“Non-linearities and upscaling in porous media“

Master’s Thesis

Dimensionless analysis of convection enhanced drug delivery to brain tissues

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Chapter 1

Introduction

1.1 Motivation

The human central nervous system is a very interesting part of the human body, in which the brain plays a vital role. To fulfil its role, the brain needs a very stable environment and a good protection against, for example, chemical disturbances. However the brain is also very fragile, any disturbance can have large effects. Among the most disastrous disturbances are brain tumours. Even though there is much ongoing research, a cure for brain tumours or even extending for the remaining life span of patients has still not been found, making the prognoses for brain tumour not good at best.

The main problem of brain tumours is getting the therapeutic agent where it is supposed to be. This is a difficult process as there are several obstacles. First of all, the blood brain barrier (BBB) is a magnificent barrier preventing most drugs from entering the brain. Groothuis (2000) gives an example of the difference of the concentration of immunoglobulin that will cross a liver capillary compared to a brain capillary; the result is an 8-log difference showing the effect of the BBB. Furthermore, the human body acts as a very effective sink term in the transport equation of the drug as most of the drug will be absorbed by other tissues than the cancer tissue. Only a minuscule fraction of the drug circulating in the body can be found in the brain, and even less in the tumour. Increasing the dose is not an option as the functioning of normal tissue will also be affected. Therefore, the toxic limit of the particular drug in question has to be taken into account, and so the concentration cannot be raised high enough to create an effective concentration in the brain.

A promising method to resolve this problem is called convection enhanced delivery (CED). In CED, a catheter is directly put into the brain tissue to avoid the blood brain barrier and to inject the therapeutic agent immediately where it is supposed to be. This, however, needs extended knowledge about the brain tissue and the natural and CED induced flow processes in the brain. So in short, we need to know the pharmacokinetics of the drug, which depend on the brain flow and material properties, drug diffusional and degradation properties and the interaction between the brain and the drug. Therefore, these characteristics will be studied and discussed in this report with the use of a dimensionless analyses. Furthermore, two side studies are made: one to research the effect of backflow along a catheter and the other one to study the effect of a simplified solid tumour area on the flow and elasticity processes.
1.2 Short Overview of the Possible Solutions for Brain Tumours

Despite ongoing research, no ideal solution exists for a cure of brain tumours. Several drug delivery methods are known, but all have their advantages and disadvantages. Some of those methods are described below to give an idea of the variety of possible solutions.

One of the ways to increase the effectiveness of chemotherapy would be to increase the permeability in the blood brain barrier. The first approach to do this would be chemical modification. In chemical modification, the drug is enhanced to make it more lipid soluble, with the intent of increasing the drug transport through the BBB. This is a promising method. Although some of the drawbacks are that an increased lipid solubility to the BBB also increases the drug permeability to all other membranes over the body. Furthermore, chemical modification increases plasma protein binding giving the opposite effect, making it less likely to pass the BBB [Patel. 2009]. An alternative chemical modification method would be to disrupt the blood brain barrier to increase its permeability for all molecules by a hyperosmolar solution or chemical agents, this is often called “hyperosmolar blood brain barrier disruption”.

The second chemical approach is prodrug therapy. In this method, the drug is chemically modified to increase its capillary permeability or to increase its residence time. If the drug is in the brain, the prodrug will transform to its active state by an enzymatic reaction. This requires detailed studying of the pharmacodynamics (the study of drug effects and mechanisms of action) and pharmacokinetics (the study of the mechanisms of distribution of the drug) of each compound.

Another method would be to infuse the drug intraarterial (intraarterial administration), which gives the tissue around the artery an increased concentration. Despite the desired increase of concentration, it has major limitations: the tumour must reside in the artery distribution area and most drugs used for treating brain tumours do not have the ideal properties for intraarterial administration.

It is also possible to use a so called “Trojan horse”. This means that the drug is attached to a so called “vector” that can access a specific catalysed transport mechanism. So the drug will join the vector and ferry across the membrane. However, this is only possible for very specific drugs [Groothuis. 2000].

A well known “solution” to brain tumours is radiation therapy: Radiation therapy uses high energy light beams (X-rays or gamma rays) or charged particles (electron beams or proton beams) to damage cells of the brain and tumour. If enough damage is done to the chromosomes of a cell, it will spontaneously die or it will die the next time it tries to divide into two cells. An advantage of radiation is that it is a non-invasive treatment and it can be given repetitively over several weeks to months. It can be aimed specifically at the area where treatment is needed, minimising side effects for uninvolved tissues. Radiation therapy usually gives a uniform dose of radiation to the entire region affected by the tumour. There is only a small variation of the dose delivered to various parts of the tumour. Besides the obvious difficulties of tumour spreading for radiation therapy, there are more side effects, among the most common are fatigue, hair loss, reddening of the scalp, loss of appetite or a change in one’s sense of taste. The most noticeable and disastrous long term side effect is a slow decline in higher brain functions. It is unknown if this decline stabilises or continues declining [Irsa. 2011].

Another group of methods for enhancing the drug content is by injecting it directly into
the brain, avoiding the BBB [Groothuis. 2000]. These methods have a very different point of interest: instead of studying the influx rate across the BBB, the main interest is the drug movement in the brain itself and the forces by which it is controlled. The first option is to infuse the therapeutic agent into the subarachnoid space or into the lateral ventricle, called intrathecal (subarachnoid space) and intraventricular (lateral ventricle) drug administration. Both processes are dominated by the cerebrospinal fluid (CSF) bulk flow. This is ideal if the targeted area is in the subarachnoid space or close to the CSF-brain interface, but it will hardly reach the extracellular space. A method that could reach the extracellular space is micro-dialysis: the drug is inserted by biodegradable polymers (which give more control over the spatial distribution). However, the distribution of the drug occurs by diffusion in both methods, and will therefore only be effective for small volumes. Another possibility has already been mentioned: convection enhanced delivery. The main principle behind this method is that the drug is injected directly in the parenchyma space and is transported in the extracellular space, which makes the distribution process to be advection instead of diffusion due to the pressure gradient created by the injection. This allows the targeted area to be larger, but highly dependent on the location and hydraulic properties, like permeability and porosity, of the brain. These properties of the brain are still unknown to some extent and need to be studied. Although CED gives rise to other problems such as neurotoxicity and limits the composition of the infusate, this will not be targeted in this study as the focus is on the transport of the infusate and the properties of the brain.
Chapter 2

The Brain

This chapter describes a biological overview of the brain, starting in the micro scale and working its way up to the macro scale to get an understanding of the functions and the structure of the brain. Special focus is drawn to the blood brain barrier, because that is what made scientists think of alternative ways for obtaining the therapeutic agent in the brain.

2.1 Biological Overview of the Brain

The brain contains two types of cells: neurons (nerve cells) and glia (neuroglia). Neurons are specialised for electrical signalling over long distances. They usually consist of three main parts: the dendrite(s), an axon and a cell body (figure 2.1.1). The dendrites collect information which is processed and transmitted at the origin of the axon. The length of the axon can be a few micrometers or extend to about a meter.

The glia cells are quite different. They do not participate in electrical signalling, but have a supporting role for the neurons by maintaining the ionic milieu around the nerve cells,
modulating the rate of nerve signal propagation, modulating the uptake of signals, providing a scaffold for neural development and aiding in recovery from neural injury. Glia cells have "tentacles" as well, but are less prominent and more radially symmetric (figure 2.1.1). Despite the fact that it is believed that they have a less important role in the central nervous system, they outnumber the neurons by 3 to 1 [Purves. 2008]. The axons from the neurons are gathered into tracts (called commissures if they cross the midline of the brain) that are more or less analogues to nerves in the periphery. Any region rich in the axons is called white matter, while any accumulation of cell bodies is called gray matter.

On a macro scale, the brain can be divided into four major brain regions: cerebral hemisphere, diencephalon, brain stem and cerebellum (see figure 2.1.2). The cerebellum is situated at the lower back of the brain and coordinates the skeletal muscles to smooth skeletal muscle movement. The brain stem is in front of the cerebellum and regulates the alertness by filtering out repetitive stimuli and transmitting important stimuli. Furthermore, it controls the blood flow system. The diencephalon is situated in the centre of the brain, it is, among other things, involved in memory processing, emotional response, body temperature and water balance. Surrounding the diencephalon are the cerebral hemispheres that control the interpretation of sensory input, skeletal muscle activity and functions in intellectual and emotional processing. This is also where the conscious mind is found [Marieb. 2004].

All of these regions can be seen in their white and gray matter components. The cerebral hemispheres and cerebellum have an outer region of gray matter that surrounds white matter, whereas the cerebellum has regions of gray matter in the white matter. The diencephalon consists of three areas of gray matter, and the brain stem is gray matter surrounded by white
matter fiber tracts with some nuclei of gray matter embedded in the tracts. This classification into white and gray matter is important because they have completely different characteristics for fluid flow and transport processes.

2.2 The Blood Brain Barrier

The blood brain barrier (BBB) is unique, and only exists in the brain (see figure 2.2.1). Its main role is to maintain a constant milieu in the brain. The BBB is impermeable for most toxicants and enhances the transfer of some solutes between the blood and the brain. Essentially, the BBB is made up of very specialised walls of the capillaries. Normal capillary walls are made of endothelial cells. These endothelial cells provide an uninterrupted network of cells joined laterally by tight junctions (see figure 2.2.1) [Marieb. 2004]. The difference between the blood brain barrier and normal capillaries is that the tight junctions in normal capillary walls are incomplete and leave gaps (called inter-cellular clefts). These are wide enough for fluids and small solutes to cross the capillary wall. So the low permeability of the blood brain barrier is obtained by the non existence of the inter-cellular cleft in the capillaries which provide a complete network of endothelial cells, that is not found anywhere else in the body [Purves. 2008, Fernstermacher. 1984].

The permeation depends on the lipid solubility and size of the substance [Fernstermacher. 1984]. Substances that traverse the walls of the brain capillaries must move through the endothelial cell membranes. Nevertheless, some ions and molecules, for example glucose that is not readily soluble in lipids, pass the BBB quite easily. For these important ions and molecules, specific transporters exist in the capillary walls [Purves. 2008]. There are two processes for the movement through the endothelial cells: 1) dissolving in and diffusing through the membranes and cytoplasm of the endothelium and 2) combined carrier-mediated and diffusional transport across the same structures. Organic substances use either the first or the second process for transport.

Figure 2.2.1: Capillary of the brain with endothelial cell membranes [Purves. 2008].
Most drugs pass the blood brain barrier via the lipid membranes of the endothelial cells because the capillary wall does not contain large enough water-filled channels for aqueous diffusion and no transport system exists for drugs in the endothelial cells [Fernstermacher, 1984]. To obtain a net transfer, a drug must leave the aqueous medium on one side of the BBB, pass into the lipid matrix of the membrane and enter the aqueous medium on the other side of the BBB. This includes absorption into and release from a lipid phase at the membrane and aqueous diffusion across the cytoplasm. Alternatively the drug is absorbed by the membrane on one side of the BBB, diffuses around the circumference of the cell within the membrane and is released on the other side. Various macromolecules are blocked within the epithelial cell membranes by tight junctions, it is very possible that the same happens for most drugs. In all cases, transfer through the BBB depends strongly on the lipid solubility of the drug. This gives rise to a lipid/water partition hypothesis of drug entry in the central nervous system (CNS). The hypothesis postulates that the permeability of the BBB is proportional to the ability of the free drug to partition or distribute between lipid and aqueous media. This is shown by experimental studies using several different kinds of drugs, but deviations were also found.
Chapter 3

Flow and Transport Processes

The transport processes in the healthy human brain can be divided into natural processes and CED induced processes\textsuperscript{1}. The difficulty lies in the fact that not all processes are well understood, but enough is known about some of them to give a rude estimate about their characteristics to take them into account in the modelling.

3.1 Natural Flow Processes

Three important natural flow processes in the brain needs to be discussed: blood flow, cerebrospinal fluid flow and interstitial fluid flow.

The most obvious process is the beating of the heart which is a pulsatile flow from the heart through the vascular system. However, the blood flow is steady at the end of the arterial tree, and therefore it is possible to assume no pulsation, and thus a constant flow, in the capillaries of the brain [Marieb. 2004].

A more important flux is the cerebrospinal fluid (CSF) flowing from its production site (the ventricles), circulating around the ventricles and the subarachnoid space to return into the blood in the dural venous sinuses or taken up via cranial and spinal nerves into the lymphatic system (see figure 3.1.1). CSF is therefore found in and around the brain and it protects the brain against blows and other trauma. The brain floats in the CSF which results in a 97\% reduced brain weight and prevents the brain from crushing under its own weight [Marieb. 2004]. CSF consists mainly of water and is very close to blood plasma in composition (sometimes values from plasma are assumed if there is no information about CSF). The importance of CSF flow arises from its contact with the interstitial fluid (ISF) of the central nervous system. It is believed that an exchange in substances exist between those two, making CSF a second source for interstitial bulk flow and CSF possibly a very effective sink.

The current hypothesis of ISF flow is that it leaves the capillaries and is driven by an ionic gradient [Bulat. 2011]. The ISF flow, often called bulk flow, is not stagnant and not uniform either, as is pointed out by Abbott (2004). Bulk flow prefers easier travel paths such as white matter fiber tracts. Due to this and the narrow space between the cells within the neuropil

\textsuperscript{1}The flow and transport process discussed in this chapter only includes those of the healthy tissue and not the tumour tissue

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an area of dendrites, axon terminals and glial cells in the gray matter), ISF flow in the gray matter is very unlikely [Linninger. 2007].

Figure 3.1.1: CSF flow in the human brain [Hanna. 2011].

3.2 Capillary Dynamics

The diffusion process transports nutrients from the capillaries into the interstitial fluid. Diffusion is driven by a concentration difference of the nutrient in the capillary and the interstitial fluid. The diffusion also exist from the interstitial fluid to the capillaries for waste like carbon dioxide. A concentration gradient of the therapeutic agent causes a transport from the interstitial fluid into the vascular system. The transport through the capillary walls also depends on the hydrostatic pressure and colloid osmotic pressure.

Capillary hydrostatic pressure (or hydrostatic vascular pressure) is the pressure exerted by the blood on the capillary walls and tends to force fluids through the capillary walls. The actual hydrostatic pressure depends on the location because the pressure decreases towards the venous end of the capillary. The capillary hydrostatic pressure is in theory opposed by the interstitial fluid hydrostatic pressure acting from outside the capillaries on the capillary wall and pushing fluid inward. These two together are called the effective vascular pressure or effective pressure. The interstitial pressure can vary from slightly positive to slightly negative, it is commonly assumed to be zero [Marieb. 2004].

The force opposing hydrostatic pressure is called the colloid osmotic pressure and is created by the presence of large non-diffusible molecules in a fluid, such as plasma proteins, that are prevented from moving through the capillary membrane [Marieb. 2004]. The large molecules cannot pass the membrane and therefore draw water towards them and thereby create a capillary colloid osmotic pressure, or called oncotic pressure. The interstitial fluid has a much lower
amount of non-diffusible molecules and has a lower oncotic pressure. Unlike the hydrostatic pressure, the oncotic pressure does not vary on the location of the vein. This can cause changes in the concentration of the therapeutic agent.

3.3 CED Induced Flow Processes

The idea of CED is to create a flow away from the catheter. Depending on the properties of the injection location, the outward flow from the catheter has an isotropic or anisotropic distribution. CED causes a high pressure difference between the pressure at the location of the source and that of its surrounds. Although this pressure difference generates a flux, that is favourable for transport, it can also be harmful to the brain tissue as it cannot withstand high pressures. Another side effect of the injection is that the tissue around the catheter will be pushed away and leaves an “open” area around the tip of the catheter. The open area causes a flow along the catheter walls: called backflow. The influence of the injection of a therapeutic agent on the flow and transport processes are discussed in this chapter.

3.3.1 Backflow

Backflow is possible because the pressure increase not only drives the fluid into the brain tissue, it also generates a small annulus around the catheter allowing flow along the catheter walls. This can lead to the spreading of the therapeutic agent into regions of the brain where it is not intended to be, resulting in a smaller concentration in the targeted area.

The importance of backflow has been studied by Morrison et al. (1999). Their results show that the pressure in the annulus diminishes gradually with distance from the catheter tip so that relative partitioning into the gray and white matter volumes is mostly controlled by the regional hydraulic conductivity and regional annular surface area. The significance of these observations is that a flow rate too large injected into a gray matter area will lead to leakage to nearby white matter regions, and perhaps to external leakage as well [Morrison. 1999].

The amount and shape of backflow depends strongly on the rate of infusion, the properties of the injected therapeutic agent, the cannula size, the catheter design and the targeted brain tissue (most importantly the hydraulic conductivity and elastic modulus). Allard et al. (2000) gives an overview of these characteristics and their effects on the volume of distribution. He states that a large volume of distribution will be reached if the catheter is placed into a region dominated by white matter and low infusion rate and a small catheter size is chosen. However, his findings cannot be generalised, because (1) sometimes white matter does not enhance the flow in the direction of interest (although gray matter still offers a more hydraulic resistance to bulk flow), (2) a high flow can rupture the brain tissue and, (3) a trade-off exists between the flow rate and the catheter diameter [Linninger. 2008].

Further, the backflow depends on the therapeutic agent that is inserted in the brain. A more viscous fluid tends to give a better convection and a larger volume of distribution. A lower viscosity of the injected fluid gives rise to more backflow [Mardor. 2005].

It is also possible to vary the catheter design, or using a micro-fluidic device [Neeves. 2006]. Another possibility would be to use a catheter with multiple ports to increase the volume of distribution and decrease the pressure. A multiport catheter generates an elliptical distribution of the therapeutic agent. However, research show that the at a large distance, the distribution was spherical for both the single port catheter and the multiport catheter [Morrison. 2007].
3.4 CED Generated Transport Processes

A direct injection of the therapeutic agent into the interstitial space of the brain causes two kinds of transport processes.

First, the drug will start to diffuse away from the injection location. For a small flow and/or a long modelling time, this could be important. The rate of diffusion depends on the characteristics of the drug. The interaction rate is also drug dependent. Evidence exist that the uptake of the drug by brain and tumour cells happen by passive diffusion [Begleiter. 1977].

Due to the increased interstitial fluid pressure, there is an increased outflow of interstitial fluid into the capillaries. The pressure difference generates a fluid flow and the concentration difference generates a diffusion across the capillary walls. This is often modelled by a form of Starling’s law [Morrison. 1994, Netti. 1997].
Chapter 4

Cancer Cells, Tumour Characteristics and the Therapeutic Agent

Brain tumours are well known and feared in western civilisation due to their high mortality rate and unpredictability. In the past, cancer has been diagnosed as being a cell growth disorder. However, the disorder has no logical pattern, no coordinated process or sequence that makes a normal cell into a cancer cell. Benign neoplasms\(^1\) are relatively harmless local phenomena that are often encapsulated, push their surroundings away, grow slowly and seldom kill their host. Malignant neoplasms (mostly called cancer) are a different kind of phenomenon. They grow relentlessly, they are nonencapsulated and often lead to the death of the host. Cancer cells resemble immature cells and invade their surroundings rather than pushing pressure on it. Cancer cells evade apoptosis\(^2\). They are insensitive to anti-growth signals and sustain angiogenesis [Hanahan. 2000]. A very destructive characteristic is their ability to break away from the primary tumour and travel to other body organs through the vascular or lymphatic system. The spreading of the tumour cells is called metastasis. Cancer cells consume an extraordinary amount of the body’s nutrients, leading to the well known weight loss [Marieb. 2004].

What actually causes the mutations that leads normal cells to transform to cancerous ones? It is well known that several factors like smoking and radiation stimulate cancer by causing mutations in the genes. They are often called carcinogens (cancer causers) and have a large effect on so called proto-oncogenes, which are genes that are essential for the cell division, growth and other things. They are, however, very fragile and are converted into oncogenes by the carcinogens, which could result in the failure to code for certain proteins\(^3\) and thus

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1. The cells from a rapid grow stage due to the cell growth disorder are called neoplasm.
2. Apoptosis is the process of programmed cell death.
3. The basic structural material of the body with a wide variety of functions like transport and body defence. Proteins are biological macromolecules consisting of polypeptides folded according to a genetic determined sequence.
leading to the loss of enzymes\textsuperscript{4} that control metabolic processes\textsuperscript{5}. Another important type of genes are called the tumour suppressor genes or anti-oncogenes. They suppress cancer by inactivating carcinogens, aiding DNA repair, or enhancing the immune system. The loss of a specific suppressor gene can have dramatic effects on the regulation of cell division. An important conclusion from this behaviour is that the rapid growth that is so characteristic of cancer is already in our genes [Marieb. 2004].

4.1 Brain Tumour Characteristics and their Relation to Life Span Prognoses

The most common brain tumour is called a glioma, because it rises from the more abundant glia cells. This particular brain tumour has a well vascularised region, extensive semi necrotic areas and a full necrotic region. The area affected by a brain tumour also suffers from hypoxia (a part of the body suffers from a lack of oxygen) and the blood brain barrier is disturbed.

