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The role of brain hyperelasticity in growth and proliferation of Glioblastoma Multiforme



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Summary

Glioblastoma Multiforme (GBM) is a highly aggressive and malignant type of brain tumour. Besides the typical hallmarks of cancer, such as uncontrolled cellular proliferation and instability, GBM also exhibits dramatic invasive potential and resistance to common therapies: even with a complete treatment including neurosurgery, chemotherapy and radiotherapy, the median survival time is about 10-16 months. Hence, there is a critical need to understand and replicate the biological complexity of the brain, in order to predict tumour evolution and arrange therapeutic strategies accordingly. For that purpose, mathematical and computational models can provide powerful instruments for investigating GBM progression: in the last decades, several models that describe brain tumour growth have been proposed, using different frameworks and accounting for different characteristics. Nevertheless, the vast majority of these models does not consider realistic mechanical and constitutive properties of brain tissue, as well as the role of stress and deformations exerted by the growing tumour. Instead, the presence of a growing mass inside the brain may be critical and dangerous for the patient: it is then important to evaluate the mechanical impact of Glioblastoma on the surrounding healthy tissue. Starting from the state-ofthe-art about brain tumour modeling, in this thesis we develop a mathematical multiphase model for GBM, based on Continuum Mechanics, which includes brain hyperelasticity, in order to study the effects of structural changes, deformations and stress on brain tissue due to the presence of a growing tumour. In particular, we consider the region occupied by the tumour as separated from the host tissue by a sharp moving interface: both the healthy and the diseased regions are treated as a saturated biphasic mixture, comprising a solid and a fluid phase. The solid phase is described as a Mooney-Rivlin hyperelastic material, while the fluid motion is determined using Darcy's law with anisotropic permeability; in the tumour region, we introduce proliferation and account for deformations subsequent to it. To include the mechanical effect of growth of the tumour mass in addition to the pure elastic deformation, we employ the natural configurations framework and the multiplicative decomposition of the deformation gradient tensor. We also include in our model an equation describing the evolution of the concentration of available nutrients, which are transported by the fluid and can diffuse into the anisotropic brain tissue. The mathematical model is then numerically solved using FEniCS, a Python-based PDE finite element solver, at first in a simplified geometry, then in a three-dimensional brain geometry using available data from MRI and DTI to build the computational domain and account for anisotropy. In the end, results are analyzed to investigate the effect of deformations and unnatural displacement induced on brain tissue by the growing Glioblastoma. Future developments might be focused on the inclusion of elastic or viscoelastic constitutive models of the brain in a diffuse-interface Cahn-Hilliard-type approach and on the plastic distorsions of brain fibers. Multiscale modelling might also be used to determine how structural changes and mechanical properties at the cellular level influence the parameters at the macroscopic scale and consequently the evolution of the tumour.

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Introduction

Cancer is nowadays the second leading cause of death worldwide, according to the World Health Organization: in particular, brain tumours constitute about 1.6% of new cancer cases every year. Among them, Glioblastoma Multiforme (GBM) is one of the deadliest: in addition to the typical features of cancer, it shows a dramatic invasive potential inside brain tissue, that makes its complete removal by surgery almost impossible leading to recurrence after a few months. Furthermore, GBM is one of the most aggressive types of cancer and exhibits a strong resistance to common therapies: the median survival time for patients undergoing a complete treatment of neurosurgery, chemotherapy and radiotherapy is about 10-16 months. Therefore, it is crucial to investigate GBM progression, in order to acquire more details and arrange efficient therapeutic strategies to fight it: to this end, mathematical and computational models can provide powerful tools to accelerate the research process, by reproducing tumour progression and predict its evolution through simulations. As a matter of fact, during the last decades several mathematical models for cancer growth in general and for Glioblastoma in particular have been proposed, proceeding alongside medical advances. The first attempts to describe GBM growth using mathematics date back to the mid-1900s, when simple equations for population dynamics were applied to cellular proliferation: nowadays, advances in Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) has allowed to refine the models, accounting for features such as heterogeneity of brain tissue, anisotropy and invasive behaviour. Recently, a consistent step forward in Glioblastoma modeling has been made thanks to the work of Colombo et al. [1] and Agosti et al. [2, 3], who developed a patient-specific computational framework capable of reproducing GBM growth including patient data obtained through DTI and MRI.

However, the vast majority of the models for GBM growth present in the literature does not account for a proper mechanical description of brain tissue. The tumour and the surrounding brain parenchyma are almost always considered either as fluids or as linear elastic materials, while experiments has clearly shown the highly nonlinear viscoelastic nature of the brain. Moreover, the presence of a growing mass inside the brain may cause unnatural displacement and stress on the host tissue that may lead to neurological damage. Hence, it is relevant to evaluate mechanical deformations subsequent to tumour growth to achieve a realistic reproduction of Glioblastoma proliferation.

Motivated by these observations, in this work we develop a mathematical model for GBM growth and proliferation which includes brain hyperelasticity, in order to evaluate the effects of structural changes and nonlinear elastic deformations of brain tissue. In particular, we propose a macroscopic model based on finite deformations and Continuum Mechanics: we treat both the tumour and the surrounding tissue as a saturated biphasic mixture, composed by a hyperelastic cell phase and an ideal fluid phase. Moreover, we consider the tumour as separated by the host tissue through a sharp interface, identified as a steep mollification of an indicator function. In order to separate the elastic deformations from the inelastic distorsions caused by growth, we employ a multiplicative decomposition of the deformation gradient. After deriving our model,

we implement it in order to perform simulations using the finite element method at first on a simplified geometry, then on a realistic brain setting with patient-specific sample data.

The work is organized as follows. In Chapter 1, we provide a short biological introduction to cancer and Glioblastoma Multiforme, so as to understand the problem we aim at reproducing. In Chapter 2, we summarize the main mechanical results that will be used to derive the model, discussing the choice of an appropriate constitutive equation for brain tissue. Then, in Chapter 3, after a brief literature review of brain tumour modeling, we thoroughly discuss the derivation of our mechanical model and of its governing equations; before moving to simulations, we provide an estimation for all the parameters that appear in the mathematical model. Chapter 4 is dedicated to numerical implementation of the model: we firstly derive a weak formulation of it and then describe how we have computationally implemented it. Lastly, in Chapter 5 we illustrate the results of our numerical simulations, both on a simplified cubic geometry and on a realistic brain geometry. Possible future developments are discussed at the end of the work, while in Appendix A the complete code employed for numerical simulation is reported.

Part I

Biological and Mechanical Introduction

Chapter 1 Biological Background

In this chapter, we provide an essential biological background: in order to develop a model for tumour growth, it is indeed necessary to firstly understand the problem at hand from the biological point of view. Then, in the first section we describe the most important features of cancer and carcinogenesis, that is, the development of a cancer. After this general introduction, we focus on brain tumours and in particular on Glioblastoma Multiforme, which is the main subject of our study. Finally, we summarize the essential characteristics of Magnetic Resonance Imaging and Diffusion Tensor Imaging.

1.1 Cancer and Carcinogenesis

The term *cancer* identifies a wide group of related diseases, which can develop almost everywhere in the human body: they are characterized by uncontrolled proliferation of some cells, the growth of which continues regardless of the mechanisms that control cellular proliferation, eventually leading to invasion of other tissues and colonization of regions normally reserved for healthy cells [4]. These malignant cells grow more and more aggressively over time, and may become lethal if they succeed to disrupt vital tissues and organs. Nowadays, cancer is the second leading cause of death globally according to the World Health Organization (WHO): it was estimated that there have been 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018 [5]. Hence, it is not difficult to understand the importance of a thorough and complete investigation of all the mechanisms involved in tumour genesis, proliferation and elimination. As a matter of fact, research in the field has consistently grown in recent years, starting to involve many subjects in addition to medicine and biology, including mathematics and physics. In order to study growth and proliferation of cancer from a mathematical and physical point of view, which is the objective of this work, it is however necessary to understand the main biological features of such a disease.

Normally, in a healthy human body, cells grow, duplicate and die according to precise mechanisms of regulation mediated by specific genes and proteins. Such activators and inhibitors allow the body to maintain a strict control over cells proliferation and programmed death, or *apoptosis*, and to induce duplication when needed. For instance, when some cells grow old or become damaged, they die and are replaced by new ones through duplication, because they are instructed to do so; similarly, when a mutation in the DNA occurs, the cell attempts to fix it: in case of failure, the cell undergoes apoptosis and eliminates itself, in order to prevent undesired changes and to protect the whole organism from dangerous alterations. However, sometimes these processes may not work properly and malfunctions may take place, causing a cell to escape control and become abnormal: this is where *carcinogenesis*, or the generation of cancer, begins.

Clearly, a single mutation is not usually sufficient to transform a healthy cell in a cancerous one; however, the mutated DNA is inherited by its descendants: over the years, an accumulation of mutations can gradually lead from an initial mild disorder in cell behaviour to the development of typical cancer characteristics, such as uncontrolled proliferation and resistance to apoptosis. An abnormal, mutated cell that starts growing and proliferating out of control will give rise to a mass of diseased cells with the same mutated DNA, and hence with the same dangerous capability to overduplicate: such a mass is called a *tumour* or *neoplasm*. As long as the neoplastic cells do not become invasive, however, the tumour is said to be *benign*: in this case, it grows slowly and does not spread into the surrounding tissues or in the vasculature; removing or destroying a local benign tumour usually achieves a complete cure and prevents clinical complications. A tumour is considered a cancer only if it becomes *malignant*, namely, if its mutated cells have acquired the ability to spread out and invade other tissues [4]. However, even in the case of a benign tumour, one needs to be careful and not to underestimate its potential danger: for instance, as regards brain tumours, the limited space within the skull means that a large growth may put pressure on brain areas and cause neurological problems.

More precisely, after the aforementioned sequence of genetic alterations, the development of cancer takes place in a multistep process. Although not all cancers share the same features, two common macro-stages are usually identified, as far as solid tumours are concerned [6, 7, 8]: an *avascular* and a *vascular* phase. During the former, the tumour remains in a localized state with dimensions of a few millimeters in diameter, and can only receive nutrients by diffusion. At this stage, tumours form three-dimensional avascular nodules called *multicell spheroids*, in which an external layer of proliferating cells surrounds a region composed of quiescent cells. Meanwhile, cells located at the centre of the spheroid, being deprived of vital nutrients and oxygen, begin to die and progressively form a *necrotic core*. During the avascular phase, in addition to excessive proliferation (*hyperplasia*), tumour cells start to appear abnormal in shape and orientation (*dysplasia*), but have not yet spread to other tissues.

The very high rate at which tumour cells reproduce causes a fast consumption of nutrients and consequently slows down the growth. Even if this situation might seem favourable at first glance, we know that it is not actually good at all. The invasive potential of a tumour can go far beyond: as a result of further mutations, the tumour may acquire the ability to invade the surrounding tissues and also colonize distant parts of the body. This new features mark the transition from the avascular to the vascular phase, which is called as such because the neoplasm starts to break the healthy host tissue and to drive angiogenesis, i.e. the formation of new blood vessels from existing capillaries. It is worth to remark that angiogenesis is in itself a physiological mechanism: oxygen and nutrients are crucial for cell function and survival, obligating virtually all cells in a tissue to stay within 100 μ m of a capillary vessel [9]. Indeed, apart from normal conditions, there exist some circumstances in which the body needs to create or expand the vascular network, such as wound healing, ischemia reperfusion, mammary gland vascularization and myocardial infarction [10]. However, angiogenesis becomes a pathological phenomenon when exploited by a growing tumoural mass suffering from hypoxia, i.e. a lack of oxygen: as a clear display of its parasitical and invasive behaviour, the tumour induces new blood vessels from the surrounding tissue to sprout towards itself, with the aim to provide itself an adequate nutrient supply.

In order to accomplish this vascularization, tumours secrete a number of diffusible chemical substances into the surrounding environment, mainly called *Tumour Angiogenic Factors* (TAFs)

and Vascular Endothelial Growth Factors (VEGFs) [11]. In response to these stimuli, nearby endothelial cells (EC) of blood vessels proliferate and migrate following the chemical gradient towards the tumour. Later, angioproteins promote the migration of muscle cells that form the intermediate layer around the new endothelial one, leading to the complete formation of a new vessel; during angiogenesis, capillaries may branch forming secondary vessels, which can fuse together and form loops: this phenomenon is known as anastomosis. The process continues with the formation of additional sprouts and loops until the development of a new vascular network which penetrates the tumour, providing it a supply of oxygen and nutrients: clearly, the vascularization of the tumour leads to an increase in its growth rate and to a faster progression. To sum up, five biological phases of angiogenesis can be identified [12]: initiation, characterized by changes in the endothelial cells shape and by increased permeability of the vessels; progression, which includes migration and proliferation of ECs; differentiation, during which ECs stop to grow and differentiate into primitive blood vessels; maturation, which includes the recruitment of smooth muscle cells and remodelling of the new vascular network; guidance, in which the architecture of the mature vasculature is delineated.

One of the most relevant and at the same time most dangerous consequences of tumour vascularization is the occurrence of *metastases*, i.e. secondary tumours arising from the primary mass at distant locations. Once it has become malignant, cancer spreads out and invades other tissues exploiting the vasculature: diseased cells can detach from the primary tumour and enter the circulatory or lymphatic system, eventually reaching another organ through blood circulation (Fig. 1.1). Six steps can be defined in the process of metastases formation [13]:

- *detachment*, which is probably allowed because of a decrease in cellular adhesive interactions with their neighbours;
- *invasion*. The cells break through the basal lamina (a layer of extracellular matrix that separates cells from the surrounding tissue) by using specific enzymes like matrix metalloproteases (MMPs);
- *intravasation*. After breaking the basal lamina, cancer cells migrate and eventually reach a blood vessel, entering the circulation: this operation is likely if the tumour is vascularised, because the new vasculature created by angiogenesis facilitates the penetration into the blood stream;
- *transport and arrest*. During their travel through circulation, cancer cells are subjected to immunological attacks: however, some of them may be able to escape and survive. Moreover, circulating cancer cells can interact with blood components and form aggregates whose size help retention and arrest in the circulation;
- *extravasation*. After stopping in the circulation, cancerous cells develop adhesive interactions with the endothelial cell lining and then migrate outside the blood stream;
- *invasion of the target organ*: diseased cells produce growth factors that induce changes in the new location, and start developing a secondary cluster of cancer cells.

Metastatic cancer dramatically increases a patient's likelihood of death, since it is a signal that the malignant tumour has become invasive: as a consequence, its complete removal or cure becomes harder. It was estimated that metastases are the cause of 90% of human cancer deaths [14].

Finally, following the work of Hanahan and Weinberg, we summarize the typical *hallmarks* of cancer, namely, some characteristics which can be considered as common to all types of cancers



Figure 1.1: Pathway from primary tumour formation to metastatic colonization [15].

and that together identify the acquired malignant capabilities of a neoplastic cell. In a first version of their work [9], six hallmarks were proposed (Fig. 1.2):

- Self-sufficiency in growth signals. Healthy cells require specific growth signals before they can move from a quiescent to a proliferative state: such behaviour contrasts with that of cancer cells, which show a greatly reduced dependence on external growth stimulation. Hence, tumour cells must generate autonomously many of their own growth signals, reducing their dependence on stimulation.
- Insensitivity to anti-growth signals. Within a normal tissue, growth-inhibitory signals act to maintain cellular quiescence and homeostasis. However, cancerous cells develop the ability to circumvent such signals, and as a consequence begin to grow out of control.
- *Evading apoptosis.* An healthy cell possesses a system of sensors which are responsible for monitoring its inside and outside environment. If conditions of abnormality are detected, for instance DNA damage or hypoxia, the sensors activate a programmed death pathway. Being themselves aberrant and dangerously mutated, neoplastic cells must find a way to avoid apoptosis, which represents an obstacle to their development.
- Limitless replicative potential. The three previous hallmarks guarantee the abnormal cell autonomy in proliferation and allow it to circumvent physiological controls. However, researches suggest that disruption of signaling is not on its own sufficient to ensure expansive growth: it was demonstrated [16] that healthy cells in culture have a finite replicative potential and, after a certain number of duplications, they stop growing. On the contrary, tumour cells in culture seem to be immortal: this result suggests that, during tumour progression, premalignant cells exhaust their allowed number of doublings. Consequently, they have to find a way to breach this barrier and to acquire limitless replicative potential.
- Sustained angiogenesis. As it was discussed above, at a certain point of tumour development vascularization becomes necessary to ensure nutrients supply and enhance neoplasm expansion.

