Idealized Simulations of Vasoconstriction and Vasodilation of Cerebral Arteries based on Mechanotransduction

Shifteh Sherafat
Master’s Thesis, Spring 2016
The front page depicts a section of the root system of the exceptional Lie group $E_8$, projected into the plane. Lie groups were invented by the Norwegian mathematician Sophus Lie (1842–1899) to express symmetries in differential equations and today they play a central role in various parts of mathematics.
Acknowledgement

I want to thank my supervisors Simon Wolfgang Funke and Kent - Andre Mardal for supervising me this year. I want to thank Simula Research Laboratories for the resources made available to me, and for a wonderful working environment. I want to thank Magne Nordaas for helping us with the code for locating cells in FEniCS. I also want to thank the master class of 2016, my family, my grandmother, my friends and a special thanks goes to my brother Pedram for always motivating and supporting me, especially through injury this year. I could not have done it without his encouragement.

Shifteh Sherafat,
June 2016
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# Abbreviations

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<td>EC</td>
<td>Endothelial Cell</td>
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<td>CFD</td>
<td>Computational Fluid Dynamic</td>
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<td>WSS</td>
<td>Wall Shear Stress</td>
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<td>ICA</td>
<td>Intercranial Aneurysm</td>
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<tr>
<td>CA</td>
<td>Cerebral Aneurysm</td>
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<td>FEM</td>
<td>Finite Element Method</td>
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<td>SAH</td>
<td>Subarachnoid hemorrhage</td>
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<td>PDE</td>
<td>Partial Differential Equations</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>CT</td>
<td>Computer tomography</td>
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Chapter 1

Introduction

Diseases that involve the heart and the blood vessels are collectively termed cardiovascular diseases (CVDs) [1]. According to the World Health Organizations webpage an estimated 17 million people die of CVDs every year. Subarachnoid hemorrhage (SAH) is a particular CVD (a type of stroke) that accounts for 3% of all strokes. Furthermore, in four out of five cases it is caused by a rupture of an intracranial aneurysm (ICA) and the rate of mortality is about 50%. In addition one out of three patients that survive need permanent help in everyday life [2]. The method used for diagnosis today is computer tomography (CT) which is a technique that uses x-rays to produce detailed 3-dimensional cross section images, termed angiography when applied to arteries and veins. If SAH is detected, the patient is quickly prepared for surgery to prevent re-bleeding. In general in vivo experiments on the patient carry too much risk. Experiments using measuring devices might even disturb physiological functions [3].

The first to propose numerical simulation techniques in the study of aneurysms was Gonzales et al. (1992) [4]. Even though he concluded that "computer modeling based on angiography images could provide important information about aneurysm hemodynamics", it would take another ten years before more researchers became interested [4]. Even then the interest was not particularly great. In 2004 there were only 12 papers published on the subject of CFD combined with CVDs [4]. If we fast forward to today, a Google scholar search of "CFD" combined with "aneurysm" match over 4 000 papers. It is not as many compared to the research done on for example some proteins, however it is a start. CFD simulations of CVD is where mathematics and medicine intersect. Interdisciplinary cooperation still requires trust and respect for each field in itself. Dr. Kallmes expressed the desire for a "treat / not treat" [5], but saw this as a long shot because of the distrust in CFD simulations. That particular button is probably a long shot but CFD simulations nevertheless have much to offer, as explained by Cebral and Meng in [6] as a counterpoint to Dr. Kallmes.

At Simula Research Laboratories, the center of biomedical computing conducts clinically relevant research with CFD on aneurysms. Published studies on CFD of aneurysms include [7, 8, 9, 10, 11]. The studies involve the wall shear stress (WSS) however arterial walls are assumed rigid in most models. There is not much done in modelling the mechanotransduction of the vessel walls.

In this thesis we study the mechanotransduction in cerebral arteries. Mechanotransduction is how the hemodynamic factors of the blood flow, particularly the WSS, is translated into chemical signals in specialized cells called endothelial cells (ECs). In turn ECs cause the arteries to contract and relax. The literature on mechanotransduction is reviewed in Chapter 1. The
Chapter 1. Introduction

cellular and physiological system is very complex. In setting up the mathematical model the most significant components are kept. The necessary components are

1. A description of the material properties of the blood;
2. The geometry of the blood vessel and the interactions between the vessel wall and the fluid;
3. How the wall moves as a response;
4. The boundary condition on the artificial boundary of the computational domain.

This is discussed in Chapter 3 together with an in depth discussion of the simplifications that we made in making the model. At the end of this chapter we reach the Stokes equations for an incompressible Newtonian fluid with a penalty term to be solved over the entire computational domain \( \Omega \in \mathbb{R}^2 \):

\[
CK\vec{u} + \frac{1}{\rho} \nabla p - \frac{\mu}{\rho} \Delta \vec{u} = 0 \quad \text{in} \; \Omega
\]

\[
\nabla \cdot \vec{u} = 0 \quad \text{in} \; \Omega
\]

where \( \vec{u} : \Omega \to \mathbb{R}^2 \) is the velocity, \( p : \Omega \to \mathbb{R} \) is the pressure, \( K \) is the level - set function. The isocontours of \( K \) divide the computational domain into the arterial interior and the surrounding layer of smooth muscle cells which we call the solid region, and \( C \) is the inverse permeability constant that removes the fluid from the solid region. The equations are solved for the pressure \( p \) and the velocity \( \vec{u} \) and the WSS is computed.

The final model derived in Chapter 3, only has explicit solutions in particular cases, and have to be approximated. We have used the finite element method (FEM) to approximate the solutions of the Stokes problem. The method is explained in Chapter 4 and the discrete model is constructed in Chapter 5. Particular difficulties arise in this section. We discovered that the choice of the discretization space turned out to be very important for the isocontours of the level set function, \( K \). After the model had been discretized, we constructed a set of experiments to which we calculated the theoretical outcome in Chapter 6, and compared these to numerical simulations. The result of which can be found in Chapter 7. Finally we round off with the verification of the model in Chapter 8, and a discussion and our conclusions of the study in Chapter 9.
Medical background

The heart, the blood and the blood vessels are part of the circulatory system. The circulatory system provides the cells of the body with nutrients and remove the waste products through the blood flow which is transported through the blood vessels [12]. Humans have three types of blood vessels [1]: arteries, veins and capillaries. For an overview of the circulatory system and the functions of the different blood vessels the reader is referred to [1, 12, 13]. The focus of this project will be on cerebral arteries, which are arteries that ensures blood supply to the brain. In general arteries carry oxygen-rich blood to the tissues of the body and consist of three layers, see Figure 2.1:

- **Tunica intima**, the inner layer consisting of flat epithelial cells called the endothelium, which is the closest layer to the blood flow;
- **Tunica media**, the middle layer consisting of smooth muscle cells;
- **Tunica adventitia**, an outer layer consisting of connective tissue.

We have specifically focused on the contraction and relaxation based on the signals sent from the endothelial cells (ECs) to the layers of smooth muscle cells in response to the blood flow.

### 2.1 Endothelial cells

Endothelial cells send signals to the layer of smooth muscle cells that cause the cells to contract or relax thereby inducing vasoconstriction or vasodilation. Which is respectively the narrowing or widening of the blood vessel [12]. These two mechanisms are controlled by

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<tr>
<td>Tunica media</td>
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<td>Tunica intima:</td>
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<tr>
<td>Endothelium</td>
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<tr>
<td>Subendothelium</td>
</tr>
<tr>
<td>Basement membrane</td>
</tr>
<tr>
<td>Lumen</td>
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<td>Elastic lamina</td>
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**Figure 2.1:** Textbook illustration of the concentric layers of an artery. The Figure is taken from [1].
Chapter 2. Medical background

- Hormones secreted by glands;
- Parasympathetic nervous system, which send impulses to smooth muscle cells that stimulate constriction or relaxation;
- Locally by the release of metabolic by-products, such as lactic acid, carbon dioxide, $K^+$-ions and other substances released by nearby tissue.

However one of the most important factor was discovered by Robert Furchgott [12]. Furchgott proved that a substance released from the endothelial lining of the blood vessels played an important role in regulating blood vessel radius. His findings showed that endothelial cells released a factor that diffused to the layer of smooth muscle cells and caused the cells to relax, which in turn caused vasodilation. Later Louis Ignarro and Ferid Murad identified the unknown vasodilator as the gas nitric oxide (NO) [12]. Their efforts were awarded a Nobel prize in 1998. Independent studies in 1998 by Masashi Yanagisawa lead to the identification of a vasoconstrictor, a peptide he named endothelin [13]. Yanagisawa concluded that endothelin was released by endothelial cells in response to hormones in the blood stream and caused vasoconstriction. Further in vitro research showed that the release of endothelin was stimulated by low shear stress [14].

The cellular pathways in the ECs activated in response to the hemodynamic have since been mapped. The mechanism by which cells convert physical stimuli to electrochemical stimuli is termed mechanotransduction. Both in vitro and in vivo experiments have shown that ECs regulate their intracellular environment in response to shear stress to maintain vascular homeostasis [15], which is the process by which a closed system regulates its internal environment to minimize the effects of perturbations in the external environment. The mechanosensors activated by the shear stress included membranproteins such as receptor tyrosine kinase, integrins, G proteins and G - protein coupled receptors, calcium channels, intracellular junction proteins and membrane lipids [15], see Figure 2.2. The mechanical signal detected by the mechanosensors was conveyed through adaptor proteins which in turn triggered a cascade of signaling pathways that resulted in altered gene expression for proliferation, growth arrest, inflammation or anti-inflammation. The changes in the gene and protein expression in turn changed the behavior or structure of the ECs. For an in depth study of the signalling pathway the reader is referred to [15]. For an overview of cellular processes the reader is referred to [16] and for an introduction to molecular biology to [13].

Further experiments with different types of flow, that is laminar or turbulent, showed that the type of flow induces different responses in the ECs. In this project the blood flow is considered laminar, and the reader is referred to [8, 15, 17] for the ECs response to turbulent flow. However the algorithm developed in this project can be generalised to include turbulent flow as well.

2.2 Cerebral Arteries and Collateral enlargement

The brain is supplied with blood from the internal carotid arteries, which arise in the neck from the common carotid arteries and the vertebral arteries, see Figure 2.4. The terminal branches of the vertebral arteries lie in the subarachnoid space and join to form the basilar artery. The basilar artery goes into a cerebral arterial circle also called the circle of Willis [1], for a general illustration of the circle of Willis see Figure 2.4, however there are individual variations as well [18]. A feature of the cardiovascular circulation is collateral enlargement [19]. In the case
2.2 Cerebral Arteries and Collateral enlargement

Figure 2.2: A schematic illustration of mechanotransduction, from a signal is received to protein expression. The figure is taken from [15].

Figure 2.3: Basilar artery before and after the internal carotid arteries were blocked. Figure found in [8].

where the main artery becomes blocked, smaller arteries can increase in radius and provide a temporary route for the blood flow. Already in 1893 Thoma used chicken embryos to show that the pathway of the fastest velocity became the main artery, while the others with slow blood velocity atrophied [20]. In an attempt to test this Kamiya and Togawa [20] surgically constructed a shunt from the carotid artery to the external jugular vein in 12 dogs, where the flow was high in some parts and low in other. Six to eight months later they determined the radius of the artery. The results showed that arterial radius increased with increased flow and decrease with decreased flow, and furthermore a new baseline WSS level was achieved after which the artery size remained unchanged. In a similar experiment Meng and others [21] surgically closed both carotid arteries in 11 rabbits. The result was a 400 % increase of blood flow to the basilar artery. Over a week the basilar artery grew radially until the new baseline WSS was reached and then stopped growing, see Figure 2.3. Thus in both animal experiments the artery had grown until a new WSS level had been reached after which it stopped growing further. Scientists started to collect data from their own research and the literature and found that in most parts of the cardiovascular system there was a WSS level of 10 to 20 dyn/cm². This was called the uniform shear hypothesis. However a structure in the brain, called the circle of Willis, would show to be an exception [8].

