Modelling of the mechanobiological adaptation to vascular occlusion in the arterial tree

Bachelor’s Thesis

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Modelling of the mechanobiological adaptation to vascular occlusion in the arterial tree
1. Introduction
It is known that there are many cardiovascular diseases caused by the alterations in the blood vessels, that affect most of the world population. The knowledge of the mechanobiological behavior of blood vessels is used for understanding how cardiovascular diseases could affect the human body. So, by studying the growth and remodeling (G&R) of the arterial tree, it is possible to predict how these diseases will develop and consequently, how they can be treated or even prevented.

The human body naturally tries to find the optimum steady-state by changing either the production of the constituents of the arteries or the flow rate through blood vessels. This effect is the phenomenon that is going to be studied in this thesis and these three main factors have to be taken into account when reproducing the diseases’ effects: the so-called transmural pressure, the blood flow rate, and the biomechanics of the constituents which form the arterial wall. Therefore, through numerical simulations the variation of these factors can be predicted, although always with a reliability supported by experimental data.

1.1. Aim

The goal of the thesis is to simulate the G&R of arterial trees as they adapt to developing disease states. However, some diseases cannot be modelled due to their complexity and the limitations of the modelling outlined herein will be presented in very general terms.

First of all, it is explained why adaptation is a concern. Then, since the arterial wall is of interest in the adaptation, its inner structure will be briefly described as well as all the main types of arteries that exist in a human body. After this, the importance of considering the pressure inside blood vessels is highlighted since it is quite related to the flow rate as well. In addition, some risk factors of hypertension and hypotension are presented in order to introduce some diseases. Especially those related to the brain since the theoretical treatment is generally applicable, although the cerebral arterial tree is used as an important application example.

Subsequently, the theoretical model is explained step by step with a set of equations that define the growth and variation of the arterial wall composition. Hagen-Poiseille’s and Kirchhoff’s laws are used for defining the relation between the transmural pressure and the flow rate, and the direction of the latter inside blood vessels respectively. Thus, numerical experiments can follow with boundary conditions suitable for modelling vascular occlusion. Once, the setup fits the physiology of the brain, some already mentioned diseases can be tested to predict the behavior of the arterial tree when adaptation to vascular occlusion occurs.

1.2. Adaptation

The inner pressure and flow rate of blood vessels can change directly due to variations in the demands of the human body. For instance, when running, more oxygen is needed and in order to supply the required energy the heart must work harder as a pump, meaning higher flow rates and pressures inside blood vessels. Hence, variations in their geometry develop until attaining the new equilibrium with these new conditions. Then, at the moment of break the supply of oxygen starts to decrease, the inner pressure of the blood vessels decreases as well as their diameter, until reaching the old equilibrium again.

This simple example explains how the human body reacts to external factors. Voluntary or not, the human body always tries to attain an equilibrium, but always under its biological limits.
At longer time-scales, the so-called growth and remodeling (G&R) of arteries is a concern. Further, when exceeding the limits or due to imbalance in the control system of G&R, instability comes to the circulatory system and if this is not controlled, diseases may develop and they could even lead to death.

The best cure is prevention and one way is through simulations of mechanobiological adaptations. Combining knowledge from medicine and engineering, it is possible to study the G&R of arteries.

1.3. Arterial wall composition

Arteries are formed by three different layers in a cylindrical model. First, the innermost is called tunica intima, which is responsible for reducing the friction due to the viscosity of the blood and where the endothelial cells, which are responsible for sensing the changes in the wall shear stress, are located. Further, the tunica media which manages the vasoconstriction and vasodilatation of the artery and where elastin and smooth muscles are present. And finally the outermost, the tunica externa or adventitia, which gives the shape of the vessels and protects them from external structures, here are mainly the collagen fibers located. Figure 1.1 illustrates this inner structure.

![Figure 1.1: Structure of an artery with its layers and main constituents. Courtesy of Blausen Medical Communications.](image)

Depending on the location of the blood vessels in the human body, the proportion of these constituents is different as well as the arterial size.

Firstly, the elastic artery whose name comes from the biggest amount of elastic tissues in its walls, allows smoothing drop pressures out. The size of their diameter is found between 1-4 mm and they manage the distribution of the oxygenated blood throughout the body. Typically, the aorta belongs to this type of vessels but its diameter is the largest in the circulatory system (25
mm), since it is in charge of buffering the impulse of the heartbeats in the bloodstream (Wiedeman, 2016).

Secondly, in the muscular artery, mainly formed by smooth muscles cells and collagen, the control of the growth of the artery walls takes place. Due to its high stiffness, it can distribute the oxygenated blood to specific organs. Its size is typically between 0.2 and 1 mm (Wiedeman, 2016).

Finally, the arterioles are the smallest arteries and they are responsible of regulating the blood pressure by the vasoconstriction and vasodilation. Here occur the biggest pressure drops and the most sudden changes in the flow rate. These are generally 10 times smaller than the muscular ones (Wiedeman, 2016).

Additionally, there are more types of blood vessels in our body, such as capillaries, where the exchange of oxygen happens; and veins, responsible for giving back the deoxygenated blood to the heart. However, for simplification this will not concern this thesis.

1.4. Pressure and flow rate

Many of the cardiovascular diseases are caused by abrupt changes in pressure of the blood flow. Depending on how far the pressure is from the equilibrium, the effects might be worse for the blood circulation. Of course it is known that the pressure is very related to the flow rate due to fluid mechanics, but this issue will be discussed later.

The pressure is employed through the motion of the heart. The phenomenon in which the left ventricle of the heart contracts and the maximum force is applied in order to pump the oxygenated blood is called systole. On the contrary, when heart expands, its muscles relax (between two heartbeats) and refills the blood, here is diastole presented. See figure 1.2.

![Figure 1.2: Systole (left) and diastole (right) of the heart. Courtesy of Blausen Medical Communications.](image_url)

Hence, it is known by the World Health Organization (WHO) that the average of normal pressure is 120/80, where the first number belongs to the systolic pressure and the second to the diastolic pressure and this ratio is to be read as “120 over 80 mmHg”. These pressures are measured in the arm usually with a sphygmomanometer. It will be mentioned later on how these pressures depend on many factors such as age, gender or even food habits. Thus, cardiovascular diseases can be classified according to whether they are caused by high or low blood pressure, although also flow rate pulsates, but one has to consider the average at a long time-scale.
INTRODUCTION

Figure 1.3 illustrates when there is high blood pressure (hypertension) and low blood pressure (hypotension). Notice that the state hypertensive crisis is synonymous to a high probability of mortal diseases.

![Blood Pressure Levels](image)

*Figure 1.3: Pressure levels according to the diastolic and systolic pressure. Courtesy of American Heart Association.*

1.4.1 Risk factors of high blood pressure (hypertension)

Over the optimal average of blood pressure 120/80, high blood pressure is considered. Some risk factors that could increase the pressure are listed as follows.

- **Family**: stressful environmental cues and/or genetic perturbations.

- **Gender and age**: men are more likely to get high blood pressure rather than women at similar ages, although after the age of menopause, the blood pressure increases much more in women because of hormonal changes. (Reckelhoff, 2001).

- **Food habits**: processed foods, big amounts of glucose, salt or saturated/trans-fat lead to hypertension, as well as overweight and obesity (Lichtenstein, 2006).

- **Drugs and depressants**: a strong alcohol consumption or smoking causes more than 10% of the cardiovascular diseases (WHO), by increasing the blood coagulability and reducing the oxygen concentration in the blood and arterial stiffness in general terms.

1.4.2. Risk factors of low blood pressure (hypotension)

Below the optimal average of blood pressure of 120/80, low blood pressure is considered. Here are some risk factors presented.

- **Age and health**: a lack of blood demand to vital organs is typical among the elderly. Medications against high blood pressure can develop enough antibodies to suddenly create a drop in the blood pressure, specially for those who suffer from other diseases like Parkinson. Also, heart failure can cause a drop in the pressure immediately to lower levels in weakest immune systems (specially with allergic reactions) or when a
serious infection is presented (sepsis). Additionally, endocrine problems (thyroid or Addison’s disease which refers to an abnormal and slow heart rhythm) can also affect or even diabetes.

- **Food habits**: a lack of B12 vitamins in the diet (anemia) or dehydration.
- **Pregnancy**: when the embryo develops a larger amount of blood is required, leading to a higher demands of nutrients from the mother.

As one can see, there are many risk factors depending on the age, gender or food habits that increase or decrease the blood pressure. However, this thesis will be focused on certain cases in order to simplify, since there are some limitations to consider.

### 1.5. Certain diseases

It is interesting to see that not only diseases might be originated by instabilities and abnormal alterations in the flow rate inside blood vessels, but also from unusual changes in the proportion of the constituents in the arterial wall.

- **Thrombosis and thromboembolisms**

They appear when an amount of blood is uncommonly coagulated locally increasing the viscosity of the blood, so that it gets accumulated as a blood clot, partially or totally blocking the flow through the vessels.

Thrombosis is mainly caused by high blood pressure and there are up to three main causes: hypercoagulability, abnormal flow of the blood and eating disorder that leads to the so-called peripheral arterial disease shown in figure 1.4. For instance, when fats deposit on the wall arteries and do not allow the legs to get the enough amount of oxygen, amputation might be required. Also, there is another trigger of thrombosis and it has to do with endothelial cells when injuring them via infection, cerebral hypoxia (local shortage of oxygen supply), local turbulent flow (Abraham & Distler, 2007) or even inflammation (Varani & Ward, 1994), wall shear stresses might be sensed incorrectly, so that some necessary substances are either not consequently involved in the adaptation or proliferated causing an obstruction in the arteries.