Like all tissues and organs in the human body, a tumour consists of vascular, interstitial and cellular spaces, but large differences exist in the structure, composition and physiology. Experiments indicate that tumours have a necrotic core, a no well-defined lymphatic network, very active cellular growth and remodelling, which may lead to an increase in temporal heterogeneities in cellular and vascular density. If the timescale of the CED infusion process is taken into account, the temporal heterogeneities can be neglected. The spatial heterogeneities in a tumour can be averaged out over a macroscopic scale [Netti. 1997].

The diffusion in or into brain tumours has been reported to be significantly lower than in normal brain tissue [Chen. 2010]. This is attributed to tumour infiltration and the destruction of the highly directional white matter fiber tracts. Determining the fractional anisotropy in MR imaging is a method to show this destruction of white matter fiber tracts. Chen et al. (2010) studied the difference between a brain tumour and normal brain tissue with diffusion tensor imaging (DTI). Their results indicate that patients having a tumour with lower apparent diffusion coefficient (ADC) have a shorter lifespan than patients having a tumour with a higher ADC. Furthermore, the diffusion is usually less restricted in the tumour compared to the brain stem indicating a destruction of the fibers. Another observation was that patients having a tumour with high anisotropic water diffusion have a faster disease progression, although the fractional anisotropy (FA) for brain tumours was still half the value of the normal brain stem. Interestingly, a higher baseline FA for the tumour causes a higher risk for the patient, while an increase in FA after radiation therapy increases the lifespan of the patients.

The different kinds of pressure existing in brain tissue are very different inside the tissue of the brain tumour. The interstitial pressure of tumours is much higher than in normal brain tissue making it harder for a therapeutic agent to reach the centre of a brain tumour. Besides, the hydrostatic pressure and the oncotic pressure are different in brain tumours as well; both are increased compared to normal brain tissue [Stohrer. 2000]. Previously, the oncotic pressure was assumed to be the same, but Stohrer et al. (2000) used a method to measure the oncotic pressure directly, and got different results. Both elevated pressures may

\textsuperscript{4}Proteins that have the function to act as a catalysator.

\textsuperscript{5}These processes allow organisms to grow and reproduce, maintain their structures, and respond to their environments.
enhance the drug transport in the direction of the blood vessels and thus have a negative effect on the concentration of the therapeutic agent in the brain tumour.

Some of the parameters used in the model describing the brain tissue, like porosity (a larger porosity in the brain tumour), vascular hydraulic conductivity (slight increase in brain tumours) and the capillary surface (larger in brain tumours) are different for brain tumours as well [Smith and Humphrey. 2007, Soltani. 2011].

Besides, the characteristics of the tumour, it is important to account for the spreading and the possible regrowth after treatment, because this is what gets most people killed. It is important to cause cell death to all the tumour cells at the first try, because a regrown tumour can have very different characteristics [Saito. 2004]. The concept of convection enhanced delivery is ideal to reach these areas affected by the spreading, and cancel the regrowth.

4.2 Therapeutic Agent and its Characteristics

The previous chapter stated that one of the most common brain tumours is the glioma, therefore a search to find a possible anti glioma-cancer drug would be most productive. Several possibilities exist: Carmustine, Bevacizumab, Lamustine, Procarbazine and Semustine [Pharma Professional Services, Nicholson. 2001]. The drug used in the modelling is Carmustine and will be explained in more detail. The other possible drugs will not be discussed. Carmustine is chosen because it can also be used for malignant glioma and belongs to the most effective drug currently in use. Although it requires mentioning that one of the reasons for its effectiveness is its ability to cross the blood brain barrier [Chae. 2005, Begleiter. 1977], which is of course of less importance in this study. The chemical name is 1,3-Bis(2-Chloroethyl)-1-Nitrosourea and therefore often called BCNU, and the name BCNU will also be used in this report from now on. The chemical formula \((C_5H_9Cl_2N_3O_2)\) is stated below in figure 4.2.1.

BCNU has a synthetic origin and, due to its mechanism, belongs to the alkylating agents\(^6\). The mechanism of action of agents like BCNU involves the chemical conversion of the parent nitrosourea to highly active alkylating species (2-chloroethyl) diazene hydro-oxide and isocyanates. However, the precise method which the drug uses to causes cell death of the tumour cells is not yet fully understood [Begleiter. 1977, Weinkam. 1983, Levin. 1978]. It has been proven that low lipophilicity, high alkylating activity and rapid chemical transformation are necessary for effective anti-tumour activity. BCNU is usually dissolved first, in for example dichloromethane (DCM), before it is injected. Like all drugs, it is toxic in high dosage, for BCNU it is dangerous to have a higher concentration than 225 \(\mu\)g/g (which is a relative low toxicity concentration) in the tissue and the side effects can be quite severe. Possible irreversible side effects are pulmonary fibrosis\(^7\) and focal neurologic deficit\(^8\), and life-threatening effects such as fibrosing alveolitis\(^9\) and interstitial pneumonitis\(^10\). Furthermore, it is known that BCNU is drained out of the system quite fast and has a relative small half life (high degradation rate),

\(^6\)Alkylation is the transfer of an alkyl group from one molecule to another.

\(^7\)Pulmonary fibrosis is the scarring or thickening of the lungs without a known cause

\(^8\)Neurologic deficit is the impairment of a part of the central nervous system functions that affect a specific region of the body, for example, a weakness in one of the limbs.

\(^9\)Fibrosing alveolitis is a progressive form of lung disease in which fibrosing (the formation of excess fibrous connective tissue) of the supporting framework of the lungs occur.

\(^10\)Interstitial pneumonitis is a form of lung disease affecting the tissue and airspace around the air sacs of the lungs
resulting in small penetration depths due to diffusion. Whether this also has a large effect in an advection driven system is not known.

The uptake of BCNU has been reported to be a diffusion-controlled process and has been studied extensively [Begleiter. 1977, Levin. 1978, Mitsuki. 1991, August. 1988]. A useful result from the experimental study of Levin et al. (1978), is that the concentration in both the tissue and tumour increases linear with the dosage given. This indicates a linear relationship for the uptake versus the concentration. Most studies that have researched the diffusion of the therapeutic agent into the tissue are experimental data and describe uptake qualitatively. However, some have gone further and quantified the rate of uptake like Mitsuki et al. (1991), or the partition coefficient like Levin et al. (1978).

The same counts for the degradation, however more studies describe a half life ranging from 20 minutes to almost 2 hours [Fung. 1996, Fung. 1998, Pharma Professional Services]. However, the degradation curve for the interstitial space depends on the tissue in which the therapeutic agent is injected: for example, an injection in the vascular system will give a very different concentration-time relationship in the brain tissue than an injection directly into the brain tissue. The degradation curve for an injection in the vascular system will first show an increase of the therapeutic agent in the brain space followed by a decrease due to degradation. The increase of the therapeutic agent concentration is caused by the time it takes the drug to reach the interstitial space. While a direct injection in the interstitial space has a higher initial concentration, but will only decrease due to degradation.
Chapter 5

Magnetic Resonance Imaging

The magnetic resonance phenomenon was discovered in 1946, resulting in the development of NMR (nuclear magnetic resonance) in the period of 1950 till 1970 for the use of chemical and physical molecular analysis. The use of phase and frequency encoding was proposed in 1975, along with the Fourier transform in the magnetic resonance imaging, which is the basis of the current MRI technique. However a fully functioning MRI technique was not developed until 1992. The following sections provide a description of MRI.

5.1 The Concept of MRI

MRI is based on the spin property of molecules. Spin is the rotation of electrons, neutrons and protons around their own axis. It can take values of +1/2 and -1/2 depending on their direction, which let them acts as small magnets.

Two or more particles, with spins having opposite signs, can eliminate the observable manifestation of spin. If an external magnetic field ($B_0$) is applied, the spins of the molecules will align with the external field (parallel or anti-parallel), and circle around the axis of the field to describe a cone (see figure 5.1.1).

The anti-parallel state is called the high energy state and the parallel state is the low energy state. At room temperature, the low energy state slightly outnumbers the high energy state. A particle can change from its low energy state to the high energy state by absorbing a photon. However, the energy of this photon has to match the energy difference between the two states.

![Figure 5.1.1: Spin movement around an external field](image)

Figure 5.1.1: Spin movement around an external field [PMRI, 2011]
exactly. This energy ($E$) is related to the frequency ($v$), called resonance frequency in MRI, and the Planck’s constant ($h$) [Hornak. 2011]:

$$E = h \cdot v.$$ (5.1.1)

Whereby, the frequency depends on the gyromagnetic ratio ($\gamma$) and the magnetic field strength:

$$v = \gamma \cdot B_0.$$ (5.1.2)

So by applying a magnetic radio-frequency pulse, spins will absorb energy, transfer to the high energy state, and release that energy when they return to the lower energy state after the pulse is stopped. That emitted energy by the spins is observed in NMR spectroscopy. Magnetic resonance is the process that describes the interaction between spins and the external magnetic field [Hoa. 2011]. The observed signal depends on the population difference between the two states as well as on the natural and biological abundance of the isotope. The natural abundance is the fraction of nuclei having a given number of protons and neutrons, while the biological abundance is the fraction of one type of atom in the human body.

### 5.1.1 Relaxation Processes

If only an external field ($B_0$) is applied, a net magnetisation occurs which is called $M_0$. This net magnetisation is in the z-direction by definition and thus is called $M_z$. The x and y direction have a zero magnetisation in the $M_0$ state. It is possible to change the $M_0$-state by exposing the system to an energy with a frequency equal to the resonance frequency (called $B_1$ in figure 5.1.2) in the x-y plane, until $M_z$ is zero. The time it costs for the system to return the magnetisation of $M_z$ to its equilibrium value $M_0$ is called the spin lattice relaxation time ($T_1$), and is governed by the following equation [Hornak. 2011]:

$$M_z = M_0 \left(1 - e^{-t/T_1}\right).$$ (5.1.3)

When the magnetisation is applied on the x-y plane, it will rotate about the z-axis at a frequency equal to the frequency of the photon which has caused the transition of the energy levels. This is called the Larmor frequency.

In addition to the spin lattice relaxation, the net magnetisation (rotation around the z-axis) will start to diphase after applying the resonance frequency. This is because the nuclei will all experience a slightly different magnetic field and rotate at their own Larmor frequency. As a result, these magnetic fields with different frequencies will interact with each other, causing a dephasing that depends on the elapsed time. The time constant describing the return of the transverse magnetisation ($M_{xy}$) is the spin-spin relaxation time ($T_2$) [Hornak. 2011]:

$$M_{xy} = M_{xy0} \cdot e^{-t/T_2}.$$ (5.1.4)

These processes ($T_1$ and $T_2$) occur simultaneously, but $T_2$ is always equal to or less than $T_1$. So, first the $M_{xy}$ goes to zero after which the relaxation of $M_z$ will continue till it returns to $M_0$. Both processes are visible in figure 5.1.2.

The decay of the transverse magnetisation is caused by pure $T_2$ molecular effects and inhomogeneous $T_2$ effects (caused by variations in the magnetic field). The combined effects of both processes is defined by a new time constant $T_2^*$. The relationship between the $T_2$
Figure 5.1.2: Relaxation of the spin after the exposure of a pulse with the resonance frequency. The vertical direction is the spin lattice relaxation and the horizontal direction is the spin-spin relaxation. The magnetisation vector rotates by the angular frequency $\omega$ [Clare. 1997].

molecular processes and that from inhomogeneities in the magnetic field can be described as in equation 5.1.5.

$$\frac{1}{T_2} = \frac{1}{T_2^*} + \frac{1}{T_{2inhomo}}. \tag{5.1.5}$$

Every sample of molecules has a distribution of frequencies, of which only the Larmor frequency affects the relaxation times. As a consequence, everything that affects the distribution of the molecules in the human body, like temperature and viscosity, affects the $T_1$ relaxation time. However, the differences in temperature observed in the human body are too low to influence the frequency, but the viscosity has a large distribution and will affect $T_1$ greatly [Hornak. 2011].

### 5.1.2 Free Induction Decay

If a frequency pulse is produced in the x-y plane, it will result in a transverse magnetisation around the z-axis. This magnetisation transverse around the magnetic field $B_0$ as well, by definition. Since the magnetisation rotates in the x-y plane and because the signal is measured in one point, it will generate a sinusoidal signal. This signal decays in time due to the $T_2^*$ relaxation process (equation 5.1.6). The decaying sinusoidal signal is called the free induction decay due to the absence of a magnetic gradient. [Clare. 1997]

$$S/S_0 = e^{t/T_2^*}\cos(ft) \tag{5.1.6}$$

If the signal is repeated, it is possible to increase the signal to noise ratio. The amplitude depends on $T_1$ and the time between the repetitions; the repetition time ($T_R$).
5.1.3 k-space and Spatial Encoding

The MRI signal is stored in something called a k-space, which is similar to a Fourier plane. It contains all the data, but is impossible to read because it is unknown where the signal comes from. To obtain a two dimensional image several steps are made to determine the origin of the signal. This means that a signal needs to include information about the location of its origin. The first step is to apply a magnetic field gradient perpendicular to the slice of interest, so that every location experiences a unique magnetic field. Simultaneously, a radio-frequency wave is applied, with the same Larmor frequency as that of the protons in the desired slice plane. This causes a shift in the magnetisation of the protons on this plane only. As none of the spins located outside the slice plane are affected by the radio frequency wave (RF), they will not emit a signal. The amplitude of the signal is proportional to the number of spins in a plane perpendicular to the gradient [Hoa. 2011]. For further encoding, only the desired slice plane is used.

The second step is the phase encoding gradient which can be applied either in the vertical or in the horizontal direction. In this case, it is applied in the vertical direction. This gradient modifies the spin resonance frequency, including dephasing, so that the spins on the same row perpendicular to the gradient have the same spin. The spins in the other rows rotate with the same frequency, but in a different phase. The third step is to apply a frequency encoding gradient in the other direction than the spatial encoding, the horizontal direction. This modifies the Larmor frequency so that it creates columns whereby each column has a different Larmor frequency. The spins in one column have an identical frequency. This process results in a unique frequency/phase relationship for every location on the slice which is shown in figure 5.1.3[Hoa. 2011].
5.2 Diffusion Tensor Imaging

One of the application of MRI is called diffusion tensor imaging (DTI). This is used to obtain the diffusion coefficient of molecules in the human body. The basic principles of DTI comes from phase contrast angiography. Angiography is the imaging of blood flow in the arteries and veins of the body [Hornak. 2011]. It can be used to obtain the anisotropic coefficient, main diffusion direction and fiber tracking (tractography).

In phase contrast angiography a bipolar magnetic gradient pulse is applied. The characteristics of a bipolar gradient are that it starts with the gradient in one direction for a certain period of time followed by a pulse in the opposite direction for the same duration. A bipolar gradient pulse has no effect on stationary spins, but spins with a velocity component, especially in the direction of the gradient, will be affected. This is because the effects of the two gradient pulses will cancel each other out if the spin is stationary. The results is a signal for non-stationary spins and no signal for stationary spins. For diffusion imaging, the phase contrast angiography has to be upgraded to image a much slower motion of molecular diffusion. This can be done by a higher amplitude of the gradients and/or by increasing the separation between gradient pulses.

The extra set of gradients is usually applied in a spin echo sequence and is placed symmetrically around the 180 degree pulse. These gradients will not have an effect on stationary spins, but will diphase the magnetisation from spins that have diffused to a new location. A stationary spin will acquire a phase given by the first pulse, gets reversed by the 180 degree pulse, gets the same pulse in another direction that cancels the effect of the first gradient. The cancelling of the effect of the first pulse is not complete if the spin has moved, because the spin will be influenced by the second pulse differently than the first pulse due to the different location. This makes it possible to visualise the diffusion of the molecules. DTI is limited to the direction of the gradient, so it has to be applied in 3 directions at least. If applied to 6 directions it is possible to extract the diffusion tensor that synthesises to all the data [Hoa. 2011]. The signal ($S_i$) in direction $i$ is related to the diffusion in the same direction ($D_i$) by the following relationship [Hornak. 2011]:

$$S/S_0 = e^{-\left[G_i \gamma \delta \frac{\Delta - \delta}{3}\right]} = e^{bD_i}. \quad (5.2.1)$$

This equation shows that the degree of diffusion weighting of the sequence depends on three characteristics: a gradient amplitude or field gradient ($G_i$), the application time ($\delta$), and the time between two gradients ($\Delta$). The effects of these are combined in one expression: the b-factor $[s/mm^2]$ (see equation 5.2.1). A stronger gradient gives a greater b-factor. A greater b-factor has the advantage of avoiding the increase of the application time and time between two gradients. This would increase $T_E$ even more. $S_0$ is the signal in direction $G_i = 0$.

The diffusion coefficient is usually calculated from a plot showing:

$$\ln(S/S_0) \text{ versus } (G_i \gamma \delta)^2 \left(\Delta - \delta/3\right). \quad (5.2.2)$$

The underlying assumption in making a diffusion map is that the bordering voxels are connected if large diffusion in the same direction is visible [Hornak. 2011].

Diffusion sequences are highly sensitive to macroscopic motions (from the patients or vascular pulsations, etc). So sequences need to have strong diffusion gradients and fast imaging.
techniques. Furthermore, any gradient dependent artifact will differ in appearance, depending on the b-factor of the image. This will cause perturbed map calculations resulting in measurement errors.

At present time, diffusion imaging is essentially used for brain exploration in clinical practice, but other applications are emerging.

5.3 Relating Self-diffusion to Effective Diffusion and Permeability

The self-diffusion of water can be obtained from spin-echo experiments. Tuch et al. (2001) used the self-diffusion of water to obtain the electrical conductivity and proposed that the same concept can be used to relate self-diffusion with several other medium characteristics such as the permeability. Linninger et al. (2008) describe a procedure for translating the information obtained from the self-diffusion tensor imaging to the effective diffusion tensor and permeability that can be used for a porous medium. In this chapter his method will be described, because it is used in obtaining the diffusion and permeability from MRI data. The main concept in the procedure of Linninger et al. (2008) is that the eigenvectors of the self-diffusion tensor (measured by DTI, see equation 5.3.1) and the eigenvectors for the permeability and diffusion tensor are assumed to be the same.

$$D_{awd} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}$$ (5.3.1)

This equation shows the self diffusion tensor for each voxel, it is defined as a positive definite symmetric tensor. The largest eigenvalue of the self diffusion tensor corresponds to the direction of the fastest diffusion. That means that the largest eigenvalue also corresponds to the direction of the white matter fiber tracts.

The method starts with splitting the self-diffusion tensor into its eigenvectors and eigenvalues.

$$D_{awd} = \zeta \cdot \Lambda \cdot \zeta^T \text{ where } \Lambda = \begin{pmatrix} \lambda_{w1} & 0 & 0 \\ 0 & \lambda_{w2} & 0 \\ 0 & 0 & \lambda_{w3} \end{pmatrix} \text{ and } \zeta = \begin{pmatrix} \zeta_{11} & \zeta_{12} & \zeta_{13} \\ \zeta_{21} & \zeta_{22} & \zeta_{23} \\ \zeta_{31} & \zeta_{32} & \zeta_{33} \end{pmatrix}$$ (5.3.2)

After this, the eigenvalues are calibrated to a literature value by dividing the eigenvalue by the average eigenvalue and multiplying it by a permeability value from the literature (experiments).

$$\bar{\lambda}_w = \frac{1}{3} \sum_{i=1}^{3} \lambda_{iw} \text{ and } \lambda'_{ik} = \bar{K} \cdot \left( \frac{\lambda_{iw}}{\bar{\lambda}_w} \right)$$ (5.3.3)

In the last step, the eigenvectors are multiplied by the new eigenvalues, calculated in equation 5.3.3, to obtain a tensor for the permeability. The same steps are done for the diffusion tensor, but because it has the same process, this will not be shown in this paper.
\[ K_0 = \zeta \cdot \Lambda' \cdot \zeta^T, \] 
\[ \text{whereby } \Lambda' = \begin{pmatrix} \lambda'_{1K} & 0 & 0 \\ 0 & \lambda'_{2K} & 0 \\ 0 & 0 & \lambda'_{3K} \end{pmatrix} \] (5.3.4)

With this method it is not necessary to implement a constant value for the diffusion or permeability parameters as is often done in the literature, but a calibration value is still needed.
Chapter 6

Mathematical Model

6.1 Assumptions

A lot of processes affect the distribution of a therapeutic agent in the brain. To model these processes and obtain the equations needed, some assumptions are made in the derivations. Furthermore, other assumptions are made to simplify the model and neglect processes that have a small effect on the actual concentration, pressure and displacement. A list of these assumptions is given below:

- Fluid and solid phases are incompressible.
- The solid matrix is assumed to behave as a linear elastic material.
- The matrix can change due to an arrangement of solid and fluid phase, but the total volume is constant.
- The therapeutic agent is completely soluble in the interstitial fluid.
- Changes of the fluid density and viscosity as a result of dissolution of the therapeutic agent are neglected.
- The fluid injected and the fluid in the brain have the same characteristics.
- The temperature is constant: it is assumed that the environment is stable despite the injection.
- The pH is assumed to be constant and has no effect on the degradation, uptake and adsorption rate.
- Unidirectional uptake exists from the fluid phase to the brain tissue (to enable to model it as a sink term).
- Steady state uptake is modelled, a fast increase of the uptake in the early seconds is neglected.
- Physical dispersion is neglected as it is assumed that the numerical dispersion is much larger.
Gravity forces are neglected.