An aneurysms life span can be divide into: genesis, enlargement and rupture [22]. A cerebral aneurysm is formed by a localized dilation of the intracranial arterial vessel wall, usually at the apex of the arterial bifurcation [23] when the mechanotransduction of the ECs fail to
suppress growth at that location [15]. In the literature there are two theories for the enlargement of an aneurysm [22]:

- High velocity flow induce enlargement. High WSS destroys the EC layer that initiates the modelling of the cell and degeneration of the cells. The cells grow out to a dilation, an aneurysm;

- Low velocity flow induce enlargement. Localized stagnation of the blood flow towards the wall on the site of an aneurysm results in dysfunction with the EC, which in turn results in enlargement.

The last stage of an aneurysms life is rupture. In the case where a CA ruptures it is called hemorrhagic stroke [1]. In a subarachnoid hemorrhage the artery ruptures and bleeds into the subarachnoid space. The risk of rupture in the literature is currently based on size [22]. However small aneurysms rupture too [24]. The reader is referred to [25] for a study on morphological and hemodynamic parameters that cause rupture and to [22] for a larger study with 210 patient specific CFD simulation for mapping of qualitative characteristics associated with rupture. The mortality rate by SAH is approximately 40 - 50 % [26]. This is attributed to brain damage caused by the initial hemorrhage. For an example of an aneurysm detected on an angiography, see Figure 2.5

Figure 2.4: Textbook illustrations from [1] of left: Arterial blood supply to the brain and right: The circle of Willis.
Figure 2.5: Angiography of cerebral arteries with an aneurysm as the spherical structure close to the center of the image. The image is taken from [27].
The Model

For our model development we model the blood flow using the Stokes equations. The Stokes equations are a system of partial differential equations, solved for the pressure and velocity. The Stokes equations are

\[
\frac{1}{\rho} \nabla p - \frac{\mu}{\rho} \Delta \vec{u} = 0, \\
\nabla \cdot \vec{u} = 0.
\]  

(3.1)

where \(\rho\) is the fluid density, \(\vec{u} = (u, v, w)\) the velocity, \(p\) the pressure and \(\mu\) the dynamic viscosity. The Stokes equations are derived using the principles of fluid mechanics which are based on the continuum hypothesis [28, 29]. According to the continuum hypothesis we can consider a material volume in the fluid [29]. The material volume contains a high number of fluid particles, so the density is definable [28]. Since the entire fluid consists of material volumes neighbouring one another with defined density, the density of the entire fluid can be determined.

Furthermore, the Stokes equations are applied over the domain, where one level-set of \(K\) represents a fluid region of the domain and the other level set the solid region of the domain. The zero level set \(K = 0\) represent the blood vessel interior and the level set \(K = 1\) represent the surrounding layer of smooth muscle cells, which we at times refer to as the solid region. The interface between the level sets can be considered the ECs and this is the place where the mechanotransduction occurs. Since the Stokes equations are applied over the entire domain a penalty term, \(CK\vec{u}\), is introduced to eliminate flow in the solid region, depending on the inverse permeability parameter, \(C\). The boundary movement is driven in terms of either sensitivity or optimality design criteria [30]. This model can be considered to have the former.

The Stokes flow on the zero isocontour produces WSS on the interface between the \(K = 0\) and \(K = 1\). We will construct an indicator function that evaluates the WSS, determines the mechanotransduction and updates the level-set function accordingly.

The aim of this section is to derive the Stokes equations, the WSS in the plane [28, 29, 31, 32, 33, 34], the level - set equation [35, 36, 37] and define all the functions needed to construct an algorithm for the mechanotransduction.
Chapter 3. The Model

3.1 Conservation of mass

Apart from nuclear reactions and realistic effects, mass is neither destroyed nor created [29]. We let an arbitrary material volume be

$$\Omega(t) \subset \mathbb{R}^3,$$  \hspace{1cm} (3.2)

and we assume \( \Omega(t) \) is a bounded domain in \( \mathbb{R}^3 \) with a smooth boundary. The boundary is denoted \( \partial \Omega \), and the surface \( S \). The material volume moves and deforms within the fluid flow. In a zone across the surface there is a rapid exchange of fluid particles [28], however the number of particles in the material volume can be considered constant. We let \( \rho \) be the density of the fluid in space and time, then that the conservation of mass can be expressed as

$$\frac{d}{dt} \int_{\Omega(t)} \rho \, d\Omega = 0$$  \hspace{1cm} (3.3)

We expand the time derivative using Reynolds transport theorem [29] to get

$$\int_{\Omega(t)} \frac{\partial \rho}{\partial t} \, d\Omega(t) + \int_{\partial \Omega(t)} \rho \, \vec{u} \cdot \vec{n} \, dS = 0$$  \hspace{1cm} (3.4)

Next we apply Gauss’ divergence theorem [29] to the surface integral

$$\int_{\Omega(t)} \frac{\partial \rho}{\partial t} \, d\Omega(t) + \int_{\Omega(t)} \nabla \cdot (\rho \, \vec{u}) \, d\Omega(t) = 0$$

$$\int_{\Omega(t)} \left( \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \, \vec{u}) \right) \, d\Omega(t) = 0$$  \hspace{1cm} (3.5)

The only possibility is that the integrand vanishes at every point in space, thus we have

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \, \vec{u}) = 0,$$  \hspace{1cm} (3.6)

which can be written out using vector calculus [28] to get

$$\frac{\partial \rho}{\partial t} + \nabla \rho \cdot \vec{u} + \rho \nabla \cdot \vec{u} = 0.$$  \hspace{1cm} (3.7)

we let the density be constant in time and space, then the fluid is termed incompressible. Hence

$$\nabla \cdot \vec{u} = 0.$$  \hspace{1cm} (3.8)

3.2 Conservation of momentum

Again we assume the material volume is \( \Omega(t) \) with surface area \( \partial \Omega(t) \) as in the previous section, then Newton’s second of motion for fluid flow can be stated as

$$\frac{d}{dt} \int_{\Omega(t)} \rho \vec{u} \, d\Omega(t) = \sum \vec{f}$$  \hspace{1cm} (3.9)
where $\rho \vec{u}$ is the momentum of the unit volume of the flowing fluid. The right hand side is the sum of the forces acting on the material volume. We apply Reynolds theorem to the left hand side to get

$$\frac{d}{dt} \int_{\Omega(t)} \rho \vec{u} d\Omega(t) = \int_{\Omega(t)} \frac{\partial \rho \vec{u}}{\partial t} d\Omega(t) + \int_{\partial\Omega(t)} \rho (\vec{u} \cdot \vec{n}) dS \quad (3.10)$$

Next we apply Gauss' theorem to get

$$= \int_{\Omega(t)} \rho \frac{\partial \vec{u}}{\partial t} + \int_{\Omega(t)} \rho \vec{u} \cdot \nabla \vec{u} + \rho \vec{u} (\nabla \cdot \vec{u}) d\Omega(t). \quad (3.11)$$

The fluid is considered incompressibility which leads to

$$\int_{\Omega(t)} \rho \frac{\partial \vec{u}}{\partial t} + \int_{\Omega(t)} \rho \vec{u} \cdot \nabla \vec{u} + \frac{\rho}{2} \Delta \vec{u} d\Omega(t). \quad (3.12)$$

The surface forces are given as the Cauchy stress tensor \[33, 34\]

$$\sigma(\vec{u}, p) = -pI + 2\mu \epsilon(\vec{u}) \quad (3.13)$$

where I is the identity matrix, and

$$\epsilon(\vec{u}) = \frac{1}{2} (\nabla \vec{u} + (\nabla \vec{u})^T). \quad (3.14)$$

is the symmetric strain tensor. We have thus assumed a linear relationship between the stress and the strain, i.e. the viscosity is Newtonian, which is the usual model for blood viscosity and the one used here. Studies on a large number of aneurysms have shown that there is not much to gain by using a complicated viscosity model as oppose to the Newtonian model \[7\]. The sum of the forces are

$$\sum \vec{f} = \int_{\Omega(t)} \vec{f}_V d\Omega(t) + \int_{\partial\Omega(t)} \vec{\sigma} \cdot \vec{n} dS \quad (3.15)$$

where $f_V$ is volume forces, e.g. gravitation. We insert for $\sigma$ from (3.13) in (3.15) and apply Gauss’ theorem

$$= \int_{\Omega(t)} \vec{f}_V d\Omega(t) + \int_{\partial\Omega(t)} \vec{\sigma} \cdot \vec{n} dS$$

$$= \int_{\Omega(t)} \vec{f}_V d\Omega(t) + \int_{\partial\Omega(t)} (-pI + 2\mu \epsilon(\vec{u})) \cdot \vec{n} dS \quad (3.16)$$

Combining equation (3.12) with (3.16) we have

$$\rho \frac{\partial \vec{u}}{\partial t} + \rho \vec{u} \cdot \nabla \vec{u} = \vec{f}_V - \nabla p + \mu \Delta \vec{u}. \quad (3.17)$$

Flow can be classified as: laminar, turbulent or transitional. We consider the flow to be laminar and stationary in time. In addition we let the viscous forces dominate and neglect the right hands side. Hence

$$0 = \vec{f}_V - \frac{1}{\rho} \nabla p + \frac{\mu}{\rho} \Delta \vec{u} \quad (3.18)$$
Chapter 3. The Model

Figure 3.1: Illustration of material volumes. Material volumes subjected to shear and caused to deform. Figure taken from [38].

Conceptually the model can be generalized to more complex types of flow. For simplicity we assume the volume forces to be zero, then the equations for the flow are

\[
\frac{1}{\rho} \nabla p - \frac{\mu}{\rho} \Delta \vec{u} = 0
\]

\[
\nabla \cdot \vec{u} = 0
\]

(3.19)

which are known as the Stokes equations for an incompressible Newtonian fluid flow. The problem is further simplified from a 3D domain to a 2D domain. The formula for the shear stress in the xy-plane becomes

\[
\tau_{x,y} = \mu \frac{1}{2} \left( \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right)
\]

(3.20)

The shear causes deformation without volume change, see Figure 3.1.

3.3 The level-set method

We want to evolve the interface. There are two ways of evolving the interface. One can either use a Lagrangian description which would require that we know the velocity on each point on the interface, this would be an infinite number. However in a discretized setting it would be a finite number of points, which is not the problematic part. The problem arises as soon as the elements are distorted as they might become for simulating an aneurysm. Topology changes might also be problematic. The Lagrangian description leads to Front tracking methods, for this the reader is referred to [35]. In the second description called the Eulerian description we have that

\[
\frac{d\vec{r}}{dt} = u(\vec{r}, t)
\]

(3.21)

where \(\vec{r} = x\vec{i} + y\vec{j} + z\vec{k}\) is the position in space. In the Eulerian description, it is supposed that each surface in the plane is the isocountour of a higher dimensional function. We have used the latter method, which is called the level-set method.
3.3 The level-set method

3.3.1 The basic idea

The basic idea of the level-set method is to define a scalar continuous function

$$\phi : \Omega \times [t_0, T] \rightarrow \mathbb{R}$$ (3.22)
on a domain $\Omega \subset \mathbb{R}^d$, $d = 2,3$, where $t_0$ is the start time and $T$ the end time, and where the zero level set of $\phi$

$$\Gamma(t) = \{ \vec{x} \in \Omega : \phi(\vec{x}, t) = 0 \}, t \in [t_0, t_f]$$ (3.23)
represents a time dependent discontinuity, such as for example an interface in an implicit way [37]. The sign of the level-set function $\phi = \phi(\cdot, t)$ can be used to divide the domain into subdomains

$$\Omega(t) = \Omega^+(t) \cup \Omega^-(t) \Gamma(t)$$ (3.24)
where $\vec{x} \in \Omega^+(t) \Leftrightarrow \phi(x, t) > 0$ and $\vec{x} \in \Omega^-(t) \Leftrightarrow \phi(x, t) < 0$, see Figure 3.2 for a visual illustration.

