.21	8.84	3.74
14.	L. ulnar	1.91	0.207	0.16	7.77	3.77
15.	Thoracic Aorta I	5.6	1.180	0.43	5.29	-
16.	Intercostals	19.5	0.412	0.27	7.07	2.59
17.	Thoracic Aorta II	7.2	1.100	0.34	4.84	-
18.	Celiac I	3.8	0.397	0.20	6.20	-
19.	Celiac II	1.3	0.431	1.25	14.9	-
20.	Splenic	19.1	0.183	0.13	7.24	3.54
21.	Gastric	19.8	0.192	0.11	6.73	4.24
22.	Hepatic	18.6	0.331	0.21	6.95	3.75
23.	Abdominal Aorta I	6.2	0.926	0.33	5.19	-
24.	L. renal	12.0	0.259	0.19	7.39	3.46
25.	Abdominal Aorta II	7.0	0.790	0.35	5.83	-
26.	R. renal	11.8	0.255	0.16	6.95	3.45
27.	Abdominal Aorta III	10.4	0.780	0.30	5.41	-
28.	R. iliac-femoral I	20.5	0.390	0.21	6.47	-
29.	R. iliac-femoral II	21.6	0.338	0.15	5.89	-
30.	R. iliac-femoral III	20.6	0.231	0.20	8.04	-
31.	L. iliac-femoral I	20.1	0.402	0.20	6.19	-
32.	L. iliac-femoral II	19.5	0.334	0.16	6.11	-
33.	L. iliac-femoral III	20.7	0.226	0.13	6.67	-
34.	R. anterior tibial	16.3	0.155	0.15	8.47	5.16
35.	R. posterior tibial	15.1	0.153	0.12	7.73	5.65
36.	L. posterior tibial	14.9	0.158	0.11	7.23	4.59
37.	L. anterior tibial	12.6	0.156	0.10	7.01	3.16

Table B2: Properties of the 37 silicon vessels used in the in-vitro model. The interval of confidence of the geometrical measurements is indicated in the heading.