• *Tissue invasion and metastasis.* The ability to create distant settlements and invade other tissues is a peculiarity of a malignant tumour, as mentioned before.



Figure 1.2: The first six hallmarks of cancer [9].

In 2011, two additional hallmarks have been identified [17]: the *reprogramming of energy metabolism* and the ability of *evading immune destruction*. The former is related to the acquired capability of tumour cells to modify their metabolism in order to sustain uncontrolled proliferation, while the latter refers to the avoidance of immunological destruction.

The acquisition of the hallmarks can happen in variable order: some genetic mutations may confer several capabilities simultaneously, while in other cases a hallmark can be accessed only through the collaboration of multiple genetic alterations. It is however made possible by two enabling characteristics: the first is the development of *genetic instability*, which generates random mutations and rearrangements that can ignite the appearance of cancer features; the second is the tumour-promoting role of *inflammation*. As regards the latter, it is nowadays known that the inflammation response associated to the presence of a tumour may have the paradoxical effect of enhancing tumour progression, by supplying fundamental molecules such as survival factors and angiogenic factors to the tumour microenvironment.

1.2 Brain Tumours and Glioblastoma Multiforme

1.2.1 Classification of brain tumours

Brain and nervous system tumours constitute about 1.6% of new cancer cases every year [5]. A first classification splits them into two major groups: *primary* and *secondary* tumours. The former are tumours that start in the brain and may spread to other parts of the central nervous system, but rarely invade other tissues of the body, while the latter are metastatic cancers coming to the brain from tumours that have started elsewhere. Metastatic brain tumours are more common than primary ones: up to a half of metastases in the brain come from lung cancer,

which is the most widespread type of malignant neoplasm [18, 5].

A second classification proposed by the WHO [19] and currently accepted within the medical community divides brain tumours into several groups according to the type of cells they affect: a summary of the principal groups is reported in Table 1.1. Before discussing the main features of each type and then focusing on the one which is primarily studied in the present work, namely, Glioblastoma Multiforme, we briefly provide an introduction to the cells of the nervous system, in order to simplify the understanding of the related classification.

The cells composing the central nervous system can be divided into two broad categories: nerve cells, or *neurons*, and supporting cells, called *neuroglia* or simply glia [20, 21]. The neuron is the information-processing and information-transmitting element of the nervous system: it is a very specialized cell with the ability of being electrically excitable. Most neurons consist of a soma, which corresponds to the cell body and contains the nucleus, and many dendrites branching from the soma: they receive and transmit information to and from other neurons through the synapses. The information conveyed by synapses on the neuronal dendrites is integrated and read out at the origin of the axon, the portion of the nerve cell specialized for signal conduction to the next site of synaptic interaction. It is a long, slender tube (it may extend even for a few hundred micrometers) which carries the action potential, a brief electrochemical impulse that permits communication between nerve cells.

However, neurons constitute only about half the volume of the central nervous system. They have a very high rate of metabolism but have no means of storing nutrients, so they must constantly be supplied with nutrients and oxygen or they will quickly die: the role played by cells that support and protect neurons is therefore very important and is performed by the glia. Glial cells hold neurons in place, control their supply of nutrients and keep the tissue clean by removing dead neurons. There are several types of glial cells: the most important ones in the central nervous system are astrocytes, oligodendrocytes, microglia and ependymal cells. Astrocytes are star-shaped cells which provide physical support and nourishment to neurons; they also control the chemical composition of the fluid surrounding the neurons by taking up or releasing substances whose concentration must be kept within critical levels. The principal function of oligodendrocytes is to provide support to axons and to produce the myelin sheath, which surrounds and insulates axons from one another. Microglia cells - together with astrocytes - act as cleaners of the nervous system, removing dead and dying neurons; they also protect the brain from invading micro-organisms and are responsible for the inflammatory reaction in response to brain damage. Finally, ependymal cells line the ventricular system of the brain: they take part in the production of the cerebrospinal fluid and promote its circulation.

We can now outline some of the main groups composing the 2016 WHO classification of central nervous system tumours [19]. There are about 150 different types of brain tumours: in this work we are mainly interested in gliomas which, as the name suggests, affect glial cells and are the most common primary malignant brain tumours. Among gliomas, we can distinguish between *astrocytic tumours* or astrocytomas, which begin in astrocytes; *oligodendroglial tumours* or oligodendrogliomas, affecting oligodendrocytes; *ependymal tumours* that involve ependymal cells; *mixed gliomas* or oligoastrocytomas, affecting both astrocytes and oligodendrocytes; *mixed neuronal-glial tumours*. According to WHO standards, central nervous system cancers are also categorized by their behaviour and malignity using four grades:

• grade I (or low grade) tumours, which are circumscribed and characterized by cells that look almost normal under a microscope, growing relatively slowly. Grade I tumours may often be cured if they are completely removed by surgery;

Tumour type	Name	Grade	Incidence
	Diffuse astrocytoma	II	10-15%
	Anaplastic astrocytoma	III	10-15%
Diffuse astrocytic/oligodendroglial	Glioblastoma	IV	12 - 15%
, <u> </u>	Oligodendroglioma	II	2-3%
	Anaplastic oligodendroglioma	III	1-2%
Other estreautie	Pilocytic astrocytoma	Ι	5-6%
Other astrocytic	Giant cell astrocytoma	Ι	$<\!1\%$
En en demaal	Ependynoma	II	5%
Ependymai	Anaplastic ependynoma	III	1%
Other gliomas	Angiocentric glioma	Ι	<1%
Mixed neuroglial	Ganglioglioma	Ι	1%

Table 1.1: Classification of some brain tumours according to the WHO standards (2016) [19].

- grade II tumours, that grow faster than grade I and may spread to nearby healthy tissue, making them incurable by only surgery. They are more likely to come back if removed and may evolve into a higher-grade neoplasm;
- grade III tumours, which are malignant and present abnormal cells. They are very likely to spread into nearby tissues and tend to come back;
- grade IV tumours, the most malignant, spread very quickly and show both pathological angiogenesis and necrosis, i.e. unnatural cellular death. They are invasive and resistant to common therapies.

Grade classification of the main mentioned gliomas and tumours is summarized in Table 1.1. In particular, the 2016 update of WHO brain tumours classification shows a relevant change from past standards: while in the past astrocytic and oligodendroglial tumours had been divided into strictly separate groups, now all *diffusely infiltrating gliomas* (both astrocytic and oligodendroglial) are grouped together. This kind of classification underlines the invasive nature of such tumours, in addition to the type of nervous cells they affect: diffuse gliomas infiltrate as single cells within the host healthy tissue, making complete removal by surgery almost impossible. More specifically, glioma cells detach from the primary tumour core as a consequence of reduction of cell-cell adhesion and microenvironmental changes: then, by degrading the ECM, they create a route and migrate to other parts of the brain [22]. Concerning this invasion mechanism, an interesting feature of glioma cells is the so-called *migration-proliferation dychotomy*: migrating cells seem to have a reduced proliferation rate with respect to actively proliferating cells. This mechanism of phenotypic plasticity, which has been called *Go-or-Grow* [23], was also included in some mathematical models, as we will discuss later.

1.2.2 Glioblastoma Multiforme

In the present work, we focus on grade IV diffusely infiltrating astrocytoma, also called Glioblastoma Multiforme (GBM). It is the most aggressive and malignant among gliomas, as well as the most common: as a matter of fact, it accounts for up to 15% of all primary brain tumours and 60-75% of all astrocytic tumours; it also accounts for the majority of gliomas (45.6%) [24, 25]. Moreover, GBM also exhibits dramatic invasive potential and resistance to common therapies: even with a complete treatment including neurosurgery, chemotherapy and radiotherapy, the median survival time is about 12-16 months [26].

From an historical point of view, the first to identify glioblastoma as a glial neoplasm was Rudolf Virchow in 1863. For many years it was known as *spongioblastoma multiforme* [27], until Bailey and Cushing [28] in 1926 proposed the name Glioblastoma Multiforme. Even if the word "multiforme" is currently no longer a part of the WHO classification, the abbreviation GBM is still commonly used and accepted in the literature to refer to glioblastoma. Moreover, the origin of such a suffix is eloquent: it was meant to describe the appearance and morphology of the tumour, which is characterized by necrosis, hemorrhages and cysts. Depending on the amount of such features, glioblastoma can take various forms and may appear very different from an individual to another.

Besides the typical hallmarks of cancer, glioblastoma shows propensity for necrosis, high invasive potential and genomic instability. It frequently seems to grow along the fibres of the white matter or along vessels, following the physical structures in the extracellular matrix of the neighbouring brain. Moreover, GBM tends to show three-dimensional and irregular growth patterns [29].

A distinction that can be made among glioblastomas, following the 2016 WHO classification, splits them into two main categories according to the presence or absence of mutations in gene IDH. IDH-wildtype glioblastoma (also called primary glioblastoma) develops *de novo* in the brain and is the most frequent form of this cancer. Instead, IDH-mutant glioblastoma, which is also referred to as secondary glioblastoma, arises from a malignant evolution of other tumours, like diffuse or anaplastic astrocytoma [19]. In Table 1.2 we report a comparison between some features of primary and secondary glioblastoma.

Feature	Primary GBM	Secondary GBM
Synonym	IDH-wildtype	IDH-mutant
Precursor lesion	None	Diffuse/Anaplastic astrocytoma
Proportion of GBMs	90%	10%
Mean age at diagnosis	62 years	44 years
Male-to-female ratio	1.42:1	1.05:1
Median survival time	15 months	31 months

Table 1.2: Comparison between some distinctive features of primary and secondary glioblastoma [19]. The median survival time is referred to patients undergoing a complete treatment, i.e. surgery, chemotherapy and radiotherapy.

As far as treatment is concerned, brain tumours in general and GBM in particular are extensively resistant to therapies, especially chemotherapy. This is mainly due to the presence of the *blood-brain barrier*, which is a selectively permeable barrier between the blood and the fluid that surrounds the cells of the brain [21]. Even if the function of the blood-brain barrier is indeed protective, since it avoids the absorption of undesired chemicals into the brain, it turns out to be a double-edged sword for tumour treatment: many drugs are not able to cross the barrier and reach the neoplasm they are supposed to target. Moreover, due to its deeply infiltrating nature and its multi-scale heterogeneity, from the molecular to the tissue level, GBM is even more difficult to treat than other tumours; at the present time, a curative treatment does not exist. Palliative treatments such as neurosurgery, chemotherapy and radiotherapy are employed to improve patients' quality of life and to extend their survival time. A complete treatment usually starts with surgery and removal of as much of tumour mass as possible: however, complete removal is almost impossible because of infiltration, so this type of cancer is very likely to appear again. Another relevant issue connected to neurosurgery is the fragility of brain tissue: the proximity of eloquent areas and structures of the brain limits the surgeon's ability to fully resect GBM [29]. Tumour resection immediately decompresses the brain, reducing intracranial pressure and delaying cancer progression, increasing at the same time the likelihood of response to chemotherapy and radiotherapy. After removal, the goal of radiation therapy is to selectively kill cancer cells without harming the healthy ones; although radiation sessions cause damage to both diseased and healthy tissues, during the time interval between treatments normal cells are able to repair themselves, while tumorous cells are not. Meanwhile, the patient is treated with chemotherapy by means of specific drugs designed to kill cancer cells.

1.3 Imaging Techniques

In this section, we briefly describe the characteristics of the main imaging techniques used in brain tumour detection, namely Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI). Medical images obtained through these techniques are employed to provide a computational reconstruction of the brain, helping to build a realistic geometry and to account for anisotropy of the brain environment. Without going into technical details, which are beyond the objectives of this work, in what follows we outline the functioning principles of MRI and DTI, so as to give an insight to the reader and favour an overall understanding. For a more detailed description of imaging physics, we refer to [30, 31].

Magnetic Resonance Imaging is a technique that allows reconstruction of detailed body images thanks to the detection of magnetic dipoles in the atomic nuclei of the organism. Basically, when protons are placed into a static magnetic field \mathbf{B} , they behave like spinning magnets and tend to align to it in spite of their thermal motion. However, since protons possess an intrinsic magnetic dipole moment due to their spin, the combination of the external field with the spin results in a precession around the direction of \mathbf{B} . This process increases the magnetization \mathbf{M} of the tissue which, under normal conditions, will be a vector aligned with the external magnetic field. The magnetization is said to be fully *longitudinal*, i.e. directed as the magnetic field, while the *transverse* magnetization (in the direction orthogonal to the magnetic field) is null.

However, if an electromagnetic radiation with a specific frequency is directed to the tissue irradiated by the magnetic field, some protons can absorb energy thanks to the *resonance* phenomenon: this results in a 90° rotation of their spin, which is the only other configuration allowed by Quantum Mechanics. Then, the protons come into phase with the external electromagnetic pulse, and therefore into phase with each other: this causes a decrease in the longitudinal magnetization, with a simultaneous increase in the transverse magnetization, which is not null anymore. If the pulse is switched off, the protons will gradually recover their original configuration: the longitudinal magnetization will return to the maximum value it had at the beginning, while the transverse magnetization will disappear. This recovery of the initial state is postulated to happen exponentially [30] and governed by two characteristic time constants:

$$M_1(t) = M_0(1 - e^{-t/T_1}), (1.1)$$

$$M_2(t) = M_0 e^{-t/T_2}, (1.2)$$

where M_1 denotes the magnitude of the longitudinal magnetization and M_2 the magnitude of the transverse magnetization, assuming that the magnetization vector was rotated by 90° at t = 0. The time constant T_1 is called *longitudinal relaxation time* and quantifies the time required for M_1 to recover: precisely, it corresponds to the time necessary for M_1 to recover 63% of its equilibrium value. T_2 is instead known as *transverse relaxation time*, related to the time that the transverse magnetization needs to disappear: more specifically, after a time T_2 the transverse magnetization drops to 37% of its starting value. By exploiting the differences in T_1 and T_2 into different tissues, it is possible to acquire signals from the M_1 and M_2 curves; two more parameters called Time to Recover (TR, the time between two consecutive pulses) and Time to Echo (TE, the time between the pulse and the acquisition of the signal) allow to associate the magnetization intensity to a colour, obtaining an MRI image. An example of T_1 and T_2 brain imaging is reported in Figure 1.3: in the T_1 -weighted MRI, the cerebrospinal fluid has the darkest appearance, grey matter is intermediate and white matter appears as the brightest; in the T_2 -weighted MRI the interstitial fluid is instead the brightest, while grey matter is brighter than white matter.



Figure 1.3: Comparison between a T_1 -weighted and a T_2 -weighted MRI brain imaging. In the T_1 image, the cerebrospinal fluid is the darkest, whilst grey matter appears dark and white matter is the brightest. Conversely, in the T_2 image the fluid is the brightest, and grey matter is brighter than white matter. Figure taken from [32].