*Figure 1.4: Peripheral arterial disease (embolism). Courtesy of Blausen Medical Communications.*
If the blood vessel is suddenly blocked, the supply of oxygen is drastically cut down, so the probability of having a heart attack or embolism is significantly increased. Particularly, the case that will be studied and what a main concern of this thesis is the (ischemic) stroke, which is exactly the same as a heart attack but here the blood flow towards the brain is cut off.

Also, thrombosis is directly linked to coronary artery disease, in which the artery walls get stiffer and narrower. So, when fats or other substances are deposited, the artery is not allowed to make the cavity wider in order to provide enough blood flow rate, meaning a gradual obstruction.

- Arteriosclerosis, arteriolosclerosis and atherosclerosis.

An endothelial dysfunction can be caused also by overactive sympathetic nervous system, and this lack of endothelial cells is the first step in the pathogenesis of atherosclerosis (Lee, Kritchevsky, & Parizaa, 1994). It is also known that prolonged or too much stress can cause an overactive response in the sympathetic nervous system. This atherosclerosis is responsible for the accumulation of a certain protein in the bloodstream that can eventually get encrusted in the arterial walls by adhesion (atheroma). As a result of this, the intima gets damaged, so that the artery cannot get rid of this protein and consequently fats are deposited obstructing the blood flow inside arteries partial or totally.

Moreover, an elastin dysfunction can be caused due to hypertension or high stresses in the arterial walls. As it has been seen before, smoking can decrease the amount of elastin of the arteries. If this happens in main arteries, this is known as arteriosclerosis, whereas if it takes place in the smallest arteries (arterioles), it is known as arteriolosclerosis.

- Anemia and polycythemia

The blood viscosity is directly related to the hematocrit, which is the percentage of red blood cells in the bloodstream. One has to remember that this type of cells is in charge of carrying the oxygen from the lungs to the tissues which require it. Usually in healthy people, the percentage of hematocrit is around 40-45% depending on the gender. However, the number of red blood cells can increase (polycythemia) or decrease (anemia) due to an abnormality in the function of the circulatory system, meaning an increase or decrease in the blood viscosity and consequently, a reduced blood flow rate and higher blood pressure. Also, polycythemia should not be confused with erythrocytosis, which means an unusual increase of the mass of the red blood cells, despite the fact that its effects are quite related to the blood viscosity as well.

- Normal aging and arrhythmia

It has been observed that a fragmentation of the elastin and an increase of the collagen start to show up in older adults because of the degeneration of the matrix of the arterial wall, basically due to aging. This is commonly known as sclerosis in the elderly and many times is quite related to hypertension. This stiffness is likely to narrow blood vessels (stenosis) and often leads to vascular occlusion.

Moreover, another common disease among the elderly is arrhythmia, which is having an abnormal heart rhythm. According to the American Heart Association (AHA), they may lead to worse effects when they are severe or long-lasting, because the heart may not be able to pump enough blood to the body.
• Ischemic cerebral disease and cerebral edema

When the cerebral flow rate is not enough in order to fulfill the oxygen and nutrients demands, the metabolism of the biological tissues degenerates, so that it may lead to the death of several cells (necrosis), a cerebral ischemic occurs. This happens when the average of the arterial pressure is under 60 mmHg. On the other hand, when the average pressure is over 140mmHg but the supply of blood flow keeps the same as in a healthy steady-state, blood might accumulate. This causes the so-called cerebral edema. Both these cerebral diseases are main symptoms of a prospective stroke (Shore, 2000).

• Fluctuating environment

In warmer environments, the vasodilatation of the artery is more active than the vasoconstriction, due to high temperatures. As said at very beginning, the human body always tries to find the equilibrium. Hence, the artery becomes wider in order to cover more surface, so that a good heat dissipation is carried out. On the contrary, vasoconstriction is more active in colder environments. Consequently, if there is a fluctuating environment, the arterial walls experience a quick change in their structure, meaning possible fractures in the matrices of elastin and collagen and a resulting mechanobiological adaptation.

• Calcification

It is well known that 99% of the ingested calcium is deposited in the bones and teeth (Horvai., 2015). Nevertheless, the rest is dissolved in the bloodstream. A disorder in the chemical process makes the calcium accumulate instead of being dissolved (Kumar, Abbas, & Aster, 2010). Then, it is usual that the stiffness of artery is increased, but it is only considered a problem when there is too much calcium accumulated or the artery is stiff enough not to allow the dilatation or constriction of itself, contributing as an important risk factor of cardiovascular diseases. Figure 1.5 shows cerebral calcifications in a 50-year-old woman from two different views of the brain.

![Figure 1.5: Cerebral calcification shown from above (left) and from the back (right) as white spots in radiographies of a 50-year-old woman. Courtesy of Hospital Severo Ochoa, Leganés, Madrid.](image-url)
• **Syndromes**

There are many syndromes and other aggressive diseases that are connected to an elastin deficiency, such as Marfan’s, emphysemas, Buschke-Ollendorff’s, Menkes’ and Williams’. The same for collagen deficiency, such as lupus, rheumatoid arthritis, scleroderma and temporal arthritis, which are very related to an abnormal functioning of the immune system (WHO).

All in all, it can be said that this amount of diseases motivates parametric studies with varying pressure, viscosity or even wall stiffness. So, as said under 1.1. Aims, it will be studied how adaptation takes place in the arterial tree when these diseases show up. This will be carried out by choosing a specific mechanical model according to physical laws suitable for what is going to be analyzed: the brain. However, this model can fit any other organ in the human body as long as the physiological setup agrees. Then, setting the boundary conditions of the problem, it will be possible to simulate some of the illnesses above as close to reality as possible by experimental data.

### 1.6. Limitations

When studying G&R of arteries, one has to considered the big amount of limitations that are involved. Also, this thesis does not go further from analysing the changes in the arterial tree when adapting to vascular occlusion.

First, as seen before, the mechanobiological behavior of the arterial wall is quite complex. Looking at the biggest artery present in the human body, the aorta cannot be modelled for instance. Its function is to soften the impulses of the bloodstream given by the heartbeats, so that every organ has a constant oxygenated blood flow rate. Despite being an elastic one, the shape of this artery is not easy to model because of its curvature. The pressure drop due to this effect will not be considered. Also, the aorta must be excluded from this study because only laminar flow is considered, and it has been shown that the bloodstream has enough speed to consider it turbulent. Additionally, the dynamics of the blood will be simplified. On one hand, the effects of the viscosity (gradients of velocity) are not considered near the wall. On the other hand, the blood will be assumed to be a Newtonian fluid (despite it is actually not) with a constant viscosity that does not depend on any temperature or shear rate. In fact, no body forces, such as gravity, will be considered neither their effect on the flow rate or the disposition of the artery in the human body.

Secondly, a simplification has been done in the arterial wall. As seen under 1.3. Arterial wall composition, there are up to three different layers with different compositions regarding elastin, collagen and smooth muscle cells mainly. So, here is only one layer considered as a compact one with a certain percentage of each of these three constituents. Moreover, uniformity in the arterial wall will be modelled as well as uniformity in the distribution of these components along the artery. So, there are identical mechanical properties for every artery of the tree.

Regarding the arterial tree itself, it will be assumed that the first node works as one located proximal to the heart, whereas the outermost works as a place in the brain where the exchange of oxygen occurs. Also, for simplification there is no artery crossing from one branch to another of the tree, owing to results from numerical experiments. As a result of this set-up, it was proved that the thickness of some other arteries became incredibly huge, because the blood always tries to find the optimal path and it could be possible that some branches get empty. Anyway, this
will be discussed in detail later. Also, although a stage of the pregnancy can be modelled (higher supply of flow rate for instance), its development is not possible to simulate, because of dealing with a fixed arterial tree and consequently, it will not be possible to create new branches from a determined section. Lastly, only two-dimensional trees will be taken into account, due to the fact that G&R of the artery is of interest, a three-dimensional tree makes the analysis more complex without any relevant information, despite its realism.

As for how the adaptation takes place, no real chemical process will be considered such as the release of NO from the endothelial cells in order to control vasodilatation or vasoconstriction.

Before finishing, it has been mentioned that many cardiovascular diseases are related to abnormal levels of pressures or compositions of the arterial wall. It is obvious that due to the limitations said so far, some diseases or conditions cannot be modelled. For example, without going any further, the brain is a piece of interest in this thesis. However, one of the most common abnormality here is the intracranial saccular aneurysm, whose effects are limited by the mechanics that will be used for modelling the arterial tree. Anyway, it will be discussed later how simulations might model certain diseases, because after all, the aim of this thesis is to predict the behavior of the arterial tree when an adaptation to vascular occlusion occurs.

Finally, the experimental data is another factor to take into consideration. It will be seen that there are many data from animals like mice or pigs, because of similarities to humans in their mechanobiological properties. Thus, it is challenging to give support to this work that will be through references.
2. Theory
2.1. Mechanical model

The model geometry of an artery used for G&R that will be used for studying the effect of G&R during vascular occlusion is shown in figure 2.1, which only depicts a segment of the final arterial tree.