### 6.2 Volume Balance

The brain can be divided into a solid part (the cells of the brain) and a fluid part (interstitial space), which need to be described together in a volume balance. To obtain this, we start by writing the two volume balances which are derived from the mass balance for the liquid part (eq:6.2.2) and solid part (eq:6.2.1).

\[
\frac{\partial ((1 - \phi)\rho_s)}{\partial t} + \nabla \cdot ((1 - \phi)\rho_s \mathbf{v}_s) = 0 \quad (6.2.1)
\]

\[
\frac{\partial (\phi \rho_l)}{\partial t} + \nabla \cdot (\phi \rho_l \mathbf{v}_l) \pm r_{s/s} = 0 \quad (6.2.2)
\]

In these equations, \(\rho\) and \(\mathbf{v}\) are the density and fluid velocity of the solid (subscript \(s\)) or liquid phase (subscript \(l\)) respectively and \(\phi\) is the porosity. The \(r_{s/s}\) term represents the source and sink terms which will be discussed in more detail later on. If the density is assumed to be constant over time due to the incompressibility assumption, and the two equations are added together, the following equation is obtained.

\[
\nabla \cdot (\phi \mathbf{v}_l + (1 - \phi)\mathbf{v}_s) \pm r_{s/s} = 0 \quad (6.2.3)
\]

This is the volume balance for the whole brain, but a lot of the terms are unknown. Therefore, the liquid velocity will be derived starting from the momentum balance (eq: 6.2.4) [Darcis. 2008/11].

\[
\frac{\partial (\phi \rho \mathbf{v}_l)}{\partial t} + \nabla \cdot (\rho_l \mathbf{v}_l \mathbf{v}_l) = \nabla \cdot (\phi \mathbf{t}_l) + F_{sl} + \rho_l \phi \mathbf{g} \quad (6.2.4)
\]

The next step is to use the material derivative \(\frac{D \mathbf{v}_l}{Dt} = \frac{\partial \mathbf{v}_l}{\partial t} + \mathbf{v} \nabla \mathbf{v}_l\) on the momentum equation and subtract the mass balance from it, which result in an equation for the fluid velocity [Hassanisadeh and Gray. 1980].

\[
\phi \rho \frac{D \mathbf{v}_l}{Dt} = \phi \rho_l \mathbf{g} + \nabla \cdot (\phi \mathbf{t}_l) + F_{sl} \quad (6.2.5)
\]

In this and the previous equation, \(\mathbf{g}\) are the gravity forces and so this term in the momentum balance represents the body forces. \(\mathbf{t}_l\) and \(F_{sl}\) represent the surface forces, whereby \(\mathbf{t}_l\) (stress tensor) is a summation of the hydrostatic pressure \((-\mathbf{p} \mathbf{I})\) and the viscous forces \(\sigma_l\) written as (eq: 6.2.6).

\[
\mathbf{t}_l = -\mathbf{p} \mathbf{I} + \sigma_l \quad (6.2.6)
\]

\(F_{sl}\) represents the friction forces between the fluid and solid phase. In a heterogeneous medium, a gradient exist in the forces exerted on the solid by the liquid. This gradient corresponds roughly to the porosity gradient, a larger porosity will create a larger force and a smaller porosity a smaller force. This has to be compensated by a force from the solid on the liquid with a gradient depending on the porosity as well. If it is assumed that the drag (often
called fluid resistance) from the solid on the liquid depends on the velocity difference between the two, a difference in velocity $\mathbf{v}_r$ is defined as:

$$\mathbf{v}_r = \mathbf{v}_l - \mathbf{v}_s \quad (6.2.7)$$

This definition can be used in the definition of $F_{sl}$ in equation 6.2.8.

$$F_{sl} = p\nabla \phi + T(\mathbf{v}_r) \quad (6.2.8)$$

The first term on the right hand side represents the force depending on the gradient of porosity and the second represents the drag depending on the velocity difference. It is possible to approximate the “drag” term with a Taylor approximation around zero, which is done in the following equation:

$$T(\mathbf{v}_r) = T(0) + \mathbf{v}_r T'(0) + \frac{\mathbf{v}_r^2}{2} T''(0) + ... \quad (6.2.9)$$

If the higher order terms are neglected and the advective inertia forces are small compared to the viscous forces, equation 6.2.9 can be written as:

$$T(\mathbf{v}_r) = -\mathbf{R} \cdot \mathbf{v}_r \quad (6.2.10)$$

$\mathbf{R}$ stands for the second order tensor in the Taylor expansion, and $T(0)$ is zero at zero velocity. With this description, we turn back to the velocity equation derived from the momentum balances. If the inertia term is neglected because it is relatively small, the velocity equation (eq: 6.2.5) can be transformed into:

$$\rho_l \phi g + \nabla \cdot (\phi \mathbf{t}_l) + p \nabla \phi - \mathbf{R} \cdot \mathbf{v}_r = 0. \quad (6.2.11)$$

This equation can be rewritten by separating the velocity term and using equation 6.2.6 to obtain equation 6.2.12.

$$\mathbf{v}_r = -\frac{1}{\mathbf{R}} \left[-\phi \rho_l g + \nabla \cdot (\phi \mathbf{t}_l) - p \nabla \phi \right] \quad (6.2.12)$$

By using the product rule $\nabla(\phi p) = p \nabla \phi + \phi \nabla p$, 6.2.12 is rewritten to 6.2.13.

$$\phi \mathbf{v}_r = -\frac{\phi^2}{\mathbf{R}} [\nabla p - \rho_l g] + \frac{\phi^2}{\mathbf{R}} (\nabla \cdot \mathbf{t}_l) \quad (6.2.13)$$

If the viscous forces are neglected due to a low velocity which result in very low viscous forces [Whitaker. 1999], the result looks very similar to Darcy’s Law.

$$q = -\frac{K}{\mu_w} [\nabla p - \rho_l g] \quad (6.2.14)$$

By comparing equation 6.2.13 to Darcy’s Law (eq: 6.2.14), it is possible to find a relationship between $\mathbf{R}$, the viscosity of water ($\mu_w$) and the hydraulic conductivity $k$ with $K = \frac{k \mu_w}{p g}$.

Now that the difference in velocity is defined, the fluid velocity can be defined as well. But first, the solid velocity needs to be defined: the solid velocity term can be represented by the partial time derivative of the displacement field $\mathbf{u}$ (eq: 6.2.15), because $\mathbf{u} \nabla \mathbf{u}$ is relatively small.
\[
\begin{align*}
\mathbf{v}_s &= \frac{Du}{Dt} = \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\nabla \mathbf{u} \approx \frac{\partial \mathbf{u}}{\partial t} & (6.2.15)
\end{align*}
\]

With this and equation 6.2.7 the fluid velocity is defined as:

\[
\mathbf{v}_{l} = -\frac{\mathbf{K}}{\mu_w \phi} \cdot (\nabla \mathbf{p} - \rho \mathbf{g}) + \frac{\partial \mathbf{u}}{\partial t} & (6.2.16)
\]

As a last step, both the velocity of the fluid phase (equation 6.2.15) and the velocity of the solid phase (equation 6.2.16) that are defined are implemented in the volume balance (equation 6.2.3). This derivation results in the solid-fluid mixture volume balance:

\[
\nabla \cdot \left( \frac{\partial \mathbf{u}}{\partial t} - \frac{\mathbf{K}}{\mu_w} \cdot (\nabla \mathbf{p} - \rho \mathbf{g}) \right) = \pm \frac{r_{s/s}}{\rho_l} = \Omega_F(\mathbf{x}, t) & (6.2.17)
\]

### 6.3 Elasticity Model

The description of the volume balance uses the displacement tensor for the solid phase movement. The solid phase behaves linear elastic in this model due to the injection of fluid from a catheter. This gives a connection between the solid and liquid phase, so the momentum balances for both phases are needed to describe a balance between the forces present. The momentum balance of the fluid phase is given in equation 6.2.4, and the one for the solid phase is written below:

\[
(1 - \phi) \cdot \rho_s \frac{\partial^2 \mathbf{u}}{\partial t^2} = \rho_s (1 - \phi) \mathbf{g} - \nabla \cdot ((1 - \phi) \mathbf{t}_s) + \mathbf{F}_{ls} & (6.3.1)
\]

In this balance, \( \rho_s \) is the solid density and \( \mathbf{t}_s \) is the stress tensor for the solid phase. \( \mathbf{F}_{ls} \) are the friction forces between the solid and the fluid phase. The forces exerted from the solid on the liquid are the same as the forces exerted from the liquid on the solid, so \( \mathbf{F}_{sl} = \mathbf{F}_{ls} \). Taking this into account, adding the two momentum balances, neglecting the acceleration term \( \frac{\partial^2 \mathbf{u}}{\partial t^2} \) due to a small displacement and an even smaller acceleration of the displacement, as well as neglecting the acceleration term of the fluid velocity field \( \frac{D\mathbf{v}_l}{Dt} \) leads to equation 6.3.2.

\[
0 = (\rho_s (1 - \phi) + \phi \rho_l) \mathbf{g} + \nabla \cdot ((1 - \phi) \mathbf{t}_s + \phi \mathbf{t}_l) & (6.3.2)
\]

Like the stress tensor of the liquid phase, the stress tensor of the solid phase can be divided in its hydrostatic pressure part and its elastic stress tensor part:

\[
\mathbf{t}_s = -p \mathbf{I} + \sigma_s & (6.3.3)
\]

If this relationship and the one for the liquid phase (eq: 6.2.6) are used, the following equation is derived:

\[
\mathbf{t}_{tot} = (1 - \phi) \mathbf{t}_s + \phi \mathbf{t}_l \approx (1 - \phi) \sigma_s - p \mathbf{I} = \sigma - p \mathbf{I} & (6.3.4)
\]

Note that in this equation, it is already assumed that the viscous forces of the liquid phase can be neglected like in the previous section. Furthermore, the elastic stress tensor is denoted...
as $\sigma$ for simplicity. This relationship can be used in the momentum balance of equation 6.3.2, to obtain the new momentum balance for a porous medium:

$$0 = (\rho_s(1 - \phi) + \phi \rho_l) g + \nabla \cdot (-p I + \sigma)$$  \hspace{1cm} (6.3.5)

After obtaining this relationship, the derivation of the elasticity model needs the definition of a linear elastic model$^1$. First, the relationship between the deformation strain tensor ($e$) and the displacement ($u$) is given by:

$$e = \frac{1}{2} (\nabla u + (\nabla u)^T)$$  \hspace{1cm} (6.3.6)

For a linear elastic model, the following relationship is used to relate stress and strain:

$$\sigma_{ij} = C_{ijkl} e_{ij}$$  \hspace{1cm} (6.3.7)

In which $C_{ijkl}$ is the fourth order stiffness tensor, that is related to the Lamé parameters $\lambda$ (bulk modulus) and $\mu$ (shear modulus) (eq: 6.3.8) under the assumption of isotropic homogeneous media$^2$.

$$C_{ijkl} = \lambda \delta_{ij} \delta_{kl} + \mu (\delta_{ik} \delta_{jl} + \delta_{il} \delta_{jk})$$  \hspace{1cm} (6.3.8)

In this equation, $\delta$ is the Kronecker delta. The Lamé parameters characterise the response of the medium to forces. Equations 6.3.7 and 6.3.8 are combined to give a stress strain relationship depending on the lamé parameters:

$$\sigma_{ij} = 2 \mu e_{ij} + \lambda e_{mm} \delta_{ij}$$  \hspace{1cm} (6.3.9)

It is now possible to return to the momentum balance of equation 6.3.5 and use equations 6.3.6 and 6.3.9 to obtain the final linear elasticity model.

$$\nabla \cdot \left( 2 \mu e_{ij} + \lambda e_{mm} \delta_{ij} - p I \right) + (\rho_s(1 - \phi) + \phi \rho_l) g_i = 0$$  \hspace{1cm} (6.3.10)

And by using equation 6.3.6, the linear elastic model is derived:

$$\nabla \cdot \left[ \left( \mu \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \right) + \lambda (\nabla \cdot u_i) I - p I \right] + (\rho_s(1 - \phi) + \phi \rho_l) g_i = 0,$$  \hspace{1cm} (6.3.11)

or in vector notation, the model is described by the following equation:

$$\left[ (\mu (\nabla u + (\nabla u)^T)) + \lambda (\nabla \cdot u) I - p I \right] + (\rho_s(1 - \phi) + \phi \rho_l) g = 0.$$  \hspace{1cm} (6.3.12)

$^1$All equations from now on are written in the Einstein summation convention to make the derivation more clear.

$^2$This only counts for the deformation and not for the flow and transport part of the model.
6.4 Transport

The transport equation is the mass balance of the infused therapeutic agent and written as:

\[
\frac{\partial (\phi c)}{\partial t} + \nabla \cdot (\phi [cv - D' \nabla c]) = r_{adsorption} + \Omega_T(x, t) \tag{6.4.1}
\]

The concentration of the therapeutic agent is denoted by \(c\) [mol/m\(^3\)]. \(D'\) [m\(^2\)/s] is the diffusion tensor, defined as \(D' = \tau D\), \(D\) [m\(^2\)/s] is the diffusion coefficient and \(\tau\) [-] the tortuosity. \(\Omega_T(x, t)\) is the source/sink term for transport (adsorption is not included in \(\Omega_T(x, t)\)). In this equation, the sink term due to adsorption is separated from the other sink terms, so that it is possible to cancel it against the desorption in the transport equation of the solid which is shown below:

\[
\rho^s \frac{\partial s}{\partial t} = -r_{desorption} \quad (6.4.2)
\]

In this equation, \(s\) is the concentration of the therapeutic agent in the solid phase, and \(\rho^s\) is the density of the solid phase. If those two equation are added, the following equation is the result:

\[
\frac{\partial (\phi c)}{\partial t} + \rho^s \frac{\partial s}{\partial t} + \nabla \cdot (\phi [cv - D' \nabla c]) = r_{adsorption} - r_{desorption} + \Omega_T(x, t) \tag{6.4.3}
\]

By considering equilibrium adsorption, it is assumed that the adsorption and desorption are related to each other and by linear equilibrium adsorption, it is assumed that they are linearly related by the following relationship: \(s = K_D c\). Whereby \(K_D [m^3/kg]\) is the distribution coefficient. This makes it possible to sum the two storage terms and cancel the sink term due to adsorption/desorption.

\[
\frac{\partial}{\partial t} \left( 1 + \rho^s K_D \right) \phi c + \nabla \cdot (\phi [cv - D' \nabla c]) = \Omega_T(x, t) \tag{6.4.4}
\]

The term in front of the storage term is called the retardation factor and usually abbreviated to \(R\):

\[
R = \left( 1 + \frac{\rho^s}{\phi} K_D \right). \quad (6.4.5)
\]

If the velocity of the liquid that is obtained in the previous section is used (eq: 6.2.16), the result will be the final transport equation:

\[
\frac{\partial (R \phi c)}{\partial t} + \nabla \cdot \left( \phi \left\{ - \frac{K}{\mu w \phi} \cdot (\nabla p - \rho g) + \frac{\partial u}{\partial t} \right\} - D' \nabla c \right) = \Omega_T(x, t) \tag{6.4.6}
\]

6.5 Therapeutic Agent Losses

The concentration of the therapeutic agent could decrease to an ineffective value in several ways. Both the volume balance (eq: 6.2.17) and the transport equation (eq: 6.4.6) have a sink term. So the sink terms can be written as:
\[ \Omega_F(x, t) = r_{\text{vascular}} + r_{\text{lymphatic}} + r_{\text{CSF}} + r_{\text{source}} \]  \hspace{1cm} (6.5.1)

and:

\[ \Omega_T(x, t) = r_{\text{vascular}} + r_{\text{CSF}} + r_{\text{lymphatic}} + r_{\text{uptake}} + r_{\text{degradation}} + r_{\text{source}} \]  \hspace{1cm} (6.5.2)

In these two equations, \( r_{\text{vascular}} \) stands for the loss of the liquid or therapeutic agent into the blood vessels which occurs by flow and transport. The same holds for the loss into the lymphatic system (\( r_{\text{lymphatic}} \)) and the cerebrospinal fluid (\( r_{\text{CSF}} \)). The other terms only affect the transport model, \( r_{\text{uptake}} \) accounts for the diffusion of the therapeutic agent into brain cells and brain tumour, and \( r_{\text{degradation}} \) accounts for the degradation of the therapeutic agent due to its half-life. The last term accounts for the source of the therapeutic agent, but this chapter focuses only on the sink terms.

A well-known equation for the vascular system is Starlings Law and is written as:

\[ r_{\text{vascular}} = L_p \frac{S}{V} (P_e - P) \] and \[ P_e = P_v - \sigma_v (\pi_v - \pi_i) \]. \hspace{1cm} (6.5.3)

Starlings Law describes the process of fluid flow across the walls of the capillaries. This equation is implemented twice, one time in the volume balance and one time in the transport equation. When implemented in the transport equation it is multiplied by the concentration.

Furthermore, the same concept can be used for the lymphatic system [Netti. 1997]:

\[ r_{\text{lymphatic}} = L_{pl} \frac{S_L}{V} (P_L - P) \] \hspace{1cm} (6.5.4)

In these two equations, the different \( P \)'s are the hydrostatic pressures for the vascular system (\( P_v \)), effective vascular pressure (\( P_e \)), and the pressure in the lymphatic system (\( P_L \)). \( P \) is the interstitial fluid pressure. \( \pi_i \) and \( \pi_v \) are the interstitial and vascular colloid osmotic pressures.

Furthermore, the group of parameters which are multiplied by the pressure difference (driving force) consist of the average hydraulic conductivity of the walls of the vascular and lymphatic system (\( L_p \) and \( L_{pl} \))[m/(Pa · s)], and (\( S/V \) [1/m]). \( (S/V) \) is the ratio of the surface of the blood vessels in the area of interest divided by the volume of the area of interest. The ratio of lymphatic (\( S_L \)) surface divided by the total volume (\( V \)) has replaced the ratio of vascular surface (\( S \)) over the total volume in the second Starlings Law for the lymphatic system. Note that these hydraulic conductivities are biological terms and are different from the hydraulic conductivity used in hydrology. Although a formulation of the sink term to the lymphatic system is defined, this can be neglected in the model because the lymphatic system in the brain has very little effect due to a small amount of lymphatic vessels and lymph nodes in the brain [Netti. 1997, Wijeratne. 2007]. So the loss due to the lymphatic system will be neglected in this study.

The uptake by tissue cells however, cannot be neglected. Nicholson (2001) mentioned that in several studies the uptake part of the transport equation had the following form:

\[ r_{\text{uptake}} = \sigma_u k \phi (c - c_i) \] \hspace{1cm} (6.5.5)

This equation is usually formulated as:
\[ r_{\text{uptake}} = k'_{u} \phi(c - c_i) \] (6.5.6)

In which \( c_i \) is the initial concentration usually taken as zero, \( \sigma_u \, [\text{m}^{-1}] \) represents a specific surface area and \( k \, [\text{m/s}] \) represents a membrane permeability. The specific surface \( (\sigma_u) \) area is a ratio of the total volume to the surface between the fluid and solid phase. \( \sigma_u \) and \( K_u \) together represent the uptake rate constant \( (k'_{u} \, [1/s]) \).

An alternative way to describe the uptake is a nonlinear model. The Michaelis-Menten-kinetics is usually used to model enzyme kinetics and describes the rates of irreversible enzymatic reactions by relating reaction rate to the concentration. If the equation is slightly enhanced, it can describe a nonlinear relationship between the uptake rate and concentration. The Michaelis-Menten-kinetics is written as:

\[ r_{\text{uptake}} = \left( \frac{V_{\text{max}} c}{K_m + c} \right) \phi c. \] (6.5.7)

\( V_{\text{max}} \, [1/s] \) is a rate constant that can be interpreted as a measure of the number of uptake sites and depends on the tissue present, and \( K_m \, [\text{kg/m}^3] \) is a dissociation constant for the binding of the agent to the membrane uptake sites [Nicholson. 2001, Ingraham. 2005]. The linear uptake is used, because the uptake of the therapeutic agent BCNU is best described by the linear uptake equation 6.5.6.

