Modelling cerebral interstitial flows and their failure in Alzheimer’s disease

by

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The human brain is the organ with the highest metabolic activity; despite this, it lacks a conventional lymphatic system responsible for clearing metabolic products. Cerebral accumulation of soluble metabolites, such as the amyloid-beta (A\textbeta) protein, has been associated with Alzheimer’s disease, the most common form of dementia. The underlying mechanisms for the clearance of the brain are not completely understood through conventional biological sciences alone. With this in mind, this thesis aims to provide a new perspective by developing novel multi-scale physiologically-realistic models that allow quantitative assessment of previously proposed clearance systems of the brain. The first model investigates the global clearance of soluble A\textbeta from the brain tissue by accounting for a realistic geometry of the human brain and heterogeneous properties of the brain tissue. Within the model, the relative contributions of different transport mechanisms of A\textbeta out of the brain tissue are assessed. Insights about physically realistic clearance mechanisms and cerebral regional deposition of A\textbeta in the brain when clearance fails are provided. The second part of this thesis aims to clarify the motive force for the intramural periarterial drainage (IPAD) of soluble A\textbeta from the brain. Failure of this clearance mechanism could explain the vascular deposition of A\textbeta as cerebral amyloid angiopathy, which is almost invariably found in Alzheimer’s dementia. The motive force of the IPAD process has yet not been clarified, hindering in this way any significant therapeutic progress. Here, a novel hypothesis, namely vasomotion-driven IPAD, is proposed and modelled by designing a novel multi-scale mathematical model of cerebral arteries. The periarterial flow rates yielded by the model suggest that vasomotion-driven IPAD is the only mechanism postulated to date capable of explaining the perivascular clearance of solutes observed experimentally.
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Declaration of Authorship

I, Roxana Aldea, declare that the thesis entitled Modelling cerebral interstitial flows and their failure in Alzheimer’s disease is my own work and it has been generated by me as a result of my own original research. I confirm that:

- this work was done wholly while in candidature for a research degree at University of Southampton;

- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

- where I have consulted the published work of others, this is always clearly attributed;

- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

- I have acknowledged all main sources of help;

- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

- parts of this work have been published as: Bakker et al., (2016).

Signed:

Date: 27.03.2018
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Nomenclature

It is remarked that
the notation is specific to each chapter and only
the symbols that are frequently used are listed here

General notation:

Aβamyloid beta
ADAlzheimer’s disease
CAACerebral amyloid angiopathy
BBBB blood brain barrier
ISFinterstitial fluid
CSFcerebrospinal fluid
SASsubarachnoid space
IPADintramural periarterial drainage
V-IPADvasomotion-driven intramural periarterial drainage
VSMCvascular smooth muscle cell
BMbasement membrane
SEFstrain energy function

Chapter 2:

cconcentration
ttime
ΨProduction rate per unit volume
Σtotal bulk removal rate
Σ_{BBB}bulk removal rate at the BBB
Σ_{IPAD}bulk removal rate along the IPAD pathways
t_{1/2}half-life
τmean time
qflux
MMtotal amount of substance diffusing
DDiffusion coefficient
Chapter 3:

\( \Omega_g \) domain of grey matter
\( \Omega_w \) domain of white matter
\( g \) subscript for grey matter
\( w \) subscript for white matter
\( q \) Darcy flux
\( k \) permeability of brain tissue
\( p \) interstitial pressure
\( \mu_m \) viscosity of ISF
\( Q \) total volumetric source
\( Q_B \) volumetric source due to BBB
\( Q_M \) volumetric source due to metabolic activity
\( \Sigma \) total bulk removal rate
\( \Sigma_{IPAD} \) bulk removal rate along the IPAD pathways
\( \Sigma_{BBB} \) bulk removal rate at the blood brain barrier
\( L_p^S \) measure of capillary hydraulic conductivity
\( \Phi \) transvascular driving pressure at capillaries
\( p_s \) pressure in the subarachnoid space
\( p_v \) pressure in the lateral ventricles
\( \Gamma_S \) subarachnoid space boundary
\( \Gamma_{LV} \) left ventricle boundary
\( \Gamma_{RV} \) right ventricle boundary
\( c \) A\( \beta \) concentration in the interstitium
\( \phi \) porosity of brain tissue
\( \Psi \) production rate of A\( \beta \)
\( D^* \) effective diffusion coefficient of A\( \beta \)
\( c_c \) A\( \beta \) concentration in the CSF

Chapter 4:

\( \sigma \) Cauchy stress
\( x \) position vector in deformed frame
\( X \) position vector in undeformed frame
\( F \) deformation gradient tensor
\( J \) Jacobian
\( C \) the right Green-Cauchy deformation tensor
\( \lambda_i \) stretch ratio with \( i = 1, 2, 3, r, \theta, z \)
Chapter 4 (continued):

\( I_i \) invariants with \( i = 1, 2, 3 \)
\( E \) Green strain tensor
\( e_{ij} \) Cauchy’s infinitesimal strain tensor
\( u \) displacement
\( \mu \) Lame constant
\( \lambda \) Lame constant
\( W \) strain energy function
\( T \) first Piola-Kirchhoff stress
\( S \) activation parameter
\( \lambda_m \) circumferential stretch for maximum active contraction
\( \lambda_0 \) circumferential stretch for minimum active contraction
\( R \) undeformed arterial radius
\( R_i \) undeformed inner radius
\( R_o \) undeformed outer radius
\( r \) deformed arterial radius
\( r_i \) deformed inner radius
\( r_o \) deformed outer radius
\( P \) arterial pressure

Chapter 5:

\( h \) deformed thickness of upper half BM
\( H \) undeformed thickness of upper half BM
\( t \) time
\( z \) axial position
\( \phi^f \) fluid volume fraction
\( \phi^s \) solid volume fraction
\( \phi^s_0 \) solid volume fraction reference state
\( v_z^f \) fluid velocity component in the z-direction
\( k \) BM permeability
\( p \) pore pressure
\( \eta \) fluid viscosity
\( \sigma_y^e \) effective Cauchy stress component in the y-direction
\( \Sigma \) external constrictive stress
\( W_{BM} \) SEF of the BM
\( S \) activation wave of the VSMCs
\( S_w \) maximum activation of the VSMCs
Chapter 5 (continued:)

$\lambda_w$ vasomotion wavelength
$\bar{c}_w$ vasomotion wave speed
$T$ time period of vasomotion wave
$\mu_s$ Lame parameter
$\lambda_s$ Lame parameter
$Q_{BM}$ volumetric flow rate through BM
$r_m$ radial position of BM
$E_i$ Green strain with $i = \theta, z$
$\lambda_i$ stretch ratio with $i = \theta, z$
$W$ SEF of the arterial wall
$P$ arterial pressure
Chapter 1

Introduction

Rather than starting with a famous quote like many do, I open my thesis with a blog post that I was invited to write by the EPSRC UK in April 2017 for the awareness month of Mathematics.

How to tackle dementia with Mathematics

A mother to her son, a husband to his wife, a grandmother to her granddaughter:
- Where did I leave my keys?
- What day is today?
- Who are you?
Are these questions part of normal ageing or symptoms of dementia?

Understanding dementia. Dementia is not normal ageing and is characterised by cognitive deficits, memory loss and personality changes that compromise the independent living of more than 46 million people worldwide. The most common form of dementia is Alzheimer’s disease (AD) and has no effective intervention. I believe that the limited success in the discovery of long-term cure for AD could partly be due to incomplete understanding of its aetiology. For many years, AD was considered solely a neurodegenerative disease. Recently, however, a new paradigm has emerged. The presence of numerous vascular risk factors of AD has led to its classification as a vascular disease, increasing the complexity of pathology and the number of research pathways that need exploring.
**Maths in medicine: a different approach.** This is the type of problem that has motivated my decision of becoming a biophysicist. Given its complexity, it is unlikely that AD can be fully understood and treated through conventional biological sciences alone. Biophysical and mathematical models are powerful tools that have not yet been explored to their full potential in the biomedical and clinical fields. I have dedicated my PhD to bridging the gap between the neurodegeneration and the vascular pathology present in AD. Rather than looking through a microscope to brain tissue samples, I have been looking at Alzheimer’s dementia through the eyes of a physicist: physical principles from fluid dynamics and solid mechanics have been my strategy, mathematical models of cerebral blood vessels my tool and the pathology of Alzheimer’s dementia my target. Such a line of action could not have been successful without the guidance and mutual interest of my supervisors from Mathematical Sciences and Clinical Neuroanatomy.

Mathematics is the language that has allowed me to quantify physiological processes, to investigate multi-scale biological systems and to link disciplines such as Physics, Computer Science, Biology and Medicine. Despite its usefulness, mathematical modelling is an underrepresented approach in biomedical and clinical applications. Could it be due to the fact that for many Mathematics sounds like a foreign language difficult to grasp or could it be because scientists from biomedicine and clinical sciences remain sceptical of reductionist thinking? The latter concern raises the question of how much physiological detail can be included in a mathematical model. My approach to this challenge can be summarised by the words of Albert Einstein: 'Everything should be made as simple as possible, but no simpler.'

**The value of interdisciplinarity.** Regarding the language of communication across the technological and biological sciences, I have learnt that the best strategy to engage with a biomedical audience is to keep the mathematical model as a black box and familiarise myself with the biological lexicon. In this way, my physical models take the shape of anatomical systems and mathematical equations express physiological processes. Embracing this strategy requires a large amount of self-teaching, high flexibility in communication and departure from the comfort zone of a mathematician or a physicist. It is nonetheless a thrilling way to develop unique skills and grow as a well-rounded scientist. The interdisciplinary funding offered by EPSRC has offered me an amazing opportunity to develop projects that combine the flexibility of mathematical and
1.1 Thesis motivation

The brain has the highest metabolic activity in the human body, with the highest consumption of energy and, subsequently, the highest waste production. Nonetheless, the brain lacks a traditional lymphatic system that, in the rest of the body, is responsible for clearing waste products, excess of fluid and any unwanted material. This raises the question about the non-conventional clearance mechanisms, especially those from the cortical region, that contribute towards maintaining the homeostasis of the brain [17, 79]. Despite gaining increased research interest over the last years, the field of clearance of the brain has been faced with many contradictory findings, debatable theories and, on top of that, limited experimental access to the brain. This thesis aims to provide novel tools for testing previously proposed clearance mechanisms, for investigating what makes physical and/or physiological sense and, finally, for providing some insights which cannot easily be obtained otherwise by biological sciences alone.

The brain contains four distinct fluids: the blood, the intracellular fluid, the interstitial fluid (ISF) and the cerebrospinal fluid (CSF). Apart from other functions, both ISF and CSF have the important role of clearing soluble metabolites and waste products from the brain. Of particular importance is the clearance of the soluble amyloid-beta (Aβ) protein which is released by neurons in the extracellular space following synaptic activity. Failure in the removal of Aβ from the brain leads to the toxic deposition of Aβ in the form of extracellular plaques commonly seen in Alzheimer’s disease (AD), the most common form of dementia [165]. Although both ISF and CSF reach the cervical lymph nodes (located along the neck), they follow distinct pathways that have been the subject of great debate over the last years [120, 185]. Moreover, given the more recent findings reviewed in [78, 79], the traditional view on the communication between ISF and CSF requires reassessment, bringing up even more fundamental questions like how water is produced in the brain. The balance between fluid production in the brain, transport within the extracellular spaces and clearance from the brain is of paramount importance for preventing highly damaging...
brain disorders such as hydrocephalus (i.e. accumulation of CSF in the brain), brain edema (i.e. brain swelling) and dementia. This work aims to elucidate some of the controversies regarding cerebral interstitial fluid flows, their contribution to the removal of Aβ from the brain and their failure in AD.

The medical and social consequences of the failure of Aβ clearance from the brain impacts millions of lives worldwide and costs billions of pounds. The already high number of patients living with dementia (46.8 million world-wide and more than 850 000 in the UK) is expected to dramatically increase to 74.4 million by 2030 and 131.5 million by 2050, given that no preventive interventions against dementia exist and, at the same time, the human lifespan is increasing. Despite numerous efforts and billions of pounds invested, all the clinical trials in AD have failed. For instance, the billion dollars Eli Lilly clinical trial in Alzheimer’s drug solanezumab unveiled the unsuccessful results in November 2016, after more than a decade of research. The failed clinical trials could be explained by their primary focus on dissolving the parenchymal amyloid plaques in patients with late-stage AD without properly understanding where the resulting soluble Aβ may be cleared and what may hinder its clearance. Moreover, the neuronal and vascular damage induced by the intracranial accumulation of Aβ is initiated 10 - 15 years before the clinical symptoms of dementia manifest. The delayed diagnostic makes it impossible to treat the irreversible damage of the brain and, consequently, dementia remains an incurable, lethal disease. Needless to say, it is critical to understand the mechanisms by which Aβ is cleared from the brain and why these fail with age, if diagnostic and therapeutic strategies for AD are to improve. The small dimensions of the clearance pathways (e.g. 10 - 150 nm) and their anatomical position within the deep layers of the brain tissue makes the investigation of Aβ elimination from the brain difficult to conduct in living humans and even in vivo in the brains of animals.

With this in mind, physiologically-oriented mathematical and computational models represent a useful tool to analyse the proposed brain clearance mechanisms in literature and provide some new mechanistic insights. By combining principles from fluid dynamics and solid mechanics of soft biological tissue with techniques from analytical mathematical modelling (e.g. lubrication theory) and computational modelling (e.g. Finite Element Method), novel multi-scale models for the clearance of ISF and Aβ from the brain are developed in the remainder of this study. The models are based on physiological experimental data available in the literature and investigate the minimum requirements for
removal of soluble Aβ from the brain at physiological production rates by accounting for: (i) global clearance from the brain, including diffusion and transport by ISF bulk flow (i.e. advection) through the brain tissue towards the CSF and (ii) bulk flow along the intramural periarterial drainage pathways (IPAD) of cerebral blood vessels. Each of these clearance mechanisms has been faced with unsolved issues over the years.

The first mathematical model of this study investigates the global clearance of soluble Aβ from the brain and is motivated by the fact that the relative contributions of the clearance mechanisms for this protein have not yet been clarified. Specifically, the model aims to clarify the percentage of ISF drained into the CSF of the human brain and, subsequently, how this drainage contributes to the removal of soluble Aβ when all the other clearance mechanisms (e.g. IPAD and transporter-mediated efflux into the blood) fail. This novel model includes a physiologically realistic geometry of the human brain and accounts for the distinct properties of the cerebral grey and white matter.

The second and the third model, both accounting for the biomechanics of cerebral arteries, aim to answer the unresolved questions regarding the motive force for the clearance of soluble metabolites, such as Aβ, along the IPAD pathways of cerebral blood vessels identified by Carare et al.\[29\]. It has been suggested that this clearance process becomes increasingly important during ageing, when the active removal of Aβ from the brain across the blood-brain barrier diminishes \[141\]. Failure of this clearance process could explain the accumulation of Aβ within the arterial wall as cerebral amyloid angiopathy (CAA), which is a vascular disorder found almost invariably in the human brains with AD \[47\]. Although the anatomical pathways for IPAD have been assessed in a detailed manner \[119, 120\], the motive force that drives the outflow of soluble metabolites along these pathways is still unclear. Successful targeted treatments for improving the Aβ clearance along the IPAD pathways do not seem likely until the motive force behind this process is understood. Recent modelling results from Diem et al., \[53\] dismissed the early hypothesis of arterial pulse-driven IPAD, motivating even more the quest for another candidate for the motive force. Here, a novel hypothesis for the mechanism that may drive IPAD in the brain (e.g. vasomotion-driven IPAD) is put forward and tested with a newly developed mathematical model based on physiological data.

This research thesis is based upon a critical analysis of the available literature, aiming to understand and quantify in new ways the physiological processes
related to the clearance of the brain. Although the research results remain theoretical and are limited by the scarcity of experimental evidence, they have the potential to put the basis of a novel theory of brain clearance that could be further tested experimentally. It is hoped that this work, at the very least, complements the experimental field (e.g. elucidates controversial findings, motivates new avenues of research) and, at its best, contributes towards early diagnosis, prevention and targeted treatment of dementia.

1.2 Thesis outline

Chapter 2 reviews the physiology of the brain relevant for the remainder of this study. In particular, Section 2.1 presents AD as a problem of clearance, describes the global impact of AD and discusses the overlap between the neurodegenerative and vascular aspects of the disease. The mechanisms for the clearance of cerebral ISF and Aβ from the brain are revised, highlighting the differences between the traditional and modern views on brain clearance. In Section 2.2, special attention is given to the clearance of solutes along the IPAD pathways. In order to better understand the IPAD process, some anatomical and physiological aspects of cerebral arteries are presented a priori. The chapter closes with a critical analysis of the IPAD experiments present in literature. Each of the following chapters contains some specific literature overview that is omitted in Chapter 2 in order to avoid repetition.

Chapter 3 presents a novel quantitative model for the global clearance of Aβ from the brain. A realistic geometry of the brain is simulated by employing image-based modelling of the human brain and accounting for the distinct properties of the grey and white matter. The model verifies some speculations from literature with respect to the distribution of pressure and fluid in the brain. Moreover, for the first time, the model predicts the accumulation of Aβ in the human brain for different levels of efficacy of the major clearance mechanisms.

Chapter 4 starts by revising the basic aspects of non-linear elasticity that are commonly employed in the modelling of the arterial wall. Further on, the first model for active cerebral arteries is built and compared with available experimental data. This model is subsequently coupled with the mathematical model from Chapter 5, in order to develop a fluid-structure interaction model.

Chapter 5 proposes a novel hypothesis for the motive force behind the IPAD
process in the brain, namely vasomotion-driven IPAD. The hypothesis is further tested with a new mathematical model, which is based on physiological data and includes elements of fluid-structure interaction of a hyperelastic porous material. The goal of the model is to quantitatively assess the flow rates along the IPAD pathways that are induced by the contractile oscillations of the cerebrovascular smooth muscle cells. The proposed mechanism of vasomotion-driven IPAD appears to be significantly better than the previously proposed mechanism of arterial pulse-driven IPAD. The possible implications of the proposed hypothesis in the clearance of soluble Aβ from the brain and in the onset of AD are discussed.

Chapter 6 draws the conclusions of this study and highlights future avenues of research.

1.3 Contributions

There are several innovative ways in which the work presented here contributes to the research field of brain clearance. Firstly, novel computational models for the quantitative assessment of cerebral interstitial flows and transport of Aβ through the human brain are developed. Secondly, a new clearance mechanism that may contribute to the removal of soluble Aβ from the brain is proposed and subsequently tested with an original mathematical model. Needless to say, the developed models are only as good as the assumptions made. However, it is emphasized that all the models are developed in line with the available experimental data for the human and rodent brain. A more detailed description of the unique contribution of this work is given below.

The experimental community focused on brain research is faced with limited access to the brain tissue, especially in the living human brain. As an alternative approach, injection of soluble tracers in the brain of rodents coupled with post-mortem analysis of brain tissue has been employed since the 1980s in order to investigate the production and clearance of ISF, CSF and Aβ protein [46, 91, 164]. Although very useful for qualitatively mapping anatomical pathways and communication between different compartments in the brain [119], the tracers studies lack robust quantitative data. Moreover, it is not clear whether the obtained experimental results describe the physiology of the brain or they are just a consequence of the experimental method employed [92, 10]. Caveats regarding these experiments are raised by Hladky et al., [78].
In order to quantitatively assess the cerebral interstitial flows under physiological conditions of the brain, a computational model is developed in Chapter 3. The equations that describe the flow of ISF and transport of A\(\beta\) through the brain tissue (e.g. the Darcy law and the advection-diffusion equation, respectively) have been commonly employed for the study of fluid flow \cite{33,76} and drug transport in different tissues \cite{159}, including the brain \cite{64,80,160,161}. However, most of these studies adopted a simplified spherical geometry of the brain, rather than a realistic geometry. Hence, the model from this study is the first computational model that employs a realistic geometry of the human brain and accounts for the heterogeneity of the brain tissue by attributing distinct properties to the regions of grey and white matter, respectively. The closest models to this work are those of Nagashima et al., \cite{123} and Linninger et al., \cite{109}. The latter study investigated the CSF flow in the normal and hydrocephalic human brain and the computational grid was reconstructed from magnetic resonance images \cite{109}. However, the brain tissue was treated as a homogenous porous medium and the authors point out that a more advanced, physiologically consistent representation would include the white matter, resulting in spatial dependence of tissue properties such as permeability, porosity and diffusivity \cite{109}.

As a step towards a more physiological representation of the human brain, the image-based model from Chapter 3 considers a coronal section of the human brain and accounts for the distinct properties of the grey and white matter. In other words, the model captures the spatial dependence of tissue properties such as permeability, porosity, diffusivity, capillary surface area and A\(\beta\) production. Moreover, the model is implemented for the first time with the software FreeFem++ \cite{75}. Nagashima et al., \cite{123} used a similar mathematical model and accounted for some distinct properties of the grey and white matter, but in the coronal section of a cat brain. The model was applied within the context of brain edema. However, the authors imposed different boundary conditions that did not capture the modern view on ISF - CSF communication and solved the model using the Finite Element Method. It is worth emphasizing that none of these studies have been extended to the clearance of A\(\beta\) from the brain, hence the A\(\beta\) model from Chapter 3 represents a novel contribution. As a consequence of its unique features, the model yields original results that show for the first time the distribution of the intracranial pressure, water and soluble A\(\beta\) in a coronal section of a human brain. These results help elucidate some of the controversies regarding the production and clearance of both ISF and CSF. The model also allows investigation of the relative contribution of different clearance mechanisms of A\(\beta\). For example, by ‘knocking out ’some of
the clearance mechanisms, the model mimics accumulation of Aβ in the human brain. Possible future extensions and applications of the model are discussed in Chapter 6.

Further on, the work from Chapter 5 shifts the perspective regarding the motive force of one of the clearance mechanisms of soluble Aβ from the brain, namely the IPAD process. The novel hypothesis of vasomotion-driven IPAD proposes the cerebral vascular smooth muscle cells (VSMCs) as the motive force generators. Since the anatomical clarification of the IPAD pathways by Carare et al., [29], the leading theory was that the arterial pulse wave, generated by the heartbeat, represents the motive force of perivascular drainage in the brain [17]. In [52], it has been reviewed how cerebral vasomotion may be impaired in AD and mentioned that vasomotion could have a secondary contribution to the driving force of IPAD. On the one hand, the arterial pulse has still been considered the motive force, despite the fact that there was no solid quantitative data to attest this and, on the other hand, no experimental or theoretical tests of the involvement of VSMCs in the perivascular drainage of the brain have been done. The theory of arterial pulse-driven IPAD has been faced with some criticism, mainly due to the direction of flow and the necessity of an intramural valve [78]. The existence of such a valve within the wall of cerebral arteries has not been confirmed. Recently, the computational model of Diem et al., [53] showed that even with an intramural valve, the arterial pulsations cannot drive physiological rates of soluble metabolites along the IPAD pathways. The mechanism of vasomotion-driven perivascular drainage, proposed and modelled for the first time here, does not require an intramural valve and generates flow rates that are comparable with the physiological clearance rates of soluble Aβ from the brain. These results stimulate further investigation of the role of cerebral vasomotion in brain clearance mainly due to the fact the the VSMCs represent an accessible therapeutic target. The originality of the modelling techniques employed for the vasomotion-driven IPAD is further emphasized in Chapter 5.

Most of this research is in progress of submission to scientific journals. For example, the material in Chapter 3 is intended as a self-contained journal article. The results from Chapter 4 and Chapter 5 will be combined for another journal article. Some parts of this work have been presented already in the following formats:
Journal article


My main contribution in the above article was revision of blood vessels and the schematic representation of the peri-and para-vascular spaces, which is also presented in this thesis in Figure 2.2.

Conferences


Chapter 2

Background

2.1 Alzheimer’s disease: a problem of clearance

2.1.1 Global issue

AD is an age-dependent neurodegenerative condition, affecting mostly those over 65 years old. AD represents the most common form of dementia. Currently, 46.8 million people worldwide are living with dementia, among which 60% to 80% of the cases have AD. Ageing is the major risk factor and, accounting for increased longevity, it is estimated that the incidence of dementia will almost double by 2030, reaching 74.4 million and 131.5 million by 2050 [135]. Some of the clinical symptoms of AD include progressive and gradual impairment in cognition and memory loss, as well as difficulty in performing familiar tasks in daily life. Ultimately, AD is a fatal disease, with no curative or preventive intervention [102].

Dementia is caused by neuron (the nerve cell of the brain) dysfunction and neuron loss. More specifically, the neuropathology of AD includes intracellular deposition of hyperphosphorylated neurofibrillary tau protein (NFTs, flame-looking tau tangles) and extracellular amyloid-beta (Aβ) deposits. The tau protein is produced in all neurons and its normal function is to stabilize the microtubules within the axons of neurons. Following hyperphosphorylation, tau disassociates from microtubules and aggregates as NFTs, causing axonal damage, impaired intracellular signalling and synaptic transmission and, ultimately, cell death. The amyloid deposits are composed of the 38-43 amino acid peptide Aβ, with Aβ40 and Aβ42 representing the most common forms. Aβ can undergo a variety of conformational changes from monomers to soluble oligomers, fibrils
and solid plaques and it is believed that the process of $A\beta$ oligomerization contributes to neurotoxicity [147]. When present in high concentrations, the extracellular $A\beta$ accumulates as parenchymal amyloid plaques [153] and as vascular deposits within the walls of cortical and leptomeningeal arteries and capillaries (i.e. cerebral amyloid angiopathy, CAA) [17].

The haemorrhages and ischemic lesions driven by CAA result in cognitive impairment and dementia [15, 144]. CAA has been reported almost invariably at autopsy in 90% cases with AD [34] 95. In sporadic or late-onset cases of AD and CAA, there is little evidence for overproduction of $A\beta$ and the pathogenic mechanism indicates failure in the clearance of $A\beta$ [126]. It is commonly believed that the $A\beta$ abnormalities enhance the tau pathology, although the exact cause and effect of AD still remains elusive [69]. Possession of Apolipoprotein E4 (ApoE4) genotype (responsible for packing cholesterol) increases the presence of amyloid plaques and vascular $A\beta$ deposits by interfering with the $A\beta$ clearance mechanisms [74].

There are also familial or early-onset AD cases, when genetic mutations lead to increased production of toxic $A\beta 42$ and subsequent predisposition of vascular $A\beta$ accumulation within the brain. One example of genetic mutation that leads to $A\beta$ overproduction is the Down syndrome. Normally, the extracellular $A\beta$ protein results from the sequential cleavage of the amyloid precursor protein (APP), which is expressed in the synapses of neurons. Following synaptic activity (communication between two neurons), $A\beta$ is released from the neurons into the extracellular space (the brain interstitium). APP is located on chromosome 21. Patients with Down syndrome who have three instances of chromosome 21 (trisomy 21), instead of the normal two, develop AD without exception due to overproduction of $A\beta$ [102]. The familial AD is rare, representing only 1% -5% of AD incidence, while the remaining 99% - 95% are sporadic cases [103, 131]. Therefore, it is essential to understand the mechanisms by which $A\beta$ is cleared from the brain, if development of therapies for CAA and AD are to progress.

### 2.1.2 Two sides of the same coin: neurodegenerative and vascular AD

The limited success in the discovery of a long-term cure for AD could be partly due to the incomplete understanding of the AD aetiology. The changing view on the nature of AD over the last century is reviewed in [89]. In the 1900s, when the
first patient was diagnosed with dementia by Alois Alzheimer, AD was thought to be caused predominantly by hardening of the arteries. As a consequence, vascular factors were considered crucial factors in dementia. The view changed in the 1980s when Aβ protein was observed in parenchymal amyloid plaques and in vascular deposits as CAA (see Fig. 2.1). The Aβ deposition was thought to cause neurodegeneration and the amyloid cascade hypothesis of AD was proposed [132, 154]. According to this hypothesis, Aβ accumulation in the brain tissue triggers numerous downstream pathological events, causing in the end neuronal death. In particular, it has been proposed that the amyloid plaques induce the tau pathology and neurotoxicity.

The amyloid cascade hypothesis has been challenged based on the fact that the presence of amyloid plaques in the human brain does not correlate with cognitive decline [60]. Although the amyloid plaques are always present in AD brains, such plaques have also been reported in the cases of healthy, normally cognitive individuals [137]. Jack et al., [94] have proposed a temporal model of AD biomarkers for guiding in vivo staging of dementia which portraits the Aβ abnormalities as the initiators of the preclinical AD stage and the tau pathology as the marker of cognitive decline and clinical progression of dementia. The concept of preclinical AD describes the stage of Aβ accumulation prior to the appearance of cognitive impairment or other symptoms of dementia [174]. The loss of balance between the production and clearance of soluble Aβ results in increased Aβ concentration, causing deposition of misfolded Aβ in the brain; this can start even 10-20 years before the AD symptoms are clinically detectable. The Aβ deposition appears to reach a plateau before the signs of mild cognitive impairment are clinical, enhancing the tau pathology which peaks at moderate to severe stages of dementia [81, 94].

The current state of knowledge suggests the need to reassess the amyloid cascade hypothesis by considering the Aβ abnormalities a necessary but not sufficient factor to produce the clinical symptoms of AD [132]. Most of the sporadic AD cases are considered vascular rather than neurodegenerative [49]. The vascular deposits of Aβ as CAA are identified almost invariably (e.g. 78% - 98%) in post-mortem brains with AD [17]. The cerebrovascular diseases (e.g. CAA, small vessel disease) seem to share the highest risk factors with AD; these include ageing, hypertension and the genetic background (e.g. ApoE4 allele) [16]. The cerebrovascular alterations impair efficient neurovascular coupling and decrease the mechanical integrity of the capillary and arterial wall, leading to altered brain perfusion and even rupture of the vessel wall. Altered
cerebral blood flow sets the stage for ischemic brain injury and increases the $A\beta$ production, while breakdown of the blood brain barrier and arterial wall results in multiple cerebral microbleeds, inflammation and decreased $A\beta$ clearance \cite{19}. The resulting cumulative vascular pathology has been suggested as an important cause of brain atrophy which enhances progression and severity of AD \cite{16}. The presence of vascular lesions increases with the severity of CAA, showing no correlation with the parenchymal amyloid plaques \cite{95}. The most recent view is that AD is a type of dementia with mixed pathologies, as illustrated in Figure 2.1.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig21Copyright.png}
\caption{Alzheimer’s disease (AD): a problem of clearance in the brain. Top layer: changes suffered by the human brain with AD compared to the healthy brain. Image source: alzheimer’s association (alz.org). Bottom layer: the $A\beta$-driven neurodegeneration and the vascular dysregulation represent the extreme of a large spectrum of pathologies. Left-hand side: parenchymal $A\beta$ plaques, image source: Nature Reviews, Molecular Cell Biology \cite{147}. Right-hand side: cross section of a human cerebral artery with AD and CAA; $A\beta$ (red) is colocalized with the cerebrovascular vascular basement membrane (blue) and, in some regions of the wall, $A\beta$ completely replaces the VSMCs (green). The illustrated CAA case is from the Newcastle Brain Tissue Resource with permission from Prof R Carare.}
\end{figure}

No treatment for the prevention or complete cure of dementia is available at the moment. The most common therapy in AD is based on acetylcholinesterase inhibitors, drugs which inhibit the cholinesterase, i.e. the enzyme that breaks down the neurotransmitter acetylcholine (ACh). The cholinergic system that releases ACh plays an important role in memory and becomes dysfunctional in AD. The cholinergic therapy increases the level and duration of action of ACh, partly compensating for the dysfunctional cholinergic areas in the AD brains. However, the cognitive deficit seen in AD is not due to the lack of a certain neurotransmitter, but rather to disruption of communicating networks between various brain regions \cite{81}. Thus, salvation of neuronal networks by preventing the accumulation of $A\beta$ and NFTs in the brain appears as a therapeutic priority. The failure of all previous clinical trials focused on dissolving the amyloid plaques, especially in advanced stages of AD, shows that the simple clearance of plaques is not the answer \cite{68}.
As discussed by Holzman et al., [81], novel therapies targeting prevention and delay of cognitive deficit are needed and the design of clinical trials has to change. The outcome of clinical trials could be improved by including a cognitively normal population that is at high risk of developing dementia, rather than late-stage AD patients. The AD neuroimaging initiative (ADNI) is a multicentre study across the world focused on developing standardized markers (e.g., clinical, imaging, genetic, biochemical) for early detection and tracking of AD. The ADNI accomplishments since its inception are reviewed in [179]. Multi-modal imaging, combining magnetic resonance imaging (MRI), positron emission tomography (PET), CSF biomarkers and cognitive tests appears as the best diagnostic method for AD [179] [186].

The abnormal levels of Aβ in the human brain can be determined non-invasively with PET and CSF samples of Aβ42 [137]. MRI and CSF samples of tau help identify the presence of tau pathology in the brain of living individuals. The CSF samples are extracted from the lumbar region and show an increased tau/amyloid ratio in AD cases compared to the healthy case. Structural MRI shows reduction of grey matter (i.e. brain atrophy) and enlargement of CSF ventricles in AD cases [167]. The microscopic structural changes in the white matter, characteristic of AD, can be detected with diffusion weighted MRI methods, including diffusion tensor imaging (DTI). The parameters detected by DTI characterise the alterations in water diffusion through the brain tissue and their values are correlated with the disease state [8, 105].

The PIB-PET-Aβ acts as an AD marker for the preclinical stages of AD in living patients and mirrors the distribution of amyloid plaques reported post-mortem at autopsy [137]. Thus, PIB-PET allows for identification of AD pathology in cognitively normal individuals, providing very valuable insights for the design of clinical trials that could include the most likely subjects to experience imminent clinical decline [179]. The FDG-PET captures the whole AD pathology (e.g. Aβ and tau), showing a reduced glucose metabolism in the AD brains which is an indirect evidence of cognitive deficits [137]. Thus, FDG-PET represents a more appropriate marker of clinical progression and late stages of AD. With this in mind, the anti-amyloid treatments for enhancing Aβ clearance and other treatments for delaying cognitive decline should be initiated in the pre-clinical stage of AD, before the tau pathology is triggered [81, 174].
2.2 Clearance of the brain

The accumulation of Aβ in the brain of patients with AD raises the question of how Aβ is normally cleared from the brain and what hinders its clearance. The major risk factor is considered ageing, but the mechanisms of clearance are still debatable [17, 165]. It has been long thought that the brain does not have a conventional lymphatic system as the rest of the body. Lymphatic vessels were first described in 1987 in the dura mater (one of the outer most membranes surrounding the brain) of rodents, but they have not been seen in other regions of the brain [9]. Owing to progress in imaging power, the dura lymphatic vessels have been ‘rediscovered’ by [14] and [110] in the rodent brain. Recently, these vessels have been visualized noninvasively also in the human brain [5]. The existence of lymphatic vessels has not been confirmed in other regions of the human or rodent brain. Therefore, the question of how do fluid and soluble metabolites clear from the brain, especially from the cerebral cortex, still remains unresolved.

The field of clearance of the brain has been dealing with "rediscovered" systems (e.g. dura lymphatics) [14, 110], "new" systems (e.g. glymphatics) [92] and "renamed" systems (perivascular space to intramural periarterial drainage pathways) [29]. In order to keep some order, terminology must be properly clarified. The spaces and membranes considered to play a role in the clearance of the brain are schematically represented in Figure 2.2. It is emphasized that the IPAD pathways are within the arterial wall, while the other perivascular spaces are along the outside of the arterial wall.
Figure 2.2: Schematic representation of the intramural, peri- and paravascular pathways in the human cerebral cortex (not to scale). The subarachnoid space (SAS), filled with cerebrospinal fluid (CSF), is separated from the subpial space by the pia matter [7]. A leptomeningeal sheath (light pink) derived from the pia matter is also reflected on the walls of both arteries and veins that are crossing the SAS, thus separating the SAS from the cerebral cortex. Bundles of collagen are interposed in the subpial space and form the adventitia of leptomeningeal vessels, which is an expandable perivascular space. The pial sheath surrounding the leptomeningeal arteries in SAS continues to coat the arteries as they penetrate the cortex and is closely applied to the outer basement membrane of vascular smooth muscle cells (VSMCs). The middle layers of basement membrane (dark green), situated between layers of VSMCs, represent the intramural perivascular drainage (IPAD) pathways for solutes out of the brain towards the lymph nodes from the neck. For the sake of simplicity, one layer of VSMCs spiralling within the arterial wall is illustrated only. The direction of clearance along the IPAD pathways is given by the green arrows. The basement membrane of the glia limitans (dark grey) is closely applied to the pia matter as the artery enters the brain; thus another narrow perivascular space is created between these two membranes [184] which has been promoted as a ‘paravascular space’ as part of the glymphatic system (dark blue arrows) [92]. Image source: [17].
Circulation in the brain. The brain has three major circulations that take place along different pathways: blood, ISF and CSF circulation, respectively. For instance, the blood circulation involves transport of nutrients and oxygen from the heart to the tissue through the lumen of arteries. Communication between the cerebral blood and the brain tissue is highly restricted by the blood brain barrier (BBB). Oxygen and important nutrients can diffuse easily across the barrier, but other substances, such as Aβ, require special transporters [4].

Secretion of water in the brain at the BBB is also a debatable and complex process dependent on hydrostatic, oncotic and osmotic pressures. The reader is referred forward to the model from Chapter 3 for modelling of this process. It is noted that the concept of BBB section of water is commonly accepted, although no direct evidence exists. The critical analysis made by Hladky et al. [79] suggests that the BBB could easily display the required properties (polarity of the BBB) for net secretion of water in the brain. For instance, within the BBB, some transporters, such as Na⁺,K⁺-ATPase pump, may be found in higher number on the abluminal side of the barrier than on the luminal one, generating in this way net secretion of Na⁺ into the brain, which implies also net water into the brain, as water follows salt.

The water secreted in the brain, together with other solutes found in the extracellular spaces of the brain form the ISF. The extracellular spaces, despite being only 20-50 nm in width, occupy all in all 20% of the brain volume and they form the brain interstitium; this is filled with ISF, providing a reservoir of ions and nutrients and also a conducting environment for chemical and electrical signals between brain cells. The ISF can be cleared out from the brain in two distinct ways: (i) bulk flow (down a pressure gradient) through the interstitium towards the CSF compartments (the subarachnoid space (SAS) and the brain ventricles) from where, subsequently, clears either into the blood or to the cervical lymph nodes by CSF flow; (ii) direct clearance to the cervical lymph nodes along the IPAD pathways, without any exchange with the CSF [17]. These two aspects are also considered in the global clearance model from Chapter 3.

Clearance of Aβ from the brain. Aβ is produced by the human brain under normal conditions and in order to prevent toxic accumulation of Aβ in the brain, it is critical that Aβ production is equally compensated by its clearance [47, 153]. Aβ is degraded by enzymes [56, 114], transported into the blood via lipoprotein receptor related protein (LRP)-1 [51] or cleared along the walls of capillaries and arteries (i.e. along IPAD pathways) [73]. Efflux of Aβ into the
2.3. PERIARTERIAL DRAINAGE OF SOLUTES FROM THE BRAIN

Blood at the BBB via the LRP-1 transporters is considered to account for up to 75% of Aβ clearance [165, 157], but this mechanism fails with aging and in AD [50]. The IPAD pathways for soluble Aβ are effectively the lymphatic drainage routes of the brain [164, 30] and may become increasingly important with ageing, in the face of failure of alternative clearance mechanisms.

The transport of ISF and CSF in the brain has also been investigated in silico [63]. The exchange of CSF with the cerebral vasculature and ISF was modelled using compartmental or lumped-parameter models [27]. Although such models are useful for investigating the transition from a normal to a diseased system, the compartmental models are limited by the absence of spatial variation, i.e. fluid velocity and pressure variation within an individual compartment cannot be modelled. One common approach for modelling the cerebral interstitial flows is based on continuum mechanics and considers the brain tissue a poroelastic biphasic material with a (deformable) solid phase and a fluid phase. Such a biomechanical strategy has been employed for modelling several brain disorders (e.g. hydrocephalus, brain edema), as well as drug delivery to the brain [123, 160, 161, 178]. Most of these studies will be discussed in more detail throughout this thesis for comparison with the novel models developed here. The relative contribution of the Aβ clearance mechanisms is modelled in Chapter 3, while the underlying mechanisms of IPAD are investigated in Chapter 5.