![Figure 2.1: Geometry used for the mechanical model of the artery](image)

In order to properly formulate the growth law, the first step will be to assume a so-called constrained mixture mechanical model, meaning an incompressible blood vessel in the axial \((z)\) direction and symmetric deformation in the azimuthal \((\varphi)\), so that there are only possible changes in the wall thickness \((\hat{r})\) and lumen radius, according to the conservation of mass. In fact, the arterial wall works as a composite material whose components are the constituents themselves. Again, due to the same deformation in each mentioned direction, the constituents will be deformed equally. Hence, they are assumed to be incompressible and orthotropic materials aligned with the axis of the vessel wall. Moreover, as seen before, there is only one layer with all the constituents, which determine the mechanical properties of the blood vessel (based on finite elasticity) and how they contribute to the wall shear stress and to the G&R. Each one has a passive contribution to the principal stresses, and only the smooth muscle will in addition have an active contribution (Otero-Martínez, Otero-Pereiro, & González-Fernández, 2014).

Once the properties of the blood vessel are set, it is time to define the force equilibrium that has to agree with the physics. Due to the moving bloodstream, there will be a variation of inner pressure. So, the direction and rate of the flow will be determined by the pressure at the upstream and at the downstream. Thus, the flow will move from the higher to the lower pressure. Therefore, the radius of the vessel will depend indirectly on the flow rate and at the timescales of G&R, adaptation follows the physiological principle of minimum work: the necessary energy to keep the blood inside the vessels is optimized, so that the blood can overcome the hydrodynamic resistance of the vessel at a given flow rate (Murray, 1926), leading to what is so-called Murray’s law, in which the lumen radius can be related to the flow rate as shown in equation (1).

\[
\hat{r}_i^3 = Ku
\]
where \( u \) is the volumetric flow rate, \( \hat{r}_i \) the optimal internal or lumen radius and \( K \) a constant that is obtained using experiments (Sherman, 1981) and (Taber, Ng, Quesnel, Whatman, & Carmen, 2001).

As said before, endothelial cells give the first signal of deformation in the geometry of the blood vessel when sensing changes in the wall shear stress. This is an account of derivations found in the reference (Lindström, Stålhand, & Klarbing, 2016). The relation between wall shear stress and flow rate is presented in equation (2).

\[
\tau_w = \frac{4\mu u}{\pi r_i^3} \tag{2}
\]

where \( \tau_w \) is the wall shear stress, \( r_i \) the current lumen radius and \( \mu \) the blood viscosity. Equation (2) is valid as long the conditions agree with the Hagen-Poiseuille solution (later in detail) of laminar Newtonian flow through a circular tube. This being said, it is possible to create a relation between the optimal and current lumen radius if inserting (1) into (2).

\[
\frac{r_i}{\hat{r}_i} = \left( \frac{\hat{\tau}_w}{\tau_w} \right)^{\frac{1}{3}} ; \quad \hat{\tau}_w = \frac{4\mu}{\pi K}
\tag{3}
\]

Therefore, this ratio is of interest for G&R of the artery.

It is known that flow conditions include a certain pressure across the arterial wall, the so-called transmural pressure which cannot be used directly to G&R control. Instead, it affects the azimuthal stress. Thus, looking at the equilibrium of forces through the thickness (as seen in figure 2.2), one finds equation (4).

![Free-body-diagram](image)

*Figure 2.2: Free-body-diagram. Equilibrium of forces for a parallel cut to the axial direction, in which all longitudinal and radial stresses are omitted.*

\[
h\sigma_{\varphi} - r_i p_{\text{trans}} = 0
\tag{4}
\]

where \( h \) is the wall thickness, \( \sigma_{\varphi} \) is the circumferential or azimuthal stress, and \( p_{\text{trans}} \) the transmural pressure. Thus, the cross-sectional area \( A \) can be defined using (4) as follows:

\[
A = 2\pi r_i h = 2\pi \frac{p_{\text{trans}} r_i^2}{\sigma_{\varphi}}
\tag{5}
In the same way as written in equation (3), one can look for the optimal cross-sectional area, which is indeed, directly proportional to the squared radius.

\[
\frac{\hat{A}}{A} = \frac{\sigma_\phi r^2}{\sigma_\phi r_i^2} = \frac{\sigma_\phi (r_W)^2}{\sigma_\phi (r_W)_i^2} \tag{6}
\]

Equation (6) shows that now, the ratio \(\frac{\hat{A}}{A}\) is ready for G&R control in order to figure the direction of growth out. Here the hat-symbol represents optimal values.

As for the constituents, it is seen that their production rates will be proportional to a factor that depends on both wall shear and circumferential stress, the optimal (or homeostatic) and the current one (Lindström, Stålhand, & Klarbring, 2016). Nevertheless, equation (6) needs a certain realism due to all the simplifications mentioned before. Thus, in order to do that, one has to start considering the constrained mixture mechanical model again.

Despite considering the blood vessel as a thin-walled tube, now it is to be considered a thick-walled tube, so that deformations can be clearly defined. According to a cylindrical coordinates system, a certain point \((R, \Phi, Z)\) is translated into a new, deformed point \((r, \varphi, z)\). Thus, the respective deformations or stretches are:

\[
\lambda_r = \frac{\partial r}{\partial R}; \quad \lambda_\varphi = \frac{r}{R}; \quad \lambda_z = \kappa; \tag{7}
\]

where \(R_i < R < R_o\) represent the physical limits of the wall-thickness, \(r = r(R)\) and \(\kappa\) a constant. One has to remember that a conservation of volume is assumed, so equation (7) can be rearranged as:

\[
\lambda_r = \frac{1}{\lambda_\varphi \lambda_z} = \frac{R}{\kappa r} \tag{8}
\]

Through equation (8), one can take into account the contribution of each constituent and this is done by strain energy functions (Lindström, Satha, & Klarbring, 2015). As said before, this contribution is divided in two main ones: passive, when finite elastic and instantaneous radial deformations occur due to sudden changes in the wall stress; and active, when smooth muscles allow the vasoconstriction due to an increase of the azimuthal stress, since they are circumferentially orientated (Otero-Martínez, Otero-Pereiro, & González-Fernández, 2014). Finally, the artery responds with G&R of its wall and its composition too.

Thus, constitutive equations can be postulated for each constituent \(k\) as shown in the following expressions.

\[
\begin{align*}
\sigma^k_{\Phi\Phi} - \sigma^k_{\Phi r} &= \lambda_\varphi \frac{\partial \psi^k}{\partial \lambda_\varphi} \\
\sigma^k_{\varphi\varphi} - \sigma^k_{\varphi r} &= \lambda_z \frac{\partial \psi^k}{\partial \lambda_z} \\
\left(\sigma^m_{\Phi\Phi} + \sigma^m_{\varphi\varphi}\right) - \sigma^m_{\Phi r} &= \lambda_\varphi \left(\frac{\partial \psi^m}{\partial \lambda_\varphi} + \frac{\partial W}{\partial \lambda_\varphi}\right)
\end{align*} \tag{9}
\]

where the subscript \(p\) denotes the passive contribution and \(a\) the active one, the superscript \(k\) denotes the type of constituent, except for the last equation which belongs to the smooth muscles, denoted by the super-index \(m\) and the smooth muscle work density \(W\), which depends on the
growth history of the material (Lindström, Ståland, & Klarbing, 2016). Hence, the active stresses from of smooth muscle are as:

$$
\sigma_{ra}^m = \sigma_{za}^m = 0; \quad \sigma_{qa}^m = \lambda_{\varphi} \frac{\partial W}{\partial \lambda_{\varphi}}
$$

(10)

Once, all the contributions of each constituent is defined, the principal stresses in the blood vessel follows a mixing rule.

According to the mechanical equilibrium in the radial direction, analogue to equation (4),

$$
\frac{\partial \sigma_r}{\partial r} + \frac{\sigma_r - \sigma_{\varphi}}{r} = 0
$$

(11)

it is indirectly given that \( \sigma_r = -p_{\text{out}} \) when \( r = r(R_{\text{out}}) \) and \( \sigma_r = -p_{\text{trans}} - p_{\text{out}} \) when \( r = r(R_{\text{in}}) \).

Here \( p_{\text{out}} \) represents the pressure applied at the external surface of the artery. More details regarding this parameter will be given in the following chapter.

Thus, integrating equation (11), rearranging constitutive equations (9) and taking into account the mentioned mixing rule and the conservation of volume, the transmural pressure can be written as:

$$
p_{\text{trans}} = \frac{1}{2\pi \lambda_{\varphi} \lambda_{z} R_{i}^2} \frac{\partial}{\partial \lambda_{\varphi}} \left( \sum_k A^k \psi^k + A^m W \right)
$$

(12)

From geometry, it is possible to define the contribution of each constituent to the cross-sectional area as follows:

$$
A^k = 2\pi \phi^k R_i^2 \ln \frac{R_o}{R_i}
$$

(13)

where \( \phi^k \) is the fraction of each constituent. Now by the thin-walled assumption, equation (13) can be rearranged as follows:

$$
A^k \approx 2\pi \phi^k R_i H \approx \pi \phi^k (R_o^2 - R_i^2)
$$

(14)

since \( H = R_o - R_i \ll R_i \). Nevertheless, equation (12) gives two unknown stretches: azimuthal \( \lambda_{\varphi} \) and axial \( \lambda_z \). Hence, it could be assumed that the strain energy and smooth muscle work density are only functions of \( \lambda_{\varphi} \) (Takamizawa & Hayashi, 1987).