Furthermore, a degradation term is implemented. In most of the literature a simple linear decay is modelled. This is also observed in several experimental data [Chae. 2005], so a linear decay is modelled in this study as well. The formulation for this is:

\[ r_{\text{degradation}} = k'_{d} \phi c. \] (6.5.8)

The sink term for the cerebrospinal fluid \( (r_{\text{CSF}}) \) is not quantified because very little information is known. If all the sink and source processes are combined, the complete sink and source term for the volume balance and transport equation are written as:

\[ \Omega_F(x, t) = L_p S \frac{V}{V} (P_e - P) + r_{\text{source}} \] (6.5.9)

\[ \Omega_T(x, t) = L_p S \frac{V}{V} (P_e - P) c - k'_{u} \phi c - k'_{d} \phi c + r_{\text{source}} \] (6.5.10)
Chapter 7

Parameter Description and Initial Values

This chapter gives an overview of the different parameters used in the mathematical model. Some, such as the permeability and porosity, are described by a relationship between the initial value and the effect of linear elasticity. Others need the calibration procedure of the DTI data to obtain an anisotropic and heterogeneous model. Nevertheless, all of them need an initial value which will also be stated, these will later be used as reference values in the parameter analysis.

7.1 Permeability

The model described in chapter 6 is linear elastic and, unlike a rigid model, the permeability can change over time due to a change in the solid phase. In case of convection enhanced delivery, the injection increases the pressure that in turn causes a displacement of the tissue located around the catheter. The displacement affects the permeability of the brain tissue. Most CED studies use a constant permeability or use the following permeability-deformation relationship [Chen. 2007, Garcia. 2008]:

$$K = K_0 e^{\beta \nabla u}. \quad (7.1.1)$$

In this equation, $K$ is the permeability, $K_0$ is the initial permeability (obtained from literature), $\beta$ is a material constant and $u$ is the displacement. The value of the material constant determines the amount of change due to the displacement. It was found out by Chen et al. (2007) in a sensitivity analysis that the material constant varies between 0 and 5. A material constant of zero gives a rigid model in case of the permeability. If no mention is made, the material constant is set to 2 [Stöverud. 2009/9]. In the case of an isotropic and homogeneous medium, the initial permeability tensor is the same in the whole domain for all directions. A more complex model, when the MRI data is used, this initial permeability is a tensor composed of the initial value from the literature multiplied by the value from the DTI procedure described in section 5.3.
7.2 Porosity

The porosity is influenced by the same processes mentioned in the previous section. One way to describe this is to define a relationship between displacement and porosity from the volume balance [Netti. 1997]. For the derivation, one volume element $V_t$ (total volume) is considered, and $\nabla u$ is defined, for small displacement, as:

$$\nabla u = \frac{\delta V_t}{V_t^0} \approx \frac{V_t - V_t^0}{V_t^0}. \quad (7.2.1)$$

Whereby $V_t$ and $V_t^0$ stand for the volume of a deformed and undeformed element. The change in the solid phase is the opposite of the change in the fluid phase for a defined volume element. If the porosity is defined as $\phi'$ and the volume of the fluid is written as $V_f = V_t \phi'$, the following equation is obtained.

$$V_t^0 \phi^0 - V_t \phi' = V_t^0 - V_t \quad (7.2.2)$$

With simple modification of this equation and the use of equation 7.2.1, a porosity-displacement relationship is derived (eq: 7.2.5).

$$V_t^0 \phi^0 - (V_t - V_t^0) \phi' + V_t^0 \phi' = V_t^0 - V_t \quad (7.2.3)$$

$$\phi^0 - \frac{(V_t - V_t^0)}{V_t^0} \phi' + \phi' = \frac{(V_t^0 - V_t)}{V_t^0} \quad (7.2.4)$$

$$\phi' = \frac{\phi_0 + \nabla u}{1 + \nabla u} \quad (7.2.5)$$

This relationship needs, like the permeability-displacement relationship, an initial value. This is a downfall because the value is obtained from experimental studies and so the porosity will have the same uncertainties as the experimental value used. Furthermore, this formulation (eq: 7.2.5) does not include the assumption of a constant volume which is made in this model. 7.2.5 can be written as:

$$\phi' = \frac{V_{pores}}{V_{new Volume}}. \quad (7.2.6)$$

Whereby $V_{new Volume}$ is the total volume after displacement, but the actual porosity that is needed is the ratio of the $V_{pores}$ over $V_{initial Volume}$. This will be defined as $\phi$. The new volume is the initial volume plus the extra volume due to a porosity increase caused by the displacement:

$$V_{new Volume} = (1 + \nabla u) \cdot V_{initial Volume}. \quad (7.2.7)$$

This gives the following relationship between the two ratio’s:

$$\phi' = \frac{V_{pores}}{V_{new Volume}} = \frac{V_{pores}}{(1 + \nabla u) \cdot V_{initial Volume}} = \frac{1}{(1 + \nabla u)} \phi \quad (7.2.8)$$

According to this relationship, equation 7.2.5 is multiplied by $(1 + \nabla u)$ to obtain the actual porosity $\phi$. The final porosity equation used in the model is therefore written as (eq: 7.2.9):
\[ \phi = \phi_0 + \nabla u \quad (7.2.9) \]

Like in the equation of the permeability, this equation needs an initial value. In this study, a porosity of 0.19 is used for gray matter and 0.21 for white matter.

### 7.3 Diffusion and Tortuosity

Diffusion is the transportation of molecules in a fluid as a result of a concentration difference and is usually described by Fick’s first law:

\[ J = -D' \nabla c. \quad (7.3.1) \]

Where \( D' \) is the effective diffusion coefficient, \( c \) is the concentration and \( J \) is the flux. The diffusion coefficient depends on the properties of the drug (the free diffusion coefficient of BCNU is \( 1.4 \cdot 10^{-10} \text{ m}^2/\text{s} \)) and on the characteristics of the volume in which the fluid is located. A volume with a larger percentage of solid particles will seriously hamper the diffusion process. This is usually taken into account with the tortuosity which is defined as the length between two points, \( L_{AB} \), divided by the length of the path that is taken by the molecule to go from one point to the other, \( C_{AB} \) (eq: 7.3.2).

\[ \tau = \frac{L_{AB}}{C_{AB}} \quad (7.3.2) \]

Due to this definition, the tortuosity can vary between zero and one. The tortuosity can decrease the diffusive flux, but never increase it, what is in accordance to the definition that a longer pathway will decrease the diffusion, but a shorter path than a straight line is, impossible.

One important point to make about the diffusion, is that the porosity is not included, therefore the effective diffusion is constant over time. The effective diffusion can be obtained from MRI data.

### 7.4 Lamé Parameters

The elasticity of the brain tissue is governed by the values chosen for the Lamé parameters. Small values for the lamé parameters indicate a very elastic model as a small pressure increase already causes displacement, while large values imply a rigid model. No significant difference in elasticity exist between gray and white matter, so the lamé parameters are set the same for both [Ozawa. 2001]. Several useful equations relate the lamé parameters with the Youngs modulus (E), Poisson’s ratio (\( v \)) and the bulk modulus (\( \kappa \)) (eq: 7.4.1).

\[ \lambda = \frac{E v}{(1 + v)(1 - 2v)}, \quad \mu = \frac{E}{2(1 + v)} \quad \text{and} \quad v = \frac{3\kappa - E}{6\kappa} \quad (7.4.1) \]

By using these equations, one can use a larger range of experimental studies and check their consistency. The Poisson’s ratio is relatively well known for brain tissue. Literature values range from 0.3 to 0.5 [Chen. 2007, Garcia. 2008, Morrison. 1999, Taylor. 2004]. The Youngs modulus however is much more difficult to determine. Despite or perhaps because of the large amount of experimental data, the actual Youngs modulus varies between 100 and 10,000
The Youngs modulus has a much larger effect on both of the lamé parameters than the Poisson ratio, due to its large uncertainty.

In the current research, uses lamé values of $1.55 \times 10^4$ for $\lambda$ and $1.72 \times 10^3$ for $\mu$ [Smith and Humphrey, 2007].

### 7.5 Vascular System

In this model, the Starlings law describes the exchange of the fluid between the interstitial space and vascular system. It contains 3 important constants which needs to be taken from experimental studies: hydraulic conductivity of the capillary walls, the capillary wall surface to total volume ratio and the effective pressure. For this study, the values for these constants are obtained from Smith and Humphrey (2007). A $L_p$ of $1 \times 10^{-9} [m/ (Pa \cdot s)]$ and a $S/V$ ratio of 100 [1/cm]. The effective pressure is assumed equal to the initial pressure of $4 \times 10^2$ Pa. This assumption causes a higher influence of the vascular system because the actual pressure of the capillaries is higher than the that of the interstitial volume.

### 7.6 Uptake and Degradation

As a first approximation, the uptake and degradation are modelled as linear equations that depend on the concentration of the therapeutic agent. A higher concentration causes a higher diffusion of the drug into the brain cell. The degradation has a linear relationship with the concentration. Both the uptake and degradation are therefore more effective in regions with a high concentration of the therapeutic agent. Due to the assumption of an initial concentration of zero, the only parameter that is taken from the literature is the rate constant: $k'_u$ and $k'_d$.

Two values are chosen specifically for BCNU: $8.79 \times 10^{-3}$ for the degradation [Chae, 2005] and $4.8 \times 10^{-4}$ for the uptake [Mitsuki, 1991].

### 7.7 Initial and Boundary Conditions

To solve the equations in the model, initial and boundary conditions need to be applied. In this case, knowledge about the concentration and pressure is applied in the initial and boundary conditions. No matter the choice of the domain, the initial concentration is set to zero, and the initial pressure is set equal to the intracranial pressure ($4 \times 10^2$ Pa).

When considering the whole brain, the boundary conditions are set at the location of the skull. Several options exist for the boundary conditions. The most obvious boundary condition at the skull is a no displacement boundary condition. However, there is evidence to suggest the existence of a “gap” between the brain and the skull which allows for the displacement of the outer region of the brain [Wittek, 2007]. If outward flow is assumed, the fluid is removed at the boundaries of the model. Alternatively, a Dirichlet boundary condition of zero concentration can be assumed.

If the whole brain is not modelled, most studies suggest a large simple radial symmetric sphere as the model domain. The boundary conditions for a large sphere are inserted at infinity [Garcia, 2008, Morrison, 1999]: free displacement (zero traction and zero pore pressure), or
Dirichlet boundary of no displacement and a fixed pressure (or fixed pressure difference) at the outer region to ensure CSF flow [Arifin. 2009, Taylor. 2004].

When a catheter is included, the model also requires boundary conditions along the side of the catheter. The boundary condition for concentration is a known concentration [Linninger. 2007, Chen. 2007, Garcia. 2008] at a constant rate [Linninger. 2007, Arifin. 2009] at the point of infusion. Another option would be to insert a constant pressure [Chen. 2007, Garcia. 2008]. A 28 (0.18 mm) or 32 (0.22 mm) gauge cannula [Chen. 2007, Garcia. 2008, Morrison. 1999] is normally. The side of the catheter is always a no slip and impermeable boundary [Morrison. 1999, Linninger. 2007].

The boundary conditions between the interstitial space and ventricles depend partly on the boundary conditions at the outer region of the model. If for example, a pressure gradient is chosen, an obvious choice would be to set these boundary condition at a constant pressure [Taylor. 2004, Arifin. 2009]. Furthermore, these boundary condition can be chosen with a zero displacement or a zero stress. The transport boundary condition at the ventricles, a permeability boundary can be assumed whereby the mass transfer depends on a driving force of the concentration [Taylor. 2004].

This study models only a part of the whole brain, in the shape of a cube. The domain has zero initial concentration and an initial pressure of pressure (4 \cdot 10^2 \text{ Pa}). The boundary conditions are set to zero concentration and a Dirichlet boundary condition of a constant pressure (4 \cdot 10^2 \text{ Pa}). A simple point source with a constant injection rate and concentration is assumed for the injection location, so no boundary conditions for the catheter are needed. The effects of a catheter is simulated by a lower permeability area mimicking the backflow of a catheter thereby neglecting the catheter itself.

### 7.8 Geometry

Anisotropy is calculated by relationship between the known characteristics of the porous medium in question, brain tissue, and the diffusion tensor obtained from DTI. Several relationships are proposed in the literature of which one of them is used in this research [Vorisek. 2009]. In chapter 2, the difference between white and gray matter is described. It is possible to say that gray matter is isotropic and white matter is anisotropic. So any flow existing in the brain will be highly directional in white matter and have no specific direction in gray matter. For example, Sarntinoranont et al. (2006) considered an anisotropic ratio of 20 between the different directions of white matter (the two direction perpendicular to white matter fiber tracts are considered the same). So the diffusion obtained by DTI is very different for white and gray matter [Sarntinoranont. 2006]. This make it possible to relate the diffusion to the sort of brain tissue [Tuch. 2001]. If more information is known about the different brain tissues, more parameters can be set at the location of that particular kind of tissue, creating an heterogeneous system.

One of the possibilities to relate diffusion from DTI to the brain tissue is described by Kim et al. (2009). In his paper, he used the fractional anisotropy as the dividing parameter assuming a higher anisotropy for white matter than for gray matter. The fractional anisotropy depend on the eigenvalues of the diffusion measure by DTI according to the following equation.
\[ FA = \sqrt{\frac{2}{3}} \sqrt{\frac{(\lambda_{w1} - \bar{\lambda})^2 + (\lambda_{w2} - \bar{\lambda})^2 + (\lambda_{w3} - \bar{\lambda})^2}{\lambda_{w1}^2 + \lambda_{w2}^2 + \lambda_{w3}^2}} \] (7.8.1)

In the case of this research, the gray and white matter is divided by a fraction anisotropy of 0.4. A lower value indicates grey matter and a a higher one indicates white matter. Furthermore, a datapoint with a tortuosity lower than 0.24, or higher than 0.54 is set as a ventricle, after Stöverud (2009/09).
Chapter 8

Dimensionless Model

To study the effect of the different processes during the injection, it is useful to change the equations of the model to their dimensionless form. For every variable, a characteristic value is chosen that is typical for the brain model. For example, the dimensionless value for pressure ($P^*$) can be written as $P^* = P/P_c$, in which $P_c$ is the characteristic value. This definition of the parameters ($P = P^*P_c$ in the case of pressure) will be substituted in the equations of the mathematical model. The characteristic values are chosen to obtain an equation where every variable is scaled to the most important variable. To explain this better, a reference is made to one of the derivations in this chapter: equation 8.0.4 and 8.0.7. Equation 8.0.7 is the dimensionless form of equation 6.2.16. The choice is made to scale the pressure term ($\nabla P$) to one in the volume balance. This results in the definition for characteristic velocity ($v_c$) that is written in equation 8.0.6, and gives equation 8.0.7. In this equation (eq: 8.0.7), only a characteristic porosity (and dimensionless parameters) remains that is multiplied by the pressure gradient. When this equation is inserted into the volume balance (eq: 8.0.9), the characteristic porosity will cancel out and only dimensionless parameters are multiplied with the pressure gradient. The other term in the velocity equation (eq: 8.0.7), the displacement term, is multiplied by a group of parameters. This group gives insight in the importance of the displacement compared to the pressure for the velocity field. What the exact characteristic values are for the different parameters will be discussed later. Before it is possible to describe the equations, it needs to be mentioned that the gravity term for this analysis is neglected and that the symbol L is the characteristic value for distance x. All other characteristic symbols should be obvious.

The linear elastic model is governed by the elasticity equation in dimensionless form (equation with dimensions: 6.3.12). So every parameter is replaced by their characteristic value and dimensionless parameter, thereafter the equation is divided by the second lamé parameter ($\mu$) to obtain no parameters in front of the first two terms.

$$\nabla^* \cdot \left(\nabla^* u^* + (\nabla^* u^*)^T + \frac{\lambda}{\mu} (\nabla^* \cdot u^*) I - \frac{LP_c}{\mu u_c} P^* \cdot I \right) = 0 \quad (8.0.1)$$

With this equation, it is possible to define the characteristic value for displacement such that the term multiplying the pressure equals unity.
\[ u_c = \frac{LP_c}{\mu} \]  

(8.0.2)

With the substitution of equation 8.0.2 in equation 8.0.1 and defining \( \frac{1}{\mu} \) as \( \lambda' \), the final linear elasticity equation for the dimensionless model is obtained:

\[ \nabla^* \cdot \left( \nabla^* \mathbf{u}^* + (\nabla^* \mathbf{u}^*)^T + \lambda' (\nabla^* \cdot \mathbf{u}^*) \mathbf{I} - P^* \cdot \mathbf{I} \right) = 0 \]  

(8.0.3)

Interestingly, if the \( \lambda \) and \( \mu \) are rewritten according to the equations in section 7.4, this elasticity equation only depends on the Poisson’s ratio and not the Youngs modulus, whereby a smaller Poisson’s ratio indicates a more elastic model on a scale of 0 to 0.5. The next step will be the equation for the velocity (eq: 6.2.16):

\[ v_c \mathbf{v}_c^* = -\frac{K_c P_c}{\mu \phi_c L} \phi^* (\nabla^* P^*) + \frac{u_c}{t_c} \frac{\partial \mathbf{u}^*}{\partial t^*} \]  

(8.0.4)

By using the definition for \( u_c \) in equation 8.0.2, defining the time as \( t_c = L/v_c \), and dividing everything by the characteristic velocity, the following equation is the result:

\[ \mathbf{v}_c^* = -\frac{K_c P_c}{\mu \phi_c L} \phi^* (\nabla^* P^*) + \frac{P_c}{\mu} \frac{\partial \mathbf{u}^*}{\partial t^*} \]  

(8.0.5)

\( P_c/\mu \) will be defined as \( 1/\mu' \) and gives insight in the importance of the displacement compared to the pressure gradient for the total velocity of the fluid. The importance is given by the ratio of characteristic pressure over the shear modulus. \( v_c \) will be defined so that the parameters grouping in front of the pressure term equals unity in the volume balance later on:

\[ v_c = \frac{P_c K_c}{\mu w L}. \]  

(8.0.6)

So that the final velocity equation is written as equation 8.0.7.

\[ \mathbf{v}_c^* = -\frac{1}{\phi_c} \frac{K_c}{\phi^*} (\nabla^* P^*) + \frac{1}{\mu'} \frac{\partial \mathbf{u}^*}{\partial t^*} \]  

(8.0.7)

With the completion of the dimensionless velocity equation, the next step will be to look at the mass balance including the sink and source terms. The mass balance has only the sink term from the vascular system and the source term for the therapeutic agent. The original mass balance can be found in section 6.2 (eq: 6.2.3).

\[ \frac{1}{L} \nabla^* \cdot (v_c \mathbf{v}_c^* \phi_c \phi^* + (1 - \phi_c \phi^*) \frac{u_c}{t_c} \frac{\partial \mathbf{u}^*}{\partial t^*}) = L \frac{S}{V} \left( P_c - P^* \right) + r_{\text{injection}} \]  

(8.0.8)

By dividing this equation with the characteristic velocity and multiplying by the characteristic length, followed by the use of the definition of the characteristic displacement (eq: 8.0.2) and time, the next equation is derived:

\[ \nabla^* \cdot (v_c \mathbf{v}_c^* \phi_c \phi^* + (1 - \phi_c \phi^*) \frac{1}{\mu'} \frac{\partial \mathbf{u}^*}{\partial t^*}) = \frac{LL_p P_c}{L} \frac{S}{v_c} \left( P_c - P^* \right) + \frac{L}{v_c} r_{\text{injection}}. \]  

(8.0.9)
The group of parameters in front of the pressure term will be defined as $E = \frac{LL_pP_c}{v_c} \frac{S}{V}$ and the second term on the right hand side will be defined as $r'_{injection} = \frac{L}{v_c} r_{injection}$. The E-number gives insight in the importance of the first term on the right hand side, so in other words, it gives information for which combinations of parameters the vascular system has an effect on the fluid flow. Basically the E-number is a ratio of loss, depending mostly on the permeability of the capillary walls, over the advective flux. This will be studied in the parameter analyses. If these definitions are used, the mass balance looks like equation 8.0.10. Note that the dimensionless form of the definition for solid velocity is already implemented.

$$\nabla^* \cdot (v_i^* \phi_c^* + (1 - \phi_c^*) \frac{1}{\mu^*} \frac{\partial u^*}{\partial t^*}) = E (P_c/P_e - P^*) + r'_{injection}$$ \hspace{1cm} (8.0.10)

Like in section 6.2, the displacement term times porosity will disappear against the displacement term in the velocity equation (eq: 8.0.7). After insertion of the dimensionless velocity equation, the following equation is the result:

$$\nabla^* \cdot (-K^* (\nabla^* P^*) + \frac{1}{\mu^*} \frac{\partial u^*}{\partial t^*}) = E (P_c/P_e - P^*) + r'_{injection}$$ \hspace{1cm} (8.0.11)