2.3 Periarterial drainage of solutes from the brain

In order to lay the foundations for the modelling the IPAD process, some brief anatomy and physiology of cerebral arteries is presented below; this is followed by a detailed discussion of the experiments that led to the discovery of the IPAD pathways. The section closes with a wider analysis of the experimental procedures and mathematical terminology commonly employed for quantifying the clearance of solutes from the brain.

2.3.1 Anatomy and physiology of cerebral arteries

The cerebral arterial wall is made of tunica intima (the endothelial cells and their basement membrane), tunica media (VSMCs and their basement membrane)
and tunica adventitia (present only in the larger extra-cerebral arteries from the surface of the brain). Other surrounding membranes are illustrated in Figure 2.2. The main features of cerebral arteries that differentiate them from the systemic (non-cerebral) arteries are the lack of external elastic lamina, the presence of tight-junctions between the endothelial cells (creating in this way the BBB) and the activity of the neurovascular unit (comprised of endothelial cells, pericytes, VSMCs, glial and neuronal cells).

The VSMCs represent the major structural component of the cerebral arterial wall; these are spindle-shaped cells approximately 20-60 $\mu$m long and 4 $\mu$m wide at nuclear region. These cells are arranged circumferentially around the arterial lumen, with the number of layers varying with species and the size of the vessels \[38, 106\]. The VSMCs synthesize their own basement membranes (BM)s as thin fibrous extracellular matrix layers and adhesion to this membranes is critical for the survival of the muscular cells. For example, biochemical signals (e.g. growth factors, signalling proteins) and mechanical signals (e.g. tensile and shear forces) are transmitted to the VSMCs through their BMs \[175\]. As it will be discussed later on, the cerebrovascular BMs are considered to play a role also in the clearance of solutes from the brain.

The arterial VSMCs are contractile cells and, under physiological conditions, they are in a sustained partial constricted state, generating a basal (or resting) vascular tone. Various mechanisms increase or decrease the basal tone, including neuronal metabolic activity, arterial pressure, shear stress and different types of innervation \[136\]. Owing to their contractile properties, the VSMCs are able to significantly alter the diameter and thickness of the artery. Further contraction of the VSMCs from their basal tone (i.e. active response) generates an active tension. During contraction, the VSMCs become thicker and shorter and, subsequently, the arterial diameter decreases, a process known as vasoconstriction. The opposite effect is known as vasodilatation, during which the VSMCs become more elongated and thinner and subsequently the arterial diameter increases. Vasodilatation is a passive process because as the VSMCs relax, the active tension is lost. Considering that the flow through a vessel depends on the fourth power of the radius of the vessel, the VSMCs of the cerebral arteries play an essential role in the regulation of cerebral vascular resistance and, subsequently, cerebral blood flow. Numerous studies address this aspect, as reviewed in \[181\]. In this study, the role of the VSMCs in the clearance of ISF and soluble A$\beta$ from the brain is investigated for the first time; a detailed analysis is given in Chapter 5.
2.3. PERIARTERIAL DRAINAGE OF SOLUTES FROM THE BRAIN

The VSMCs have the ability to sense the changes in arterial pressure inside the lumen of the vessel and respond accordingly. This response is known as myogenic tone and is an intrinsic property of the VSMCs. Moreover, the VSMCs may present spontaneous contractions due to changes in the intracellular concentration of calcium \[127\]. The local contraction of one VSMC is transmitted to the neighbouring muscular cells via gap junctions, generating in this way a contraction wave \[155\]. The spontaneous rhythmic oscillation in vascular tone conducted along the arteries is known as vasomotion and is independent of heart beat and respiration cycle \[133\]. Although vasomotion has been observed in numerous vascular beds, not only cerebral ones, its physiological implications remain unclear \[1\]. Modelling studies suggested that vasomotion may have a role in facilitating blood and oxygen transport to the tissue, especially under hypoxia conditions \[31, 62, 67, 170\]. The ways in which vasomotion is affected in AD have been reviewed in \[52\]. In this study, the ways in which vasomotion could contribute to clearance of solutes from the brain are investigated in Chapter 5.

2.3.2 Intramural periarterial drainage (IPAD)

Early tracer experiments showed that ISF is cleared from the brain tissue by bulk flow (down a pressure gradient). The ISF bulk flow occurs along preferential channels, such as the perivascular spaces of arteries and the white matter fibre tracts \[45, 164\]. The anatomical details of these pathways remained unclear until the era of confocal and multiphoton microscopy, when the BMs interposed between layers of arterial VSMCs have been identified as the IPAD pathways in the rodent brain \[29, 120\]. Extensive work has been done in order to assess the transport of solutes along the IPAD pathways during aging \[72\] and under physiological and pathological conditions, such as presence of CAA \[73\], possession of APOE4 \[183\], consumption of a high-fat diet \[71\] and after ischemic stroke \[10\]. The aforementioned experiments suggest that soluble tracers injected in the brain interstitium mix with the cerebral ISF and enter the BMs of capillaries. Subsequent drainage towards the leptomeningeal arteries from the surface of the brain occurs along the BMs of arterioles and small arteries. Eventually, the solutes reach the lymph nodes in the neck along major cerebral arteries. In other words, an outflow of solutes appears to take place within the walls of cerebral capillaries and arteries, in the opposite direction of arterial pulsations and blood flow, as illustrated in Figure 2.2. The distribution of tracers within the capillary and arterial wall is similar to that of the vascular...
Aβ deposits specific to CAA \[134, 180\]. These findings suggest that Aβ is eliminated from the human brain along the IPAD pathways and failure of this clearance mechanism leads to the onset of CAA.

The IPAD process seems to be a relatively fast clearance mechanism. A total time for the clearance of solutes from the brain interstitium into the wall of cerebral arteries can be inferred to be between 30 minutes and 3 hours based on the observations of Carare et al., \[29\]. Five minutes after injection in the deep layers of grey matter (the striatum), tracers were diffused in the brain interstitium and some tracers were detected in the wall of cerebral capillaries and arteries. Thirty minutes after injection, tracers were still present in the brain interstitium and in the basement membranes of the intra-cerebral arteries, while no tracers were seen in the walls of cerebral capillaries. An explanation for the latter observations has not yet been provided. Three hours after injection, no tracers were present in the interstitium or in the basement membranes of any cerebral blood vessels. However, some tracers were identified in the macrophages (cells that engulf debris and pathogens) sitting on the wall of cerebral arteries. Such a pattern was observed in different cerebral arteries, including the small intra-cerebral ones and the large leptomeningeal ones, even 24 hours later \[29\]. It is believed that the solutes from the brain interstitium reach the wall of arteries from the surface of the brain by bulk ISF flow along the basement membranes of the cerebral arteries. Although very useful in mapping the anatomical pathways of clearance, the experiments from \[29\] are limited by the fact that the analysis of drainage is usually performed with histological stains and microscopy in post mortem tissue. Recently, real-time imaging confirmed the perivascular drainage of solutes along the cerebral arteries (not veins), as well as the presence of solutes within the BMs of arterial VSMCs \[10\].

### 2.3.3 Critical analysis of tracer experiments

Here, a quantitative analysis of the most representative animal experiments in the field of clearance of solutes from the brain is made. The high discrepancy in the experimental values (e.g. time of clearance between 20 min - 15 hrs) reported by different groups, which assessed the same type of clearance problem (e.g. perivascular drainage), motivates a close analysis of their experiments and their mathematical interpretation of experimental data. By doing so, also important parameters that will appear in the quantitative physiological models from the next chapters are determined. The spatial variation in the production
and clearance of solutes from the brain is ignored for now, but is included in the model from Chapter 3.

In an attempt to map the clearance pathways of ISF and soluble Aβ from the brain, injection of anatomical tracers in the rodent brain has been commonly employed over the years. Removal of tracers from the brain tissue can occur by various mechanisms. One instance is the ‘bulk’ clearance mechanism that acts (nearly) uniformly across the brain. The ‘bulk’ clearance defined here can be seen as a sink effect created by the LRP-1 transporters, found on the endothelium of cerebral capillaries, facilitating the Aβ efflux into blood. Similarly, the cerebrovascular BM that represent the IPAD pathways and display a rich distribution over the entire brain tissue can act as suction pipes that substract the ISF from the neighbourhood of the vessels in a (nearly) uniform manner. In a different manner, the soluble tracers can move by advection through the interstitium, i.e. transported by bulk ISF flow down a pressure gradient. As long as the pressure in the ISF is higher than that in CSF, solutes will flow towards the CSF compartments. Lastly, tracers could simply move by diffusion (movement down a concentration gradient) through the brain tissue towards the CSF compartments.

When taken separately, each of the above transport mechanisms is mathematically described by different equations. The bulk clearance mechanism can be modelled as an exponential decay - type problem

$$\frac{dc}{dt} = \Psi - \Sigma c, \quad \text{with} \quad \Sigma = \Sigma_{BBB} + \Sigma_{IPAD}. \quad (2.1)$$

Here, $c$ is the concentration of the solute at time $t$, $\Psi$ is the production rate per unit volume and $\Sigma$ is the clearance constant, representing the total ‘bulk’ clearance of soluble Aβ. $\Sigma_{BBB}$ and $\Sigma_{IPAD}$ denote the removal rate of Aβ across the BBB due to specific transporters and along the IPAD pathways, respectively.

In order to maintain a constant Aβ concentration in the brain, its production must be counterbalanced by its clearance. Hence, at steady state, the left-hand side of equation (2.1) is zero and $\Psi = \Sigma c$. This is useful for determining the production of Aβ, given that the normal concentration of Aβ in the brain tissue and the half-life for its total clearance are known. The total soluble Aβ in the brain tissue, under normal condition, has a concentration of 6.4 ng·g$^{-1}$ and the half-life for its total clearance from the brain tissue was found to be
25 minutes by Shibata et al., [157]. This means that the total Aβ clearance, including efflux at the BBB, lasts nearly 35 minutes. Substituting these values in the relationship \( \Psi = \Sigma c \), yields an approximate Aβ production rate of 0.17 ng·min\(^{-1}\)g\(^{-1}\).

In the case of tracer experiments, relatively high amounts of soluble molecules are injected into the brain over a short period of time. The molecules that are commonly used (e.g. dextran) are not produced by the brain, so there is no source term (i.e. \( \Psi = 0 \)). Moreover, such solutes are not (usually) cleared at the BBB (i.e. \( \Sigma_{BBB} = 0 \)), providing a way to measure the effectiveness of other removal mechanisms such as the IPAD routes. In this instance, equation (2.1) reduces to

\[
\frac{dc}{dt} = -\Sigma_{IPAD}c, \tag{2.2}
\]

with solution

\[
c(t) = c_i e^{-\Sigma_{IPAD}t}, \tag{2.3}
\]

where \( c_i \) denotes the initial concentration.

The removal rate \( \Sigma \) can be expressed in terms of half-life, denoted \( t_{1/2} \), or in terms of the mean life, denoted \( \tau \), as

\[
t_{1/2} = \frac{\ln(2)}{\Sigma} = \tau \ln(2). \tag{2.4}
\]

In the absence of production, the half-life is the time required for the decaying concentration of solutes to reach half of the initial value.

Equation (2.3) show that clearance via the IPAD pathways describes an exponential decay. Such an analysis has been adopted by Arbel-Ornath et al., [10] where perivascular drainage of dextran along cerebral arteries was observed in vivo following injection of the solute in the mouse cortex. From their experiments, a half-life of 10 minutes can be inferred, suggesting that perivascular drainage is very fast (e.g. \( \Sigma_{IPAD} \approx (15 \text{ min})^{-1} \)). It is noted that the values reported by Arbel-Ornath et al., [10] \( t_{1/2} = 10 \text{ minutes} \) are smaller than those reported by Shibata et al., [157] \( t_{1/2} = 25 \text{ minutes} \) and this difference may arise from different experimental procedures. In [10], the fluid was injected into the cortex at very high rates and pressures, which may have damaged the
Another set of experiments from Cserr and colleagues adopted an exponential decay-type problem for interpretation of their experiments on clearance of tracers from the rodent brain. Very different removal rates, with a half-life of 10 hours ($\Sigma = (15 \text{ hrs})^{-1}$), for albumin tracers injected in the grey and white matter of the rat brain were reported in [164]. The authors adopted an exponential decay analysis for their experimental data. It is worth mentioning that the quantitative analysis was made with very few data points (e.g. 3 points) over a time-span of 18 hours. Therefore, it is not clear if clearance truly occurred in an exponential manner. Future experiments of this kind should include more data points. Moreover, the exponential analysis adopted in [164] is justified only if the clearance of tracers is assumed to be due to a sink mechanism such as IPAD. Indeed, accumulation of tracers within the perivascular spaces of large cerebral arteries (e.g. Circle of Willis) by 2 hours after injection was reported. However, the authors also concluded that ‘bulk flow’ occurs along the white matter; this should actually be seen as advection due to hydrostatic pressure gradients between the ISF and CSF, rather than a sink mechanism. If this is the case, then a more appropriate equation for describing the clearance of solutes observed in [164] is

$$\frac{dc}{dt} + \nabla \cdot (q c) = -\Sigma_{IPAD} c,$$

where $q$ is the interstitial Darcy flux through the brain interstitium driven by a pressure gradient.

If no sink effect is considered, i.e. $\Sigma_{IPAD} = 0$, then the movement of solutes by convection through the brain tissue is described by

$$\frac{dc}{dt} + \nabla \cdot (q c) = 0,$$

which has a travelling wave type solution. In other words, experiments investigating the clearance of solutes from the brain by advection, without considering the sink effect of the BBB or that of the IPAD pathways, cannot be fitted with an exponential decay.

Careful differentiation between the curves of exponential decay and diffusion should also be made. The substance injected in some restricted area of the brain may diffuse from the source point and the concentration at distance $r$ from the
source will be given by

\[ c = \frac{M}{8(\pi Dt)^{3/2}}e^{-r^2/(4Dt)}, \quad (2.7) \]

where \( M \) denotes the total amount of substance diffusing and \( D \) is the diffusion coefficient ([44], p 29).

The common belief is that the anatomical tracers injected into rodent brains are cleared by advection along the IPAD pathways, given that tracers with different molecular weights (e.g. 3 kDa dextran, 40-70 kDa albumin) presented similar clearance patterns [29, 45]. Diffusion is believe to dominate in the grey matter, where the very low permeability of the brain tissue does not allow for significant bulk ISF flow to develop [13, 80, 96].

In the light of the above, it is difficult to reach a consensus and determine the characteristic time of fluid clearance along the IPAD pathways. A very wide range of clearance rates for perivascular drainage of soluble tracers, e.g. from 15 minute to 15 hours, has been reported by \textit{in vivo} and post-mortem analysis, respectively. The reason for this may be the lack of standardized experimental and mathematical procedures for assessing the clearance of tracers injected in the brain. Additional experiments are needed and they should be designed in a consistent manner. For example, a standard amount of solutes injected in the brain and a well controlled pressure of injection should be used in all experiments. More importantly, the experiments should be tailored according to the mathematical analysis used for their interpretation. Accounting for the complexity of brain, most probably all of the above clearance mechanisms act simultaneously and therefore the most appropriate model would be the advection-diffusion equation with both a source term (for A\( \beta \) production) and a sink term (for A\( \beta \) ‘bulk’ clearance).
Chapter 3

Modelling the global clearance of soluble Aβ from the human brain

3.1 Introduction

The regulation of ISF volume and movement in the brain has been a subject of debate for years. For instance, the ways in which the unique features of the brain (e.g. the lack of a conventional lymphatic system and the presence of the BBB) impact the regulation of ISF are still not clarified [79]. In order to maintain a relatively constant amount of ISF in the human brain (e.g. 280 ml), it needs to be cleared at rates similar to the rates of production. As these rates are difficult to determine in the living brain, they are commonly estimated from tracer studies in the animal brain [3]. This approach has yielded various and controversial findings, which means that the production and clearance of ISF in the brain still remain unresolved. Here, a physiologically-based model of the human brain is developed in order to test the plausibility of the main production and clearance mechanisms of ISF proposed in literature. Early views, as well as contemporary ones, are tested.

The contribution of the ISF flow to the clearance of soluble molecules, including Aβ, is also a debatable process. The most common view is that substances released into the brain interstitium move predominantly by diffusion [124]. Diffusion is driven by concentration gradients and, over short distances, is efficient and essential for the function of brain cells. For example, the nutrients delivered by blood vessels diffuse through the interstitium for approximately 20 micrometers in order to reach the brain cells. Similarly, Aβ produced by
neurons diffuses over tens of micrometres towards capillaries for subsequent removal across the BBB or drainage along the vascular basement membranes \[165\]. The efficacy of diffusion is limited by the molecular weight of the solutes. However, diffusion is also inefficient over longer distances as can be seen from estimating the diffusion timescale for diffusive transport of Aβ across the human brain. The diffusion timescale \(\tau\) for a solute over a distance \(L\) (i.e. the typical time required for appreciable transport over length \(L\)) is given by the formula \(\tau = L^2 / D\), where \(D\) is the diffusivity of the solute. The effective diffusivity of Aβ in the grey matter of the brain is around \(8 \times 10^{-7}\) cm\(^2\)/s \[163\] and for it to diffuse over 1 cm (a significant fraction of the human brain \[57\]) would take over 14 days. Nonetheless, recent modelling studies have reported that diffusion is the dominant transport process through brain tissue in the absence of significant interstitial flow of soluble tracers through the interstitium \[13, 80, 96\]. It is emphasized that these studies have only looked at the properties of the grey matter, over relatively short distances at the order of hundreds of micrometres. On the other hand, early tracer studies reported interstitial flow velocities in the range of 5-14.5 µm min\(^{-1}\) that seemed to occur in the white matter towards the CSF compartments \[46, 146, 164\].

A global quantitative picture of the cerebral interstitial flows and the dynamics of soluble Aβ in the human brain is still missing. Moreover, the distribution of intra-cerebral pressure in the human brain is also unknown. The physiological value of intracranial pressure (ICP) is considered to be within the range of 5-15 mmHg \[138\]. However, the experimental methods employed to determine the ICP do not allow for a full description of pressure distribution within the intra-cerebral regions \[18\]. With this in mind, this study aims to investigate the distribution of intra-cerebral pressure in the human brain, clarify the extent to which ISF contributes to the production of CSF due to efflux into the lateral ventricles and SAS and, subsequently, how the global ISF flow through the interstitium contributes to the removal of soluble Aβ from the brain. To this end, this study involves: (i) development of a mathematical model for global ISF flow through the brain interstitium accounting for the distinct properties of the grey matter and the white matter, (ii) theoretical application of the flow model to predict Aβ concentration within the brain based on physiological production rates in a healthy person and (iii) assessment of the efficacy of ISF flow through the interstitium in the clearance of Aβ from the brain in the event of failure of other clearance mechanisms. This is the first model that includes both a realistic geometry of the human brain and a heterogeneous distribution of tissue properties.
An early computational study employed a realistic geometry of the cat brain with numerous physiological parameters in order to investigate the pressure and elastic deformations of the brain within the context of vasogenic brain edema [123]. The focus was on how a brain injury affects the intracranial pressure, the tissue deformation and the water content. The model does not capture the modern concept of ISF-CSF communication across the pial layer lining the SAS and it has not been applied to the transport of Aβ in the brain. Linninger et al.[109] investigated the CSF dynamics in the normal and hydrocephalic brain using image-based modelling of the human brain and accounting for the ISF-CSF communication. As the author remarked, their homogeneous model does not include physiologically-advanced assumptions such as the contribution of the white matter [109]. The presence of the white matter increases the complexity of the system by introducing a spatial dependence of material parameters, such as tissue permeability, diffusivity, capillary surface area and metabolic water production. Other studies modelled the brain tissue by using a simplified circular geometry of the brain and their focus was on the elastic deformation of the brain under edema and hydrochephalic conditions [64, 160, 161]. In the model developed here, a coronal section of the human brain is used, the differences between the grey and white matter are accounted for, the ISF-CSF communication is assessed at both brain-ventricle and brain-SAS interface and the model is applied to the clearance of soluble Aβ from the brain.

The rest of this chapter is structured as follows. Section 3.2 presents the model formulation and the physiological significance of the equations. The results for the distribution of intra-cerebral pressure in the human brain, interstitial flows and the clearance of Aβ are presented in Section 3.3. The implications of the obtained results and their comparison with experimental findings available in literature are discussed in Section 3.4. Details of the computational implementation of the model are given in Section 3.5.

### 3.2 Model formulation

The computational model of this study is comprised of two parts: the flow model for the movement of ISF (which has density and viscosity close to water) through the brain interstitium and the clearance model for the global removal of Aβ from the human brain. The possible presence of ions in the ISF is not explicitly considered in this model. The flow model is based on the early view on the ISF volume regulation proposed by Bradbury [26]. Accordingly, in this model, the
following are assumed: ISF (i) is secreted into the brain at the BBB, (ii) moves by interstitial flow through the brain interstitium towards the CSF compartments due to intra-cerebral pressure gradients and (iii) communicates with the CSF compartments via permeable membranes lining the lateral ventricles and the SAS. Further on, the model is extended by including the metabolic production of ISF and also the clearance of ISF due to bulk mechanisms, such as the IPAD mechanism. The contribution of brain metabolic activity to the production of water in the brain has been recently reviewed in [79]. Once the flow model is solved, the efficacy of interstitial flows to the removal of Aβ from the brain at physiological production rates of the proteins, in the face of progressive failure of all the other clearance mechanisms, is investigated.

The domain containing the brain tissue enclosed by the CSF compartments (e.g. lateral ventricles and SAS) represents a coronal section of the human brain shown in Figure 3.1 and it is extracted from an image of the human brain using the computational method described in Section 3.5. The brain domain is denoted by $\Omega(x, y) \subset \mathbb{R}^2$ with the boundary $\delta \Omega = \Gamma_S \cup \Gamma_{LV} \cup \Gamma_{RV}$, where $\Gamma_S$ is the SAS boundary, $\Gamma_{LV}$ is the left lateral ventricle and $\Gamma_{RV}$ is the right lateral ventricle. The position vector of any point within the brain domain is denoted by $x \subset \Omega$. For the purpose of this study, the cerebellum is ignored, as it is disconnected from the cerebrum. The particular coronal section of the human brain, shown in Figure (3.1), has been chosen because it captures both the grey and the white matter and also regions of grey matter of significantly different sizes. It is noted that some significant regions of grey matter, such as the putamen and the caudate nucleus, are not included in this model. Such regions may be captured by different coronal sections, moving from the middle of the brain towards the edges of the brain. By doing so, the presence of the grey matter will decrease, while that of the white matter will increase. Owing to its relatively lower permeability, the grey matter may hinder the transport of fluid and solutes (e.g. Aβ) out of the brain more than the white matter, increasing in this way the risk of fluid and amyloid deposition. Therefore, special attention is given to the removal of ISF and Aβ from the grey matter. Consequently, the particular coronal section of the human brain chosen here may be considered the most representative one for the purposes of this model due to the fact that it contains the highest amount of grey matter (e.g. cerebral cortex and thalamus).

The brain tissue consists of two distinct components, the grey matter and the white matter, here denoted by $\Omega_g$ and $\Omega_w$, respectively. In general, the grey matter is composed mainly of cell bodies that produce Aβ and has a relatively
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Figure 3.1: Image-based construction of brain mesh. Top image: anatomical coronal section of a human brain and the segmented version representing the input geometry of the model (middle image); bottom image: brain mesh generated in FreeFem++. The image with the anatomical coronal section is from the Laboratory of Affective Neuropharmacology from University of Michigan.

low permeability to interstitial flow. The cerebral cortex is a thin layer of grey matter and presents regional differences in thickness between 1-4.5 mm [57]. On the other hand, the thalamus (the walnut looking structure) is a large region of grey matter up to 5 cm long. The white matter contains mostly myelinated axons and very few cell bodies. The bundles of axons, also known as fibre tracts, provide a much higher permeability to interstitial flow. This suggests that the movement of ISF and subsequent clearance of Aβ may not only differ between the grey and white matter, but also between different regions of the grey matter.

The brain tissue, especially the grey matter, is supplied by a rich network of capillaries. The secretion of ISF at the BBB of cerebral capillaries has not been confirmed experimentally due to technical difficulties, but numerous studies
suggest that ISF secretion into the brain occurs and leads to a cumulative interstitial flow, as it has been reviewed in [79]. ISF can also be produced from the oxygenation of glucose subsequent to metabolic brain activity. Here, the relative contributions of the metabolic activity and secretion across the BBB to the total production of cerebral ISF is investigated. The metabolic production of water is integrated into the model as a constant source term, while the secretion rate of water at the BBB depends on the pressure difference between the capillaries and the brain interstitium. The capillary surface area per unit volume of brain tissue is three-fold higher in the gray matter than in the white matter [162]. This is in agreement with the recent results from [88], showing that the extraction of oxygen and the glucose oxygenation is three-fold higher in the grey matter than in the white matter. Taken together, these findings suggest different rates of ISF production in the grey matter compared to the white matter.

In this model, the ISF bathing the brain tissue communicates with the CSF compartments through encapsulating membranes, namely the ependymal and pial-glial layers which line the lateral ventricles and the SAS, respectively. The direction and amount of ISF flow is determined by the hydrostatic pressure gradient between the brain ISF and CSF. As long as the interstitial pressure is higher than the CSF pressure, the ISF flows towards the CSF compartments. It is emphasized that the interstitial pressure gradient is not imposed, but rather an output of the model; this is a notable improvement on previous studies which impose a pressure gradient for transport of solutes in the grey matter, e.g. [80]. The flux of ISF into the CSF compartments is expected to wash away the soluble Aβ protein released into the interstitium and, here, it is investigated to what extent this transport mechanism contributes to the total removal of soluble Aβ from the human brain. There is one way coupling between the interstitial fluid and the Aβ protein; that is the dynamics of ISF influences the Aβ concentration in the brain, but changes in the Aβ concentration do not impact the interstitial pressures and flows. Another possible way for ISF efflux from the brain is via the IPAD pathways, which may be seen as a sink term, as it was discussed in Section 2.3.3.

The brain tissue is modelled as a heterogeneous fluid-filled porous medium accounting for the distinct properties of the grey and white matter in a healthy human brain. Specifically, brain properties such as the capillary surface area per unit tissue, the interstitium permeability and porosity, as well as the metabolic production of water and Aβ in the brain, have a spatial-dependence over the simulated domain, i.e. different values in $\Omega_g$ and $\Omega_w$, respectively. The $\Omega_g$ and
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$\Omega_w$ domains are each considered to be homogeneous and isotropic, making this aspect one of the limitations of this study. The anisotropy of the white matter (direction dependent properties) that arises from the arrangement of the axonal fibres is not included. This approach is justified by the scarcity of experimental information on the properties of the human brain and possible extensions of the model are discussed in Section 3.4.

$A\beta$ production is assumed to occur at physiological production rates and only in the grey matter where most of the neurons' nuclei are found (see Appendix A for exact values). The production of $A\beta$ must be efficiently counteracted by its clearance, in order to prevent accumulation of pathological levels of $A\beta$ in the brain. There are numerous clearance mechanisms that may act at the same time, but over different time-scales. Although the exact contribution of all $A\beta$ clearance mechanisms is still debatable, there is some consensus that some of the mechanisms are fast, with a timescale of less than one hour [157], while others are slower, taking up to three hours to fully remove $A\beta$ from the brain tissue [39]. The fastest clearance mechanism is considered the efflux of $A\beta$ into the blood at the BBB via specific transporters [157]. The precise time span for the complete clearance of soluble $A\beta$ from the brain tissue into the cervical lymph nodes along the IPAD pathways is unknown and difficult to determine experimentally, given that various transport mechanisms of $A\beta$ act concomitantly. Instead, similar solutes, like dextran, which are cleared only by ISF flow, disappeared from the IPAD pathways by three hours after injection [29]. In order to account for both types of clearance along privileged pathways (e.g. BBB and IPAD), a sink term with two components is included in the model. It is emphasized that none of the privileged pathways are modelled explicitly, only their bulk effect.

Bringing it all together, the concentration of $A\beta$ in the brain yielded by the model is the balance between the $A\beta$ production by the grey matter and its clearance by various mechanisms, namely: (i) diffusion and (ii) interstitial flow through the brain interstitium and (iii) transport via privileged pathways modelled by the sink term. The efficacy of $A\beta$ transport through the brain interstitium, in the face of progressive failure of the privileged pathways, is investigated.
CHAPTER 3. MODELLING THE GLOBAL CLEARANCE OF SOLUBLE Aβ FROM THE HUMAN BRAIN

3.2.1 ISF flow through the brain interstitium

The brain tissue is commonly treated as a porous medium [124] and the movement of ISF through the interstitium is described by Darcy’s model

\[ q(x) = -\frac{k(x)}{\mu} \nabla p(x), \quad (3.1) \]

with

\[ k(x) = \begin{cases} 
  k_g & \text{in } \Omega_g, \\
  k_w & \text{in } \Omega_w,
\end{cases} \]

where \( k(x) \) is the permeability of the interstitium, taking different values in the white and grey matter, as given in [160]. In addition, \( q[m \cdot s^{-1}] \) is the ISF flux through the interstitium, \( p[Pa] \) is the interstitial pressure and \( \mu[kg \cdot m^{-1} \cdot s^{-1}] \) is the ISF viscosity.

In order to account for the production of ISF in the brain, a volumetric source term \( Q[cm^3 \cdot s^{-1} \cdot cm^{-3}] \) is added to the mass conservation equation, such that the conservation of ISF mass reads

\[ \nabla \cdot \left( -\frac{k(x)}{\mu} \nabla p(x) \right) = Q(x), \quad \text{where } Q(x) = Q_B(x) + Q_M(x). \quad (3.2) \]

Here, \( Q \) comprises of contributions from the metabolic activity of the brain (denoted \( Q_M \)) and from the BBB (denoted \( Q_B \)). These terms will be explained in detail below, but first an important remark is made. Although the model given by equation (3.2) has been used previously by other authors [63, 109, 161], the model is not complete because it does not account for the existence of sink mechanisms that could clear uniformly the ISF from the brain. Hence, equation (3.2) must be extended to the form

\[ \nabla \cdot \left( -\frac{k(x)}{\mu} \nabla p(x) \right) = Q(x) - \Sigma_{IPAD}, \quad (3.3) \]

where \( \Sigma_{IPAD} \) represents the removal rate of ISF by bulk clearance along the IPAD pathways. Even this model may not be complete, as other potential clearance mechanisms of ISF could exist. For instance, researchers have been talking about perivascular and/or paravascular spaces (PVS), or equally, Virchow-Robin spaces [78]; such spaces are between the arterial wall and the brain tissue and are different than the IPAD pathways located within the arterial wall. Given that the existence of PVS in the grey matter is questionable [17], the potential
clearance of ISF along the PVS is ignored in this model.

Regarding the production of ISF, in this model, $Q_M$ is a known function, taking different values in the grey and white matter according to the experimental findings in [88] and is written as

$$Q_M(x) = \begin{cases} 
Q_{Mg} & \text{in } \Omega_g, \\
Q_{Mw} & \text{in } \Omega_w. 
\end{cases}$$

$Q_M$ may be seen as the volume of ISF produced per unit time per unit volume of brain tissue following metabolic activity. The form of $Q_B$ is explained below.

The Starling equation is commonly employed to describe the fluid filtration across the capillaries of the systemic circulation supplying the peripheral tissue, i.e. the peripheral capillaries [33, 108, 159]. However, the Starling equation requires some modification in order to incorporate the unique properties of the cerebral arteries. Following the standard method described in [99], $Q_B$ is calculated from the modified Starling equation, accounting for the hydrostatic pressure difference and for the total osmotic pressure difference (this results from the difference in oncotic pressure generated by proteins and difference in osmotic pressure generated by ions), as follows:

$$Q_B(x) = L_pS_V(x)[(p_c - p(x))] - \sigma_{\text{oncotic}}\Delta\pi_{\text{oncotic}} - \sigma_{\text{ions}}\Delta\pi_{\text{ions}}. \quad (3.4)$$

Here, $Q_B$ may be seen as the volume of ISF secreted by the capillary wall per unit time per unit volume of brain tissue. $L_p[cm \cdot s^{-1} \cdot Pa^{-1}]$ is the hydraulic conductivity per unit surface area of capillary and $S_V[cm^{-1}]$ is the capillary surface area per unit volume of brain tissue. Henceforth, it is written $L^{S_V}_p = L_pS_V$, which can be physically interpreted as the volumetric flow rate of ISF across the capillary wall into the brain per unit brain tissue per unit pressure difference [64]. Throughout this study, $L^{S_V}_p$ should be seen as a measure of capillary hydraulic conductivity. It should be noted that different studies used various symbols to characterize the capillary hydraulic conductivity [26, 64, 99], hence the comparison between studies should be made in terms of units. $p_c - p[Pa]$ is the hydraulic pressure difference, where $p_c[Pa]$ is the capillary pressure. $\Delta\pi_{\text{oncotic}}[Pa]$ and $\Delta\pi_{\text{ions}}[Pa]$ are the osmotic pressure differences between capillary blood and brain interstitium due to proteins and ions, respectively. $\sigma_{\text{oncotic}}$ and $\sigma_{\text{ions}}$ are the dimensionless reflection coefficients for proteins and ions, respectively; in general, each of these can take values
between 0 and 1. For the cerebral capillaries, both reflection coefficients are equal to 1, which means that all the proteins and ions are retained in the plasma of cerebral capillaries because the BBB is highly impermeable to proteins and ions. Consequently, proteins and ions can enter the brain only by active transport via specific transporters (e.g. Na\(^+\), K\(^+\)-ATPase pump). This is in contrast to the peripheral capillaries, where only oncotic contributions are present and \(\sigma_{\text{ions}} = 0\) because these vessels are permeable to ions. Although the term \(L_p^{SV}\) offers some resistance (e.g the hydraulic conductivity for water is 10-fold lower in the cerebral capillaries compared to the peripheral ones), water can still move passively across the BBB following the actively transported ions (i.e. water follows salt) \[78\].

The above equation can be used to show that flow of water across the BBB rapidly equilibrates, generating an hydrostatic pressure difference that balances the total osmotic pressure difference. The study \[99\] shows that when water is forced into the brain by the hydrostatic pressure causing as little as 1% dilution of the ISF, a high osmotic pressure difference (e.g. 51 mmHg) is generated. However, this is not the case for cerebral capillaries under normal conditions because water only follows solute movement and this movement occurs fast enough to maintain a constant osmotic pressure difference between blood and brain interstitium, i.e. plasma and brain ISF remain isosmotic fluids. Here, for simplicity, it is assumed that the oncotic and ionic pressure, along with the capillary pressure, are constant throughout the brain, as in \[64\]. Hence, equation (3.4) reads

\[
Q_B(x) = L_p^{SV}(x)(\Phi - p(x)),
\]

where \(\Phi = p_c - \sigma_{\text{oncotic}}\Delta \pi_{\text{oncotic}} - \sigma_{\text{ions}}\Delta \pi_{\text{ions}}\) and \(L_p^{SV}(x) = \begin{cases} \ L_g & \text{in } \Omega_g, \\ \ L_w & \text{in } \Omega_w. \end{cases}\)

The effect of \(\Phi\) on the levels of cerebral ISF is investigated. Here, the values of \(L_p^{SV}\) in the grey matter \((L_g)\) and white matter \((L_w)\) are taken from \[58\ \[130\] and account for the fact that the capillary surface area per unit volume of brain tissue in the white matter is one third of that in the grey matter \[162\].

**Boundary conditions.** Equations (3.1) and (3.2) need to be solved in conjunction with two boundary conditions. There are two different kinds of possible boundary conditions:
3.2. MODEL FORMULATION

Option 1:

\[ q \cdot n = \beta_s(p - p_s) \quad \text{on} \quad \Gamma_S, \quad (3.6a) \]
\[ q \cdot n = \beta_v(p_v - p) \quad \text{on} \quad \Gamma_{LV} \cup \Gamma_{RV}, \quad (3.6b) \]

which describe the semi-permeable nature of the encapsulating membranes, namely the pial-glial layer (i.e. the interface between the SAS and brain tissue) and the ependymal layer (i.e. the interface between brain tissue and ventricles) \[143\]. Here, \[\beta_s[cm \cdot s^{-1} \cdot Pa^{-1}]\] represents the pial-glial hydraulic conductivity, or, equally, the filtration coefficient of the pial-glial layer per surface area of the membrane. Similarly, \[\beta_v[cm \cdot s^{-1} \cdot Pa^{-1}]\] represents the ependymal hydraulic conductivity, or, equally, the filtration coefficient of the ependymal layer per surface area of the membrane. \[p_s\] and \[p_v[Pa]\] are the pressure in the SAS and in the ventricles, respectively. It is assumed that the pressure in the left lateral ventricle is equal to the pressure in the right lateral ventricle. \( n \) is the unit outward pointing normal to the brain surface on \( \delta \Omega \).

Option 2:

\[ p = p_s \quad \text{on} \quad \Gamma_S, \quad (3.7a) \]
\[ p = p_v \quad \text{on} \quad \Gamma_{LV} \cup \Gamma_{RV}, \quad (3.7b) \]

which represent the simplest boundary conditions (Dirichlet-type), imposing continuity of pressure at the boundaries.

Limited by the lack of experimental data on the pial-glial and ependymal hydraulic conductivity, the Dirichlet boundary conditions are chosen for the remainder of this study. This choice is also justified by the fact that, owing to its low permeability, the grey matter close to the boundaries is not expected to allow significant fluid flows that require confinement by the encapsulating membranes.

It is noted that no interface conditions are required at the interface between the grey and white matter, despite the apparent need of continuity raised by the presence of the discrete term \( k(x) \). This approach is acceptable because \(3.2\) and \(3.3\) is implemented in weak form; hence, \( k(x) \), rather than \( \nabla k(x) \), will appear under the integral sign. The weak form of equation \(3.2\) and details about its computational implementation are given in Section \(3.5\).
3.2.2 The global clearance of Aβ from the brain

Once the interstitial pressure and the flow rates of ISF through the brain interstitium are determined, their contribution to the transport of soluble Aβ towards the CSF compartments is assessed. The removal of Aβ from the brain tissue is studied by accounting not only for interstitial flow of ISF, but also for diffusion of Aβ through the brain interstitium and all the other clearance mechanisms acting along privileged pathways (e.g. BBB and IPAD pathways). The total action of the privileged pathways is incorporated in a bulk sink term $\Sigma$, where the constant $\Sigma$ can be seen as the decay rate of Aβ from the brain owing to fast acting clearance mechanisms. The action of the sink term is assumed homogeneous over the entire domain, i.e. the same in the grey and the white matter. Hence, the evolution of Aβ concentration within the human brain is described by the following conservation equation:

$$\phi(x) \frac{\partial c(t,x)}{\partial t} + \nabla \cdot (q(x)c(t,x)) = \Psi(x) + \nabla \cdot (D^*(x) \nabla c(t,x)) - \Sigma c(t,x),$$

where $\Sigma = \Sigma_{BBB} + \Sigma_{IPAD}$,

and

$$\phi(x) = \begin{cases} \phi_g & \text{in } \Omega_g, \\ \phi_w & \text{in } \Omega_w, \end{cases} \quad \Psi(x) = \begin{cases} \Psi_g & \text{in } \Omega_g, \\ \Psi_w & \text{in } \Omega_w, \end{cases} \quad D^*(x) = \begin{cases} D_g & \text{in } \Omega_g, \\ D_w & \text{in } \Omega_w. \end{cases}$$

Here, $c(x,t)[g \cdot cm^{-3}]$ is the Aβ concentration per unit volume of brain tissue, $\phi$ is the porosity of the interstitium (the volume fraction of ISF), $\Psi[g \cdot cm^{-3} \cdot s^{-1}]$ is the production rate of Aβ per unit volume of brain tissue per unit time and $D^*[cm^2 \cdot s^{-1}]$ denotes the effective diffusion coefficient of Aβ in the interstitium.