The main advantages of MRI lie in its noninvasive nature and in its efficiency in detecting brain tumours, as well as its capability to highlight the different tissue types composing the brain. Nevertheless, MRI does not provide any information concerning the direction of the fibers, which is an important feature when dealing with invasive brain tumours as we pointed out previously: a possible way to overcome this limitation is to use Diffusion Weighted Imaging (DWI), and in particular Diffusion Tensor Imaging (DTI). DWI is a type of magnetic resonance imaging able to estimate the rate of water diffusion, due to random Brownian motion of molecules, into each element of the image; essentially, the functioning principle of DWI is the following: if a pulsed field gradient is applied to a uniform magnetic field in MRI, it will cause a phase shift in protons which depends on the position of protons themselves. However, if another pulse with the same magnitude but opposite direction is applied, phase alignment between protons should be recovered, and the original signal should be captured again; if this is not the case, it means that some molecules have moved during the time interval between the two opposite gradients. Such a loss in MRI signals is due to diffusion and can be measured to estimate the diffusion coefficient of water molecules in a specific region of the brain. Mathematically, the signal loss due to diffusion in a zone can be quantified through the equation proposed by Stejskal and Tanner [33]:

$$S = S_0 e^{-bD} \,, \tag{1.3}$$

where S_0 is the MRI signal intensity when no diffusion-field gradient is imposed, D is the diffusion coefficient and b is a parameter, called *diffusion weighting factor*, that includes all the quantities characterizing the field gradient. Equation (1.3) allows to evaluate D carrying out two measurements, one with b = 0 followed by one with $b \neq 0$, and calculating the signal intensities:

$$D = -\frac{1}{b}\ln\frac{S}{S_0}.\tag{1.4}$$

From these measurements, values of D can be inferred and assigned to each portion of the image, building a map of diffusion coefficients inside the brain. It is worth to remark that what is measured that way is not properly the diffusion coefficient, since it depends on many factors such that the microscopic structure of the brain environment, experimental conditions and so on: this is why it is often more correctly referred to as *apparent diffusion coefficient* (ADC).

If a tissue is isotropic, i.e. no preferential directions exist, the quantification of the ADC is sufficient to describe diffusion properties. However, in anisotropic tissues like white matter, where there are preferential directions, a single measurement of the ADC along a certain direction is not enough to fully characterize diffusion: as a matter of fact, performing measurements with different directions of the field gradient leads to different results. To account for this effect and describe diffusion more precisely, Diffusion Tensor Imaging (DTI) is employed. In this technique, diffusion is not characterized by a single coefficient but rather by a second-order symmetric tensor, called *diffusion tensor*:

$$\mathbb{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}.$$
 (1.5)

The diagonal components of \mathbb{D} are proportional to the apparent diffusivity along the three directions, while the off-diagonal elements are related to the magnitude of diffusivity in a direction when a gradient is applied in an orthogonal direction. With this assumption, Equation (1.3) needs to be modified as follows:

$$S = S_0 e^{-\mathbb{B}:\mathbb{D}},\tag{1.6}$$

where the diffusion-weighting factor \mathbb{B} is now a tensor as well. Hence, seven measurements are now requested to estimate the components of the diffusion tensor: one giving S_0 and six for the independent components of \mathbb{D} .

Diagonalization of the diffusion tensor allows to calculate its eigenvalues λ_1 , λ_2 , λ_3 which quantify the diffusivity along the eigenvectors \mathbf{e}_1 , \mathbf{e}_2 , \mathbf{e}_3 , respectively. They can be used to visualize the so-called *diffusion ellipsoid*, that is, an ellipsoid that spatially describes the distance covered by water molecules in a time interval Δt : the main axes of the ellipsoid are directed along the eigenvectors, and their lengths coincide with the eigenvalues. So, the ellipsoid equation is

$$\frac{\tilde{x}^2}{2\lambda_1 \Delta t} + \frac{\tilde{y}^2}{2\lambda_2 \Delta t} + \frac{\tilde{z}^2}{2\lambda_3 \Delta t} = 1, \qquad (1.7)$$

where $O \tilde{x} \tilde{y} \tilde{z}$ is the reference frame defined by the eigenvectors of \mathbb{D} , which are orthogonal since the tensor is symmetric; the eigenvalues are often considered in decreasing order, i.e. $\lambda_1 > \lambda_2 > \lambda_3$. The greatest eigenvalue λ_1 is also referred to as *longitudinal diffusivity*, since it quantifies the magnitude of diffusion along the main direction, i.e. the direction of the fibers. A scalar parameter used to quantify diffusion anisotropy is the *fractional anisotropy* (FA), that coincides with the diffusion ellipsoid eccentricity:

$$FA = \sqrt{\frac{1}{2} \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}.$$
 (1.8)

A fractional anisotropy of 0 defines an isotropic medium, where the eigenvalues are all coincident and the ellipsoid is actually a sphere, with no preferential direction of diffusion. Instead, an FA value of 1 indicates the existence of a totally preferred direction, making diffusion to occur only along one of the eigenvectors.

Other useful measures of anisotropy are given by three indices, c_l , c_p and c_s that are called *linear*, *planar* and *spherical* index, respectively. They are defined as follows [34]:

$$c_l = \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}, \quad c_p = \frac{2(\lambda_2 - \lambda_3)}{\lambda_1 + \lambda_2 + \lambda_3}, \quad c_s = \frac{3\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3}, \quad (1.9)$$

where the eigenvalues are considered in decreasing order. The meaning of these coefficients is evident from their definitions: if $c_l \approx 1$ there is only one preferential direction, identified by the first eigenvector of the tensor; if $c_p \approx 1$ there are two dominating directions that do not prevail over each other; finally, if $c_s \approx 1$, there is no preferential direction at all and the tensor is isotropic. Clearly, $c_l + c_p + c_s = 1$.

In the following chapters, after describing our mathematical model, we will run simulations on a brain geometry that has been constructed through images coming from MRI and DTI. Moreover, the diffusion tensor \mathbb{D} and the tensor of preferential directions \mathbb{A} of the brain will be estimated starting by DTI data, as we will discuss in Section 4.2.

Chapter 2

Mechanical Framework and Preliminary Results

In this chapter, we outline the mechanical framework that will be employed to derive the mathematical model of GBM growth. In summary, the theoretical foundations of the model proposed in this work lay on four main cornerstones: the theory of finite deformations and Continuum Mechanics; the theory of mixtures; the evolving natural configurations framework and the choice of appropriate constitutive equations to reproduce the mechanical behaviour of brain tissue. We collect in the following the principal results related to these four theoretical bases of our theory, establishing at the same time notations that will be used hereafter. For contents of section 2.1, refer to [35].

2.1 Kinematics and Dynamics of Continua

We consider a continuum C that occupies a fixed reference configuration \mathcal{B}_* , also known as *material or Lagrangian configuration*, in a three-dimensional space. After a fixed time t, the body will occupy a region \mathcal{B}_t , called *deformed or Eulerian configuration*. A point **X** in \mathcal{B}_* is called a *material* point.

Definition 1 A finite deformation from \mathcal{B}_* to \mathcal{B}_t is a smooth function

$$\chi: \quad \mathcal{B}_* \longrightarrow \mathcal{B}_t \tag{2.1}$$

$$\mathbf{X} \longmapsto \mathbf{x} = \chi(\mathbf{X}) \tag{2.2}$$

that maps each material point \mathbf{X} to a spatial point \mathbf{x} in the deformed configuration.

If A denotes a set of material points, or more simply a material set, then

$$\mathcal{A}_t = \chi(A)$$

represents the set of spatial points occupied by the material points of A at time t, and we say that A deforms to A_t at time t. Consistent with this definition, we say that a time-dependent spatial set A_t convects with the body if there is a set A of material points such that $A_t = \chi(A)$ for all t.

A finite deformation only describes the transition between the reference configuration and the deformed one, without accounting for how that happens and what happens during the time interval. If t is allowed to vary, we obtain a deformation for each time instant: this collection represents a *motion* of the body, denoted by

$$\mathbf{x} = \chi(\mathbf{X}, t), \qquad (\mathbf{X}, t) \in \mathcal{B}_* \times (0, T).$$
(2.3)

Basically, by fixing t in a motion we have a finite deformation of the body, while by fixing **X** we obtain the trajectory described by the particle that occupied position **X** in \mathcal{B}_* .

Definition 2 The tensor field

$$\mathbb{F} := \nabla \chi, \qquad F_{ij} = \frac{\partial \chi_i}{\partial X_j} \tag{2.4}$$

is referred to as the deformation gradient. Its determinant, also called Jacobian, is denoted by

$$J := \det \mathbb{F} \tag{2.5}$$

and needs to be strictly positive, in order to avoid unphysical effects.

By definition, the deformation gradient maps material vectors to spatial vectors, that is, if $d\mathbf{X}$ is an infinitesimal vector in $\mathbf{X} \in \mathcal{B}_*$, the corresponding infinitesimal vector in the deformed configuration is

$$d\mathbf{x} = \mathbb{F}d\mathbf{X}.\tag{2.6}$$

The deformation gradient and its Jacobian are also involved in deformation of volumes and areas from the reference configuration to the deformed one. The following results, which will be widely employed in the next chapter, hold.

Theorem 1 Let $d\Sigma^*$, dV^* and **N** be an element of area, an element of volume and a unitary normal vector in the reference configuration \mathcal{B}_* , respectively, and $d\Sigma$, dV and **n** the corresponding elements in \mathcal{B}_t . Then, the following relationships hold:

$$d\mathbf{\Sigma} = J \mathbb{F}^{-T} d\mathbf{\Sigma}^*, \tag{2.7}$$

$$dV = JdV^*, (2.8)$$

$$\mathbf{n} = \mathbb{F}^{-T} \mathbf{N}.\tag{2.9}$$

The deformation of a continuum from the reference configuration \mathcal{B}_* to the deformed one \mathcal{B}_t can be equivalently described using the *displacement field* $\mathbf{u}(\mathbf{X})$, defined through

$$\mathbf{x}(\mathbf{X}) = \mathbf{X} + \mathbf{u}(\mathbf{X}). \tag{2.10}$$

In other words, the vector field \mathbf{u} quantifies the displacement of a point from its position in the material configuration:

$$\mathbf{u}(\mathbf{X}) = \mathbf{x}(\mathbf{X}) - \mathbf{X}.\tag{2.11}$$

Differentiating (2.10) with respect to the material coordinates, we obtain the relation

$$\mathbb{F} = \mathbb{I} + \operatorname{Grad} \mathbf{u},\tag{2.12}$$

where \mathbb{I} is the second order identity tensor and

Grad
$$\mathbf{u} := \frac{\partial \mathbf{u}}{\partial \mathbf{X}},$$
 (Grad \mathbf{u})_{*ij*} := $\frac{\partial u_i}{\partial X_j},$ (2.13)

is referred to as the *displacement gradient*.

An important distinction that needs to be underlined is the one between material and spatial description of fields. In general, if φ denotes a scalar, vector or tensor field defined on the body for all time, if we consider φ to be a function $\varphi(\mathbf{X}, t)$ of the material point \mathbf{X} and time t we say that we are using a *material description* of the field. But we may also consider φ to be a function $\phi(\mathbf{x}, t)$ of the spatial point \mathbf{x} and time t: this is called *spatial description* and is related to the material description through the motion, by setting:

$$\phi(\mathbf{x},t) = \varphi(\chi^{-1}(\mathbf{x},t),t). \tag{2.14}$$

In the following, unless there is danger of confusion, we will use the same symbol for both the material and spatial description. Instead, we decide to employ a different notation to distinguish between differential operators acting on different configurations: henceforth, we will use the symbols Grad and Div to denote the *material gradient* and *material divergence*, respectively, i.e. gradient and divergence with respect to the material point \mathbf{X} in the reference body. Meanwhile, ∇ and ∇ · will refer to the *spatial gradient* and *spatial divergence*, respectively, with respect to the spatial point $\mathbf{x} = \chi(\mathbf{X}, t)$. By the chain rule, for φ a scalar field and \mathbf{u} a vector field, we have

Grad
$$\varphi = \mathbb{F}^T \nabla \varphi$$
, Grad $\mathbf{u} = \nabla \mathbf{u} \mathbb{F}$. (2.15)

The velocity of a particle at time t and position \mathbf{x} is defined as

$$\mathbf{v}(\mathbf{x},t) = \frac{\partial \mathbf{x}}{\partial t} = \frac{\partial \chi(\mathbf{X},t)}{\partial t} = \frac{\partial \chi(\chi^{-1}(\mathbf{x},t),t)}{\partial t}.$$
(2.16)

Following a similar reasoning as before, given a field φ we can define a *material time-derivative*, or Lagrangian derivative, as

$$\dot{\varphi}(\mathbf{X},t) = \frac{\partial \varphi(\mathbf{X},t)}{\partial t},\tag{2.17}$$

where \mathbf{X} is hold fixed. The material derivative is then related to the spatial one through the chain rule, namely

$$\dot{\varphi} = \frac{d\varphi(\mathbf{x},t)}{dt} = \frac{\partial\varphi(\mathbf{x},t)}{\partial t} + \mathbf{v}(\mathbf{x},t) \cdot \nabla\varphi(\mathbf{x},t).$$
(2.18)

We now introduce some other useful quantities that will be used in the model.

Definition 3 Let χ be a motion and \mathbb{F} be its deformation gradient. Then

- $\mathbb{C} := \mathbb{F}^T \mathbb{F}$ is called right Cauchy-Green deformation tensor. By definition, it is a symmetric tensor that maps the material configuration into itself.
- The spatial tensor field $\mathbb{L} := \nabla \mathbf{v} = \dot{\mathbb{F}}\mathbb{F}^{-1}$ is called the velocity gradient. An important property of such a tensor that follows from its definition is the following:

$$\operatorname{tr} \mathbb{L} = \operatorname{tr} \nabla \mathbf{v} = \nabla \cdot \mathbf{v}. \tag{2.19}$$

Another relevant identity expressing transport of volume is

$$\dot{J} = J \operatorname{tr} \mathbb{L} = J \nabla \cdot \mathbf{v}. \tag{2.20}$$

Definition 4 Let \mathbb{M} be a generic tensor. The scalar quantities

$$I_{\mathbb{M}} := \operatorname{tr} \mathbb{M},\tag{2.21}$$

$$II_{\mathbb{M}} := \frac{1}{2} \left[(\operatorname{tr} \mathbb{M})^2 - \operatorname{tr} \mathbb{M}^2 \right], \qquad (2.22)$$

$$III_{\mathbb{M}} := \det \mathbb{M}, \tag{2.23}$$

are called first, second and third principal invariant of \mathbb{M} , respectively. By definition, they are invariant under frame of reference changes.

Proposition 1 Let \mathbb{M} be a generic non singular tensor. Then, the following identities hold:

$$\frac{\partial I_{\mathbb{M}}}{\partial \mathbb{M}} = \mathbb{I}, \tag{2.24}$$

$$\frac{\partial \mathrm{II}_{\mathbb{M}}}{\partial \mathbb{M}} = \mathrm{I}_{\mathbb{M}}\mathbb{I} - \mathbb{M}^{\mathrm{T}},\tag{2.25}$$

$$\frac{\partial \mathrm{III}_{\mathbb{M}}}{\partial \mathbb{M}} = (\mathbb{M}^2 - \mathrm{I}_{\mathbb{M}}\mathbb{M} + \mathrm{II}_{\mathbb{M}}\mathbb{I})^{\mathrm{T}}.$$
(2.26)

(2.27)

A relevant result widely employed in Continuum Mechanics is Reynolds' transport theorem.

Theorem 2 (Reynolds) Let V_t be a spatial volume that convects with the body. If ψ is a scalar field of class C^1 , then

$$\frac{d}{dt} \int_{V_t} \psi \, dV = \int_{V_t} \left(\dot{\psi} + \psi \nabla \cdot \mathbf{v} \right) \, dV = \int_{V_t} \left(\frac{\partial \psi}{\partial t} + \nabla \cdot (\psi \mathbf{v}) \right) \, dV. \tag{2.28}$$

If the set V_t is not convecting, Reynolds' relation needs to be modified as follows.