The next step is to transform the transport equation to its dimensionless form (for the original equation, see equation 6.4.6, section 6.4 and section 6.5 for the sink terms):

$$\frac{c_c \phi_c}{t_c} \frac{\partial (c^* \phi^*)}{\partial t^*} + \frac{1}{L} \nabla^* \cdot \left( \phi_c \phi^* \left[ c_c c^* v_c v_i^* - \frac{D'}{L} \nabla^* c^* \right] \right)$$

$$= c_c c^* L_p S \left( P_c - P_e P^* \right) + \phi_c \phi^* c_c c^* \left[ -k_u - k_d + k_{in} \right]$$ \hspace{1cm} (8.0.12)\n
Note that the retardation factor written in the original model is gone. Not using this parameter is a result of a lack of information about the retardation in the human brain in the literature. Rearranging the transport equation results in the following:

$$\frac{L}{v_c t_c} \frac{\partial (c^* \phi^*)}{\partial t^*} + \nabla^* \cdot \left( \phi^* \left[ c^* v_i^* - \frac{D'}{v_c L} \nabla^* c^* \right] \right)$$

$$= c^* \left[ \frac{LL_p S P_c}{\phi_c V v_c} (P_c/P_e - P^*) \right] + \phi^* c_c \frac{L}{v_c} \left[ -k_u - k_d + k_{in} \right].$$ \hspace{1cm} (8.0.13)

To simplify this equation, the definition of the characteristic time value: $t_c$, is used and $D'/(v_c L)$ can be written as one over the Peclet number $(1/P_e^*)$, this number gives the importance of diffusion compared to advection. The $k$ values are sink/source rates of the uptake due to cells, degradation of the therapeutic agent or source injection of the catheter, they have a dimension of $[1/s]$. Furthermore, the group of parameters in front of the sink rates are written as one symbol. As long as the rates are constant values, they can be written as one rate, but they are kept separate for completeness (note that the sink and source terms affect different areas as well).

$$\frac{\partial (c^* \phi^*)}{\partial t^*} + \nabla^* \cdot \left( \phi^* \left[ c^* v_i^* - \frac{1}{P_e^*} \nabla^* c^* \right] \right) = c^* A'_{st} (P_e^* - P^*) + \phi^* c^* \left[ -A_u' - A_d' + A_{in}' \right]$$ \hspace{1cm} (8.0.14)
This equation introduces some new symbols which need to be described shortly: \( P^*_e \) is the dimensionless effective pressure \( P_e / P_c \). \( A'_{st} \) is a dimensionless parameter representing the group of parameters in the first term on the right hand side: \( A'_{st} = \frac{LL_p SP_c \phi_c Vv_c}{\phi_c Vv_c} \), the other \( A' \) symbols represent the dimensionless uptake, degradation and injection: \( A'_u = \frac{L_v c k_u}{\phi_c} \), \( A'_d = \frac{L_v c k_d}{\phi_c} \) and \( A'_in = \frac{L_v c k_{in}}{\phi_c} \). Like the E-number, these dimensionless parameters give information about the importance of the therapeutic agent loss due to the vascular system, uptake, degradation and the injection term in the transport equations. The values of the characteristic pressure \( \frac{S}{P} \) -ratio and characteristic length are relatively stable. If these are considered as constants, the E and \( A'_{st} \) numbers can be expressed as a loss ratio, in which a higher velocity causes less loss of the interstitial fluid in the volume balance and therapeutic agent in the transport equation, and a higher vascular hydraulic conductivity causes more loss. The other dimensionless parameters for degradation and uptake are both a ratio between the rate of degradation respectively uptake over the advective flux. Like the volume balance, the dimensionless velocity equation can be inserted, which gives the final transport equation used in the model.

\[
\frac{\partial (c^* \phi^*)}{\partial t^*} + \nabla^* \cdot \left[ c^* \left( \frac{1}{\phi_c} K^* (\nabla^* P^*) + \frac{\phi^*}{\mu^*} \frac{\partial u^*}{\partial t^*} \right) - \frac{\phi^*}{P_c E} \nabla^* c^* \right]
= c^* A'_{st} (P^*_e - P^*) + \phi^* c^* [-A'_u - A'_d + A'_in] \tag{8.0.15}
\]

The permeability and porosity are, just like the model described in chapter 6, not constant, so a dimensionless equation for them is needed. The following equations are used in the mathematical model:

\[
K = K_0 e^{\beta \nabla u} \text{ and } \phi = \phi_0 + \nabla u \tag{8.0.16}
\]

By making these equations dimensionless and using the definition of \( u_c \) (eq: 8.0.2) and \( P_e / \mu = \mu^* \) from the beginning of this chapter, they are rewritten as:

\[
K^* = \frac{K_0}{K_c} e^{\beta (1/\mu') \nabla^* u^*} \text{ and } \phi^* = \frac{\phi_0}{\phi_c} + \frac{\nabla^* u^*}{\phi_c \mu'} \tag{8.0.17}
\]

In the case of a homogeneous and isotropic medium \( K_0 = K_c \) and \( \phi_0 = \phi_c \), which simplifies these porosity and permeability equations to equation 8.0.18.

\[
K^* = e^{\beta (1/\mu') \nabla^* u^*} \text{ and } \phi^* = 1 + \frac{\nabla^* u^*}{\phi_0 \mu'} \tag{8.0.18}
\]

After this transformation, it is important to define the correct characteristic values. Some are defined along the way such as the characteristic velocity and time values. One other characteristic value is already mentioned: the distance \( L \). This is the length of the model domain that is chosen to be one in all directions. The other values need to be defined for this particular problem as well. The characteristic values of porosity and permeability are set to their initial values to obtain a dimensionless value of around one, and the characteristic value for the concentration is set equal to the concentration of the source term. The characteristic value for pressure is more difficult to define because the maximum pressure in the system is unknown, in this study the characteristic pressure will be set to the to the maximum pressure in the model with dimensions.
Chapter 9

Numerical Model

For this research, the mathematical model is implemented in an openSource code called DuMu\(^x\). This is a C++ based program developed at Stuttgart University and comes as an extra module of the openSource program DUNE, which in turn is developed by several universities in Germany and one in the United Kingdom. This chapter will describe DUNE and DuMu\(^x\) shortly, and after that, the transfer from mathematical to the numerical equations are explained.

9.1 DUNE and DuMu\(^x\)

DUNE stands for the Distributed and Unified Numerics Environment, and is a toolbox for solving differential equations with different grid based methods. The main concept of DUNE is to create slim interfaces allowing an efficient use legacy and new libraries [DUNE. 2011]. Due to the available C++ techniques, DUNE allows to use different implementations of the same concepts, like a grid, using one common interface with a low overhead. DUNE is based on 3 basic principles: one is the separation of data structures and algorithms by abstract interfaces to provide more functionality and less code. The second is to obtain an efficient implementation of the interfaces using generic programming techniques. And last is the reuse of existing finite elements packages which have a large body functionality. The framework of DUNE consist of several classes of which DuMu\(^x\) can be one of them to provide an easy and efficient multi-scale and multi-physic toolbox for the simulation of flow and transport in porous media [Flemisch. 2007]. DuMu\(^x\) stands for DUNE and Multiple, whereby the \(x\) indicates that multiple multiples exist. The possible implementations of DuMu\(^x\) range from problem formulation, the selection of discretisation schemes to general concepts for model coupling. So far, DuMu\(^x\) is an academic research code and targeted towards researchers to apply new mathematical and numerical approaches. No knowledge of DUNE is needed to use DuMu\(^x\), but knowledge of C++ programming is necessary. DuMu\(^x\) contains a lot of different files for different scenarios, but the user is able to pick the parts that are needed for his or her problem, so this research only uses a small part of the DuMu\(^x\) module [Flemisch. 2010].
9.2 Box Method

DuMuX uses the box method in the discretisation process of the mathematical model. In the box method (see figure 9.2.1), the model domain is discretised with a finite element (FE) mesh of nodes $i$ and corresponding elements $E_k$ (blue box). So that node $i$ is the corner points of the finite element mesh. The second step is to construct a finite volume mesh and define the box $B_i$ (red box) by connecting the midpoints of the elements from the finite element mesh. The finite element mesh divides the volume $B_i$ in four subcontrol volumes (the green square in figure 9.2.1 indicates one subcontrol volume of box $B_i$). These subcontrol volumes belong to four different $B_i$ boxes. The faces between the subcontrol volumes (the orange line) are necessary for the discretisation as well as the integration point (the black dot) and the normal vector at the integration point. The idea behind this method is to apply the finite volume method to each finite volume box $B_i$ and to obtain the fluxes across the interfaces at the integration point between the subcontrol volumes from the finite element approach [Dumux Handbook. 2011].

9.3 Numerical Equations

For the actual simulations, the mathematical model should be transformed into their discretised form using the box method. First, the space discretisation and then the time discretisation, that are used to write the dimensionless model, that is described in chapter 8, in its discretised form.

9.3.1 Space Discretisation

The fully upwind BOX method is used for the space discretisation, and uses the integration form of the model equations. Therefore, the primary variables are approximated by finite element approximations using linear shape functions. The equation in question is integrated
by a finite volume approach over a volume \( V \) [Class. 2007, Stöverud. 2009/9]. The primary values are approximated values in the integration form, so they are replaced by \( \tilde{c}^*, \tilde{u}^* \) and \( \tilde{P}^* \). The space discretisation is explained with the dimensionless transport equation.

\[
\int_V \frac{\partial \tilde{c}^*}{\partial t^*} \text{d}V + \int_V \nabla^* \cdot \left( \phi^* \left[ \tilde{c}^* \mathbf{v}_l^* - \frac{1}{P_e^*} \nabla^* \tilde{c}^* \right] \right) \text{d}V = \int_V \phi^* \tilde{A}_{st}^* \left( P_e^* - \tilde{P}^* \right) \text{d}V + \int_V \varepsilon \text{d}V \quad (9.3.1)
\]

The approximated values are defined in the following way:

\[
\tilde{c}^* = \sum_{i=1}^{n} \hat{c}_i^* N_i, \quad \tilde{u}^* = \sum_{i=1}^{n} \hat{u}_i^* N_i, \quad \text{and} \quad \tilde{P}^* = \sum_{i=1}^{n} \hat{P}_i^* N_i. \quad (9.3.2)
\]

In this approximation, \( N_i \) stands for the basis function, \( n \) for the total number of nodes of an element and \( \hat{c}_i^* \) for the discrete values of the primary variables at each node. The discrete primary variables are approximated between the nodes by basis function. A common choice for the basis function are linear basis function. Linear basis functions are 1 at the node and decrease linearly to zero at the neighbouring nodes.

The discrete values of the primary variables have to be founded for the nodes so that the error function, which is the last term in equation 9.3.6, is minimised. To do this, the discrete nodal values are determined so that the weighted local average of the error \( \varepsilon \) vanishes. This is done by a weighting function related to the Galerkin method: \( W_i \). Equation 9.3.6 is multiplied by this weighting function so that the last term on the right hand side vanishes, because the weighting function has the condition \( \int_V W_i \varepsilon \text{d}V = 0 \). Furthermore, the sink and source term are written as \( \Omega_T^* (x,t) \).

\[
\int_V W_i \frac{\partial \tilde{c}^*}{\partial t^*} \text{d}V + \int_V W_i \nabla^* \cdot \left( \phi^* \left[ \tilde{c}^* \mathbf{v}_l^* - \frac{1}{P_e^*} \nabla^* \tilde{c}^* \right] \right) \text{d}V = \int_V W_i \Omega_T^* (x,t) \text{d}V \quad (9.3.3)
\]

In the BOX-method, the weighting function is chosen in a way that it equals one at node \( i \) and zero at the neighbouring nodes. Therefor, the integrals do not have to be evaluated in the entire domain, but just in a subdomain around node \( i \):

\[
W_i = \begin{cases} 
1 & \text{in box } B_i \\
0 & \text{outside } B_i \end{cases} \quad \nabla^* W_i = 0 \quad (9.3.4)
\]

The next step is to apply a mass lumping technique to the storage and sink/source terms, this means that all coefficients of a row of a matrix are lumped together in the diagonal position of the matrix. Furthermore, the sum of all the values of the weighting function \( W_i \) at a certain node \( i \) equals one and the weighting functions are linearly independent. The result will be that the storage and sink terms are concentrated at the nodes, and that the weighting and basis function can be cancelled in the storage and sink/source term. This is done in equation 9.3.6.

The diffusion and convection terms are rewritten using the Gauss theorem:
\[
\int_V W_i \nabla^* \cdot \left( \phi^* \left[ \bar{c}^* v^*_i - \frac{1}{P_c^*} \nabla^* \bar{c}^* \right] \right) dV = \int_V \nabla^* \cdot \left[ W_i \left( \phi^* \left[ \bar{c}^* v^*_i - \frac{1}{P_c^*} \nabla^* \bar{c}^* \right] \right) - \int_V \left( \phi^* \left[ \bar{c}^* v^*_i - \frac{1}{P_c^*} \nabla^* \bar{c}^* \right] \right) \right] dV
\]

\[
= \int_{S_{B_i}} \left[ W_i \left( \phi^* \left[ \bar{c}^* v^*_i - \frac{1}{P_c^*} \nabla^* \bar{c}^* \right] \right) \right] \cdot n dS_{B_i}
\] (9.3.5)

According to equation 9.3.4, the second term on the right hand side is zero and an integral over the surface of the element around node \(i\) is left. The integrals are evaluated at the boundaries of the volume elements (boxes) denoted by \(S_{B_i}\).

\[
\int_V \partial_t^* \phi^* \bar{c}^* + \int_{S_{B_i}} \left( \phi^* \left[ \bar{c}^* v^*_i - \frac{1}{P_c^*} \nabla^* \bar{c}^* \right] \right) \cdot n dS_{B_i} = V_i \Omega^*_i(x, t)
\] (9.3.6)

In this equation, \(V_i\) is the volume of the box around the node. The convective part is calculated by a fully upwind scheme, and the diffusion by a central scheme. An upwinding scheme calculates the solution at node \(i\) based on the solution of the equation at the node upstream of node \(i\). Upstream is defined with respect to the direction of the transport velocity. This is used for advection dominated transport because the physical process of advection creates a sharp front. While a central scheme creates a more gradual decrease between the nodes. This is more realistic for the diffusion process.

### 9.3.2 Time Discretisation

A finite difference method derived from the Taylor expansion is used for the time discretisation. If the higher order terms are neglected and thus a linear approximation is assumed, the Taylor expansion looks like:

\[
(\phi^* \bar{c}^*)^{t^*+\Delta t^*} = (\phi^* \bar{c}^*)^{t^*} + \frac{\delta (\phi^* \bar{c}^*)}{\delta t^*} \cdot \Delta t^* + O(\Delta t^*).
\] (9.3.7)

Whereby, \(O(\Delta t^*)\) stands for the error of the approximation caused by neglecting the higher order terms. Rearranging this equation and neglecting the error results in equation 9.3.8.

\[
\frac{\delta (\phi^* \bar{c}^*)}{\delta t^*} = \frac{\left( \phi^* \bar{c}^* \right)^{t^*+\Delta t^*} - \left( \phi^* \bar{c}^* \right)^{t^*}}{\Delta t^*} = f\left( c^{t^*+\Delta t^*} \right)
\] (9.3.8)

This is called an implicit Euler scheme which is a coupled system of equations causing a more expensive computation model, but it is unconditionally stable.

### 9.3.3 Equations in DuMu\(^x\)

The source injection is in most cases inserted in one node, which in combination to a high injection rate or low permeability values, creates a high pressure difference over short time span and small distances. Although this is useful in a convection driven model, it also causes less stable models. Aguilar (2008) found a solution for this with an extra term in the calculation of the velocity written in equation 9.3.9.
\[
(\mathbf{v}_i^{t^*})^{t^*+\Delta t^*} = -\frac{1}{\phi_c} \phi^* (\nabla^* (\tilde{P}^*)^{t^*+\Delta t^*}) + \frac{1}{\mu'} \left[ \frac{(\tilde{u}^*)^{t^*+\Delta t^*} - (\tilde{u}^*)^{t^*}}{\Delta t^*} \right]
\]
(9.3.9)

\[
+ \frac{P_c}{L^2} \left[ \frac{(\Delta x)^2}{4\phi_c\phi^*(\lambda + 2\mu)} \nabla^* \left( \frac{(\tilde{P}^*)^{t^*+\Delta t^*} - (\tilde{P}^*)^{t^*}}{\Delta t^*} \right) \right]
\]

The third term on the right hand side is the correction term and depends partly on the grid
spacing \((\Delta x)^2\). A small grid spacing gives a smaller correction term. Furthermore, it depends
on the porosity, lamé parameters and the gradient of pressure over time. The derivation of the
transport equation is used for the example of time and space discretisation.

\[
\int_{S_{B_i}} \left[ \phi^* \phi^* (\mathbf{v}_i^*)^{t^*+\Delta t^*} + (1 - \phi_c) \phi^* \frac{1}{\mu'} \left( \frac{(\tilde{u}^*)^{t^*+\Delta t^*} - (\tilde{u}^*)^{t^*}}{\Delta t^*} \right) \right] \cdot \mathbf{n} dS_{B_i} = V_i \Omega^*_F(x, t)
\]
(9.3.12)
\[
\frac{V_i}{\mu'} \nabla \cdot \left( \frac{\left( \tilde{u}^* \right)^{t^*+\Delta t^*} - \left( \tilde{u}^* \right)^{t^*}}{\Delta t^*} \right) \\
+ \nabla^* \cdot \int_{S_{Bi}} \left( -K^* (\nabla^* \tilde{P}^*) + \frac{P_c}{L^2} \left[ \frac{(\Delta x)^2}{4(\lambda + 2\mu)} \nabla^* \left( \frac{\left( \tilde{P}^* \right)^{t^*+\Delta t^*} - \left( \tilde{P}^* \right)^{t^*}}{\Delta t^*} \right) \right] \right) \cdot ndS_{Bi}
\]

\[= V_i \Omega^*_F(x, t) \quad (9.3.13)\]

And finally, the linear elasticity model is written as

\[
\int_{S_{Bi}} \nabla^* \cdot \left( \left[ \nabla^* \tilde{u}^* + (\nabla^* \tilde{u}^*)^T \right] + \lambda' \left[ \nabla^* \cdot \tilde{u}^* \right] I - P^* \cdot I \right)^{t^*+\Delta t^*} \cdot ndS_{Bi} = 0 \quad (9.3.14)
\]

These equations are implemented in DuMu-x, to calculate the distributions of several parameters, among them the concentration and pressure.
Chapter 10

Parameter Analysis

The goal of a parameter analysis is to study the effect of different dimensionless parameters on the results. This gives information about the importance of decreasing the range of values for the parameters. A large range of values does not necessarily mean a high or low influence of that parameter on the results. Or a low range in the parameter value could have drastic effects on the results of the model. Furthermore, a dimensionless analysis gives information about the importance of the terms of the mathematical model. The results included in this analysis are the distribution profiles of concentration, pressure, displacement, permeability and porosity. To test the effect of one parameter, the specific parameter is changed whilst all other parameters are kept constant. A parameter analysis is done with a homogeneous and isotropic domain (called simple model), and an anisotropic and heterogeneous domain (called complex model). The parameters for the analysis are taken from MRI data (only for the complex model) and from literature values.

The ranges of values are shown in table 10.0.1. When studying one parameter, the other parameters are set to their reference values. Those are also mentioned in the table. Not all parameters are tested with a range of values, in those cases, the total group of parameters is more interesting. For example, the vascular hydraulic conductivity is varied to test the effect of the E- and $A'_{st}$ parameters on the results. The vascular area is not varied because a change in the vascular area would have similar effect as the vascular hydraulic conductivity on the dimensionless parameters. Therefore, both parameters have a similar effect on the results, making it unnecessary to vary all parameters in a dimensionless parameter like $A'_{st}$.

10.1 A homogeneous and Isotropic Case

The simple model has a homogeneous and isotropic domain of dimensionless length, one in all three directions. These are unrealistic conditions for the brain tissue. However, they lead to more simple results of the used model and the effect of one parameter will be more clear. Most models are run for a dimensionless time number, which corresponds to 3300 seconds in real time. The final stage of the model simulation is not always shown, because only the most interesting results are given.