Equation (3.8) requires one initial condition and two boundary conditions.

**Initial condition.** The Aβ concentration is considered zero in the initial state

$$c|_{t=0} = 0, \quad x \subset \Omega.$$  \hspace{1cm} (3.9)

**Boundary conditions.** As in the case of the flow model, at least two kinds of boundary conditions are possible, as follows.
Option 1:
\[ c \mathbf{q} \cdot \mathbf{n} = \gamma_s (c - c_c) \quad \text{on} \quad \Gamma_S, \]  
\[ c \mathbf{q} \cdot \mathbf{n} = \gamma_v (c_c - c) \quad \text{on} \quad \Gamma_{LV} \cup \Gamma_{RV}, \]

which impose a concentration jump dependent on the flux across the encapsulating membranes and the membrane permeability to Aβ. Here, \( c_c \) is the Aβ concentration in the CSF compartment (assumed equal in the SAS and the lateral ventricles). \( \gamma_s [cm \cdot s^{-1}] \) and \( \gamma_v [cm \cdot s^{-1}] \) represent the permeability to Aβ of the pial-glial layer lining the SAS and of the ependymal layer lining the ventricles, respectively.

Option 2:
\[ c = c_c \quad \text{on} \quad \Gamma_S, \]  
\[ c = c_c \quad \text{on} \quad \Gamma_{LV} \cup \Gamma_{RV}. \]

which are the simplest boundary conditions (Dirichlet type) showing continuity of concentration at the boundaries.

Applying the same reasoning as in the flow model, the Dirichlet boundary conditions are chosen. Moreover, no interface conditions are required despite the discrete values of \( D^*(x) \), as equation (3.8) is also implemented computationally in weak form (see details in Section 3.5).

### 3.2.3 Physiological parameter values

It should be kept in mind that little quantitative data for the material properties of the human brain tissue is available and the reported values may vary due to different experimental methodologies. The computational model developed here can be further employed for a more thorough analysis of the material parameters that are given within a large range in the literature. This is however beyond the scope of this study. It is believed that a reasonable choice of physiological parameters has been made here and the chosen parameters are described in details in Appendix A and listed in Table 3.4. Some parameters of the model (e.g. \( \Phi \) and \( \Sigma \)) are varied in order to evaluate the relative contribution of different mechanisms involved in the production and clearance of ISF and soluble
CHAPTER 3. MODELLING THE GLOBAL CLEARANCE OF SOLUBLE Aβ FROM THE HUMAN BRAIN

Aβ from the brain.

Here, all the parameters employed correspond to healthy brain tissue and the transition from a physiological to a pathological case is simulated by decreasing the value of the sink term denoted Σ, i.e. the transport of ISF and Aβ out of the brain via privileged pathways takes longer, making clearance less efficient. In this way, the role of a particular Aβ transport mechanism in progression from a physiological to a pathological Aβ concentration in the brain is assessed. Diffusivity and anisotropy of the brain tissue varies between young, aged and diseased human subjects and such parameters can be determined with non-invasive methods (e.g. diffusion MRI) in living subjects [8, 105]. Therefore, by varying these parameters, the effect of disease-driven changes in the diffusivity of brain tissue on the distribution of intra-cerebral pressure and interstitial cerebral flows could be investigated. This aspect is left for a future cohort study steered by image-based modelling (see future directions in Chapter 6). The parameters which are not clearly stated in the literature, such as the transvascular driving pressure of capillaries (denoted φ) and the removal rate of the IPAD process (denoted Σ_{IPAD}) have been investigated over a wide range and their effect on the intra-cerebral pressure and bulk ISF flow are given in Table 3.3. By allowing a 100-fold increase in the value of φ, failure of the BBB can be simulated as in the study of Waters et al., [64]. This aspect may also be included in a future comparative study between physiological and pathological cases.

In terms of parameter importance for assessing the physiological case, most probably, the permeability of the brain tissue has the highest influence on the magnitude of the cerebral interstitial flows. Specifically, the low permeability of the grey matter has been proposed to hinder any significant bulk ISF flow towards the CSF compartments, increasing the risk of pressure build up and Aβ accumulation. Most of the previous studies have focused only on the grey matter permeability, while the white matter permeability relative to that of the grey matter has not been determined experimentally, but approximated by numerical analysis only [160]. Therefore, further attention is worth giving to the differences between the grey and the white matter in terms of permeability to fluid flow, as the white matter may allow for significant convective interstitial flows, aiding the elimination of ISF into CSF. A very recent study [80], based on the 3D electron microscope reconstruction of the grey matter from the rat brain, showed a 10-fold lower permeability than the one considered in this study. Lower grey matter permeability does not change the significance of the results from this study. However, the grey matter permeability may increase up to three orders of
magnitude during pressure infusion of drugs into the brain, as reviewed in [80]. Therefore, future versions of the model focused on the transport of injected drugs into the brain should account for a larger range of brain interstitium permeability.

**Cases for cerebral ISF flow.** The investigated cases for the flow model are shown in Table 3.1. The value of $\Phi$, which can be seen as the transvascular driving pressure of capillaries, is not clearly given in the literature. In order to calculate $\Phi$, the capillary pressure, the oncotic and osmotic pressures on both sides of the BBB need to be measured simultaneously. Such an experiment appears impossible in the human brain and also yields variable results in animal studies, depending on the species and the methodologies employed [161]. Different studies investigated values between 3-10 mmHg [64, 161]. Here, the values of $\Phi$ are estimated as follows. When $\Phi$ equals the interstitial pressure $p$, no net secretion of ISF into the brain takes place. In this model, $p$ is the unknown to be determined, but values of normal intracranial pressure between 5-15 mmHg have been estimated in the literature [38]. In order to allow the possibility of ISF secretion at the BBB, two distinct values of $\Phi$ are investigated here, specifically $\Phi = 10 \text{ mmHg}$ and $\Phi = 20 \text{ mmHg}$.

Cases a and b represent the situation when ISF is secreted at the BBB, for different $\Phi$ values, and moves by convection through the brain interstitium only. In other words, the metabolic production of ISF is ignored, as well as the possibility of bulk clearance along the IPAD pathways ($\Sigma_{IPAD} = 0 \text{ hrs}^{-1}$). This scenario has been put forward by Bradbury as a theory for ISF production in the brain [26] and it has been assumed in numerous mathematical and computational models of brain edema and hydrocephalus [64, 109, 161].

Case c represents the situation when the net amount of ISF present in the brain is due to both BBB secretion and metabolic production. Also in this case, ISF moves by convection through the brain interstitium only (i.e. $\Sigma_{IPAD} = 0 \text{ hrs}^{-1}$). This possibility has also investigated in [123], but in a different geometrical setting.

Cases d and e account for the removal of ISF from the brain tissue by bulk clearance along the IPAD pathways. Given the lack of a clear value for the removal rate of ISF and $A_\beta$ along the IPAD pathways, two significantly different values are investigated here, specifically $\Sigma_{IPAD} = (3 \text{ hrs})^{-1}$ ($t_{1/2} = 2.1 \text{ hrs}$) in line with the findings of Carare et al., [29] and $\Sigma_{IPAD} = (15 \text{ hrs})^{-1}$ ($t_{1/2} = 10.5 \text{ hrs}$) as reported by Cserr et al., [164]. It is noted that in the latter study, the
authors described the clearance pathways as perivascular sleeves because the tracers were observed in the wall (adventitia) of large cerebral arteries. However, more recent experiments of Carare et al., [29], employing state of art imaging techniques, argue that the actual spaces are the basement membranes of the arteries, i.e. the IPAD pathways.

**Cases for Aβ transport.** The investigated cases for the Aβ transport model are listed in Table 3.2. Two distinct cases for the flow model (e.g. c and e) are coupled with the Aβ transport model. A range of values for Σ (the total sink term describing the loss of Aβ along privileged pathways, including both BBB and IPAD) is tested. [157] reported a half-life of 34.6 minutes for the efflux of soluble Aβ across the BBB in the young mice. Here, a value of Σ_{BBB} = (0.83 hrs)^{-1} (t_{1/2} = 34.6 min) is taken for normal transport conditions of Aβ into the blood across the BBB. By decreasing the value of Σ (i.e. the sink effect is less present), progressive failure in the clearance of Aβ out of the brain via the privileged pathways is simulated and complete failure in such clearance is described by taking Σ = 0 hrs\(^{-1}\). Cases I, II and III focus on the importance of Aβ clearance at the BBB, while case IV investigates the efficacy of the IPAD pathways in the clearance of Aβ from the brain when Aβ efflux at the BBB fails.

<table>
<thead>
<tr>
<th>Case</th>
<th>Q_B (Φ = 10)</th>
<th>Q_B (Φ = 20)</th>
<th>Q_M</th>
<th>Σ_{IPAD} 0 hrs(^{-1})</th>
<th>Σ_{IPAD} 3 hrs(^{-1})</th>
<th>Σ_{IPAD} 15 hrs(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>b</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>c</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>d</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>e</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Table 3.1:** Cases investigated in the fluid model. Φ is given in mmHg. The ✓ symbol indicates that a certain mechanism is considered, while the X symbol shows that the mechanism is ignored.

<table>
<thead>
<tr>
<th>Case</th>
<th>Flow case</th>
<th>Σ_{BBB} (0.83 hrs)^{-1}</th>
<th>Σ_{BBB} (1.6 hrs)^{-1}</th>
<th>Σ_{BBB} 0 hrs(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>c</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>II</td>
<td>c</td>
<td>X</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>III</td>
<td>c</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>IV</td>
<td>e</td>
<td>X</td>
<td>X</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Table 3.2:** Cases investigated in the Aβ transport model. The ✓ symbol indicates that a certain mechanism is considered, while the X symbol shows that the mechanism is ignored.
3.3 Results

3.3.1 Interstitial pressure and flows

The various levels of permeability and capillary hydraulic conductivity used in the model are shown in Figure 3.2. By accounting for different material properties of the grey matter and the white matter, the weak form of equation (3.2), together with the boundary conditions (3.7), is solved numerically for the unknown interstitial pressure (see equation (3.14) in Section 3.5). The relative effect of the two sources of water (BBB and metabolic activity) on the values of interstitial pressure and total volumetric source of ISF in the human brain is given in Table 3.3. It is noted that the volumetric source represents the production rate of ISF at the BBB per unit volume of wet (not dry) brain tissue and this approach is chosen for ease of comparison with experimental data; this rate can also be seen as the total clearance rate of ISF per unit volume of brain tissue. The production rate of ISF per unit volume of dry tissue can be obtained by multiplying the value of the volumetric source with the ratio of wet tissue to dry tissue (e.g. 1/0.25, given that almost 75% of the brain tissue is water).

In Figure 3.3, the interstitial pressure and the volumetric source is plotted for two scenarios, e.g. case a and case a-idealised. In both cases, the highest pressure arises in the areas containing significant amounts of grey matter, e.g. the thalamus. This effect is caused by the relatively low permeability of the grey matter to interstitial flows (100-fold smaller than in the white matter). The lowest pressure is found in the corpus callosum of the white matter and on the outer most layer of the cerebral cortex, both regions having a pressure close to the CSF pressure from the lateral ventricles and SAS.

Case a-idealised. The effect of the interstitial pressure on the secretion of water at the BBB is illustrated in the ‘Idealised Homogenous’ case from Figure 3.3, where \( L_p^{Sv} \) is uniform across the entire brain. For this particular case, the largest secretion rate of water at the BBB per unit volume of wet brain tissue, is found to be in the corpus callosum (white matter) and in the outer most layer of the cortex (grey matter); both these regions have the smallest interstitial pressure. The lowest volumetric source is in the thalamus which has the highest pressure. This outcome can also be easily inferred from equation (3.5) once the interstitial pressure is known. However, this scenario is different than the more complicated physiological situation and it was presented just for clarity purposes.
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Figure 3.2: Heterogeneous material properties of the brain tissue. Top image: tissue permeability taking distinct values in the grey and white matter. Bottom image: the $L_{pV}^h$ term as a result of three-fold higher capillary surface area per unit volume of brain tissue in the grey compared to the white matter.

Case a. The physiological case accounting for the combined effect of the interstitial pressure and the uneven distribution of capillaries in the grey and white matter (i.e. $L_{pV}^h$ heterogenous), is shown in the ‘Physiological Heterogenous’ case in Figure 3.3 and exhibits a complex behaviour that cannot be easily inferred from relationship (3.5): the highest volumetric source is found in the cerebral cortex, while the lowest one in the white matter. The secretion rates of water at the BBB per unit volume of wet brain tissue are within the range of $0.02 - 0.12 \mu l \cdot min^{-1} \cdot g^{-1}$ for a given transvascular driving pressure $\Phi$ of 10 mmHg. Almost three-fold higher secretion rates within the range of $0.05 - 0.33 \mu l \cdot min^{-1} \cdot g^{-1}$ are found for a transvascular pressure of 20 mmHg (case b), as shown in Table 3.3. These results show that the local production of ISF
3.3. RESULTS

Figure 3.3: The secretion of water at the BBB for case a. The top layer illustrates the situation in which the term $L_S V_p$ is homogeneous, meaning that the capillary surface area per unit volume of brain tissue is equal in the grey and white matter. The influence of the resulting interstitial pressure (left-hand side image) on the volumetric source of water (right-hand side image) is immediately obvious. The bottom layer illustrates the physiological situation where the term $L_S V_p$ is heterogeneous: interstitial pressure (left-hand side image) and volumetric source of water (right-hand side image).

significantly varies across the human brain. This implies that also the clearance of ISF from various regions of the brain occurs at different rates.

Case c. Another physiological case is shown in Figure 3.4 where both sources of water are considered. The highest interstitial pressure is found again in the areas containing significant amounts of grey matter, e.g. the thalamus. The pressure values remain, nonetheless, in the normal range of intracranial pressure for the adult human brain (lower than 15 mmHg). The pressure differences that arise in the brain interstitium drive the ISF flow towards the CSF compartments, as shown in Figure 3.4. For example, the large pressure difference between the thalamus and the corpus callosum generates high fluxes of ISF towards the lateral ventricles; the highest bulk ISF flow develops in the white matter, with
no significant bulk ISF flow in the grey matter. Notably, the interstitial flows are not unidirectional. There seems to be a point of continental divide from where ISF flows either towards the ventricular system or towards the SAS. According to Figure 3.4, the continental divide arises close to the interface between the grey and white matter. The effect of the generated interstitial flows on the removal of Aβ from the brain interstitium into the CSF compartments is investigated below. For this particular case, ISF can leave the brain only by convection through the interstitium and efflux into the CSF. It is found that 88% of ISF clears into the SAS, while the remaining 12% drains into the lateral ventricles.

Case d and e. The sink effect of the IPAD pathways is enforced in case d and case e, which are shown in Figure 3.5 and Figure 3.6, respectively. Some striking behaviour is observed. Specifically, the pressure in the brain becomes negative, leading to remarkably higher volumetric sources of ISF, compared to the cases a-c. This suggests that the removal rate of the IPAD mechanism is significantly higher than the secretion of ISF at the BBB. Consequently, the sink effect of the IPAD pathways will create local decreases in pressure. The high negative pressures from case d do not appear physiological. As the interstitial pressure decreases, the secretion rate of ISF at the BBB increases, according to equation (3.5). Given that the intra-cerebral pressure becomes lower than the pressure in the CSF compartments, the direction of convective flow through the brain interstitium is reversed, i.e. fluid flows from the CSF border towards the interior of the brain.
Figure 3.4: Production of water in the brain, accounting for both the BBB source and the metabolic source (case c). Top image: interstitial pressure in the brain. Middle image: the total volumetric source of water. Bottom image: the field of the ISF flux. The arrows indicate the direction of ISF flux; the colour indicates the relative magnitude of flux. A point of continental divide for ISF flows is noted at the interface between the grey and the white matter. The flows from the cerebral cortex are towards the outer SAS.
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Figure 3.5: Interstitial pressure and flows for case d. Top image: interstitial pressure in the brain. Middle image: the total volumetric source of water. Bottom image: the field of the ISF flux. The arrows from the bottom image indicate the direction of ISF flux; the colour indicates the relative magnitude of flux. The flows from the cerebral cortex are towards the interior of the brain.
Figure 3.6: Interstitial pressure and flows for case e. Top image: interstitial pressure in the brain. Middle image: the total volumetric source of water. Bottom image: the field of the ISF flux. The arrows from the bottom image indicate the direction of ISF flux; the colour indicates the relative magnitude of flux. The flows from the cerebral cortex are towards the interior of the brain.
### 3.3.2 Aβ transport

Using the material properties from Table 3.4 and the set of parameters from Table 3.2, the evolution of Aβ concentration in the human brain is assessed.

**Case I** Initially, the brain starts producing Aβ at a constant physiological rate, while three different Aβ clearance mechanisms are fully activated, namely diffusion and convective flow (with ISF) through the brain tissue, together with removal via the BBB. It is recalled that the sink term Σ describes the efficacy of the privileged pathways by showing how long it takes to remove Aβ along such routes and \( t_{1/2} \) denotes the corresponding half-life. For the particular case of \( t_{1/2} = 35 \) minutes and the interstitial flows illustrated in Figure 3.4, the brain reaches an equilibrium where the Aβ concentration is 10 ng · g\(^{-1}\) in the grey matter and no Aβ is present in the white matter (see Figure 3.7).

**Case II.** In order to assess the relative contribution of interstitial flows to the removal of Aβ from the brain, complete failure of the privileged pathways is simulated by assuming the sink term zero. This means that removal of Aβ along privileged pathways takes an infinitely long time and the dominant clearance mechanisms for Aβ are diffusion and ISF convection through the brain interstitium towards the CSF compartments. The Aβ concentration in the brain in the steady state becomes higher than 2500 ng · g\(^{-1}\), with significant Aβ deposition also in the white matter, despite the fact that Aβ is produced at physiological rates (i.e. no overproduction). The highest values for the Aβ concentration is obtained in the thalamus and the concentration decreases

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**Table 3.3:** Intra-cerebral pressure, interstitial velocity and volumetric source for different production and clearance mechanisms of ISF in the human brain.

<table>
<thead>
<tr>
<th>Case (flow)</th>
<th>min pressure [mmHg]</th>
<th>max pressure [mmHg]</th>
<th>max velocity [( \mu m \cdot min^{-1} )]</th>
<th>( Q ) [( \mu l \cdot min^{-1} \cdot g^{-1} )]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>3.8</td>
<td>8.9</td>
<td>2.63</td>
<td>0.02 - 0.12</td>
</tr>
<tr>
<td>b</td>
<td>3.8</td>
<td>17.3</td>
<td>6.89</td>
<td>0.05 - 0.33</td>
</tr>
<tr>
<td>c</td>
<td>3.8</td>
<td>10.6</td>
<td>3.49</td>
<td>0.02 - 0.17</td>
</tr>
<tr>
<td>d</td>
<td>-225</td>
<td>4.8</td>
<td>115.1</td>
<td>0.05 - 4.94</td>
</tr>
<tr>
<td>e</td>
<td>-36.6</td>
<td>4.04</td>
<td>20.2</td>
<td>0.06 - 1.01</td>
</tr>
</tbody>
</table>
3.4 Discussion

A comparison of the main results of this model with the available experimental data is presented below.

The presence of a continental divide for interstitial flows in the human brain

Previous numerical studies have argued against bulk ISF flow being a dominant transport mechanism in the grey matter, showing that diffusion prevails instead [13, 80, 96]. However, little attention has been given to the possibility of bulk flows in the white matter, which is considered more permeable compared to the grey matter. The simulation results from this study confirm that no significant bulk ISF flows take place in the grey matter, owing to its low permeability. Nonetheless, assuming the white matter permeability 100-fold higher than that of the gray matter, the model shows that significant bulk flow can be developed in the white matter and this contributes to the transport of ISF towards CSF. The velocity of ISF through the white matter is comparable with the experimental velocity of 10 $\mu$m-s$^{-1}$ reported by [146]. The model also predicts that the cerebral interstitial flows are not unidirectional, as will be discussed below.
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Figure 3.7: The concentration of Aβ in the human brain. Top image: the steady state for case I. Bottom image: the steady state for case II when the clearance of Aβ along privileged pathways completely fails, i.e. Aβ clears into CSF by diffusion and ISF convection through the brain interstitium. Both results correspond to the flow model from case c. It is noted that the color bar is specific to each image.
3.4. DISCUSSION

Figure 3.8: The concentration of Aβ in the human brain when clearance of Aβ along privileged pathways progressively fails. Top image: the steady state for case III. Bottom image: the steady state for case IV. It is noted that the color bar shows specific values for each image.

The production of water in the brain by secretion at the BBB may be seen like a watershed in which the numerous cerebral capillaries generate a cumulative flow of water. The interstitial flows remain small at the level of capillaries but become larger closer to the ventricles. A similar view has been proposed in [21] based on their experimental findings from tracer studies in mice, which suggested ISF flows through the interstitium towards the brain ventricles. Moreover, the study [21] also speculated a point of ‘continental divide’ close to the cortical surface from where ISF flows either towards the ventricles or towards the SAS. Such a continental divide close to the interface of the grey and white matter has also been found in the human brain in this computational model.
CHAPTER 3. MODELLING THE GLOBAL CLEARANCE OF SOLUBLE Aβ FROM THE HUMAN BRAIN

The biological implications of the above modelling predictions are far reaching, providing insights about the exchange of ISF-CSF, as well as guidance for drug delivery to the brain. Controversies regarding the flow of CSF into and out of the brain have emerged over the last few years [18, 92] and this model may help find a consensus. For instance, the model shows that as long as the intra-cerebral pressure is higher than the CSF pressure, bulk ISF flow occurs through the white matter towards the CSF compartments. This may provide an efficient way for clearing soluble waste products that are co-transported with the ISF out of the brain. At the same time, drugs injected into the brain tissue may be derailed from their target due to the multi-directional interstitial flows. Future versions of this model could be extended with an external pressure term for pressure-induced drug delivery to the brain, in a similar way to previous models [161], and predict the most likely trajectory of the drugs through the brain tissue. Reversed directions of flow are obtained when the sink IPAD mechanism, acting between 3-15 hours, is forced into the model, simulating in this way various conditions under which CSF may enter the brain parenchyma. According to these findings, it is encouraged that future experiments, involving injection of drugs or anatomical tracers in the brain, should carefully consider the existence of the continental divide, as the direction of drug flow through the interstitium may differ depending on the injection site.

ISF secretion into the brain at the BBB

By allowing the ISF secretion at the BBB to depend on the intra-cerebral pressure, which in turn is a function of brain tissue properties, regional differences in the production of ISF in unit volume of (wet) brain tissue are found. This implies that the ISF is also cleared from the various brain regions at different rates. The study [164] was the first one to estimate the clearance rates of ISF from the brain by injecting different soluble tracers in the rat brain. They have estimated maximum values of 0.18 - 0.19 µl·min⁻¹·g⁻¹ for clearance from the caudate nucleus (grey matter) and interna capsule (white matter), respectively. These values were used to estimate the secretion rate of ISF in the BBB and, since then, have been the most cited values for ISF clearance from the brain. The $Q$ values yielded by the model can be seen as the clearance rate of ISF by unit volume of (wet) brain tissue and be compared with the experimental values from [164]. Hence, it appears that case c from the flow model compares best with the experiments. However, there are some fundamental differences between the conditions assumed in experiments and those in the model; they are discussed below.
In case c from the model, both ISF production in the brain by BBB secretion and metabolic activity is assumed. Moreover, no bulk clearance of ISF along the IPAD pathways takes place. This means that the ISF is cleared from the brain only by convection through the brain interstitium (no sink terms) and clearance cannot be assessed with an exponential decay. In contrast, the values from [164] were calculated by assuming production of ISF at the BBB only and quantifying clearance with an exponential decay. By assessing clearance in an exponential manner, the existence of a sink term is implicitly assumed in [164]. If a sink term is included in the model (e.g. case d and e), then much higher production rates of ISF within the range $0.05 - 4.94 \, \mu l \cdot min^{-1} \cdot g^{-1}$ are obtained. Moreover, non-physiological negative intra-cerebral pressures (e.g. $-225$ mmHg and $-35$ mmHg, respectively) are generated. These findings suggest that some discrepancies may exist between the design of experiments from [164] and their mathematical interpretation.

The simulations also suggest that bulk ISF flow through the white matter towards the CSF is efficient enough to clear the ISF from the brain at physiological production rates of the fluid. The inclusion of a sink mechanism, such as IPAD, speeds up the clearance of fluid, creating very low local pressures due to the imbalance between production and clearance. However, it is not obvious at this stage how the bulk ISF flow into CSF contributes to the A\textsubscript{\textbeta} removal from the human brain; hence, the A\textsubscript{\textbeta} transport model is required for a full appreciation of the role of IPAD in the clearance of the brain.

The imbalance between the production and clearance of A\textsubscript{\textbeta} in the human brain

Starting from a healthy scenario, with physiological material properties and physiological production/clearance rates of A\textsubscript{\textbeta}, a significant amyloid deposition in the human brain is obtained by decreasing the clearance rates corresponding to two sink mechanisms (e.g. BBB and IPAD). In this way, progressive impairment in the clearance of A\textsubscript{\textbeta} from the BBB seen during aging and AD progression [50] is simulated and the corresponding values of A\textsubscript{\textbeta} concentration obtained numerically are comparable with the experimental reports. For example, when BBB clearance acts up to 50 minutes, the A\textsubscript{\textbeta} concentration yielded by the model (e.g. 10 ng \cdot g^{-1}) is comparable with the total A\textsubscript{\textbeta} concentration found experimentally in the normal human brain tissue [176]. Experimental data [176] showed that, compared to the normal level of soluble A\textsubscript{\textbeta}
(6.4 ng·g⁻¹), a statistically significant increase of 20-fold was found in the case of pathological ageing, while the total levels of Aβ₄₀ and Aβ₄₂ were increased 330-fold and 1050-fold, respectively, in the AD patients compared to healthy patients. A more recent study reported levels of water-soluble Aβ monomer between 0-69 ng·g⁻¹ in the normal non-demented cases (with insignificant presence of amyloid plaques); this concentration increased up to 802 ng·g⁻¹ in the brains diagnosed with moderate/severe dementia (with high frequency of amyloid neuritic plaques) [117].

Comparison of the modelling results with the above experiments indicates that as long as efflux of Aβ across the BBB occurs in less than one hour, then the Aβ produced by the entire grey matter is efficiently cleared from the brain, making the need for the IPAD unnecessary. According to the model, even 50% failure in the removal of parenchymal Aβ across the BBB does not cause pathological accumulation of Aβ. However, complete hindrance of Aβ efflux across the BBB, in the absence of other privileged clearance pathways, leads to high Aβ concentration both in the grey matter and white matter (see Figure 3.7), which is in line with the experimental reports of Aβ concentration for the demented cases [117]. These findings suggest that clearance of Aβ from the brain across the BBB is the main clearance mechanism, as was shown in mouse experiments [157]. The authors have shown that the low-density lipoprotein receptor related protein-1 (LRP) found at the BBB act as sinks for parenchymal Aβ and that their expression level is decreased in aged and AD patients [51]. The modelling results from here show that the IPAD mechanism gains more importance when removal of Aβ at the BBB completely fails. In such an instance, the IPAD mechanism, acting over 15 hours, is able to save the white matter from significant Aβ deposition and decrease the Aβ concentration in the grey matter down to 100 ng·g⁻¹, which is in line with the experimental reports of Aβ concentration for the non-demented cases. This situation, however, may represent the initial stage for precipitation of parenchymal Aβ, as seen during ageing and AD [117]. A more solid appreciation of the biological implications of the modelling results will be obtained once the model accounts for the heterogeneous distribution of the sink mechanisms of ISF and Aβ.

The most exposed areas for Aβ accumulation are in the grey matter, namely the cerebral cortex and the thalamus. These results are not surprising, considering that Aβ is produced only in the grey matter where no significant interstitial flows can take place. High deposition of extracellular Aβ has been seen in the thalamus in AD cases [6, 25]. Nonetheless, regional differences in the drainage
of solutes along the IPAD pathways (e.g. most efficient in the thalamus) were found in mice studies \[70\]. This suggests that brain areas with the highest risk of Aβ deposition are empowered by more efficient alternative clearance mechanisms, which can compensate for the disadvantage created by the local material properties of the brain. A more solid appreciation of the biological implications of the modelling results will be obtained once the model accounts for the heterogeneous distribution of the sink mechanisms of ISF and Aβ. Here, the action of the sink term is assumed uniform across the entire brain, but this limitation will be improved in the next version of the model. Moreover, the anisotropy of the human white matter needs to be considered in future versions of the model. It is noted that no differentiation between the Aβ40 and Aβ42 is made in this model and the consequences of Aβ aggregation in the brain, i.e. the shift from soluble to insoluble is not considered, although such a change may exacerbate the deposition of Aβ in the brain \[72\]. This work will be extended to a three-dimensional (3D) model in order to account for other significant regions of grey matter like the caudate nucleus and the putamen.

The extension to a 3D model is not expected to lead to significantly different results in terms of pressure distribution, magnitude of cerebral interstitial flows and Aβ concentration in the brain. This expectation is supported by two main reasons: (i) the input parameters which influence the outcome of the model through boundary conditions (e.g. CSF pressure, Aβ concentration in CSF), as well as the capillary pressure, do not change in a 3D setting and (ii) the coronal section considered here already captures the most significant regions of the grey matter with the highest risk for Aβ accumulation (owing to the high resistance to advective interstitial flows). Nonetheless, a 3D model will allow assessment of the relative contribution of different intra-cerebral regions to the clearance of ISF and Aβ from the brain, identifying other cerebral areas at risk of Aβ deposition. Moreover, a 3D model will also allow a realistic guidance of drug delivery to the brain.

In conclusion, a novel model for the global clearance of Aβ from the human brain has been developed accounting for physiological experimental data, a realistic geometry of the human brain and distinct properties of the grey and white matter. The distribution of intra-cerebral pressure, the corresponding ISF flow through the interstitium and its role in the clearance of soluble Aβ into the CSF compartments have been modelled for the first time in the human brain. The model addresses modern controversial aspects regarding the production of ISF in the brain and its subsequent contribution to the production of CSF.
Moreover, the relative contribution of different clearance mechanisms of A\(\beta\) is investigated for the first time in the human brain. The model developed here may be seen as the basis of a complex computational platform that allows implementation of realistic models of the human brain, aiming to enhance the current understanding of clearance of the brain.

### 3.5 Numerical solution of the model

Here, both the model for the fluid flow (3.2)-(3.7) and for the A\(\beta\) transport (3.8)-(3.11) are solved by using the Finite Element Method from FreeFem++, which is an open source software for solving partial differential equations based on C++ [75]. FreeFem++ is a relatively high-level language in which the user only needs to supply a definition of the computational domain and the weak form of the problem to be solved. The program automatically deals with many of the subtleties such as mesh generation and numerical manipulation.

In order to solve the equation (3.2) with the boundary conditions (3.7) for \(p\), the pressure equation must be first written in weak form, i.e. the pressure equations has weak solutions only with respect to certain test functions. Here, \(p\) is assumed to be made of continuous piecewise linear test functions \(\xi\), such that

\[
p(x) = \sum_{i=1}^{M} P_i \xi_i(x) \quad \text{with} \quad \xi_i|_{\partial \Omega} = 0.
\]  

(3.12)

where \(P_i\) is the value of \(p\) at node \(n_i\) and \(M\) is the dimension of the finite element space (i.e. the number of vertices). The choice of a test function is motivated later on.

By multiplying equation (3.2) with the test function \(\xi\) and integrating over the domain \(\Omega\), gives

\[
\int_{\Omega} \nabla \cdot \left( \frac{k}{\mu} \nabla p \right) \xi \, dV = \int_{\Omega} Q \xi \, dV,
\]  

(3.13)

which on integration by parts becomes

\[
- \int_{\partial \Omega} \frac{k}{\mu} \nabla p \cdot n \, dS + \int_{\Omega} \frac{k}{\mu} \nabla p \cdot \nabla \xi \, dV = \int_{\Omega} Q \xi \, dV,
\]  

(3.14)
3.5. NUMERICAL SOLUTION OF THE MODEL

where $S$ denotes the surface that encloses the volume $V$ and $n$ is the unit outward pointing normal to the surface.

Given that $\xi$ vanishes on the boundaries according to equation (3.17), the surface integral is zero. Hence, the final weak form of the pressure equation reduces to

$$\int_{\Omega} \frac{k}{\mu} \nabla p \cdot \nabla \xi \ dV = \int_{\Omega} Q \xi \ dV,$$

(3.15)

which is implemented in FreeFem++ in order to obtain a solution for $p$.

The tissue parameters are identified by the mesh parameter region which is defined when the command buildmesh is called. Here, the mesh parameter region takes two integer values corresponding to each connected component of the entire mesh (e.g. 0 and 3 in the grey and white matter, respectively). The reserved word region returns the corresponding region number of the current point $(x,y)$. The jumps in the values of tissue permeability (denoted $k$) and other material parameters do not raise any issues when integrating over the entire domain because both the pressure and concentration equations are solved in the weak form. This means that $k$, rather than the gradient of $k$, appears under the integral sign and this is similar for other discrete material parameters. Consequently, this avoids a term with singularities and obviates the need for imposing an interface condition.

The choice of the test function $\xi$ from (3.12) is justified as follows. A continuous piecewise linear test function is chosen for simplicity reasons, while the assumption of the test function being null on the boundary facilitates the integration by parts (as done in [75]). Choosing the test function to be null on the boundary still leads to a solution $p$ that satisfies the boundary conditions (3.7) which require a non-zero pressure. This is shown to be true by separating the pressure into two distinct parts: one part that is zero on the boundaries and made of continuous piecewise linear test functions $\xi$ (denote $p_0$) and another part that is non-zero on the boundaries (denoted $p_n$)

$$p = p_n + p_0 \quad \text{with} \quad p_n|_{\partial \Omega} = n \quad \text{and} \quad p_0|_{\partial \Omega} = 0,$$

(3.16)

where $n$ denotes the value of the pressure on the boundaries (e.g. $p_s$ on $\Gamma_S$ and $p_v$ on $\Gamma_{LV} \cup \Gamma_{RV}$).
This time $p_0$ is assumed to be made of continuous piecewise linear test functions $\xi$, such that

$$p_0(\mathbf{x}) = \sum_{i=1}^{M} P_0, i \xi_i(\mathbf{x}) \quad \text{with} \quad \xi_i|_{\partial \Omega} = 0. \quad (3.17)$$

The solution form (3.16) is replaced in the original pressure equation (3.2) to find $\xi$ that satisfies the condition from (3.17).

$$\nabla \cdot \left( -\frac{k}{\mu} \nabla p_0 \right) = Q - \nabla \cdot \left( -\frac{k}{\mu} \nabla p_n \right), \quad (3.18)$$

By multiplying equation (3.18) with the test function $\xi$ and integrating over the domain $\Omega$, gives

$$\int_{\Omega} \nabla \cdot \left( -\frac{k}{\mu} \nabla p_0 \right) \xi \ dV = \int_{\Omega} Q \xi \ dV + \int_{\Omega} \nabla \cdot \left( \frac{k}{\mu} \nabla p_n \right) \xi \ dV; \quad (3.19)$$

which on integration by parts becomes

$$-\int_{\partial \Omega} \xi \frac{k}{\mu} \nabla p_0 \cdot \mathbf{n} \ dS + \int_{\Omega} \frac{k}{\mu} \nabla p_0 \cdot \nabla \xi \ dV = \int_{\Omega} Q \xi \ dV + \int_{\partial \Omega} \xi \frac{k}{\mu} \nabla p_n \cdot \mathbf{n} \ dS - \int_{\Omega} \frac{k}{\mu} \nabla p_n \cdot \nabla \xi \ dV \quad (3.20)$$

Accounting for the fact that $\xi$ vanishes on the boundary, the surface integrals in the above equation become zero and equation (3.20) reduces to

$$\int_{\Omega} \frac{k}{\mu} \nabla p_0 \cdot \nabla \xi \ dV + \int_{\Omega} \frac{k}{\mu} \nabla p_n \cdot \nabla \xi \ dV = \int_{\Omega} Q \xi \ dV, \quad (3.21)$$

which is the weak form (3.15). In other words, the same test function $\xi$ which is null on the boundaries can be found by solving either equation (3.15) or equation (3.18). The latter equation clearly shows that the part of the pressure solution that satisfies the boundary conditions (3.7) is not lost by using a test function that is null on the boundary.

In a similar manner, the concentration equation (3.8) with the boundary conditions (3.11) is formulated in weak form by multiplying (3.8) with the test function $\chi \subset \Omega$ and integrating the result over $\Omega$. $\chi$ is a continuous piecewise linear test function, such that

$$c(\mathbf{x}, t) = \sum_{j=1}^{M} C_j \chi_j(\mathbf{x}, t) \quad \text{with} \quad \chi_j|_{\partial \Omega} = 0, \quad (3.22)$$
where the choice of $\chi$ follows the same rationale as in the case of the test function $\xi$ described above.

An (implicit) backward Euler finite difference approximation in time is applied for the time derivative. Consequently, the following weak form for equation (3.8) is obtained

$$
\int_{\Omega} \left( \phi \frac{c_{n+1} - c_n}{\delta t} + \nabla \cdot (qc) \right) \chi \ dV = 
\int_{\Omega} \Psi \chi \ dV + \int_{\Omega} \nabla \cdot (D^{*} \nabla c) \chi \ dV - \int_{\Omega} \Sigma c \chi \ dV,
$$

(3.23)

where $n$ is the number of discrete time points and $\delta t$ is the time step. Here $\delta t = 0.001$ hrs for a total time interval of 3 hrs.

The second integral in the right-hand side of equation (3.23) can be simplified using integration by parts as follows

$$
\int_{\Omega} \nabla \cdot (D^{*} \nabla c) \chi \ dV = 
\int_{\partial \Omega} \chi D^{*} \nabla c \cdot \mathbf{n} \ dS - \int_{\Omega} D^{*} \nabla c \cdot \nabla \chi \ dV,
$$

(3.24)

where the surface integral becomes zero due to the fact that $\chi$ vanishes on the boundary according to (3.22)

Consequently, the weak form for the concentration equation reduces to

$$
\int_{\Omega} \left( \phi \frac{c_{n+1} - c_n}{\delta t} + \nabla \cdot (qc) \right) \chi \ d\Omega = 
\int_{\Omega} \Psi \chi \ dV + \int_{\Omega} D^{*} \nabla c \cdot \nabla \chi \ dV - \int_{\Omega} \Sigma c \chi \ dV,
$$

(3.25)

which is implemented in FreeFem++ to determine $c$.

Image segmentation was made using a bespoke script written in MATLAB. First, the greyscale image underwent a simple thresholding in which pixels with a greyscale value smaller than $p_1$ were set equal to 0, those with a value larger than $p_2$ were set equal to 1 and those between $p_1$ and $p_2$ were set equal to 0.5. On setting $p_1 \approx 0.59$ and $p_2 \approx 0.95$ the three phases shown in Figure 3.1 (background, white matter and grey matter) were fairly well identified. Next, interfaces between regions were smoothed and small features (typically incorrectly identified bright or dark spots) were ‘cleaned’ from the image by sequentially ‘dilating’ (connected regions of a phase are expanded by a given number of pixels) and ‘eroding’ (connected regions are shrunk by a given number
of pixels) each of the three phases. Finally, the isocline function in FreeFem++ was used to identify level sets (e.g. values 0.5 and 0.99 for different material interfaces) in the image. The final domain was then constructed by selecting the longest isocline of each type, corresponding to the external boundary of the brain, internal boundaries of the ventricles and internal interface between the white and grey matter, respectively.