3.3.2 The level-set method in the model

In this project we define the level-set function as

$$K : \Omega \subset \mathbb{R}^3 \rightarrow \mathbb{R},$$ (3.25)
where $K$ represents the arterial vessel in $\mathbb{R}^3$. The isocontours of $K$ are defined such that

$$K(\vec{r}, t) = \begin{cases} 0, & \text{if } (x_0, y) - (R, 0) < (x, y) < (x_0, y) + (R, 0) \text{ (artery interior subdomain)} \\ 1, & \text{otherwise (solid subdomain),} \end{cases}$$ (3.26)
where $(x_0, t)$ is the center of the fluid domain and $R$ the radius of the blood vessel from the center, see Figure 3.3 for an overview. We want to evolve the interface over time. Thus by

Figure 3.2: An example of the basic idea of the level-set function $\phi$ and its zero isocontour. The image is taken from [39].
differentiating \( K(\vec{r}, t) \) as defined in (3.26) with respect to time we have that

\[
\frac{\partial K(\vec{r}, t)}{\partial t} = 0
\]

\[
\frac{\partial K(x(t), y(t), z(t), t)}{\partial t} = 0
\]

\[
\frac{\partial K}{\partial x} \frac{dx}{dt} + \frac{\partial K}{\partial y} \frac{dy}{dt} + \frac{\partial K}{\partial z} \frac{dz}{dt} + \frac{\partial K}{\partial t} = 0
\]

\[
\frac{\partial K}{\partial x} u + \frac{\partial K}{\partial y} v + \frac{\partial K}{\partial z} w + \frac{\partial K}{\partial t} = 0
\]

\[
\vec{u} \cdot \nabla K + \frac{\partial K}{\partial t} = 0.
\]  

Equation (3.27) is called the level set equation and was first introduced by Osher and Sethian [35], however it had been used in the combustion field under the name G-equation. In general the level set equation is a particular case of a Hamilton – Jacobi equation

\[
\frac{\partial K}{\partial t} + H(\nabla K) = 0,
\]  

where \( H \) is a function of space and time. During vasoconstriction of vasodilation the arterial walls move in the normal direction. Thus we move the interface in the normal direction. We decompose the velocity vector into the linear combination

\[
\vec{u} = u_n \vec{n} + u_t \vec{t},
\]  

where \( \vec{t} \) is the tangential unit vector and \( \vec{n} \) the normal unit vector. We insert (3.29) into the level set equation (3.27)

\[
\frac{\partial K}{\partial t} + \vec{u} \cdot \nabla K = 0,
\]

\[
\frac{\partial K}{\partial t} + (u_n \vec{n} + u_t \vec{t}) \cdot \nabla K = 0,
\]

\[
\frac{\partial K}{\partial t} + u_n \vec{n} \cdot \nabla K + u_t \vec{t} \cdot \nabla K = 0,
\]

\[
\frac{\partial K}{\partial t} + u_n \vec{n} \cdot \nabla K = 0,
\]  

where we have used that the tangential unit vector \( \vec{t} \) and the gradient to the level set function \( \nabla K \) are perpendicular. Furthermore, since \( \nabla K \) is normal to \( K \), the normal unit vector \( \vec{n} \) can be written as

\[
\vec{n} = \frac{\nabla K}{|\nabla K|},
\]  

which we insert into (3.30) such that

\[
\frac{\partial K}{\partial t} + u_n \vec{n} \cdot \nabla K = 0
\]

\[
\frac{\partial K}{\partial t} + u_n \frac{\nabla K}{|\nabla K|} \cdot \nabla K = 0
\]

\[
\frac{\partial K}{\partial t} + u_n |\nabla K| = 0
\]  

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3.4 The Stokes equations with penalty term

The factor driving the vasoconstriction and dilation is the mechanotransduction. The ECs "indicate" to the smooth muscle cell layer to constrict or dilate based on the WSS from the blood flow. Thus the evolution in the normal direction is to be determined by an indicator function over the WSS, \( \gamma(\tau_{x,y}) \), therefore we set

\[ u_n = \gamma(|\tau_{x,y}|). \]  

The indicator function is defined such that

\[ \gamma(|\tau_{x,y}|) = \begin{cases} < 0 & |\tau_{x,y}| \leq d_1, \\ > 0 & |\tau_{x,y}| \geq d_2, \\ 0 & \text{otherwise}, \end{cases} \]  

where \( d_1 \) and \( d_2 \) are chosen threshold values based on analytical calculations of the WSS for an explicit solution of the Stokes formulation, see Chapter 6. What the indicator function does is simply evaluate the shear from the Stokes flow at the interface. For \( \gamma(|\tau_{x,y}|) < 0 \) the interface moves in the direction of concavity, i.e. the blood vessel contracts and becomes narrower. When \( \gamma(|\tau_{x,y}|) < 0 \) the interface moves in the direction of convexity, i.e. the blood vessel expands and becomes wider. If the WSS fall between the threshold values nothing happens.

We use a Backward Euler scheme to discretize the temporal term in the level - set equation (3.27), letting the time step be one time unit. After the indicator function is calculated we advance isocontours in time in an iterative loop where the new isocontours are found by updating the old isocontours such that

\[ K^n = K^{n-1} - \Delta t \gamma(|\tau_{x,y}|)^{n-1} |\nabla K|^{n-1} \]  

for the time discretization

\[ 0 = t_0 < t_1 < \cdots < t_N = T, \]  

where \( t^{n+1} = t^n + \Delta t \). The new isocontours are processed by setting the new level - set as

\[ K_{1/2}(\vec{r}, t) = \begin{cases} 0, & (x, y) < \frac{1}{2}, \\ 1, & (x, y) \geq \frac{1}{2}. \end{cases} \]  

3.4 The Stokes equations with penalty term

We added a penalty term in the momentum equation of the Stokes equations. The penalty term is defined as

\[ \alpha(\vec{u}, K) = CK\vec{u}, \]  

where \( K \) is the level - set function defined in (3.26), \( C >> 0 \) is a high inverse permeability constant for the solid isocontour, and \( \vec{u} \) the velocity field determined by the Stokes equations. This allows us to solve the Stokes equations on the entire physical domain, and remove the flow from the solid isocontour depending on the parameter \( C \). The greater the value of \( C \), the less permeable the solid isocontour will be. The Stokes formulation with penalty term become

\[
\begin{align*}
\alpha(u, K) + \frac{1}{\rho} \nabla p - \frac{\mu}{\rho} \Delta \vec{u} &= 0 \\
\nabla \cdot \vec{u} &= 0
\end{align*}
\]
Figure 3.3: Sketch of the level set function top left: 3D blood vessel in blue and surrounding solid in pink, top right: horizontal plane cut through the blood vessel and the surrounding solid, bottom left: surface made from the cut, bottom right: surface in 1D where $x_0$ is the center and $R$ the radius.
3.5 Boundary conditions

The fluid is the zero isocontour of $K$, so the penalty term vanishes and the Stokes equations are recovered. Whereas, the solid isocontour is when $K(r, t) = 1$, then for $C \to \infty$ one obtains $\vec{u} \to 0$.

3.5 Boundary conditions

Finally we let the boundary conditions be

\begin{equation}
\vec{u} = \vec{g}, \quad \partial \Omega_D
\end{equation}

on the inlet and

\begin{equation}
\vec{u} = 0, \quad \partial \Omega_D
\end{equation}

on the walls. Thus the walls are considered smooth surfaces with the no-slip condition applied. This is enforced for $C \to \infty$. Which is not the case in a discretized setting, therefore there will be some leakage, this is discussed in Chapter 8. Both of the boundary conditions above are Dirichlet boundary conditions. On the outlet we applied

\begin{equation}
\frac{\partial u}{\partial n} - \rho n = 0, \quad \partial \Omega_N
\end{equation}

called the traction boundary condition.

We have assumed that the walls are smooth. However at the cellular level, the endothelial cells lining the arterial walls are wavy with hills and valleys [38]. The hills and valleys will form nonuniform shear stress even if the shear far above is uniform. The no slip condition applied on the cell membranes facing the blood is a simplification. However, as previously mentioned the technique we have developed can be generalized to a more complex blood flow model in the future.

3.6 Dimensions and units

The internal carotid artery (ICA) varies in men and women and in relation to the body and neck [40]. [40] reports a diameter of approximately 4.7 millimeters for women and approximately 5.1 millimetre in men, and [38] reports an internal diameter as 0.5 centimetre for canine. Therefore a centimetre - gram - second (cgs) system is used in this project. This is also the most common [33]. That is we use centimetre for length, gram for mass, and seconds for time, see Table 3.1. The derived units are in Table 3.2.

<table>
<thead>
<tr>
<th>Table 3.1: Base units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity</td>
</tr>
<tr>
<td>Length</td>
</tr>
<tr>
<td>Mass</td>
</tr>
<tr>
<td>Time</td>
</tr>
</tbody>
</table>

Table 3.2: Derived units
### 3.7 Hypothesis

The hypothesis is:

The mechanotransduction in cerebral arteries as a response to WSS that results in vasoconstriction and vasodilation, can be modeled by the letting the indicator function (3.34) represent the mechanotransduction in the ECs to the layer of smooth muscle cells.

The isocontour $K = 0$ represents the arterial interior, $K = 1$ represents the Tunica media, and the interface between the two represents the ECs in the Tunica intima. The blood is modelled using the Stokes equations with a penalty term. The WSS can be found using the Stokes equations and the interface of the level - sets. In an iterative process the level - sets will be updated representing vasoconstriction or dilation. For low WSS the level - sets will change so that the vessel shows vasoconstriction, and conversely for high WSS the level - sets will change so that the vessel shows vasodilation. In both cases a new baseline WSS level will be reached and the wall will stop moving.

The algorithm suggested will be, see Figure 3.4:

- Create a blood vessel geometry using the level - set equation $K$;
- Let Stokes flow enter the domain and vanish on the solid isocontour by means of the penalty term in the Stokes formulation;
- Calculate the shear;
- Find the interface between the two isocontours;
- Combine the interface and the shear to calculate the WSS;
- Update the indicator function based on the WSS and chosen threshold values;
- Update the isocontours $K^{n-1} \rightarrow K^n$ based on the indicator function;
- Post - process the isocontours by choosing the new level - set at a half.

### 3.8 Materials

The literature used in this project can be found in the bibliography. The implementation is written in the programming language Python, version 2.7.6, using the FEniCS library, particularly the DOLFIN interface, version 1.6.0 [41]. The open-source application, Paraview [42] have been used for visualization of the data sets, using the tutorial [43].
Figure 3.4: A schematic illustration of the algorithm.
4 Methods

4.1 The finite element method

In general the finite element method (FEM) is a method to numerically solve PDEs. In this project the FEM is used to approximate the solution of the Stokes equations. In this section the method will be emphasized by an implementation of a model problem in FEniCS [44]. For more information on FEniCS, we refer the reader to [44]. It will be most expedient to illustrate the FEM using a simple model problem. We will therefore use the Poisson equation. Let the spatial domain be denoted \( \Omega \) with boundary \( \partial \Omega \). The Poisson equation in the strong form with boundary conditions is

\[
-\nabla^2 u = f \quad \text{in } \Omega \\
u = g \quad \text{on } \partial \Omega_D \\
\frac{\partial u}{\partial n} = h \quad \text{on } \partial \Omega_N
\]  

(4.1)

where \( u \) is the solution and \( f \) is a known source term. The solution is known on the boundary as \( g \) on the Dirichlet part of the boundary \( \partial \Omega_D \) and the derivative of the solution in the normal direction as \( h(\vec{x}) \) on the Neumann part of the boundary \( \partial \Omega_N \). We define

\[
\Omega = [0,1] \times [0,1],
\partial \Omega_D = \{(0,y) \cup (1,y) \subset \partial \Omega\},
\partial \Omega_N = \{(x,0) \cup (x,1) \subset \partial \Omega\},
g(x,y) = 0,
h(x,y) = \sin(5x) \quad \text{and} 
\]

\[
f(x,y) = 100 \exp(-((x-0.5)^2 + (y-0.5)^2)/0.02)
\]  

(4.2)

To implement the mesh and the above functions, the DOLFIN library is imported. DOLFIN interfaces the Python code to the underlying C++ code in FEniCS.

```python
from dolfin import *
mesh = UnitSquareMesh(32, 32)
g = Constant(0.0)
h = Expression("\sin(5*x[0])")
f = Expression("100*exp(-((x[0] - 0.5)^2 + (x[1] - 0.5)^2)/0.02)")
```
Next, (4.1) is reformulated in the weak form, that is (4.1) is multiplied by a test function $v$ from the Hilbert space $H^1(\Omega)$, which is defined as

$$H^1(\Omega) = \{ u : \Omega \to \mathbb{R} : \int_{\Omega} ||u||^2 + ||\nabla||^2 dx < \infty \}. \quad (4.3)$$