Theorem 3 Let V_t be a non-convecting set, $\psi \in C^1$ scalar field and $w_n := (\mathbf{v}_{\Sigma} - \mathbf{v}) \cdot \mathbf{n}$ the velocity of the boundary ∂V_t relative to the velocity of the body \mathbf{v} . Then,

$$\frac{d}{dt} \int_{V_t} \psi \, dV = \int_{V_t} \left(\dot{\psi} + \psi \nabla \cdot \mathbf{v} \right) \, dV + \int_{\partial V_t} \psi w_n \, d\Sigma.$$
(2.29)

In the present work, we will assume that stresses can be represented by the *Cauchy stress* tensor: formally, if **t** denotes the traction per unit area of the body, there exists a tensor field \mathbb{T} such that

$$\mathbf{t}(\mathbf{n}) = \mathbb{T}\mathbf{n}.\tag{2.30}$$

Since we will be working extensively with Lagrangian coordinates, it is useful to recall the laws for transformations of vectors and tensors from the deformed configuration to the reference one, known as *Piola transformations*.

Definition 5 Let \mathbf{u} and \mathbb{M} be a vector and a tensor field, respectively, defined on the current configuration. If \mathbb{F} is the deformation gradient associated to a motion χ , then the material field

$$\mathbf{u}^* := J \mathbb{F}^{-1} \mathbf{u} \tag{2.31}$$

is said to be the Piola transform of **u**. Similarly, the material tensor field

$$\mathbb{M}^* := J\mathbb{M}\mathbb{F}^{-T} \tag{2.32}$$

is said to be the Piola transform of \mathbb{M} .

In particular, the Piola transform of the Cauchy stress

$$\mathbb{P} := J \mathbb{T} \mathbb{F}^{-T} \tag{2.33}$$

is known in Continuum Mechanics as first Piola-Kirchhoff stress tensor.

2.2 Mixture Theory

Since in our model the brain and the tumour will be represented as a mixture of cells and fluid, in this section we outline the main features of mixture theory. Basically, such a theory allows to describe mathematically a continuum C composed by an arbitrary number of phases interacting with one another; there are no sharp boundaries between the phases: it would be almost impossible, in a complex domain, to trace those microscopical interfaces. Even if we tried, it would be impractical to deal with fields which, given the different nature of the phases, would be discontinuous. Instead, the properties of a multiphase body are defined at every material point and at every time instant as an average over a proper spherical neighbourhood of the point called microscopic representative elementary volume (REV): the system is then schematized as a mixture of interacting and "overlapping" continua [36]. This approach permits to exploit all the instruments of Continuum Mechanics presented in Section 2.1 and to treat the problem at a macroscopic scale using continuous fields for macroscopic variables. The macroscopic effects of the microscopic configuration are retained in the form of coefficients that are created in the process of averaging.

A basic feature of mixture theory and porous media mechanics is that all the phases are supposed to be distributed throughout the whole domain. This implies that samples of a sufficiently large volume (the REV), taken at different locations within the domain, will always contain all the involved phases: we denote such a volume by $V_t := V(\mathbf{x}, t)$. Inside V_t , each phase α has a mass $m_{\alpha}(\mathbf{x}, t)$ and occupies a volume $V_{\alpha}(\mathbf{x}, t)$: we can then define a *true* mass density for the α -th phase

$$\gamma_{\alpha}(\mathbf{x},t) := \frac{m_{\alpha}(\mathbf{x},t)}{V_{\alpha}(\mathbf{x},t)},\tag{2.34}$$

which is the density of the phase relative to its own volume inside the REV, and an *apparent* mass density

$$\rho_{\alpha}(\mathbf{x},t) := \frac{m_{\alpha}(\mathbf{x},t)}{V(\mathbf{x},t)},\tag{2.35}$$

calculated instead with the REV as reference. They are related through the concept of *volume* fraction, that is, the volume occupied by the α -th constituent over the total volume:

$$\phi_{\alpha}(\mathbf{x},t) := \frac{V_{\alpha}(\mathbf{x},t)}{V(\mathbf{x},t)} = \frac{\rho_{\alpha}(\mathbf{x},t)}{\gamma_{\alpha}(\mathbf{x},t)}.$$
(2.36)

Obviously, for any phase, we have $\phi_{\alpha} \in [0,1]$. It follows that the apparent mass density can be obtained by the true mass density using the relation:

$$\rho_{\alpha} = \phi_{\alpha} \, \gamma_{\alpha}. \tag{2.37}$$

The mixture is said to be *saturated* if the phases fill the entire control volume without voids: this implies that

$$\sum_{\alpha=1}^{N} \phi_{\alpha} = 1 \qquad \forall \mathbf{x} \in \mathcal{B} \ \forall t.$$
(2.38)

Starting from these concepts, we can derive the mass balance equations for a mixture: in principle, each phase has to satisfy its own mass balance, which can be written in integral formulation as

$$\frac{d}{dt} \int_{V_t} \rho_\alpha \, dV = \int_{V_t} \Gamma_\alpha \, dV \qquad \forall \alpha = 1, \dots, N,$$
(2.39)

where $\Gamma_{\alpha}(\mathbf{x}, t)$ is a mass source term per unit volume of the body. Using Reynolds' transport theorem 2, one obtains

$$\int_{V_t} \left(\frac{\partial \rho_\alpha}{\partial t} + \nabla \cdot (\rho_\alpha \mathbf{v}_\alpha) \right) \, dV = \int_{V_t} \Gamma_\alpha \, dV, \tag{2.40}$$

where \mathbf{v}_{α} is the velocity field of the α -th phase. If all the involved quantities are smooth and we require that (2.40) holds for every volume, we arrive at the Eulerian local form of the mass balance for a single phase:

$$\frac{\partial \rho_{\alpha}}{\partial t} + \nabla \cdot (\rho_{\alpha} \mathbf{v}_{\alpha}) = \Gamma_{\alpha}, \qquad (2.41)$$

or equivalently

$$\dot{\rho_{\alpha}} + \rho_{\alpha} \nabla \cdot \mathbf{v}_{\alpha} = \Gamma_{\alpha}. \tag{2.42}$$

Recalling (2.37) and assuming that all phases are *incompressible*, that is $\dot{\gamma}_{\alpha} = 0$, we can write

$$\dot{\phi_{\alpha}} + \phi_{\alpha} \nabla \cdot \mathbf{v}_{\alpha} = \frac{\Gamma_{\alpha}}{\gamma_{\alpha}}.$$
(2.43)

The mass balance equation can then be rephrased, under the hypothesis of incompressibility of constituents, with the volume fraction as unknown:

$$\frac{\partial \phi_{\alpha}}{\partial t} + \nabla \cdot (\phi_{\alpha} \mathbf{v}_{\alpha}) = \frac{\Gamma_{\alpha}}{\gamma_{\alpha}}.$$
(2.44)

In order to determine the velocity fields appearing in the mass balance equations, each component of a mixture must satisfy its own momentum balance equation:

$$\rho_{\alpha}\left(\frac{\partial \mathbf{v}_{\alpha}}{\partial t} + \mathbf{v}_{\alpha} \cdot \nabla \mathbf{v}_{\alpha}\right) = \nabla \cdot \widetilde{\mathbb{T}}_{\alpha} + \rho_{\alpha} \mathbf{b}_{\alpha} + \mathbf{m}_{\alpha}, \qquad (2.45)$$

where $\overline{\mathbb{T}}_{\alpha}$ is the partial Cauchy stress tensor of the α -th phase, \mathbf{b}_{α} is the body force acting on the α -th constituent and the term \mathbf{m}_{α} is the momentum supply that accounts for the interaction between different phases [37]. Since in most biological applications the motion of cells and interstitial fluid is very slow, inertial terms can be neglected when compared to the stress terms; moreover, body forces such as gravitational force are often assumed to be negligible and dominated by the stresses.

To close the model for a multiphase continuum, it is necessary to specify constitutive equations for the stresses, in order to properly account for the mechanical response to deformations. The choice of appropriate constitutive equations, especially in the case of brain tissue, is quite a delicate matter and will be discussed thoroughly in Section 2.4. Here, we recall that the saturation assumption of the constitutive equations for each phase can be characterized by a pressure contribution and an excess part:

$$\mathbb{T}_{\alpha} = -\phi_{\alpha} p \mathbb{I} + \mathbb{T}_{\alpha}. \tag{2.46}$$

The first term on the right-hand side of (2.46) accounts for the amount of pressure sustained by the α -th phase, while the second term \mathbb{T}_{α} is connected to the purely mechanical response of the constituent and needs to be derived from an appropriate constitutive equation for the α -th phase. In our case, we will have to deal with a fluid phase and a solid phase composed by brain tissue: more details regarding the choice of a constitutive expression for \mathbb{T}_{α} of the brain will be provided in Section 2.4.

2.3 Evolving Natural Configurations Framework

A fundamental aspect for the development of a realistic model is a proper description of the growing tumour, especially from the mechanical point of view. Even if in some cases it might be sufficient to treat the tumour as an ideal fluid, as it was done in early mathematical models of cancer, this approach neglects the role of deformations and stresses. As a consequence, it does not allow to investigate the role of mechanical aspects that has been shown to be relevant for tumour growth and development [40]. Furthermore, in dealing with brain tumours, it is crucial to quantify the mechanical impact that tumour growth may have on the surrounding healthy tissue: a growing cancer may exert stress and pressure on nearby brain areas and induce unnatural displacement, with possible damage. The relevance of a detailed mechanical description of a tumour is then clear: to that end, Continuum Mechanics and mixture theory represent indeed a powerful and well established framework to work with.

However, in developing a mathematical model that includes mechanics, some non trivial difficulties arise: cells duplicate and die, the environment is continuously modified and remodelled as a result of tumour growth, and when dealing with solid tumours it is not clear which reference configuration should be used to measure deformations, since the material is constantly changing [41]. In the context of tumour growth and biological applications, this problem was tackled in [42, 40, 43] by applying the concept of *evolving natural configurations*, which consists in splitting the evolution in pure elastic deformations and deformations subsequent to growth. In this section, following the modelling background proposed in [42, 44], we outline the main aspects of the natural configurations framework, which will be employed to derive our mechanical model of GBM growth.

A possible, immediate way of describing growth using classical Continuum Mechanics is to imagine that particles composing a body can be labelled in a certain reference configuration and, in going from the starting configuration to the final one, new particles appear. However, this approach turns out to be not theoretically suitable, since it makes the definition of a motion from the original configuration onto the current one impossible; as a matter of fact, with this assumption, the new particles arising from growth process would have no counterpart in the starting configuration, causing the motion to be non invertible. A possible solution to overcome this difficulty could be to solve the problem in an Eulerian frame of reference; the Eulerian approach is still not feasible when dealing with solid bodies undergoing large deformations, since boundary conditions can only be formulated in the current configuration which is an unknown of the problem. In the modeling context proposed in [42], growth is not seen as an increase in the number of particles, but rather as an increase in the mass of already existing particles. Doing so, the body has exactly the same number of particles at any time - which allows to define a motion - while the mass of the body may have changed, because of an increasing or decreasing in the mass of each particle.

Starting from this idea, we consider a body which is in a configuration \mathcal{B}_0 at time t = 0, and we suppose that such a body undergoes deformations and growth so that at time t its configuration is \mathcal{B} . During this motion, each particle of the body may have grown, and the consequent state of stress might be different from zero. We now imagine to remove a particle from the current configuration and relieve its state of stress while keeping its mass constant: at the end of this process, relaxing the constraint that the body remains integer [40], the considered particle will have a configuration which will be, in general, different from both the one it had in \mathcal{B}_0 and \mathcal{B} ; the particle is said to be in its *natural state*: the collection of all the particles taken in their natural states builds up the *natural configuration* of the body at time t, denoted by \mathcal{B}_g .

The natural configuration then represents an intermediate, useful state of the body which can

be used to decompose the global deformation \mathbb{F} into two different contributions, as pictured in Figure 2.1. As discussed first by Rajagopal [45], the deformation from the natural configuration to the current one can be measured through a tensor \mathbb{F}_{e} , while the path from \mathcal{B}_{0} to \mathcal{B}_{g} is described by another tensor \mathbb{F}_{g} . Hence, the following decomposition holds:



Figure 2.1: Multiplicative decomposition of the deformation gradient (from Lubarda, 2004 [44]). \mathcal{B}_0 denotes the reference configuration, \mathcal{B} the current configuration and \mathcal{B}_g the natural configuration of the body. We note that mass is preserved from \mathcal{B}_g to \mathcal{B} , while growth takes place in the path from \mathcal{B}_0 to \mathcal{B}_g .

The physical meaning of the two tensors introduced in this manner can be understood bearing in mind the observations of Skalak [46], who proposed the idea that growth is accompanied by incompatible deformations and residual stresses, and Rodriguez et al. [47], suggesting to decompose the deformation gradient into an elastic part and an inelastic part connected to growth. As a matter of fact, since we assumed that mass is preserved from \mathcal{B}_g to \mathcal{B} , the tensor \mathbb{F}_e in (2.47) is not directly related to growth: hence, the whole contribution of deformations due to growth processes is carried by the other tensor \mathbb{F}_g . Therefore, the multiplicative decomposition of the deformation gradient allows to separate the inelastic distortions related to growth from the pure elastic contribution, which determines the stress response of the material. In summary, recalling that the deformation gradient describes how the body is deforming locally in going from \mathcal{B}_0 to \mathcal{B} , we can say that \mathbb{F}_e tells how the body is deforming elastically from the natural configuration \mathcal{B}_g to \mathcal{B} , whilst \mathbb{F}_g are invertible as well; additionally, the determinant of the deformation gradient can be expressed as

$$J = J_{\rm e} J_{\rm g}, \tag{2.48}$$

(2.47)

where $J_{e} := \det \mathbb{F}_{e}$ and $J_{g} := \det \mathbb{F}_{g}$.

Using the same principles of reasoning, more complex decompositions of the deformation gradient may be considered to take into account other biological phenomena. For instance, one could introduce another intermediate configuration between \mathcal{B}_{g} and \mathcal{B} to model the internal plastic reorganization of the growing tissue. However, for the moment we will not include these effects in our model: for a more detailed description, the reader is referred to [43, 48].

2.4 Constitutive Equations for Brain Tissue

In order to close the model, it is necessary to prescribe constitutive equations that properly characterize the mechanical response of a material to deformations. We begin this section by briefly recalling the main results related to nonlinear elasticity, or *hyperelasticity*. Then, we discuss the problem of choosing an appropriate constitutive equation capable to represent the mechanical behaviour of brain tissue. Since our main goal is to study how a growing glioblastoma affects the healthy host tissue from a mechanical viewpoint, such a choice is crucial and not trivial at all, due to the extremely complex nature of the brain. For contents of section 2.4.1, the main references are [35] and [49].

2.4.1 Hyperelasticity

In classical mechanics, the force and energy within an elastic spring depend only on the change in length of the spring; moreover, the force is independent of the past history of the length as well as the rate at which the length is changing in time. In Continuum Mechanics, local length changes are characterized by the deformation gradient \mathbb{F} : therefore, we can extend the definition of *elastic body* by introducing a dependence of stress only on local deformation.

Definition 6 A continuum C is said to be hyperelastic if there exists a function $\sigma(\mathbb{F})$ such that

$$\mathbb{T}(\mathbb{F}) = \rho \frac{\partial \sigma}{\partial \mathbb{F}} \mathbb{F}^T, \tag{2.49}$$

where \mathbb{T} is the Cauchy stress tensor, ρ the density of the material and \mathbb{F} the deformation gradient. Equivalently, a continuum is hyperelastic if there exists a function $\mathcal{W}(\mathbb{F})$, called strain energy density function, such that

$$\mathbb{T}(\mathbb{F}) = \frac{1}{J} \frac{\partial \mathcal{W}}{\partial \mathbb{F}} \mathbb{F}^{T}, \qquad (2.50)$$

where $J = \det \mathbb{F}$.