Last but not least, the growth dynamics of the living constituents of a blood vessel is of interest (Satha, Lindström, & Klarbing, 2014). The effective areas comprise two different concepts: an initial remainder of the constituents and what is left from the components formed at a certain time. This growth model can be seen in the following equation (Baek, Rajagopal, & Humphrey, 2007):

$$
A^k = A^k(0) Q^k(t) + \int_0^t a^k(\tau) q^k(t - \tau) d\tau, \quad t \geq 0
$$

(15)

where \( A^k(0) \) is the original effective area of the component \( k \), \( Q^k(t) \) is the fraction of the constituent \( k \) that was produced before an initial time \( t = 0 \) and remains at time \( t \), \( a^k(t) \) is the rate of production of effective area at time \( t \), and \( q^k(t) \) is a monotonically decreasing survival function so that \( q(0) = 1 \).
Additionally, it will be also assumed that this degradation of the constituents (15) will follow a Poisson process as shown in the following equation (16):

$$Q^k(t) = q^k(t) = e^{-\nu^k t}$$  \hspace{1cm} (16)

where \(\nu^k\) is a rate constant which captures the turnover of constituent \(k\) and whose value is approximately 1/80 per day for the collagen and smooth muscle. It is assumed that \(\nu^{\text{elastin}} = 0\). Moreover, \(a^k\) can be represented by the following formula (17),

$$a^k = A^k \phi^k \left[ 1 + \beta \left( \frac{A}{A^k} - 1 \right) \right]$$  \hspace{1cm} (17)

which includes the ratio from equation (6) and many other assumptions as for the effective areas of the constituents and their fractions in the arterial wall (Lindström, Stålahnd, & Klarbing, 2016), which is normally 22% for the collagen, 76% for smooth muscles and only 2% for elastin (Bæk, Rajagopal, & Humphrey, 2007) for the middle cerebral artery.

### 2.2. Hagen-Poiseuille law

A relation between the blood pressure and the flow rate of the bloodstream can be modelled by the Hagen-Poiseuille law due to the already mentioned simplifications: the blood flow through a cylinder of constant cross-sectional area is considered laminar, incompressible and uniformly viscous, i.e. Newtonian fluid (Vera Coello, Iglesias Estradé, & Sánchez Pérez, 2012). Thus, considering a cylindrical tube of fluid with radius \(r\) and thickness \(dr\); with length \(L\) in the chosen model, the shear force due to the blood viscosity can be calculated from an equilibrium of forces in the axial direction as:

$$F + p_1\pi r^2 - p_2\pi r^2 = 0$$  \hspace{1cm} (18)

where \(F\) is the shear force, \(p_1\) is the inner pressure upstream and \(p_2\) the inner pressure downstream. This force is directly proportional to the speed of the flow by a constant called viscosity in an analogous manner as in equation (2).

$$\frac{F}{A_L} = \mu \frac{dv}{dr}$$  \hspace{1cm} (19)

Since the lateral area where the shear force is applied is \(A_L = 2\pi rL\), it is possible to introduce (18) into (19) so:

$$2\pi rL\mu \frac{dv}{dr} + p_1\pi r^2 - p_2\pi r^2 = 0$$  \hspace{1cm} (20)

and isolating the differential speed:

$$dv = - \frac{\Delta p}{2L\mu} r dr, \ \Delta p = p_1 - p_2$$  \hspace{1cm} (21)

Thus, integrating equation (21) gives,
\[ v = -\frac{\Delta p}{4L\mu} r^2 + C \]  
\[ (22) \]
in which the constant can be determined by the condition that there is no speed \( v=0 \) at the wall, i.e. \( r = r_i \). So, equation (22) becomes:
\[ v = \frac{\Delta p}{4L\mu} (r_i^2 - r^2) \]  
\[ (23) \]
Once the blood flow rate is defined, it is possible to consider a differential volume flow rate as:
\[ du = 2\pi rvdr \]  
\[ (24) \]
Then, introducing (23) into (24) and integrating,
\[ u = \int_0^u du = \int_0^{r_i} 2\pi rdr \frac{\Delta p}{4L\mu} (r_i^2 - r^2) dr = \]  
\[ = \frac{\Delta p\pi r_i^4}{2L\mu} \int_0^{r_i} r(r_i^2 - r^2) dr = \frac{\Delta p\pi r_i^4}{8L\mu} \]  
\[ (25) \]
Hagen-Poiseuille law is obtained in equation (25). This law will establish the relation between the pressure and the flow rate throughout the whole arterial tree.

### 2.3. Kirchhoff’s law

An additional law will be used for properly building the model for the arterial tree and it is related to the flow rates of a bifurcation. This issue can be explained by two different ways: first, from a more complete point of view regarding the fluid mechanics and secondly, by a direct and simpler way according to Kirchhoff’s postulates.

First of all, it is known that from the divergence theorem (also commonly known as Gauss’s theorem), a conservation of mass equation in differential form can be expressed as:
\[ \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{u}) = g \]  
\[ (26) \]
where the first term belongs to the variation in the density \( \rho \) with respect to the time, the second term to the flow rate \( \vec{u} \) as a vector with all the components for each direction and eventually \( g \) the generation of flow per unit time, whose sign depends on whether it is referred to a source or a sink. Nevertheless, this Euler’s equation (26) can be simplified in our case due to two reasons. One is that the flow is incompressible, so density does not vary with respect to the time and consequently the first term is zero and the density of the second term is not affected by the gradient. And the second reason is that there is no generation, so \( g = 0 \). Hence, taking into account this, (26) becomes:
\[ \nabla \vec{u} = 0 \]  
\[ (27) \]
by which it is implied that all the flow rates that go into a certain differential volume must be the same as those flow rates that go away from it, so to say, conservation of mass and volume.

Secondly, the conservation of mass captured by Kirchhoff’s law can be formulated more directly. It is common to find this postulate in circuits or heat transfer because of the similarity of the functioning of an arterial tree if flow rates are considered as electric currents or heat flow respectively. Kirchhoff’s law says that at any node or junction the sum of the blood flowing into that node must be equal to the blood flowing out of that node. Somehow, it can be related perfectly to equation (25) and agree with the described fluid mechanics.

This being said, one can look at a volume control in a node $j$ from an specific configuration of arterial tree so that equation (27) can be explained by a representative example as follows, supported by figure 2.3:

\[ \sum_{i=1}^{n=4} u_i = u_{\text{out},j} \iff -u_1 + u_2 - u_3 - u_4 = 0 \]  

Figure 2.3: Volume control that consists of four different arteries from a determined configuration of an arterial tree that are connected among one another through their node $j$.

Here equation (27) becomes simplified as:

\[ \sum_{i=1}^{n=4} u_i = u_{\text{out},j} \iff -u_1 + u_2 - u_3 - u_4 = 0 \]  

where flow rates with a positive coefficient are defined outwards, whereas those with a negative coefficient are defined inwards. Notice that in this case, there is no flow rate that goes in/outwards directly from node $j$, as could happen in a sudden cut of the arterial network due to injury for instance.
3. **Numerical experiments**
In order to be able to build a model that fits with all the aforementioned equations described under 2. Theory, some considerations have been taken into account since numerical simulations have certain restrictions.

- **Wall shear stress**

  Since the viscosity is a desired parameter to be changed when simulating diseases related to it, such as anemia or polycythemia, equation (2) and (3) will change respectively to:

  \[ \tau_W = \frac{4f\mu_0u}{\pi r_f^2}; \quad \hat{\tau}_W = \frac{4\mu_0}{\pi K} \]

  where \( \mu = f\mu_0 \) for equation (2), since endothelial cells cannot sense changes in the blood viscosity directly, i.e. \( \tau_W \) is not to change. Thus, by setting \( \mu_0 \) to the initial value as a constant, \( f \) will be the factor that makes the cells believe that there is a change in the blood viscosity, so that variations in the blood flow rate, \( u \), will play the role instead of variations in the blood viscosity, \( \mu \). For instance, if anemia is presented, viscosity is reduced normally 10 times, so that \( \mu = 0.1\mu_0 \).

- **Boundary conditions**

  The arterial tree defined in the model is to have a certain number of boundary conditions, so that on one hand a supply of flow rate is required at the exists and on the other, the pressure of the starting node (close to the heart) is known as well. However, pressure drops will be solved for the numerical experiments, so this method can be applied for any human condition, either healthy or already ill.

  It is known that despite the fact that the brain represents just 2% of the total human body weight, it demands 20% of the total oxygen and around 15% of the cardiac output. Research done in (Lassen, 1959) showed that the local cerebral blood flow in a healthy man agrees with the following figure 3.1:

  ![Figure 3.1: Local cerebral blood flow and blood pressure in the middle-cerebral artery (Lassen, 1959)](image)

  Here, the local cerebral blood flow has different values according to the blood pressure, so that the whole brain has a blood consumption from 750 up to 900 ml/min, depending on the person.
Thus, for a normal person without any alteration in the blood flow, 50-55 ml/min will be the normal demand of blood as a boundary condition at the exits.

- **Pressures and flow rates**

Since pressures and flow rates at each pipe of the arterial tree are of interest in this thesis, a system of equations is to presented. Once the boundary conditions are known, i.e. the pressure at the entrance (heart) and the flow rates at the exits (different locations within the brain), through Hagen-Poiseuille law (25), it will be possible to calculate them.