The robustness of the model is checked for case I by refining the size of the time step $\delta t$ from equation (3.25). Here, $t_n$ denotes the time at the $n$th time step and $c_n = c(t = t_n, x)$ denotes the computed solution at the $n$th time step at a fixed grid position $x$. The time step, assumed constant, is given by $\delta t = t_n - t_{n-1}$. According to the (implicit) backward Euler method,

$$c_{n+1} = c_n + \delta t f(c_{n+1}, t_{n+1}),$$  \hspace{1cm} (3.26)

where the function $f(c_{n+1}, t_{n+1})$ is unknown, thereby giving an implicit equation for the computation of $c_{n+1}$.

Considering that the exact concentration solution is unknown a priori, the solution obtained with a sufficiently small time step is chosen as the ‘exact’ solution for studying the convergence characteristics. Specifically, here, $\delta t = 0.0002$ is chosen as the time step corresponding to the ‘exact’ solution denoted $c^e_n$ and compared with the concentration solution computed at with higher time steps, e.g. $\delta t = 0.001, 0.002, 0.004, 0.008, 0.016, 0.032$.

$$\epsilon = |c^e_n - c_n|,$$  \hspace{1cm} (3.27)

where the $n$th time step is the final time step (e.g. $t = 3$ hrs) when the steady state has already been reached. As expected, the backward Euler method is stable, i.e. the solution $c_n$ becomes more accurate as $\delta t$ decreases and the small global error scales linearly with $\delta t$, as shown in Figure 3.9.
3.5. NUMERICAL SOLUTION OF THE MODEL

Figure 3.9: Convergence of the backward Euler method in FreeFem++. The marks give the error $\epsilon$ for computations with a time step $\delta t$ of 0.001, 0.002, 0.004, 0.008, 0.0016 and 0.032 against the numerical solution with $\delta t = 0.0002$. The line shows the linear convergence of the method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_g$</td>
<td>$10^{-12}$</td>
<td>cm$^2$</td>
<td>permeability in $\Omega_g$</td>
</tr>
<tr>
<td>$k_w$</td>
<td>$10^{-10}$</td>
<td>cm$^2$</td>
<td>permeability in $\Omega_w$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$10^{-3}$</td>
<td>Pa$\cdot$s</td>
<td>ISF viscosity</td>
</tr>
<tr>
<td>$\rho$</td>
<td>1</td>
<td>g$\cdot$cm$^{-3}$</td>
<td>ISF density</td>
</tr>
<tr>
<td>$Q_{Mg}$</td>
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<td>cm$^3$$\cdot$s$^{-1}$cm$^{-3}$</td>
<td>metabolic source in $\Omega_g$</td>
</tr>
<tr>
<td>$Q_{Mw}$</td>
<td>$3.1 \cdot 10^{-3}$</td>
<td>cm$^3$$\cdot$s$^{-1}$cm$^{-3}$</td>
<td>metabolic source in $\Omega_w$</td>
</tr>
<tr>
<td>$S_V$</td>
<td>33 – 100</td>
<td>cm$^2$$\cdot$cm$^{-3}$</td>
<td>capillary surface area</td>
</tr>
<tr>
<td>$L_g$</td>
<td>$2.6 \cdot 10^{-9}$</td>
<td>s$^{-1}$$\cdot$Pa$^{-1}$</td>
<td>$L_pS_V$ in $\Omega_g$</td>
</tr>
<tr>
<td>$L_w$</td>
<td>$0.85 \cdot 10^{-9}$</td>
<td>s$^{-1}$$\cdot$Pa$^{-1}$</td>
<td>$L_pS_V$ in $\Omega_w$</td>
</tr>
<tr>
<td>$\Phi$</td>
<td>1333</td>
<td>Pa</td>
<td>driving pressure across BBB</td>
</tr>
<tr>
<td>$p_s$</td>
<td>507</td>
<td>Pa</td>
<td>pressure in SAS</td>
</tr>
<tr>
<td>$p_v$</td>
<td>517</td>
<td>Pa</td>
<td>pressure in lateral ventricles</td>
</tr>
<tr>
<td>$\phi_g$</td>
<td>0.24</td>
<td>1</td>
<td>porosity in $\Omega_g$</td>
</tr>
<tr>
<td>$\phi_w$</td>
<td>0.21</td>
<td>1</td>
<td>porosity in $\Omega_w$</td>
</tr>
<tr>
<td>$\Psi_g$</td>
<td>$3 \cdot 10^{-12}$</td>
<td>g$\cdot$cm$^{-3}$$\cdot$s$^{-1}$</td>
<td>$A\beta$ production rate in $\Omega_g$</td>
</tr>
<tr>
<td>$\Psi_w$</td>
<td>0</td>
<td>g$\cdot$cm$^{-3}$$\cdot$s$^{-1}$</td>
<td>production rate of $A\beta$ in $\Omega_w$</td>
</tr>
<tr>
<td>$D_g$</td>
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<td>cm$^2$$\cdot$s$^{-1}$</td>
<td>$A\beta$ diffusivity in $\Omega_g$</td>
</tr>
<tr>
<td>$D_w$</td>
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<td>cm$^2$$\cdot$s$^{-1}$</td>
<td>$A\beta$ diffusivity in $\Omega_w$</td>
</tr>
<tr>
<td>$c_c$</td>
<td>$9.9 \cdot 10^{-9}$</td>
<td>g$\cdot$cm$^{-3}$</td>
<td>$A\beta$ concentration in CSF</td>
</tr>
</tbody>
</table>

Table 3.4: Physiological parameters described in details in Appendix A.
Chapter 4

Modelling the arterial wall

The purpose of this chapter is to lay the foundations for the novel vasomotion-driven IPAD model from Chapter 5 by taking a close look at the biomechanics of cerebral arteries. The previous model from Chapter 3 assessed the global clearance of soluble $A\beta$ from the human brain. The remainder of this work presents a detailed investigation of one particular clearance mechanism, namely the IPAD process. In order to develop a physiologically-realistic model for the IPAD mechanism, first the biomechanics of cerebral arteries needs to be understood and then the IPAD model is to be integrated in Chapter 5. This will result in a multi-scale fluid-structure interaction model. The particular aspects that are of interest include: the distribution of deformation and corresponding stresses across the arterial wall, as well as their spatial propagation, in response to arterial pressure and muscular contractions. This chapter is structured as follows. An overview of the elastic theory commonly employed for modelling the arterial wall is presented in Section 4.1. The most representative three-dimensional models of arteries are reviewed in Section 4.2. A model for the active cerebral artery is developed in Section 4.3.

Under physiological conditions, the arteries are subjected to numerous external factors, including inflation by arterial pressure and longitudinal tethering by the surrounding tissue. Accounting for the difficulty of conducting $in vivo$ investigations, the elastic response of arteries is assessed by employing mathematical modelling [166]. The first models for arteries appeared in 1733 as the Windkessel models. A brief history of the arterial wall modelling can be found in [97]. The Windkessel models comprise of ordinary partial equations (ODEs) and are associated with electrical circuits. These models are able to simulate the inflation and constriction of elastic arteries following heart systole.
and diastole, respectively. However, the Windkessel models do not account for the sophisticated structure of the arterial wall and for the spatial propagation of arterial deformations. Nonetheless, these models are still useful and popular in modelling global hemodynamics (dynamics of blood flow); one instance is the vascular coupling between various organs of the body.

In a different manner, for local investigations of the arterial biomechanics, cardiovascular partial differential equation (PDE) models are employed. These models appeared since the XIX century and gained increased interest with advancements in computational technologies. The PDE models account for both spatial and temporal dependence of arterial deformations. The one-dimensional PDE models allow implementation of the wave character of arterial pulsations and blood flow and are able to determine the deformed cross-sectional area of the vessel [48]. The arteries are modelled as extensible tubes, but are lacking physiological details such as the composition of the arterial wall [97].

Finally, the three-dimensional (3D) PDE models are able to incorporate the heterogeneous composition and response of the deformable arterial wall. The 3D PDE arterial models are based on methods from continuum mechanics and require constitutive laws that describe the behaviour of soft biological tissues under different in vivo and in vitro conditions [86]. Numerous material laws formulated for the arterial wall have been empirical, using functional relations that fit the experimentally observed behaviour; this is know as the phenomenological approach [85, 97]. In a more physiologically-realistic way, the microstructure-based constitutive models of arteries account for the individual contribution of various layers (e.g. collagen, elastin, smooth muscle) within the arterial wall [36, 82]. As the complexity of the models increases, the experimental validation becomes more challenging. The set of material parameters, determined by fitting the model against experimental data, applies to that specific vessel and those experimental conditions only. In other words, models of the large arteries, such as the aorta for instance, are not able to capture the specific response of cerebral arteries and vice versa.

The elastic response of the arterial wall to external loads is commonly assessed in terms of strains and stresses [111]. The strain describes the finite deformation of a solid body relative to the initial configuration. The stress (elastic force per unit cross-sectional area) is related to the strength of a material. The strains and stresses within a material are related by a constitutive relation, which does not describe the material itself, but rather the behaviour
of the material under specific conditions (e.g. normotensive, hypertensive, etc). Therefore, various constitutive relations are required to describe the elastic behaviour of the same material under different circumstances \[86\]. For example, under the assumption of small displacements relative to any other length-scale, i.e. infinitesimal strain theory, a linear relationship can be postulated between the strains and stresses and no distinction is made between the undeformed and deformed configuration. This is in contrast with the framework of finite strain theory, i.e large strain theory or large deformation theory, in which deformations are relatively large and where a clear distinction needs to be made between the undeformed and deformed state of the system and the stress-strain relationship becomes non-linear. The latter one is the most popular approach for describing the response of biological soft tissues such as arteries. The hyperelastic material is a non-linear model for which the constitutive stress-strain relationship arises from a strain energy function (SEF) and is commonly used to quantify the strains and stresses in arteries under physiological and pathological conditions \[86\]. In the section below, basic aspects of hyperelasticity are revised and then applied to the cerebral arterial model and also to the poroelastic model from Chapter 5.

### 4.1 Overview of finite hyperelasticity

None of the material in Section 4.1 is of original creation. Three books \[59, 83, 98\] are used as main references for the overview of finite hyperelasticity in the remainder of this section.

**Principal stress state.** The response of a deformable body to applied external forces and body forces has been commonly presented in terms of stress. The concept of stress is related to the strength of a material and describes the force \(dF\) per unit area \(dS\) acting on the material surface:

\[
T^{(n)} = \frac{dF}{dS}, \tag{4.1}
\]

where \(T^{(n)}\) represents the traction or stress vector oriented in the direction of the unit normal vector \(n\) of the surface. The stress tensor \(\sigma\) relates the stress vector to the unit normal vector of the material surface, according to:

\[
T^{(n)} = \sigma n \quad \text{or} \quad T_{j}^{(n)} = \sigma_{ij} n_{i} \quad (i, j = 1, 2, 3), \tag{4.2}
\]
where $\sigma = (\sigma_{ij})$ is known as the Cauchy stress tensor or the true stress tensor.

For a continuous body in a 3D coordinate system $Ox_1x_2x_3$, $\sigma$ is a symmetric second-order tensor with nine components that completely describe the state of stress at a point within the deformed body. The Cauchy stress tensor has 6 distinct components owing to symmetry: 3 normal stresses ($\sigma_{11}, \sigma_{22}, \sigma_{33}$) and 3 distinct shear stresses ($\tau_{12} = \tau_{21}, \tau_{23} = \tau_{32}, \tau_{13} = \tau_{31}$), i.e.

$$\sigma_{ij} = \begin{bmatrix} \sigma_{11} & \tau_{12} & \tau_{13} \\ \tau_{21} & \sigma_{22} & \tau_{23} \\ \tau_{31} & \tau_{32} & \sigma_{33} \end{bmatrix}. \quad (4.3)$$

The components of stress depend on the orientation of the coordinate system at the point under consideration. Nonetheless, the stress tensor itself is a physical entity and its magnitude is independent of the coordinate system. In other words, the way a deformable body responds to stress should be the same, regardless of the frame in which it is observed.

Every second-order symmetric tensor has components that are independent of the coordinate system. These components are the eigenvalues of the tensor and are said to be the invariants of the tensor, i.e. the eigenvalues of a second-order tensor are invariant under any orthogonal transformation (e.g. rotation). The eigenvectors corresponding to the eigenvalues of the tensor give the principal directions.

A given system $Ox_1x_2x_3$ can be rotated such that the axes of the new coordinate system $Ox'_1x'_2x'_3$ are orientated along the eigenvectors of the stress tensor which represent the principal directions and correspond to the eigenvalues $\sigma_1, \sigma_2$ and $\sigma_3$. The shear stress components vanish, while the normal components of stress are oriented in the principal directions and represent the principal stresses. Thus, the matrix of components of the stress tensor becomes diagonal:

$$\sigma_{ij} = \begin{bmatrix} \sigma_1 & 0 & 0 \\ 0 & \sigma_2 & 0 \\ 0 & 0 & \sigma_3 \end{bmatrix}, \quad (4.4)$$

where $\sigma_1, \sigma_2$ and $\sigma_3$ are the principal stresses.

**The deformation tensor.** In a continuous, deformable material, the stress response to an imposed force results in deformations. The undeformed (reference)
4.1. OVERVIEW OF FINITE HYPERELASTICITY

Configuration is described in the Lagrangian frame. The material is deformed in such a way that, at a later time, the position $\mathbf{X}$ of an arbitrary material point is displaced to a new position $\mathbf{x}(\mathbf{X},t)$, where $\mathbf{x}$ denotes the position vector in the deformed (current) configuration described in the Eulerian frame. The material deformation is captured by the deformation gradient tensor $F = (F_{ij})$

$$F = (F_{ij}) = \frac{\partial x_i}{\partial X_j} \quad (i, j = 1, 2, 3),$$

(4.5)

where the ratio $\frac{\partial x_i}{\partial X_j}$ relates the position of an arbitrary point of the material in the reference configuration to the position of the same point in the deformed state ([83], p. 216). $F$ is useful to define the Jacobian (denoted by $J$) of a material.

$$J = \det \left( \frac{\partial x_i}{\partial X_j} \right) = \det F_{ij},$$

(4.6)

where $J$ is a measure of volume change. If $J$ is positive and less than one, it means that the material’s volume decreased following deformation, while values of $J$ higher than one show that the material’s volume increased. If $J$ remains equal to one, then the volume is conserved and the material is said to be incompressible.

The deformation gradient tensor $F$ does not only contain information on the local stress-induced deformations but also on the local rotations and translations of the body. The rigid body movement (e.g. translation and rotation) causes displacement of the body, but does not induce any stress. The action of $F$ can be expressed via its polar decomposition:

$$F = M^T U,$$

(4.7)

where $M$ is an orthogonal matrix describing the rotation of the body and $U$ a positive definite symmetric matrix that stretches the elastic body along a set of orthogonal axes.

For any real symmetric second-order tensor it is possible to choose a set of principal axes, such that the matrix of components of the tensor is diagonal. Thus, in response to a stress field acting along the principal directions, the material will be stretched along those directions. If $\epsilon_i (i = 1, 2, 3)$ are eigenvectors of $U$ corresponding to real, positive eigenvalues $\lambda_i (i = 1, 2, 3)$, then $U$ can be diagonalized under the action of an orthogonal matrix $R$. 
CHAPTER 4. MODELLING THE ARTERIAL WALL

\[ U = R^T \Lambda R, \]  \hspace{1cm} (4.8)

where \( \Lambda = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}, \quad R = \begin{bmatrix} e_1^T \\ e_2^T \\ e_3^T \end{bmatrix} \) and \( U e_i = \lambda_i e_i, e_i e_j = \delta_{ij}. \)

where \( \delta_{ij} \) represent the delta Kronecker symbol.

Consequently, the deformation gradient tensor \( F \) becomes:

\[ F = M^T R^T \Lambda R \]  \hspace{1cm} (4.9)

and the transformation of a line segment can be described by

\[ dx = M^T R^T \Lambda RdX. \]  \hspace{1cm} (4.10)

Here, \( dX \) denotes the line segment that joins two particles in the undeformed material and \( dx \) denotes the line segment that joins the same two particles displaced to new positions in the deformed material. The line element can be decomposed into its components along each of the eigenvectors \( e_i \)

\[ dx = M^T \sum_i \lambda_i e_i (e_i \cdot dX). \]  \hspace{1cm} (4.11)

Therefore, the transformation of a line segment described by \( F \), could be regarded as: a stretch by a positive factor \( \lambda_i \) along the eigenvectors \( e_i \), followed by a rotation under the action of the orthogonal matrix \( M \). The eigenvalues \( \lambda_i \) represent the principal stretch ratios ([83], p. 222).

The deformations due to the stretch of the material are contained in the symmetric part of \( F \), while the rotational information is captured in the skew-symmetric part of \( F \). Since a rotation is not supposed to affect the deformation ability of a material and induce any stresses, it is convenient to exclude rotations when measuring a material deformation in response to stress ([83], p.5). However, the gradient deformation tensor is not rotation-independent. For instance, suppose that a rigid-body motion (e.g. translation and rotation) is superimposed on the deformed state, such that each point \( x \) is further displaced...
4.1. OVERVIEW OF FINITE HYPERELASTICITY

\[ x' = c + P x. \] (4.12)

where the translation vector \( c \) and the rotation matrix \( P \) are constant ([3], p.216). By substituting the expression of \( x' \) in expression \([4.5]\), the deformation gradient tensor becomes:

\[ F'_{ij} = \frac{\partial x'_{i}}{\partial X_{j}} = P_{ik} F_{kj}. \] (4.13)

The new configuration is measured by a new deformation gradient tensor \( F'_{ij} \), although no stress response or additional deformations are present. In order to account locally only for the stress-induced deformations (e.g. stretches) and eliminate the transformations of the system due to the rigid-body motion, the Cauchy-Green deformation tensor is introduced. Considering that a rotation, followed by its inverse rotation yields no change, local rotations can be excluded by multiplying equation \([4.9]\) with the transpose of \( F \):

\[ C = F^T F = U^T M M^T U = U^2, \] (4.14)

with the remark that \( U^T = U \) and \( M M^T = I \), where \( I \) is the identity matrix.

The above expression is called the right Green-Cauchy deformation tensor or simply the Green deformation tensor. \( C \) is a symmetric tensor that completely describes the state of deformation induced by the stress field in the local neighbourhood of a material point at which it is evaluated. The left Green-Cauchy deformation tensor can also be defined as \( B = F F^T \). Considering expression \([4.5]\), \( C \) appears in index notation as

\[ C_{ij} = F_{ik}^T F_{jk} = \frac{\partial x_k}{\partial X_i} \frac{\partial x_k}{\partial X_j}. \] (4.15)

Physically, \( C \) describes the square of local changes in distance due to deformations. By substituting the form of \( U \) from \([4.8]\) in \([4.14]\), \( C \) becomes:

\[ C = U^2 = R^T \Lambda^2 R. \] (4.16)

It results that \( C \) shares the same eigenvectors \( e_i \) as \( U \), although it has different eigenvalues (e.g. \( \lambda_i^2 \), \( i = 1, 2, 3 \)). It is worth recalling that the eigenvalues of a second order symmetrical tensor are independent of the coordinate system and are said to be invariants of the tensor. Any function \( f(\lambda_1^2, \lambda_2^2, \lambda_3^2) \) whose value
remains unchanged after reordering $\lambda_1^2, \lambda_2^2, \lambda_3^2$ is said to be symmetric in $\lambda_1^2, \lambda_2^2, \lambda_3^2$ and is an invariant of $C$. The invariants of $C$ play an important role in designing constitutive equations and the most commonly used invariants are

\begin{align}
I_1(C) &= \lambda_1^2 + \lambda_2^2 + \lambda_3^2, \\
I_2(C) &= \lambda_1^2\lambda_2^2 + \lambda_2^2\lambda_3^2 + \lambda_3^2\lambda_1^2, \\
I_3(C) &= \lambda_1^2\lambda_2^2\lambda_3^2.
\end{align}

For a coordinate system with axes oriented along the principal directions, $C$ is diagonal and the three invariants become:

\begin{align}
I_1(C) &= \text{Tr}(C), \\
I_2(C) &= \frac{1}{2}(\text{Tr}(C)^2 - \text{Tr}(C^2)), \\
I_3(C) &= \det C.
\end{align}

**Principal strains.** The strain, $(d\mathbf{x} - d\mathbf{X})/d\mathbf{X}$ describes the extension of a line segment relative to its initial length. The Green strain tensor is defined as

$$E_{ij} = \frac{1}{2} \left( \frac{\partial x_k}{\partial X_i} \frac{\partial x_k}{\partial X_j} - \delta_{ij} \right)$$

which rewritten in tensor notation, appears as

$$E = \frac{1}{2}(C - I) = \frac{1}{2}(F^T F - I).$$

In the light of the invariance requirements, only the symmetric part of the gradient deformation tensor, corresponding to the stretch, is retained in the definition of $E$. If the axes of the system are oriented along the principal directions of the deformation, the normal strains will represent the principal strains ($E_{11} = E_1, E_{22} = E_2, E_{33} = E_3$) and all the other components of the strain tensor will go to zero (i.e. $E_{ij} = 0$ for any $i \neq j$). The principal strains are related to the principal stretch ratios by

$$E_i = \frac{1}{2}(\lambda_i^2 - 1).$$

The strains can also be expressed as a function of displacement $u(\mathbf{X}, t)$:

$$u(\mathbf{X}, t) = x(\mathbf{X}, t) - \mathbf{X},$$

which gives the difference between the current and the initial position of the point that underwent deformation.
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Substituting in the definition of $E$ from (4.19), gives

\[
E_{ij} = \frac{1}{2} \left( (\delta_{ki} + \frac{\partial u_k}{\partial X_i}) (\delta_{kj} + \frac{\partial u_k}{\partial X_j}) - \delta_{ij} \right),
\]

(4.23)

\[
E_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial X_j} + \frac{\partial u_j}{\partial X_i} + \frac{\partial u_k}{\partial X_i} \frac{\partial u_k}{\partial X_j} \right).
\]

(4.24)

**Linear elasticity** The particular case of linear elasticity can be obtained if for small finite deformation, the quadratic term from equation (4.24) is neglected, considering the smallness of $\frac{\partial u_i}{\partial X_j}$. The resulting linearised strain tensor, also known as the *Cauchy’s infinitesimal strain tensor* is:

\[
E_{ij} \approx e_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial X_j} + \frac{\partial u_j}{\partial X_i} \right)
\]

(4.25)

It is emphasized that the deformation gradient tensor from (4.5) and the strain tensors from (4.24) are defined in terms of Lagrangian variables $X$, describing the deformation relative to the reference state. On the other hand, the Cauchy stress tensor is defined in the Eulerian space, relating the stress to the deformed configuration. Consequently, it is a challenging task to formulate a constitutive equation (or stress-strain relationship) between two variables defined in different frames of reference. A constitutive equation specifies the physical properties of a material. As the value of a physical property should be the same, regardless of the frame of reference with respect to which the physical quantity is calculated, the constitutive equation must be independent of the coordinate system. There exist some simplified, idealized constitutive equations, such as in the context of linear elastic theory, where the Lagrangian and Eulerian variables can be approximated as equal. Hence, $X$ can be replaced by $x$ and $\frac{\partial u_i}{\partial X_j}$ by $\frac{\partial u_i}{\partial x_j}$. Consequently, in linear elasticity, the corresponding Cauchy stress tensor can be expressed as a linear function of the strain from (4.25) according to:

\[
\sigma_{ij} = \lambda (e_{kk}) \delta_{ij} + 2\mu e_{ij},
\]

(4.26)

where $\lambda$ and $\mu$ are Lamé constants and $\delta_{ij}$ is the Kronecker delta symbol.

However, in materials which are exposed to large finite deformations and still remain elastic (e.g. rubber, biological tissue), the linear stress-strain relationship does not hold and the quadratic term from expression (4.24) cannot be neglected. Moreover, the Lagrangian and Eulerian frames cannot be assumed as being identical. Consequently, the stress corresponding to the Green
strain needs to be defined relative to the Lagrangian frame; this is realised by introducing the Piola-Kirchhoff stress tensor, as shown below.

The strain energy function. The derivation of stress-strain relationships within the context of non-linear elastic theory can be simplified for hyperelastic materials for which the stress and strain are related through the partial derivatives of an appropriate empirical strain energy function (SEF), which gives the amount of stored energy per unit volume. This is the case of biological tissues, such as the arterial wall and the brain tissue.

As an illustrative example, the stress-strain relationship for the linear elastic model from equation (4.26) can also be obtained from a SEF as follows

\[ \sigma = \frac{\partial W}{\partial e_{ij}} \quad \text{with} \quad W = \frac{1}{2} \lambda e_{kk}^2 + \mu e_{ij} e_{ij}, \tag{4.27} \]

where \( W \) denotes the SEF.

Considering that a large variety of materials exist, there are also numerous corresponding constitutive equations describing the material physical properties. Certain constitutive relations could characterize an elastic material that is a limitless energy source, which is physically impossible. In order to exclude such a behaviour, it is sufficient for the SEF to satisfy the following condition

\[ T = \frac{\partial W}{\partial F} \tag{4.28} \]

where \( T \) is the non-symmetric second-order tensor known as the first Piola-Kirchhoff stress tensor expressed relative to the Lagrangian frame.

Underlying again the fact that the way a material responds to stress should not change in different frames of reference, the SEF must be independent of the coordinate system. Moreover, the SEF must be a convex function of the stretch ratios, with global minima when the material does not experience any deformation. In other words, when there is no strain, no stress can be generated. Additionally, the SEF should adequately describe the experimental data. The non-symmetry of the \( T \) stress raises difficulties in designing the constitutive equations. Therefore, the second Piola-Kirchhoff stress tensor \( S \) is introduced as \( S = F^{-1}T \).

The Cauchy stress (i.e. the true stress) is related to the Piola-Kirchhoff
stresses as follows

\[ T = \det(F)\sigma(F^T)^{-1} \quad (4.29) \]

and

\[ S = F^{-1}T = \det(F)F^{-1}\sigma(F^T)^{-1}. \quad (4.30) \]

The above relationships allow for the Cauchy stress to be determined from a SEF

\[ \sigma = \frac{1}{\det F} \frac{\partial W}{\partial F} F^T, \quad (4.31) \]

where expression (4.28) was considered. For an incompressible material with axes oriented along the principal directions of the Cauchy stress, a stress-strain relationship between the principal Cauchy stresses and the principal Green strains is obtained:

\[ \sigma = \lambda_i \frac{\partial W}{\partial \lambda_i} = \lambda_i^2 \frac{\partial W}{\partial E_i}, \quad (4.32) \]

noting that the deduction of expression (4.32) is explained in Appendix B.

The SEF can be expressed as function of the invariants (i.e. \( W = W(I_1, I_2, I_3) \)), or as a function of principal stretch ratios (i.e. \( W = W(\lambda_1, \lambda_2, \lambda_3) \)) or, equally, as a function of principal Green strains (i.e. \( W = W(E_1, E_2, E_3) \)). The problems of non-linear solid mechanics are usually solved in the Lagrangian framework where the first or the second Piola-Kirchhoff stress is defined. Nonetheless, the orientation of the system along the principal directions makes the analysis in the Eulerian framework tractable, as it will be shown below in the model of the elastic active cerebral artery.

### 4.2 Representative hyperelastic models of arteries

Arteries are exposed to a significant amount of mechanical stress during the pumping of the blood and the composition of the arterial wall is critical for withstanding such stresses. The arterial wall consists of elastic material that allows distension and recoil of the wall, collagenous fibres that contribute to the
stiffness of the wall and contractile muscular cells that impose a vascular tone. The type of stresses that arise in an arterial wall are discussed below.

**Passive and active stress.** The deformation of the arterial wall modulated by the elastic and collagenous elements yields passive stresses, while the contractile VSMCs generate an active stress, i.e. hoop stress, distributed mainly circumferentially [97]. The passive stresses are a function of the mechanical properties of the artery, while the active stresses reflect its autoregulatory abilities (e.g. myogenic tone). The vascular tone of VSMCs was proposed as an important parameter in arterial adaptation to blood flow, vascular remodelling and in the distribution of strains and stresses in the arterial wall [140, 139]. If the contribution of the VSMCs in the arterial elastic response is accounted for, then the non-linear elastic theory should be employed, because the stress-strain relationship of VSMCs is non-linear, as it will be shown below.

**Residual stress.** The residual strains and stresses are those present in the arterial wall when the entire external load is removed. Early experiments have shown that when a ring segment from an unloaded artery is cut radially, it springs open taking a circular form. Chuong and Fung (1986) were the first ones to suggest the presence of residual strain and stress, which proved to reduce the stress gradient along the wall thickness [37]. Considering that a nearly uniform distribution of stress in the arterial wall is essential for an optimal performance of arteries, it is important to account for the contribution of the residual strains and stresses when assessing the biomechanics of arteries in health and disease. When modelling the deformation of arteries, the reference state should be considered the zero-stress state when the artery springs open releasing the residual stresses [140]. Given that the residual stresses are specific to each arterial segment from the body, the experimental information about such stresses is very scarce. Consequently, the existence of residual stresses is often ignored and the reference state is considered to be the zero-load state, rather than the zero-stress state.

### 4.2.1 Models of passive arteries

The most commonly employed 3D hyperelastic models of the arterial wall are reviewed in [82, 97]. One of the earliest SEFs was proposed by Yuan Cheng Fung, who is considered the father of biomechanics [37]. The most general form
of the 3D Fung-type model looks like

\[ W = \frac{c}{2}(e^Q - 1) \tag{4.33} \]

where

\[ Q = b_1 E_{\theta\theta}^2 + b_2 E_{zz}^2 + b_3 E_{rr}^2 + 2b_4 E_{\theta\theta} E_{zz} + 2b_5 E_{rr} E_{zz} + 2b_6 E_{rr} E_{\theta\theta} + b_7 E_{\theta z}^2 + b_8 E_{rz}^2 + b_9 E_{r\theta}^2. \tag{4.34} \]

c is a material parameter with units of pressure and \( b_i \) with \( i = 1, ..., 9 \) are non-dimensional material parameters determined from fitting the model against experimental data; this is known as a phenomenological approach. \( E_{jk} \) with \( j, k = r, \theta, z \) are the components of the Green strain in cylindrical coordinates.

The above expression is further simplified for arteries that do not experience torsion (i.e. \( E_{r\theta} = E_{z\theta} = 0 \)) and for incompressible arteries when the radial strains can be expressed as a function of the circumferential and axial strains only; this aspect is discussed in more details in the cerebral arterial model from Section 4.3.

The Fung-type SEF assumes a homogeneous arterial wall, in the way that no differentiation between the material layers of the arterial wall is made. More complex SEFs that capture the specific behaviour of each arterial layer (e.g. elastin, collagen) have been introduced by Holzapfel and are known as fibre-reinforced models \[82\].

### 4.2.2 Models of active arteries

All the arterial models mentioned above have been experimentally validated in passive arteries when the VSMCs are a priori relaxed. One of the earliest models for the active response of the VSMCs was proposed by Rachev et al.\[140\] in the form of

\[ \sigma_\theta^a = S \lambda_\theta f(\lambda_\theta) \quad \text{with} \quad f(\lambda_\theta) = 1 - \left( \frac{\lambda_m - \lambda_\theta}{\lambda_m - \lambda_0} \right)^2, \tag{4.35} \]

where \( \lambda_m \) is the circumferential stretch at which maximum active contraction may develop and \( \lambda_0 \) is the minimum stretch possible at which active force can be generated. \( S \) captures the activation of the SMCs and it has units of stress, e.g. \( S = 0, 50 \) and 100 kPa in the passive, basal and fully activated state, respectively.
The model (4.35) shows that the SMCs are able to generate an active force only at certain lengths. For example, if the SMC is over-stretched or over-contracted, it will not be able to generate any active stress. This property is captured in the length-tension relationship $f(\lambda)$ which describes a parabolic curve and is in line with more recent studies that considered intracellular mechanisms that lead to contractions of the VSMCs \cite{121}. The model (4.35) assumes that the SMCs generate an active stress only in the circumferential direction. Experimental studies have shown that the SMCs may also generate an active axial stress \cite{122} and the model (4.35) has been developed to account for this property \cite{187}.

The major limitation of the model (4.35) is the fact that the activation parameter $S$ takes fixed values inferred from experimental data on carotid arteries \cite{43, 140}. A more physiologically-advanced model would include an activation function that depends on the intracellular calcium concentration, accounting for the fact that the VSMC contraction is calcium-dependent (an elevated intracellular calcium concentration generates VSMC contraction through coupling of actin and myosin filaments). Such models have been developed by Zulliger et al., \cite{188} who proposed a conceptually similar model to the fibre-reinforced model of Holzapfel et al., \cite{82} by accounting for the orientation of the elastic and collagenous fibres, as well as for the contribution of the VSMC contraction to load bearing in conductive arteries (e.g. rat carotid artery).

### 4.3 Radial deformation of an active cerebral artery

This section deals with the axisymmetric uniform radial deformation of an incompressible non-linear active elastic artery exposed to radial inflation with intraluminal pressure and constant axial extension. A hyperelastic model for an active middle cerebral artery is built by bringing together the passive and active models reviewed in the section above. This is actually a simplified model motivated by the linear analysis from Appendix B. The objective of the model is to estimate the deformation of an cerebral artery induced by the active VSMCs, as this aspect plays an important role in the IPAD model from Chapter 5. Given also the non-linear elastic nature of the arterial wall, the complexity of the problem increases significantly. However, some reasonable simplifications can be made by exploiting the disparity between the length scale of the system
4.3. RADIAL DEFORMATION OF AN ACTIVE CEREBRAL ARTERY

(the arterial radius of around 100 µm is much smaller than the wavelength of muscular contractions of 2000 µm). Hence, the axial variations in arterial deformations are longer in comparison to the arterial radius. For simplicity reasons, the implications of this assumption are studied in the linear elastic model presented in Appendix B. By applying the lubrication approximation, it is obtained that, at leading order, only the normal stresses are non-zero and have radial dependence only. By analogy, it is assumed that also the hyperelastic artery behaves similarly at leading order; hence, the model for the active cerebral artery developed below has radial dependence only.

4.3.1 Model formulation

The system (e.g., cerebral hyperelastic artery) is described in cylindrical coordinates as a thick-walled cylinder, where the reference configuration is given in terms of \((R, \Theta, Z)\) and the deformed configuration in terms of \((r, \theta, z)\). The reference state is considered to be the zero-load state (i.e., the intraluminal pressure and the axial strain are both zero). This assumption ignores the existence of residual stresses in the arterial wall after the external load is removed, but is, nonetheless, an acceptable assumption motivated by the limited experimental data on cerebral arteries. As justified above, all variables depend only on \(r\). The problem is further simplified by considering the axes of the cylindrical coordinate system oriented along the principal directions, i.e., in the same direction of the principal components of the Cauchy stress tensor and the Green strain tensor. Thus, the only non-zero physical components of the Cauchy stress tensor are \(\tau_{rr}(r) = \sigma_r(r)\), \(\tau_{\theta\theta}(r) = \sigma_\theta(r)\) and \(\tau_{zz}(r) = \sigma_z(r)\), respectively.

**Deformation.** The deformation gradient tensor, that relates the deformed configuration to the reference configuration, becomes

\[
\mathbf{F} = \text{diag} \left[ \frac{\partial r}{\partial R}, \frac{r}{R}, \frac{l}{L} \right],
\]

where \(R\) and \(r\) are the radial coordinates of an arbitrary point in the initial and deformed state, respectively. \(L\) and \(l\) are the undeformed and deformed length, respectively.

A common approach is to describe the deformation in terms of the principal
stretches
\[ \lambda_r = \frac{\partial r}{\partial R}, \quad \lambda_\theta = \frac{r}{R}, \quad \lambda_z = \frac{l}{L}, \] \hfill (4.37)

where \( \lambda_r, \lambda_\theta, \) and \( \lambda_z \) are the principal stretches in the radial, circumferential and axial direction, respectively. Here, \( \lambda_z \) is a known constant from the experiments in [22].

The principal Green strains are related to the principal stretches, by
\[ E_i = \frac{1}{2} (\lambda_i^2 - 1), \quad i = r, \theta, z. \] \hfill (4.38)

The arterial wall is assumed incompressible (i.e. the wall volume is preserved during deformation), which means imposing \( J = \det F = 1 \). Therefore, the principal stretches must satisfy the condition
\[ \lambda_r \lambda_\theta \lambda_z = 1. \] \hfill (4.39)

Accounting for equation (4.39), one of the principal stretches can be expressed as a function of the other two stretches and still maintain the three-dimensional response of the system, i.e.
\[ \lambda_r = \frac{1}{\lambda_\theta \lambda_z}. \] \hfill (4.40)

Similarly, the radial strain can be expressed as a function of the circumferential and axial strains by considering relationship (4.38). Consequently, any 3D SEF that describes this particular case can be a function of the circumferential and axial strains only, i.e. \( W = W(E_\theta, E_z) \) and still describe the 3D nature of the system. Here, the Fung-type SEF from (4.33)-(4.34) is chosen and, for these particular assumptions (incompressible, no torsion, radial inflation and longitudinal extension), reduces to
\[ W = \frac{1}{2} c(e^Q - 1) \quad \text{with} \quad Q = c_1 E_\theta^2 + c_2 E_z^2 + 2c_3 E_\theta E_z \] \hfill (4.41)

where \( c \) is a material parameter with units of pressure, \( c_1, c_2 \) and \( c_3 \) are non-dimensional material parameters and the principal Green strains \( (E_\theta, E_z) \) are given in (4.38). The material parameters need to satisfy certain requirements imposed by energy conservation, e.g. \( c_1, c_2, c_3 > 0 \) and \( \sqrt{c_1 c_2} > c_3 \). These material parameters were determined experimentally by [22] for passive rat middle cerebral arteries that were exposed to inflation with pressure and constant axial
extension (see Table 4.1). The same SEF form was used by [84] for modelling passive cerebral arteries (e.g. porcine basilar artery) and compared well with other models such as the Holzapfel model [82] and its extension to the 4-fibre family model.

The incompressibility condition yields a relationship between the undeformed and deformed radius of the artery, as follows. Substituting equations (4.37) into condition (4.39), gives the differential equation

\[ \frac{dr}{dR} = \frac{R}{\lambda z} r. \]  

(4.42)

After integrating the above

\[ \int_{r_i}^{r} r dr = \frac{1}{\lambda z} \int_{R_i}^{R} R dR, \]

(4.43)

a relationship between the undeformed radius \( R \) and the deformed radius \( r \) is obtained

\[ r = \sqrt{r_i^2 + \frac{R^2 - R_i^2}{\lambda z}}. \]

(4.44)

The only input of the model is the reference configuration (e.g. \( R_i \), denoting the undeformed inner radius and \( R_o \), denoting the undeformed outer radius), the constant arterial pressure \( P \) and the constant axial stretch \( \lambda z \). The deformed state of the system is completely unknown. Therefore, in order to calculate the stresses and strains of the arterial wall under physiological conditions, the deformed inner radius \( r_i \) must be determined first. The derivation of the equation that requires solving in order to determine \( r_i \) is given below.

**Force-balance equation.** The balance of the generated forces during the deformation of the arterial wall, in a specific point, is captured in the conservation of momentum equation, which for a material point is given in the Lagrangian framework, while for a spatial point is given in the Eulerian framework. Here, the latter approach is chosen. In the absence of time-dependence and any body forces, the conservation of momentum equation reduces to the force-balance equation:

\[ \nabla \cdot \sigma = 0, \]

(4.45)

where \( \nabla \) denotes the spatial divergence of the Cauchy stress \( \sigma \), in the current deformed configuration of the system. Given the assumed geometry, the Cauchy
stress is a function of principal stresses only, i.e. \( \sigma = \sigma(\sigma_r, \sigma_\theta, \sigma_z) \). The only non-trivial component of equation (4.45), in cylindrical coordinates, is

\[
\frac{d\sigma_r}{dr} + \frac{\sigma_r - \sigma_\theta}{r} = 0,
\]

with boundary conditions

\[
\sigma_r|_{r=r_i} = -P, \quad \sigma_r|_{r=r_o} = 0,
\]

that impose continuity of stress at the inner and outer boundaries. A constant arterial pressure \( P \) is applied on the inner boundary of the wall, while zero pressure is assumed on the outer boundary. Two boundary conditions are required because equation (4.46) becomes a second-order differential equation in terms of the deformed radius \( r \), as will be obvious below.