It is worth to remark that $\mathcal{W}(\mathbb{F})$, which expresses the elastic energy per unit volume of the material, satisfies $\mathcal{W}(\mathbb{F}) = \rho_* \sigma(\mathbb{F})$, where ρ_* is the density in the reference configuration.

In order to satisfy the material frame indifference principle, which states that a constitutive equation must not depend on the adopted frame of reference, it can be shown that the following theorem holds.

Theorem 4 A hyperelastic material satisfies the frame indifference principle if and only if its strain energy density function depends on the deformation through the right Cauchy-Green strain tensor \mathbb{C} :

$$\mathcal{W}(\mathbb{F}) = \mathcal{W}(\mathbb{C}). \tag{2.51}$$

Consequently, Theorem 4 and Definition 6 impose that the general constitutive equation for a hyperelastic material reads

$$\mathbb{T}(\mathbb{F}) = 2\rho \mathbb{F} \frac{\partial \widetilde{\sigma}}{\partial \mathbb{C}} \mathbb{F}^T$$
(2.52)

$$= \frac{2}{J} \mathbb{F} \frac{\partial \widetilde{\mathcal{W}}}{\partial \mathbb{C}} \mathbb{F}^T.$$
(2.53)

An additional simplification on the constitutive equation can me made if the material is assumed to be isotropic with respect to the mechanical response: in such a case, the strain energy density is an isotropic function of \mathbb{C} , leading to the following result.

Theorem 5 A hyperelastic material that satisfies the frame indifference principle is isotropic if and only if its strain energy density function depends on \mathbb{C} only through the principal invariants, namely,

$$\widetilde{\mathcal{W}}(\mathbb{C}) = \widehat{\mathcal{W}}(I_{\mathbb{C}}, II_{\mathbb{C}}, III_{\mathbb{C}}).$$
(2.54)

In summary, the most general form of the constitutive equation describing a hyperelastic frame-indifference isotropic material is

$$\mathbb{T}(\mathbb{F}) = 2\rho \mathbb{F} \frac{\partial \widehat{\sigma}(\mathbf{I}_{\mathbb{C}}, \mathbf{II}_{\mathbb{C}}, \mathbf{III}_{\mathbb{C}})}{\partial \mathbb{C}} \mathbb{F}^{T}$$
(2.55)

$$=\frac{2}{J}\mathbb{F}\frac{\partial\widehat{\mathcal{W}}(\mathbf{I}_{\mathbb{C}},\mathbf{II}_{\mathbb{C}},\mathbf{III}_{\mathbb{C}})}{\partial\mathbb{C}}\mathbb{F}^{T}.$$
(2.56)

2.4.2 Mechanical Modeling of the Brain

Modeling the mechanical behaviour of the brain has become increasingly important over the past decades. Despite the progresses and research initiatives on how the brain functions and operates, comparatively little is known about how the brain behaves at the mechanical level. According to Goriely et al. [50], two main factors contribute to this relatively poor state of knowledge: first, the brain is a fully enclosed organ that is particularly difficult to examine and to deal with physically; second, viewed as a solid, it is extremely soft and its mechanical response is heavily influenced by a fluid phase. Nonetheless, the last decade has seen fundamental advances in brain mechanics, which was proved to have a key role in several situations and pathologies such as traumatic brain injury, brain development and brain tumours, the latter being the focus of the present work. In what follows, we review the main perspectives regarding the constitutive modeling of brain tissue, so as to make a choice for our model; it is however essential to notice that, even if many constitutive models have been proposed so far, no general consensus on which model is the best exists. In fact, several difficulties arise when dealing with experimental settings involving brain tissue: human brain specimen are not always available and must be treated carefully, since they are extremely delicate; moreover, in vitro tests need to be generalized to in vivo conditions, providing an additional complication.

A first, important remark put forward by experimental studies of Budday et al. [51] concerns the anisotropy of brain tissue. In their work, the authors have established that despite the intrinsic microstructural anisotropy due to the presence of nerve fibers, the human brain tissue is nearly isotropic from a mechanical viewpoint. As a matter of fact, no significant mechanical directional dependency was observed in their assays, even in highly anisotropic regions of the brain. Therefore, we will align ourselves to these results and consider the brain as isotropic as far as mechanics is concerned; when it comes to diffusion of substances and fluids, however, anisotropy cannot be neglected, as the same authors pointed out.

As regards the mechanical characterization, the vast majority of experimental results agree upon the highly nonlinear and viscoelastic nature of brain tissue [50, 51, 52], under different loading conditions [53, 54, 55, 56] and even with multiple loading modes [51]. In more detail, Miller [57] and Miller and Chinzei [56, 58] observed a strong stress-strain rate dependence and a tension-compression asymmetry on porcine brain tissue; they proposed firstly a linear, then a nonlinear viscoelastic model for brain behaviour at low strain rates, suitable for neurosurgical simulations. As confirmed by experimental settings performed by Rashid et al. at intermediate and dynamic strain rates both in compression [53] and in tension [54], porcine brain specimen showed a pronounced difference between the two loading conditions and a stiffer response with increasing strain rates. These results have been further reinforced by Budday et al. [51], who tested human brain specimen under shear in two orthogonal directions, compression and tension. Brain tissue showed again a nonlinear mechanical response, which was significantly stiffer in compression than in tension; shear stresses were also found to increase with increasing compressive strain but not with increasing tensile strain. Hystereses also showed up during cyclic loading: the pre-conditioning of the samples was substantial between the first and the second cycle, while it became less evident during all subsequent cycles. The authors attributed this characteristic to the porous nature of brain tissue, where interstitial fluid is gradually squeezed out of the sample; this observation is also supported by the fact that, if the specimen underwent a 60 minutes recovery period in a saline solution, their pre-conditioning behaviour was very similar to that of the initial test. Stress relaxation experiments confirmed the highly time-dependent response of the tissue, with a relaxation of up to 80% within only 300 seconds.

Once established the nonlinear viscoelastic nature of the brain, it is mandatory to identify a mechanical constitutive model able to capture its essential features. For the purposes of our work, we are interested in brain tissue's elastic response under small strain rates: in the first instance, we will not include explicit viscous contributions, assuming that all inelastic deformations are included in the growth term of the multiplicative decomposition (2.47). Therefore, we neglect time-dependent behaviour and focus on time-independent, hyperelastic constitutive modeling of brain tissue.

To that end, several models have been proposed in the literature [52]: there is a general agreement that the generalized Ogden model [59] with strain energy density function

$$\mathcal{W}^{\text{Ogd}}(\mathbb{C}) = \sum_{i=1}^{N} \frac{\mu_i}{\alpha_i} (\lambda_1^{\alpha_i} + \lambda_2^{\alpha_i} + \lambda_3^{\alpha_i} - 3), \qquad (2.57)$$

where λ_i are the principal stretches (i.e. the square roots of the eigenvalues of $\mathbb{C} = \mathbb{F}^T \mathbb{F}$), and N, μ_i, α_i are the material parameters, is suitable to represent the mechanical behaviour of soft brain tissue. In particular, fitting to experimental data by Budday et al. [51], Rashid et al. [53, 54, 55] and Mihai et al. [60] showed that a modified one-term Ogden model

$$\mathcal{W}^{\text{Ogd}}(\mathbb{C}) = 2\frac{\mu}{\alpha^2} (\lambda_1^{\alpha} + \lambda_2^{\alpha} + \lambda_3^{\alpha} - 3), \qquad (2.58)$$

where

$$\mu = \frac{1}{2}\mu_1\alpha_1$$

corresponds the classical shear modulus and $\alpha_1 = \alpha$, is able to capture the compression-tension asymmetry and the elastic behaviour of the brain with multiple loading modes simultaneously.

Budday et al. also remark the fact that parameter α needs to be given a negative value, in order to represent the effect that stresses are higher in compression than in tension; a positive value for α would yield the opposite result, not respecting experimental evidence. Some authors, including Mihai et al. [60], employed the Mooney-Rivlin model [61, 62], whose strain energy function is

$$\mathcal{W}^{\mathrm{MR}}(\mathbb{C}) = \frac{1}{2}\mu_1(\mathrm{I}_{\mathbb{C}} - 3) + \frac{1}{2}\mu_2(\mathrm{II}_{\mathbb{C}} - 3), \qquad (2.59)$$

where the parameters μ_1 and μ_2 are related to the shear modulus μ through $\mu = \mu_1 + \mu_2$. The Mooney-Rivlin model can be viewed as a special case of the Ogden model (2.57) by choosing N = 2, $\alpha_1 = 2$, $\alpha_2 = -2$:

$$\mathcal{W}^{\mathrm{MR}}(\mathbb{C}) = \frac{1}{2}c_1\left[\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3\right] - \frac{1}{2}c_2\left[\lambda_1^{-2} + \lambda_2^{-2} + \lambda_3^{-2} - 3\right]$$
(2.60)

$$= \frac{1}{2}\mu_1(I_{\mathbb{C}} - 3) + \frac{1}{2}\mu_2(II_{\mathbb{C}} - 3).$$
(2.61)

Mihai et al. [60] also proposed a four-parameter constitutive model by adding a Mooney-Rivlin-type energy (2.59) to the one-term Ogden strain energy function (2.58):

$$\mathcal{W}(\mathbb{C}) = \frac{C_0}{2\alpha} \left(\lambda_1^{2\alpha} + \lambda_2^{2\alpha} + \lambda_3^{2\alpha} - 3 \right) + \frac{C_1}{2} \left(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3 \right) + \frac{C_2}{2} \left(\lambda_1^{-2} + \lambda_2^{-2} + \lambda_3^{-2} - 3 \right).$$
(2.62)

Their model turns out to be capable of predicting the elastic behaviour of human brain tissue under combined multi-axial loading.
Part II

Model and Simulations

Chapter 3

Mathematical Model of GBM Growth

After having established both the biological and the mechanical framework in the previous chapters, we are now ready to derive our mathematical model for Glioblastoma growth and proliferation. First of all, we provide a review on brain tumour modeling and analyze the results that have been obtained so far in this field: in particular, we distinguish between macroscopic, mesoscopic, microscopic and hybrid models, discussing their strong and weak points. Afterwards, we provide a thorough derivation of our model: it is a continuum multiphase model that includes the hyperelastic nature of brain tissue, in order to investigate the mechanical impact of GBM growth. The governing equations are firstly derived in an Eulerian framework and then reformulated into a Lagrangian one. In the last part of the chapter, we provide an appropriate estimation for all the parameters, so as to simulate tumour progression realistically.

3.1 Review of Brain Tumour Modeling

As we pointed out in Chapter 1, cancer growth is an extremely complex process, involving many phenomena which occur at different scales: even if research in the field has drawn a lot of attention during the last decades, there is still much to be understood as far as tumours are concerned. In particular, concerning Glioblastoma Multiforme, there is a critical need to understand and replicate the biological complexity of the brain, in order to predict tumour evolution and arrange therapeutic strategies accordingly. The study of cancer proliferation has gradually involved researchers with different backgrounds, including mathematicians and physicists: several mathematical models of tumour growth have been proposed, with the purpose of providing a better understanding of the phenomenon while speeding up the research process through the use of computer simulations. As a matter of fact, mathematical and computational models can provide powerful instruments for investigating cancer progression, especially in those cases which are particularly difficult to be treated with current therapeutic protocols such as GBM. Before deriving our model, we review some of the main models of brain tumour growth that have been proposed: they have become increasingly sophisticated and refined during the years, using different frameworks and accounting for different characteristics of brain tissue. Advances in experimental and mechanical study of the brain progressively provided new features to the modeling process: nevertheless, as we will discuss soon, the vast majority of these models does not consider realistic mechanical and constitutive properties of brain tissue, as well as the role of deformations and stresses exerted on and by the growing tumour. Hence, in order to get a better insight into an highly lethal cancer as GBM, it is important to include a proper mechanical framework in models and simulations.

Excellent reviews on mathematical modeling of brain tumours and gliomas are the ones by Harpold et al. [63], Hatzikirou et al. [29], Rockne et al. [64] and more recently those by Goriely et al. [50], Martirosyan et al. [65] and Alfonso et al. [22].

In general, mathematical modeling of tumour growth should reproduce as much as possible the complexity of the process and the different scales on which cancer evolution takes place. As a consequence, a first distinction among models can be done by considering the scale they are meant to describe: authors usually distinguish between microscopic, mesoscopic and macroscopic scale [66, 29].

The *microscopic* scale includes all the phenomena that occur at the subcellular level, such as gene expression, cell functioning and protein cascades, while the *mesoscopic* scale focuses on interactions between single cells and structural changes at cellular level. These two scales are strongly connected to molecular biology and to the emerging field of mechanobiology, which aims at understanding how physical forces act at the cellular level. Instead, the *macroscopic* scale concentrates on processes and phenomena that take place at the tissue level, studying for instance convection and diffusion of nutrients, mechanical properties of tissues and tumours, cell migration and diffusion of metastases, visible effects of therapies. Cancer proliferation involves all these scales, which are also reciprocally influenced: this is particularly evident in invasive gliomas, where, for example, genetic mutations in signalling pathways at the microscopic level or changes in cell-cell interaction at the mesoscopic level are thought to be related to altered capability of cell migration. Progresses in mechanobiology suggest that alterations in cell mechanics have a significant role in the progression of brain tumours [50]: the attempts to develop realistic multi-scale models that might provide a link between different phenomena, however, lie on a consolidated knowledge of cellular biology of Glioblastoma, which is currently not available.

In the last decades, researchers have developed a wide variety of mathematical models for GBM growth, reflecting the previous scale classification: different approaches have contributed to explore and unravel distinct features of this cancer, as well as to address different biological questions. In the following, we firstly provide a brief overview of micro-mesoscopic models of glioma invasion; then, we focus more thoroughly on macroscopic approaches, providing a comparison between models and putting in evidence their main mathematical and biological foundations.

3.1.1 Microscopic and Mesoscopic Models

Microscopic and mesoscopic models of brain tumour proliferation mainly fulfill two objectives: the first is to reproduce the early growth of gliomas at the very beginning, when the tumour is composed by a few diseased cells and is still in its avascular phase; the second is to investigate the effects of cell interactions and microenvironmental conditions on cancer progression and invasive behaviour. Such models are based on *in vitro* experiments and allow a potentially detailed study of biophysical processes at the cellular level: since cell-cell adhesion and cell-microenvironment interactions are believed to have an important role in invasive migration [23], their investigation is of crucial importance.

At those levels, cellular automata (CA) or agent-based models (ABMs) are mostly used [29]. CA are discrete models that treat cells as points in a regular spatial two- or three-dimensional lattice: each cell is described by a state, which is updated at each discrete time step according to a precise rule. The choice of such a rule is critical and makes the difference between models: it can be deterministic, stochastic or both, and the new state may depend on several variables such as the state of the cell at the previous time step and the states of its neighbours. Instead, ABMs treat the cells as agents that interact with each other and can make simple decisions according to a set of fixed rules which are biologically justified: the goal of such models is to analyze the collective emerging behaviour of the system as a result of the possibly complex interactions between its agents. ABMs also differ from cellular automata in the fact that they are usually lattice-free, so that cells are allowed to move and change their orientation, providing a more realistic description of the phenomenon. Even if this kind of mathematical models can provide a powerful instrument to examine growth patterns at the first stages of tumour proliferation, they can be difficult to study analitically and their computational cost may become unacceptable as the number of cells increases. In fact, a tumour spheroid of 1 mm radius may include several hundred thousand cells, making the use of CA or ABMs inadequate for the simulation of significant cancer sizes [67].