A test function in this space is such that it is zero on the Dirichlet part of the boundary. The weak formulation of the Poisson problem becomes: Find $u \in H^1(\Omega)$ such that $\forall v \in H^1_0(\Omega)$

$$\int_{\Omega} \nabla u \cdot \nabla v \, dx - \int_{\partial\Omega} \frac{\partial u}{\partial n} v \, ds = \int_{\Omega} f v \, dx \quad (4.4)$$

where the boundary has been divided into the Dirichlet boundary and the Neumann boundary, where the integral on the Dirichlet part of the boundary vanished. So far the problem has been converted from the strong formulation to the weak formulation. The FEM defines finite dimensional function spaces as subspaces, $V_h \subset H^1(\Omega)$ and $\hat{V}_h \subset H^1_0(\Omega)$. The discrete FEM formulation follows directly from the weak formulation: Find $u_h \in V_h$ such that $\forall v \in \hat{V}_h$

$$\int_{\Omega} \nabla u_h \cdot \nabla v \, dx = \int_{\Omega} f v \, dx + \int_{\partial\Omega_N} h v \, ds. \quad (4.5)$$

We introduce the abstract notation

$$a(u, v) = L(v) \quad \forall v \in V, \quad (4.6)$$

where the left hand side, called the bilinear form is

$$a(u, v) = \int_{\Omega} \nabla u_h \cdot \nabla v \, dx \quad (4.7)$$

and the right hand side, the linear form is

$$L(v) = \int_{\Omega} f v \, dx + \int_{\partial\Omega_N} h v \, ds. \quad (4.8)$$

The finite dimensional function space, $V_h$ is constructed from a finite element. There is a rich set of finite element. For a nice overview we refer the reader to the femtable.org (the periodic table of finite elements). In this example we choose a function space with first order Lagrange elements, which we denote $CG_1$. We let $CG_1 = \{ \phi \}_{j=0}^N$ be the test functions and $\hat{CG}_1 = \{ \hat{\phi} \}_{i=0}^N$ the trial functions. Given this basis we make the ansatz that the approximate solution, $u_h$ is a linear combination of the basis functions, i.e.

$$u_h = \sum_{j=0}^N c_j \hat{\phi}_j. \quad (4.9)$$
4.1 The finite element method

The space of basis function, the test - and trial - functions are implemented as

```python
V = FunctionSpace(mesh, 'Lagrange', 1)
u = TrialFunction(V)
v = TestFunction(V)
```

Inserting this ansatz, the FEM variational form of the Poisson problem become

\[
\sum_{j=0}^{N} c_j \int_{\Omega} \nabla \phi_j \cdot \nabla \hat{\phi}_i \, dx = \int_{\Omega} f \hat{\phi}_i \, dx + \int_{\partial \Omega_N} h \hat{\phi}_i \, ds \quad \forall i = 0, \ldots, N.
\] (4.10)

The above equation gives a linear system of algebraic equation which can be written in the matrix form

\[
A_{ij} x_j = b_i,
\] (4.11)

where \( A \) is the discretized Laplace operator. After the Dirichlet boundary condition is incorporated, the system is solved by the linear algebra back - end of FEniCS. The way we can define the Dirichlet boundary condition is by the syntax

```python
def boundary(x):
    return x[0] < DOLFIN_EPS or x[0] > 1.0 - DOLFIN_EPS

g = Constant(0.0)
bc = DirichletBC(V, g, boundary)
```

After the system has been solved it can be plotted by the built - in VTK plotter or saved for post-processing by

```python
u = Function(V)
solve(a == L, u, bc)
plot(u, interactive = True)  # VTK plotter

# Save solution in VTK format
file = File('poisson.xdmf')
file << u
```

The result can be seen in Figure 4.1. After a solution is obtained the validity of the solution can be investigated.
Figure 4.1: FEM solution to the Poisson equation
The Discrete Model

We will discretize the model derived in Chapter 3 with the FEM described in Chapter 4. Let the computational domain denoted \( \Omega \) be a rectangle mesh with opposite corners in \((-1, -1)\) and \((1, 1)\) of \(N \times N\) elements, see Figure 5.1. The elements used are \((CG_2)^2\), \(CG_1\) and \(DG_1\), where \((CG_2)^2\) is the vector function space of second order Lagrange elements, \(CG_1\) is the scalar function space of first order Lagrange elements, and \(DG_1\) the scalar function space of first order discontinuous Lagrange elements. \((CG_2)^2\) and \(CG_1\) combined are termed the Taylor-Hood elements, which have been shown to be a good approximation for the solutions of the Stokes equation that does not lead to instabilities [45]. \(DG_1\) is used for the WSS, the interface and the indicator function, and \(CG_1\) for the isocontour of the level-set function \(K\). The implementation of the mesh and the finite elements in FEniCS is

\begin{verbatim}
N = 64
mesh = RectangleMesh(Point(-1.0,-1.0) ,Point( 1.0, 1.0), N, N, "right")

# Function spaces
V = VectorFunctionSpace(mesh, 'Lagrange', 2)
P = FunctionSpace(mesh, 'Lagrange', 1)
DG1 = FunctionSpace(mesh, 'DG',1)
\end{verbatim}

where traditionally the capital letters V and P have been used to denote the velocity function space and the pressure function space respectively.

### 5.1 The discrete level-set isocontours

Equation (3.26) introduced in Chapter 3, separates two regions in the computational domain. It is repeated here for reference

\[
K(\vec{r}, t) = \begin{cases} 
0, & (x_0 - R, y) < (x, y) < (x_0 + R, y) \\
1, & \text{otherwise}
\end{cases}
\]  

(5.1)

which has a jump discontinuity at the interface of the isocontours, at \((x_0 - R, y)\) and \((x_0 + R, y)\). To model the jump discontinuity exactly, one would have to represent \(K\) on a space of discontinuous functions. To avoid this, we have chosen to interpolate \(K\) on \(CG_1 = \text{span}\{L_j\}_{j=0}^N\). For
Figure 5.1: The computational domain, where (R,0) is the radius out from \((x_0, y)\), where \(x_0 = 0\). In FEniCS x is called \(x[0]\) and y, \(x[1]\).
5.2 The interface

\( K_h \in CG_1 \) to be the best approximation to \( K \) we demand that

\[
K_h(x_i, y_i) = K(x_i, y_i), \quad \text{for } i, j = 0, ..., N
\]  

such that

\[
K_h(x_i, y_i) = \sum_{j=0}^{N+1} K_j L_j(x_i, y_i) = K(x_i, y_i).
\]  

The result is the linear system

\[
\sum_{j=0}^{N} A_{i,j} K_j = b_i, \quad i = 0, ... N
\]  

where \( A_{i,j} = L_j(x_i, y_i) \) and \( b_i = K(x_i, y_i) \). Thus by the choice of space we have removed the jump discontinuity. The smeared \( K_h \) can be described as

\[
K(\vec{r}, t) = \begin{cases} 
0 & \text{when } (x_0 - R, y) \leq (x, y) \leq (x_0 + R, y) \\
L_0(x, y) & \text{when } (x_0 - R - \frac{1}{N}, y) < (x, y) < (x_0 - R, y) \\
L_1(x, y) & \text{when } (x_0 + R, y) < (x_0 + R + \frac{1}{N}, y) < (x, y) \\
1 & \text{otherwise}
\end{cases}
\]  

where \( N \) is the number of elements and \( L_0(x, y) \) and \( L_1(x, y) \) are basis functions in \( CG_1 \). For \( N \to \infty \), \( K_h \to K \), that is the smeared function approached the step function. In FEniCS, first the isocontour of \( K_h \) is created as an Expression then interpolated into \( CG_1 \):

```python
1 K = Expression("' \(( x[0] > (x0 - R) \&\& x[0] < (x0 + R ) ) ? 0.0 : 1.0'",
2 x0 = x0, R = R )
3 # create the surface
4 K_h = interpolate(K, P) # interpolate in a space of linear functions
```

Physically we have constructed a channel, see Figure 5.2.

5.2 The interface

In the discrete setting we call gradient of \( K_h \) the interface. As a consequence of \( K \) being approximated by \( CG_1 \) functions, \( |\nabla K| \) is suppose to be zero everywhere except on the elements between the isocontours. \( |\nabla K| \) of \( K_h \) is suppose to be a positive constant function over these elements, see Figure 5.3. Then \( |\nabla K| \) can be represented exactly in \( DG_0 \), which are piecewise constant basis function.

However, since the shear will be in \( DG_1 \), for consistency the interface is projected on to \( DG_1 \) as well. Since a constant function in \( DG_0 \) can be exactly reproduced by a linear combination of the basis functions of \( DG_1 \), since \( DG_0 \subset DG_1 \), we have used the space \( DG_1 \) for \( |\nabla K| \) as well. In other words, the constant function over the interface elements, are represented exact in \( DG_1 \) as well, see Figure 5.3. The formal formulation for the projection becomes: Find \( |\nabla K|_h \in DG_1 \) such that \( \forall v \in DG_1 \)

\[
\int_{\Omega} |\nabla K|_h v dx = \int_{\Omega} |\nabla K| v dx
\]  

(5.6)
Figure 5.2: The $K_h$ function. Top left: sketch of a 1D vertical cross section view. Top right: The channel where red represents the solid isocontour and blue the fluid isocontour on a mesh of $64 \times 64$ elements. Bottom: Isocontours of $K_h$ as viewed from above.

where

$$|\nabla K|_h = \sum_{j=0}^{N} d_j D_j$$

(5.7)

where $D_j$ and $D_i$ are discontinuous linear trial- and test- functions respectively. This gives the algebraic system

$$\sum_{j=0}^{N} d_j \int_{\Omega} D_j D_i dx = \int_{\Omega} |\nabla K| D_i dx$$

(5.8)

which can be written as

$$M_{i,j} x_j = b_i$$

(5.9)

where $M_{i,j} = \int_{\Omega} D_j D_i dx$, $x = d_j$ and $b_i = \int_{\Omega} |\nabla K| D_i dx$.

We would expect that $|\nabla K|_h \geq 0$, since

$$|\nabla K|_h = \sqrt{\nabla K_h \cdot \nabla K_h},$$

(5.10)

However, after interpolating $K$ on $CG_1$, zeros indicating fluid domain have been converted to negative machine precision zero. Therefore we first have to take the absolute value when ap-
5.3 Stokes flow through the channel

![1D sketch of how \( \nabla K_h \) and \( \nabla K_h \cdot \nabla K_h \) were supposed to look like based on our smearing of the isocontour interface.]

**Figure 5.3:** 1D sketch of how \( \nabla K_h \) and \( \nabla K_h \cdot \nabla K_h \) were supposed to look like based on our smearing of the isocontour interface.

![The interface represented on a mesh of 64 x 64 cells proximating (5.10):]

**Figure 5.4:** The interface represented on a mesh of 64 x 64 cells proximating (5.10):

```python
def interface(K):
    return sqrt(abs(grad(K)**2))  # inner product

wall_proj = project(interface, DG1)
```

As the number of elements increase the linear basis functions at the interface become steeper and the gradient becomes larger in magnitude. For the interface on a 64 \( \times \) 64 mesh, see Figure 5.4.