The analysis for the simple model is the same as described in the previous section. One parameter is changed while the others are kept constant. Analysing the parameters is done with
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Range</th>
<th>Reference value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion coefficient BCNU (D)</td>
<td>[m²/s]</td>
<td>1.4 · 10⁻¹⁰ - 1.43 · 10⁻⁹</td>
<td>1.4 · 10⁻¹⁰</td>
<td>[Fung. 1996, Fung. 1998]</td>
</tr>
<tr>
<td>Permeability (K)</td>
<td>[m²]</td>
<td>1.82 · 10⁻¹⁴ - 1.82 · 10⁻¹⁶</td>
<td>1.82 · 10⁻¹⁵</td>
<td>Specific values used for gray and white matter in the more complex model.</td>
</tr>
<tr>
<td>Poisson ratio (v)</td>
<td>[-]</td>
<td>0.3 - 0.475</td>
<td>0.45</td>
<td>[Morrison. 1999, Garcia. 2008, Taylor. 2004]</td>
</tr>
<tr>
<td>Shear modulus* (μ)</td>
<td>[Pa]</td>
<td>1.38 · 10⁴ - 3.45 · 10⁴</td>
<td>1.72 · 10⁴</td>
<td></td>
</tr>
<tr>
<td>second Lamé parameter* (λ)</td>
<td>[Pa]</td>
<td>1.24 · 10³ - 3.22 · 10³</td>
<td>1.55 · 10³</td>
<td></td>
</tr>
<tr>
<td>Lamé parameters: λ*</td>
<td></td>
<td>0.5 - 15</td>
<td>155/17.2</td>
<td>[Smith and Humphrey. 2007, Garcia. 2008, Morrison. 1999]</td>
</tr>
<tr>
<td>porosity (φ)</td>
<td>[-]</td>
<td>0.1 - 0.3</td>
<td>0.2</td>
<td>[Linninger. 2008, Chen. 2007, Morrison. 1999]</td>
</tr>
<tr>
<td>tortuosity (τ)</td>
<td>[-]</td>
<td>0.24 - 0.67</td>
<td>0.4</td>
<td>[Linninger. 2008, Vorisek. 2009]</td>
</tr>
<tr>
<td>uptake rate (k_up)</td>
<td>[1/s]</td>
<td>3.0 · 10⁻¹⁴ - 6.3 · 10⁻¹⁴</td>
<td>0</td>
<td>[Mitsuki. 1991]</td>
</tr>
<tr>
<td>degradation rate (k_d)</td>
<td>[1/s]</td>
<td>5.18 · 10⁻³ - 15.97 · 10⁻³</td>
<td>0</td>
<td>[Chae. 2005]</td>
</tr>
<tr>
<td>vascular conductivity (L_p)</td>
<td>[m/(Pa · s)]</td>
<td>1 · 10⁻¹¹ - 1 · 10⁻¹⁴</td>
<td>0</td>
<td>[Smith and Humphrey. 2007]</td>
</tr>
<tr>
<td>vascular area (S/V)</td>
<td>[1/m]</td>
<td>-</td>
<td>1 · 10⁴</td>
<td>[Smith and Humphrey. 2007]</td>
</tr>
<tr>
<td>effective pressure (P_e)</td>
<td>[Pa]</td>
<td>-</td>
<td>400</td>
<td>[Smith and Humphrey. 2007, Wijeratne. 2007]</td>
</tr>
<tr>
<td>interstitial pressure (P_i)</td>
<td>[Pa]</td>
<td>400</td>
<td>400</td>
<td>[Smith and Humphrey. 2007]</td>
</tr>
</tbody>
</table>

Table 10.0.1: An overview of the parameters used in this study

*Maximum Poisson’s ratio is set to 0.475 because 0.5 gives a zero shear modulus causing model problems. This counts for both λ and μ.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Characteristic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porosity ($\phi_c$)</td>
<td>[-]</td>
<td>0.2</td>
</tr>
<tr>
<td>Permeability ($K_c$)</td>
<td>[m$^2$]</td>
<td>$1.82 \cdot 10^{-15}$</td>
</tr>
<tr>
<td>Concentration ($c_c$)</td>
<td>[mol/cm$^3$]</td>
<td>$c_{initial}$</td>
</tr>
<tr>
<td>Pressure ($P_c$)</td>
<td>[Pa]</td>
<td>15000</td>
</tr>
<tr>
<td>Length ($L$)</td>
<td>[m]</td>
<td>1</td>
</tr>
<tr>
<td>Displacement ($U_c$)</td>
<td>[m]</td>
<td>$\frac{L}{v_c} = 9.01 \cdot 10^{-2}$</td>
</tr>
<tr>
<td>Velocity ($v_c$)</td>
<td>[m/s]</td>
<td>$\frac{K_c P_c}{L v_c} = 2.997 \cdot 10^{-6}$</td>
</tr>
<tr>
<td>Time ($t_c$)</td>
<td>[s]</td>
<td>$\frac{L}{v_c} = 2.997 \cdot 10^4$</td>
</tr>
</tbody>
</table>

Table 10.1.1: Characteristic values of the homogeneous and isotropic case.

the dimensionless model. Due to the transformation of the equations into their dimensionless form, the results are dimensionless as well (chapter 8). The characteristic values have to be chosen specifically for every dimensionless model. The characteristic values for the simple model are shown in table 10.1.1. Some of those are defined by the derivation, so no specific value needs to be chosen. Others, like the porosity, do need to be chosen and will reflect the results. For example, a porosity of 0.2 gives a dimensionless porosity of 1, as an initial value. This also holds for the characteristic permeability, concentration and length. The pressure is a more complicated parameter because the injection of the therapeutic agent is implemented as a flux term and no logical constraint for the pressure is known. The characteristic pressure is therefore determined from the output of the model with dimensions, using the reference values from the dimensionless model. In this study a value is chosen so that the pressure will go from 0 to roughly 1, because not much is known concerning the pressure that human brain cells can withstand.

The boundary conditions also change due to the transformation from the mathematical model to its dimensionless form. Normally, the Dirichlet boundary conditions have a pressure of 400 Pa and an initial pressure of 400 Pa. These boundary values should be divided by the characteristic pressure value. The initial and boundary conditions for the concentration are zero, and so will not change in the dimensionless model. The source term in the volume balance is multiplied by $L/v_c$ (8.0.11), changing the injection rate. The source term in the transport equation is multiplied by $\frac{L}{v_c \phi_c}$ (eq: 8.0.14).

The results are 3-dimensional images such as shown in figure 10.1.1. However, it is much easier to study the parameters by the use of cross sections for a homogeneous and isotropic model. Therefore, the 3D images are not shown for the analyses of the simple model, and solely cross sections are used. The cross sections show values in reference to its initial values.
10.1.1 Diffusion

In this section, the diffusion is studied to investigate the importance of the diffusion flux compared to the advection flux. The importance of diffusion is studied through the Peclet number (defined as $1/P'_e = \frac{D}{v_c L}$) in the dimensionless transport model (equation 8.0.14). The Peclet number is a ratio of advective flux over the diffusive flux. So, a high Peclet number indicates a small effect of the diffusion on the concentration distribution. One over the Peclet number is varied from $4.7 \cdot 10^{-5}$ to $4.7 \cdot 10^{-1}$, with a value of $4.7 \cdot 10^{-3}$ as the reference value. This is calculated for a length one, a reference velocity of $2.997 \cdot 10^{-4}$ and diffusion values of BCNU specifically. The diffusion value only has an effect on the transport model and therefore only the concentration distribution is plotted (figure 10.1.2).
These results show a small difference of the concentration curves for the higher Peclet numbers. It is possible to say that one over a Peclet number of $4.7 \times 10^{-4}$ or lower results in negligible diffusion and could be left out of the model. The reference value is not much different than the green curve (high Peclet number), but it decreases the steepness of the curve a little. Lower Peclet numbers give an obvious and important difference compared to the reference value.

For BCNU specifically, the diffusion can be neglected, as the diffusion coefficient of BCNU is close to the reference value. However, other therapeutic agents could have a higher diffusion coefficient. These results show that a higher diffusion coefficient has obvious influence on the concentration distribution. The gradient of the curve with a very high Peclet numbers is a result of numerical diffusion. If the numerical diffusion would be very small, the curve would look like a step function.
In the dimensionless form of the elasticity model, the lamé parameters affect the third term in equation 8.0.3: $\frac{1}{\mu} (\nabla^* \cdot \mathbf{u}^*) \mathbf{I}$. In other words, a change in one of the lamé parameters will change the contribution of this term compared to the other terms in the elasticity model. The intention is to find the influence of varying $\lambda'$ on the elasticity of the model.

The reference model uses a $\lambda$ of $1.55 \cdot 10^4$ Pa and a $\mu$ of $1.72 \cdot 10^3$ Pa; this correspond to $\frac{\lambda}{\mu} = \lambda' \approx 9$. The $\lambda'$ is varied between 1 and 15 to correspond to changes in the literature stating a variance of the Young’s modulus between 500 and 10,000 and a Poisson’s ratio between 0.3 and 0.5.

By changing the Lamé parameters, the concentration is only influenced to a small extent according to figure 10.1.4a. A low $\lambda'$ value will decrease the width of the concentration distribution a little. The pressure distribution is more different due to the change in $\lambda'$ (figure 10.1.4b). A high $\lambda'$ value shows an increase in the maximum pressure at the location of the source. The higher pressure results in a higher displacement, higher porosity and higher permeability values (figures 10.1.5 and 10.1.4b).

The difference in concentration can be explained by the elasticity of the model. A higher elasticity generates a higher displacement and thus a higher porosity. This increase in porosity will increase the storage term, giving a delay in the concentration distribution. The pressure distribution has lower maximum values for lower $\lambda'$ values, already indicating a higher elasti-

**Figure 10.1.3:** An overview of the effect of a varying $\lambda'$.

**Figure 10.1.4:** Concentration and pressure distribution with different lamé values.
city (figure 10.1.3). This is confirmed by the distribution of displacement and divergence of displacement (figure 10.1.5). A lower $\lambda'$ value results in a higher displacement due to higher elasticity. The higher elasticity can therefore explain the lower pressure distribution. Figure 10.1.6 show the same relationship between elasticity and $\lambda'$, because a more elastic model (low $\lambda'$ value) results in high porosity and increased permeability. The high increase in these parameters values is due to their relationship to the elasticity by the divergence of displacement.

Interestingly, one would expect a feedback effect because a higher elasticity (and thus a higher displacement) causes lower pressure values. However, a lower pressure corresponds to a lower displacement. Causing a negative feedback on the displacement. Eventually a steady state is reached. Obviously, a larger $\lambda'$ has a larger effect than the lower pressure on the displacement distribution. With this knowledge, it is possible to conclude that the difference in the concentration term is mostly caused by the elasticity, because a higher $\lambda'$ generates a higher storage and a lower volume of distribution.

Furthermore, only a small change in this parameter can give very different maximum pressures at the location of the source term. This seems very important because very little agreement exist about the Youngs modulus, which partly determines the lamé parameters. However, if $\lambda'$ is rewritten using the definition of the lamé parameters in section 7.4, the result will be: $\lambda' = 2\nu/(1-2\nu)$. This shows that the dimensionless elasticity model only depends on the Poisson’s ratio. Despite that the range of possible Poisson ratio value is much smaller than that of the Youngs modulus, this can still cause large changes in the $\lambda'$ parameter. Although the Youngs modulus has no influence in this term, keep in mind that due to definitions that are used, the lamé parameters return in other equations, like the transport equation, and so influence the model in several places. This will be studied in the next section.
Figure 10.1.6: Porosity and permeability distribution with different Lamé values.

10.1.3 The Displacement Parameter $\frac{1}{\mu'}$

The velocity equation (eq: 8.0.7) contains a pressure and a displacement term. The displacement term is multiplied by $\frac{1}{\mu'}$, or in real parameters: $P_c/\mu$. The same parameter ($\frac{1}{\mu'}$) returns in the equation for porosity and permeability. In this section, the influence of the displacement parameter on the results is studied. This is done by varying $\frac{1}{\mu'}$ from 0.872 to 87.2, with a reference value of 8.72. The reference value is calculated with a characteristic pressure of $1.5 \cdot 10^4$ Pa and $\mu$ of $1.72 \cdot 10^3$ Pa. The range of the displacement term corresponds to the possible changes in the second Lamé parameter $\mu$. The displacement term gives insight into the importance of the displacement of the solid compared to the pressure gradient in the flow velocity.

Theoretically, a greater displacement results in a larger volume for flow and as such a lower flow velocity. In the volume balance and transport equation, the displacement parameter is always multiplied by the temporal change in displacement. In the porosity and permeability equation, the displacement parameter is multiplied by the divergence of displacement. For example, the porosity equation is written as $\phi = 1 + \frac{1}{\mu'} \nabla^* \mathbf{u}^*$. Therefore, changing the actual displacement or the displacement parameter have similar effects on the flow and transport. So, although the actual displacement is kept the same, a greater displacement or an increased displacement parameter should have similar effects on the results.
Figure 10.1.7: The effect of $1/\mu'$ on the concentration and pressure distribution.

Figure 10.1.7a shows the concentration distribution with different $1/\mu'$ values. The concentration distributions are very similar, but a higher displacement parameter generates a delayed concentration distribution. The pressure curve is more affected by the displacement parameter (figure: 10.1.7b). An increased $1/\mu'$ results in lower pressure values. The displacement and divergence of displacement are also less if the displacement parameter is increased. However, the permeability and porosity show the opposite response to an increase in $1/\mu'$ than the actual displacement.

An increase of the displacement term gives more influence of the elasticity on the flow and transport properties. To explain the different concentration distributions, the porosity equation is needed (eq: 8.0.18). A higher displacement term enhances the effect of the actual displacement and so increases the porosity more, compared to a lower displacement term. The increased porosity generates a higher storage. This higher storage causes a delayed flow and a smaller concentration distribution.

A higher displacement parameter is similar to a higher actual displacement in the volume balance and transport equation. This is similar to a more elastic model. Therefore a lower pressure is needed to generate the same flow velocity. The lower pressure decreases the displacement. However, a lower displacement causes a higher pressure, leading to negative feedback until a steady state is reached (very similar to the feedback effect of the Lamé parameters). Despite this negative feedback, an increase in the displacement parameter has a stronger effect on the results than the lower pressure. This is illustrated by figures 10.1.7b and 10.1.8.

The porosity and permeability equations depend on the divergence of the displacement, which is smaller in case of an increased displacement parameter (figure: 10.1.8). Nevertheless, the porosity is the greatest for the lowest displacement due to the higher influence of the increased displacement parameter. Thus, the increase in the displacement parameter is more important than the decrease in the divergence of the displacement. This behaviour is shown in the porosity distribution in figure 10.1.9. Due to the equations of the porosity and permeability (eq: 8.0.18), the permeability distribution is expected to behave in the same way as the
porosity. This similar behaviour of porosity and permeability is also visible in the previous section, in figure 10.1.6.

10.1.4 Source Injection Rate

This section explains the influence of a different injection rate at the source location. The reference injection rate is 0.1 ml/hr, and the range of injection rates is from 0.05 ml/hr to 2 ml/hr. No other parameters are changed for this analysis. The injection rate of the source
term is very important, because it is one of the few parameters that can actually be varied in convection enhanced delivery operations.

The results are clear for the different injection rates: a higher rate gives a greater concentration distribution and higher pressure, displacement, porosity and permeability.

A higher source injection rate results in a larger concentration distribution, but also a higher pressure at the injection point. While a greater concentration distribution is favourable, a higher pressure distribution does not have to be so. A high pressure gradient increases the flow, but could also be harmful to the brain tissue. Furthermore, the injection rate seems to have a larger influence on the pressure than on the concentration distribution. This could be due to an increase of porosity for high injection rates, generating a higher storage.

If sink terms do not play a major role, it could be preferable to inject with a very low injection rate for a longer time. If it is impossible to implement the catheter close to the targeted area, a higher injection rate could help.

(a) Concentration distribution.
(b) Pressure distribution.

Figure 10.1.10: The concentration and pressure curves for injection rates.
The displacement and divergence of displacement show an increase for increased pressure values (increased injection rate) in figure 10.1.12. The increased displacement also generates higher porosity and permeability values in figure 10.1.11. The porosity and permeability react differently to the divergence of displacement; the porosity is obviously more influenced by these differences in the displacement, and thus these different injection rates, than the permeability.
10.1.5 Grid Resolution

The importance of the grid resolution will be studied by testing four different resolutions. The grid resolution is important because a trade-off exists between the accuracy of the results and the modelling time. A different grid resolution has a more prominent effect on the results if they are irregular, and has less influence on smooth functions. The results of CED show very steep curves and thus are highly influenced by the choice of grid size. Therefore, the pressure and concentration curves for different grids are shown in figure 10.1.13. The results show 4 different resolutions; a 40x40x40 grid means that in every direction 40 cells exist. So the grid size is 1/40 because the total volume of the model is 1x1x1 in dimensionless distance.

The curves in the graphs are smoother with a higher resolution. For the low resolutions, the results do not show the correct shape of the distribution anymore.

![Concentration and Pressure Distributions](image)

Figure 10.1.13: The concentration and pressure distributions for different grids.

According to these results, the second to highest resolution graph is close to the highest resolution and gives the same features for the concentration. So, it is acceptable to use a 1/20 grid size. The pressure curves for the two highest resolutions also show the same features. However, the actual values at the point of injection are very different. Most importantly, the results do not seem to converge to a maximum value. Therefore, it is unknown if the pressure at the injection point with the highest grid resolution is the actual value. A lower resolution is not preferable for the concentration graph, whilst it is unacceptable for the pressure curve as it loses the form it has for the higher resolutions.
The divergence distributions (figure 10.1.14a) of the 1/20 and 1/10 resolutions are surprisingly close to the 1/40 resolution when keeping the pressure difference in mind. This disappears when the divergence of the displacement is taken (figure: 10.1.14b). The porosity and permeability distributions (figure: 10.1.15) are almost constant in the case of a low resolution caused by the low divergence of the displacement. Therefore a low grid resolution makes the coupling of the porosity and permeability to the elasticity model and their dependence on the displacement unnecessary.

The displacement and divergence of displacement distributions for different grids.

Porosity and permeability distributions for different grids.
10.1.6 Vascular System

To study the influence of the vascular system on the transport and flow processes, the hydraulic conductivity of the walls of the capillaries \((L_p)\) is varied between \(1 \cdot 10^{-7}\) and \(1 \cdot 10^{-10}\) \([m/(Pa\cdot s)]\). So as to vary \(A_{st}'\) and \(E\) too. The ratio \(\frac{\hat{S}}{P_c}\) and \(v_c\) are all kept constant, and the reference \(L_p\) value is \(1 \cdot 10^{-9}\) \([m/(Pa\cdot s)]\). Varying these parameters show the effect of the vascular system on the concentration and pressure distribution, and their importance in CED. The results are shown in figure 10.1.16.

These distributions show that the range of chosen \(L_p\) values all have negligible effects on both the concentration and pressure distribution. Even a value 100 times higher than the reference value hardly leads to a difference in the distributions. Hence, if there is no special situation, the effect of the vascular system can be neglected.

![Concentration and pressure distribution](image)

(a) Concentration distribution.  
(b) Pressure distribution

Figure 10.1.16: Concentration and pressure distribution with different \(E\) and \(A_{st}'\) numbers, changed by changing the hydraulic conductivity of the walls of the vascular system.

10.1.7 Degradation

The degradation is modelled for a range of experimental values. It is also investigated what degradation rate a therapeutic agent should have so that degradation can be neglected in the model. Both results are shown in figure 10.1.17. The degradation rate of the therapeutic agent is important to know, because a higher degradation results in a smaller concentration distribution. Thus, the degradation influences the time length and injection rate needed to obtain the preferred concentration distribution.
The dimensionless uptake parameter $A_d' = \frac{L}{v_c} k_d$ is varied by varying $k_d$, whilst $L$ and $v_c$ are kept constant. The degradation constant is varied between $5.18 \cdot 10^{-3} - 15.97 \cdot 10^{-3}$ s$^{-1}$, meaning that the $A_d'$ is varied between 17.3 and 53.3. Furthermore, it is tested which degradation rate would result in it being negligible in the model; both investigations are shown in figure 10.1.17.

The results show an obvious influence of the varying degradation on the concentration distribution. Only a degradation rate 100 times lower than the literature value of BCNU shows a negligible effect. It is therefore important to include the degradation in convection enhanced delivery models. An interesting conclusion is that even the experimental range shown in figure 10.1.17 have very different results. This indicates that a smaller range from experiments is necessary.

Furthermore, these results give some measure of quantification of the effect of degradation on the effectivity of the drug. The dimensionless parameter $A_d'$ can roughly be described as the loss of the therapeutic agent divided by the advective flux. To obtain a lower degradation rate, another drug can be chosen with a longer half life and thus decreasing the loss, or the characteristic velocity must be increased. This can be done by enhancing the parameters in the characteristic velocity. However, these parameters are set to literature values or the values

Figure 10.1.17: Concentration distribution for a range of degradation values.
are specifically chosen for this case, so changing them would mean changing the setup of the model.