In order to make a system of equations some matrices are first defined. Considering the fact that a segment of an artery is defined by two nodes and the pipe that connect them, the $\overline{A}$ matrix is described by the difference of two matrices $\overline{A}_{in}$, which represents from which pipe a blood flow comes to a node; and $\overline{A}_{out}$, which represents to which pipe a flow rate goes out from a certain node. The size of $\overline{A}$ is determined by the number of nodes and elements, so that $\overline{A}_{ij}$ is the element for node $i$ and pipe $j$. Thus, for a simple bifurcation illustrated in figure 3.2:

\[
\begin{pmatrix}
1 & p\text{ipe }j\text{ away from node }i \\
0 & otherwise
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 & p\text{ipe }j\text{ directed into node }i \\
0 & otherwise
\end{pmatrix}
\]

Thus, both matrices for the example showed above would be:

\[
\overline{A}_{in} = \begin{bmatrix}
0 & 0 & 0 \\
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix}; \quad \overline{A}_{out} = \begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & 1 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}
\]

Looking for instance at node 2, it can be seen that the pipe 1 is directed into it ($A_{in_{21}} = 1$) and pipes 2 and 3 are away from it ($A_{out_{22}} = A_{out_{32}} = 1$). Notice also that the complexity can be
increased for a larger tree, although the notation for nodes and pipes would be applied in a similar way. Hence, it is only needed to define which direction the flow rate should have in all the pipes, according to the boundary conditions imposed.

Then, once the matrix $\vec{A}$ is calculated, all the flow rates can be obtained if the boundary condition at the entrance is a flow rate as well. However, there is a known pressure here. So, equation (25) has to be considered for the system of equations. Consequently, it will be defined a matrix $\vec{R}$ by using equation (25):

$$
\vec{R} = \frac{\pi}{8\mu} \vec{D}
$$

(29)

where $\vec{D} = \text{diag}(\frac{r_1^4}{L_1}, \ldots, \frac{r_n^4}{L_n})$. In the experiments, all segments are assumed to have the same length, so to say $L_i = L$. This simplification will be explained later on by figure 3.5.

Therefore, the following set of equations can be solved for a tree with $n$ pipes and $m$ nodes: on one hand, the Kirchoff’s law or continuity equation (27); and on the other hand, the Hagen-Poiseuille law (25) for a volumetric flow rate $u$.

$$
[\vec{A}_{in} - \vec{A}_{out}] \cdot [u_1, \ldots, u_n]^T = [u_{out,1}, \ldots, u_{out,m}]^T
$$

(30)

$$
\frac{\Delta p_i \pi r_i^4}{8L\mu} = u_j \iff \frac{8L\mu}{\pi r_i^4} u_j - \Delta p_i = 0 \iff
\Rightarrow \vec{R}^{-1} \cdot [u_1, \ldots, u_n]^T - [\vec{A}_{in} - \vec{A}_{out}] \cdot [p_1, \ldots, p_m]^T = \vec{0}
$$

(31)

Notice that equation (30) uses an analogue notation as equation (28). Hence, rearranging Kirchoff’s (27) and Hagen-Poiseuille’s (25) in such a way one set of equations is solved for a general solution which includes pressures and flow rates at the same time, it is obtained (32) as,

$$
\vec{M} \cdot \vec{a} = \vec{a}_0 \rightarrow
[\vec{A}_{in} - \vec{A}_{out}] \vec{R}^{-1} (\vec{A}_{in} - \vec{A}_{out})^T \cdot \begin{bmatrix} u_1 \\ \vdots \\ u_n \\ p_1 \\ \vdots \\ p_m \end{bmatrix} = \begin{bmatrix} u_{out,1} \\ \vdots \\ u_{out,m} \end{bmatrix}
$$

(32)

where $\vec{a}$ is the solution which is being looking for and $\vec{a}_0$ the vector which includes the boundary conditions at each node. Notice again that the second part of the latter is a vector $\vec{0}$ with $n$ rows, because equation (27) is used.

However, it is known that there will be some problems of bad-scaling because pressure and flow rate do not have the same units. The reference pressure $p_{ref}$ is of the order of 10 kPa, whereas the latter $u_{ref}$ is of the order of 10 ml/min. Then, nondimensionalization is required and it will be done by using a new matrix, called $\vec{R}$, which includes both mentioned parameters as a reference in their diagonal, so that with the help of the square unit matrix $\vec{I}$,

$$
\vec{R} = \begin{bmatrix} I_{u_{ref}} & \vec{0} \\ \vec{0} & I_{p_{ref}} \end{bmatrix}
$$

(33)

where the index of $\vec{I}$ represents its size. Thus, introducing the inverse of $\vec{R}$ from (33) into (32), so that the parameters of the solution vector $\vec{a}$ are dimensionless,

$$
\vec{R}^{-1} \cdot \vec{M} \cdot (\vec{R} \cdot \vec{R}^{-1}) \cdot \vec{a} = \vec{R}^{-1} \cdot \vec{a}_0
$$

(34)
Notice that a unit matrix is introduced between $\bar{M}$ and $\bar{a}$ to agree with the units and end with the wanted nondimensionalization. Now, new vectors and matrices are defined as:

$$\bar{M}_r = \bar{R}^{-1} \cdot \bar{M} \cdot \bar{R}$$

$$\bar{a}_r = \bar{R}^{-1} \cdot \bar{a}$$

$$\bar{a}_0 = \bar{R}^{-1} \cdot \bar{a}_0$$

(35)

Then, one only has to set the initial boundary condition at the entrance, i.e. no pressure at all, in such a way that $\bar{M}_r$ is $[\bar{b}_1 = 1 \quad \bar{b}_{m-1}]$ and $\bar{a}_0 = 0$. It is possible to isolate the vector solution $\bar{a}$, so that the flow rates and pressures at the nodes can be obtained without any problem and eventually Murray’s law (1) can be used to get the target radii of every segment of the arterial tree.

However according to the theory explained before, the pressure at the external surface is not of interest, but the inner or transmural pressure. So, in order to get the transmural pressure for each pipe $i$ in an arterial tree of $n$ pipes, it is to be followed this set of equations:

$$p_{\text{out}} = \min \{p_1, \ldots, p_i, p_{i+1}, \ldots, p_n\} - p_0$$

$$p_{\text{trans}, i} = p_i - p_{\text{out}}$$

(36)

where the $p_0$ will be the pressure at pipe $i$ that determines whether there is high or low blood pressure, since it is defined as the difference in pressure across a membrane between two fluids.

Notice that every value of the pressure $p_i$ is calculated from $\bar{a}$. Next step then will be setting the homeostatic initial conditions for the arteries according to the theory (from equation (3) to (15)).

- **Vascular occlusion**

Finally, once the initial arterial tree is built, it is time to add the changes in the flow rate and pressures and simulate what is subject of this thesis, the vascular occlusion.

First of all, one has to consider that vascular occlusions in reality does not show up instantly. In fact, only after a while its first big effect appears. This said, despite the fact that it is possible to vary the demand of blood flow, the stability range of G&R simulations is very restricted, meaning some limitations in the differential equations governing G&R. For example, looking back at the simple bifurcation from figure 3.2, the upper and lower limits of the blood flow at the exists are respectively around 40% more and less of the initial value. Actually, even step-changes larger than 20% makes the system unstable. Therefore, larger gradual changes are only simulated.

Using the present model, it is not possible to simulate an instantaneous vascular occlusion itself, because it is only possible to simulate a 60% remainder of the initial blood flow that is passing through the obstructed arteries and in reality there is a much less blood flow rate left inside arteries after vascular occlusion. Actually, step changes in the flow rate are only 20% of the initial value (Lindström, Satha, & Klarbring, 2015) due to stability limitations. Then, this is to be simulated as required, so in order to do this an arctangent function with respect to the time might be used for instance as a good tool to solve this problem.

Later on, figure 3.3 illustrates the smooth transition from one value to another of the arctangent function, so that sudden changes can be avoided. Considering this, the function can
be modified in such a way that the flow rate goes from its initial value to a desired value by using the following factor of the flow rate dependence on time:

\[
u_{\text{factor}}(t) = \frac{1}{\pi} \cdot \left( \frac{\pi}{2} - \tan \left( \frac{t - t_d}{\tau} \right) \right)
\]  

(37)

where \( t_d \) controls when the sudden change takes place and \( \tau \) controls how fast the transition occurs, i.e. the smoothness.

Thus, it has been how useful this factor might be because it allows a gradual control of the decrease of the blood flow rate by changing the two aforementioned parameters, \( t_d \) and \( \tau \).

However, any value for each parameter does not give a feasible solution and their limits are thus studied below. A total occlusion is actually impossible to simulate due to instability of the differential equations, so it has been decided that the minimum and possible remaining blood flow will be 10% which is also more realistic. Hence, these parameters are to be related somehow with the duration of the numerical simulation in the following way:

\[
T = B \cdot C \cdot \tau
\]

\[
t_d = C \cdot \tau
\]

(38)

where \( T \) is the duration of the simulation, \( R \) the remaining fraction of the fluid flow after infinite time, and \( B \) and \( C \) the parameters that will be carefully changed. By fixing \( B = 10 \) and \( C = 4 \) to have a proper smoothness and delay time agreeing with the duration of the simulation, the bisection method was used to find the minimum \( \tau \) corresponding to each value of the remainder \( R \) for different configurations of arterial trees, so that the work stability limits can be defined. In addition, the properties of the fluid flow are those commonly found in a healthy person, i.e. 3 mm for each pipe segment’s length and \( 4 \cdot 10^4 \) Pas for the blood viscosity (Cote & Caron, 1989). The boundary conditions are similar between configurations. For example, in the simple artery with a blood demand of 20 ml/min, if there is a vascular occlusion in it the total flow rate must go down. However, in the other configurations with bifurcations, the vascular occlusion is located in one of the two main branches (as a result of the bifurcation) after the trunk. Then, the blood demand in the non-obstructed one increases as much as it decreases in the occluded one (39).
Numerical experiments

Before going any further it will be explained how the boundary conditions actually are simulated for a vascular occlusion. Using equation (36) as a factor to control the decrease of the flow rate, so that according to figure 3.6, it could be assumed a vascular occlusion in Pipe 2 that makes the demand of flow rate decreases until a certain percentage \( R \) in each exit. Thus, the following set of equations dependant on time agrees with the mentioned scenario:

\[
\begin{align*}
    u_{out,1}(t) &= u_{out,1}(0)(R + (1 - R)u_{factor}(t)) \\
    u_{out,2}(t) &= u_{out,2}(0)(R + (1 - R)u_{factor}(t)) \\
    u_{out,3}(t) &= u_{out,1}(0) + u_{out,3}(0) - u_{out,1}(t) \\
    u_{out,4}(t) &= u_{out,2}(0) + u_{out,4}(0) - u_{out,2}(t)
\end{align*}
\]

(39)

where a total symmetry in flow demands is considered.