A commonly employed approach [32, 86, 140] for modelling active arteries is to calculate the total circumferential stress as the sum of passive stress and active stress, here denoted by \( \sigma^p_\theta \) and \( \sigma^a_\theta \), respectively

\[
\sigma_\theta = \sigma^p_\theta + \sigma^a_\theta.
\]

**The passive stresses.** The general expression of the Cauchy stresses determined from a SEF was discussed above, e.g. equation (4.32). Given the assumed incompressibility of the arterial wall, some constraints are required and the expression of the Cauchy stress modifies accordingly. The incompressibility constraint can be enforced directly or via a Lagrange multiplier denoted \( p \) ([87], p. 93-97). The latter approach says that the normal stresses can be determined from the SEF \( W \) only up to an arbitrary \( p \) and the expression of the principal stresses becomes

\[
\sigma_r = \lambda^2_r \frac{\partial W}{\partial E_r} - p, \quad \sigma^p_\theta = \lambda^2_\theta \frac{\partial W}{\partial E_\theta} - p, \quad \sigma_z = \lambda^2_z \frac{\partial W}{\partial E_z} - p,
\]

where \( p \) is the Lagrange multiplier that remains to be determined from the equilibrium and boundary conditions of the system ([87], p. 289).

Alternatively, the incompressibility constraint can be imposed directly by
giving only the differences between the three principal stresses as

\[ \sigma^p_{\theta} - \sigma_r = \lambda^2_{\theta} \frac{\partial W}{\partial E_{\theta}}, \quad (4.50) \]

\[ \sigma_z - \sigma_r = \lambda^2_{z} \frac{\partial W}{\partial E_{z}}, \quad (4.51) \]

where \( W = W(E_\theta, E_z) \). This approach reveals that only two of the three principal components of stress are independent and determined from the SEF. The third component (e.g. \( \sigma_r \)) can also be determined by imposing equilibrium and boundary conditions, which is similar to the determination of the Lagrange multiplier \( p \).

Imposing incompressibility directly requires for the direction of the principal stresses and strains to coincide. Overall, the Lagrange multiplier approach is more general, i.e. does not apply only to the principal components, but, on the other hand, introduces an extra unknown that needs to be determined. Moreover, the search for a SEF that depends on three or more strain components, as is the case for the Lagrange multiplier method, is more challenging than determining a functional form for a SEF that depends only on two strain components. Here, incompressibility is imposed directly, i.e. using equations (4.50)-(4.51), in order to comply with the approach from the experimental study [22] that determined the material parameters of rat middle cerebral arteries.

The active stress. The choice of a model for the active cerebral artery is very difficult because all the previous active models contain fitted parameters and none of them have been validated for cerebral arteries. For simplicity reasons, the model (4.35) from [4] is chosen and recalled below

\[ \sigma^a_{\theta} = S\lambda_{\theta} f(\lambda_{\theta}) \quad \text{with} \quad f(\lambda_{\theta}) = 1 - \left( \frac{\lambda_m - \lambda_{\theta}}{\lambda_m - \lambda_0} \right)^2, \quad (4.52) \]

where \( S \) represents the level of VSMC activation, e.g. \( S = 0, 50 \) and 100 kPa in the passive, basal and fully activated state, respectively. By taking these values, it is assumed that the VSMCs of the rat middle cerebral artery develop the same contractile force as those in the rat carotid artery.

The pressure equation. The deformation of the arterial wall is determined by employing the local radial equilibrium equation (4.46) and boundary conditions (4.47). Both radial and circumferential stresses are known functions of the deformed radius \( r \), i.e. \( \sigma_r = \sigma_r(r) \) and \( \sigma_{\theta} = \sigma_{\theta}(r) \), so the equilibrium equation
is solved for $r$ which varies between the inner radius $r_i$ and outer radius $r_o$. Rearranging and integrating equation (4.46) over the thickness of the wall by following the approach from numerous studies (see [140], [87], p. 299), gives

$$
\int_{r_i}^{r_o} d\sigma_r = \int_{r_i}^{r_o} (\sigma_\theta - \sigma_r) \frac{dr}{r} \tag{4.53}
$$

$$
\sigma_r|_{r=r_o} - \sigma_r|_{r=r_i} = \int_{r_i}^{r_o} (\sigma_\theta^a + \sigma_\theta^p - \sigma_r) \frac{dr}{r}, \tag{4.54}
$$

where $r_o$ is a known function of $r_i$. The expression for the total circumferential stress from (4.48) was considered in the above equation.

Substituting the values of the radial stress on the inner and outer wall from the boundary conditions (4.47) in the left-hand side and replacing expressions (4.52) and (4.50) for the active and passive stresses, respectively, in the right hand side, equation (4.54) becomes

$$
P = \int_{r_i}^{r_o} \left( \lambda_\theta^2 \frac{\partial W}{\partial E_\theta} + S\lambda_\theta f(\lambda_\theta) \right) \frac{dr}{r} \tag{4.55}
$$

where

$$
r_o(r_i) = \sqrt{r_i^2 + \frac{R_o^2}{\lambda_z} - \frac{R_i^2}{\lambda_z}}, \quad \lambda_\theta = \frac{r}{R}, \quad E_\theta = \frac{1}{2} \left( \lambda_\theta^2 - 1 \right). \tag{4.56}
$$

The pressure equation plays a critical role in describing the behaviour of the system. Essentially, every time the deformation of the artery is assessed, one will return to the pressure equation to calculate the deformed inner radius $r_i$ and, only subsequently, the strains and stresses within the wall will be determined.

**Stresses within the arterial wall.** Once $r_i$ is determined from (4.55), the principal radial stress at any radial position $r$ within the arterial wall is calculated by integrating equation (4.46) from $r_i$ to any $r$ and applying the first boundary condition in (4.47); this gives

$$
\sigma(r) = \int_{r_i}^{r} \left( \lambda_\theta^2(r) \frac{\partial W(r)}{\partial E_\theta(r)} + S\lambda_\theta f(\lambda_\theta(r)) \right) \frac{dr}{r} - P. \tag{4.57}
$$

The radial position at the middle of the wall (i.e. $r = r_m$, where $r_m = (r_i + r_o)/2$) and the corresponding radial stress (i.e. $\sigma_r(r_m)$) represent the input of the IPAD model from Chapter 5.
4.3.2 Physiological parameter values

The artery modelled here is considered a rat middle cerebral artery (MCA) whose passive elastic response to pressure inflation and axial stretch was investigated experimentally in [22]. The corresponding material parameters that appear in the Fung-elastic model are given in Table 4.1 and were determined in [22] by fitting the theoretical stress-strain curve against the experimental stress-strain curve. The conditions of axial stretching under which the material parameter were determined are not clearly specified in [22]. Thereby, here, each artery is investigated under different conditions of axial stretch mentioned in [22] in order to see which case provides the best fit.

The reference (undeformed state) of the artery is described by a wall thickness of 40 \( \mu \text{m} \) and an external diameter of 250 \( \mu \text{m} \), in line with the reports in [22]. Regarding the parameters specific to the VSMCs, the minimum stretch ratio for active stress (\( \lambda_0 \)) is 0.8 and the maximum stretch ratio for active stress (\( \lambda_m \)) is 1.5, as in [86].

![Table 4.1: MCA material parameters for inflation test from the study of Bell et al. [22].](image)

<table>
<thead>
<tr>
<th>Artery sample (rat MCA)</th>
<th>Fung-type material parameters (kPa)</th>
<th>( c_1 )</th>
<th>( c_2 )</th>
<th>( c_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>M10</td>
<td>13.19</td>
<td>3.12</td>
<td>12.47</td>
<td>0.48</td>
</tr>
<tr>
<td>M12</td>
<td>5.59</td>
<td>12.25</td>
<td>37.03</td>
<td>6.60</td>
</tr>
</tbody>
</table>

4.3.3 Results

Experimental validation of the model. The comparison of the cerebral arterial model with the experimental data on passive rat middle cerebral arteries in [22] is shown in Figure 4.1. Two different arteries with the material parameters given in Table 4.1 are investigated. Each artery is inflated with a large range of physiological pressures (e.g. 0 - 20 kPa) and exposed to three different levels of axial stretch. The lack of a perfect fit of the model with experiments may be explained by possibly different reference states used in the model and in the experiments, respectively. The study [22] does not provide full information about the reference state of the artery (e.g. arterial inner/outer radius or wall thickness when pressure is zero and axial stretch is one). Consequently, here, the undeformed wall thickness of rat middle cerebral artery is estimated by
extrapolation of their graphs, which may cause the discrepancies between the model and the experiment. For the M10 artery, the model describes a slightly stiffer behaviour compared to experiments, while for the M12 artery, the model yields a relatively more elastic behaviour. The active response of cerebral arteries is more difficult to validate experimentally. The general form of the active stress from equation (4.35) is illustrated in Figure 4.2. The bell-shape curve compares qualitatively well with the previous models that considered the intracellular electromechanics of VSMCs [121]. The artery displaying the best experimental fit (e.g. M10 with $\lambda_z = 1.27$) is considered for the following analysis.

![Figure 4.1: Experimental validation of the passive cerebral arterial model.](image)

**Figure 4.1:** Experimental validation of the passive cerebral arterial model. Two different rat cerebral arteries, M10 (top-image) and M12 (bottom image), are inflated with a wide range of pressures (0 - 20 kPa) and exposed to a constant axial stretch denoted by $\lambda_z$. The stress-stretch curves generated by the model are fitted against the experimental data in [22].

The combined influence of arterial pressure and VSMC contraction. The elastic response of the M10 artery is illustrated in Figure 4.3. Firstly, the effect of intraluminal pressure is assessed. The artery is kept at a constant axial stretch and inflated with a wide range of arterial pressure, causing radial distension of the artery. More specifically, a larger arterial diameter and a thinner arterial wall is observed (similar to blowing an elastic balloon). Contraction of the
4.3. RADIAL DEFORMATION OF AN ACTIVE CEREBRAL ARTERY

VSVMCs causes decrease in arterial diameter and thickening of the arterial wall; this effect becomes more predominant with increase in the value of the activation parameter $S$ (see Figure 4.3). The stress-strain relationship for various levels of activation is shown in Figure 4.4.

![Figure 4.2](image)

**Figure 4.2:** The general form of the active stress used in the model of active cerebral artery presented here. Circumferential stretches varying between 0 and 300% are considered for illustration purposes.

![Figure 4.3](image)

**Figure 4.3:** Deformed arterial radius and wall thickness in response to a wide range of arterial pressures. Left-hand side image: deformed inner radius as a function of arterial pressure. Right-hand side image: deformed wall thickness as a function of arterial pressure. A middle cerebral artery (here, M10 from Table 4.1) exposed to a constant axial stretch of 1.27 is considered.

The analysis of the M10 artery continues by looking at the distribution of the stretches and stresses across the arterial wall for two instances: (i) the arterial wall deforms due to the action of the VSVMCs only, i.e. there is no distension due to arterial pressure, as the intraluminal pressure is assumed zero; (ii) both the contractile VSVMCs and intraluminal pressure cause deformation of the arterial wall. The results are illustrated in Figure 4.5, where negative stresses indicate constrictive stresses. The former case allows separate evaluation of the effect of muscular contractions on the configuration of the arterial wall. In the case of
zero muscular activation a gradient both in stretch and stresses (radial and total circumferential) develops across the arterial wall. In contrast, in the basal state of the artery, there is nearly uniform distribution of stretch and stresses across the wall.

A non-uniform wall deformation also appears when the VSMCs remain relaxed and the artery is inflated with a physiological pressure of 100 mmHg. Once the VSMCs become activated, the distribution of the circumferential stretch and total circumferential stress across the wall becomes more uniform. The gradient in radial stress across the arterial wall is still maintained (via continuity of stress condition) due to the high pressure differences between the luminal and abluminal side of the arterial wall.

**The activation parameter.** It is emphasized that the middle of the arterial wall displays the highest variation in radial stress for different levels of VSMC activation (i.e. different values of $S$). The gradient in radial stress across the arterial wall has implications in the vasomotion model from Chapter 5; this aspect is, therefore, assessed in more cerebral arteries that exposed to various levels of axial stretch. For example, the additional cases M12 with $\lambda_z = 1.07$ and M12 with $\lambda_z = 1.13$ are considered. The value of the radial stress at the middle of the arterial wall changes with the muscular activation level and this variation becomes more significant as the axial stretch decreases, as illustrated in Figure 4.6.
4.3. **RADIAL DEFORMATION OF AN ACTIVE CEREBRAL ARTERY**

Figure 4.5: Distribution within the arterial wall of the circumferential stretch (top), total circumferential stress (middle) and radial stress (bottom). The left-hand side column: the artery has zero intraluminal arterial pressure. Right-hand side column: the artery is inflated with a physiological pressure of 100 mmHg. A middle cerebral artery (here, M10 from Table 4.1) exposed to a constant axial stretch of 1.27 is considered. Three levels of activation are investigated: S=0 kPa (black), i.e. fully relaxed VSMCs, S=50 kPa (green), i.e. basal state, and S=100 kPa (red), i.e. maximum activation of VSMCs.
Figure 4.6: Circumferential stretch and radial stress distribution within the arterial wall. Left-hand side image: M12 artery with a constant axial stretch of 1.07. Right-hand side image: M12 artery with a constant axial stretch of 1.13. Both arteries are inflated with a physiological pressure of 100 mmHg. The dotted blue line indicates the radial stress distribution at the middle of the arterial wall. Three levels of activation are investigated: S=0 kPa (black), i.e. fully relaxed VSMCs, S=50 kPa (green), i.e. basal state, and S=100 kPa (red), i.e. maximum activation of VSMCs.

The case M12 with $\lambda_z = 1.07$ is further considered as it displaced the highest variation in radial stress at the middle of the wall. A relationship between the activation parameter and the resulting deformed inner radius and corresponding radial stress is shown in Figure 4.7 and is obtained as follows. While the artery is maintained at constant arterial pressure and constant axial stretch, the activation parameter $S$ is varied continuously between 0 kPa (zero activation) and 100 kPa (maximum activation). The resulting arterial deformation for each $S$ is determined by solving the pressure equation (4.55). Subsequently, the curve between the deformed radius and $S$, as well as the curve between the resulting radial stress and $S$, are fitted with a polynomial function. e.g. $r_m(S) = p_1 S^2 + p_2 S + p_3$ and $\sigma_r(S) = m_1 S^2 + m_2 S + m_3$, respectively. The fitting coefficients are:
4.3. RADIAL DEFORMATION OF AN ACTIVE CEREBRAL ARTERY

\[ p_1 = -3.6 \cdot 10^{-8} \text{[mm}^{-1}], \quad p_2 = -2.5 \cdot 10^{-4}, \quad p_3 = 0.1233 \text{[mm]} \text{ and } m_1 = 2.6 \cdot 10^{-4} \text{[kPa}^{-1}], \quad m_2 = -0.051, \quad m_3 = -3.56 \text{[kPa].} \]

\[ S \text{[kPa]} \]

![Graph showing deformed radius vs. S and radial stress vs. S](image)

**Figure 4.7:** Dependence of the deformed arterial radius and corresponding radial stress on the activation level of the artery. Left-hand side image: deformed radius at the middle of the wall as a function of the activation parameter \( S \). Right-hand side image: radial stress at the middle of the wall as a function of the activation parameter \( S \). A middle cerebral artery (here, M12 from Table 4.1) exposed to a constant intraluminal pressure of 100 mmHg and axial stretch of 1.07 is considered. Goodness of fit: \( sse = 3.48 \cdot 10^{-5}, \ R\text{-square} = 0.99, \ \text{adjusted R-square} = 0.99, \ \text{rmse} = 5.99 \cdot 10^{-4} \) (left-hand side graph) and \( sse = 0.383, \ \text{R-square} = 0.99, \ \text{adjusted R-square} = 0.99, \ \text{rmse} = 0.06 \) (right-hand side graph).

4.3.4 Discussion

Here, a model for the passive and active response of cerebral arteries has been presented. The linear elastic model from Appendix B is valid only for relatively small deformations of the artery and may be seen as a toy model, which presents the problem in a more familiar framework. The toy model is useful for understanding which simplifications are reasonable in order to make the non-linear elastic model analytically tractable.

The non-linear elastic response displayed by the cerebral arteries, namely the J-shape for the passive stress-strain relationship and the bell-shape for the active response, compares qualitatively well with the behaviour reported by other studies [42, 121]. The VSMCs found in a basal state of activation assure uniform distribution of circumferential stress within the arterial wall, as proposed in [140]. In contrast, the radial stress is non-uniform across the wall in all states of activation; this is due to differences between the intraluminal pressure exerted
by the blood on the inner side of the arterial wall and the intracranial pressure present on the outer side of the wall. The differences in radial stress at a fixed point within the arterial wall, for various levels of activation, has important implications for the IPAD model from Chapter 5.

The purpose of this chapter has been to provide a mechanistic understanding of the cerebral arterial wall. The deformed radius of the artery and the corresponding radial stress at the middle of the wall, both quantities being functions of the muscular activation, represent the input of the vasomotion-driven IPAD model from Chapter 5.
Chapter 5

Modelling the vasomotion-driven IPAD of the brain

5.1 Introduction

This part of the study aims to unravel the motive force for the clearance of ISF and solutes from the brain tissue along the walls of cerebral arteries, more specifically along the IPAD pathways. It is recalled that these pathways are tiny compartments of basement membrane (BM), hundreds of nanometres thick, located within the arterial wall around the VSMCs of cerebral arteries. Tracer studies suggest that solutes, similar to $\text{A}_\beta_40$, are able to enter the IPAD pathways and flow out of the brain against the direction of arterial pulsations [10, 29, 120].

The accumulation of soluble tracers along the IPAD pathways resembles the pathological $\text{A}_\beta$ deposition during CAA, a key vascular pathology in dementia. Improvement of $\text{A}_\beta$ drainage along the IPAD pathways holds great therapeutic promise for CAA. However, such progress is not possible until the underlying mechanisms of the IPAD process, including its motive force, are clarified.

The anatomical properties of the IPAD pathways have been extensively investigated under different physiological and pathological conditions and clarified to a certain degree in the brain of rodents [10, 29, 72, 73, 120]. Despite all the experimental efforts, the motive force for the transport of fluid along the IPAD pathways remains unclear. It is emphasized again that the IPAD process
is different than the cerebral blood flow, which occurs in the arterial lumen in same direction as arterial pulsations.

The observations of no perivascular drainage following cardiac arrest motivated the theory of arterial pulse-driven IPAD in the brain. Assuming the motive force to be the arterial pulse, numerous mathematical models simulated various mechanisms that could explain the perivascular fluid flows against the direction of the arterial pulse [41, 150, 156, 177]. It has been suggested that some degree of attachment between solutes and the BM [150], or different flexible structures within the BM [156] are required for generating greater resistance to forward flow than to retrograde flow (against the direction of the arterial pulse). The existence of these structures within the cerebral arterial wall still awaits experimental confirmation. A different mechanism was proposed in [41], suggesting that the reflected boundary waves created at arterial branching junctions are enough to generate preferential transport along the BM against the forward-propagating arterial pulse. In [177], the fluid mechanics was modelled in the perivascular spaces outside the arterial wall, rather than along the intramural BM, in the context of convection-enhanced delivery in the brain.

The hypothesis of pulse-driven IPAD has been widely promoted over the last 10 years, despite the lack of solid quantitative data about the magnitude of the perivascular flows generated by the heart pulsations [17, 29, 78, 150]. None of the aforementioned mathematical studies provided dimensional flow rates along the IPAD pathways. Recently, by employing quantitative modelling, it has been shown that the arterial pulsations cannot generate physiologically-significant fluid flow rates out of the brain along the IPAD pathways, even when valve-like structures are present within the BM [53]. It was suggested that the valve-like structure could be created by specific pulse-induced deformations of the protein network that makes up the BM; this was accounted for by a pressure gradient dependent permeability. However, the very long wavelength of the arterial pulsations (higher than 1 m) is incapable of inducing significant pressure gradients over distances specific to the brain (mm in rodents, cm in humans). In the lack of strong enough pressure gradients, the generated periartrial fluid velocities and flow rates are too small to explain the sort of flows observed experimentally (e.g. four to eight orders of magnitude smaller, respectively), as reported in [53]. These modelling findings suggest that forces other than cardiac pulsations are more likely to drive IPAD in the brain and the quest for other candidates is still open.
5.1. INTRODUCTION

Here, it is proposed that the VSMCs of cerebral arteries, responsible for the vasomotion waves, may act as the main force generators of IPAD in the brain. The vasomotion wave has significantly different properties than the wave of arterial pulsation, e.g. vasomotion has a wavelength of the order of mm, which is three orders of magnitude lower than that of arterial pulsations. Moreover, the time response of the VSMC is around 10 seconds, while the time response of an artery to the arterial pulse is less than 1 second [1, 127]. The contribution of the cerebral VSMCs to the periarterial drainage of fluid from the brain has not been previously investigated, neither experimentally nor by any modelling technique. The goal of this work is to provide the first quantitative method for assessing the flow rates along the IPAD pathways induced by the cerebral vasomotion waves. Some of the long-term implications of this work include: (i) clarification of the underlying mechanisms for transport of ISF and soluble Aβ from the brain, (ii) quantification of the impact of age-induced vascular changes and drug-altered arterial contraction on fluid transport in the brain and (iii) guidance of new experiments focused on clearance of ISF and Aβ from the brain.

The proposed hypothesis of vasomotion-driven IPAD, denoted V-IPAD for the remainder of this study, is tested by developing a novel multiscale mathematical model based on physiological data and solving the model with the lubrication theory. The model couples the deformation of an active cerebral artery (i.e. arterial wall model) with the fluid flow along a deforming poroelastic BM (i.e. the BM model) situated within the arterial wall and it has numerous distinct features compared to the previous mathematical implementations of cerebral perivascular drainage. The unique feature of the model is the fact that the motive force of IPAD along the BM is considered to be the cerebral vasomotion wave generated by the muscular contractions of the VSMCs, rather than the heart-derived arterial pulse. In order to account for the contractions of the VSMCs, a full elastic analysis of the stresses within the arterial wall is necessary, including both the passive elasticity and the active contraction of the artery (see details in Chapter 4). The BM model that describes the deformation of the BM and the resulting flows along the IPAD pathway is developed separately and this approach is justified in Section 5.2. Nonetheless, there is coupling between the arterial wall model and the BM model due to the continuity of (radial) stress across the arterial wall. For instance, the external wave acting upon the fluid-filled BM, causing deformation of its boundaries, depends on the activation wave of muscular contractions and on the radial stress within the arterial wall; this is similar to squeezing a water-filled sponge and is shown in Figure 5.1. It is emphasized that none of the previous studies included
an elastic model for the BM.

In the study [53], the heart pulse-induced arterial deformation was determined from an elastic analysis of the arterial wall, but the artery was modelled with the simplest non-linear elastic model, e.g. the Hookean hyperelastic material that did not capture the active contraction generated by the VSMCs. In the present model, the arterial wall is assumed to be a passive Fung-type hyperelastic material with active elements. In a more realistic way, here, the BM is modelled as a fluid-filled hyperelastic porous material with deformation dependent permeability, rather than just a fluid-filled channel [150, 41] or a fluid-filled porous medium [53, 177]. The magnitude of the fluid flows along the BM induced by the cerebral vasomotion may contribute significantly to the transport of ISF and soluble Aβ out of the brain and this aspect is investigated in the next sections.

Although it is the first time that vasomotion is investigated within the context of fluid drainage from the brain, it has been previously modelled as a contributing mechanism to the transport of blood [170] and oxygen [67, 62] from blood vessels to different tissues in the body. Also the potential underlying mechanisms of vasomotion were investigated numerically in various studies [11, 101]. The closest study to the V-IPAD model is the one in [31] which assessed the peristaltic pumping in the ureter by modelling periodic activation waves in an infinite tube. In [31], authors used as input the elastic and contractile properties of the ureter wall, including an activation wave of muscular contractions. They also used the lubrication theory to solve the mathematical model for small-amplitude activation waves. Although there are some obvious similarities between the mathematical techniques employed, there are also several key differences between the two models with respect to the geometry of the systems and the physiological application of the models. For instance, the previous model [31] investigated deformation-induced flows through a large lumen (600 µm in diameter) and the deforming soft material between the contracting muscular layer and the lumen was considered a thin-shell. By analogy with the problem of perivascular drainage in the brain, the cerebral arterial wall would be a thin-shell and the activation waves would induce flows through the lumen of the artery (where cerebral blood is flowing). In contrast, in the V-IPAD model developed here, the material deforming in the presence of the activation wave is the BM which is modelled as a porous hyperelastic medium rather than just a thin-shell. Moreover, the perivascular flow induced by the waves of muscular contractions occurs through the BM (0.4 µm thick) rather than through the arterial lumen (≈ 200µm in diameter). In addition, the
cerebral arterial wall is considered a thick incompressible hyperelastic material and assessed in a three-dimensional geometry (see details in Chapter 4).

The governing equations of the V-IPAD model and their physiological significance are described in Section 5.2. A quick guide to the equations and the main assumptions that couple the arterial wall model from Chapter 4 with the BM model from this chapter, leading to the multiscale model of V-IPAD, is provided in Section 5.2.2. The numerical implementation of the BM model is given in Section 5.2.3. The anatomical and physiological observations that support the proposed hypothesis of V-IPAD are reviewed in Section 5.3. The results are presented and discussed in Section 5.4 and 5.5, respectively. Finally, the detailed derivation of the governing equations is given in Section 5.6.

5.2 Model formulation

The V-IPAD model consists of: (i) the BM model for intramural periarterial flows and the elastic response of the BM coupled to (ii) a model for the active elastic response of the cerebral arterial wall. The BM (0.4 \( \mu \)m thick) is embedded in the arterial wall (40 \( \mu \)m thick) and, although the two models are coupled, in practice the BM is small in comparison to the arterial wall such that it does not affect the elastic deformation of the artery. Hence, the arterial wall model decouples from the BM model. The problem can be solved for the elastic stresses in the arterial wall without the need to consider the response of the BM and then the calculated stresses can be used as input in the BM model. The latter model is developed in order to determine the flow driven along the BM by the cerebral vasomotion wave. The arterial wall model has been presented in detail in Chapter 4 and it will be briefly recalled in Section 5.2.2 but now the BM model is discussed.

5.2.1 Lubrication model of the BM

The perivascular drainage of fluid through the vascular BM of a cerebral artery, i.e. the IPAD pathway, is investigated. The vascular BM is modelled as a slow varying channel of width \( 2h \), running along the z-axis, exposed to external compressive stresses on the top and bottom boundaries (see Figure 5.1). Both the bottom and top boundaries of the BM are assumed impermeable. Given its anatomical properties (e.g. a fluid-filled protein matrix), the BM is treated as a fluid-filled poroelastic medium comprised of a porous solid phase (the matrix of proteins) denoted by the superscript ‘s’ and a fluid phase (the ISF) denoted by
the superscript ‘f’. The pores of the solid matrix provide a path for the movement of interstitial fluid.

Figure 5.1: Schematic representation of the system (not to scale). A leptomeningeal artery (e.g., middle cerebral artery) is modelled as a long thick-walled cylinder with uniform material properties along its length, maintained at a constant intraluminal pressure $P$ and constant longitudinal stretch and exposed to the active contraction of the VSMCs. The top layer shows the cross section of the artery with a layer of BM (blue compartment) embedded in the wall (left) and the longitudinal section of the BM (right). For simplicity reasons, only one layer of BM is considered at the middle of the wall and the two layers of the VSMCs surrounding the BM are assumed to behave identically. The remaining wall components are not shown, but their effect on the wall elasticity is captured by the radial ($\sigma_r$) and circumferential stress ($\sigma_\theta$). The deformed inner radius and middle radius of the arterial wall are denoted by $r_i$ and $r_m$, respectively. The BM position is assumed at $r_m$ and, owing to stress continuity across the wall, the radial stress $\sigma_r$ at that point represents the external compressive stress $\Sigma$ which acts on the BM, i.e. $\Sigma = \sigma_r(r = r_m)$, coupling in this way the arterial wall model with the BM model. Both $r_m$ and $\Sigma$ depend on the prescribed activation wave $S(z, t)$ generated by the contractile VSMCs. The BM thickness is significantly smaller than the arterial radius and, hence, the BM is assumed to be a thin axially-symmetric material whose thickness is $2h$, with $h = h(z, t)$ representing the thickness of the upper-half part. The area delimited by the rectangular is illustrated in the bottom schematic: a layer of BM deforming under the action of $-\Sigma$, assessed in a two-dimensional Cartesian system. The BM is modelled as a poroelastic compartment whose fluid-filled pores are squeezed during VSMC contraction, driving the fluid out of the BM pores in the direction of the contraction wave.
5.2. MODEL FORMULATION

The poroelastic basement membrane is a compressible hyperelastic medium subjected to deformations in response to an external compressive stress and to changes in fluid pressure in the pores of the matrix. Specifically, the external compressive stress, denoted $\Sigma$, is a known input function of time and position, i.e. $\Sigma = \Sigma(z,t)$; its value is previously determined from the elastic analysis of a contractile middle cerebral artery from the rat brain in Chapter 4. $\Sigma$ is generated by the contractile VSMCs during cerebral vasomotion and affects the fluid flow along the BM through the deformation of its boundaries. Thus, the system depends on time only through the boundary conditions. It is noted that the model is developed for a general external stress $\Sigma$ and the characteristic properties of the vasomotion wave are applied only at the end of the model. This allows for the model to be used in future studies for investigating the effect of different waves that may act upon the BM of cerebral arteries. Accounting for the symmetry of the system illustrated in Figure 5.1 it suffices to solve the BM model in the upper half plane in order to determine the deformed BM thickness. For visual purposes, the following notation is adopted: $2H$ is the undeformed thickness of the BM and $2h$ is the deformed thickness of the BM.

**Governing equations.** The vasomotion-induced deformation of the BM and the generated fluid flows are calculated using the lubrication approximation, owing to the disparity between the length scales of the system. For instance, the wavelength of the muscular contractions of the VSMCs is significantly longer (2 mm) compared to the radius of the cerebral artery (0.1 mm). This means that it is possible to assume that the variations in the $r$-direction of the BM are weak and the solution is, at leading order, one-dimensional with the form $h = h(z,t)$. The detailed application of the lubrication approximation is given in Section 5.6.3 and the resulting one-dimensional model comprises a system of 5 equations, as follows:

\[
\frac{\partial(\phi_f h)}{\partial t} + \frac{\partial}{\partial z}(\phi_f v_z h) = 0, \quad (5.1)
\]

\[
-\frac{\partial \phi_f}{\partial t} + (1 - \phi_f) \frac{1}{h} \frac{\partial h}{\partial t} = 0, \quad (5.2)
\]

\[
\phi_f v_z = -\frac{k(h)}{\eta} \frac{\partial p}{\partial z}, \quad (5.3)
\]

\[
\sigma_y^e - p = \Sigma(z,t), \quad (5.4)
\]

\[
\sigma_y^e = f \left( \frac{h}{H} \right) \quad \text{where} \quad f \left( \frac{h}{H} \right) = \frac{\partial W_{BM} \left( \frac{h}{H} \right)}{\partial \lambda_y \left( \frac{h}{H} \right)}, \quad (5.5)
\]
CHAPTER 5. MODELLING THE VASOMOTION-DRIVEN IPAD OF THE BRAIN

for the 5 dimensional unknowns: $\phi^f = \phi^f(z, t)$ is the volume fraction of fluid, $h = h(z, t)$ the deformed thickness of the BM, $v^f_z = v^f_z(z, t)$ the fluid velocity in the $z$-direction, $p = p(z, t)$ the pore pressure in the basement membrane and $\sigma^e_y = \sigma^e_y(z, t)$ the principal effective Cauchy stress, where $t$ denotes time and $z$ the position along the $z$-axis. $k$ is the deformation dependent permeability of the porous medium and $\eta$ the fluid viscosity. $H$ denotes the undeformed thickness of the upper half BM and $\Sigma$ denotes the external constrictive stress; these two terms are the input of the model. $f \left( \frac{h}{H} \right)$ is a function of deformation and gives the stress-strain relationship, calculated from deriving the strain energy function $W_{BM}$ with respect to the principal stretch ratio $\lambda_y$ from the $y$-direction. The reader is referred forward to equation (5.8) for the particular form of $W_{BM}$.

Physiological interpretation of the system (5.1) - (5.5) The physiological significance of the BM model is outlined below.

Equation (5.1) and equation (5.2) represent conservation of fluid and solid mass, respectively, in the deformed configuration of the system. Assuming that the BM is comprised only of fluid and solid phases, the volume fractions $\phi^s$ (solid) and $\phi^f$ (fluid) satisfy $\phi^s + \phi^f = 1$.

Equation (5.3) is the lubrication approximation of Darcy’s law which relates the interstitial fluid velocity to the pore pressure gradient, the fluid viscosity and the deformation-dependent permeability. Various functions for deformation-dependent permeability have been proposed in literature and, here, the model described in [113] is chosen, which holds for a large range of material compression as well as distension,

$$k(h) = k_\ast \left( \frac{h}{H} - \frac{\phi^s_\ast}{1 - \phi^s_\ast} \right)^\kappa,$$

where $k_\ast$ is the permeability of the undeformed BM, $\kappa$ is a positive parameter and $\phi^s_\ast$ is the volume fraction of the solid in the fluid-filled reference configuration. At leading order, the term $\frac{h}{N}$ represents the Jacobian of the system, as shown in the lubrication approximation from Section 5.6.3. Equations (5.3) and (5.6) account for the fact that any change in the BM volume will affect its porosity and, subsequently, its permeability to fluid flow. In this particular case, it is assumed that the fluid volume fraction can decrease to zero due to finite compressive forces that reduce the pores and, as a consequence, close the path for fluid drainage. The state of zero porosity is reached when $\frac{h}{N} = \phi^s_\ast$. 
5.2. MODEL FORMULATION

Equation (5.4) represents the force-balance equation derived from the conservation of momentum. \( \Sigma = \Sigma(z, t) \) is the external compressive stress which is derived by solving the arterial wall model. A close look at the elasticity of an arterial segment shows that \( \Sigma \) is the radial stress at the radial position of the basement membrane (see derivation in Chapter 4) and equation (5.4) follows from the continuity of radial stress across the BM embedded in the wall. The dependence of the radial stress on the magnitude of the activation parameter \( S \) (describing active tone of the contractile VSMCs) is also determined in Chapter 4. Here, the propagation of the muscular contractions of the VSMCs are modelled by a periodic activation wave \( S(z, t) \), where

\[
S = A \cdot \sin^2 \left( \frac{\pi}{\lambda_w} (z - c_w t) \right) \cdot S_m. \tag{5.7}
\]

This was previously used for the muscular activation wave of the ureter wall in [31]. Moreover, the activation wave \( S \) has the same pattern as the arterial vasomotion wave observed experimentally [24, 116, 65, 173, 142]. \( S \) accounts for the available experimental data on the mechanical properties of the VSMCs and on the cerebral vasomotion wave. \( S_m \) represents the maximum activation of the VSMCs and \( A \) is the amplitude of change in the maximum activation. \( \lambda_w \) and \( c_w \) denote the wavelength and the speed of the vasomotion wave, respectively. \( t \) is time and \( z \) is the spatial coordinate.

Finally, equation (5.5) represents the constitutive equation for the hyperelastic BM. This means that the principal effective Cauchy stress is derived from a strain energy function, denoted here \( W_{BM} \). In general, the strain energy function is a function of deformation. It is emphasized that the form of \( W_{BM} \) does not describe the material itself, but its elastic behaviour under particular deforming conditions and its choice requires careful attention. Limited by the lack of experimental data on the elasticity of the cerebrovascular BM, a minimum number of material parameters able to describe the physiological response is desired. With this in mind, the neo-Hookean model with only two material parameters is chosen from the study [182] which combined hyperelasticity and permeability constitutive relations that describe the deformation of biological poroelastic materials. Hence, the elastic response of the poroelastic BM to the external constrictive stress is captured by the following strain energy function [182]
\[
W_{BM}\left(\frac{h}{H}\right) = \frac{\mu_s}{2} \left( I_1 \left(\frac{h}{H}\right) - 2 - 2(1 - J) \log \frac{J \left(\frac{h}{H}\right) - 1}{1 - J} \right) + \frac{1}{2} \left( \lambda_s \mu_s J_s \left(\frac{h}{H}\right) - 1 \right)^2,
\] (5.8)

with the material parameters \(\mu_s\) and \(\lambda_s\) which denote the first and second Lamé parameters, respectively. \(I_1\) is the first invariant and \(J\) is the Jacobian of the system that describes the change in the BM volume; both terms are functions of deformation, i.e. \(I_1 = I_1 \left(\frac{h}{H}\right)\) and \(J = J \left(\frac{h}{H}\right)\) and are explained in detail in Section 5.6.1. Briefly, for the BM system considered here, \(I_1 = \lambda_z^2 + \lambda_y^2\), where \(\lambda_z^2\) and \(\lambda_y^2\) denote the principal stretch ratios in the z- and y-direction, respectively. The asymptotic analysis from 5.6.3 shows that, at leading order, the thickness of the BM is the only one that changes significantly, i.e. \(\lambda_z = 1\) and \(\lambda_y = \frac{h}{H}\). Hence, at leading order \(J = \frac{h}{H}\) and \(I_1 = \left(\frac{h}{H}\right)^2 + 1\). The full non-dimensional analysis is presented in Section 5.6.3. \(J_* = \phi^*_s\) is the lower bound on \(J\) and represents the lower limit of physical validity of the employed elastic model, meaning that \(J\) remains positive, i.e. no material interpenetration. As \(J \to J_*\), a compression of the BM to zero void volume occurs.

In particular, \(W_{BM}\) from (5.8) gives the non-linear elastic stress-strain response which is derived from (5.5) and the resulting stress-strain response of the BM is plotted in Figure 5.5 for two sets of proposed material parameters. Then, the stress derivative with respect to \(z\) is

\[
\frac{\partial \sigma_y^e}{\partial z} \left(\frac{h}{H}\right) = \left( \mu_s \frac{1 - \phi^*_s}{\left(\frac{h}{H} - \phi^*_s\right)^2} + \mu_s \frac{1 - 2\phi^*_s}{1 - \phi^*_s} + \lambda_s \right) \frac{\partial \left(\frac{h}{H}\right)}{\partial z},
\] (5.9)

The system of equations from (5.1) - (5.5) is simplified by replacing (5.2) - (5.3) in (5.1), which yields the non-linear equation for \(h\)

\[
\frac{\partial h}{\partial t} = \frac{\partial}{\partial z} \left( k(h) \frac{\partial p(h, \Sigma(z,t))}{\partial z} \right),
\] (5.10)

recalling that

\[
k(h) = k_* \left( \frac{h}{\phi^*_s} \right) ^\kappa, \quad p = \sigma_y^e(h) - \Sigma(z,t)
\] (5.11)

and \(\sigma_y^e(h)\) is calculated using (5.8)
The parabolic equation (5.10) plays a paramount role in the dynamics of the system and is solved for \( h(z,t) \) for a given \( \Sigma = \Sigma(S) \) and \( W_{BM} \). Equation (5.10) requires one initial condition and two boundary conditions.