10.1.8 Uptake

In this section, the uptake rate is included in the model for different rates. The uptake is described in two ways in section 6.5. The BCNU uptake, however, is linear and thus only the linear uptake is shown here (figure 10.1.18). The loss of uptake corresponds to the amount of therapeutic agent diffusing into the cells. This gives an indication of the effectivity of the drug. The uptake rate is varied by changing the $k_u$ from $3.0 \cdot 10^{-4}$ to $6.3 \cdot 10^{-4}$. Hence, $A_u'$ is varied between 1 and 2.1. Figure 10.1.18 shows concentration distributions with different uptake rates. The uptake rate has a clear effect on the concentration distribution, but it is still close to no uptake. This indicates that the uptake rate used for BCNU is not favourable. Just as for the degradation, different drug characteristics or another characteristic velocity will influence the actual uptake. Compared to the degradation, a lower characteristic velocity is favourable. Unfortunately, the loss of the therapeutic agent due to uptake is much less than that due to degradation.
10.1.9 Tortuosity

Due to the definition of tortuosity ($\tau$) that is used in this model, its value ranges from zero to one. However, zero tortuosity means no diffusion and is related to a porous medium with a very low porosity. A tortuosity of one, on the other hand, is related to a very high porosity. The brain has neither of those situations at the location of injection and so the tortuosity is varied between 0.2 and 0.7. This is in accordance with literature values (see table 10.0.1). The tortuosity is analysed because it partly determines the importance of diffusion. In the equation of transport, tortuosity is included in the diffusion term and so will only have an effect on the concentration distribution, see figure 10.1.19.
The effect of changing the tortuosity has similar effects on the concentration distribution as changing the diffusion coefficient. However, it still depends strongly on the diffusion value that is used. This is because the tortuosity determines the effective diffusion, which in turn is based on the diffusion coefficient used. Therefore the diffusion can be varied in this way from zero diffusion to the diffusion coefficient. Figure 10.1.19 shows that a higher tortuosity results in more diffusion and vice versa, but has a minimal effect on the concentration distribution.

10.1.10 Permeability

The influence of the permeability is studied next. Permeability is a somewhat different kind of dimensionless parameter. The dimensionless parameters studied so far are constants. However, the permeability changes over time due to its dependence on elasticity. Nevertheless, the effects of changing the initial permeability on the distributions are studied. The reference initial permeability is $1.82 \cdot 10^{-15} \text{ m}^2$, and the range simulated is $1.82 \cdot 10^{-14} - 1.82 \cdot 10^{-16} \text{ m}^2$. The characteristic permeability values are changed together with the initial permeability values. In this way, the permeability equation will not change, and the initial dimensionless value ($K^*$)
is still one. The reason behind this is that the characteristic permeability of $1.82 \cdot 10^{-15} \, [m^2]$ would not be a characteristic value for the model anymore if the initial permeability is changed. The dimensionless permeability is unchanged, because both the initial and characteristic value of permeability are enhanced in the same way. The permeability does change in the characteristic velocity, influencing all the sink and source terms. The results are plotted in figures 10.1.20, 10.1.22 and 10.1.21.

![Figure 10.1.20: Concentration and pressure distribution with different permeability values.](image)

![Figure 10.1.21: Displacement and divergence of displacement distribution with different permeability values.](image)
The results show a high value for all distributions at a low permeability, and a large concentration distribution. This gives an indication of the importance of the permeability for convection enhanced delivery.

The concentration distribution (figure 10.1.20a) is very different for the different permeabilities. However, by changing the characteristic permeability, the characteristic velocity \( v_c = \frac{K_c P_c}{L \mu_w} \) and the characteristic time \( t_c = \frac{L}{v_c} \) are changed as well. These simulations are done for the same dimensionless time span \( t^* = t/t_c \), but the definition of the dimensionless time span is different. Therefore the simulation results are from different real time values. If the different timespan is taken into account, the concentration distribution is almost the same.

The pressure, displacement, porosity and permeability distributions are correct, because they all reached steady state. The pressure distribution shows a high dependence on the results of the permeability. The injection rate in all the simulations are the same, therefore the fluid flow is the same. However, a lower permeability causes a greater resistance to flow. Due to the greater resistance, a higher pressure is needed to generate the same flow velocity. This high pressure generates a greater displacement as well, as shown in figure 10.1.22. The high displacement increases the porosity and permeability values (figure 10.1.21). The changing initial permeability can thus influence the permeability change. This is possible because the initial permeability influences the pressure. The pressure influences the displacement, and the displacement influences the permeability change due to elasticity. Interestingly, the lowest initial permeability used increases the effective permeability more than the porosity, whilst the other two initial permeabilities values increase the porosity more than the effective permeability. Take into account that this is a relative increase. Thus, the real permeability with a lower initial permeability will not be higher than the other real permeabilities despite its large increase. This shows that the porosity and permeability are related differently to the elasticity model. The porosity has a linear relationship with the displacement, while the relationship between displacement and permeability is exponential. Furthermore, a displacement value exists above which the permeability is most influenced, and below which the porosity is most
influenced. The actual value could be narrowed down with further research.

10.1.11 Porosity

Figure 10.1.23: This figure shows three different aspects from different starting porosities: porosity, permeability and displacement distribution. Note that porosity is also dimensionless in figure c, so that the porosity increase to the injection is relative to its starting value. This means that a starting porosity of 0.1 gives the greatest relative changes but not the highest absolute porosity.

The next parameter studied is the initial porosity. The porosity is varied between 0.1 and 0.3 (this is in accordance to literature values), whereby most values lie in the range of 0.2 to 0.3 (see table 10.0.1). The characteristic porosity is changed in the same way as the initial
porosity. This means that the dimensionless porosity is kept the same. Figure 10.1.23 shows the results from changing the initial porosity. The other distributions are not shown, because they show no differences related to the porosity changes.

The concentration distribution is shown in figure 10.1.23a and shows a clear result of changing the porosity. A lower porosity generates a wider distribution area of the therapeutic agent. This is due to the lower storage term in a less porous medium. Furthermore, the characteristic porosity influences the advection term and injection rate in the transport equation. These two will cancel each others effects in the results, because a porosity difference will affect the advection flux term in the same way as the source injection.

The pressure distribution shows no difference due to the change in porosity, because the porosity does not influence volume balance. A logical result would be that the displacement is the same in all cases because the pressure is the same. This is indeed the case and therefore these results are not shown. The permeability and porosity changes depend on the divergence of the displacement, and so no difference is expected. However, because the base porosity is different, the relative change is different, and that is shown in 10.1.23c.

10.2 A Heterogeneous and Anisotropic Case

The more complex model makes use of MRI data for the diffusion and permeability parameters. The initial values for permeability are $1.82 \times 10^{-19}$ m$^2$ for ventricles, $1.3 \times 10^{-16}$ m$^2$ for gray matter and $1.82 \times 10^{-15}$ m$^2$ for white matter. Furthermore, the permeability is changed by the calibration procedure to make the domain anisotropic and heterogeneous. The initial effective diffusion coefficient depends on the drug, but is enhanced by the calibration process. The porosity, however, is only changed due to the different tissues visible in MRI: 0.25 for the ventricles, 0.19 for white matter and 0.21 for gray matter. The MRI data has a grid resolution of 0.2 cm$^3$, but this is too coarse to effectively model the pressure. Due to this and the large volume of the brain, it costs a lot of computational time to model the whole brain. Therefore, only a piece is used for the analyses and can be seen in figure 10.2.1. This box has dimensionless lengths of 6x9.6x5.4.

Due to the low grid resolution, the pressure will not reach the same values as for the simple case. Furthermore, the dimensionless model requires small model timesteps, because a small dimensionless time value relates to a much greater real time value. This causes a problem because the model is unstable for small timesteps, and so a higher initial timestep is used than in the homogeneous/isotropic case. All these model difficulties mean that it is not possible to simulate the pressure, and thus the displacement and all effects due to the displacement, well enough to do an effective parameter analyses. This means that the inclusion of elasticity hardly has any effect on this model. Therefore, the more complex model analysis focuses on the concentration. The Peclet number and initial permeability are analysed, as they are both derived from the diffusion tensor imaging. Note that the elasticity model is not influenced by the MRI data, and is still isotropic and homogeneous in the complex model. Only the coupling of the transport and flow with the elasticity model is influenced.
Figure 10.2.1: Initial porosity field of the heterogeneous and anisotropic case. The dark blue indicates white matter and light blue indicates gray matter. The red part of the model indicates the ventricles with very low permeability.

Like in the easier model, the characteristic values need to be set. They do not differ much from the previous simulation, although this time the initial dimensionless values will not always be one. The porosity and permeability initial values are location dependent (see table 10.2.1). To be consistent with the simple model, the characteristic pressure is set to $1.5 \cdot 10^4 \text{ Pa}$, but this will hardly make any difference because pressure distribution cannot be modelled satisfyingly with the used grid resolution.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Characteristic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porosity ($\phi_c$)</td>
<td>$[-]$</td>
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</tr>
<tr>
<td>Permeability ($K_c$)</td>
<td>$[m^2]$</td>
<td>$1.82 \cdot 10^{-15}$</td>
</tr>
<tr>
<td>Concentration ($c_c$)</td>
<td>$[mol/cm^3]$</td>
<td>$c_{initial}$</td>
</tr>
<tr>
<td>Pressure ($P_c$)</td>
<td>$[Pa]$</td>
<td>15000</td>
</tr>
<tr>
<td>Length ($L$)</td>
<td>$[m]$</td>
<td>1</td>
</tr>
<tr>
<td>Displacement ($U_c$)</td>
<td>$[m]$</td>
<td>$\frac{LP_c}{\mu} = 9.01 \cdot 10^{-2}$</td>
</tr>
<tr>
<td>Velocity ($v_c$)</td>
<td>$[m/s]$</td>
<td>$\frac{K_cV_c}{L_Pc} = 2.997 \cdot 10^{-6}$</td>
</tr>
<tr>
<td>Time ($t_c$)</td>
<td>$[s]$</td>
<td>$\frac{L}{\nu} = 2.997 \cdot 10^4$</td>
</tr>
</tbody>
</table>

Table 10.2.1: Characteristic values of the heterogeneous and anisotropic case.
The permeability is changed for the white and gray matter separately. The analyses of the simple model have already shown that a higher permeability at the location of the injection points generates a lower pressure. In a heterogeneous model, it is possible to study the ratio of the permeability between gray and white matter. To visualise the changing values of the permeability, 2 dimensional images are shown. With 2 dimensional images, it is more difficult to quantify the data, but they are more informative for a heterogeneous medium. Figure 10.2.2a shows the distribution of the gray and white matter. The dark blue indicates white matter and light blue indicates gray matter. The reference value is set to the highest permeability. The red part of the model indicates the ventricles with very low permeability. Figure 10.2.2b shows the results for the reference values. In this study, the gray matter is varied from $1.3 \cdot 10^{-15}$ to $1.3 \cdot 10^{-17} \text{ m}^2$. The white matter is varied between $1.82 \cdot 10^{-14}$ and $1.82 \cdot 10^{-16} \text{ m}^2$. The reference values are $1.82 \cdot 10^{-15} \text{ m}^2$ for white matter and $1.3 \cdot 10^{-16} \text{ m}^2$ for gray matter.

To study the effect of the permeability, first the gray matter is varied and then the white matter. Figure 10.2.3 shows the results from the variation of gray matter, and figure 10.2.4 that from the variation of white matter. The variation in gray matter permeability shows a more anisotropic distribution for a low gray matter permeability and more isotropic for high gray matter permeability. The results from varying the white matter permeability is the opposite: a low white matter permeability gives a more isotropic distribution and a high white matter permeability gives a more anisotropic concentration distribution. Actually, all these figures indicates the same: if the permeability values of gray and white matter are closer, the concentration distribution is more similar to an isotropic distribution of the concentration.
It is interesting to note is that only a small permeability difference causes noticeable anisotropy in the concentration distribution, as seen in figure 10.2.3b and 10.2.4a. A larger difference between the permeability values than that of the reference model is not much different. So it seems that when a threshold ratio is achieved, a more varying permeability value is less important.

### 10.2.2 Diffusion

From the analyses of the simple model, it is known that the diffusion only has a slight influence on the concentration distribution, unless it has a much higher value than the reference value. However, what makes it an interesting parameter to study is that the diffusion value is enhanced...
Figure 10.2.5: Two 2 dimensional figures of the concentration distribution with different diffusion coefficients on a heterogeneous and anisotropic domain.

by the DTI data. Therefore, the diffusion is varied from $212$ to $213 \cdot 10^2$ for the Peclet number. Figure 10.2.5 shows the results of a different diffusion values in a heterogeneous and anisotropic model.

Figure 10.2.5a portrays the concentration distribution for a high diffusion coefficient (low Peclet number) and figure 10.2.5b portrays the concentration distribution for a lower diffusion coefficient (high Peclet number). These figures show that a higher diffusion generates a more equal distributed concentration. This can be explained by the permeability tensor: a lower diffusion means relative more influence of the heterogeneous permeability distribution. When the diffusion is higher, it generates a transport that is concentration dependent. So, the therapeutic agent will transport along the boundary of white to gray matter decreasing the concentration difference. This is especially effective in areas where a small part of gray matter is surrounded by white matter with a high concentration as the diffusion causes a transport from all the surroundings into the gray matter with a low concentration.
Chapter 11

Tumour Model Characteristics

In this chapter, the CED process is applied to a synthetic tumour. The actual goal of convection enhanced delivery, is to apply it on a brain dataset, including a tumour. Due to the lack of a MRI dataset including tumour tissue, a synthetic tumour is modelled in the homogeneous and isotropic model. To generate a synthetic tumour, the characteristics of a tumour have to be known. Tumour tissue has different characteristics than normal brain tissue, and thus a tumour can be modelled by changing the parameters in a specific part of the domain to approximate a real tumour. The characteristics of the tumour are a lower permeability, higher porosity and a higher shear modulus. This is implemented as a perfect sphere. An overview of the most important processes that are affected by the the tumour tissue are shown in figure 11.0.1. In general, the pressure is high in a tumour causing an outward flux. The increased pressure and lower permeability cause less advection of the therapeutic agent into the tumour tissue, and because diffusion processes have a short reach, it is difficult for the therapeutic agent to reach the core of a tumour.

Figure 11.0.1: The processes in a brain tumour that differentiate from normal brain tissue [Soltani. 2011].

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To model this, the characteristics of the tumour area is changed according to the values in table 11.0.1. To simulate the increase in pressure in the tumour, a source term without a concentration is implemented in the centre of the tumour. Simulations are done with and without an increased tumour pressure to investigate the effect of the high tumour pressure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Brain tumour tissue</th>
<th>healthy brain tissue</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peclet number ( (P'_{e}) )</td>
<td>-</td>
<td>( 1.43 \cdot 10^{-3} )</td>
<td>( 1.43 \cdot 10^{-3} )</td>
<td>[Smith and Humphrey. 2007]</td>
</tr>
<tr>
<td>Permeability ( (\kappa) )</td>
<td>([m^2])</td>
<td>( 9.1 \cdot 10^{-17} )</td>
<td>( 1.82 \cdot 10^{-15} )</td>
<td>[Smith and Humphrey. 2007]</td>
</tr>
<tr>
<td>Lamé parameters: ( \lambda^* )</td>
<td></td>
<td>( \frac{1.55 \cdot 10^3}{5.16 \cdot 10^2} )</td>
<td>( \frac{1.55 \cdot 10^3}{7.20 \cdot 10^2} )</td>
<td>[Smith and Humphrey. 2007, Wittek. 2007]</td>
</tr>
<tr>
<td>porosity ( (\phi) )</td>
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<td>0.2</td>
<td>[Linninger. 2008, Vorisek. 2009]</td>
</tr>
<tr>
<td>tortuosity ( (\tau) )</td>
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<td>0.4</td>
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</tr>
<tr>
<td>uptake rate ( (k_{up}^') )</td>
<td>([1/s])</td>
<td>( 4.8 \cdot 10^{-4} )</td>
<td>( 4.8 \cdot 10^{-4} )</td>
<td>[Mitsuki. 1991]</td>
</tr>
<tr>
<td>degradation rate ( (k_{d}^') )</td>
<td>([1/s])</td>
<td>( 8.79 \cdot 10^{-3} )</td>
<td>( 8.79 \cdot 10^{-3} )</td>
<td>[Chae. 2005]</td>
</tr>
<tr>
<td>vascular conductivity ( (L_p) )</td>
<td>([m^2]/[Pa\cdot s])</td>
<td>( 1 \cdot 10^{-10} )</td>
<td>( 1 \cdot 10^{-13} )</td>
<td>[Smith and Humphrey. 2007]</td>
</tr>
<tr>
<td>vascular area ( (S/V) )</td>
<td>([1/m])</td>
<td>( 2 \cdot 10^4 )</td>
<td>( 1 \cdot 10^4 )</td>
<td>[Smith and Humphrey. 2007, Soltani. 2011]</td>
</tr>
<tr>
<td>effective pressure ( (P_e) )</td>
<td>([Pa])</td>
<td>( 1500 - 15322 )</td>
<td>( 400 )</td>
<td>[Smith and Humphrey. 2007, Wijeratne. 2007]</td>
</tr>
<tr>
<td>interstitial pressure ( (P_i) ) (BC)</td>
<td>([Pa])</td>
<td>( 1500 - 15322 )</td>
<td>( 400 )</td>
<td>[Smith and Humphrey. 2007, Wijeratne. 2007]</td>
</tr>
</tbody>
</table>

Table 11.0.1: An overview of the parameters used in this study for the brain tumour.

### 11.1 Brain Tumour Simulations

The simulations in this section are mainly done for the reference values mentioned in table 11.0.1. Nevertheless, several different scenarios are modelled. In the first case, a tumour is simulated by enhancing the medium properties at a certain location. The location is shown in figure 11.1.1. This one will be called the “normal tumour”. The only parameters changed are the Lamé parameters, permeability and porosity [Smith and Humphrey. 2007]. In the second case, a pressure increase in the tumour region is simulated by a constant influx of a flow without a therapeutic agent concentration. All other parameters are the same as for the normal tumour, and will be called the “high pressure tumour”. The last case is the same as the first, but includes the sink terms for uptake and degradation. The sink term of the vascular system is not modelled, because its influence is very small (see chapter 10).
The results are shown in figure 11.1.2c. The simulation of the normal tumour shows only the effect of changing the medium properties of that of a tumour (no increased pressure). In this timespan, the therapeutic agent is hardly found in the tumour area, indicating the low flux into the tumour area. This is mainly caused by the lower permeability of the tumour. At later time steps (not shown) the therapeutic agent will reach the centre of the tumour. However, the long infusion time also causes a high concentration of the drug in a large volume of healthy tissue. The high pressure tumour has even less concentration in the tumour area. A higher pressure means that the pressure gradient between the source location is less than the pressure gradient between the source location and healthy tissue. The therapeutic agent will flow in the direction of the highest pressure gradient. So, when the tumour has a higher pressure than the normal brain tissue, the therapeutic agent will flow into the normal brain tissue. The last 2 dimensional images show the importance of the sink terms in convection enhanced delivery. The image is shown for the same time length, but the concentration distribution has hardly started to surround the tumour area. These simulation indicate the convection enhanced delivery is a difficult process through which to get the drug into a large tumour, especially if sink terms are considered. The last image of figure 11.1.2c shows the cross section of the concentration distribution along the source and the tumour to quantify the concentration distribution of the 2D figures.
(a) A tumour simulated by a lower permeability, higher porosity and less elasticity.

(b) A tumour simulated by a lower permeability, higher porosity, less elasticity and an increased pressure at the centre of the tumour.

(c) A tumour simulated by a lower permeability, higher porosity and less elasticity. This simulation also includes the loss of the therapeutic agent in the brain (brain tissue uptake and degradation only).

(d) The concentration distribution of a cross section over the brain tumour.

Figure 11.1.2: Visualisation of a synthetic brain tumour in a otherwise homogeneous and isotropic grid.
Chapter 12

Backflow and Catheter Design

The insertion of a catheter for convection enhanced delivery causes, apart from outward flow, backflow. Morrison et al. (1999) describe and have simulated the flow mechanics around the catheter, with specific reference to the backflow. They conclude that permeability is one of the most important parameters for determining the shape of backflow [Morrison. 1999].

The simulations that are done in this study research the effect of backflow as a result of a catheter. The actual catheter is not modelled, but the backflow is resembled by the implementation of a low permeability / high porosity region. The size of that region is determined after the findings of Morrison et al. (2009). Figure 12.0.1 gives an overview of the model setting. For the investigation of the backflow process, an inflow rate of 0.06 ml/s is used, that generates a backflow of 0.21 cm [Morrison. 1999]. So the backflow is modelled by a high permeability region with dimensionless length of 0.2. This is referred to as the backflow distance. The width of the backflow is one volume element.

The backflow process creates a free flow area around the catheter. The free flow area will be filled by the fluid injected by the CED first, before the therapeutic agent is transported away from the source injection. This creates a delay similar to a higher porosity. Therefore, a higher porosity is modelled at the region of backflow (purple area in figure 12.0.1) to simulate this delay and to give an idea about the amount of therapeutic agent left behind along the catheter.
Figure 12.0.1: The left figure shows the location of the 2D section for the 2 dimensional images. The right figure shows that 2D section. The black line indicates the catheter, that is actually not implemented, but the backflow it generates is modelled. The purple area indicates the area of backflow (the length of this region is referred to as the backflow distance). The multiport catheter length is the total length of injection to simulate a catheter with multiple ports. This is half the length of the backflow distance. Furthermore, the two striped lines are the cross section locations used in this chapter.