Appendix C

Python Script

C1 Phyton Script

```
# ------------------------------------------------------------
# SHEAR FORCE SECTION
# ------------------------------------------------------------
# Ok. For this routine, Shear Stress components is NOT GIVEN,
# and therefore calculated with the velocity gradient, fluid dynamic
# viscosity, and fluid shear routine therefore, we will have to do
# some pre-operations.
# ------------------------------------------------------------
# NOTE:
#   Using Solution (FAQ) "Fluid Forces, Drag Calculations in
#   EnSight" (#3), under "II. Shear Forces" steps a-i we have:
#
##################################################
#Procedure:
# a. in  the fluid  domain surrounding  the surface, define vx,
#   vy, vx, the velocity components, as three new scalars
# b. using the Grad operator in the variable calculator, compute the
#  gradient of each of  these components  in the  fluid, resulting
#  in new  gradient vectors of these components,
#  i.e. grad_vx, grad_vy, grad_vz
# c. these gradients must be mapped from the fluid onto the surface.
#  This is done either by using the Case Map feature in EnSight, or
#  creating an isosurface (velocity = 0.) or a clip plane that
#  corresponds to the surface of interest.
# d. Compute the fluid shear stress components using the FluidShear
#  function in the variable calculator and the mapped velocity gradients.
#  A value  for the fluid's dynamic viscosity must be provided.
#  This may also be a scalar variable.
# e. Create a fluid shear stress vector from these components using
#  the MakeVect function in the variable calculator.
# f. We need the tangential component of the fluid shear stress
```

```
#   vector in order to integrate the shear stress forces and moments.
#  The tangential  component may be  displayed by projecting
#  this from the Feature Detail Editor (Vector Arrows)
# g. Compute the  tangential component of the shear stress.
#  This is done using vector algebra.
#  First, create a surface normal vector variable using
#  the Normal function in the variable calculator.
#  Next, dot this with the shear stress vector, and multiply
#  this product by the surface normal vector.
#  This produces the normal component of the shear stress vector.
#     The tangential component is now computed by subtracting this normal
#     component from the shear stress vector, or Vt = V - Vn, where V
#     represents the shear stress vector.
# h. We now use the tangential component of the surface shear stress,
#     itself a vector, to compute a shear stress force vector,
#     simple by multiplying the  x/y/z components of the tangential
#     component of the shear stress by the incremental surface area.

# Part #1 is Fluid Domain
# Part #2 is the Wall of interest.
# vel_name is velocity vector
#  Begin
vel_name = "_VelocityVEC"
fluid_part_num = 2
surface_part_num = 1
viscosity = 3.5
tbegin=0
tend=4
num_steps = tend-tbegin+1 #added 1 for total num timesteps if start
#                                 from 0
ensight.part.select_begin(fluid_part_num)
ensight.variables.activate(vel_name)
#
# b. With ONLY fluid part(s) selected...
# Calculate a gradient vector from each component these velocity
#              components
ensight.part.select_begin(fluid_part_num)
#  Note gradient function requires additional step of extracting
#    vector components of velocity prior to calling it. You cannot,
#    for example, directly reference Velocity[X], and etc.
ensight.variables.evaluate("VelX = "+vel_name+"[X]")
ensight.variables.evaluate("VelY = "+vel_name+"[Y]")
ensight.variables.evaluate("VelZ = "+vel_name+"[Z]")
ensight.variables.evaluate("GradU = Grad(plist,VelX)")
ensight.variables.evaluate("GradV = Grad(plist,VelY)")
ensight.variables.evaluate("GradW = Grad(plist,VelZ)")
# c. Now select boundary part(s).
#    Map the 3 component gradient vectors from the fluid part(s)
```

```
#    to the surface part(s) via CaseMap using 1 case on itself.
#    Case Map CaseMap(2D or 3D part(s), case to map from, scalar/vector/
#    tensor). Finds the specified scalar, vector, or tensor variable
#    values for the specified part(s) from the indicated case.
ensight.part.select_begin(surface_part_num)
ensight.variables.evaluate("CaseMap_GradU = CaseMap(plist,1,GradU,1)")
ensight.variables.evaluate("CaseMap_GradV = CaseMap(plist,1,GradV,1)")
ensight.variables.evaluate("CaseMap_GradW = CaseMap(plist,1,GradW,1)")
#
# d. With boundary part(s) selected...
#    Compute the Fluid Shear stress (Tau) components
#    Compute the fluid shear stress components using the FluidShear
#    function in the variable calculator and the mapped velocity
#    gradients. A value for the fluid's  dynamic viscosity must
#    be provided. This may also be a scalar variable.
ensight.variables.evaluate("TauU = FluidShear(plist,CaseMap_GradU," +
str(viscosity) + ")")
ensight.variables.evaluate("TauV = FluidShear(plist,CaseMap_GradV," +
str(viscosity) + ")")
ensight.variables.evaluate("TauW = FluidShear(plist,CaseMap_GradW," +
str(viscosity) + ")")
#
# e. With boundary part(s) selected...
#    Create the fluid shear stress vector
#    Create a fluid shear stress vector from these components using
#    the MakeVect function in the variable calculator.
ensight.variables.evaluate("Tau = MakeVect(plist,TauU,TauV,TauW)")
#
# f. With boundary part(s) selected...
#    You can visually inspect the vector arrows of Tau on the boundary
#    part by creating these vector arrows and displaying the tangential
#    component
# g. With boundary part(s) selected...
#    Compute the decomposed tangential vector components of the Tau:
#    1. Computing the surface Normal vector on the boundary part(s)
ensight.variables.evaluate("Normal = Normal(plist)")
#    2. Creating the decomposed normal vector component of the Tau
#       vector: by dotting Tau with the surface Normal and
#       multiplying this scalar by the surface Normal again.
ensight.variables.evaluate("TauN = DOT(Tau,Normal)*Normal")
#    3. Creating the decomponed tangential vector component of the
#       Tau vector: by subtracting, i.e. TauT = Tau - TauN
ensight.variables.evaluate("TauT = Tau-TauN")
#
# h. With boundary part(s) selected...
#    Compute the element shear-stress force
#    1. Extract the 3 component scalars from TauT
ensight.variables.evaluate("TauTx = TauT[X]")
```

```
ensight.variables.evaluate("TauTy = TauT[Y]")
ensight.variables.evaluate("TauTz = TauT[Z]")
#    2. Compute the element area scalar
ensight.variables.evaluate("EleSize = EleSize(plist)")
#    3. Compute the tangential shear-stress component forces
ensight.variables.evaluate("FtauTx = TauTx*EleSize")
ensight.variables.evaluate("FtauTy = TauTy*EleSize")
ensight.variables.evaluate("FtauTz = TauTz*EleSize")
#
# i. With boundary part(s) selected...
# Now, sum up each shear-stress force component into constant values
ensight.variables.evaluate("sumFSX = StatMoment(plist,FtauTx,0)")
ensight.variables.evaluate("sumFSY = StatMoment(plist,FtauTy,0)")
ensight.variables.evaluate("sumFSZ = StatMoment(plist,FtauTz,0)")
# These three constant variables should contain the components of the
# shear stress. Grab the variables from EnSight to be able to store
# in a python register or print
sumFX=ensight.ensvariable("sumFX")
sumFY=ensight.ensvariable("sumFY")
sumFZ=ensight.ensvariable("sumFZ")
sumFSX=ensight.ensvariable("sumFSX")
sumFSY=ensight.ensvariable("sumFSY")
sumFSZ=ensight.ensvariable("sumFSZ")
# place these variables into storage array for printing
print "---------------- Force Summary --------------------"
print "                        Fx              Fy         Fz"
print "Shear Force      : ",sumFSX[0], sumFSY[0], sumFSZ[0]
ensight.part.select_begin(surface_part_num)
# WSS = TauU,TauV,TauW
#|WSS| =Mod_Tau
ensight.variables.evaluate("Mod_Tau=SQRT(TauU^2+TauV^2+TauW^2)")
ensight.variables.evaluate("I_Mod_WSS = TempMean(plist,Mod_Tau, "
+  str(tbegin) + " , " + str(tend) + ")")
ensight.variables.evaluate("I_WSS = TempMean(plist,Tau, "
+ str(tbegin) + " ,  " + str(tend) + ")")
ensight.variables.evaluate("Mod_I_WSS=SQRT(I_WSS[X]^2+I_WSS[Y]^2+
I_WSS[Z]^2)")
ensight.variables.evaluate("OSI=0.5*(1-(Mod_I_WSS/I_Mod_WSS))")
ensight.variables.evaluate("RRT = 1/((1-2*OSI)*Mod_I_WSS)")
ensight.variables.evaluate("ECAP = OSI/Mod_I_WSS")
```

Appendix

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