For the study of gliomas, Kansal et al. [68] proposed in 2000 the first three-dimensional cellular automaton to simulate glioma growth: their model included several new features, such as a distinction between necrotic, proliferative and non-proliferative cells, and an isotropic, adaptive grid lattice, which allowed to simulate even small tumours accurately within a three orders of magnitude increase in radius. Starting from an initial distribution of about 1000 cells, the model was able to simulate growth until a fully developed tumour of 10^{11} cells; the authors also included a stochastic component in their work, giving each cell a certain probability of division at each time step.

More recently, an interesting experimental result obtained by Khain et al. [69] was explained by the same authors thanks to a 2D stochastic cellular automaton. They studied glioma cell migration in two different settings: initially away from a glioma spheroid placed on a substrate, then in a wound-healing geometry, where a scratch was made to separate cells. By measuring the migrated distance of both normal and hypoxic cells, they found that in the spheroid case there were no significant differences between the two types of cells; instead, in the wound-healing setting hypoxic cells migrated less than normal cells. This counter-intuitive result was well explained by their cellular automaton model, suggesting that hypoxia not only reduces cell motility, but also cell-cell adhesion; as a consequence, hypoxic glioma cells can detach more easily from the tumour core, enhancing their capability of invasion. Glioma cells migration on substrates of collagen and astrocytes was also investigated by Aubert et al. [70] employing a two-dimensional CA model: results indicated that interactions between tumoural cell and normal astrocytes have a role in GBM invasion; in particular, the authors showed that inhibiting glioma cells interactions favours migration, while inhibition of glioma cells-astrocytes interactions reduces it.

The ability of glioma cells to change their phenotype from proliferative to migratory according to the characteristics of the microenvironment, the so-called *phenotypic plasticity* discussed in the first chapter, has also been investigated through the use of cellular automata. Tektonidis et al. [71] proposed a lattice-based model to reproduce the migration-proliferation dychotomy: in order to achieve that, they introduced two different parallel lattices, each hosting a different cell phenotype. Resting cells reside on one lattice, while moving cells on the other. At each time step, cells can switch between phenotypes with constant probabilities. Their work shed light on the *Go-or-Grow* mechanism and, coupling it with the self-repulsion between glioma cells that was demonstrated experimentally [72], was able to reproduce experimental results. Other cellular automata models which provided insight into the duality between proliferation and migration in glioma cells are the ones by Hatzikirou et al. [73] and Bottger et al. [74]. In particular, Hatzikirou and coworkers address hypoxia as the main cause of phenotypic switching and find support to their theory in GBM resection and subsequent recurrence: when the tumour is removed, hypoxic cells that remain in the tissue become normoxic and convert themselves from an invasive to a proliferative phenotype. This observation should explain the fast recurrence after glioma removal since, if only mutations were responsible for phenotypic plasticity, repopulation would require a longer time. Although many researchers agree upon the hypotesis of migration-proliferation dichotomy as a relevant characteristic of invasive gliomas, not all the authors consider it to be a necessary property: for instance, Scribner and Fathallah-Shaykh [75] proposed a single cell model able to replicate the key features of GBM, such as the formation of a multilayer structure with necrosis and poor survival times, without including the *Go-or-Grow* mechanism.

An agent-based modeling framework was instead used by Mansury et al. [76, 77, 78] to simulate early avascular GBM growth. Starting from the assumption that tumours behave like complex self-organising systems, the authors proposed a 2D variable lattice model in which the agent-cells migrate by looking for attractive nodes, i.e. nodes that have higher nutrients concentration, low toxic metabolites concentration and reduced mechanical confinement.

3.1.2 Macroscopic Models

Discrete computational approaches such as cellular automata and agent-based models represent useful tools to explore invasive migration, phenotypic plasticity and early growth of GBM. However, they are not suitable to be studied from an analytical viewpoint and may reach an overwhelming computational cost when it comes to simulate fully developed cancers. Furthermore, CA and ABMs are not able by themselves to capture some features of Glioblastoma that may be relevant, such as the intricate anisotropy of brain tissue and its mechanical response. On the other hand, macroscopic models neglect the intrinsically discrete nature of tumours as cell aggregates, in exchange for a more flexible description provided by the instruments of Continuum Mechanics. At the macroscopic level, a cancer is treated as a continuum and described through continuous variables such as cell and nutrient concentrations, volumetric fractions and densities, whose variations are regulated by differential equations.

Throughout the years, macroscopic modeling of GBM growth has become increasingly detailed, following the experimental advances and discoveries to develop realistic models. The first attempts to provide a continuous description of tumours, in the mid-1900s, were guided by the hypotesis that cancer cells divided at almost constant rates, depending on the different types of tumours and following a simple exponential law for growth [63]. In subsequent years, several other population growth models, such as logistic or gompertzian laws, were proposed to describe cancer proliferation [64]: however, none of them accounted for the spatial distribution of cells or for their motility, which are crucial aspects when dealing with invasive gliomas.

The first development of a more refined, although still very simple, mathematical model for GBM growth is attributed to Murray and his group in the 1990s [79, 80]. In order to include cell motility and spatial dynamics together with proliferation, they proposed a conservation-diffusion equation as follows:

$$\frac{\partial c}{\partial t} = D\nabla^2 c + \rho c. \tag{3.1}$$

In (3.1), the unknown $c(\mathbf{x}, t)$ is the concentration of Glioblastoma cells at point \mathbf{x} and time t, while D is the diffusion coefficient of tumour cells and ρ is their net proliferation rate. This basic model paved the way for subsequent works and was taken as a starting point by many researchers, who tried to improve it adding more complex features. The first extension, by the same authors, considered two different cell populations c_1 and c_2 with different responses to chemotherapies:

$$\frac{\partial c_1}{\partial t} = D\nabla^2 c_1 + \rho_1 c_1 - K_1 c_1 - K_2 c_1 \,, \tag{3.2}$$

$$\frac{\partial c_2}{\partial t} = D\nabla^2 c_2 + \rho_2 c_2 - K_2 c_2. \tag{3.3}$$

In particular, population c_1 is sensitive to both the first and the second type of therapy, while population c_2 is resistant to the first and sensitive to the second. A year later, Woodward et al. [81] employed the two-population model (3.2), (3.3) to perform simulations of surgical GBM resection, by setting to zero the concentration of cells in the assumed region of removal, and studied the effects on survival time. So far, simulations assumed two-dimensional tumour growth in a homogeneous tissue and relied on clinical data derived from Computed Tomography (CT) observations.

Advances in MRI technology, however, suggested that a constant and uniform diffusion coefficient was not a proper approximation: as a matter of fact, glioma cells tend to exhibit greater motility in white matter than in grey matter. To include this heterogeneity into the model, Swanson et al. [82] allowed the diffusion coefficient to depend on position \mathbf{x} :

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\nabla c) + \rho c, \qquad (3.4)$$

where $D(\mathbf{x}) = D_w$ in white matter zones and $D(\mathbf{x}) = D_g$ in grey matter ones, with $D_w > D_g$. An assumption that has to be pointed out [82] regards the fact that equation (3.4) only represents a second phase of growth process, where a small mass has already formed before diffusion starts: otherwise, the model would only simulate a case in which tumour cells spread out in the brain, but no bulk tumour exists. The same researchers also performed simulations on a realistic brain geometry and exploited their model to investigate the effect of brain heterogeneity on drug delivery, resection and GBM invasion [83, 84, 85, 86]. Specifically, concerning chemotherapy, they proved that it may be ineffective on glioma invasion due to cell motility: invading cells not targeted by the treatment remain undetectable by MRI and lead to recurrence of cancer [64, 84]. Later, an extension of the proliferation-invasion model was proposed including hypoxia, necrosis and angiogenesis [87], so as to quantify their role in tumour progression.

To capture the specific behaviour of tumour spheroids of reduced dimensions, Stein et al. [88] relaxed the assumption made by Swanson and coworkers, proposing an advection-reactiondiffusion equation only for the invasive fraction of cells, with a source term that models the appearance of new motile cells coming from the tumour core.

Afterwards, a further relevant step in GBM modeling was made thanks to the work of Jbabdi et al. [34] who provided a refinement of Swanson's model by incorporating the effect of brain anisotropy. Indeed, it is commonly recognized that glioma cells not only migrate faster in white matter, but also move preferentially along blood vessels and white matter fiber tracts. This feature is included in the model by considering diffusion guided not by a single coefficient $D(\mathbf{x})$ but by a tensor $\mathbb{D}(\mathbf{x})$, which is reconstructed through the use of Diffusion Tensor Imaging (DTI). A more formal description of anisotropic proliferation together with a kinetic model was proposed by Painter and Hillen [89], whose results underline the importance of anisotropy in glioma development.

Other models in the literature that make use of differential equations to describe different phenomena related to Glioblastoma growth and treatment are the one by Yangjin et al. [90], which explores the evolution of the tumour microenvironment through reaction-diffusion equations for cancer cells, microglia cells and several growth factors concentrations; and the one by Hathout et al. [91] who extended Swanson's model to include an advection term, in order to refine the mathematical description of migration. Finally, as far as radiotherapy is concerned, extensions of Swanson's model including a death term due to radiation effects have been proposed [92, 93].

The continuum models presented so far are able to capture both qualitatively and quantitatively some peculiar characteristics of Glioblastoma growth: however, none of them accounts for a mechanical description of brain tissue and for the influence of a growing tumour on the surrounding healthy areas from a mechanical viewpoint. Instead, since the skull encompasses a fixed volume, the presence of a growing mass may be critical: the growth of a neoplasm could induce an unnatural displacement of the healthy tissue, known as *mass effect*, which may result in neurological injury [94].

Continuum Mechanics provides a powerful and suitable theoretical framework to model tumour growth: the employment of kinematics and balance laws is well-established, as proved by the works of Ambrosi and Mollica [42, 40], Ambrosi and Preziosi [37, 43], Ambrosi et al. [95, 96], Ben Amar and Goriely [97]. As regards brain tumours and pathologies, Clatz et al. [98] coupled diffusion with biomechanical deformation, treating brain tissue as a linear elastic material. Lang et al. [99] developed a model for propagation of damage and oedema in brain tissue using an iterative approach and Continuum Mechanics. However, more recent works on macroscopic models for Glioblastoma Multiforme growth has been developed using mixture theory in addition to classical Continuum Mechanics: the main features of such a theory were summarized in Section 2.2. Here, we review some of the main multiphase models concerning biomechanical modeling of the brain.

As much as Continuum Mechanics, the use of mixture theory in the field of mathematical biology is not a novelty: for unspecific tumour growth modeling, it has been used by Ambrosi and Preziosi [37, 43], Ambrosi et al. [100], Byrne and Preziosi [38], Sciumè et al. [101] and more recently by Giverso et al. [48] and Mascheroni et al. [102]. Concerning brain mechanics specifically, Mascheroni et al. [103] developed a multiphase model to describe the growth of Glioblastoma Multiforme spheroids: in their work, they considered the tumour as a saturated biphasic mixture, composed by a solid and a fluid phase; the constitutive equation for the stress, however, resembles the one for an elastic fluid. Ehlers and Wagner [104] proposed a more elaborated model for brain tumour growth and drug delivery, assuming the presence of three phases: an hyperelastic and mechanically anisotropic solid skeleton, the blood and the interstitial fluid, the latter further split into a liquid solvent and a dissolved therapeutic agent. Other attempts to investigate the role of biomechanical forces in brain tumour growth have been carried out by Angeli et al. [105, 106] using a biphasic isotropic model of brain tissue; unlike the previous reviewed models, they also introduce a multiplicative decomposition of the deformation gradient to distinguish the elastic and inelastic contribution to the overall deformation.

A recently developed approach for Glioblastoma Multiforme modeling employs multiphase diffuse interface models of Cahn-Hilliard [107] type. From a physical viewpoint, in the diffuse interface approach, sharp interfaces are replaced by transition layers: this is translated into mathematics by introducing a fourth-order nonlinear advection-reaction-diffusion equation analogous to the phase-field model of Cahn and Hilliard. This kind of approach has two relevant advantages: it avoids the need to impose interface conditions between the tumour and the host tissue and eliminates the necessity of tracking the interface motion explicitly. A theoretical framework for diffuse interface tumour models was proposed by Wise and coworkers [108] and was used for instance to study microstructural patterns in skin cancer [109] and tumour growth in complex microenvironmental geometries [110]. However, the application of diffuse interface to Glioblastoma growth is of our major interest: Colombo et al. [1] firstly proposed a GBM multiphase proliferation model making use of a Cahn-Hilliard-type equation, accounting also for anisotropy and heterogeneity of brain tissue through the use of DTI and MRI imaging. Agosti et al. [2, 3] then introduced and simulated therapies in the GBM diffuse interface model. Such an approach to brain tumour modeling is innovative and has all the benefits of a diffuse interface description; however, as many of the reviewed models, it treats both the healthy tissue and the tumour as fluids from a constitutive point of view, which might not be suitable to investigate mass effect and consequences of cancer-induced deformations on the brain.

3.1.3 Hybrid and Multi-Scale Models

Cancer onset and progression are inherently multi-scale processes: they consist of phenomena that take place at all the previously discussed scales. This multi-scale nature and the strong coupling between scales should be considered as much as possible in mathematical modeling, always maintaining an appropriate balance between realism and possible unnecessary complications: hybrid and multi-scale models aim at providing a connection between microscopic and macroscopic representations. They integrate both discrete and continuous variables that are used to represent individual cells or concentration fields for microenvironmental factors, respectively. Excellent reviews on hybrid mathematical models in the field of tumour growth and treatment are the ones by Rejniak and Anderson [111] and by Chamseddine and Rejniak [112]. Here, we report the main multi-scale models concerning glioma proliferation.

Frieboes et al. [113] proposed a 3D multi-scale computational model for Glioblastoma growth based on what they call functional collective cell migration units (FCCMU). Their approach is based on theoretical principles and numerical algorithms that link the tissue scale behaviour of the tumour to the underlying molecular biology: the bridging is realized through the use of experimentally tested functional relationships between the microscopic properties of cancer cells and tissue scale model parameters. The model is based on mass and momentum conservation equations nonlinearly coupled to a hybrid lattice-free model of tumor-induced angiogenesis. Simulations were able to reproduce morphological features of a growing GBM such as hypoxia, necrosis and neovascular structures around the tumour.

A different kind of hybrid model is the one developed by Khain et al. [114] which is an extension of an aforementioned microscopic model by the same authors [69]. Starting from a simple Fisher-Kolmogorov equation with constant diffusion coefficient and logistic growth term, they analyze the dependence of the propagation velocity of the resulting traveling wave upon a parameter q that quantifies cell-cell adhesion.

The work by Zhang et al. [115] investigated the impact of clonal heterogeneity on tumour growth by modeling a simplified glioma progression pathway. They employed a 3D multi-scale model which incorporates five types of glioma cells having different peculiarities and emerging sequentially. The simulated heterogeneity seems to influence glioma growth patterns and leads to asymmetries that resembles clinical observations.

Other interesting models focused on Glioblastoma phenotypic switching are proposed by Gerlee and Nelander [116, 117], who start from an agent-based stochastic model to derive a system of partial differential equations. The unknowns of this system are the densities of both proliferative and motile cells, according to the proliferation-invasion dichotomy. Their model gives insight into the dependency between microscopic parameters and macroscopic dynamics of GBM growth: simulations support the fact that tumour expansion (i.e. the velocity of the resulting traveling wave solution of the PDE system) depends non-trivially on proliferation and migration switching rates; moreover, they put in evidence that there exists a critical apoptosis rate above which the tumour cannot grow.