If no mention is made of the chosen value, the same reference values are used as in the dimensionless parameter analysis for the simple model. This means that outside of the catheter a porosity of 0.2 and a permeability of $1.82 \cdot 10^{-15} \ [1/m^2]$ are used. The same domain and grid resolution are used as in the simple model in the parameter analysis.

Two types of catheters are modelled: one with a point injection and the other with a line injection. The line injection has a dimensionless distance of 0.1, and so is half of the total length of the backflow found by Morrison et al. (1999). In all cases, the same amount of fluid is injected into the domain. An overview of the different parameter sets of the simulations is given in table 12.0.1. For both the single point source and multiport source, four different simulations are done. The first simulation does not include backflow. This one is called “no backflow model” or “base model”. The second does include backflow by a higher permeability (5 times the reference permeability) for the purple region in figure 12.0.1. This simulation is referred to as the “normal backflow model” or “normal catheter model”. The third simulation includes backflow with an even higher permeability (10 times the reference permeability) for the purple region. Therefore, it is called the “high permeability model”. The last simulation includes a higher permeability and a higher porosity, and is named the “high porosity model”.

This section shows the results of the backflow processes generated by a point source and by a line source. All the results are shown for the same modelled time span.
Table 12.0.1: The different cases with the parameters for simulating the backflow around the catheter. These parameters are used for the purple region in figure 12.0.1. The abbreviations PI and MI stands Point Injection and Multiport Injection.

### 12.1 Backflow and a Point Influx Catheter

The backflow is modelled for the 3 different cases described in table 12.0.1: 5 times the normal permeability, 10 times the normal permeability, and 5 times the normal permeability and high porosity for the area simulating a backflow along the catheter walls (see table 12.0.1). To visualise the effect of these different models, the concentration distribution is shown in 2 dimensions. Note that the 2 dimensional images are mirrored compared to 12.0.1. Furthermore, all the distributions that are shown in the parameter analyses are also given in cross sections in this chapter. The cross section locations are shown in figure 12.0.1.

The two dimensional concentration distributions are shown in figure 12.1.1 for all the cases. It also includes the 2 dimensional view of the concentration distribution if no backflow is implemented.
(a) Point source injection without backflow processes (the base model for a single injection point).

(b) Point source injection with normal backflow region.

(c) Point source injection with a high permeability backflow region.

(d) Point source injection with a high porosity backflow region.

Figure 12.1.1: 2 dimensional concentration distributions of different settings for the backflow region and a point source injection. Note that these images are mirrored compared to 12.0.1.

These 2 dimensional figures clearly show the effect of a higher permeability for the backflow region. Figure 12.2.1b and c have a clear increase of the transport of the therapeutic agent in the direction of the catheter. This could be important in an anisotropic and heterogeneous domain because the therapeutic agent could leak into white fiber tracts with a higher velocity. The higher velocity would transports the therapeutic agent away from the area of interest. The higher porosity on the other hand cancels the effect of 5 times higher permeability for
the catheter almost completely in the 2 dimensional view. This is due to a high delay caused by a higher porosity. The cross sections are taken along the catheter to best show the same anti-symmetric form visible in the 2 dimensional figures (the green striped line in figure 12.0.1).

![Concentration distribution](image1.png) ![Pressure distribution](image2.png)

Figure 12.1.2: The effect of different implementation of the catheter on the concentration and pressure distribution with a point source injection.

The concentration of the therapeutic agent (figure: 12.1.2a) is spread further in the direction of the higher permeability generating backflow. The increase in concentration along the catheter is compensated by a small decrease along most of the outer region of the distribution circle (figure 12.1.1). The high permeability model shows more influence of the backflow than the normal backflow model, indicating the importance of permeability to generate backflow. The angle in the blue curve (high permeability model) shows the end of the backflow and a decreased permeability at a distance of 0.2 from the injection point. At this point the permeability is decreased and a smaller flow speed is reduced. The higher porosity case shows the same effect as the normal catheter model, but at a delay due to the high storage.

The shape of the pressure distribution (figure: 12.1.2b) shows little variation for the different models. A higher backflow generates a slightly higher pressure along the catheter, despite its lower permeability. So the extra flow in the direction of the catheter creates more pressure despite the lower resistance. This is, however, much less than the change in the maximum pressure between the models. The insertion of backflow causes the maximum pressure to be much lower and more divided. The kind of permeability that is used to generate backflow is less important than the actual implementation of a permeability difference on the pressure distribution. The green line (normal backflow/catheter) is invisible in the pressure and displacement distributions because it shows exactly the same distribution as the red one (high porosity) Therefore it is clear that porosity has no effect on the pressure and displacement distributions and thus, will not be discussed in relationship to this.

Figure 12.1.3 shows the displacement and divergence of displacement. The increased pressure next to the catheter (at the backflow area) shows a small increase in the displacement further away from the injection point. The main difference due to backflow is the lower max-
Figure 12.1.3: The effect of different implementation of the catheter on the displacement and divergence distribution with a point source injection.

imum displacement at the location of the source. This also causes less influence of the injection on the permeability and porosity distributions (figure 12.1.4). The porosity distribution has a smaller increase everywhere, except in the backflow area, compared to an injection without backflow. The high porosity model looks very different, but the relative increase is less than the base model (no catheter model). The permeability profile shows that a higher initial permeability also causes a higher permeability change, even while the maximum displacement is lower. This is logical if the equation of permeability is taken into account: 

$$K^* = \frac{K_0}{K_c} e^{\beta(1/\mu)'\nabla^* u^*}.$$ 

The $K_0/K_c$ term in case of a higher $K_0$ is increased so much that it more than compensates for the lower displacement.

The last figure (figure: 12.1.5) shows a cross section of the domain that is situated perpendicular to the catheter, at a distance of 0.15 from the point injection (the blue striped line in figure 12.0.1). These two figures quantify what the 2 dimensional figures already show: a higher concentration next to the catheter due to backflow. It is interesting to see that the width of the distributions are very similar for models with or without the implementation of the backflow. This indicates that outside the backflow area, the influence of the backflow process is sharply reduced in the homogeneous and isotropic medium that is used for these models. The pressure distribution (figure12.1.5b) shows the same as 12.1.2b: a higher pressure due to a lower permeability further away from the injection point. Furthermore, it also shows that difference between the models is very small outside the influence of the backflow process.
Figure 12.1.4: The effect of different implementation of the catheter on the porosity and permeability distribution with a point source injection.

Figure 12.1.5: The effect of different implementation of the catheter on the concentration and pressure distribution with a point source injection. The distributions cut the catheter at a distance of a length of 0.15 from the point.

The concentration distribution of a model with and without backflow included turns out to be very similar for larger modelling time. So, the concentration distribution will resemble a perfect sphere. After the area of backflow is surrounded by the therapeutic agent, the transport of the agent goes with the same velocity in every direction. Therefore, the peak in the concentration distribution in the 2D images will disappear. The other distributions (pressure, displacement, porosity and permeability) are the same as shown in this section for
longer modelling time.

12.2 Backflow and a Multiport Catheter

The previous chapter describes the effect of the backflow process with a point source injection, but a catheter can have more than one outlet point. A catheter with multiple outlet points would decrease the pressure and increase the volume of distribution. This is simulated by a line injection of a dimensionless length of 0.1 and the same backflow distance as for the point injection (see figure 12.0.1). The scenarios are the same as in the previous section, but than with a line source. That the backflow distance (purple region) is the same is not totally illogical despite that the distance between the source and the end of the backflow is much less. The line injection also decreases the pressure which generates a smaller backflow distance from the source. Furthermore, the figures plotted are all for the same modelled timespan as in the case of the point injection, so it is possible to compare these results with that of the previous section.

The influence of backflow and multiport catheter is visualised with 2D images and cross section of the parameter distributions in the same way as the previous section. The 2 dimensional results are shown in figure 12.2.1. Figure 12.2.1a shows only the multipoint injection and not the backflow. This already results in an asymmetric distribution, cancelling the clear effect of the backflow that was visible in 12.1.1. The process of backflow still enhances the concentration distribution in 12.2.1b, c and d, but less strongly than for a point source. The simulations with only a higher permeability value for the backflow (figure 12.2.1b and c) are very similar. This indicates that the permeability difference used has less effect on the results than with a point source injection. However, both figures are still significantly different from the simulation without backflow (figure 12.2.1a).
(a) Line source injection without backflow processes (the base model for a line injection).

(b) Line source injection with a normal backflow region.

(c) Line source injection with a high permeability backflow region.

(d) Line source injection with a high porosity backflow region.

Figure 12.2.1: 2 dimensional concentration distributions of different settings for the backflow region and a line source injection. Note that these images are mirrored compared to 12.0.1.

The cross sections along the catheter (figures 12.2.2, 12.2.3 and 12.2.4) show the line source by broader peaks in the curves than in the case of a point source injection. These are made at the location of the green striped line in figure 12.0.1. Figure 12.2.2a shows a higher concentration along the catheter due to the backflow process stimulated by the higher permeability, and the delay in the transport by the porosity due to a higher storage. These findings were also visible in the simulations with a point source. The pressure distribution (figure 12.2.2b)
is similar to those of the point source injection except that the peak is wider and its maximum value is lower. Thus, a lower maximum pressure is reached when a higher permeability is used for the backflow. Yet it has a slightly higher pressure in the area where backflow occurs (left of the peak). Again, the porosity has no influence on the pressure field, and thus no influence on the displacement field either (figure 12.2.3). The displacement and divergence of displacement distributions have the same differences between the point and line injection as the pressure distribution: a lower maximum value and a wider peak.

Figure 12.2.2: The effect of different implementation of the catheter on the concentration and pressure distribution with a line source injection.

Figure 12.2.3: The effect of different implementation of the catheter on the displacement and divergence distribution with a line source injection.
The same conclusions can be made about the porosity and permeability distribution for the multi point source injection (figure 12.2.4) as for the point source injection. The only difference is the lesser effect of the injection due to a lower pressure as it effects a broader area.

![Porosity and Permeability Distribution](image)

(a) Porosity distribution.  
(b) Permeability distribution.

Figure 12.2.4: The effect of different implementation of the catheter on the porosity and permeability distribution with a line source injection.

The cross sections perpendicular to the catheter (blue striped line in figure 12.0.1), and thus the backflow (figures 12.1.5 and 12.2.5), give the best view of the difference between a point source and a line source. Due to the line injection, the concentration distributions peak is not as small as for the point source, indicating less influence of the backflow and more influence of the source. The difference between pressure distributions of the point and line injection is the opposite from that of the concentration. At this distance, the maximum pressure is more and the peak is smaller for the line injection, indicating a closer distance to the actual source.
Figure 12.2.5: The effect of different implementation of the catheter on the concentration and pressure distribution with a line source injection. The distributions cut the catheter at a distance of a length of 0.15 from the point.

Just like in the previous section, the concentration distribution will resemble a perfect sphere after long modelling time. Even the effect of a line injection does not influence the concentration distribution that much. When the region of backflow is surrounded, the elliptical shape of figure 12.2.1a slowly transforms to a sphere. The other distributions (pressure, displacement, porosity and permeability) are the same as shown in this section for longer modelling time.
Chapter 13

Discussion and Outlook

This study exists of three parts: a dimensionless analysis, a backflow study and a tumour study. These parts will be discussed separately after which an outlook is given.

13.1 Dimensionless Analysis

The main focus of this study was to analyse the parameters of the convection enhanced delivery model. The goal of doing such an analysis is to obtain knowledge of the importance of the different parameters. This could be used to focus further research on specific parameters that have the most influence on the final results, i.e. the concentration and pressure distributions. This study could also be used for modelling purposes: the analysis indicates which part of the mathematical model is worthwhile to simulate under certain conditions. For example, if a therapeutic agent has a low diffusion coefficient, it is unnecessary to include this in the model, improving its efficiency. A short overview of the most important findings of the parameter analysis is given in this section.

In all the parameters that were varied, with exception of the injection rate, the concentration distribution are very similar for the different values. This indicates the importance of the flux rate of the source. The injection rate analysis shows its influence on the concentration distribution. The importance of the injection rate comes from the maximum pressure that is reached in the model (a high pressure can damage the brain tissue), and the spreading of the therapeutic agent. The minimal changes in the concentration distribution in most models is due to a constant and continuous influx rate. This causes the same amount of injected fluid in the same volume, resulting in the same volume of distribution. The only difference comes from an enhancement of the volume by enhancing the porosity. Changing the initial porosity proves this. However, several parameters influence the porosity indirectly due to the contribution of linear elasticity on the porosity.

In the case of a different permeability, the concentration is also different because a lower permeability increases the resistance and thus the pressure that is needed to overcome this resistance. A higher pressure means a higher displacement and thus a higher porosity that influences the concentration distribution. The permeability is also increased due to the higher pressure, but not enough to decrease the resistance drastically. The actual pressure difference due to a varying initial permeability is large. This is important because the literature values do
not agree concerning the permeability, and high pressure in the brain could be unfavourable. The permeability studies on a heterogeneous and anisotropic grid show that especially the ratio of gray and white matter permeability is important for the distribution of the therapeutic agent

The diffusion is analysed by varying the Peclet number. A wide range is simulated to include other therapeutic agents that might have a different diffusion coefficient. The diffusion of BCNU is almost negligible (Peclet number of around 200). Only a Peclet number of less than 20 shows an important influence on the diffusion in the simple model. This correlates to a diffusion coefficient of $1.4 \times 10^{-9} \text{ m}^2/\text{s}$ or larger. For the complex model, the diffusion rate of BCNU has a significant effect in smoothing the concentration distribution.

The elasticity model includes two dimensionless parameters. The first is the combination of the two Lamé parameters $\lambda'$. This parameter influences the elasticity and thus the displacement of the medium due to a pressure gradient. The ratio depends solely on the Poisson’s ratio; a value close to 0.5 corresponds to a higher $\lambda'$ number and simulates a rigid model. This is visible in the pressure and displacement distributions. A more rigid model generates a higher pressure and a lower displacement. Even the changes corresponding to the literature values of the Poisson’s ratio show significant differences. This indicates that it is important to understand the elasticity of the brain better. The elasticity also affects the effective porosity and permeability remarkable. The porosity, for example, could reach almost 4 times its initial value for large elasticity, creating a much higher storage around the catheter. This influences the amount of therapeutic agent that is needed to reach the targeted area of the brain.

The second parameter from the elasticity model is the displacement parameter $1/\mu'$. This parameter enhances the influence of the elasticity model on the volume balance and transport equation. A higher displacement parameter generates a higher influence of the elasticity on the results, and is thus similar to the effect of a lower $\lambda'$. This is visible in the pressure and displacement distribution. An increase of the displacement parameter generates a lower pressure and a lower displacement, because according to the volume balance and the transport equation, the porous medium is more elastic. The porosity and permeability distributions are not in accordance with the displacement. A higher displacement parameter gives a lower pressure and displacement, but a higher porosity and permeability. This means that the influence of the increased displacement parameter has a larger effect than the lower actual displacement on these parameters. Interestingly, both the displacement parameter and the $\lambda'$ parameter depends on the shear modulus $\mu$ in different ways. An increase in $\mu$ will decrease $\lambda'$ making the model more elastic. Whilst an increase in $\mu$ generates a lower displacement parameter, making the model more rigid. While these two parameters are tested differently, they are connected by the Lamé parameter. This does not mean that if $\lambda'$ is changed, $1/\mu'$ should be changed as well.

Despite that the grid resolution is not an actual parameter, it is important to know for what grid size the model clearly visualises the processes involved in convection enhanced delivery. The grid size used for the dimensionless analysis (1/40) results in a good distribution of the parameters. Decreasing the resolution will generate unacceptable results, especially for the pressure distribution. Interestingly, the grid resolutions used in the analysis do not seem to convert. So it is unsure if the 1/40 grid resolution is high enough for the model to calculate the exact pressure values. This can be important for the pressure that is allowed in the brain before the process of CED damages the brain tissue. When an injection rate of 0.1 ml/hr (the reference value for injection rate used in all models except the injection rate analyses) and grid resolution of 1/10 or higher, it will be unnecessary to model an elastic influence on the
porosity and permeability. The influence of the elasticity model on these parameters is not captured with low grid resolutions.

The uptake of, degradation in and flux into the vascular system are all modelled as sink terms. The flux into the vascular system is negligible. It is unlikely that a loss into the vascular system will influence the CED model with other realistic parameter values. The degradation and uptake both have a large effect on the concentration distribution. The parameters used are unfavourable, because the degradation is much larger than the uptake. The best way to enhance this, is by choosing a different drug with other characteristics.

13.2 Tumour

The tumour is modelled in a homogeneous and isotropic medium, and produced by enhancing the parameters locally. The results show that for a large solid tumour, the convection enhanced delivery is not effective. When a higher pressure in the tumour is considered, it is almost impossible for the therapeutic agent to reach the centre of the tumour. However, this does not mean that CED is ineffective against tumour cells. It is probably more effective for the spreading of the tumour that cannot be cured with other methods. CED does not have the downfalls of the effective BBB, like intraarterial administration, or damaging brain tissue such as the radiation therapy. Furthermore, transport in CED is dominated by convection, giving an advantage of all diffusion dominated therapy’s.

The implementation of a higher pressure in the tumour by an injection of a fluid without a concentration has a side effect. Not only increases it the tumour pressure, but it also creates an outflow of flow. The outflow will also hamper the therapeutic agent travelling into the brain tumour. However, this is not realistic and should be taken into account.

13.3 Backflow and Catheter Design

The backflow is simulated with a multiport (line source) and a single port (point source) catheter. Both create an asymmetric distribution of the concentration and pressure. This leads to the area of backflow having a higher concentration and a slightly higher pressure, but the maximum pressure value being lower. Furthermore, the effect of both processes (backflow and line injection) disappears over time, because the distribution surrounds the backflow area. When the concentration distribution is seen from a distance, it is similar with or without backflow and with a point or line source.

Before the backflow is surrounded by the concentration distribution, backflow could be important if the source is located in a gray matter area and the backflow reaches an area of white matter. White matter has a higher permeability and will transport the therapeutic agent away from the source, decreasing the amount of drug in the targeted area. Furthermore, the backflow process lowers the pressure at the location of the source due to lower resistance (higher permeability). This could be favourable if the pressure of the system would otherwise damage the brain tissue.

A source injected over a line creates a broader area with a high concentration and a high pressure than that of the point source injection. However, the maximum pressure is much lower for a line source injection. Both backflow and a multiport catheter have similar effects on the concentration distribution. However, their combined influence on the concentration
distribution will only partly add up, showing a more asymmetric distribution. Injection of the therapeutic agent as a line source and backflow both decrease the maximum pressure at the location of the source, whereby the effect of backflow and multiport catheter partly adds up.

The backflow can be simulated with different permeability values. The use of a higher permeability generates a stronger and faster backflow. This results in a better visible peak in the concentration distribution for smaller modelling time. However, the concentration distribution is quite similar for different permeabilities. This shows that the value of the permeability is not a main concern.

An increase in porosity along the catheter will delay the effect of backflow because of the higher storage. Due to this delay, it seems that the backflow process has less effect on the concentration distribution. The reason for this is that the backflow is generated more slowly, but the formation of the volume of distribution over the rest of the domain is very similar.

The simulations show that backflow is important if CED is applied for a short time, but negligible for a longer time.

13.4 Outlook

This research studies the effect of different parameters on the process of convection enhanced delivery. A better knowledge is needed about the parameters effecting convection enhanced delivery process. The focus of further research should therefore be on the parameters influencing CED the most. For example, it would improve the accuracy of the model to narrow down the value of the initial permeability or displacement parameter.

A side study in this research has shown that it is difficult to cure a large tumour with CED. However, it is promising for the spreading of the tumour. CED can be targeted to influence a certain area with a good knowledge of the processes and the brain characteristics. Therefore, the most influential parameters should be studied in greater detail. After this, the model can be used with high resolution MRI data, including a tumour with spreading.

Another possibility would be to improve the model to be able to simulate the linear elasticity combined with the MRI data. One possibility to do this is to increase the grid resolution, but not the MRI data. This would be useful because high resolution MRI data are harder to obtain. However, a high resolution model requires a long modelling time for the volume that is used in this study. Furthermore, it would be better to model the full brain instead of a small part, which increases the modelling time even more. To be able to model the full brain, it should be divided in certain areas with different complexities. For example, the area close to the catheter has an increased pressure, which is important for the elasticity model. Further from the catheter, no pressure increase is noticeable and it is acceptable to model the brain as a rigid porous medium. This would decrease the modelling time and increase the efficiency.
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