It has been researched in rats how cerebral blood flow alterations take place when a cerebral thrombosis is induced by a specified method (kaolin-cephalin suspension after frontal and caudal ligation of the sagittal sinus) (Ungersböck, Heimann, & Kempski, 1993). Here it has been seen that the mean blood flow velocity is increased twice of the initial values in those rats who did not experience arterial damage and were able to adapt to the thrombosis. This being said, equation (39) agrees with this experiment, since the flow rate in branches which are not obstructed will be doubled.

\[\text{Figure 3.4: } \tau_{min} \text{[years] vs } R \text{ [-] for different configurations of arterial trees and their respective tendency equation defined next to them.}\]

Figure 3.4 illustrates that there is a clear exponential dependence of \( \tau_{min} \) on \( R \): the more flow rate is left the more abrupt can the change in the flow rate be. There are not many visible differences due to the complexity, that is the depth, of the arterial tree. It is seen that for those simpler configurations, \( \tau_{min} \) is increased up to 2 years more for the lowest \( R \) and on the other hand, \( \tau_{min} \) is decreased up to 0.2 years for the highest \( R \). Notice that there is no interest in investigating higher values for \( R \) than 0.6 since vascular occlusions are typically for \( R \) around 0.2 (Cote & Caron, 1989).
Other interesting aspect to take into account is how the length of the arterial segments affect the stability. It has also been investigated how this dependence changes for a configuration with double bifurcation as depicted in figure 3.7.

![Graph showing \( \tau_{\text{min}} \) vs \( R \)](image)

*Figure 3.5: \( \tau_{\text{min}} \) [years] vs \( R \) [-] for different lengths for arterial trees with double bifurcations and their respective dependence equation next to them.*

It has been found that the longer the segments of the arterial tree, the smaller \( \tau_{\text{min}} \) when the bigger \( R \). Notice that \( L \), which is the length of the pipe, has been taken for a mean value of 3 mm (Pai, Varma, & Kulkarni, 1981). Again, since small \( R \) are of interest in this thesis, it is seen there will be no visible differences in \( \tau_{\text{min}} \): less than a year for \( R = 0.1 \) and \( R = 0.2 \) between experiments. Therefore, this idea will be taken into account for the final configuration of study.

Finally, there is one more factor to take into consideration and that is the number of segments that a pipe consists of which does not change the final solution, so to say, convergence. This problem now is not to be confused with the previous case in which there were one segment per pipe whose length was changeable. This is done in a proper way by looking at the target radius of each segment of artery and comparing it to the initial or reference radius. A configuration with a double bifurcation will be used, as seen in figure 3.6:
To assess intermediate structures of the developing tree, the radius of each branch will be compared to its sub-branch in case of bifurcation. Also, when there is more than one segment per artery (named as pipe in figure 3.8) the segment that is the most distant to the heart will be chosen for the comparison. Hence, fixing $B = 10$ and $C = 4$ in order to achieve a smooth transition, $\mathbf{R} = 0.2$ is chosen (Cote & Caron, 1989) and the duration of the simulation is long enough ($\tau = 3$ years, far from the stability limit defined by figure 3.4) to be able to resolve changes according to figure 3.6.

![Image of arterial tree with double bifurcation](image)

**Figure 3.6:** Arterial tree with double bifurcation

![Graphs showing radius ratios](graphs)

**Figure 3.7:** Radii ratios for an arterial tree with single-segment and double bifurcation of Fig. 3.8.
Figure 3.7 shows how the radii, cross-sectional areas and circumferential stresses change when vascular occlusion of $R = 0.2$ arises in pipes 3 and 4 of figure 3.6 for different discretization levels, i.e. different number of segments per pipe of the arterial tree. Another experiment has been carried out doubling the number of segments per pipe and despite having more segments to compare, results from numerical simulations had negligible deviations. In fact, only tiny changes show up in those segments which are close to the exits, but even the difference in percentage is of the order of $10^4\%$. Later on, figure 3.8 shows this in detail and quantifies why a configuration with just one segment per pipe is enough.

Additionally, the average radius of the segments when they belong to the same pipe was studied. However, the values of the final radii do not change significantly comparing between each other, meaning division of pipes in multiple segments does not help to provide a more accurate solution. Actually, small changes in the arterial lumen radius show up due to the pressure drop from Hagen-Poiseuille’s law (25).

<table>
<thead>
<tr>
<th>Pipe</th>
<th>Radius SS [μm]</th>
<th>Difference DS [%]</th>
<th>Pressure SS [Pa]</th>
<th>Difference DS [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,541</td>
<td>-2.20E05</td>
<td>-7.23</td>
<td>3.75E04</td>
</tr>
<tr>
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<td>0.732</td>
<td>1.74E-05</td>
<td>-14.90</td>
<td>2.13E-04</td>
</tr>
<tr>
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<td>0.581</td>
<td>-3.16E-05</td>
<td>-32.24</td>
<td>1.47E-04</td>
</tr>
<tr>
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<td>-41.91</td>
<td>2.31E-04</td>
</tr>
<tr>
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<td>-2.05E-04</td>
<td>-11.00</td>
<td>7.52E-05</td>
</tr>
<tr>
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<td>1.176</td>
<td>-3.22E-05</td>
<td>-19.52</td>
<td>8.60E-05</td>
</tr>
<tr>
<td>7</td>
<td>1.176</td>
<td>-3.22E-05</td>
<td>-19.52</td>
<td>8.60E-05</td>
</tr>
</tbody>
</table>

*Figure 3.8: Radii and pressures data for an arterial tree with a single-segment (SS) compared to a double-segment one (DS). DS data is obtained by the average of both segments that form a segment. Both configurations agree with Fig. 3.6.*

Figure 3.8 quantifies errors between the single-segment (SS) and double-segment (DS) arterial tree. Looking at the differences in percentage of both parameters (radius and pressures of the pipes), it can be seen that they have values of the order of $10^4\%$. Thus, as a results of this, it will be perfectly assumed that convergence is reached by using just one segment per pipe, since a meaningful error would be several percents.

- **Murray’s law**

Furthermore, it will be interesting to study the difference between results from the numerical simulations and those which theoretically would come from Murray’s law when assuming instantaneous adaptation. Once all the radii and flow rates are updated to the target solution, new radii will be calculated by using Murray’s law (1) with the target flow rates in order to see that this law cannot be used for calculating the target flow rate with the lumen radius as input.
Figure 3.9: Radii ratios for an arterial tree with single-segment and double bifurcation of Fig. 3.8.

Figure 3.11 illustrates the differences mentioned above when a vascular occlusion develops in one of the main branches after the bifurcation. As seen in figure 3.7, only the most relevant pipes are shown. One can see the numbering of the pipes in figure 3.8. Despite the fact that Murray’s law follows the development of the experimental prediction, small differences come from some ratios: 1/2, 1/3, 1/5 and 1/7. Looking at this in detail, the largest differences have a value around 10 % (10^2 or even 10^3 smaller for the ratios between sub-branches 2/3 and 5/7). Even though this happens only in the transition, Murray’s law fits very well with the experiments at the very beginning and at the end of the simulation when comes stabilized with errors of almost 0.5%.
4. Discussions
In this section diseases will be simulated following the method previously described. Hence, the parameters that are of interest for this thesis are: the pressure of the outside of the artery, which controls whether there is a high or low blood pressure condition; the blood viscosity; the demand of cerebral blood flow and finally, the properties of the constituents of the arterial wall.

But without going any further, the setup already described has to be related somehow with the physiology of the brain, that is the main concern of this thesis. Since there are up to 17 different main branches in the middle cerebral arterial network (see figure 4.1), the setup which agrees with figure 3.8 will represent any local area in the brain that has a double bifurcation. As said in 3. Numerical experiments, the length of each pipe will be 3 mm and the blood viscosity for a healthy person is $4 \times 10^{-3}$ (Cote & Caron, 1989).

![Figure 4.1: The main 17 different arteries in the middle cerebral arterial network](Hacking & Jones, 2016).

According to figure 3.1, the blood demand at every exit will be 20 ml/min and the pressure of the outside of the artery, i.e. $p_o$, agreeing with (36), will be set to 90 mmHg. Then, it is possible to define what will be the initial and healthy state of this arterial tree in figure 4.1.