**Initial condition.** The BM is considered initially undeformed and uniform along the vessel, i.e.

\[
\begin{align*}
    h|_{t=0} &= H, \quad 0 \leq z \leq L_s.
\end{align*}
\]  

(5.12)

where \( z = 0 \) represents the proximal end of the BM, while \( z = L_s \) represents the distal end of the BM, i.e. the length of the simulated system. Both the deformation of the BM induced by the external compressive stress and the resulting flow through the BM are investigated later.

**Boundary conditions at the ends of the BM.** The ends of the BM are assumed to be at the same pressure (i.e. any significant pressure driven flow along the BM is discounted)

\[
\begin{align*}
    p|_{z=0} &= p|_{z=L_s} = 0, \quad t > 0.
\end{align*}
\]  

(5.13)

These boundary conditions show that all the external factors will affect the ISF flow only through the deformations of the boundaries, rather than via a directly imposed pressure gradient.

Once \( h \) is determined, all the other variables of the system can be calculated given their dependency on \( h \). Further on, once the Darcy flux from equation (5.3) is determined, the fluid flow rate through the poroelastic BM can be calculated as shown below. Equation (5.10) is solved with the method of lines described in Section 5.2.3.

**Volumetric flow rate through a poroelastic medium.** An infinitesimal element of the cerebral artery is considered, as shown in Figure 5.1. The annular region represents the poroelastic BM. Radial symmetric deformation of the artery is assumed and the deformation of BM depends solely on the external compressive stress induced by the vasomotion wave. The total flow rate of fluid through the infinitesimal volume of BM, generated by the vasomotion-induced deformation of the BM boundaries, is calculated by using the differential form of the Darcy’s law and recalling that the y-sectional area of the BM is
2\pi r_m (2h) [\mu m^2]; hence, it follows that

\[ Q_{BM}(z, t) = -2\frac{2\pi r_m h k(h)}{\eta} \frac{\partial p}{\partial z}, \]  

(5.14)

where \( Q_{BM} = Q_{BM}(z, t) [\mu m^3 \cdot s^{-1}] \) is the volumetric flow rate through the entire thickness of the BM, approximated by doubling the flow rate along the deformed upper half BM, owing to the symmetry of the system. \( r_m [\mu m] \) denotes the radial position of the BM and is a function of the activation wave, i.e. \( r_m = r_m(S) \).

It is emphasized that the form of \( r_m \) is not prescribed, but is rather determined from the arterial wall model in Chapter 4.

The average volumetric flow rate over one cycle of vasomotion (with time period \( T = \lambda_w / c_w \)) is

\[ \bar{Q}_{BM} = \frac{1}{T} \int_0^T Q_{BM} dt = \frac{1}{\lambda_w} \int_0^{\lambda_w} Q_{BM} dz. \]  

(5.15)

### 5.2.2 Modelling the elastic response of the arterial wall

The assumptions and equations from Chapter 4 that are used to calculate the radial position of the deformed BM (e.g. \( r_m \)) and the corresponding stresses (e.g. constrictive stress \( \Sigma \)) are recapped below. The rat middle cerebral artery is modelled as a thick-walled cylinder that undergoes deformations due to axial extension and pressure inflation. The material properties of the artery are assumed uniform along its entire length. The resulting deformation and stresses are calculated under the assumption that deformation is axisymmetric (no \( \theta \)-dependence) and axial variations in arterial deformations are long in comparison to the artery radius. Consequently, the deformation can be approximated by a quasi one-dimensional solution in which the dependent variable is the \( r \) (radial) coordinate, while the \( z \) (axial) coordinate has the role of a parameter. Moreover, no time-dependence is considered. A fluid-filled thin compartment of BM (only 0.4 \( \mu m \) thick), is embedded in the arterial wall (40 \( \mu m \) thick). Assuming continuity of stress across the wall, the radial stress at the middle of the wall acts as external constrictive stress on the BM. The BM is small enough such that it does not affect the stresses in the wall, but, on the other hand, the deformation of the arterial wall drives the flow in the BM. Hence, there is only one-way coupling and the elastic analysis of the artery can be made independent of the existence of the BM. The resulting solution for the deformation of the arterial wall is used as input for the BM model; specifically, the deformed radius at the middle of
5.2. MODEL FORMULATION

the wall and the corresponding radial stress. The equations from Chapter 4 that have implications in the V-IPAD model are recalled below.

**The arterial wall model.** The arterial wall is modelled as a Fung-type hyperelastic material with the strain energy function $W$ given by

$$
W = \frac{1}{2}c(e^Q - 1), \quad \text{with} \quad Q = c_1 E_\theta^2 + c_2 E_z^2 + 2c_3 E_\theta E_z,
$$

(5.16)

and where

$$
E_\theta = \frac{1}{2} (\lambda_\theta^2 - 1), \quad E_z = \frac{1}{2} (\lambda_z^2 - 1), \quad \lambda_\theta = \frac{r}{R}
$$

with $\lambda_z$ being a known constant. $R$ and $r$ are the undeformed and deformed arterial radii, respectively. $\lambda_\theta$ and $\lambda_z$ are the principal stretches in the circumferential and axial directions, respectively; the latter one is a known constant from the experiments in [22]. $E_\theta$ and $E_z$ denote the principal Green strains in the circumferential and axial direction, respectively. $c[kPa], c_1, c_2, c_3$ are the material parameters determined experimentally in [22] for rat middle cerebral arteries. For a given $R$ in the undeformed configuration, the only unknown in the above expressions is $r$.

The deformation of the inner radius of the artery (denoted $r_i$) following axial extension and inflation with pressure is calculated from the pressure equation (solved in Chapter 4)

$$
P = \int_{r_i}^{r_o(r_i)} \left( \lambda_\theta^2 \frac{\partial W}{\partial E_\theta} + S\lambda_\theta f(\lambda_\theta) \right) \frac{dr}{r},
$$

(5.17)

where it is recalled that

$$
f(\lambda_\theta) = 1 - \left( \frac{\lambda_m - \lambda_\theta}{\lambda_m - \lambda_0} \right)^2,
$$

with $\lambda_m$ and $\lambda_0$ two known constants.

Here, $P$ is the constant arterial pressure. $r$ takes values between $r_i$ and $r_o$, where $r_o$ is the deformed outer radius, which is related to the $r_i$ by the incompressibility condition of the arterial wall, e.g. $r_o = \sqrt{r_i^2 + \frac{R_o^2 - R_i^2}{\lambda_z}}$; $R_i$ and $R_o$ are the undeformed inner and outer radius, respectively. The first and second terms under the integral represent the circumferential passive and active stress. It is noted that the contractile VSMCs, that generate the active stress, are not
modelled as individual cells within the wall. The form of the active stress was originally proposed in [140]. $S$ is the activation parameter with values of stress and reflects the level of contractile activity of the VSMCs; it is used as input in the BM model as $S(z,t)$, in order to describe the spatial and temporal oscillations in the activation of the VSMCs. A high value of $S$ corresponds to a high ability of the VSMCs to generate active stress. Whether the active stress actually develops, depends on the level of stretch of the arterial wall. This mechanical property is modelled by including $\lambda_\theta$ and the length-tension relationship $f(\lambda_\theta)$ in the expression of the active stress, where $\lambda_m$ is the circumferential stretch that yields maximum active contraction and $\lambda_0$ is the minimum stretch possible at which active force can be generated.

The distribution of the radial stress $\sigma_r$ within the wall has implications for the BM model, so its expression is given below. Once $r_i(S)$ is calculated from (5.17), the corresponding radial stress is calculated as

$$\sigma_r(r(S)) = \int_{r_i}^{r(r_i)} \left( \lambda_\theta \frac{\partial W}{\partial E_\theta} + S \lambda_\theta f(\lambda_\theta) \right) \frac{dr}{r} - P. \quad (5.18)$$

**Coupling.** For simplicity, the BM is assumed to be positioned at $r = r_m$ where $r_m$ denotes the radial position of the middle arterial wall, i.e. $r_m(S(z,t)) = \frac{r_i + r_o}{2}$.

The external load that deforms the BM is the constrictive radial stress in the middle of the wall, i.e. $\Sigma(S(z,t)) = \sigma_r|_{r=r_m}$.

### 5.2.3 Numerical solution: method of lines

**Method of lines, general description.** In this method, the parabolic partial differential equation (5.10) for the quantity $h(z,t)$ is approximated by a set of coupled ODEs for $h_i(t)$, where $h_i(t) \approx h(z_i,t)$ and $z_i$, with $0 \leq i \leq n$, represents the position on a spatial computational grid. In this instance, a uniform computational grid with $n + 1$ grid points is used, such that the total domain $x \in [0, L_s/L]$ is partitioned into $n$ subintervals, where $L_s$ denotes the length of the system and $L$ the characteristic length. The central difference operator notation is adopted such that the operator $\delta_z$ is centred in the $z$-dimension at position $z_i$ over an interval $\Delta z$, where $\Delta z$ is the spacing between points.

The spatial derivatives are discretised using second order accurate finite
differences on an uniform grid. Thereby, using central differences, the first derivative is approximated as

\[
h_z = \frac{1}{\Delta z} \delta_z h_i(t) = \frac{h_{i+1/2} - h_{i-1/2}}{\Delta z} \tag{5.19}
\]

and the second derivative as

\[
h_{zz} = \frac{1}{\Delta z^2} \delta_z^2 (\delta_z h_i(t)) = \frac{h_{i+1} - 2h_i + h_{i-1}}{\Delta z^2}. \tag{5.20}
\]

The values of \( h \) at the intermediate grid points can be approximated using the known values at the adjacent grid points:

\[
h_{i+1/2} \approx \frac{h_{i+1} + h_i}{2} \quad \text{and} \quad h_{i-1/2} \approx \frac{h_{i-1} + h_i}{2}. \tag{5.21}
\]

where \( i = 1, \ldots, n - 1 \).

For an application of the method of lines to a different problem (e.g. diffusion), the reader is referred to [171].

**Method of lines, the BM model.** Before applying the method of lines to this problem, equation (5.10) is rewritten in terms of \( z \), \( t \) and \( h(z,t) \) only and a simpler notation is adopted, as follows. Firstly, the expression of the effective Cauchy stress derivative with respect to \( z \) (5.9) is replaced in (5.10). Thus, the \( h \)-equation becomes:

\[
\frac{\partial \hat{h}}{\partial t} = \frac{k_s}{\eta} \frac{1}{\hat{h} - \phi_s^*} \frac{\partial}{\partial z} \left( \left( \frac{1}{1 - \phi_s^*} \right) \left( \frac{1}{\hat{h} - \phi_s^*} + \frac{1 - 2\phi_s^*}{(\hat{h} - \phi_s^*)^2} + \frac{2\phi_s^*}{1 - \phi_s^*} + \lambda_s \right) \frac{\partial \hat{h}}{\partial z} - \frac{\partial \Sigma}{\partial z} \right), \tag{5.22}
\]

where the notation \( \hat{h} = \frac{h}{H} \) is adopted for visual purposes.

Secondly, the initial condition from (5.12) is rewritten in terms of \( \hat{h} \) as

\[
\hat{h}|_{t=0} = 1, \quad 0 \leq z \leq L_s, \tag{5.23}
\]

as well as the boundary conditions from (5.13)

\[
0 = \mu_s \left( \frac{\hat{h} - 1 - \phi_s^*}{\hat{h} - \phi_s^*} \right) + \left( \lambda_s - \mu_s \frac{\phi_s^*}{1 - \phi_s^*} \right) (\hat{h} - 1) - \Sigma(0,t), \quad \text{for } t > 0 \quad \text{for } z = 0 \tag{5.24}
\]
\[ 0 = \mu_s \left( \frac{\hat{h} - 1 - \phi_s^*}{\hat{h} - \phi_s^*} \right) + \left( \lambda_s - \mu_s \frac{\phi_s^*}{1 - \phi_s^*} \right) \left( \hat{h} - 1 \right) - \Sigma(1, t), \]

for \( t > 0 \) for \( z = L_s \). (5.25)

By distributing the outer spatial derivative only to the last term in the RHS of equation (5.22) gives

\[
\frac{\partial \hat{h}}{\partial t} = \frac{k_s}{\eta} \left( \frac{\partial}{\partial z} \left( A \frac{\partial \hat{h}}{\partial z} \right) - C \frac{\partial B}{\partial z} - BD \right),
\]

with the notation

\[
A(\hat{h}(z, t)) = \hat{h} \left( \frac{\hat{h} - \phi_s^*}{1 - \phi_s^*} \right)^\kappa \left( \mu_s \frac{1 - \phi_s^*}{(\hat{h} - \phi_s^*)^2} + \mu_s \frac{1 - 2\phi_s^*}{1 - \phi_s^*} + \lambda_s \right),
\]

(5.27a)

\[
B(\hat{h}(z, t)) = \hat{h} \left( \frac{\hat{h} - \phi_s^*}{1 - \phi_s^*} \right)^\kappa,
\]

(5.27b)

\[
C(z, t) = \frac{\partial \Sigma}{\partial z},
\]

(5.27c)

\[
D(z, t) = \frac{\partial^2 \Sigma}{\partial z^2}.
\]

(5.27d)

The specific expression of \( \Sigma = \Sigma(z, t) \) is discussed in section (5.2). Equation (5.26) is solved with the method of lines by discretizing with respect to the \( z \)-variable using central differences

\[
\frac{d\hat{h}_i(t)}{dt} = \frac{k_s}{\eta} \left( \frac{1}{\Delta z^2} \delta_i \frac{A_i A_{i+1/2} \delta_i \hat{h}_i - C_i \delta_i B_i - B_i D_i}{\Delta z} \right)
\]

\[
= \frac{k_s}{\eta} \left( \frac{1}{\Delta z^2} \delta_i \left( A_i (\hat{h}_{i+1/2} - \hat{h}_{i-1/2}) - C_i (B_{i+1/2} - B_{i-1/2}) - B_i D_i \right) \right)
\]

\[
\approx \frac{k_s}{\eta} \left( \frac{1}{2\Delta z^2} \left( A_i (\hat{h}_{i+1} - \hat{h}_i) - A_{i-1/2} (\hat{h}_{i+1/2} - \hat{h}_{i-1/2}) - \frac{C_i}{2\Delta z} (B_{i+1} - B_{i-1}) - B_i D_i \right) \right)
\]

\[
\approx \frac{k_s}{\eta} \left( \frac{1}{2\Delta z^2} (A_{i+1} (\hat{h}_{i+1} - \hat{h}_i) + A_i (\hat{h}_{i+1} - 2\hat{h}_i + \hat{h}_{i-1}) + A_{i-1} (\hat{h}_{i-1} - \hat{h}_i)) \right)
\]

\[
- \frac{k_s}{\eta} \left( \frac{C_i}{2\Delta z} (B_{i+1} + B_{i-1}) - B_i D_i \right)
\]

(5.28)

for \( i = 1, ..., n - 1 \) and \( t > 0 \).
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It is denoted:

\[ \hat{h}_i = \hat{h}_i(t) = \hat{h}(z_i, t), \]
\[ A_i = A(\hat{h}_i) = \hat{h}_i \left( \frac{\hat{h}_i - \phi_s^*}{1 - \phi_s^*} \right) \kappa \left( \mu_s \frac{1 - \phi_s^*}{(\hat{h}_i - \phi_s^*)^2} + \mu_s \frac{1 - 2\phi_s^*}{1 - \phi_s^*} + \lambda_s \right), \]
\[ B_i = B(\hat{h}_i) = \hat{h}_i \left( \frac{\hat{h}_i - \phi_s^*}{1 - \phi_s^*} \right)^\kappa, \]
\[ C_i = C(z_i, t), \]
\[ D_i = D(z_i, t). \]  

The values of \( \hat{h}(z_i, t) = \hat{h}_i \) for \( i = 1, ..., n - 1 \) are obtained by solving the system of ODEs from (5.28), while the remaining values \( \hat{h}(z_0, t) = \hat{h}_0 \) and \( \hat{h}(z_n, t) = \hat{h}_n \) are obtained from solving the boundary conditions (5.24) and (5.25), respectively.

The temporal integration of the system of ODEs is solved in MATLAB using the solver *ode15s* which has an adaptive time step and so overcomes stability issues associated with discretizing the parabolic PDE (5.10). The spatial grid of length \( L_s \) on which computations are performed is long enough such that up to five wavelengths of vasomotion are able to develop along it. This allows for evaluation of the solution far away from the extremes of the spatial grid where rapid variations in the solution may occur. The investigation of all plotted quantities was carried out on a uniform grid with 1000 spatial points (i.e. a discretization step \( \Delta z \) of \( 10^{-3} \)).

The convergence of the employed numerical method is tested by refining the spatial grid, repeating all the computations and checking the changes in results. In particular, the ‘Lymphatic’ material is considered and the pointwise convergence of the scheme is demonstrated by interrogating the value of \( h \) at the end of one temporal cycle of vasomotion in two distinct positions, the beginning and middle of the third wavelength, respectively. These values are chosen because, regardless of the number of grid points employed, they are easily accessible following temporal integration without requiring additional interpolation. Given the lack of exact experimental solutions of the problem, the convergence is verified by calculating the error relative to a solution computed on a highly refined grid. Here, the maximum number of points considered is denoted \( n_M \) (e.g. \( n_M = 8000 \)) and the corresponding solution, assumed to be the most accurate one, is denoted \( h^{(n_M)} \).
The following error is defined

\[ \epsilon(n) = |h^{(n)} - h^{(n_M)}|, \quad (5.30) \]

where \( h^{(n)} \) is computed using \( n \) points, with \( n \ll n_M \) (e.g., \( n = 250, 500, 1000, 2000, 4000 \)). The pointwise convergence of \( h \) is shown in Figure 5.2 demonstrating the second order convergence of the scheme.

\[ \begin{align*} 
5.5 & \quad 6 \quad 6.5 \quad 7 \quad 7.5 \quad 8 \quad 8.5 \\
-12 & \quad -11 \quad -10 \quad -9 \quad -8 \quad -7 \quad -6 \\
-5 & \quad -6 \quad -7 \quad -8 \quad -9 \quad -10 \\
\end{align*} \]

**Figure 5.2:** Illustration of pointwise convergence of the numerical method. The pointwise error, \( \epsilon \), is shown against the number of grid points \( n \) for \( h \) at the beginning (stars) and middle (open circles) of a wavelength. The markers give the errors for computations with \( n = 250, 500, 1000, 2000 \) and \( 4000 \), respectively, against the numerical solution with \( n_M = 8000 \) grid points. The lines show second order convergence of the method.

### 5.2.4 Physiological parameter values

The parameters chosen for the V-IPAD model are justified below and given in Table 5.1. Some parameters specific to the cerebrovascular BM have not been reported in the literature. In order to estimate the necessary values, the interstitium of the extracranial lymphatic system and the interstitium of the brain are taken as reference materials, for two reasons. Firstly, the extracellular matrix of the BM has a similar composition to that of the brain interstitium, including collagen and laminin proteins. The second reason is based on the fact that the BM is supposed to have a role in the clearance of the brain, similar to the role of the lymphatic system outside the brain; hence, these two tissues may have similar properties.
5.2. MODEL FORMULATION

**BM parameters.** The thickness of the cerebral BM was commonly reported to be within 100-150 nm in the previous experimental studies of perivascular drainage [70]. However, it should be kept in mind that the analysis was made in post-mortem tissues where the BM is dehydrated. By employing atomic force microscopy, [28] reported that the hydrated BM of the retina is 4-fold thicker than the dehydrated BM and its thickness increases with age. Hence, here, the thickness of the adult hydrated BM is taken to be 400 nm (which gives $H = 200$ nm), in line with the study of [28].

The BM is embedded in the wall of a cerebral artery which has the following features: an approximate undeformed radius of 0.1 mm, wall thickness of 0.04 mm and uniform material properties along its length. The artery experiences axial extension and radial inflation. The elastic parameters of the artery are specific to a rat middle cerebral arteries (approximately 2 mm in length) and given in Chapter 4, where the arterial wall model was fitted against the experimental data of [22]. Here, the particular artery M12 with an axial stretch of 1.07 is taken. The assumed arterial pressure that causes radial inflation is 100 mmHg and falls within the range of pressures used in the model of [53]. Although the investigation of the V-IPAD mechanism would be more physiologically-realistic in a network of cerebral arteries (e.g. the middle cerebra artery and its branches), here a single long vessel (the equivalent of approximately five middle cerebral arteries) is considered; this approach makes the model more tractable and avoids the complex behaviour of the arterial bifurcations.

No measurements for the permeability of the cerebrovascular BM are available in the literature. [107] reported values for the permeability of other biological tissues within the range of $10^{-2} \mu m^2$ to $10^{-6} \mu m^2$. Here, the initial permeability of the BM is chosen to be $10^{-2} \mu m^2$ and allowed to decrease in a deformation-dependent manner. The chosen arterial pressure that causes radial inflation is 100 mmHg and falls within the range of pressures used in the model of [53]. The value of the $\kappa$ parameter from equation (5.6) is chosen in accordance with the analysis made by [182] who showed that $\kappa$ must be higher than 1 in order to have the possibility of complete closed fluid pores, when combining deformation-dependent permeability of the form (5.6) with strain energy function of the form (5.8).

The first and second Lamé parameters, $\mu_s$ and $\lambda_s$, that appear in the form of the strain energy function (5.8) are chosen in line with the elasticity of drained soft tissues and apply to the lymphatic system [77], as well as to the brain tissue [160]. Hence, here is taken $\mu_s = 3700$ Pa and $\lambda_s = 8640$ Pa, which yield
a Young’s modulus of $10^4$ Pa. These values describe the first case investigated which is referred to as the ‘Lymphatic’ BM. Given that no elasticity information exists for the drained cerebrovascular BM of cerebral arteries, some other elastic parameters (e.g. $\mu_s = 74$ Pa, $\lambda_s = 6912$ Pa with a Young’s modulus of 221 Pa) are investigated in a case that is referred to as the ‘Spongy’ BM. Compared to the ‘Lymphatic’ BM, the ‘Spongy’ BM is a more elastic material, i.e. it deforms more under the action of a finite stress compared to the ‘Lymphatic’ BM. In this way, the deformation of the ‘Spongy’ BM could lead to a full closure of the pores and more efficient elimination of fluid, similar to the behaviour of a fluid-filled sponge. The reason the ‘Spongy’ BM is considered is because if the BM is indeed a clearance pathway, its properties may have evolved to improve clearance of debris from the brain. This makes it sensible to investigate what can be achieved with the right material properties.

<table>
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</thead>
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<tr>
<td>$S_m$</td>
<td>$10^5$</td>
<td>$Pa$</td>
<td>maximum active tone</td>
</tr>
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</table>

Table 5.1: Dimensional physiological parameters

Vasomotion parameters. The frequency of vasomotion has been identified at $\approx 0.1$ Hz in different arteries and species, as reviewed in [1, 142]. The spatial characteristics of vasomotion are not so well understood, but they may be inferred from the propagation of arterial diameter variations in response to vasoactive drugs or induced synaptic activity. [55] induced conducted vasodilation of arterioles by administration of acetylcholine and the vascular response propagated with a longitudinal velocity of $200 \mu m/s$. Furthermore, local synaptic activity in the cerebellum induced retrograde dilatation of larger arteries located 2-3 mm upstream, as shown by [90]. A longitudinal velocity of the conducted vascular response of $280 \mu m/s$ can be estimated from their
experiments. [155] estimated a velocity of 100 $\mu$m/s for the intercellular calcium waves that are associated with the vasomotion wave. Here, a frequency of 0.1 Hz and a wave velocity of 200 $\mu$m/s is assumed for the cerebral vasomotion wave; this yields the corresponding wavelength of 2000 $\mu$m.

5.3 Proposed mechanism: vasomotion-driven IPAD

The strongest support for the V-IPAD hypothesis probably comes from the experiments of [20] who assessed the deposition of Aβ in the rabbit brain as a result of cortical cholinergic deafferentation (i.e. interruption of acetylcholine neurotransmitter to the cerebral blood vessels and other cells of the brain). [20] induced lesions to the main source of cholinergic innervation (e.g. the nucleus basalis) which resulted in 31% reduction of cholinergic activity. The deposition of Aβ in the lesioned animals was up to 8-fold higher than in the healthy subjects, with the highest accumulation in the arteriole wall within the abluminal basement membrane of VSMCs, as illustrated in Figure 5.3. The authors concluded that the observed deposition may be due to overproduction of Aβ by the neurons that were deprived of access to acetylcholine neurotransmitters. Their conclusion was based on earlier findings that such neurons overproduced APP, the precursor of Aβ [129]. As the authors noted, their conclusion cannot explain why most of the Aβ deposition was in the wall of arterioles and only sparsely in the brain tissue as amyloid plaques.

The cholinergic innervation directly affects the activity of the VSMCs and, therefore, here it is proposed that the vascular deposition of Aβ in the arterial wall could be explained by the impaired activity of the VSCMs. Given that the rich cholinergic innervation of the cerebral arteries regulated their vascular tone [66], the cholinergic deafferentation induced by [20] may hinder the activity of the VSMCs and their contribution to the clearance of Aβ along their BM.
Further on, [10] reported significantly reduced efficiency in perivascular drainage during induced ischaemic stroke (i.e. focally disrupted blood perfusion to the brain) within 30 min of imaging. It is worth remarking that the contractile fillaments of the VSMCs of arterioles and arteries are significantly damaged after 15-45 min of ischaemia in a duration-dependent manner, as shown by [104]. Unfortunately, this aspect was not investigated in the study of [10], but ischaemia-induced damage to the VSMCs seems likely and this could explain the observed impaired perivascular drainage. On a similar note, [29] reported lack of perivascular drainage following cardiac arrest.

Additional experimental evidence that suggests a relationship between the activity of the VSMCs and the IPAD of the brain comes from the study of [112]. In their work, the authors administered the vasoactive drug cilostazol in the brain of mice and found improved perivascular drainage. As reviewed by [112], cilostazol has numerous effects on blood vessels, such as regulation of the VSMCs, improved arterial elasticity and vasodilatation. The positive effects of cilostazol, including reduced cognitive decline, are also seen in human patients suffering mild cognitive impairment. Other drugs such as cholinesterase inhibitors, commonly used in the treatment of AD, have proven to improve cognition, attention and executive functions in demented patients who responded to treatment [23]. [40] have proposed that the reported improvements may be a consequence of direct effects on blood vessels. Given the cholinergic-vasculature hypothesis of [40], it remains an interesting question how various vasoactive agents (e.g. anti-cholinergic drugs) affect the perivascular drainage of Aβ.

Although no direct evidence is given, the aforementioned experiments strongly support the proposed hypothesis that the activity of the VSMCs may be a key element in the IPAD of the brain. The novel V-IPAD model developed here brings quantitative evidence that the intramural periarterial fluid flow may be driven by the contractile VSMCs. This work encourages new research directions in the clearance of the brain, specifically, future experiments that assess in more
details the state of the VSMCs during perivascular drainage.

**Relationship between the VSMCs and the IPAD pathways.** How can the VSMCs contribute to the IPAD of the brain? As reviewed in Chapter 2, the VSMCs represent the major structural component of the tunica media within the walls of cerebral arteries and they are arranged circumferentially around the arterial lumen, with the number of layers varying with species and the size of the vessels [38, 106]. The VSMCs synthesize their own BM and adhesion to the surrounding membrane is critical for their survival [175]. The position of the VSMCs within the arterial wall seems to be ideal in order to allow immediate effect of these cells on the surrounding BM. As reviewed in Chapter 2 and Chapter 4, the VSMCs are contractile cells and, under physiological conditions, they generate a basal vascular tone. Different mechanisms induce oscillations in the basal tone and further contraction of the VSMCs from their basal tone (i.e. active response) generates an active tension. During contraction, the VSMCs become thicker and shorter and, subsequently, the arterial diameter decreases while the wall thickness increases (i.e. vasoconstriction). On the other hand, during relaxation, the VSMCs become more elongated and thinner, leading to increased arterial diameter and thinner arterial wall (i.e. vasodilatation). The oscillations in the contractile state of the VSMCs may affect the conformation of the attached BM and, subsequently, the fluid flow along these drainage pathways. More specifically, the VSMCs may create a squeeze-release mechanism of the attached BM driving the fluid out of this compartment.

Furthermore, the rhythmic oscillations of the VSMCs are conducted along the arterial network, generating the vasomotion wave [133, 155]. The initial site of the vasomotion wave and the dominant direction of propagation are key elements in order to generate the outflow of fluid along the IPAD pathways of the brain. Slow 0.1 Hz sinusoidal oscillations have been confirmed in the awake human brain by [142]. The oscillations were associated with pial arterioles and seemed to propagate as a spatial wave across the human cortex, from distinct regions of arterioles towards larger arteries (i.e. in the direction of IPAD) [142]. The authors suggested that the observed oscillations are primarily of myogenic origin, driven by the properties of the vessels themselves and therefore independent of neuronal activity. Spontaneous, low-frequency oscillations of cerebral arteries, within the range 0.1-1 Hz, were also reported in awake mice, propagating over several hundred micrometres across the cortex; these oscillations resulted presumably from vasomotion [54]. Considering the complex vascular response during the functional hyperaemia of the brain consisting of
the vasodilation of arterioles communicated remotely to their parent arteries \[90\], the cerebral arterial network appears to be equipped with the appropriate features for allowing vasomotion to propagate in the optimal direction of IPAD \[61\] \[152\].

5.4 Results

The active VSMCs induce deformations and stresses within the arterial wall and the solutions at leading order are presented below. In Chapter 4, the relationship between the activation of the VSMCs, the deformed arterial radius and the corresponding radial stress, at a local point within the wall, was shown.

Here, the conducted muscular contractions of the VSMCs along the BM are modelled with equation (5.7) where \(S(z, t)\) is the activation wave with characteristics resembling those of the vasomotion wave, as shown in Figure 5.4. The induced propagated deformation of the arterial middle wall, denoted \(r_m(z, t)\), and the corresponding radial stress, denoted \(\Sigma(z, t)\), are also shown in Figure 5.4; both are functions of the activation wave. \(r_m\) and \(\Sigma\) are the input of the BM model, representing the position of the deformed BM and the external constrictive stress, respectively; these are calculated from equations (5.17) and (5.18), respectively. One full cycle of vasomotion comprises both the contraction and the relaxation of the VSMCs and the corresponding oscillation in the arterial radius has an amplitude of 20\%. The highest negative value of \(\Sigma\) is generated during maximum activation of the VSMCs, while the lowest negative value corresponds to the relaxed (inactive) state of the VSMCs. The negative values signal the fact that \(\Sigma\) is a constrictive stress. It is noted that \(\Sigma\) is non-zero in the inactive state due to presence of passive stresses within the arterial wall which yield a non-zero radial stress. The reader is referred to the elastic analysis from Chapter 4 for a full proof.

The response of the poroelastic BM to the external constrictive stress is described by the stress-stretch relationship calculated using the strain energy function from equation (5.8). The ability of the chosen strain energy function to describe the non-linear elastic behaviour for a general large range of deformations is shown in Figure 5.5, where the elastic responses of the ‘Lymphatic’ and ‘Spongy’ BMs are compared. The stress-permeability relationship accounts for the deformation-dependence relationship from equation (5.6). As expected, the ‘Spongy’ material undergoes larger deformations and experiences larger changes in permeability
5.4. RESULTS

Figure 5.4: The arterial wall response to the contractile VSMC oscillations over one wavelength. Top image: the activation wave. Bottom image: the radial position of the BM (left-hand side) and the constrictive stress acting on the BM (right-hand side). Both $r_m$ and $\Sigma$ depend on $S(z, t)$ and represent the input of the BM model. For clarity purposes, only 15 consecutive time points are illustrated, representing 2.5 seconds from one vasomotion cycle of 10 seconds. Progressive change in colour from red to green shows increase in time.

than the ‘Lymphatic’ BM. It appears that a compressive stress of 6 kPa nearly shuts the pores of the ‘Spongy’ BM, decreasing its permeability by almost 100%, while the same stress only decreases the permeability of the ‘Lymphatic’ BM by 50%. In other words, the stiffer ‘Lymphatic’ BM requires more force to be squeezed shut. The behaviour exhibited by the ‘Spongy’ BM makes the contractile VSMCs a more efficient pump for pushing fluid out of the pores.

The constrictive stress from Figure 5.4 induces deformations of the BM that are propagated longitudinally and vary in time. The evolution of the BM thickness and the resulting fluid flow through the BM are shown in Figure 5.6 and Figure 5.7. The deformation models a vasomotion wave, having a period of ten seconds. The vasomotion-induced flow rate through the entire BM compartment is calculated using equation (5.14). It appears that during a vasomotion cycle, at a given spatial point of the BM, both positive (i.e. in the direction of the vasomotion wave) and negative flows (i.e. in the reverse direction) occur at
different times. However, the net flow is always in the direction of the vasomotion wave.

Although high flow rates of nearly 4000 $\mu$m$^3$·s$^{-1}$ are obtained for the ‘Lymphatic’ BM, the net flow rate during one cycle of vasomotion is only 360-480 $\mu$m$^3$·s$^{-1}$, depending on the BM material properties. The positive net values indicate that the flow propagates in the same direction as the vasomotion wave. The net flow is calculated with equation (5.15), which is implemented in MATLAB with the trapezoidal method ([151], p.330).

The remainder of the results are given for one cycle of vasomotion when the BM system settles to a periodic behaviour. The deformation of the upper half BM, the corresponding deformation-induced permeability and the resulting pressure wave are illustrated in Figure 5.8. The upper half of the ‘Lymphatic’ BM undergoes up to 13% and 25% changes in its thickness and permeability, respectively. By taking the minimum value of $k$ from Figure 5.8 (e.g. nearly $5 \cdot 10^{-3}$ $\mu$m$^2$) and comparing it to the $k$ value from the undeformed state (e.g. $10^{-2}$ $\mu$m$^2$), it is observed that the permeability of ‘Lymphatic’ BM actually decreased as much as 50%. This change in permeability is much less than in the case of the ‘Spongy’ BM, which is nearly squeezed shut, as its permeability decreases down to 12% compared to the undeformed state. It is also noted that the pore pressure in the ‘Spongy’ BM is significantly higher compared to the ‘Lymphatic’ BM; this is due to the fact that the former material is very elastic and the solid component cannot withstand high stresses. Consequently, a higher fraction of the external
compressive stress is transmitted to the fluid filling the pores of the ‘Spongy’ BM.

The minus sign of the pressure $p$ does not mean less than nothing, but its signals that the basement membrane (BM) has lower pressure than the region around it. In all biological systems, the pressure value within a compartment is relative to the atmospheric pressure and is known as the gauge pressure. The bottom and top left-hand plots in Figure 5.8 illustrate that during compression of the ‘Lymphatic’ BM, the pressure within its pores is slightly smaller than the atmospheric pressure, thus the gauge pressure becomes slightly negative. The pressure gradient observed in Figure 5.8 develops due to the BM deformations induced by the travelling contraction wave of the VSMCs and is negative for some part of the vasomotion cycle and positive for the other part.
CHAPTER 5. MODELLING THE VASOMOTION-DRIVEN IPAD OF THE BRAIN

Figure 5.7: Vasomotion-induced flows through the ‘Spongy’ BM. Oscillations in the upper-half of the BM thickness in time, at different fixed locations (left-hand side) and the corresponding volumetric flow rates along the whole BM compartment (right-hand side). The transitory part of the solution is shown in the left-hand side, while only the last three time periods are plotted in the right-hand side. Progressive change in colour from red to purple shows six distinct spatial points over 750 µm (out of a wavelength of 2000 µm).

5.5 Discussion

The most likely motive force of IPAD in the brain. A new hypothesis has been proposed for the motive force of IPAD in the brain, namely the vasomotion-driven IPAD. The hypothesis has been tested with a novel mathematical model based on the available physiological experimental data. By exploiting the disparity between the length scales of the system, the V-IPAD model was solved with the lubrication approximation. This is the first study that investigates the possible contribution of the vasomotion wave in the perivascular drainage of the brain. It is also one of the few studies that provides quantitative values for the predicted flow rates along the IPAD pathway.

It is found that the cerebral vasomotion induces high flow rates along the IPAD pathway of up to 4000 µm³·s⁻¹, depending on the material elastic properties of the BM. Given that one cycle of vasomotion incorporates both the contraction and the relaxation of the VSMCs, the fluid flow along the BM can be bidirectional at different moments of time. In other words, there is positive flow in the direction of the vasomotion wave and negative flow in the reverse direction. Nonetheless, the net flow rate during one cycle of vasomotion is always in the direction of the wave (a consequence of the much reduced BM permeability as it is squeezed) and falls within the range of 360 µm³·s⁻¹.
- 488 \( \mu m^3 s^{-1} \), depending on the material properties of the BM. Based on the experimental observations reviewed in Section 5.3, it is reasonable to assume that the vasomotion wave propagates from the smallest arterioles closest to the brain tissue towards the largest arteries at the base of the neck. Within the context of clearance of the brain, the model predicts that fluid and soluble metabolites will be transported along the IPAD pathways from inside the brain tissue, i.e. the intracerebral region, towards the cervical lymphatic nodes situated in the neck, i.e. the extracerebral region. Therefore, the V-IPAD model generates net flow rates from inside the brain out. It is noted that comparison with other studies should be made with caution, as others may have defined the net flows out of the brain as negative flows relative to the direction of arterial pulsations.

The BM is modelled as a poroelastic material with a deformation-dependent permeability. The vasomotion-induced deformation of the BM causes partial closure of the pores, providing in this way a higher resistance to the reverse flows. Consequently, the net flow rates are always in the direction of the vasomotion wave without the need of additional intramural attachment or flexible structures as proposed in [150, 156].

Comparison of the results generated by the V-IPAD model with previous studies is given in Table 5.2. Even the lowest net perivascular flow rate of 360 \( \mu m^3/s \) generated by the V-IPAD mechanism along only one layer of ‘Lymphatic’ BM is five orders of magnitude higher than the net perivascular flow rate induced by arterial pulsations [53]. The studies from [12, 13] also reported perivascular flow rates driven by the arterial pulsations, but in a different perivascular space positioned outside the arterial wall. Nonetheless, their results bring further evidence that arterial pulsations are unable to generate significant perivascular flow rates out of the brain. The values reported in [12, 13] differ from those reported in [53] due to the fact that the former authors assumed the thickness of the perivascular space up to two orders of magnitude higher. Based on the values given in Table 5.2, the vasomotion wave seems to be the best candidate proposed to date for the motive force of IPAD in the brain.
CHAPTER 5. MODELLING THE VASOMOTION-DRIVEN IPAD OF THE BRAIN

Figure 5.8: Deformation-dependent permeability of the BM, over one wavelength. For clarity purposes, only 15 consecutive time points are illustrated, representing approximately 1.5 seconds from one vasomotion cycle of 10 seconds. Progressive change in colour from red to green shows increase in time. The response of the ‘Lymphatic’ BM is shown in the left-hand side, while the one of the ‘Spongy’ BM in the right-hand side. Top image: BM thickness; middle image: deformation-dependent permeability of the BM; bottom image: fluid pressure within the BM. Progressive change in colour from red to green shows increase in time during one period of vasomotion.

V-IPAD in the clearance of ISF and soluble $\text{A}_\beta$ produced by the brain. Although the V-IPAD mechanics generates significantly higher net perivascular flow rates than the mechanisms proposed by others [53] (e.g. up to five orders
of magnitude higher), it is important to see where it fits in the picture of brain clearance. The model developed here gives the fluid flow rate along only one BM compartment of a rat middle cerebral artery. The total number of cerebral BMs involved in the drainage of solutes from the brain is currently unknown. Given that each layer of VSMCs has an adjacent BM that could be involved in perivascular drainage, the number of IPAD pathways is similar to the number of VSMCs layers. It has been reported that the number of VSMC layers in the large cerebral arteries of rats varies between 3 and 6, depending on the vessel type (e.g. up to 6 layers are found in the basilar artery) [106]. However, the total number of arteries and arterioles supplying the rat brain is also unknown.