### 5.3 Stokes flow through the channel

In Chapter 3 we derived the equations for Stokes flow. The results was the classical form of the Stokes equation also called the **strong formulation**. We wish to convert the equations to the **weak (modern) formulation** and apply the FEM, see Chapter 4. This is achieved by multiplying with test functions \( \vec{v} \) and \( q \) and integrating over the domain, \( \Omega \). The weak
formulation becomes: Find $\vec{u} \in (H^1(\Omega))^2$ and $p \in L^2(\Omega)$ such that

$$
\int_{\Omega} CK_h \vec{u} \cdot \vec{v} dx + \int_{\Omega} \frac{1}{\rho} \nabla \cdot \vec{v} p dx + \int_{\Omega} \nabla \vec{u} : \nabla \vec{v} dx = 0 \quad \forall \vec{v} \in H^1_0(\Omega)
$$

$$
\int_{\Omega} \nabla \cdot \vec{u} q = 0 \quad \forall q \in L^2(\Omega)
$$

(5.11)

where we have used that traction boundary condition and that the test functions vanish on the Dirichlet boundary. And where $L^2(\Omega)$ is

$$
L^2(\Omega) = \{q : \Omega \rightarrow \mathbb{R} : \int_{\Omega} q dx < 0\}.
$$

(5.12)

The FEM formulation follows directly from the weak formulation: Find $u_h \in V_h^2 \subset (H^1(\Omega))^2$ and $p_h \in P_h \subset L^2(\Omega)$ such that

$$
\int_{\Omega} CK_h \vec{u}_h \cdot \vec{v}_h dx + \int_{\Omega} \frac{1}{\rho} \nabla \cdot \vec{v}_h p_h dx + \int_{\Omega} \nabla \vec{u}_h : \nabla \vec{v}_h dx = 0, \quad \forall \vec{v}_h \in \hat{V}_h, g
$$

$$
\int_{\Omega} \nabla \cdot \vec{u}_h q_h = 0, \quad \forall q_h \in \hat{P}_h
$$

(5.13)

We let the approximation to the velocity be $u_h = \sum_{j=0}^N U_j N_j$ and the approximation to the pressure be $p_h = \sum_{j=0}^N P_j L_j$. Letting the test functions be $\vec{v}_h = N_i$ for the velocity and $q_h = L_i$ for the pressure, we get

$$
CK_h \sum_{j=0}^N U_j \int_{\Omega} N_j \cdot N_i dx + \frac{1}{\rho} \sum_{j=0}^N P_j \int_{\Omega} \nabla \cdot N_i L_j dx + \sum_{j=0}^N U_j \int_{\Omega} \nabla N_j : \nabla N_i dx = 0,
$$

$$
\sum_{j=0}^N U_j \int_{\Omega} \nabla \cdot N_j L_i = 0,
$$

(5.14)

where $K_h$ is resolved on the mesh as before. Rearranging the terms, with $K_h = 0$ for the fluid domain, we arrive at the system

$$
\begin{bmatrix}
A & B^T \\
B & 0
\end{bmatrix}
\begin{bmatrix}
U_j \\
P_j
\end{bmatrix}
= 
\begin{bmatrix}
0 \\
0
\end{bmatrix}
$$

(5.15)

where $A_{i,j} = \int_{\Omega} \nabla N_j : \nabla N_i dx$ and $B_{i,j} = \int_{\Omega} \nabla \cdot N_j L_i dx$. Equation (5.15) is an indefinite matrix. We refer the reader to [45] for an introduction to the numerical analysis of the indefinite matrix problem.

Implementation wise, $K_h$ is sent as an argument to the Stokes solver. Inside the channel defined by $K_h = 0$ is Stokes flow, while outside the flow vanishes by means of the penalty term, which will be addressed in the next section. See Figure 5.5 for an illustration of the flow in the channel using a Poiseuille flow at the inlet (which is derived in Chapter 6).
5.4 The penalty term

The discrete penalty term is

$$CK_h \sum_{j=0}^{N} U_j \int_{\Omega} N_j \cdot N_i dx. \tag{5.16}$$

For the fluid domain $K_h = 0$, the Stokes equations are recovered. However, the value of the inverse permeability constant $C$ allow for different amounts of leakage from the channel. We consider the extreme cases

- $C \to 0$
- $C \to \infty$

Let $K_h$ be the entire computational domain $\Omega$. For the case of $C \to 0$, the Stokes equations are recovered which results in Stokes flow in the entire computational domain

$$\frac{1}{\rho} \sum_{j=0}^{N} P_j \int_{\Omega} \nabla \cdot N_i L_j dx + \sum_{j=0}^{N} U_j \int_{\Omega} \nabla N_j : \nabla N_i dx = 0 \quad \text{in } \Omega. \tag{5.17}$$

Whereas for the case of $C \to \infty$, the penalty term will dominate the momentum equation and we can neglect the viscosity and pressure to get

$$C \Omega \sum_{j=0}^{N} U_j \int_{\Omega} N_j \cdot N_i dx = 0. \tag{5.18}$$

**Figure 5.5:** The velocity in the fluid isocontour of $K$ on a mesh of $64 \times 64$ cells.
Chapter 5. The Discrete Model

We have implemented the penalty term as a separate function called \( \alpha \):

```python
def alpha(u, K):
    C = Constant(1E5) # inverse permeability constant
    return C*K*u
```

Figure 5.6 illustrates the effects of the penalty term, for more we refer to Chapter 7.

5.5 The shear stress

Since the shear is the derivative of the velocity components it is natural for it to be projected onto a space of linear functions. However it can be discontinuous over the elements. The function is therefore projected into \( DG_1 \): Find \( \tau_{x,y,h} \in DG_1 \) such that \( \forall v \in DG_1 \)

\[
\int_{\Omega} \tau_{x,y,h} v dx = \int_{\Omega} \tau_{x,y} v dx
\]

(5.19)

where

\[
\tau_{x,y,h} = \sum_{j=0}^{N} t_j D_j
\]

(5.20)

where \( D_i \) and \( D_j \) are discontinuous linear trial- and test -functions respectively and \( t_j \) the linear coefficients. We get the algebraic system

\[
M_{i,j}x_j = b_i
\]

(5.21)

where \( M_{i,j} = \int_{\Omega} D_i D_j dx \), \( x = t_j \) and \( b_i = \int_{\Omega} \tau_{xy} D_i dx \). We implemented and projected the shear as shown below:

```python
def tau_xy(u):
    return mu*0.5*(u[0].dx(1) + u[1].dx(0))

tau_xy_ = tau_xy(u=u)
tau_xy_proj = project(tau_xy_, DG1)
```

Figure 5.7 shows how the shear looks like in the computational domain. The shear is zero on the solid isocontour, and a linear function on the fluid isocontour. We have made a cut over the shear in the middle of the channel as indicated on Figure 5.7 to get the graph of the shear over that line.

The theoretical shear, see equation (3.20) is a linear function. As Stokes flow enters the channel, the artificial model boundaries give rise to nonphysical oscillations in the shear, see Figure 5.8. These oscillations are inlet effects. The human body circulation is a closed circuit with no cuts and thus no inlets. The inlet effects may dominate and deter the solution. This is remedied by the introduction of a domain we called the interesting domain. Which is a smaller domain for calculation of the WSS that is to be evaluated in the indicator function. This is explained in the next section.
5.5 The shear stress

Figure 5.6: Effects of the inverse permeability parameter: Top: C = 1; Bottom: C = 10.
Figure 5.7: Top: Shear represented in Parview with a cut through the middle. Bottom: The shear function over the cut.
5.6 The indicator function

5.6.1 Constructing the indicator

The indicator function, \( \gamma(\tau_{x,y,h}) \), evaluates the WSS, and based on chosen threshold values determines if the interface should move according to

\[
\gamma(\tau_{x,y,h}) = \begin{cases} 
-\epsilon & \text{if } |\tau_{x,y,h}| \leq d_1 \\
\epsilon & \text{if } |\tau_{x,y,h}| \geq d_2 \\
0 & \text{otherwise}
\end{cases}
\]

where \( \epsilon \) is a small constant and \( d_2 \) and \( d_1 \) are the maximum and minimum threshold values respectively. The indicator function is constructed as a function in \( DG_1 \). First we corrected for the inlet effects. They were observed to extend 0.01 cm from the inlet. This small area is neglected and the remaining we call, interesting domain, see Figure 5.9.

For constructing the indicator function we need the WSS, that is the values of the shear function at the interface. The function values of the shear and the interface, also living in \( DG_1 \), are accessed to determine the WSS by the code

```python
skjaer = tau_xy.vector().array()  # create array objects
vegg = interface.vector().array()
assert len(skjaer) == len(vegg)
indikator = Function(space)  # create indicator function
indikator_array = indikator.vector().array()
```
Since both the interface and the shear are in $DG_1$, their function values are evaluated at the same nodes in the mesh. We tested if a node is on the interface by requiring that its value be larger than 0.1. See the below code

```
if abs(vegg[i]) > 0.1:
    # we are on the interface
```

Next we determined threshold values for the shear on the interface. We use the value obtained by the processing of the shear as in Figure 5.7, which we denote $\hat{\tau}$. Then we set the maximum - and minimum threshold values as 120 - and 80 percent of the model shear respectively, i.e.

$$d_2, d_1 = \hat{\tau} \pm 20\% \hat{\tau}. \quad (5.23)$$

We evaluated the shear at the interface. If it was above or below the threshold values the indicator function was updated with the value $\pm \epsilon$ respectively. Consider the below code:

```
if abs(skjaer[i]) > maks_terskel_verdi:    # growing
    indikator_array[i] = epsilon * domene[i]

elif abs(skjaer[i]) < min_terskel_verdi:  # shrinking
    indikator_array[i] = -epsilon * domene[i]

else:
    indikator_array[i] = 0 * domene[i]    # otherwise
```

where we have multiplied with $domene$ which is the interesting domains function values. If we are outside the interesting domain the values are 0, then the indicator takes the value 0 for those areas, in that way the inlet is excluded. For examples of two different indicator functions, see Figure 5.10. One is zero everywhere except at the interface, where it is negative, which
5.6 The indicator function

Figure 5.10: The indicator function, $\gamma$ on a $32 \times 32$ rectangle mesh. Top: The indicator function takes negative values on the interface indicating that the interface will shrink inwards. Bottom: the indicator takes positive values on the interface indicating that the interface will grow outwards.

indicates constriction. While the other is positive at the interface, which indicates dilation. We remark that the indicator is in $DG_1$, and the FEniCS plotter can not display such functions, thus it has automatically been projected to $CG_1$ for the plotting.

5.6.2 Projecting the indicator

The indicator function updates the isocontours of $K_h$. We have that $K_h \in CG_1$ while the $\gamma_H \in DG_1$. We chose the shear, the interface and the indicator consistently as function in $DG_1$. However we cannot avoid a projection from a richer space, $DG_0$ to a less rich space, $CG_1$ we our set up. When we update $K_h$, we have to projection the indicator from $DG_1$ to $CG_1$. Consider the projection: Given $\gamma(\tau)_H \in DG_1$ Find $\gamma(\tau)_h \in CG_1 \forall v \in CG_1$ such that

$$\int_{\Omega} \gamma(\tau)_H vdx = \int_{\Omega} \gamma(\tau)_h vdx, \quad (5.24)$$
where $\gamma(\tau)_h = \sum_{j=0}^{N} \gamma_j L_j$, $v = L_i$. Before the projection the indicator function was a discontinuous function over the interface elements. After the projection it is piecewise continuous. FEniCS averages between jumps to get the function value at the nodes in $CG_1$.

### 5.6.3 An improved indicator

We observed that the indicator function identified nodes that were set up to shrink perfectly. But when the set up was such that the indicator should indicate growth, it failed. It worked only in the case where the inflow speed was very high, i.e. ten times the control velocity and the maximum threshold was zero or very low. We concluded that in those fine-tuned cases where the indicator showed growth the leakage had been higher than in the control because the high inlet velocity was dramatically increased. In other words the combination of the increase in velocity and decrease in the maximum threshold value lead to growth. Theoretically if there was no leakage then there would never be a low degree of shear on the solid domain, and the vessel would never grow.

Theoretically, we can consider six cases:

1. For a fluid element:
   - (a) $0 \to 1$, i.e. the fluid element has become solid;
   - (b) $0 \to 0$, i.e. the fluid element remained unchanged;
   - (c) $0 \to -1$, i.e. the fluid became ’more’ fluid;

2. For a solid element:
   - (a) $1 \to 0$, i.e. the solid element has become fluid;
   - (b) $1 \to 1$, i.e. the solid element remained unchanged;
   - (c) $1 \to 2$, i.e. the solid element became ’more’ solid.

Theoretically since the WSS is zero in the solid domain, case 2a) never will occur. Therefore we improved the indicator such that for a degree of freedom (dof) on a cell indicating growth, we found the index of that cell. Then we found the facets of that cell to locate its neighbouring cells. Finally we found the dofs of the neighbouring cells as well. And sat the dofs of the neighbouring cells to indicate dilation, that is to $\epsilon$. We also did the same for the constriction, except then we sat the value to $-\epsilon$.