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![Figure 4.2: Radii, cross-sectional areas, azimuthal component stresses and drop pressures in every pipe of the initial (healthy) arterial tree, whose configuration follows Fig. 3.8.](

Eventually with figure 4.2, the setup is now related to the physiology of the brain.
• **Vascular occlusion (thrombosis)**

It is already well-known that vascular occlusion restricts the flow rate that goes through an artery totally or partially. Depending on its dimension, it makes the flow rate increase in those branches which do not have this obstruction, because the supply of blood is the same from the heart and there is a redundancy in the arterial tree. In this thesis, this is an object of huge interest and this is why its effects on the G&R of the arteries will be studied.

First of all, a vascular occlusion in the upper branch (pipe 5 in figure 3.8) of the arterial tree will be studied, meaning a reduction of blood flow rate on the other branch until a certain value. In (Ungersböck, Heimann, & Kempski, 1993) the local cerebral blood flow was measured during vascular occlusion and it was concluded that it was reduced until a 60% of the its steady-state value with variations of ±30%. Thus, these situations will be reproduced for the worst case ($\mathcal{R} = 0.3$) and the average case ($\mathcal{R} = 0.6$). Eventually, and as said before, the demands of cerebral blood flow rate will be set according to equation (39).

![Graph showing effects of vascular occlusion](image)

*Figure 4.3: Effects of vascular occlusion (thrombosis) on the lumen radius, cross-sectional area and circumferential stress component of the arterial wall for a configuration of the arterial tree similar to the presented in figure 3.8. Continuous lines represent an occlusion of $\mathcal{R} = 0.3$, whereas dashed lines represent a vascular occlusion of $\mathcal{R} = 0.6$.]*

Notice that in figure 4.3, results from pipe 2 are hidden behind pipe 3 in all the cases, because they follow the same behavior. It is clear that the more severe occlusion, the bigger changes in all these parameters. For $\mathcal{R} = 0.6$, the lumen radii, cross-sectional area and circumferential stress component is almost doubled compared to $\mathcal{R} = 0.3$.

Here, both lumen radii and cross-sectional area become stabilized at the same time ($t = 5\times10^6$ s), whereas the circumferential stress component after almost the double of time. For smaller $\mathcal{R}$, bigger changes happen later than those for higher $\mathcal{R}$, and consequently equilibrium is attained earlier.
• Calcification

One has to remember that with calcification the arterial wall becomes stiffer due to an enrichment of the calcium. It restricts the growth of the artery when it has to adapt to new conditions, so that the vasodilatation and vasoconstriction are inhibited. Thus in order to quantify the changes in the numerical experiments, it will be assumed a person with a certain calcification that doubles the stiffness of the collagen. Additionally, this person has a partial obstruction due to cholesterol in the upper branch of the arterial tree of figure 3.8 (pipe 2, 3 and 4) that decreases the supply of blood 50% of its initial value.

Figure 4.4: Effects of stiffer collagen (calcification) combined with vascular occlusion at different parts of the arterial tree regarding the lumen radius, cross-sectional area and circumferential stress component of the arterial wall. The number of the pipes agree with Fig. 3.8. Continued lines represent calcification and vascular occlusion, whereas dashed ones only the latter.

Figure 4.4 illustrates the differences when modifications in collagen stiffness are made. Notice also that the pipe 3 and 2 (hidden behind) have the same geometrical behavior since they belong to the branch where the vascular occlusion is located. Bigger peak circumferential stress components appear comparing to the previous figure 4.3 when the arteries have difficulties to dilate or contract, i.e. when calcification is presented. Nevertheless, the mechanobiological adaptation for the lumen radii and cross-sectional areas seem to work the same comparing to both situations, especially for the latter, although it is seen that arteries of the person with calcification are likely to adapt later than arteries of the person who does not have it. Notice also, that this example of calcification can be applied for a smoker, because it is known that the substances that cigarettes contain can adhere to the arterial walls in a similar way to the calcium that make its collagen stiffer.

As seen previously in the section about vascular occlusion (figure 4.3), bigger changes in radii and cross-sectional areas come to the branch which has the vascular occlusion itself (pipes 2, 3 and 4 in figure 3.8). On the contrary, higher circumferential stress components come to the branch that increase the flow rate that goes through it (pipes 5, 6 and 7 in figure 3.8). So this pattern is still followed for modifications in the properties of the collagen.
- **Ischemic cerebral disease and cerebral edema**

  Cerebral ischemia is a condition in which there is a local shortage in the supply of oxygen to the brain, basically achieved in the model by decreasing the prescribed flow rate, as explained at the beginning. Sometimes a blood clot makes the pressure increase around it (cerebral edema) and due to this, other areas nearby have to decrease the blood pressure (ischemia). When this effect is abnormally abrupt or blood vessels cannot adapt to it easily, necrosis shows up to these areas. Here a clear example of changes in the cerebral pressure is presented, and consequently can be simulated through numerical simulations, whose durations are 9.5 years in order to make sure that the new equilibrium with its target conditions is reached.

  First of all, ischemia will be treated as a great decrease in the blood pressure. Then, the parameter \( p_0 \) is to be increased. It is known from (Shore, 2000) that per each increase or decrease of 10 mmHg in this pressure, the mortality increases 20%. This experiment will be carried out for a general person with normal conditions and follow the same boundary conditions and arterial configuration from figure 3.8 said at the very beginning of this section.

As expected, the more pressure the higher the rate of adaptation shows up in the arterial wall according to figure 4.5, which represents a cerebral edema. Notice also that on one hand when \( p_0 \) changes, the whole arterial tree adapts to the alteration, meaning all the pipes increase their geometrical properties at the same time; and on the other that each level of pressure at the capillary represents a level of mortality: the blue line (100 mmHg) will represent a probability of death of 20%, whereas the black line plays the role of 100% of mortality, i.e. death.

This said, numerical simulations illustrate that ischemia can lead to death when the cross-sectional area (i.e. the wall thickness) reaches a 53% larger size and in last term, the circumferential stress component becomes 62% greater than the value of the steady-state.

Moreover, looking at the tendency of the parameters with respect to the time, it can be seen that the lumen radius adapts more slowly (a stabilized value is reached when \( t = 1.5 \times 10^6 \) s, i.e. 4.75 years), whereas the cross-sectional area (or even the azimuthal stress) adapts faster than the
radius (a stabilized value is reached when $t = 0.4 \times 10^5$ s, i.e. 1.25 years). This being said, if a radiography of the brain shows that the arteries from here present a thicker wall than normal, it could be said that a person is likely to have a cerebral edema.

![Graphs showing the effects of hypotension (ischemia) at different levels on the lumen radius, cross-sectional area, and circumferential stress component of the arterial wall. The number of the pipes agree with Fig. 3.8.](image)

Figure 4.6: Effects of hypotension (ischemia) at different levels on the lumen radius, cross-sectional area and circumferential stress component of the arterial wall. The number of the pipes agree with Fig. 3.8.

In an analogue way to the hypertension, low blood pressure is investigated in different levels representing steps of 20% of mortality, so that the blue line (80 mmHg) is the more harmless level whereas the black line (40 mmHg) illustrates the limit of the death. Thus, figure 4.6 represents the effect of the ischemia cerebral disease. Notice again that all the segments of the arterial tree behave geometrically exactly in the same way. Here, it is seen that the probability of stroke attains its 100% when the cross-sectional area is reduced 53% (in a symmetric way as compared to cerebral edema) and eventually, the target circumferential stress component is decreased almost until a value of 60% with respect to the initial value.

Moreover, it is seen again that the stabilizing effect is longer for the lumen radius and much shorter (same values for the time as seen in the cerebral edema) for the area and the azimuthal stress. Thus, it could be added that if a radiography of the brain shows that the arteries here display a small thickness, this person is likely to have ischemia and even a mortal stroke after a while.

Since vascular occlusion is of interest, two more simulations will be carried out for two different people: one with a cerebral edema with 80% mortality, i.e. $p_\theta = 50$ mmHg; and a second one with ischemia also with an 80% mortality, with $p_\theta = 130$ mmHg. Both cases are modelled with a vascular occlusion of $R = 0.3$, so that it could be seen how hypertension and hypotension affect to an unhealthy person.
Both figures 4.7 and 4.8 illustrate the overlap of hyper/hypotension with vascular occlusion. Notice again that the behavior of the second pipe is hidden behind the third one, i.e. following the same adaptation. Moreover, it is seen that the effect of changing $p_0$ is clearer at the very beginning of the simulation: one has to remember from 4.7 and 4.8 that the steady-state is attained for every parameter at $t = 1.5 \times 10^8$ s. However, vascular occlusion from figure 4.3 is somehow combined with this effect. For instance, the lumen radius does not change due to an initial change of pressure; however, the cross-sectional area is somehow displaced due to it: for cerebral edema
higher thickness of the arterial wall is reached (equal to the enlargement due to the pressure change, i.e. around 40%), whereas for cerebral ischemia the thickness is reduced (around 40% as well). Thus, from lumen radius could be difficult to distinguish if a person with a vascular occlusion has a cerebral edema or ischemia, but it might be clearer looking at the thickness or cross-sectional area of the arteries, which present bigger changes than just vascular occlusion. Eventually, the azimuthal stress component does not help to the diagnosis to see if edema or ischemia is presented in the patient. In any case, if this stress was measured somehow during the time, a small oscillation could be seen after the effect of the pressure change, although the maximum/minimum stress reached would be 10 times smaller than the reached at the very beginning of the simulation. Then, it can be concluded that the main cause for stress fluctuations is variation in blood pressure and not G&R.