Modern imaging techniques, such as multi-photon microscopy, allow in vivo visualisation of the surface arterial vascular network in rodent brains. By considering the rat brain images from [149], minimum 8 arteries branching from the middle cerebral artery can be detected in a 4 mm x 3 mm area. A reasonable assumption is to consider that the surface arterial network supplies (blood through the lumen) and clears (ISF and soluble metabolites through the wall) the cortex through its entire depth (e.g. 1 mm in the rat brain [172]). In this way, a brain volume of 4 mm x 3mm x 1 mm appears to be supplied and cleared by at least 8 surface arteries branching from the middle cerebral artery. Each of these arteries presumably has at least 3 BM compartments [106] that could contribute to the periartrial drainage of fluid out of the brain, i.e. a total of 24 BMs. This gives a total intramural fluid flow rate of $0.86 \cdot 10^4 - 1.15 \cdot 10^4 \mu m^3 \cdot s^{-1}$ out of 12 mm$^3$ of grey matter through the ‘Lymphatic’ and ‘Spongy’ BMs, respectively. The cerebral ISF occupies 20% of the brain volume, which means that a volume of 2.4 mm$^3$ ISF needs to be eliminated from the volume of grey matter considered here (e.g. 12 mm$^3$). The exact amount of ISF and diluted soluble Aβ that needs to be cleared along the IPAD routes versus other routes (e.g. convection through the interstitium towards the CSF) has been largely debated. These modelling results suggest that 19% of the cerebral ISF could be cleared by the V-IPAD mechanism through the ‘Lymphatic’ BM in up to 15 hours (a characteristic time for perivascular drainage found by [164]).

With ageing, the efficacy of the V-IPAD mechanism may decrease. The contractile and relaxing abilities of the VSMCs are impaired in old arteries [169]. The cholinergic innervation of cerebral arteries also decreases with age and in the presence of AD [168]. All these age-driven changes may translate into altered vasomotion waves and, consequently, into a decreased motive force for the perivascular drainage Aβ from the brain. The mechanism for the removal of Aβ
across the BBB also becomes inefficient with ageing \cite{157}, resulting in a higher burden of intracerebral Aβ that needs to be cleared along the IPAD pathways. All in all, the likelihood of CAA development will increase. The V-IPAD model could be further developed in order to simulate the effect of vascular ageing on the perivascular drainage of solutes from the brain and this aspect is discussed in Chapter 6.

<table>
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Table 5.2: Comparison of results between the V-IPAD model and previous models. BM represents the compartment within the arterial wall, while PVS represents the perivascular space between the arterial wall and the glial layer of the brain.

Major assumptions of the model

In designing the V-IPAD model, three major assumptions have been made. The first major assumption is the shape of the activation wave of the muscular contractions and the generated active stress within the arterial wall. These two terms determine the radial stress within the arterial wall, and, subsequently the external constrictive stress acting upon the BM, as shown in the elastic analysis from Chapter 4. The qualitative shape of the activation wave is similar to the vasomotion waves observed experimentally \cite{21, 65, 93, 142}. However, the magnitude of the maximum activation $S_m$ has not been confirmed in the cerebral muscular arteries. Given the lack of experimental data, $S_m$ is taken in accordance with the value reported in \cite{140} for the carotid arteries. The assumed $S_m$ induced a 20% amplitude of oscillation in the arterial diameter, which is comparable with the amplitude of vasomotion reported in the microcirculation of rodent skin \cite{92}. The cerebral arteries are very muscular arteries, with varying contractile abilities across the entire brain network of vessels; hence, the corresponding vasomotion wave may be stronger in different areas of the brain, leading to even higher flow rates along the IPAD pathways.

The second major assumption is the form of the strain energy function of
5.5. **DISCUSSION**

the BM. No experimental data on the elastic behaviour of the cerebrovascular BM exists, therefore the simplest non-linear elastic model was chosen. The stress-permeability relationship from Figure 5.5 describes qualitatively the same behaviour seen in Matrigel matrices exposed to compression by physiological pressures [100]. Matrigel is commonly used for reproducing basement membranes in vitro. Different material parameters have been considered to describe significantly different elastic behaviours of the BMs. The cerebrovascular BM denoted by the word ‘Lymphatic’ has similar properties to the interstitium of the systemic lymphatic system and to the interstitium of the brain, therefore it appears as a physiologically reasonable assumption. The cerebrovascular BM denoted by the word ‘Spongy’ describes a more elastic material and the corresponding net flow rates of 488 \( \mu m^3 \cdot s^{-1} \) may be seen as the upper limit for the potential perivascular flows induced during cerebral vasomotion. It is not excluded that the cerebrovascular BMs may have very specific properties, if it has the purpose of clearing most of the waste products of the brain. With increasing availability of experimental data, a new strain energy function can be easily implemented in the V-IPAD model.

The third major assumption is that the cerebral vasomotion must propagate from the networks of small arterioles towards the largest arteries in order to drive a net fluid flow out of the brain along the IPAD pathways. Although it was reported that similar waves with the frequency of 0.1 Hz in the awake cortex of the human brain propagate from small arterioles towards large arteries [142], further studies that clarify the origin of those waves are needed. In contrast, if the predominant direction of the cerebral vasomotion is from the largest arteries towards the smallest ones, i.e. in the reverse direction of IPAD, then there will be high net perivascular flows driven by the vasomotion wave towards the brain tissue. Further experimental investigation of the spatial pattern of vasomotion is needed and in vivo optical imaging (e.g. two-photon microscopy, optical intrinsic signal imaging) of contractile cerebral vascular networks [35, 128, 142] will prove useful in such an endeavour.

In conclusion, this study has demonstrated that the vasomotion wave initiated by the contractile VSMCs of cerebral arteries could represent the driving force of IPAD in the brain. The V-IPAD model is the first one that investigates the role of cerebral vasomotion in the clearance of fluid from the brain. The model offers mechanistic insights about the behaviour of the cerebrovascular BM and its interaction with the adjacent VSMCs. Once the hypothesis of V-IPAD gains more experimental confirmation, the model can help assess the efficacy of IPAD.
under different physiological, aged or pathological states of the cerebral arteries. The hypothesis proposed and tested here brings some promise for the future treatments of CAA and AD, highlighting the cerebral VSMCs as potential drug targets.

5.6 Derivation of equations for the poroelastic BM model

5.6.1 Governing equations

Poro-hyperelastic material. The fluid-filled poro-elastic BM is described in the reference (Lagrangian) configuration by the material coordinate $Z$. Its position after deformation is described in the current (Eulerian) configuration by the spatial coordinate $z = \chi(Z,t)$ as

$$
\begin{align*}
    z &= Z + u(Z,t),
\end{align*}
$$

where $t$ is time and $u(Z,t)$ is the BM displacement. The mapping $z = \chi(Z,t)$ is invertible, such that $Z = \chi^{-1}(z,t)$.

The velocity of a material point with coordinate $Z$ is

$$
\begin{align*}
    v(Z,t) = \dot{z}(Z,t) = \frac{\partial z(Z,t)}{\partial t} = \frac{\partial u(Z,t)}{\partial t},
\end{align*}
$$

where the right-side represents the convective (i.e. material) derivative of the displacement.

The deformation gradient tensor which describes relative deformations locally is

$$
\begin{align*}
    F = \frac{\partial z}{\partial Z} = I + \frac{\partial u}{\partial Z} \quad \text{with} \quad J = \det(F),
\end{align*}
$$

where $F$ is a mixed tensor and $J$ is its determinant. $J$ is known as the Jacobian of the transformation from $Z$ to $z$ and its physical significance is that it measures the changes in the current volume compared to the initial volume. $I$ denotes the identity matrix.

The BM is compressible (i.e. $J \neq 1$) as its volume changes due to changes in pore size during fluid drainage. For example, squeezing the pores under a compressive
force will result in reduction of BM volume and hindered permeability of the fluid paths. The matrix of proteins of the solid component can be incompressible, such that all the volume changes in the BM are due to changes in pores.

Due to its symmetry properties, the Right-Green deformation tensor $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is commonly used to describe the deformation of a system. It is recalled that every second-order symmetric tensor has components that are independent of the coordinate system, i.e. are invariant under any orthogonal transformation (e.g. rotation). These components are the eigenvalues of the tensor and are said to be the invariants of the tensor. The eigenvectors corresponding to these eigenvalues give the principal directions ([98], p. 272). In the special case when the axes of a three-dimensional system are oriented along the principal direction, $\mathbf{F}$ and $\mathbf{C}$ reduce to a diagonal matrix

$$\mathbf{F} = \text{diag}[\lambda_1, \lambda_2, \lambda_3] \quad \text{and} \quad \mathbf{C} = \text{diag}[\lambda_1^2, \lambda_2^2, \lambda_3^2],$$

(5.34)

where $\lambda_i$ with $i = 1, 2, 3$ represent the principal stretches in the principal directions of a three-dimensional system.

The most commonly used invariants of $\mathbf{C}$ are

$$I_1 = \text{Tr}(\mathbf{C}) = \lambda_1^2 + \lambda_2^2 + \lambda_3^2,$$

(5.35a)

$$I_2 = \frac{1}{2}(\text{Tr}(\mathbf{C}^2) - \text{Tr}(\mathbf{C}^2)) = \lambda_1^2 \lambda_2^2 + \lambda_2^2 \lambda_3^2 + \lambda_3^2 \lambda_1^2,$$

(5.35b)

$$I_3 = \text{det}(\mathbf{C}) = \lambda_1^2 \lambda_2^2 \lambda_3^2,$$

(5.35c)

which are discussed in detail in ([98], p. 222). Given that the BM is modelled as hyperelastic material, its properties can be described in terms of a strain energy function $W_{BM}(\mathbf{F})$ defined per unit volume. The constitutive stress-strain relation must be invariant under rigid-body motions of the reference state, i.e. the way an elastic material responds to stress should not depend on the frame in which it is observed. Therefore, for isotropic materials, $W_{BM}$ depends only on the invariants of $\mathbf{C}$, i.e. $W_{BM} = W_{BM}(I_1, I_2, I_3)$. The choice of $W_{BM}$ is discussed in detail in Section 5.2.3.

**Force-balance equation.** Treating the solid matrix and the fluid from the pores as a homogeneous continuum, the stress within the BM is related both to the deformation of the solid phase and to the pressure in the fluid phase. Neglecting inertia and assuming no body forces, conservation of momentum leads
to the force-balance equation, according to which the divergence of the BM stress is zero

$$\nabla_z \cdot (\sigma^e - \alpha p I) = 0,$$  \hspace{1cm} (5.36)

where $\sigma^e$ is the effective Cauchy stress of the solid matrix, $p$ is the pore pressure and $\alpha$ is a material parameter ($\alpha = 1$ for perfectly saturated mixtures). The divergence is taken in the Eulerian configuration with respect to the deformed coordinate $z$ and is denoted by $\nabla_z$.

For an hyperelastic material, the Cauchy stresses are derived from a strain-energy function, denoted here $W_{BM}$, as

$$\sigma^e = I_3^{-1/2} \frac{\partial W_{BM}}{\partial F} F^T$$  \hspace{1cm} (5.37)

and the expression of the principal Cauchy stresses (in index notation with no summation) simplifies to

$$\sigma_i^e = I_3^{-1/2} \lambda_i \frac{\partial W_{BM}}{\partial \lambda_i},$$  \hspace{1cm} (5.38)

where, for example, $i = 1, 2, 3$ for a three-dimensional coordinate system.

**Mass conservation.** The conservation of solid mass and fluid mass are given by

$$\frac{\partial \phi^s}{\partial t} + \nabla_z \cdot (\phi^s v^s) = 0,$$  \hspace{1cm} (5.39)

$$\frac{\partial \phi^f}{\partial t} + \nabla_z \cdot (\phi^f v^f) = 0,$$  \hspace{1cm} (5.40)

where $v^s$ and $v^f$ represent the solid and fluid velocity, respectively, while $\phi^s$ and $\phi^f$ represent the volume fraction of solid and fluid, respectively, in the current deformed configuration of the system. $v^s$ is defined as in (5.32).

**Flow through a poroelastic medium.** The fluid velocity relative to the solid matrix is determined by the pore pressure gradient and the deformation-dependent permeability via a Darcy-type relation

$$\phi^f (v^f - v^s) = -\frac{k}{\eta} \nabla p,$$  \hspace{1cm} (5.41)
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where \( p [Pa] \) is the pore pressure, \( \eta [Pa \cdot s] \) is the viscosity of the interstitial fluid and \( k [m^2] \) is the deformation-dependent permeability of the BM given by

\[
k = k_s f(J), \tag{5.42}
\]

where \( k_s \) represents the permeability of the basement membrane in the fluid-filled reference configuration. \( f(J) \) is a dimensionless function that relates permeability to the material volume changes given by the Jacobian \( J \)

\[
f(J) = \left( \frac{J - \phi_s^*}{1 - \phi_s^*} \right)^\kappa \tag{5.43}
\]

where \( \kappa \) is a positive parameter and \( \phi_s^* \) is the volume fraction of the solid in the reference configuration. The state of zero porosity is reached when \( J = \phi_s^* \).

5.6.2 Geometry, initial and boundary conditions

Accounting for the difference in scale (BM thickness \( \approx 400 \text{ nm} \ll \text{arterial radius} \approx 100 \mu m \ll \text{wavelength} \approx 2 \text{ mm} \)), the model is restricted to a two-dimensional Cartesian system in the \((z,y)\) plane, as shown in 5.1. The BM is a narrow poroelastic fluid-filled channel running along \( z \)-axis; its deformation and the subsequent flow induced by the external load from the top and bottom boundaries are investigated. The top and bottom boundaries represent the layers of contracting VSMCs. In the reference fluid-filled configuration the BM has thickness \( 2H \), length \( L_s \) and spatially uniform properties, such as the permeability \( k_s \), the solid porosity \( \phi_s^* \) and the fluid porosity \( 1 - \phi_s^* \) (assuming perfectly saturated mixture). The reference configuration of the system is described by the Lagrangian coordinates \((Z,Y)\) and the current deformed configuration by the Eulerian coordinates \((z,y)\). Here, for visual purposes, the upper half of the undeformed BM is denoted \( H \) and the upper half of the deformed BM is denoted \( h \). For simplicity reasons, it is enough to solve the problem only in the upper half-plane accounting for the symmetry of the system.

Therefore, the displacement is given by

\[
u = u_z(Z, Y, t)e_z + u_y(Z, Y, t)e_y, \tag{5.44}
\]
where \( \mathbf{e}_z \) and \( \mathbf{e}_y \) are the unit vectors in the z- and y-direction, respectively. The corresponding deformation gradient tensor becomes

\[
\mathbf{F} = \begin{pmatrix} 1 + \frac{\partial u_z}{\partial Z} & \frac{\partial u_z}{\partial Y} \\ \frac{\partial u_y}{\partial Z} & 1 + \frac{\partial u_y}{\partial Y} \end{pmatrix} \quad \text{with} \quad J = \left( 1 + \frac{\partial u_z}{\partial Z} \right) \left( 1 + \frac{\partial u_y}{\partial Y} \right) - \frac{\partial u_y}{\partial Z} \frac{\partial u_z}{\partial Y}
\]

The effective Cauchy stress takes the form

\[
\sigma^e = \begin{pmatrix} \sigma_{zz}^e & \sigma_{zy}^e \\ \sigma_{yz}^e & \sigma_{yy}^e \end{pmatrix}
\]

and the corresponding velocity of a material point is

\[
v^* = v_z^*(Z,Y,t)e_z + v_y^*(Z,Y,t)e_y,
\]

with the components

\[
v_z^* = \frac{\partial u_z}{\partial t} \quad \text{and} \quad v_y^* = \frac{\partial u_y}{\partial t}.
\]

The governing equations from (5.36) and (5.39)-(5.41) need to be considered with the appropriate initial and boundary conditions.

**Initial conditions.** The initial BM is considered to be uniform and undeformed, i.e.

\[
h|_{t=0} = H, \quad 0 \leq Z \leq L_s.
\]

The BM deforms under the known external load \( \Sigma(z,t) = \Sigma(z,t)\mathbf{e}_y \).

Accounting for the symmetry axis at \( y=0 \), the boundaries of the system transform as follows

\[
Z = 0 \rightarrow z = 0, \quad Z = L_s \rightarrow z = l, \quad Y = 0 \rightarrow y = 0, \quad Y = H \rightarrow y = h(z,t),
\]

where \( l \) is the deformed length and \( h \) is the deformed thickness in the current configuration.
Boundary conditions at the ends of the BM. The ends of the BM are assumed to be at the same pressure (i.e. any significant pressure driven flows along the BM are discounted)

\[ p |_{z=0} = p |_{z=l} = 0, \quad t > 0. \quad (5.50) \]

Boundary conditions on the top and bottom surface. A constricting stress \(-\Sigma(z, t) = -\Sigma(z, t)e_y\) is applied on both sides of the BM, at \(h\) and \(-h\), as shown in Figure 5.1. It is noted that the top boundary, whose height above the z-axis is given by \(y = h(z, t)\), is a moving surface and its position remains unknown until the problem is solved. Consequently, it is necessary to specify a kinematic boundary condition concerning the fluid motion and a dynamic boundary condition concerning the stresses.

The kinematic boundary condition requires that the material fluid elements on the moving boundary remain on the boundary. Let the top boundary be described by the function

\[ F(z, y, t) = h(z, t) - y \quad (5.51) \]

It follows that

\[ \frac{D}{Dt} (h(z, t) - y) = 0 \quad \text{on} \quad y = h(z, t) \quad (5.52) \]

and, by expanding the convective derivative (e.g. \(\frac{D}{Dt} = \frac{\partial}{\partial t} + v \cdot \nabla\)), the kinematic boundary condition becomes

\[ \frac{\partial h}{\partial t} + v_f^z \frac{\partial h}{\partial z} = v_y^f \quad \text{on} \quad y = h(z, t). \quad (5.53) \]

The other boundary considered here is the symmetry axis \(y = 0\), which means that no flux condition apply

\[ v_y^f = 0 \quad \text{on} \quad y = 0. \quad (5.54) \]

The dynamic boundary condition requires the stress to be continuous across the top boundary

\[ \sigma_{yy}^e - p = \Sigma \quad \text{on} \quad y = h(z, t), \quad (5.55) \]
while the symmetry boundary condition applies on the line $y = 0$,

$$\frac{\partial (\sigma_{yy}^e - p)}{\partial y} = 0 \quad \text{on} \quad y = 0,$$  \hfill (5.56)

where $\sigma_{yy}^e$ is the normal Cauchy stress component in the $y$-direction. Condition (5.56) ensures that the stress gradients normal to the axis of symmetry are zero.

The external load $\Sigma(z, t)$ acts as the normal compressive stress and is represented as a sinusoidal oscillation both in time and space. A detailed description is given in 5.2.

### 5.6.3 Lubrication approximation

In this section, the key parameters of the model are determined by making use of the difference in scale between the length and the thickness of the vascular BM, which is considered a long and thin layer of fluid-filled poroelastic material.

**Non-dimensional model.** It is non-dimensionalized as follows:

\[
\begin{align*}
    z &= L \hat{z}, \quad y = H \hat{y}, \quad h = H \hat{h}, \quad l = L \hat{l}, \quad Z = L \hat{Z}, \quad Y = H \hat{Y}, \\
    u_z &= \varepsilon H \hat{u}_z, \quad u_y = H \hat{u}_y, \\
    \sigma^e &= (\lambda_s + 2\mu_s) \hat{\sigma}, \quad W_{BM} = (\lambda_s + 2\mu_s) \hat{W}_{BM}, \quad p = (\lambda_s + 2\mu_s) \hat{p}, \\
    \Sigma &= (\lambda_s + 2\mu_s) \hat{\Sigma}, \quad S = (\lambda_s + 2\mu_s) \hat{S}, \\
    v_z^f &= \frac{k_s(\lambda_s + 2\mu_s)}{\eta L} \hat{v}_z^f = V \hat{v}_z^f, \quad v_y = \varepsilon V \hat{v}_y^f, \quad v_z^s = \varepsilon^2 V \hat{v}_z^s, \quad v_y^s = \varepsilon V \hat{v}_y^s, \\
    k &= k_s \hat{k}, \quad t = t^* \hat{t} = \frac{\eta L^2}{k_s(\lambda_s + 2\mu_s)} \hat{t},
\end{align*}
\]

(5.57a-f)

where the dimensionless constants are denoted as

\[
\varepsilon = H/L \ll 1, \quad \hat{\mu}_s = \frac{\mu_s}{\lambda_s + 2\mu_s}, \quad \hat{\lambda}_s = \frac{\lambda_s}{\lambda_s + 2\mu_s}, \quad \hat{S}_m = \frac{S_m}{\lambda_s + 2\mu_s}. \hfill (5.58)
\]

$\varepsilon$ represents the aspect ratio of the system, with $H$ being the characteristic thickness and $L$ the characteristic length in the direction of flow equal to the wavelength. $\lambda_s + 2\mu_s$ is chosen as the characteristic pressure. In the light of the compressibility of the BM, it is assumed that the deformations of the BM are larger in the $y$-direction than in the $z$-direction. Taking $V = \frac{k_s(\lambda_s + 2\mu_s)}{\eta L}$ to be the scale of fluid velocity $v^f$ in the $z$-direction, the scale of $v^f$ in the $y$-direction must be $\varepsilon V$ in order not to violate the fluid mass conservation from (5.40). The fluid velocity has been scaled using Darcy’s equation (5.41). $t^* = L/V$ is the timescale.
for a flow with characteristic viscosity $\eta$ that travels distance $L$ under the pressure gradient $(\lambda_s + 2\mu_s)/L$ through a medium of characteristic permeability $k_\ast$. The solid velocity has been scaled using (5.47). $S$ and $S_m$ appear in the activation wave. The values of the constants of the system are given in Table (5.1).

Given that the top and bottom boundaries of the BM are assumed incompressible, no fluid can escape from the poroelastic BM, hence fluid mass conservation needs to be imposed (i.e. exactly the same amount of fluid entering the BM at the left end must exit at the right end). This aspect is assured during the scaling of the fluid equation (5.40) as demonstrated below. Equation (5.40) is rewritten as

$$\frac{\partial \phi^f}{\partial t} + \frac{\partial (\phi^f v^f_y)}{\partial z} + \frac{\partial (\phi^f v^f_z)}{\partial y} = 0,$$

(5.59)

The assumption of a thin layer means that $\epsilon = \frac{H}{L} \ll 1$, where $H$ is the characteristic thickness and $L$ is the characteristic length in the direction of flow. The time $t$ is scaled with $L/V$, where $V$ denotes the characteristic fluid velocity. This gives $z = L\hat{z}$ and $y = H\hat{y}$ which are replaced in equation (5.59), leading to

$$\frac{V}{L} \frac{\partial \phi^f}{\partial \hat{t}} + \frac{\partial (\phi^f \hat{v}^f_y)}{\partial \hat{z}} + \frac{\partial (\phi^f \hat{v}^f_z)}{\partial \hat{y}} = 0,$$

(5.60)

At this stage, by taking the scale of both velocity components $v^f_y$ and $v^f_z$ to be identical, e.g. $v^f_y = V\hat{v}^f_y$ and $v^f_z = V\hat{v}^f_z$, the last term in the left-hand side of equation (5.60) will be dominant (since the term $\frac{1}{\epsilon}$ becomes very high, tending to infinity, as $\epsilon$ goes to zero). In other words, at leading order, the fluid flowing in the $y$-direction will be the only one that matters and equation (5.60) reduces to

$$\frac{\partial (\phi^f \hat{v}^f_y)}{\partial \hat{y}} = 0$$

(5.61)

In order to keep both fluid velocity components equally important, reflecting in this way fluid mass conservation, the scale of the fluid velocity in the $z$-direction is $V$, while that of the fluid velocity in the $y$-direction is $\epsilon V$. This gives

$$\frac{\partial \phi^f}{\partial \hat{t}} + \frac{\partial (\phi^f \hat{v}^f_z)}{\partial \hat{z}} + \frac{\partial (\phi^f \hat{v}^f_y)}{\partial \hat{y}} = 0$$

(5.62)

which means that the equation for fluid mass conservation remains practically unchanged in the non-dimensional framework.
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Considering the above scaling, the non-dimensional displacement is

\[ \dot{\mathbf{u}} = \varepsilon H \hat{u}_z \mathbf{e}_z + H \hat{u}_y \mathbf{e}_y \]  \hspace{1cm} (5.63)

and the boundaries of the system from (5.49) transform as follows

\[ \begin{align*}
\hat{Z} = 0 &\rightarrow \hat{z} = 0, \quad (5.64a) \\
\hat{Z} = L_s/L &\rightarrow \hat{z} = \hat{l}, \quad (5.64b) \\
\hat{Y} = 0 &\rightarrow \hat{y} = 0, \quad (5.64c) \\
\hat{Y} = 1 &\rightarrow \hat{y} = \hat{h}(z, t). \quad (5.64d)
\end{align*} \]

The corresponding deformation gradient tensor is

\[ \mathbf{F} = \begin{pmatrix} 1 + \varepsilon^2 \frac{\partial \hat{u}_z}{\partial \hat{Z}} & \varepsilon \frac{\partial \hat{u}_y}{\partial \hat{Y}} \\ \varepsilon \frac{\partial \hat{u}_y}{\partial \hat{Y}} & 1 + \varepsilon^2 \frac{\partial \hat{u}_z}{\partial \hat{Z}} \end{pmatrix} \]

with \[ J = \left( 1 + \frac{\partial \hat{u}_y}{\partial \hat{Y}} \right) + \varepsilon^2 \left( \frac{\partial \hat{u}_z}{\partial \hat{Z}} \frac{\partial \hat{u}_z}{\partial \hat{Y}} - \frac{\partial \hat{u}_z}{\partial \hat{Z}} \frac{\partial \hat{u}_y}{\partial \hat{Y}} \right) \]  \hspace{1cm} (5.65)

Further on, substituting the above scaling into (5.36) and (5.39)-(5.43), the non-dimensional governing equations are obtained

\[ \begin{align*}
\varepsilon \frac{\partial \hat{\sigma}^e_{zz}}{\partial \hat{z}} - \varepsilon \frac{\partial \hat{p}}{\partial \hat{Z}} + \frac{\partial \hat{\sigma}^e_{zy}}{\partial \hat{y}} &= 0, \quad (5.66) \\
\varepsilon \frac{\partial \hat{\sigma}^e_{yz}}{\partial \hat{z}} + \frac{\partial \hat{\sigma}^e_{yy}}{\partial \hat{y}} - \frac{\partial \hat{p}}{\partial \hat{Y}} &= 0, \quad (5.67) \\
\frac{\partial \phi^s}{\partial \hat{t}} + \varepsilon \frac{1}{\varepsilon^2} \frac{\partial \phi^s_{zz}}{\partial \hat{Z}} + \frac{\partial \phi^s_{yy}}{\partial \hat{y}} &= 0, \quad (5.68) \\
\frac{\partial \phi^f}{\partial \hat{t}} + \frac{\partial \phi^f_{zz}}{\partial \hat{Z}} + \frac{\partial \phi^f_{yy}}{\partial \hat{y}} &= 0, \quad (5.69)
\end{align*} \]

\[ \phi^f \left( \left( \hat{v}^f_z e_z - \varepsilon^2 \frac{\partial \hat{u}_z}{\partial \hat{t}} \right) e_z + \varepsilon \left( \hat{v}^f_y - \frac{\partial \hat{u}_y}{\partial \hat{t}} \right) e_y \right) = -\hat{k}(J) \left( \frac{\partial \hat{p}}{\partial \hat{Z}} e_z + \frac{1}{\varepsilon} \frac{\partial \hat{p}}{\partial \hat{Y}} e_y \right), \quad (5.70) \]

with the initial condition,

\[ h|_{t=0} = 1, \quad 0 \leq \hat{Z} \leq L_s/L \]  \hspace{1cm} (5.71)
and the boundary conditions

\[ \hat{p}|_{\hat{z}=0} = \hat{p}|_{\hat{z}=l} = 0, \quad t > 0, \quad (5.72a) \]
\[ \frac{\partial \hat{h}}{\partial t} + \hat{v}_f \frac{\partial \hat{h}}{\partial \hat{z}} = \hat{v}_f \text{ on } \hat{y} = \hat{h}(z, t), \quad (5.72b) \]
\[ \hat{v}_y = 0 \text{ on } \hat{y} = 0, \quad (5.72c) \]
\[ \hat{\sigma}_{yy} - \hat{p} = \hat{\Sigma} \text{ on } \hat{y} = \hat{h}(z, t), \quad (5.72d) \]
\[ \frac{\partial (\hat{\sigma}_{yy} - \hat{p})}{\partial \hat{y}} = 0 \text{ on } \hat{y} = 0. \quad (5.72e) \]

In non-dimensional form, the solid velocity is

\[ \hat{\mathbf{v}}^s = \varepsilon^2 \hat{v}_z^s \mathbf{e}_z + \varepsilon \hat{v}_y^s \mathbf{e}_y, \quad (5.73) \]

with the components

\[ \hat{v}_z^s = \frac{\partial \hat{u}_z}{\partial \hat{t}}, \quad \text{and} \quad \hat{v}_y^s = \frac{\partial \hat{u}_y}{\partial \hat{t}}, \]

the fluid velocity is

\[ \hat{\mathbf{v}}^f = \hat{v}_z^f \mathbf{e}_z + \varepsilon \hat{v}_y^f \mathbf{e}_y, \quad (5.74) \]

and the Cauchy stress components (in index notation) are

\[ \hat{\sigma}_{ij} = \frac{1}{J} \hat{W}_{BM} F_{ik} F^T_{kj}, \quad (5.75) \]

with the dimensionless strain-energy function \( \hat{W} \).

The deformation-dependent permeability (5.42) becomes

\[ \hat{k}(J) = \left( \frac{J - \phi_s}{1 - \phi_s} \right)^\kappa. \quad (5.76) \]

**Asymptotic solution**  In the light of the smallness of the parameter \( \varepsilon \), the dependent variables are expanded asymptotically as follows, dropping the hat on the dimensionless variables but keeping the hat on the dimensionless constants
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from (5.58)

\[ u_z = u_{z,0} + \varepsilon u_{z,1} + ..., \quad u_y = u_{y,0} + \varepsilon u_{y,1} + ..., \tag{5.77a} \]

\[ v_f^z = v_{f,0}^z + \varepsilon v_{f,1}^z + ..., \quad v_f^y = v_{f,0}^y + \varepsilon v_{f,1}^y + ..., \tag{5.77b} \]

\[ \phi_f = \phi_{0}^s + \varepsilon \phi_{1}^s + ..., \quad \phi_s = \phi_{0}^s + \varepsilon \phi_{1}^s + ..., \tag{5.77c} \]

\[ J = J_0 + \varepsilon J_1 + ..., \quad k = k_0 + \varepsilon k_1 + ..., \tag{5.77d} \]

\[ \sigma_{zz}^e = \sigma_{zz,0}^e + \varepsilon \sigma_{zz,1}^e + ..., \quad \sigma_{yy}^e = \sigma_{yy,0}^e + \varepsilon \sigma_{yy,1}^e + ..., \tag{5.77e} \]

\[ \sigma_{zy}^e = \varepsilon \sigma_{zy,0}^e + \varepsilon^2 \sigma_{zy,1}^e + ..., \quad \sigma_{yy}^e = \sigma_{yy,0}^e + \varepsilon \sigma_{yy,1}^e + ..., \tag{5.77f} \]

Omitting terms of order \( \varepsilon \) and smaller, the deformation at the leading order becomes

\[ \mathbf{u} = u_{y,0} \mathbf{e}_y + O(\varepsilon), \tag{5.78} \]

with the corresponding deformation gradient tensor

\[ \mathbf{F} = \begin{pmatrix} 1 & 0 \\ 0 & 1 + \frac{\partial u_{y,0}}{\partial Y} \end{pmatrix} + O(\varepsilon) \quad \text{with} \quad J_0 = 1 + \frac{\partial u_{y,0}}{\partial Y} + O(\varepsilon) \tag{5.79} \]

and the corresponding material velocity

\[ \mathbf{v}^s = v_{y,0}^s \mathbf{e}_y + O(\varepsilon), \tag{5.80} \]

where

\[ v_{y,0}^s = \frac{\partial u_{y,0}}{\partial t}. \]

Given the deformation in the y-direction only from (5.78), at leading order the length of the basement membrane does not change, i.e. \( l = L_s \).

By solving the characteristic equation \( \text{det}(\mathbf{C} - \lambda^2 \mathbf{I}) = 0 \) (recalling that \( \mathbf{C} = \mathbf{F}^T \mathbf{F} \) and \( \mathbf{I} \) is the identity matrix), at leading order the principal stretches are identified

\[ \lambda_z = \frac{\partial Z}{\partial Z} = 1, \quad \lambda_y = \frac{\partial Y}{\partial Y} = 1 + \frac{\partial u_{y,0}}{\partial Y}. \tag{5.81} \]
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Therefore, at leading order the deformation tensors reduce to a diagonal matrix, i.e. $\mathbf{F} = \text{diag}[\lambda_z, \lambda_y]$ and $\mathbf{C} = \text{diag}[\lambda_z^2, \lambda_y^2]$, with the invariants

\begin{align*}
I_1 &= \lambda_z^2 + \lambda_y^2, \\
I_2 &= I_3 = \lambda_z^2 \lambda_y^2, \\
J_0 &= I_3^{-1/2} = \lambda_z \lambda_y.
\end{align*}

(5.82a, 5.82b, 5.82c)

The system is a special case when the axes of system are oriented along the principal directions, such that the effective Cauchy stress components at leading order are the principal Cauchy stresses:

\begin{align*}
\sigma_{zz,0}^e &= \sigma_z^e = J_0^{-1} \lambda_z \frac{\partial W_{BM}}{\partial \lambda_z}, \\
\sigma_{yy,0}^e &= \sigma_y^e = J_0^{-1} \lambda_y \frac{\partial W_{BM}}{\partial \lambda_y}, \\
\sigma_{zy,0}^e &= 0.
\end{align*}

(5.83a, 5.83b, 5.83c)

This leads to the following expansion

\begin{align*}
\sigma_{zz}^e &= \sigma_z^e + O(\varepsilon), \\
\sigma_{yy}^e &= \sigma_y^e + O(\varepsilon), \\
\sigma_{zy}^e &= O(\varepsilon).
\end{align*}

(5.84a, 5.84b, 5.84c)

Therefore, the force balance equations from (5.66)-(5.67) at leading order reduce to

\[
\frac{\partial \sigma_y^e}{\partial y} - \frac{\partial p_0}{\partial y} = 0
\]

(5.85)

By substituting the expressions (5.77) into the governing equations (5.68)-(5.69), the solid and fluid mass conservation equations at leading order are obtained in the form:

\begin{align*}
\frac{\partial \phi_0^s}{\partial t} + \frac{\partial (\phi_0^s v_{y,0}^s)}{\partial y} &= 0, \\
\frac{\partial \phi_0^f}{\partial t} + \frac{\partial (\phi_0^f v_{z,0}^f)}{\partial z} + \frac{\partial (\phi_0^f v_{y,0}^f)}{\partial y} &= 0
\end{align*}

(5.86, 5.87)

with the solid velocity at leading order

\[
v_{y,0} = \frac{\partial u_{y,0}}{\partial t}
\]

(5.88)
The Darcy’s equation (5.70) at the first two leading orders becomes
\[
\frac{\partial p_0}{\partial y} = 0 \quad (5.89)
\]
and
\[
(\phi_0^f v_{z,0}^f) e_z = -k \left( \frac{\partial p_0}{\partial z} e_z - \frac{\partial p_1}{\partial y} e_y \right), \quad (5.90)
\]
with
\[
k = k(J_0) = k(\lambda_y) = \left( \frac{\lambda_y - \phi_s^*}{1 - \phi_e^*} \right) + O(\varepsilon). \quad (5.91)
\]
At leading order, the initial condition from (5.71) and boundary conditions from (5.72) become:

\[
h|_{t=0} = 1, \quad 0 \leq Z \leq L_s/L, \quad (5.92a)
\]

\[
p_0|_{z=0} = p_0|_{z=1} = 0, \quad t > 0, \quad (5.92b)
\]

\[
\frac{\partial h}{\partial t} + v_{z,0}^f \frac{\partial h}{\partial z} = v_{y,0}^f \quad \text{on} \quad y = h(z,t), \quad (5.92c)
\]

\[
v_{y,0}^f = 0 \quad \text{on} \quad y = 0, \quad (5.92d)
\]

\[
\sigma_{yy,0}^e - p_0 = \Sigma \quad \text{on} \quad y = h(z,t), \quad (5.92e)
\]

\[
\frac{\partial (\sigma_{yy,0}^e - p_0)}{\partial y} = 0 \quad \text{on} \quad y = 0, \quad (5.92f)
\]

By solving (5.85) and applying the boundary condition (5.92e), it follows that the force-balance equations reduce to
\[
\sigma_y^e - p_0 = \Sigma(z,t) \quad (5.93)
\]

Equations (5.89)-(5.90) show that
\[
p_0 = p_0(z,t), \quad (5.94)
\]
\[
p_1 = p_1(z,t), \quad (5.95)
\]
\[
\phi_0^f v_{z,0}^f = -k \frac{\partial p_0}{\partial z}. \quad (5.96)
\]

Considering (5.94), equation (5.93) leads to
\[
\sigma_y^e = \sigma_y^e(z,t), \quad (5.97)
\]
which implies that

\[ \lambda_y = \lambda_y(z, t), \]  
(5.98)

and according to equation (5.86),

\[ \phi_0^s = \phi_0^s(z, t). \]  
(5.99)

By saturation condition \((\phi^s + \phi^f = 1)\),

\[ \phi_0^f = \phi_0^f(z, t). \]  
(5.100)

Considering only the \((z,t)\)-dependence of variables from (5.94) and (5.97) - (5.100), the Darcy’s equation (5.96) shows that

\[ v_{z,0}^f = v_{z,0}^f(z, t) \]  
(5.101)

Integrating the fluid mass conservation (5.87) over the entire domain

\[ \int_{y=0}^{y=h(z,t)} \frac{\partial \phi_0^f(z, t)}{\partial t} dy + \int_{y=0}^{y=h(z,t)} \frac{\partial (\phi_0^f(z, t)v_{z,0}^f(z, t))}{\partial z} dy + \left[ \phi_0^f(z, t)v_{y,0}^f(z, y, t) \right]_{y=0}^{y=h(z,t)} = 0, \]  
(5.102)

\[ \frac{\partial \phi_0^f}{\partial t} h + \frac{\partial (\phi_0^f v_{z,0}^f)}{\partial z} h + \phi_0^f v_{y,0}^f(z, h, t) = 0 \]  
(5.103)

and applying the boundary conditions from (5.92c)-(5.92d), the conservation of fluid mass becomes

\[ \frac{\partial (\phi_0^f h)}{\partial t} + \frac{\partial (\phi_0^f v_{z,0}^f h)}{\partial z} = 0. \]  
(5.104)

Regarding the conservation of solid mass, it is recalled that \(v_{y,0}^s\) needs to be calculated at a spatial point in the Eulerian configuration. Making use of the fact that at leading order the only non-trivial deformation is

\[ y = Y + u_{y,0}(Z, Y, t) \]  
(5.105)

and that the stretch ratio \(\lambda_y = \lambda_y(z, t)\) from (5.81) can be expressed in dimensionless form as

\[ \lambda_y = \frac{y}{Y} = h(z, t), \]  
(5.106)
the dimensionless BM displacement at leading order is expressed as

$$u_{y,0} = (h - 1)Y.$$  \hfill (5.107)

Given that the reference configuration has no time dependence, the solid velocity at a spatial point at leading order from (5.80) is now given by

$$v_{y,0} = \frac{\partial((h - 1)Y)}{\partial t} = \frac{\partial h_y}{\partial t} Y = \frac{\partial h_y}{\partial t} h.$$  \hfill (5.108)

The last term in (5.108) is obtained by transforming from a Lagrangian representation to an Eulerian representation using (5.106). Hence, the equation for the conservation of solid mass (5.86) becomes

$$\frac{\partial \phi_s^0}{\partial t} + \phi_s^0 \frac{1}{h} \frac{\partial h}{\partial t} = 0.$$  \hfill (5.109)

By substituting (5.81) and (5.107), it is immediately obvious that, at leading order, the Jacobian of the system that shows the volumetric change of the BM reduces to $J_0 = h$, while the other two invariants become $I_1 = h^2 + 1$ and $I_2 = h^2$, respectively. Moreover, the principal Cauchy stress in the normal direction from (5.83) reduces to

$$\sigma_y^e(h) = \frac{\partial W_{BM}}{\partial \lambda_y} = \frac{\partial W_{BM}}{\partial h},$$  \hfill (5.110)

while the deformation-dependent permeability from (5.91) becomes

$$k(h) = \left( \frac{h - \phi_s^*}{1 - \phi_s^*} \right)^\kappa.$$  \hfill (5.111)

Bringing it all together, the equations (5.109), (5.104), (5.96), (5.93) and (5.110) represent the non-dimensional form of the system of 5 equations with 5 unknowns presented in section (5.6). It is recalled that the hat symbol of the non-dimensional variables was dropped in the above analysis. The dimensional form is regained by using the relationships from (5.57).
Chapter 6

Conclusions and future directions

This thesis has been a journey down into the deep layers of the brain and then back again to the surface via privileged pathways. The objective of this journey was to first provide a critical assessment of the available experimental data on the clearance of solutes from the brain. The main clearance mechanisms were then modelled in a novel physiologically-based framework and their relative contribution was assessed. A special focus was on the role of cerebral blood vessels in the clearance of Aβ from the brain. The conclusions drawn from this study are given below. In addition, the ways in which the model developed here could serve as guidance tools for future experiments in the field of clearance of the brain are discussed.