### 5.7 Evolving the interface

We evolved the interface as in equation (3.35), repeated here for reference

$$K^n_h = K^{n-1}_h - \Delta t \gamma(\tau)^{n-1}_h |\nabla K|^{n-1}_h$$  \hspace{1cm} (5.25)

where we used a time step $\Delta t$ as seconds. The update was constructed in a Python function:
5.8 Post- processing of the surface

Figure 5.11: The new surface $K^n$ before it has been processed.

```python
def K_update(indikator, K):
    K_ny = Function(K.function_space())  # space is CG1
    indikator_proj = project(indikator, K.function_space())
    K_ny.vector()[:] = K.vector()[:] - indikator_proj.vector()[:]
    return K_ny
```

We advanced in time by iterating over the entire program in the loop:

```python
# Time loop
time_start = 0
time_stop = T  # choose a stopping time
for t in range(time_start, time_stop):
    K_cap_proj = time_stepping(K, t)  # Call the program
    K = K_cap_proj  # update the surface
```

Figure 5.11 shows the updated surface, i.e. $K^n$, for the growth indicator in Figure 5.10. We remove the non-smooth effects in the next section by what we call post-processing.

5.8 Post- processing of the surface

In the final stage we have processed the surface as described in (3.37) and repeated here for easy reference

$$K_{\frac{1}{2}}(\vec{r}, t) = \begin{cases}
0, & (x, y) < \frac{1}{2} \\
1, & (x, y) > \frac{1}{2}
\end{cases} \quad (5.26)$$

We also project $K_{\frac{1}{2}}$ into $CG_1$, the same space as $K_h$. This gives a nice surface into which the flow can enter and the process is repeated and iterated over. For an example of a new surface
Chapter 5. The Discrete Model

Figure 5.12: The new surface post-processing.

see Figure 5.12
Chapter 6

Analytical solution

Assuming Poiseuille flow we have derived an analytical solution to the Stokes equation in a straight pipe and used it as the inlet boundary condition on the flow. It is also used to verify the Stokes implementation. In addition we use it to calculate the theoretical WSS values to which we compare the model WSS values. We make six assumptions to apply the Poiseuille flow:

1. The fluid is Newtonian, i.e. the stress and the strain are linearly dependent;
2. Laminar flow, i.e. the flow is parallel with the walls (see Figure 3.1);
3. The flow is fully developed, i.e. it is far enough from the inlet for it not to exhibit boundary layer effects;
4. Stationary, i.e. it is not time dependent;
5. The channel is straight and cylindrical in the plane;
6. There is a pressure gradient across the channel.

In the model, we achieved assumption number three by neglecting the flow at the boundary by introducing the *interesting domain*, see Chapter 5.

We use the explicit solution we have derived from the Poiseuille assumptions as the inlet boundary condition and furthermore we use it to constructed three experiments to predict the mechanotransduction in the simulations. In the next sections the analytical solution for the velocity and the shear is derived, then the experiments are set up using these.

### 6.1 Analytical solutions to the Stokes equations

To derive the Poiseuille solution we consider a cylindrical coordinate system \((r, y)\) where \(y\) is the axis in the direction of the channels length and \(r\) is the distance out from the \(y\) - axis. Let the radius of the channel be \(R\). Let the pressure gradient across the channel in the \(y\) - direction be written as \(\frac{\partial p}{\partial y} = \beta\) for simplicity, where \(p\) is the pressure. In the fluid region, \(K = 0\), the penalty term vanishes and the Stokes equations are recovered. We called the velocity in the \(y\) - direction \(u\), and the velocity in the \(r\) - direction \(v\), where \(v\) is a function of the radial distance. The velocity vector becomes

\[
\vec{u} = (u, v) = (0, v(r))
\]  

(6.1)
Chapter 6. Analytical solution

and then the Stokes equations

\[
\frac{1}{\rho} \nabla p + \frac{\mu}{\rho} \Delta \vec{u} = 0, \\
\nabla \cdot \vec{u} = 0,
\]

become

\[
\frac{1}{\rho} \beta - \frac{\mu}{\rho} \frac{1}{r} \frac{d}{dr} (r \frac{dv}{dr}) = 0, \\
\frac{\partial v}{\partial y} = 0,
\]

where \( \beta, \mu, \rho \) are as in Table 6.1. We integrate the momentum equation twice to get

\[
v(r) = \frac{\beta}{4\mu} r^2 + C_1 \ln(r) + C_2.
\]

For \( r \rightarrow 0 \), \( C_1 \ln(r) \rightarrow \infty \), which says that the velocity in the center of the tube is infinitely high. This is nonphysical and to avoid this case we choose \( C_1 = 0 \). Next, the no-slip boundary condition at the walls, i.e. \( v(r = R) = 0 \), determines the remaining coefficient

\[
C_2 = -\frac{\beta R^2}{2\mu}.
\]

The velocity profile becomes

\[
v(r) = \frac{\beta}{4\mu} (r^2 - R^2).
\]

In addition we multiply equation (6.6) with a constant, \( s \) denoting speed to get

\[
v(r) = s \frac{\beta}{4\mu} (r^2 - R^2).
\]

The purpose of the constant \( s \) is to alternate between different values in the experiments. The function implementation follows directly from the mathematical formulation see the code:

```python
# In the case of control
speed = 1
analyticalVelocity = Expression(['0', 'speed*0.25*dpdy*((x[0])*(x[0]) - R*R)'], x0 = x0, R = R, dpdy = dpdy, speed = speed)
```

Equation (6.7) is used as the inlet boundary condition in the model and implemented as the analytical solution in the verification where it is projected on a fine mesh, see Chapter 8. Moreover the analytical solution is used to calculate the shear function and the theoretical WSS. The theoretical values of these functions will serve as the values against which the model WSS values will be compared to in the experiments.
The analytical shear function becomes

\[ \tau_{x,y} = \mu \left( \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \]

\[ = \mu \frac{1}{2} \left( \partial_y \left( \int_{-R}^{R} u \, dr \right) \right) \]

\[ = \mu \frac{1}{2} \left( \int_{-R}^{R} (s \beta 4 \mu (r^2 - R^2)) \, dr \right) \]

\[ = \mu \frac{1}{2} \left( s \beta 2r \right) \]

\[ = \frac{s \beta r}{4}. \tag{6.8} \]

To get the wall shear stress, equation (6.8) is evaluated at the wall, i.e. \( \pm R \). The wall shear stress is hence

\[ |\tau_{r,y}| = \left| \frac{s \beta r}{4} \right|_{r=R}. \tag{6.9} \]

In the experiments of both Kamiya and Togawa [20] and the experiment of [21] the flow is increased or decreased and this effects the radius of the artery. Thus we have to relate the WSS to the flow. The total volume flow \( Q \) through a duct is found by integrating the velocity over the cross section of the duct. And dividing by the area gives the average velocity [29]. We call the average velocity \( \bar{u} \), hence we have that

\[ \int_{-R}^{R} \bar{u} \, dr = \int_{-R}^{R} u \, dr \]

\[ 2R \bar{u} = \int_{-R}^{R} s \beta 4 \mu (r^2 - R^2) \, dr \]

\[ \bar{u} = \frac{1}{2} \frac{s \beta}{4 \mu} R^3 \]

\[ \bar{u} = \frac{s \beta R^2}{8 \mu} \]

\[ \beta = \frac{8 \mu \bar{u}}{s R^2} \tag{6.10} \]

We insert (6.10) into (6.9) to get

\[ |\tau_{r,y}| = \frac{2 \bar{u} \mu}{R}. \tag{6.11} \]

Since the average velocity and the pressure have a proportional relationship, we can find a value for \( \beta \) to use in the velocity profile by the choice of the mean velocity. Also if we double the average velocity, then we have to double \( \beta \). Thus it is helpful to have the parameter \( s \) in the velocity profile. The chosen values of the parameters are summed in Table 6.1. The radius is chosen based on the report of [40], that found the diameter of the ICA to be about 0.4\text{cm} in females and about 0.5\text{cm} in males. Since ICA are more likely to occur in females [23] we choose a radius of 0.2\text{cm}. The average velocity was chosen as 0.0105 cm/s for the control case, which gave the pressure gradient \( \beta = 2.1 \text{g/cm s}^2 \).
Table 6.1: Channel parameters and blood constants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chosen value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average velocity, $u$</td>
<td>0.0105 cm/s</td>
</tr>
<tr>
<td>Radius, $R$</td>
<td>0.2 cm</td>
</tr>
<tr>
<td>Density, $\rho$</td>
<td>1.0 g/cm³</td>
</tr>
<tr>
<td>Dynamic viscosity, $\mu$</td>
<td>1.0 g/(cm·s)</td>
</tr>
</tbody>
</table>

6.2 Experiments

The aim of this section is to set up *a priori* experiments, i.e. experiments were we can predict the outcome before we do the numerical simulations. Thus the outcome tells us if the model is correct or not. Based on the derived formulas we choose a control velocity and find the WSS. Based on the control WSS we set threshold values that are 80 and 120 percent of the control WSS as minimum - and maximum threshold values for vasoconstriction and dilation respectively. If the model WSS falls between the threshold values we expect neither vasoconstriction nor dilation.

In the second experiment we halved the average velocity. According to (6.11) the WSS is halved as well and the WSS will fall below the minimum threshold value. Thus in this case we expect vasoconstriction. Conversely, when the average velocity is doubled the WSS is doubled as well. In this case the WSS increase above the maximum threshold value resulting in vasodilation.

Control

We have set the average velocity in equation (6.11) as in Table 6.1. Then the WSS was calculated to be

$$|\tau_{r,y}| = 0.105 \frac{g}{cm \cdot s^2}. \quad (6.12)$$

We have defined the theoretical threshold values according to the formula

$$d_2, d_1 = |\tau_{r,y}| \pm |\tau_{r,y}| r\%.$$

We have chosen percentage $r\% = 20\%$, then using (6.12) the threshold values become $d_2 = 0.126 \frac{g}{cm \cdot s^2}$ and $d_1 = 0.084 \frac{g}{cm \cdot s^2}$, where $d_2$ is the maximum threshold value and $d_1$ the minimum threshold value. In the control case we except the vessel to neither contract nor dilate when the solution is advanced in time.

Experiment 2: Halved speed

In this experiment we halved the average velocity of the control and calculated the WSS to be

$$|\tau_{r,y}| = 0.0525 \frac{g}{cm \cdot s^2}. \quad (6.14)$$

This experiment and the next are examples of *positive controls*, which means that we are supposed to observe an effect. The WSS in this case is below the threshold value $d_1$. Thus we predict that, if the model is correct, we will observe vasoconstriction. However, as the vessel contracts the WSS will starts to increase because of the inverse relationship between the radius
and the shear according to (6.11) and the vessel either stops contracting or starts expanding. This is continued until an new baseline WSS level is reached, as in the animal experiments of [20] and [21] described in Chapter 2.

**Experiment 3: Doubled speed**

In the third experiment we double the average velocity. The theoretical value for the WSS becomes

$$|\tau_{r \gamma}| = 0.210 \frac{g}{cm \cdot s^2}.$$

(6.15)

The WSS in this case is above the threshold value $d_2$. Thus we expect the vessel to radially dilate. As the blood vessel becomes wider the WSS will be reduced according to (6.11). When the WSS falls below $d_2$ the vessel stops expanding and a new baseline WSS between $d_1$ and $d_2$ is reached. Table 6.1 summarises the theoretical values and outcomes of the three experiments.

<table>
<thead>
<tr>
<th>Average velocity factor, $s$ (cm/s)</th>
<th>$\tau_{r \gamma}$ (g/cm$s^2$)</th>
<th>$d_1$ (g/cm$s^2$)</th>
<th>$d_2$ (g/cm$s^2$)</th>
<th>Expected outcome in K</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.105</td>
<td>0.084</td>
<td>0.126</td>
<td>No change</td>
</tr>
<tr>
<td>0.5</td>
<td>0.0525</td>
<td>$&lt;$</td>
<td>$&lt;$</td>
<td>Vasocontraction</td>
</tr>
<tr>
<td>2</td>
<td>0.210</td>
<td>$&gt;$</td>
<td>$&gt;$</td>
<td>Vasodilation</td>
</tr>
</tbody>
</table>

Table 6.2: Theoretical WSS and threshold values.
Chapter 7

Vasoconstriction and Vasodilation experiment results

We have used the baseline WSS for the control average velocity \((s = 1)\). To obtain this value we used the Plot over Line filter in Paraview [42], see Figure 7.1, at the line \((r, 0)\), i.e \(|\tau_{r,0}|\). This line is used for all the reported WSS in the experiments. We found the model baseline WSS to be \(|\tau_{r,0}| = 0.098g/cms^2\). Which is not that far from the theoretical value \((0.105g/cms^2)\). The model threshold become \(d_2 = 0.118g/cms^2 \) (120 % of control), \(d_1 = 0.078g/cms^2 \) (80 % of control). The wall evolution factor, \(\epsilon\) is kept fixed for all the experiments as \(\epsilon = 2\). We denoted dilation by ‘+’, constriction by ‘−’, and no change by ‘0’. The parameter values are summed in Table 7.1.

\[
\begin{array}{|c|c|}
\hline
\text{Parameters} & \text{Values} \\
\hline
\text{WSS measurements line} & (r,0) \\
\text{Baseline WSS, } |\tau_{r,0}| & 0.098g/cms^2 \\
\text{Max threshold } d_2 & 0.118g/cms^2 \\
\text{Min threshold } d_1 & 0.078g/cms^2 \\
\text{Wall factor } \epsilon & 2 \\
\text{Dilation} & + \\
\text{Constriction} & - \\
\text{No change} & 0 \\
\hline
\end{array}
\]

We have obtained the results for three experiments: the first is the results of our original algorithm; the second is the results of a fine tuning of the original algorithm to get dilation, and the third is the results of our improved algorithm. A general remark on the results are that in some figures the original channel is included for illustration, however this is not included in the time steps.
Chapter 7. Vasoconstriction and Vasodilation experiment results

Figure 7.1: Baseline WSS at the line (r,0). Shows a plot of the shear function in Paraview with a line drawn through (r,0) (left). A plot of the shear function at the drawn line (right).