Lastly, we mention the hybrid mathematical model of glioma proliferation by Tanaka et al. [118]: working in radial symmetry, they employ a compartmental continuous model to describe the variation of proliferative, migrative and dead glioma cells. Then, they add a diffusion equation for the nutrients to distinguish between the proliferating rim, the hypoxic region and the necrotic core of the tumour. Finally, these equations are coupled to a stochastic invasion model for the cells that are in the migration compartment.

3.2 Model Derivation

We are now ready to derive the governing equations of our continuum, multiphase model for Glioblastoma Multiforme growth and proliferation. Although a wide variety of macroscopic models concerning brain tumour growth has been proposed in the last decades, as discussed in Section 3.1.2, the vast majority of them still lacks a proper mechanical description of brain tissue. Instead, since the mass effect due to the presence of a growing tumour inside the brain may be critical and dangerous for the patient, it is relevant to evaluate deformations, stresses and unnatural displacement caused by GBM. We then develop a mathematical model which includes brain hyperelasticity, in order to study the effects of structural changes and nonlinear elastic deformations of brain tissue. At the same time, to achieve a realistic description of Glioblastoma proliferation, we employ a sample of patient-specific data to include the anisotropy of the brain: following the path paved by Colombo et al. [1] and Agosti et al. [2, 3], the goal is to make a step forward towards the development of a mathematical and computational model able to accurately represent GBM growth.

3.2.1 Multiphase Model with Sharp Interface

In this section, we derive a macroscopic, Continuum Mechanics-based model for GBM growth using a multiphase approach and the evolving natural configurations framework, introduced in Sections 2.2 and 2.3 respectively. Following [38, 37], we consider the brain as a saturated domain comprising two distinct phases, which represent the cell population (labelled with subscript "s") and the interstitial fluid (labelled with subscript " ℓ "). Moreover, we assume that the region occupied by the tumour is well defined and completely separated from the healthy host tissue, so that the boundary between the tumour and the surrounding environment can be described by a moving interface. In particular, we denote by $\Omega_t(t)$ the subregion occupied by the growing tumour and by $\Omega_{\rm h}(t)$ the subregion occupied by the healthy tissue: they are both treated as biphasic, including a cellular and a fluid phase. In our description, we assume that the cellular phase includes healthy, diseased and necrotic cells, while the fluid phase resumes interstitial brain fluid, blood and nutrients; the distinction between cancer and host tissue is then realized through the use of a separating interface rather than through the introduction of different phases for tumorous and healthy cells. Indeed, since our main focus concerns the mass effect and the mechanical impact of the growing Glioblastoma on its surrounding tissues, this approach seems more appropriate and allows to fully distinguish the tumour from the rest of the brain tissue, accounting for the porous nature of the brain at the same time. Moreover, since we want to evaluate tissue deformation resulting from tumour proliferation, the cell phase is supposed to behave as an hyperelastic solid, whose constitutive equation will be detailed in the following sections. The liquid phase is instead considered constitutively as an ideal fluid.

The multiphase approach we employ to describe tumour growth is based on the theory of mixtures and consists of a set of mass and momentum balance equations. First of all, we assume that both the phases are intrinsically incompressible and external body forces (such as the gravitational force) as well as inertial effects are negligible: this hypotheses are reasonable when dealing with biological problems [37], since the motion of cells and interstitial fluid is very slow. Under these assumptions, recalling (2.44), (2.45) and (2.46), the general balance laws write

$$\frac{\partial \phi_{\alpha}}{\partial t} + \nabla \cdot (\phi_{\alpha} \mathbf{v}_{\alpha}) = \Gamma_{\alpha} , \quad \alpha = \mathbf{s}, \ell , \qquad (3.5)$$

$$\nabla \cdot \widetilde{\mathbb{T}}_{\alpha} + \widetilde{\mathbf{m}}_{\alpha} = \mathbf{0}, \quad \alpha = \mathbf{s}, \ell.$$
(3.6)

Equation (3.5) represents the mass balance of the α -th phase, while Equation (3.6) corresponds to the momentum balance of each phase neglecting inertia and body forces. For each phase α , ϕ_{α} denotes the volumetric fraction, \mathbf{v}_{α} is the velocity, $\widetilde{\mathbb{T}}_{\alpha}$ is the partial Cauchy stress tensor, Γ_{α} is the mass growth rate and $\widetilde{\mathbf{m}}_{\alpha}$ represents the rate at which the α -th phase exchanges momentum with the other phase.

Since we consider the medium as saturated, i.e. the two phases fill all the available space in the domain, the constraint

$$\sum_{\alpha=s,\ell} \phi_{\alpha} = \phi_s + \phi_{\ell} = 1 \tag{3.7}$$

has to hold. Consequently, summing Equation (3.5) over both phases and using (3.7) yields

$$\nabla \cdot \left(\sum_{\alpha=\mathbf{s},\ell} (\phi_{\alpha} \mathbf{v}_{\alpha}) \right) = \nabla \cdot (\phi_{\mathbf{s}} \mathbf{v}_{\mathbf{s}} + \phi_{\ell} \mathbf{v}_{\ell}) = \sum_{\alpha=\mathbf{s},\ell} \Gamma_{\alpha} = \Gamma_{\mathbf{s}} + \Gamma_{\ell} = 0, \qquad (3.8)$$

where in the last passage we have assumed that mass exchanges occur only among the constituents taken into account (the mixture is said to be *closed* with respect to mass).

The term $\widetilde{\mathbf{m}}_{\alpha}$ in Equation (3.6) contains all forces acting on the α -th phase due to its interactions with the only other present phase. Using thermodynamics arguments, one can show that it is given by a dissipative and a non-dissipative part [48, 119]:

$$\widetilde{\mathbf{m}}_{\alpha} = \widetilde{\mathbf{m}}_{\alpha}{}^{(\mathbf{d})} + p\nabla\phi_{\alpha}, \tag{3.9}$$

where p is the pressure of the interstitial fluid. The dissipative part can be expressed as

$$\widetilde{\mathbf{m}}_{\alpha}^{(\mathrm{d})} = \overline{\mathbf{m}}_{\alpha\beta} \,, \tag{3.10}$$

where the term $\overline{\mathbf{m}}_{\alpha\beta}$ represents the force acting on the α -th phase due to the other phase, denoted by subscript β . By invoking the action-reaction principle, in our case it holds that

$$\widetilde{\mathbf{m}}_{\mathbf{s}}^{(d)} = \overline{\mathbf{m}}_{\mathbf{s}\ell} = -\overline{\mathbf{m}}_{\ell\mathbf{s}} = -\widetilde{\mathbf{m}}_{\ell}^{(d)}.$$
(3.11)

3.2.2 Mass and Momentum Balance Laws

Firstly, we consider the region occupied by the tumour $\Omega_t(t)$ and write equations (3.5) and (3.6) for the two phases. We assume that, in this region, cells proliferate since the tumour is growing: from the closed mixture assumption, it follows that the mass exchange in the cellular phase happens at the expense of the liquid phase. The mass balances of the cellular and fluid phase then read:

$$\frac{\partial \phi_{\rm s}}{\partial t} + \nabla \cdot (\phi_{\rm s} \mathbf{v}_{\rm s}) = \Gamma_{\rm s} \,, \tag{3.12}$$

$$\frac{\partial \phi_{\ell}}{\partial t} + \nabla \cdot (\phi_{\ell} \mathbf{v}_{\ell}) = \Gamma_{\ell} = -\Gamma_{\rm s}.$$
(3.13)

As regards the momentum balance, we recall that, in a saturated mixture, the partial Cauchy stress associated with the α -th phase of the mixture can be written as

$$\mathbb{T}_{\alpha} = -\phi_{\alpha} \, p\mathbb{I} + \mathbb{T}_{\alpha},\tag{3.14}$$

where \mathbb{T}_{α} is referred to as *effective* (or extra-) stress, and the purely hydrostatic contribution $-\phi_{\alpha} p\mathbb{I}$ indicates the amount of pressure sustained by the α -th phase. We underline that, in the

present theory, p is a Lagrange multiplier rather than a constitutively determined quantity. Using the definitions of $\widetilde{\mathbb{T}}_{\alpha}$ and $\widetilde{\mathbf{m}}_{\alpha}$ given in (3.14) and in (3.9), (3.10) respectively, Equation (3.6) can be specialized for each phase as:

$$-\phi_{\rm s}\nabla p + \nabla \cdot \mathbb{T}_{\rm s} + \overline{\mathbf{m}}_{s\ell} = \mathbf{0}, \qquad (3.15)$$

$$-\phi_{\ell}\nabla p + \nabla \cdot \mathbb{T}_{\ell} + \overline{\mathbf{m}}_{\ell s} = \mathbf{0}.$$
(3.16)

Coherently with the hypotheses usually made to deduce Darcy's Law, we require that the extra-stress of the fluid phase \mathbb{T}_{ℓ} is negligible with respect to the pressure gradient and to the interaction forces between fluid and solid phase. As a consequence, we take Darcy's Law as a momentum balance for the fluid phase:

$$\mathbf{v}_{\ell} = \mathbf{v}_{\mathrm{s}} - \frac{\mathbb{K}(\phi_{\ell})}{\mu\phi_{\ell}}\nabla p, \qquad (3.17)$$

where \mathbf{v}_{ℓ} is the velocity of the fluid, \mathbf{v}_{s} is the velocity of the cellular phase, μ is the dynamic viscosity of the fluid component and \mathbb{K} is the permeability tensor. The dependence upon ϕ_{ℓ} can be made explicit, for instance, by taking $\mathbb{K}(\phi_{\ell}) = \frac{\phi_{\ell}^{2}}{1-\phi_{\ell}}\mathbb{K}_{0}$, with \mathbb{K}_{0} independent of ϕ_{ℓ} . However, if the fluid volumetric fraction does not significantly vary - as it is in many situations - \mathbb{K} can be assumed independent of ϕ_{ℓ} .

The momentum balance for the solid phase can then be obtained by summing (3.15) and (3.16) recalling the saturation condition (3.7) and the action-reaction principle (3.11):

$$-\nabla p + \nabla \cdot \mathbb{T}_{s} = \mathbf{0}. \tag{3.18}$$

To model the presence of white and gray matter fibers in the brain tissue and account for the consequent anisotropy in the fluid motion, we can take the permeability tensor as

$$\mathbb{K}(\phi_{\ell}) = K(\phi_{\ell})\mathbb{A},\tag{3.19}$$

where \mathbb{A} denotes the tensor of preferential directions derived through DTI and MRI imaging that will be described in Section 3.3.

In the domain occupied by the healthy tissue $\Omega_{\rm h}(t)$, the mass and momentum balance equations are similar and can be derived through an analogous reasoning: however, we assume that in the healthy region the proliferation of cells is compensated by natural cell death, so that the rate of growth $\Gamma_{\rm s}$ is equal to 0. The closed mixture assumption (3.8) immediately implies that also the source term Γ_{ℓ} must be null. Hence, the mass balances in the healthy region can be written as

$$\frac{\partial \phi_{\rm s}}{\partial t} + \nabla \cdot (\phi_{\rm s} \mathbf{v}_{\rm s}) = 0, \qquad (3.20)$$

$$\frac{\partial \phi_{\ell}}{\partial t} + \nabla \cdot (\phi_{\ell} \mathbf{v}_{\ell}) = \Gamma_{\ell} = 0.$$
(3.21)

The momentum balances are exactly the same as the ones in the tumour region (3.18) and (3.17).

3.2.3 Stress Tensors and Constitutive Equations

To close the system of mass and momentum balance equations derived in the previous section, it is necessary to determine an appropriate evolution law for the Cauchy stress tensor \mathbb{T}_s associated with the cellular tumour population, both in the diseased and in the healthy region. This

is a relevant part of this mathematical model, since our primary aim is to study how GBM growth influences mechanically the surrounding tissues and to quantify the entity of stress and deformation as a consequence of tumour proliferation. The definition of a realistic constitutive equation for brain tissue is a non trivial problem, that we summarized in Section 2.4.2 and reviewed in Section 3.1.2: in the following, we derive stress-deformations relationships employing the evolving natural configurations framework [42], whose main features have been described in Section 2.3; moreover, we treat the brain as a nonlinear elastic material: this is an innovative aspect in Glioblastoma mathematical modeling, as we pointed out in the literature review, since only very few works introduced an appropriate mechanical brain behaviour.

Tumour Cells Stress Tensor

As we mentioned previously, in the tumour region we introduce a growth term in order to study GBM proliferation. Since we are mostly interested in studying the mechanical effect of the growing tumorous mass inside the brain, we recall that a tissue undergoing growth experiences inelastic deformations and residual stresses [46, 47]. To account for this fact, a possible way is to employ a multiplicative decomposition of the deformation gradient: if we denote by \mathbb{F}_s the deformation gradient tensor of the cellular population, we have

$$\mathbb{F}_{s} = \mathbb{F}_{e} \mathbb{F}_{g}. \tag{3.22}$$

In Equation (3.22), \mathbb{F}_{e} is the purely elastic contribution to the overall deformation gradient, whereas \mathbb{F}_{g} represents the inelastic distortions related to growth. Recalling the description provided by Ambrosi and Mollica [42] and summarized in Section 2.3, the physical meaning of the multiplicative decomposition can be related to the assumption that a third configuration, called *natural configuration*, is inserted between the reference and the actual ones traditionally used in Continuum Mechanics. This natural state of the material is stress-free and corresponds to the configuration of a body undergoing inelastic deformation processes: the transition between the reference configuration and the natural one is then described by the tensor \mathbb{F}_{g} , while the subsequent elastic accomodation is included in \mathbb{F}_{e} . We also recall that throughout the path between the natural configuration and the current configuration mass is assumed to be preserved, so that growth contribution is entirely carried by \mathbb{F}_{g} .

A consequence of Equation (3.22) is that the volumetric part of the deformation gradient, $J_s = \det \mathbb{F}_s$, can be written as

$$J_{\rm s} = J_{\rm e} J_{\rm g},\tag{3.23}$$

with $J_e := \det \mathbb{F}_e$ and $J_g := \det \mathbb{F}_g$. Since the overall deformation gradient \mathbb{F}_s is assumed to be non singular, from (3.23) it follows that each tensor introduced in (3.22) is non singular as well.