Chapter 2. From the experimental and clinical evidence revised in Chapter 2, it is obvious that impaired clearance of soluble Aβ from the brain has implications in the onset of AD. The drainage of soluble tracers from the brain of rodents was intensively investigated in the early 80s and the drainage rates of ISF from the brain tissue, calculated back then, are the reference values for the modern studies of clearance of the brain. The modern experiments benefit from high imaging power and this has helped pinpoint the anatomical details of the clearance pathways of the brain. However, solid quantitative assessment of the rates of clearance along the vascular pathways is still lacking.

Future direction. Future experiments should make a clear distinction between the possible clearance mechanisms of solutes from the brain (e.g. convection, diffusion or bulk removal via sink terms) and tailor the experimental methodology according to the mathematical analysis used for the interpretation of their results.
For instance, the clearance of solutes along the IPAD pathways may be assessed with an exponential decay, but flows along the perivascular spaces on the outside of the artery should be analysed as a convection-type problem. The previous experiments [164] seem to describe multiple types of clearance mechanisms and, yet, they only use exponential decay-type problems to assess their data.

Chapter 3. The model of the human brain developed in Chapter 3 represents a physiologically-realistic framework for testing various clearance mechanisms of Aβ out of the brain which have been proposed in the literature. A realistic geometry of the human brain and heterogeneous material properties of the brain tissue, (e.g. permeability, porosity, diffusivity), are the input of the model. On the other hand, the intra-cerebral pressure, the interstitial fluxes and the secretion rate of ISF at the BBB are determined. This yields regional differences in the clearance of fluid and Aβ from the brain, which are difficult to infer experimentally. Moreover, previous speculations about the existence of a continental divide for interstitial flows in the brain is confirmed by the model.

The relative efficacy of different transport mechanisms of Aβ out of the brain were investigated, confirming that the fast-clearance of Aβ at the BBB is essential for maintaining physiological concentrations of Aβ in the brain [157]. In contrast, the importance of clearance mechanisms with a half-life of 10 hours, which were reported by the early experiments of Cserr et al. [46, 164], was downplayed, due to the fact that such mechanisms do not act fast enough to compensate for the physiological production rates of Aβ by the human brain; this results in high pathological Aβ concentrations in the grey matter. Not all possible combinations of clearance mechanisms were assessed here, but the model allows relatively easy inclusion of different experimental assumptions.

Future directions. The intra-cerebral pressure and flow maps of the normal brain generated by the model from Chapter 3 cannot be directly validated against experimental data with the current imaging technologies. The model developed in Chapter 3 is setup just for the physiological case. Nonetheless, a future comparative study between physiological and pathological cases, with predictive capability of cerebral pressure distribution and interstitial flows, is possible owing to the non-invasive imaging methods of the living human brain. For instance, methods like diffusion weighted imaging, including diffusion tensor imaging, are able to determine the alterations in water diffusion resulting from microscopic structural changes in the grey and white matter due to various pathological
conditions (e.g. AD, traumatic brain injury). In this way, a measure of the diffusion coefficient of water in the brain and anisotropy of the brain tissue can be obtained and correlated with different brain disorders [8, 105]. The model from Chapter 3 could predict how micro-structural alterations in the grey and white matter influence the clearance of fluid and soluble Aβ from the brain, by using as input various diffusivity properties of the brain corresponding to healthy, aged and AD brains. Further on, access to human data from PET or functional-MRI allows assessing the changes in the metabolic activity of the brain in young, aged and diseased patients. These imaging methods could provide input data for the model, such as metabolic production rates of ISF and Aβ in the human brain. Consequently, the clearance of cerebral ISF and Aβ could be investigated as a function of brain activity.

It is set out to develop a three-dimensional model for the global clearance of ISF and Aβ from the human brain. This future challenge could be met by employing a similar modelling approach to that in Chapter 3 to consecutive sections of the entire human brain, including coronal and transversal sections. Such a model will have far-reaching applications, as it could be employed for studying the clearance of other solutes from the brain (e.g. the tau protein which is the other hallmark of AD) or the distribution of drugs delivered to the brain.

Chapter 4. An attempt to build a model for active cerebral arteries based on previously employed methods was presented. Here, again, issues are raised by limited experimental data for the biomechanics of contractile cerebral arteries. The previous models of cerebral arteries have only considered the passive response (when the VSMCs are fully relaxed), while the few experimental studies that assessed the active response of cerebral arteries did not provide sufficient details about the reference state of the system. This hinders development of a non-linear elastic model that differentiates between the undeformed (reference) and the deformed state of the active artery. In the end, a compromise was made. The passive response of cerebral arteries was validated by experimental data on rat middle cerebral arteries [22], while the active response of cerebral VSMCs was assumed equal to that of the VSMCs from the carotid artery [140]. The elastic deformation of the arterial wall determined in Chapter 4 served as input in the multi-scale model from Chapter 5.

Future directions. Models of active cerebral arteries could be used to study processes of high importance for the brain, such as neurovascular coupling (the influence of brain activity on the contractile levels of the arteries), cerebrovascular
ageing, or, as it was shown in Chapter 5, vascular clearance of solutes from the brain. It is hoped that these important problems motivate the community of experimentalists to consider also active cerebral arteries in their work. In the end, any model, regardless of how sophisticated is, becomes valuable only when it is coupled with experiments.

Chapter 5. A mechanistic analysis of the role of cerebral arteries in the clearance of fluid from the brain was presented in Chapter 5. The V-IPAD model was motivated by the counter-intuitive reports of intramural periarterial flows out of the brain against the direction of arterial pulsations [10, 29]. The objective was to identify what process may occur in the brain under normal conditions in the opposite direction to arterial pulsations. Consequently, the cerebral vasomotion was proposed and modelled as the driving force for the transport of solutes along the cerebrovascular BMs. The removal rate of the vasomotion-driven IPAD mechanism compares well with the clearance observed experimentally in [29, 164]. This has shifted the view from a heart-driven clearance of the brain to an intrinsic mechanism of cerebral arteries (e.g. vasomotion-driven IPAD).

Future directions. Although there is supporting evidence that failure of the V-IPAD mechanism could explain the vascular deposition of Aβ as CAA, the hypothesis of vasomotion-driven IPAD requires more direct experimental validation. If validation is obtained, then the model could be further developed for investigating the effect of aging (e.g. changes in arterial elasticity) on the IPAD clearance of solute from the brain. Such progress will be possible given that the vasomotion activation wave from the V-IPAD model allows alterations that capture the effect of ageing.

The V-IPAD model showed that the contractions of the VSMCs are strong enough to induce net intramural periarterial flow rates of significant magnitude for efficient transport of fluid along the IPAD routes, but the predominant direction of vasomotion remains elusive. Non-invasive techniques such as the diffusion tensor MRI could detect the fluid presence and directionality in the intramural and perivascular spaces of surface cerebral arteries, although owing to resolution limitations, it may be difficult to differentiate between various compartments filled with similar fluids (e.g. the BM within the arterial wall filled with ISF and the perivascular spaces of leptomeningeal arteries filled with CSF). Multi-photon microscopy allows in vivo visualisation of penetrating cerebral arteries, hundreds of micrometres deep into the rodent cortex [128, 158],
whereas optical-spectroscopy can detect the vasomotion waves spreading across the cerebral cortex even in humans [112]. Coupling such imaging techniques of cerebral vasomotor processes with studies of Aβ clearance from the brain, could offer useful insights about the force generators behind the IPAD mechanism.

Further on, vasoactive agents that modulate the oscillations in the contractile state of VSMCs may represent potential therapeutic approaches for CAA. It is hoped that the high potential of the VSMCs in the clearance of the brain, brought to light by the V-IPAD model from Chapter 5, stimulates future experiments that account for the active tone of cerebral arteries. For example, it has been previously found that administration of the vasoactive drug cylostazol improved the efficacy of the IPAD mechanism in mice [112]. Therefore, the search for other vasoactive agents with similar properties is worth continuing.

Bringing it all together, the puzzling effect of the IPAD process on the dynamics of cerebral ISF (found in Chapter 3) raises questions about the time response of the IPAD mechanism and its actual physiological role. Although the cerebral vasomotion could provide the necessary force for the fast-acting IPAD mechanism (as shown in Chapter 5), it remains to be further investigated if this is actually a predominantly occurring physiological process in the human brain. From the transport model of Aβ, it appear obvious that the dominant transport mechanism of Aβ out of the brain is efflux at the BBB. Moreover, the Aβ transport out of the brain by ISF flow via alternative pathways becomes increasingly important when Aβ efflux across the BBB fails. Therefore, solving the mechanisms for ISF transport into, through and out from the brain remains of great importance.

The ISF may be cleared from the brain by bulk flow through the brain tissue towards the CSF compartments and along the IPAD pathways towards the cervical lymph nodes. As shown in Chapter 3, the former mechanism alone appears to be able to remove ISF from the brain at a pace comparable with the secretion rate of ISF into the brain across the BBB, leading to physiological intra-cerebral pressures. However, this mechanism is not fast enough compared to the Aβ production rate by the normal brain and, when acting alone, produces pathological Aβ concentrations in the brain tissue. This implies that faster-acting mechanisms for the co-transport of Aβ and ISF out of the brain are required in order to prevent Aβ accumulation in the brain tissue, especially when protein clearance across the BBB fails. In such a situation, the IPAD mechanism can significantly slow the cerebral Aβ
deposition. A surprising effect (e.g. high negative intra-cranial pressure) was observed when a sink IPAD term acting over 3 hours was included in the model from Chapter 3. However, if the IPAD mechanism acts more slowly (e.g. over 15 hours), more reasonable interstitial pressure values are found and the parenchymal Aβ deposition is also decreased. Based on the results from Chapter 5, the vasomotion-driven IPAD can facilitate elimination of significant amounts of ISF within 15 hours. These modelling results suggest that the IPAD mechanism, contributing to the clearance of ISF and soluble Aβ from the brain, takes longer than previously suggested (e.g. between 30 min and 3 hours) by the experiments of Carare et al., [29]. Although a full explanation for the accumulation of Aβ within the brain cannot be provided at this stage, mathematical and computational models similar to those developed in this thesis are useful for testing the plausibility of various clearance mechanisms of the brain.

This thesis started off with the aim of enhancing our understanding about how cerebrovascular aspects could play a role in the pathology of AD. It has become clearer that the frontiers between brain neurodegeneration and vascular disorders are vanishing. Given that the brain tissue remains mainly a black box allowing for limited experimental access, the cerebrovascular response, which is more experimentally accessible, could provide insights about the state of brain tissue. Mathematical and computational models of cerebrovascular mechanisms, coupled with state of art imaging techniques, could significantly contribute towards tackling various brain disorders.
Appendix A

Chapter 3: parameter details

The physiological parameters used in Chapter 3 are discussed below and listed in Table 3.4. The particular coronal section of the human brain used in this model contains 60% grey matter and 40% white matter. It is noted that the relative amount of grey and white matter may vary in different coronal sections of the brain and a more detailed consideration of regional differences is left for future work. The density and viscosity of ISF occupying the brain interstitium is considered similar to that of water, e.g. $\rho = 1 \text{ g} \cdot \text{cm}^{-3}$ and $\mu = 10^{-3} \text{ Pa} \cdot \text{s}$.

The permeability of the brain tissue is 100-fold higher in the white matter compared to the grey matter, as it was approximated in the computational study [160]. The hydraulic conductivity of the capillaries ($L_p$) was estimated within the range of $0.8 - 2 \cdot 10^{-9} \text{ cm} \cdot \text{s}^{-1} \cdot \text{cmH}_2\text{O}^{-1}$ in the rabbit and the frog brain [58]. A summary of the reported values is presented by [26]. A value of $L_p = 2.6 \cdot 10^{-9} \text{ cm} \cdot \text{s}^{-1} \cdot \text{cmH}_2\text{O}^{-1}$ ($L_p = 2.6 \cdot 10^{-11} \text{ cm} \cdot \text{s}^{-1} \cdot \text{Pa}^{-1}$) was found for the BBB in the human brain [130]. The capillary surface area per unit volume of brain tissue was found to be $S_V = 100\text{-}150 \text{ cm}^{-1}$ in the grey matter and one third of this value in the white matter [162]. Hence, a value of $L_p^{SV} = 2.6 \cdot 10^{-9} \text{ s}^{-1} \text{ Pa}^{-1}$ is taken for capillaries in the grey matter and $L_p^{SV} = 0.85 \cdot 10^{-9} \text{ s}^{-1} \text{ Pa}^{-1}$ for capillaries in the white matter.

With respect to the secretion of ISF by the cerebral capillaries, the reflection coefficients are considered to be $\sigma_{\text{oedetic}} = \sigma_{\text{ions}} = 1$, which means that the capillary wall is totally impermeable to proteins and solutes [99]. Therefore, both the oncotic and osmotic pressure gradients influence the transvascular flow of water.
The metabolic volumetric source term is calculated using a constant production rate of metabolic water of 60 ml · day\(^{-1}\) by the entire human brain [79]. [88] reported that the extraction of oxygen and the glucose oxygenation is three-fold higher in the grey matter compared to the white matter. Taking all this into account, together with the volumetric fraction of the grey (0.6) and white matter (0.4) for the particular coronal section of this study, yields a metabolic volumetric source of 6.2 \(\cdot 10^{-7}\) cm\(^3\) · s\(^{-1}\) cm\(^{-3}\) in the grey matter and of 3.1 \(\cdot 10^{-7}\) cm\(^3\) · s\(^{-1}\) cm\(^{-3}\) in the white matter.

Given that the grey matter contains most of the cell bodies of the brain responsible for producing A\(\beta\), it is assumed that the soluble A\(\beta\) is produced only in the grey matter at a constant rate of 3 \(\cdot 10^{-12}\) g · cm\(^{-3}\) · s\(^{-1}\). This value is calculated based on the normal level of total soluble A\(\beta\) concentration in the grey matter of 6.4 ng · g\(^{-1}\) reported by [176] for the human brain and the half-life \((t_{1/2})\) of 25 min for the total clearance of A\(\beta\) from the rodent brain reported by [157]. The decay rate corresponding to \(t_{1/2} = 25\) min is 0.028 min\(^{-1}\). Multiplication of the decay rate with the concentration of A\(\beta\) in the brain tissue yields the total clearance rate of A\(\beta\) by the unit volume of brain tissue. The assumption that the total clearance of A\(\beta\) from the brain equals the total production of A\(\beta\) in the brain is made. The study [145] used the same concentration of A\(\beta\) for calculating the total clearance rate of A\(\beta\) from the human brain. However, the employed decay rate of 0.14 hrs\(^{-1}\) was based on samples of CSF from the lumbar spinal region. It is known, however, that only one fraction of the total cerebral A\(\beta\) reaches the spinal CSF [165]. Therefore, the values reported in [115] should only be seen as the efflux rate of A\(\beta\) into the spinal CSF, rather than the total clearance rate by all contributing mechanisms.

In healthy brains, the volume fraction of the brain interstitium (i.e the porosity) is commonly taken to be 0.2, which means that the interstitium occupies 20% of the total brain tissue [125]. However, regional differences may exist across the entire brain tissue. The human cortex (region of grey matter) was found to have a porosity of 0.24, while the corpus callosum (bundles of white matter fibres) has a porosity of 0.21 [163]. Here, it is taken \(\phi_g = 0.24\) and \(\phi_w = 0.21\). The diffusion of soluble 4.5 kDa A\(\beta\) through the brain interstitium differs in the grey and white matter, due to the different levels of tortuosity of these regions. Based on the experimental values reviewed in [163], the effective diffusion coefficient for A\(\beta\) is calculated to be \(8.5 \cdot 10^{-7}\) cm\(^2\) · s\(^{-1}\) in the grey matter and \(10 \cdot 10^{-7}\) cm\(^2\) · s\(^{-1}\) in the white matter, respectively.
The pressure and the $\alpha\beta$ concentration in the CSF compartments are taken from [109] and [118], respectively. By employing image-based computational modelling, the study [109] showed that even a very small pressure difference between the lateral ventricles and SAS, i.e. a transmantle pressure of 10 Pa (0.07 mmHg), is enough to drive CSF flow through the ventricular system towards SAS of the human brain. The minimum and the maximum values of the CSF pressure within the lateral ventricles to be 490 Pa and 517 Pa, respectively, were calculated under normal conditions of the human brain. Accordingly, here the pressure in the lateral ventricles is assumed to be $p_v = 517$ Pa (3.87 mmHg) and the pressure in the SAS $p_s = 507$ Pa (3.80 mmHg). The concentrations of $\alpha\beta$ in the lateral ventricles and in the SAS are assumed equal and the value of $9.8 \cdot 10^{-9}$ g·cm$^{-3}$ is taken from [118] who assessed the levels of $\alpha\beta$ in CSF in healthy patients and in patients with AD.
Appendix B

Chapter 4: mathematical details

B.1 3D axisymmetric deformation of a linear elastic artery

This problem may be seen as a toy model that is useful for understanding which simplifications are reasonable in order to make the non-linear elastic model from Section 4.3 analytically tractable. In this section, a novel three-dimensional mathematical model is developed for a linear elastic incompressible artery which undergoes axisymmetric deformations in the radial (circumferential) and axial direction, respectively.

Consider an elastic artery represented as a linearly elastic cylinder of radius \( r_i \leq r \leq r_o \) and length \( L \). The elastic cylinder undergoes deformations under the action of an arterial pressure \( P_a(z,t) \) applied on the inner boundary. The arterial pressure is allowed to vary along the z-axis. The system is quasi-steady (i.e. has no time derivatives but may depend on time through the boundary conditions) and has no body forces. Thus, the Cauchy momentum equations, in index notation, take the form

\[
\frac{\partial \tau_{ij}}{\partial x_j} = 0, \quad (B.1)
\]

where \( \tau_{ij} \) represents the Cauchy stress tensor. For small deformations, it is acceptable to model the arterial wall as a linear elastic material, for which the linear stress-strain constitutive equation is

\[
\tau_{ij} = 2\mu e_{ij} + \lambda(e_{kk})\delta_{ij}, \quad (B.2)
\]
where the linearised strain tensor $e_{ij}$ is defined by

$$e_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right). \quad (B.3)$$

Here $u$ is the displacement and $\lambda, \mu$ are the first Lamé constant and the second Lamé constant (also known as the shear modulus), respectively [83].

Substituting equations (B.2)-(B.3) into (B.1) leads to the Navier equation, also known as the Lamé equation [83]

$$0 = (\lambda + \mu) \nabla (\nabla \cdot u) + \mu \nabla^2 u \quad (B.4)$$

The arterial wall is considered a nearly incompressible material, given that $\lambda >> \mu$

$$\frac{\lambda}{\mu} = \frac{1}{\epsilon} \quad (B.5)$$

where $\epsilon$ is a small parameter. For $\epsilon << 1$, it is expected that the $\nabla \cdot u$ will be of order $\epsilon$. This motivates the introduction of the scalar function $p_\epsilon$

$$p_\epsilon = -\lambda \nabla \cdot u \quad (B.6)$$

which has magnitude $O(\mu)$. The scalar function $p_\epsilon$ represents the isotropic hydrostatic pressure in the arterial wall and is determined from the governing equations and boundary conditions of the problem. Hence, in the limit $\epsilon << 1$, the Navier equation becomes

$$0 = -\nabla p + \mu \nabla^2 u, \quad (B.7)$$

along with the incompressibility constraint

$$\nabla \cdot u = 0, \quad (B.8)$$

where $p_\epsilon \to p$ as $\epsilon \to 0$. Moreover, the stress-strain constitutive equation takes the form

$$\tau_{ij} = 2\mu e_{ij} - p\delta_{ij}, \quad (B.9)$$
B.1. 3D AXISYMMETRIC DEFORMATION OF A LINEAR ELASTIC ARTERY

Problem in cylindrical polar coordinates

Consider a radial symmetric deformation of the cylinder, i.e. deformation with no \( \theta \)-dependence, in response to the applied pressure. The resulting displacement has the form

\[
\mathbf{u} = u_r(r,z)\mathbf{e}_r + u_z(r,z)\mathbf{e}_z. \quad (B.10)
\]

The incompressibility condition (B.8) and the force balance condition (B.1) are given in cylindrical polar coordinates by

\[
\frac{\partial u_r}{\partial r} + \frac{u_r}{r} + \frac{\partial u_z}{\partial z} = 0, \quad (B.11)
\]

\[
\frac{\partial \tau_{rr}}{\partial r} + \frac{\tau_{rr} - \tau_{\theta\theta}}{r} + \frac{\partial \tau_{rz}}{\partial z} = 0, \quad (B.12)
\]

\[
\frac{\partial \tau_{rz}}{\partial r} + \frac{\tau_{rz}}{r} + \frac{\partial \tau_{zz}}{\partial z} = 0, \quad (B.13)
\]

where the non-zero stress components for an incompressible material described in terms of the cylindrical displacements are:

\[
\tau_{rr} = 2\mu \frac{\partial u_r}{\partial r} - p, \quad (B.14a)
\]

\[
\tau_{\theta\theta} = 2\mu \frac{u_r}{r} - p, \quad (B.14b)
\]

\[
\tau_{zz} = 2\mu \frac{\partial u_z}{\partial z} - p, \quad (B.14c)
\]

\[
\tau_{rz} = \mu \left( \frac{\partial u_z}{\partial r} - \frac{\partial u_r}{\partial z} \right). \quad (B.14d)
\]

Boundary conditions

The arterial pressure \( P_a(z,t) \) is applied on the inner boundary \( (r = r_i) \) of the arterial wall, while zero traction is assumed on the outer boundary \( (r = r_o) \).

\[
\tau_{rr} \Big|_{r=r_i} = -P_a(z,t) \quad \tau_{rr} \Big|_{r=r_o} = 0. \quad (B.15)
\]

Further on, the following two remarks are made: (i) the flow-induced wall shear stress at the inner wall is several orders of magnitude smaller than the pressure-induced axial and circumferential (radial) stresses \([55]\); (ii) the tethering force from the surrounding tissue is neglected. Therefore, the boundary conditions for
the non-zero shear stress components become:

\[ \tau_{rz} |_{r=r_i} = 0 \quad \tau_{rz} |_{r=r_o} = 0. \quad (B.16) \]

**Nondimensionalisation**

Accounting for the difference in scale between the length and the radius of the artery, let us non-dimensionalise as follows:

\[ r = R\hat{r} \quad z = L\hat{z} \quad (B.17a) \]

\[ u_r = U\hat{u}_r \quad u_z = U\hat{u}_z \quad (B.17b) \]

\[ p = \frac{\mu U}{R} \hat{p} \quad P_a = \frac{\mu U}{R} \hat{P}_a \quad (B.17c) \]

\[ \tau_{rr} = \frac{\mu U}{R} \hat{\tau}_{rr} \quad \tau_{\theta\theta} = \frac{\mu U}{R} \hat{\tau}_{\theta\theta} \quad \tau_{zz} = \frac{\mu U}{R} \hat{\tau}_{zz} \quad \tau_{rz} = \frac{\mu U}{R} \hat{\tau}_{rz}. \quad (B.17d) \]

Substituting the above expressions into (B.11)-(B.16) and dropping the hats, the non-dimensional governing equations are obtained

\[ \frac{\partial u_r}{\partial r} + \frac{u_r}{r} + \delta \frac{\partial u_z}{\partial z} = 0, \quad (B.18) \]

\[ \frac{\partial \tau_{rr}}{\partial r} + \frac{\tau_{rr} - \tau_{\theta\theta}}{r} + \delta \frac{\partial \tau_{rz}}{\partial z} = 0, \quad (B.19) \]

\[ \frac{\partial \tau_{rz}}{\partial r} + \frac{\tau_{rz}}{r} + \delta \frac{\partial \tau_{zz}}{\partial z} = 0, \quad (B.20) \]

with boundary conditions

\[ \tau_{rr} |_{r=r_i} = -P_a(z,t) \quad \tau_{rr} |_{r=r_o} = 0, \quad (B.21) \]

\[ \tau_{rz} |_{r=r_i} = 0 \quad \tau_{rz} |_{r=r_o} = 0 \quad (B.22) \]

and stress components

\[ \tau_{rr} = 2 \frac{\partial u_r}{\partial r} - p, \quad (B.23a) \]

\[ \tau_{\theta\theta} = 2 \frac{u_r}{r} - p, \quad (B.23b) \]

\[ \tau_{zz} = 2\delta \frac{\partial u_z}{\partial z} - p, \quad (B.23c) \]

\[ \tau_{rz} = \frac{\partial u_z}{\partial r} - \delta \frac{\partial u_r}{\partial z}, \quad (B.23d) \]

where \( \delta = \frac{R}{L} \) is the aspect ratio of the artery. \( \delta \) is considered very small and the above equations are solved asymptotically.
Lubrication solution

In the light of the smallness of the parameter $\delta$, the dependent variables asymptotically are expanded as follows

$$u_z = \frac{1}{\delta} u_{z,0} + u_{z,1} + ..., \quad u_r = u_{r,1} + ..., \quad (B.24a)$$

$$\tau_{rr} = \tau_{rr,0} + \delta \tau_{rr,1} + ..., \quad \tau_{\theta\theta} = \tau_{\theta\theta,0} + \delta \tau_{\theta\theta,1} + ..., \quad (B.24b)$$

$$\tau_{zz} = \tau_{zz,0} + \delta \tau_{zz,1} + ..., \quad \tau_{rz} = \frac{1}{\delta} \tau_{rz,0} + \tau_{rz,1} + \delta \tau_{rz,2} + ..., \quad (B.24c)$$

$$p = p_0 + \delta p_1 + .... \quad (B.24d)$$

Substituting these expressions into (B.23) and taking the leading order terms, gives

$$\tau_{rr,0} = 2 \frac{\partial u_{r,1}}{\partial r} - p_0 \quad (B.25a)$$

$$\tau_{\theta\theta,0} = 2 \frac{u_{r,1}}{r} - p_0 \quad (B.25b)$$

$$\tau_{zz,0} = 2 \frac{\partial u_{z,0}}{\partial z} - p_0 \quad (B.25c)$$

$$\tau_{rz,0} = \frac{\partial u_{z,0}}{\partial r} \quad (B.25d)$$

By substituting the above into the governing equations (B.18)-(B.20), the incompressibility equation at the leading order is obtained in the form

$$\frac{1}{r} \frac{\partial}{\partial r} (ru_{r,1}) + \frac{\partial u_{z,0}}{\partial z} = 0 \quad (B.26)$$

and the $e_z$- component of the force balance equation at the leading order is given by

$$\frac{\partial \tau_{rr,0}}{\partial r} + \frac{\tau_{rr,0} - \tau_{\theta\theta,0}}{r} + \frac{\partial \tau_{rz,0}}{\partial z} = 0. \quad (B.27)$$

The $e_z$-component of the force balance equation at the first two leading orders becomes

$$\frac{1}{r} \frac{\partial}{\partial r} (r \tau_{rz,0}) = 0, \quad (B.28)$$

$$\frac{1}{r} \frac{\partial}{\partial r} (r \tau_{rz,1}) = 0, \quad (B.29)$$
with boundary conditions that come from (B.21) and (B.22):

\[ \tau_{rr,0}|_{r=r_i} = -P_a(z,t), \quad \tau_{rr,0}|_{r=r_o} = 0, \quad (B.30) \]
\[ \tau_{rz,0}|_{r=r_i} = 0, \quad \tau_{rz,0}|_{r=r_o} = 0, \quad (B.31) \]
\[ \tau_{rz,1}|_{r=r_i} = 0, \quad \tau_{rz,1}|_{r=r_o} = 0. \quad (B.32) \]

By solving (B.28)-(B.29) and applying the boundary conditions (B.31) - (B.32), it follows that

\[ \tau_{rz,0} = \frac{\partial u_{z,0}}{\partial r} = 0 \quad (B.33) \]
\[ \tau_{rz,1} = \frac{\partial u_{z,1}}{\partial r} = 0 \quad (B.34) \]

which implies that

\[ u_{z,0} = u_{z,0}(z,t) \quad (B.35) \]
\[ u_{z,1} = u_{z,1}(z,t). \quad (B.36) \]

Given that \( \tau_{rz,0} = 0 \), the \( e_r \)-component of the force balance equation at the leading order (B.27), becomes

\[ 2 \frac{\partial}{\partial r} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( ru_{r,1} \right) \right) = \frac{\partial p_0}{\partial r}. \quad (B.37) \]

By substituting (B.26) into (B.37) and recalling that \( u_{z,0} = u_{z,0}(z,t) \), it is noticed that \( \frac{\partial p_0}{\partial r} = 0 \) and so

\[ p_0 = p_0(z,t), \quad (B.38) \]

which allows us to solve equation (B.37). From this, the radial displacement at leading order is determined as

\[ u_{r,1} = f_1(z) \frac{r}{2} + \frac{f_2(z)}{r}, \quad (B.39a) \]
\[ 2 \frac{\partial u_{r,1}}{\partial r} - p_0 = -P_a(z,t), \quad r = r_i, \quad (B.39b) \]
\[ 2 \frac{\partial u_{r,1}}{\partial r} - p_0 = 0, \quad r = r_o, \quad (B.39c) \]

where the arbitrary functions \( f_1(z) \) and \( f_2(z) \) are determined from the boundary conditions (B.39b) and (B.39c), respectively. The boundary conditions (B.39b)
B.1. 3D AXISYMMETRIC DEFORMATION OF A LINEAR ELASTIC ARTERY

and (B.39c) represent just another form of the boundary conditions (B.30). This yields the expression of the radial displacement at the leading order

\[
u_{r,1} = P_a(z) \frac{r_i^2}{2 \left( r_0^2 - r_i^2 \right)} \left( r + \frac{r_0^2}{r} \right) + p_0(z) \frac{r}{2},
\]

(B.40)

Determining the tension in the vessel

Substituting the above expression for \( u_{r,1} \) into the incompressibility equation (B.26) yields

\[
\frac{d u_{z,0}}{d z} = -P_a(z) \frac{r_i^2}{(r_0^2 - r_i^2)} - p_0(z), \tag{B.41}
\]

where \( p_0(z,t) \) is still unknown. In order to determine \( p_0(z,t) \), we make use of the \( e_z \)- component of the force balance equation at the third order, namely

\[
\frac{1}{r} \frac{\partial}{\partial r} (r \tau_{rz,2}) = - \frac{\partial \tau_{zz,0}}{\partial z}, \tag{B.42}
\]

which satisfies the boundary conditions

\[
\tau_{rz,2} \big|_{r=r_i} = \tau_{rz,2} \big|_{r=r_o} = 0. \tag{B.43}
\]

Since \( u_{z,0} = u_{z,0}(z,t) \) and \( p_0 = p_0(z,t) \), the axial stress at the leading order becomes

\[
\tau_{zz,0} = \tau_{zz,0}(z). \tag{B.44}
\]

A solvability condition arises from multiplying equation (B.42) by \( r \) and integrating between \( r = r_i \) and \( r = r_o \)

\[
\left[ r \tau_{rz,2} \right]_{r=r_o}^{r=r_i} = - \frac{d \tau_{zz,0}}{d z} \frac{(r_o^2 - r_i^2)}{2} \tag{B.45}
\]

Applying the boundary conditions from (B.43) yields \( \frac{d \tau_{zz,0}}{d z} = 0 \). In other words, the axial stress at the leading order is constant

\[
\tau_{zz,0} = 2 \frac{d u_{z,0}}{d z} - p_0(z) = T. \tag{B.46}
\]

Here the constant \( T \) represents the axial tension per unit area in the arterial wall.

From (B.46), the isotropic pressure of the material \( p_0(z,t) \) is expressed in terms
of $T$

$$p_0(z) = -T + 2 \frac{du_{z,0}}{dz}. \quad (B.47)$$

By substituting (B.47) into (B.41), it is obtained

$$\frac{du_{z,0}}{dz} = \frac{T}{3} - \frac{P_a(z)}{3} \frac{r_i^2}{(r_0^2 - r_i^2)}. \quad (B.48)$$

Integrating (B.48) along the vessel length, gives

$$\int_{z=0}^{z=L} du_{z,0} = \int_{z=0}^{z=L} \left( \frac{T}{3} - \frac{P_a(z)}{3} \frac{r_i^2}{(r_0^2 - r_i^2)} \right) dz. \quad (B.49)$$

In order to solve (B.49), different boundary conditions could be applied.

**Boundary conditions I**

Equation (B.49) could be assessed for the particular case when the ends of the vessel are free to move, i.e. when $T \equiv 0$ and

$$\tau_{zz,0}|_{z=0} = \tau_{zz,0}|_{z=L} = 0 \quad (B.50)$$

**Boundary conditions II**

For the particular case when the artery is fixed at both ends, as in most experimental procedures when the artery is excised and studied *in vitro*, the boundary conditions

$$u_{z,0}|_{z=0} = u_{z,0}|_{z=L} = 0 \quad (B.51)$$

are applied to (B.49) and give

$$T = \frac{r_i^2}{L(r_0^2 - r_i^2)} \int_{z=0}^{z=L} P_a(z) dz. \quad (B.52)$$

For a particular arterial pressure, the constant tension can be determined from (B.52). The arterial pressure causes circumferential expansion and longitudinal
B.2 MATHEMATICAL DETAILS NON-LINEAR ELASTICITY

retraction of the artery. However, when the ends of the artery are held fixed, the positive tension $T$ counteracts the longitudinal retraction.

Determining the displacements and stresses in the arterial wall

Once $T$ is determined, all the stress components at the leading order from (B.25) are calculated

\[
\begin{align*}
\tau_{rr,0} &= \frac{P r_i^2}{r_o^2 - r_i^2} \left(1 - \frac{r_o^2}{r_i^2}\right) \quad \text{(B.53a)} \\
\tau_{\theta\theta,0} &= \frac{P r_i^2}{r_o^2 - r_i^2} \left(1 + \frac{r_o^2}{r_i^2}\right) \quad \text{(B.53b)} \\
\tau_{zz,0} &= T \quad \text{(B.53c)} \\
\tau_{rz,0} &= 0 \quad \text{(B.53d)}
\end{align*}
\]

with $r_i \leq r \leq r_0$.

An expression for $p_0(z, t)$ is obtained by substituting (B.48) into (B.47)

\[
p_0(z, t) = -\frac{2}{3} P_a(z, t) \frac{r_i^2}{r_o^2 - r_i^2} - \frac{T}{3}.
\]

The extra unknown $p_0(z, t)$ introduced in order to satisfy the incompressibility constraint is, therefore, determined. Hence, the radial $u_r(r, z, t)$ and axial $u_z(z, t)$ displacements at the leading order can be calculated from (B.40) and (B.41), respectively, for different sets of boundary conditions.

B.2 Mathematical details non-linear elasticity

The calculations below show the deduction of the stress-strain relationship between the principal Cauchy stress and the principal Green strain from Section 4.1. The polar decomposition from equation (4.9) is rewritten in index notation as

\[
F_{ij} = M_{ki} R_{lk} \Lambda_{lm} R_{mj},
\]

where $M_{ki} = M_{ik}^T$ and $R_{lk} = R_{kl}^T$.

By considering the definition of the first Piola-Kirchhoff stress tensor from
and applying the chain rule, it is noticeable that

\[ T_{ij} = \frac{\partial W}{\partial F_{ij}} = \frac{\partial W}{\partial \Lambda_{lm}} \frac{\partial \Lambda_{lm}}{\partial F_{ij}}, \]

(B.56)

where \( \Lambda = R M F R^T \) or \( \Lambda_{lm} = R_{lp} M_{pq} F_{qr} R_{mr} \),

with the remark that \( R_{mr} = R_{rm}^T \).

Substituting (B.55) in (B.56), gives

\[ \frac{\partial W}{\partial F_{ij}} = \frac{\partial W}{\partial \Lambda_{lm}} R_{lp} M_{pi} R_{mj}. \]

(B.57)

After rearranging the indices, the above expression becomes

\[ \frac{\partial W}{\partial F_{ij}} = M^T R_{pi} R_{pl} \frac{\partial W}{\partial \Lambda_{lm}} R_{mj}, \]

(B.58)

which in tensor notation appears as

\[ \frac{\partial W}{\partial F} = M^T R^T \frac{\partial W}{\partial \Lambda} R. \]

(B.59)

Substituting expression (B.59) and the transpose of (B.55) in (4.31), the following expression for the Cauchy stress tensor is obtained

\[ \sigma = \frac{1}{\det F} M^T R^T \frac{\partial W}{\partial \Lambda} R R^T \Lambda M, \]

(B.60)

which reduces to

\[ \sigma = \frac{1}{\det F} M^T R^T \frac{\partial W}{\partial \Lambda} \Lambda M. \]

(B.61)

For an incompressible material, \( \det F = 1 \). Recalling that \( R \) and \( M \) are orthogonal matrices, their product may be regarded as a single rotation acting on \( \frac{\partial W}{\partial \Lambda} \). In addition, it should be accounted for the fact that under the change of coordinate system, the Cauchy stress tensor transforms as a contravariant tensor:

\[ \sigma' = A \sigma A^T, \]

(B.62)

where \( \sigma' \) represents the corresponding Cauchy stress tensor in the new coordinate system and \( A \) is a rotation matrix. Thus, it is implied that \( \frac{\partial W}{\partial \Lambda} \) represent the components of the Cauchy stress tensor in a new coordinate system. Given that
\( \Lambda \) is a diagonal matrix comprised of the principal stretch ratios, the rotation from (B.62) orientates the axes of the system with the principal directions. The eigenvalues corresponding to the eigenvectors of the Cauchy stress tensor parallel to the principal directions define the principal stresses

\[
\sigma_i = \lambda_i \frac{\partial W}{\partial \lambda_i}, \tag{B.63}
\]

Considering the relationship between strains and stretches from (4.21) and by applying the chain rule, the constitutive relation between the Cauchy stress and the Green strains is given by

\[
\sigma_i = \lambda_i \frac{\partial W}{\partial E_i} \frac{\partial E_i}{\partial \lambda_i} = \lambda_i \frac{1}{2} \frac{\partial W}{\partial E_i} \frac{\partial (\lambda_i^2 - 1)}{\partial \lambda_i} = \lambda_i^2 \frac{\partial W}{\partial E_i}. \tag{B.64}
\]
Bibliography