7.1 Results

7.1.1 Original algorithm - experiment results

The Control Case: $s = 1$;

For the control case of $s = 1$ and $N = 32$ the vessel constricts, see Figure 7.2. The constriction is through time steps $t_2$ to $t_5$ where the vessel stabilizes with the new baseline WSS at 0.36 g/cms$^2$, see Table 7.2. All the WSS values are above $d_2$, thus according to the data we expected dilation, not constriction. When we refined the mesh size to $N = 64$ we observed shrinking for $t_1$ and $t_2$, see Figure 7.3. According to the data in Table 7.3, the vessel should have stabilized immediately. We also measured the minimum WSS on the interface to be 0.08 g/cms$^2$ for $t_1$ and 0.11 g/cms$^2$ for $t_2$. In both these cases constriction is the expected outcome. The mesh was further refined to $N = 128$. In this case we observed neither shrinking nor expanding, see Figure 7.4, which is compatible with the data in Table 7.4.

In conclusion, for the case of $s = 1$, as we refined the mesh we achieved the expected outcome of no change in vessel radius.

Table 7.2: Data for $s=1; N=32$

<table>
<thead>
<tr>
<th>time step</th>
<th>$\tau_{r,y}$ values (g/cms$^2$)</th>
<th>Expected outcome</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.18</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
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</tr>
<tr>
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<td>+</td>
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</tr>
<tr>
<td>5</td>
<td>0.36</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>
## 7.1 Results

**Table 7.3**: Data for $s=1; N=64$;

| time step | $|\tau_{r,y}|$ values (g/cms$^2$) | Expected outcome | Observed |
|-----------|----------------------------------|------------------|----------|
| 1         | 0.095                            | 0                | -        |
| 2         | 0.12                             | 0                | -        |

**Table 7.4**: Data for $s=1; N=128$;

| time step | $|\tau_{r,y}|$ values (g/cms$^2$) | Expected outcome | Observed |
|-----------|----------------------------------|------------------|----------|
| 1         | 0.098                            | 0                | 0        |
| 2         | 0.098                            | 0                | 0        |

**Halved average velocity: $s = 0.5$**;

For $N = 32$ we observed constriction through five time advances, and no dilation. According to the WSS in Table 7.5 we expected the vessel to dilate for time step $t_3$. However it collapsed at $t_5$, see Figure 7.5. When we refined the mesh to $N = 64$, the vessel constricted at $t_1$ and $t_2$, as expected according to the data, see Table 7.6, then stabilized which was also expected, see Figure 7.6. In addition we observe some holes close to the boundary at $t_3$. Using $N = 128$ the vessel stabilizes at the second time step with the new baseline WSS $0.06g/cms^2$, see data in Table 7.7 and Figure 7.7. However this falls below $d_1$ and we expected constriction.

**Table 7.5**: Data for $s=0.5; N=32$;

| time step | $|\tau_{r,y}|$ values (g/cms$^2$) | Expected outcome | Observed |
|-----------|----------------------------------|------------------|----------|
| 1         | 0.05                             | -                | -        |
| 2         | 0.09                             | 0                | -        |
| 3         | 0.18                             | +                | -        |
| 4         | 0.18                             | +                | -        |
| 5         | 0.12                             | +                | -        |

**Table 7.6**: Data for $s=0.5; N=64$;

| time step | $|\tau_{r,y}|$ values (g/cms$^2$) | Expected outcome | Observed |
|-----------|----------------------------------|------------------|----------|
| 1         | 0.05                             | 0/-              | -        |
| 2         | 0.06                             | 0                | 0        |
| 3         | 0.098                            | 0                | -        |
| 4         | 0.12                             | 0/+              | 0        |
| 5         | 0.12                             | 0/+              | 0        |

**Table 7.7**: Data for $s=0.5; N=128$;

| time step | $|\tau_{r,y}|$ values (g/cms$^2$) | Expected Outcome | Observed |
|-----------|----------------------------------|------------------|----------|
| 1         | 0.05                             | -                | -        |
| 2         | 0.06                             | -                | 0        |
| 3         | 0.06                             | -                | 0        |
Chapter 7. Vasoconstriction and Vasodilation experiment results

Figure 7.2: $s=1; N = 32$; First row: The original channel (left), at $t_0$ the channel has constricted (right). Second row: at $t_2$ the channel constricts (left), at $t_3$ the channel stabilizes (right). Third row: at $t_4$ no change is seen (left), at $t_5$ constriction can be observed (right). Fourth row: The channels at $t_6$ did not show change from $t_5$. 

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7.1 Results

Figure 7.3: $s=1$; $N=64$; The channel constricts from the $t_1$ (left) to the $t_2$ (right).

Figure 7.4: $s=1$; $N=128$; The channel does not exhibit any change from $t_1$ (left) to $t_2$ (right).

Doubled average velocity: $s=2$;

For $N=32$ we observed constriction at $t_1$ then stabilization for the resulting, see Figure 7.8. As read from Table 7.8 the WSS at $t_2$ is much higher than $d_2$, however we do not observe dilation. We refined the mesh to $N=64$ and still did not observed any change in the vessel diameter through five iterations. In addition the WSS was found to be $0.19g/cm^2$ for which dilation was the expected result. This was also the case for $N=128$.

| time step | $|\tau_{r,y}|$ values (g/cm$^2$) | Expected outcome | Observed |
|-----------|----------------------------------|-----------------|----------|
| 1         | 0.19                             | +               | -        |
| 2         | 0.37                             | +               | 0        |
| 3         | 0.37                             | +               | 0        |

Table 7.8: Data for $s=2$; $N=32$;

7.1.2 Dilation - experiment results

The effect we did not observe in the previous experiments was dilation. We wanted to test the algorithm for dilation, so we changed the model WSS parameter to $|\tau_{r,y}| = 0.023g/cm^2$, and the threshold values ten percent above and below, that is $d_2 = 0.0253g/cm^2$ as maximum threshold value and $d_1 = 0.0207g/cm^2$ as minimum threshold value. We doubled the average velocity, i.e. $s = 2$, and tested for $N=32$ and $N=64$. We observed dilation for both cases. For $N=32$ the WSS became stable at $0.11g/cm^2$. The WSS at $t_1$ was $0.19g/cm^2$, it then reduced to $0.11g/cm^2$ for $t_2$ to $t_5$, see Figure 7.10. For $N=64$ we observed dilation as well,
Figure 7.5: $s=0.5; N = 32$. From the first row: we observed constriction at $t_1$ (right). From the second row: the channel constricts further at $t_2$ (left) and $t_3$ (right). From the third row: it starts to collapse at $t_4$ (left) and is completely collapsed at $t_5$ (right).
Figure 7.6: $s=0.5; N=64$. From the top row: We observe constriction at $t_1$ (left) through to the second row for $t_2$ (left) and $t_3$ (right) here we observe two holes close to the boundary. In the third row the vessel has stabilized for $t_4$ (left) and $t_5$ (right).
Figure 7.7: s=0.5; N= 128. From top row: The first channel is the original channel without flow (left). After flow was introduced, the channel constricted at \( t_1 \) (right). Second row: The channel constricted further at \( t_2 \) (left) and then became stable at \( t_3 \) (right).

Figure 7.8: s=2; N= 32. From the top row: At \( t_1 \) the vessel has constricted (right). Second row: we observe no more change at \( t_2 \) (left) to \( t_3 \) (right).
7.1 Results

Figure 7.9: $s=2; N = 64$. No change was observed in $t_1$ (right).

see Figure 7.11. In this case the vessel wall was more smooth and less jagged compared to $N = 32$.

7.1.3 Improved algorithm - experiment results

The model WSS was set back to its original value $0.098 g/cms^2$, as well as the threshold values, see Table 7.1. We changed the algorithm, specifically the indicator function, as explained in Chapter 5. In short we located the neighbours of cells at the interface indicated to dilate and had them dilate as well. Or conversely contract.

$s = 1$;

For $N = 32$ the vessel constricts and collapses, see Figure 7.12. We observed holes in the solid domain from where it used to be fluid, and peaks of solid in the fluid domain, therefore the data in 7.9 includes these as well, since the WSS is determined at the line $(r, 0)$. For $N = 64$ the vessel at $t_7$ has been shaped from the flow, i.e. it has dilated and constricted in different regions of the wall and as a result is has become curved, see Figure 7.13. And overall it has remained the same radius, which is what we expected.

Table 7.9: Data for $s=1; N=32$;

| time step | $|\tau_{r,y}|$ (g/cms$^2$) | Expected outcome | Observed outcome |
|-----------|-----------------|-----------------|-----------------|
| 1         | 0.095           | 0               | both + and -    |
| 2         | 0.19            | +               | both + and -    |
| 3         | 0.4             | +               | +               |
| 4         | 0.2             | +               | -               |
| 5         | 0.3             | +               | +               |
| 6         | indeterminable  | indeterminable  | indeterminable  |
| 7         | indeterminable  | indeterminable  | indeterminable  |

Table 7.10: Data for $s=1; N=64$;


Figure 7.10: $s=2$; $N=32$. From top row: The indicator function indicated growth (left), the original domain (right). Second row: the vessel dilated at $t_1$ (left), it became stable at $t_2$ (right). Third row: at $t_3$ a couple of cells at each inlet dilate (left), at $t_4$ a few more dilate (right). Fifth row: A few cells become solid at $t_5$. 
Figure 7.11: $s = 2$; $N=64$. First row: The vessel dilated at $t_1$ (right). Second row: The vessel dilated further at $t_2$ (left) and continued to dilate at $t_3$ (right). Third row: the vessel became stable at $t_4$ (left) and remained stable at $t_5$ (right) to $t_6$ in the fifth row.
Chapter 7. Vasoconstriction and Vasodilation experiment results

| time step | $|\tau_{r,y}|$ values (g/cms²) | Expected outcome | Observed |
|-----------|-------------------------------|------------------|----------|
| 1         | 0.095                         |                  | -        |
| 2         | 0.12                          | +                | both - and + |
| 3         | 0.19                          | +                | +        |
| 4         | 0.17                          | +                | + (left) / - (right) |
| 5         | 0.14                          | +                | + (left) / - (right) |
| 6         | 0.11                          | 0                | + (left) / - (right) |
| 7         | 0.3                            | +                | 0        |

$s = 2$

For $N = 32$ the vessel dilates with some irregularities and holes, see Figure 7.14. It dilates close to the inlet at $t_4$ but then constricts at $t_5$ and stabilizes. However there are some solid peaks inside the fluid domain at $t_7$.

For $N = 64$ the vessel dilates at $t_1$ on the left side. It continues to dilate on the left side at $t_2$, which continues until a curves shape is attained at the final time step, see Figure 7.15. We observe from that it has dilated and become somewhat wider compared to the original vessel radius.