- **Anemia and polycythemia**

Experiments done in transgenic mice (Vogel, et al., 2003) show that the blood viscosity in these animals increases up to 10000-fold that of water in those areas where the flow rate was lower and around 10 times more where the flow rate was higher. However, not only anemia and polycythemia are diseases that directly affect the fluid properties of the blood, but coronary heart diseases also do this.

In men at the age of 40 with anemia, the blood viscosity is reduced 10 times of its normal value, whereas in those with polycythemia it is increased 100 times more (Dintenfass, 1969). Since a new factor $f$ has been introduced in equation (2, the results from investigations in humans done by (Dintenfass, 1969) cannot be used due to numerical limitations, which will later on be explained more in detailed by the results from figure 4.10. Thus, for polycythemia $f = 1.5$ will be used, whereas for anemia $f = 0.65$, because they give the highest and lowest possible values for blood viscosity without jeopardizing numerical stability.

![Figure 4.9: Effects of high blood viscosity ($\mu_{new} = 1.\mu$, polycythemia) and low blood viscosity ($\mu_{new} = 0.65\mu$, anemia) on the the lumen radius, cross-sectional area and circumferential stress component of the arterial wall. The number of the pipes agree with those from figure 3.8.](image)
Figure 4.9 shows how high and low viscosity are involved in the adaptation of the arteries. Notice that all the pipes of the arterial tree behave in the same way. It can be seen that the lumen radius attains almost 15% of difference in both cases; the cross-sectional area reaches 30% and 25% of difference respectively for polycythemia and anemia; and the stress peak is almost 20% for both cases. Then, if one wants to predict properly anemia or polycythemia by looking at some radiographies, it is possible to see how big the thickness of the arterial wall is compared to the lumen radius, since the latter needs 6.3 years \( t = 2 \cdot 10^8 \text{ s} \) for reaching an equilibrium and the cross-sectional area needs less than the half \( t = 0.6 \cdot 10^3 \text{ s} \) for stabilizing itself. Hence, thicker walls points to polycythemia.

Comparing figures 4.9 and 4.5 it is almost impossible to distinguish if a patient suffers from edema or polycythemia just by looking at the cross-sectional area and lumen radius. Probably, it could be better to simply measure the viscosity from a blood sample. It may be worth mentioning that blood viscosity has a huge impact on G&R and this could have very important implications for the treatment of patients with vascular malformations, which are coupled to G&R.

Now in order to go a bit further and since vascular occlusion is of interest of this thesis, both of these diseases (polycythemia and anemia) will be combined with vascular occlusion to see their contribution, as did with ischemia and edema, in figure 4.7 and 4.8.

\[ \mu_{new} = 1.5 \mu, \text{ polycythemia} \]

\[ R = 0.3 \]

\[ \text{number of the pipes agree with those from figure 3.8} \]

Figure 4.10 shows the effect of combining the vascular occlusion of \( R = 0.3 \) and the hypercoagulability. Notice again that results from the second pipe (red line) are hidden behind those from the third one (green line). As expected, this figure 4.10 can be treated as the figure 4.2 displaced with the values from polycythemia from figure 4.9, so that the system is more sensitive specially for the lumen radius and cross-sectional area for every pipe, except the trunk (pipe 1). Both radii and sections become much bigger (actually almost the double), although the value of the stress in its first peak does not differ, from the case without the vascular occlusion.
Figure 4.11: Effects of low blood viscosity ($\mu_{new} = 0.63\mu$, anemia) and vascular occlusion of $R = 0.3$ on the lumen radius, cross-sectional area and circumferential stress component of the arterial wall. The number of the pipes agree with those from figure 3.8.

Figure 4.11 illustrates the effect a vascular occlusion of $R = 0.3$ with hypocoagulability. Notice again, that results from the pipe 2 (red line) are hidden behind the third pipe (green line). Here, there is an interesting effect comparing to the previous figure 4.10. The radius and practically the cross-sectional area of one of the pipes that does not suffer from occlusion (pipe 7) reach the same value as initially has. Therefore, it can be concluded that if radiographies of the arterial network show that some arteries are narrower and thinner and other remain with their same geometrical parameters as in the steady-state, this could imply a vascular occlusion and anemia at the same time. Eventually, this could be also a point to highlight if one wants to distinguish anemia (figure 4.11) from ischemia (figure 4.8) for instance.

However, one has to remember that the results from neither of figures 4.10 and 4.11 are not representing the real effects of anemia and polycythemia. In fact, they show the tendency of the lumen radius, cross-sectional area and circumferential stress when the blood viscosity is changed. As said before, when anemia is present, the blood viscosity is reduced even 100 times whereas the blood of a person with polycythemia is 10000-fold of the water (Vogel, et al., 2003). A numerical instability shows up when limits are exceeded (1.5 times for polycythemia and 0.65 times for anemia), meaning a huge impact on G&R can be expected in realistic cases of polycythemia or anemia.
5. Conclusions
CONCLUSIONS

Gathering all the numerical experiments and discussions from this thesis, many conclusions can be extracted.

It has been seen that this arterial tree is suitable for modelling the G&R of the arteries. By setting the proper boundary conditions it is possible to see how the adaptation takes place, i.e. how the arteries’ radius, section or circumferential component stress respond to changes in the blood pressure and flow rate changes according to some variations from diseases. The setup of this model is applicable to a cerebral arterial tree, but it can fit perfectly to any other organ’s physiology (for instance, arteries near the wrist) as long as it fulfills the requirements stated in the limitations section.

Even due to all the simplifications and limitations, the method used in this thesis is able to simulate diseases and even predict the behavior of the arterial tree during diseases and simultaneously vascular occlusion. It has been shown herein that Murry’s law (1) fits very well to the radii ratios obtained, because it follows the mechanobiological adaptation of the arteries as seen in figure 3.11. The convergence is always a concept that has to be considered in these simulations in order to have a criterion. It has been shown in figures 3.9 and 3.10 that only one segment or division per pipe is enough to attain sufficient accuracy. Of course, nodal pressures are not the same since they depend on the length of the segment but these differences are not great enough to distort the relevant data (figure 3.10). Lastly, since this arterial tree (figure 3.8) is a model consisting of 3 bifurcations, 4 exits and 1 entrance, a local effect can be modelled as well, so that it does not mean that the entrance has to be specifically the heart and the exists the final destination where the exchange of oxygen takes place. Again, it works as a generic arterial tree.

Under the section 4, Discussions, some diseases were successfully tested to quantify their effects on the lumen radius, cross-sectional area and circumferential stress component. Actually, here the main aim of this thesis is achieved, which is predicting the G&R response to arterial diseases. It was seen particularly in figure 4.5 and 4.6 that cerebral edema and ischemia disease could be diagnosed if looking at the adaptation of the thickness of the arterial wall throughout the time. For instance, if a radiography of the arterial networks shows that suddenly a local area of the tree presents thicker arteries, it is a clear signal that this subject is likely to have this kind of diseases. Furthermore, it can also be distinguished if this person has a vascular occlusion on the cerebral arterial tree, since the thickness is larger (edema) or smaller (ischemia) than normal. Actually, further investigations have been carried out regarding viscosity. Here it has been seen that one hand, variations only in the viscosity can be diagnosed by looking at the quick development of the thickness and lumen radius (arteries become thicker faster rather than the lumen radius bigger, in polycythemia from figure 4.9). On the other hand, when combining these diseases with vascular occlusion, it has been investigated that polycythemia could be more difficult to predict than anemia, since lumen radii and section are doubled in the first one, whereas for the latter some arteries keep the same size and other become narrower and thinner at the same time. In addition, it can also be concluded that there is a potentially huge impact of viscosity changes on G&R. In a person with hypercoagulability with vascular occlusion for example, some precautions have to be taken if this person takes some medications in order to lower the viscosity. Since polycythemia could mean an increase of 10000-fold of the water, a vascular occlusion could lead to bigger risks in the G&R of the arteries. Therefore, those people who suffer from abnormal levels of blood viscosity are to be given special attention if they need medication, because arteries could develop
thick walls with huge lumen radius and cause malformations in the arterial tree when it tries to attain a steady state.

Therefore, it can be concluded that the method used in this theoretical model can be used for simulating many diseases and dysfunctions at the same time: starting by changing basic parameters, such as supplies of blood flow rate or pressures; passing through fraction of the constituents, in such a way that all type of arteries can be modelled (elastic, muscular, etc); and ending up with changing the mechanical properties of the constituents themselves.

All in all, it will be said that despite the complexity of real arterial trees and the secondary effects from certain diseases, the method used in this thesis could be used as a simple tool for predicting essentially vascular diseases and their effects on the sensitivity of G&R to sudden changes in the flow rate. Of course, some improvements could be done in order to simulate other interesting cerebral diseases such as aneurysms, so that this thesis could be a much more powerful tool to further investigations in G&R of the arteries, so that better accuracy can be achieved. However, it is not to be forgotten that a theoretical model has been used in this thesis and one has to expect some differences from real experiments. Uncertainties in the physiological system are different from one subject to another. Since always, it has been difficult to make experiments with humans, and animals (owing to their similarities) have to be used instead. Even in this simple idea, there is some uncertainty because a cerebral network of a mouse will never behave as a human’s and this complexity is still nowadays an issue that needs answers. Nevertheless, analysing the G&R of the arteries deeply can lead not only to predict but also to help to plan treatment for certain diseases, but it is always a hard work since lots of variables are involved.
6. References


References