Table 7.11: Data for s=2; N=32;

| time step | $|\tau_{r,y}|$ values (g/cms²) | Expected outcome | Observed |
|-----------|-------------------------------|------------------|----------|
| 1         | 0.19                          | +                | both + and - |
| 2         | 0.4                            | +                | - on left side |
| 3         | 0.80 (0.32 solid peak)        | +                | +        |
| 4         | 0.04 (0.13 peak)              | -                | -        |
| 5         | 0.13                          | +                | + / 0    |
| 6         | 0.14 (0.19)                   | +                | 0        |
| 6         | 0.12                          | 0                | 0        |

Table 7.12: Data for s=2; N=64;

| time step | $|\tau_{r,y}|$ values (g/cms²) | Expected Outcome | Observed |
|-----------|-------------------------------|------------------|----------|
| 1         | 0.19                          | +                | +        |
| 2         | 0.17                          | +                | +        |
| 3         | 0.15                          | +                | + (left) / - (right) |
| 4         | 0.17                          | +                | + (left) / - (right) |
| 5         | 0.17                          | +                | + (left) / - (right) |
| 6         | 0.14                          | +                | + (left) / - (right) |
| 6         | 0.19 +                        | + (left) / - (right) |

$s = 0.5$;

For $N = 32$ we observed that the vessel constricted until it collapsed at $t_4$, see Figure 7.16. However for $N = 64$ the vessel constricted close to the inlet and dilated at its center, see Figure 7.17. Compared to the original vessel radius it has constricted and become narrower, which is what we expected in this case.
Figure 7.12: \( s=1; \) \( N=32 \). From first row: At \( t_1 \) the vessel constricted and we saw holes of fluid in the solid domain (right). Second row: At \( t_2 \) the vessel constricted, but dilated on a few elements into the holes seen in \( t_1 \) (left). It dilated further at \( t_3 \) (right). Third row: the vessel constricted at \( t_4 \) (left), and continues to constrict at \( t_5 \) (right). Fifth row: At \( t_6 \) the vessel starts to collapse (left) and keeps collapsing at \( t_7 \) (right).
Figure 7.13: $s=1; \ N = 64$. First row: at $t_0$ the vessel constricts (right). Second row: At $t_1$ the vessels constricted but grew to the right to produce holes (left). The vessel dilated slightly at $t_3$, where the shadow on the right wall is a thin wall (an artifact from $t_2$) (right). Third row: At $t_4$ the vessel dilated on the right side of the wall farthest from the inlet, and constricted closest to the inlet on the same side (left). At $t_5$ the vessel dilated on the left side farthest from the inlet and contracted on the right side farthest from the inlet at the same location it dilated in the previous time step, $t_4$ (right). Fourth row: At $t_6$ the vessel started to exhibit a curved shape (left), the curved shape becomes more accentuated at $t_7$ (right).
Figure 7.14: \( s=2; \ N=32 \). First row: At \( t_1 \) the vessel dilated on the left side and constricted on the right side (right). Second row: At \( t_2 \) the vessel constricted back at the left side and there is no changes on the right side. A few solid peaks are observed in the fluid (left). At \( t_3 \) the vessel dilated close to the inlet on both sides and constricted farthest from the inlet on both sides (right). Third row: At \( t_4 \) the vessel continued to dilate close to the inlet (left). It also continued to dilate close to the outlet at and center \( t_5 \) (right). Fifth row: At \( t_6 \) (left) and \( t_7 \) the vessel became stable.
Figure 7.15: $s=2$; $N=64$. First row: At $t_0$ the vessel dilated to the left (right). Second row: The vessel dilated more to the left for $t_2$ (left). For $t_3$ is started constricting on the right side of the wall in the center and continued to dilate to the left on the left side of the wall (right). Third row: At $t_4$ a hole is observed on the right side of the wall, while the wall continues to dilate slightly on the left side (left). The same is observed for $t_5$ as was for $t_4$ (right). Fourth row: The evolution of $t_5$ continued to $t_6$ (left) and $t_7$ (right).
Figure 7.16: $s=0.5$, $N=32$. First row: At $t_1$ the vessel constricted on the right side and dilated on the left side of the wall (right). Second row: The vessel dilated on both sides for $t_2$ (left) and kept constricting for $t_3$ (right). Third row: The vessel collapsed at $t_4$. 
Figure 7.17: $s = 0.5$, $N = 64$. First row: At $t_1$ the vessel contracted on both sides (right). It kept contracting on the second row at $t_2$ (left) where it developed holes to $t_3$ (right). This is still continued to the third row: At $t_4$ (left) to $t_5$ (right) and to the fourth row at $t_6$ (left) where it has a big hole on the right side of the wall. Finally it dilated at the center at $t_7$ (right).
In Chapter 5 the effects of the penalty term was illustrated using the extreme cases of the inverse permeability constant, $C$. In practice the values of $C$ will never be either. The value can not be 0 and for obvious reasons it can not be $\infty$ in a computer simulation. In practice the value of $C$ needs to be large enough for there to be as little leakage as possible into the solid domain. However since it is not $\infty$ there will always be some leakage. Using a series of rising $C$-values, we will show the velocity solution converges.

The effects of the inverse permeability term $C$

To study the effects of the $C$ - values in the plots, the colors of the the solid domain is set to a yellowish brown for better distinction between the velocity field and the domain, see Figure 8.1. For $C = 0.1, 1, 10$ there is a high degree of leakage as seen in Figure 8.1, and it is basically Stokes flow in the entire computational domain. For $C = 100, 1000, 1E4$ we can hardly see the flow in the solid domain except at the inlet, see Figure 8.2. For $C = 1E5$ the flow is considered practically gone in the solid done, even though it is not entirely the case. As mentioned it is entirely vanished in the solid domain when $C = \infty$. Another consideration is that for higher values of $C$ the computational time is increased.

Velocity convergence for a fixed $C$ value

We used the $C = 1E5$ in our simulations. For this value the experimental velocity solution is compared to the analytical solution for mesh sizes $N = 16, 32, 64, 128$. The analytical solution is resolved on the mesh size $N = 128$, see Figure 8.4. In Figure 8.5 we can see that the experimental velocity field converge to the analytical velocity field. To better depict this, we have plotted the discrepancy fields, see Figure 8.6. We observe that the discrepancy almost vanished in the center of the vessel, but remained in regions close to the vessel walls. In this region the flow leaks out to the solid domain and thus there will be a level of discrepancy at the walls.

Velocity convergence for different $C$ - values

We investigated the velocity convergence for different $C$ - values. That is we found the discrepancy between the analytical solution and the experimental solution for mesh sizes $N = 16, 32, 64, 128$ and $C$- values $C = 0.1, 1, 10, 100, 1000, 1E4, 1E5$. The $H^1$ - errornorm were calculated, see Table 8.1, and used to make a log - log plot of the error values as a function of
Figure 8.1: The series of $C$ values on a $32 \times 32$ mesh with control average velocity, where $C$ is equal to 0.1 (top), 1 (middle), 10 (bottom).
Figure 8.2: The series of C values on a $32 \times 32$ mesh with control average velocity, where C is equal to 100 (top), 1000 (middle), 1E4 (bottom)
Chapter 8. Verification

**Figure 8.3:** C = 1E5 for a 32 × 32 mesh with control average velocity

**Figure 8.4:** Analytical velocity on a fine mesh 128 × 128
Figure 8.5: Experimental velocity field for N= 16,32,64,128 from the top (N=16) to the bottom (N=128)
Figure 8.6: Velocity Discrepancy fields for $N = 16, 32, 64, 128$ from the top ($N=16$) to the bottom ($N=128$)
the mesh size, see 8.7. We observed that for C values lower than a 1000 the error is not reduced when the mesh is refined. For the $C = 1000$ we observed a very slow decline, that eventually stagnates. For $C = 10^4$ the slope is steep but also stagnates. This is because there will be some leakage for any value of C. For $C = 10^5$ the slope is steep. As observed in the figure and data the first error for $C = 10^5$ is higher than any other error. This is because for a high C-value, most of the leakage is removed. However the mesh is very coarse for $N = 16$ thus the velocity solution is just one arrow as seen in Figure 8.5, while the analytical velocity field is very different, see Figure 8.4, therefor the discrepancy becomes large.

<table>
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<tr>
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<th>$h = 1/N$</th>
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<th>$C = 10$</th>
<th>$C = 100$</th>
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</table>
Chapter 9

Discussion

9.1 Results

Before arriving at the results presented in Chapter 7, other strategies were explored as well. In particular we experimented with different elements. Before developing the improved algorithm, we tried to use $CG_1$ elements for the shear, the interface and the indicator. However this approach did not work. The reason can possibly be because the interface would still be a constant over one element with one node on the fluid region and one node close to the solid region. And the shear evaluated at the node on the solid region would still always be a small value.

Another challenge was the choice of element for $K$. If we had chosen $K \in DG_1$, then we would have used the jump functionality in FEniCS. This approach also turn out not to work. The jump was not detected possibly because in general $DG_1$ also contains continuous linear functions, e.g. $CG_1 \subset DG_1$. We did not attempt the use of $CG_2$ elements. In the latter case $K$ would have been smoother and the last post-processing step might not have been necessary. This approach can be explored. Which element to use turned out to be one of the most challenging parts of the study.

Turning to some of the aspects of the final model. With the original algorithm, experiments never showed dilation. We hypothesized that the shear was evaluated at the solid parts of the interface. In earlier experiments we had observed dilation for $s = 10$. Thus we created the "Dilation experiment". In this experiment we saw that when the parameters were fine-tuned, that is when $d_2$ was very low and $s$ high we observed dilation. Which indicated that the flow had leaked enough for the WSS at the solid to be above the threshold value. Thus we improved the indicator function to dilate neighbouring cells as well. Earlier experiments showed that the constriction would benefit from the same improvement. The reason for the latter is unclear. If we look at the final time steps for the improved algorithm on the finer mesh (N=64), we see that the model indeed

- Has remained approximately the same size for $s = 1$ although the shape has become curved, see Figure 9.1;
- Exhibits vasodilation for $s = 2$, see Figure 9.2;
- Exhibits vasoconstriction for $s = 0.5$, see Figure 9.3.

The downside this algorithm compared to the old one is that the computational time increased. The reason for this is most likely because we locate cells in the mesh. A parallel code might
Chapter 9. Discussion

Figure 9.1: Baseline results for s=1; N=64. The original vessel (left), and the final vessel (right).

Figure 9.2: s=2; N=64. The original vessel (left) and the vasodilated vessel (right)

reduce the computational time. Another downside is the peaks of solid in the fluid domain and the holes of fluid in the solid domain. The holes of fluid in the solid domain are probably fluid cells from previous time steps. The solid peaks in the fluid region tend to remain there if they are in the middle of the vessel because at the center of the vessel the WSS is at its lowest. And thus the maximum threshold is never reached. We also observed that the vessel collapsed when the mesh was coarse. A reason for this can be that the flow did not enter the vessel as it became narrower. Without flow the WSS is zero leading to atrophy of the vessel. However we observed that when the mesh is refined the vessel did not collapse and had fewer peaks and holes.

Figure 9.3: s=0.5; N=64. The original vessel (left) and the vasoconstricted vessel (right)
9.2 Conclusion and Future work

A comment on the average velocity has to be made, it is lower than what is reported in the literature [33]. Unfortunately at the time we discovered this is was to late to change. However, the experiments we constructed are such that the WSS will be below or above the WSS threshold values and thus we to get the desired effects of vasoconstriction and dilation regardless of the chosen average velocity.

We suggest for further work that the blood is simulated using the Navier-Stokes equations to simulate turbulence. It would be interesting to see the effects of different types of flow on the mechanotransduction. The Stokes equations can not simulate turbulence because they lack the advective term. Thus the simulations are fitted for narrow capillaries where the viscous term dominates over the advection. However the model can conceptually be generalized to more complex types of flow. In addition the model can be applied to branched or bifurcated geometries. We made different types of geometries but because of the time constraints did not have the time to perform experiments on them. The branched geometry could be used in the study of a stagnation point and the bifurcated geometry in the study of aneurysm formation at the apex of the bifurcation. However more experiments using the straight vessel can be performed as well, e.g. using a wider vessel than the inflow, and observe if the vessel constricts. Which would be similar to the experiments in this project.

We could not find many publications where the mechanotransduction was considered in CFD simulations of blood flow or the combination of the level-set method for mechanotransduction modelling. One interesting paper that used the level-set method in aneurysm simulations was [30]. The results of this thesis might inspire future work.


[27] Center of biomedical computing webpage.


[42] Paraview webpage.