Furthermore, we suppose that the tumour cell population behaves as an hyperelastic material exhibiting isotropic behaviour from its natural state, despite the anisotropic alignment of fibers: this assumption is justified by the previously mentioned results by Budday et al. [51], whose experimental assays revealed that anisotropy is not involved in the mechanical response of the brain. The choice of modeling only the elastic behaviour of the material is a simplification since, as we discussed previously, the brain response would be better approximated by a viscoelastic equation: however, in the case of tumour growth which is a very slow process, the rate dependent response can be neglected without introducing significant errors [42]. Then, proceeding as depicted in Section 2.4.2 and recalling Definition 6, we assume that the strain energy density function $W_{\rm sn}$, expressed per unit volume of the natural state, is of Mooney-Rivlin type [61, 62]. Making use of Theorems 4 and 5 as a consequence of frame indifference and isotropy, one can

write

$$\widehat{\mathcal{W}}_{\rm sn}(\mathbb{C}_{\rm e}) = \frac{1}{2} \mu_{\rm 1t} \left(I_{\mathbb{C}_{\rm e}} - 3 \right) + \frac{1}{2} \mu_{\rm 2t} \left(II_{\mathbb{C}_{\rm e}} - 3 \right), \qquad (3.24)$$

where μ_{1t} and μ_{2t} are the material parameters of the tumour while

$$I_{\mathbb{C}_{e}} = tr(\mathbb{C}_{e})$$

and

$$II_{\mathbb{C}_{e}} = \frac{1}{2} \left[\left(tr \ \mathbb{C}_{e} \right)^{2} - tr \left(\mathbb{C}_{e}^{2} \right) \right]$$

are respectively the first and second principal invariant of the right Cauchy-Green elastic deformation tensor $\mathbb{C}_{e} = \mathbb{F}_{e}^{T} \mathbb{F}_{e}$. Recalling (2.49), we know that, given the elastic energy $\sigma_{s}(\mathbb{F}_{e})$ of an isotropic hyperelastic material, the Cauchy stress tensor \mathbb{T}_{s} of the cellular phase can be expressed constitutively as

$$\mathbb{T}_{s} = \rho_{s} \frac{\partial \sigma_{s}}{\partial \mathbb{F}_{e}} \mathbb{F}_{e}^{T}.$$
(3.25)

In order to satisfy the material indifference principle, the elastic energy must depend only on the right Cauchy-Green tensor $\mathbb{C}_{e} = \mathbb{F}_{e}^{T} \mathbb{F}_{e}$: we will denote it by $\hat{\sigma}_{s}(\mathbb{C}_{e})$. The constitutive relation (3.25) is then modified as follows:

$$\mathbb{T}_{s} = 2\rho_{s}\mathbb{F}_{e}\frac{\partial\widehat{\sigma}_{s}}{\partial\mathbb{C}_{e}}\mathbb{F}_{e}^{T}.$$
(3.26)

Finally, since - as usual in the multiplicative decomposition framework - mass is supposed to be preserved during the pure elastic deformation defined by \mathbb{F}_{e} , we can relate the energy function to the strain energy density function in the natural configuration through the relation:

$$\widehat{\mathcal{W}}_{\mathrm{sn}} = \widehat{\sigma}_{\mathrm{s}} \rho_{\mathrm{sn}} = \widehat{\sigma}_{\mathrm{s}} \rho_{\mathrm{s}} J_{\mathrm{e}} = \widehat{\sigma}_{\mathrm{s}} \rho_{\mathrm{s}} \phi_{\mathrm{s}}^{-1} \phi_{\mathrm{sn}} = \widehat{\sigma}_{\mathrm{s}} \widehat{\rho}_{\mathrm{s}} \phi_{\mathrm{sn}}, \qquad (3.27)$$

where $\hat{\rho}_{s}$ denotes the true mass density of the solid phase, J_{e} is the determinant of the elastic part of the deformation gradient, while $\rho_{s} = \hat{\rho}_{s}\phi_{s}$ is the apparent mass density and ϕ_{sn} is the volumetric fraction of the cell phase in the natural state. In (3.27), we have imposed mass conservation between the natural and the current configuration:

$$\rho_{\rm sn} = J_{\rm e} \rho_{\rm s}. \tag{3.28}$$

Then, we enforced the assumption that the solid phase is incompressible, i.e. $\hat{\rho}_s$ is a constant: this allows to rewrite (3.28) in a stronger form as

$$\phi_{\rm sn} = J_{\rm e}\phi_{\rm s}.\tag{3.29}$$

As a consequence, using (3.26), (3.27) and (3.29), we can derive the expression for the Cauchy stress of the solid phase:

$$\begin{split} \mathbb{T}_{\mathrm{s}} &= 2\rho_{\mathrm{s}} \mathbb{F}_{\mathrm{e}} \frac{\partial \widehat{\sigma}_{\mathrm{s}}}{\partial \mathbb{C}_{\mathrm{e}}} \mathbb{F}_{\mathrm{e}}^{T} \\ &= 2 \frac{\widehat{\rho}_{\mathrm{s}} \phi_{\mathrm{s}}}{\widehat{\rho}_{\mathrm{s}} \phi_{\mathrm{sn}}} \mathbb{F}_{\mathrm{e}} \frac{\partial \widehat{\mathcal{W}}_{\mathrm{sn}}}{\partial \mathbb{C}_{\mathrm{e}}} \mathbb{F}_{\mathrm{e}}^{T} \\ &= 2 \frac{\phi_{\mathrm{s}}}{\phi_{\mathrm{sn}}} \mathbb{F}_{\mathrm{e}} \frac{\partial \widehat{\mathcal{W}}_{\mathrm{sn}}}{\partial \mathbb{C}_{\mathrm{e}}} \mathbb{F}_{\mathrm{e}}^{T} \\ &= 2 J_{\mathrm{e}}^{-1} \mathbb{F}_{\mathrm{e}} \frac{\partial \widehat{\mathcal{W}}_{\mathrm{sn}}}{\partial \mathbb{C}_{\mathrm{e}}} \mathbb{F}_{\mathrm{e}}^{T} \quad \text{ in } \Omega_{\mathrm{t}}(t). \end{split}$$

The constitutive expression of the Cauchy stress tensor \mathbb{T}_s must be accompanied by equations determining \mathbb{F}_s and \mathbb{F}_g . However, the tensor \mathbb{F}_s , which is entirely determined by the motion of the cell phase, is not an additional unknown for the model, whereas \mathbb{F}_g has to be determined by solving appropriate evolution equations. The evolution of \mathbb{F}_g can be obtained self-consistently by working out Equation (3.12) [48, 102, 120]. First of all, we multiply Equation (3.12) by J_s , i.e. the determinant of the overall deformation gradient \mathbb{F}_s , and rewrite it on the reference configuration as

$$\overline{J_{\rm s}\phi_{\rm s}} = J_{\rm s}\Gamma_{\rm s}.\tag{3.30}$$

Secondly, recall that we denote by $\hat{\rho}_{\alpha}$ the true mass densities of the phases and by $\rho_{\alpha} = \hat{\rho}_{\alpha}\phi_{\alpha}$ the apparent mass densities; then, $\rho_{\rm sr} = J_{\rm s}\rho_{\rm s}$ is the mass density of the solid phase in the reference configuration, while $\rho_{\rm sn} = J_{\rm e}\rho_{\rm s}$ is the mass density of the solid phase in the natural configuration. Since we are considering the cell phase as incompressible, we have

$$\phi_{\rm sr} = J_{\rm s}\phi_{\rm s} = J_{\rm e}J_{\rm g}\phi_{\rm s} = J_{\rm g}\phi_{\rm sn},\tag{3.31}$$

where ϕ_{sr} stands for the volumetric fraction of the solid phase in the reference configuration, and we have used (3.23) and (3.29). Then, substituting into the Lagrangian mass balance equation of the solid phase (3.30) and recalling (3.31) we obtain

$$\overline{J_{\rm g}\phi_{\rm sn}} = J_{\rm s}\Gamma_{\rm s},\tag{3.32}$$

$$\dot{\phi}_{\rm sn}J_{\rm g} + \dot{J}_{\rm g}\phi_{\rm sn} = J_{\rm s}\Gamma_{\rm s}.\tag{3.33}$$

Since from standard calculus it holds that $J_{g} = J_{g} \operatorname{tr}(\mathbb{L}_{g})$, where \mathbb{L}_{g} is the strain rate tensor (or velocity gradient) associated to \mathbb{F}_{g} , namely,

$$\mathbb{L}_{g} = \dot{\mathbb{F}}_{g} \mathbb{F}_{g}^{-1}, \qquad (3.34)$$

introducing this result into (3.33) one obtains

$$\dot{\phi}_{\rm sn}J_{\rm g} + J_{\rm g}\phi_{\rm sn}\operatorname{tr}(\mathbb{L}_{\rm g}) = J_{\rm s}\Gamma_{\rm s}.\tag{3.35}$$

We now make the assumption that the rate of mass change of the solid phase is entirely compensated by the volume change due to growth [42, 48, 102, 120]: this requirement leads to the condition

$$\phi_{\rm s} \operatorname{tr}(\mathbb{L}_{\rm g}) = \Gamma_{\rm s} \,. \tag{3.36}$$

Multiplying both sides of (3.36) by J_s yields

$$J_{\rm s}\phi_{\rm s}\operatorname{tr}(\mathbb{L}_{\rm g}) = J_{\rm s}\Gamma_{\rm s} \tag{3.37}$$

which, if we recall (3.31), is equivalent to

$$J_{\rm g}\phi_{\rm sn}\,{\rm tr}(\mathbb{L}_{\rm g}) = J_{\rm s}\Gamma_{\rm s}.\tag{3.38}$$

From (3.38) and (3.35) it follows immediately that ϕ_{sn} is constant in time, and it can be assumed to be known from the outset.

In the following, we will consider an isotropic growth of the form

$$\mathbb{F}_{g} = g\mathbb{I} \tag{3.39}$$

with I being the identity tensor and g a scalar field. Therefore, (3.39) leads to

$$\operatorname{tr}(\mathbb{L}_{g}) = 3\dot{g}g^{-1}.$$

Consequently, (3.36) yields

$$\frac{\dot{g}}{g} = \frac{1}{3} \frac{\Gamma_{\rm s}}{\phi_{\rm s}}, \qquad \text{in } \Omega_{\rm t}(t).$$
(3.40)

Equation (3.40) is an ordinary differential equation that, equipped with an initial condition, determines g univocally, provided that Γ_s is given constitutively. Hence, it completely determines the evolution of the growth tensor \mathbb{F}_g .

Healthy Cells Stress Tensor

As stated above, in the present work we will assume that in the host healthy tissue, i.e. in the region $\Omega_{\rm h}(t)$, the net source term $\Gamma_{\rm s}$ is null, since the death of healthy cells is compensated by proliferation. Therefore, in this case the multiplicative decomposition is not needed and the Cauchy stress tensor for the cell phase can be derived using a plain hyperelastic constitutive equation.

We still consider that the host cell population behaves as an elastic material exhibiting an isotropic behaviour, despite the anisotropic alignment of fibers which is not relevant from the mechanical point of view. As done for the tumour cell population, we will assume that the strain energy density function W_s in the healthy region, expressed per unit volume, is of Mooney-Rivlin type:

$$\widehat{\mathcal{W}}_{s}(\mathbb{C}_{e}) = \frac{1}{2} \mu_{1h} \left(I_{\mathbb{C}_{e}} - 3 \right) + \frac{1}{2} \mu_{2h} \left(II_{\mathbb{C}_{e}} - 3 \right), \qquad (3.41)$$

where μ_{1h} , μ_{2h} are the material parameters of the host tissue, \mathbb{F}_{e} is the elastic deformation gradient tensor of the healthy region, while $\mathbb{C}_{e} = \mathbb{F}_{e}^{T} \mathbb{F}_{e}$ is the right Cauchy-Green deformation tensor associated to it. Hence, the Cauchy stress tensor of the solid phase in the healthy domain is given by

$$\mathbb{T}_{s} = \frac{2}{J_{e}} \mathbb{F}_{e} \frac{\partial \widehat{\mathcal{W}}_{s}}{\partial \mathbb{C}_{e}} \mathbb{F}_{e}^{T} \qquad \text{in } \Omega_{h}(t).$$
(3.42)

We remark that, in principle, the strain energy density function of the healthy tissue might be different from the one describing the elastic behaviour of the tumour tissue.

3.2.4 Nutrients

The rate of tumour growth Γ_s is influenced by many different factors, such as the stress and the availability of nutrients [42, 40, 96, 102]. In particular, the amount of nutrients that diffuse inside the tissue and are transported by the liquid moving in the interstitial space strongly affects the cells capability to duplicate: in order to insert this kind of dependency in the growth term, it is necessary to introduce in our model an equation describing the evolution of these chemicals in the domain.

We assume that nutrients are transported by the fluid phase and can diffuse into it; at the same time, they are taken by the growing tumour and uniformly supplied by the vasculature. We introduce the hypotesis that the nutrients uptake by the healthy tissue is negligible compared to the one by the tumour tissue: biologically, this is equivalent to say that the nutrients absorbed by the host tissue are immediately replaced by the vasculature. Hence, if we denote by c_n the

concentration of available nutrients normalized with respect to the physiological concentration, so that $c_n \in [0,1]$, the mass balance of nutrients in both regions $\Omega_t(t)$ and $\Omega_h(t)$ reads

$$\frac{\partial}{\partial t}(\phi_{\ell}c_n) + \nabla \cdot (\phi_{\ell}c_n \mathbf{v}_{\ell}) = \nabla \cdot (\phi_{\ell} \mathbb{D} \nabla c_n) + \Gamma_{\ell}c_n + G_n , \qquad (3.43)$$

where ϕ_{ℓ} is the volumetric fraction of the fluid phase, \mathbf{v}_{ℓ} is the velocity of the same phase, \mathbb{D} is the diffusion tensor obtained through DTI imaging and G_n is the source term which accounts for absorption of nutrients by the tumour and increasing in concentration due to incoming nutrients. The use of a tensor in the diffusion term allows to account for the anisotropy of the brain tissue [34], that induces fluids to diffuse preferentially along certain directions. Actually, the tensor \mathbb{D} describes how water diffuses along specific directions: however, if we consider that the main nutrient for cells is oxygen which is carried by water molecules, we can take the same tensor as a descriptor of the diffusion values of nutrients.

Using standard calculus techniques, one can rewrite (3.43) as

$$c_n \frac{\partial \phi_\ell}{\partial t} + \phi_\ell \frac{\partial c_n}{\partial t} + \phi_\ell \mathbf{v}_\ell \cdot \nabla c_n + c_n \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \nabla \cdot (\phi_\ell \mathbb{D} \nabla c_n) + \Gamma_\ell c_n + G_n.$$
(3.44)

If we recall the mass balance equation of the fluid phase (3.13), (3.44) can be rephrased as

$$\frac{\partial c_n}{\partial t} + \mathbf{v}_{\ell} \cdot \nabla c_n = \frac{1}{\phi_{\ell}} \nabla \cdot (\phi_{\ell} \mathbb{D} \nabla c_n) + \frac{G_n}{\phi_{\ell}} \,. \tag{3.45}$$

In particular, in a first formulation of our model, we will consider the following form for the source term:

$$G_n = \left[-\zeta \phi_{\rm s} \phi_\ell c_n + S_n (1 - c_n) \phi_\ell\right] H_{\Omega_{\rm t}(t)} , \qquad (3.46)$$

where $H_{\Omega_t(t)}$ is the indicator function of the tumour domain $\Omega_t(t)$. This expression describes the fact that nutrients are consumed by the tumour with a constant rate ζ : the uptake depends on the volumetric fractions of cells and liquid in the tumour region, as well as on the available concentration of nutrients. Concurrently, nutrients are supplied by the vasculature at a rate S_n as far as their concentration is below the physiological value, i.e. $c_n < 1$. The delivery of nutrients is also weighted with a factor ϕ_ℓ to mathematically assert that the more fluid phase is available, the greater supply of nutrients can be provided. The whole expression is multiplied by the tumour indicator function: in the healthy region we assume that production and absorption of nutrients are reciprocally balanced. Accounting for the functional formulation of G_n assumed in (3.46), the final equation describing the evolution of normalized nutrients concentration becomes:

$$\frac{\partial c_n}{\partial t} + \mathbf{v}_{\ell} \cdot \nabla c_n = \frac{1}{\phi_{\ell}} \nabla \cdot (\phi_{\ell} \mathbb{D} \nabla c_n) + \left[-\zeta \phi_{\mathrm{s}} c_n + S_n (1 - c_n) \right] H_{\Omega_{\mathrm{t}}(t)}.$$
(3.47)

3.2.5 Constitutive Equation for the Tumour Growth Rate

Once we have introduced an equation describing the evolution of available nutrients, we can express the cell net proliferation rate Γ_s . In a first approximation, one can assume the following constitutive equation:

$$\Gamma_{\rm s} = \nu \phi_{\rm s} (1 - \phi_{\rm s}) \left(c_n - c_0 \right)_+, \qquad (3.48)$$

where $(\cdot)_+$ denotes the positive part and ν is a positive coefficient. We see that the proliferation rate depends linearly on the available concentration of nutrients c_n , provided that it is greater than a threshold c_0 : this can be thought of as the hypoxia threshold, below which tumour cells do not receive enough nourishment and stop duplicating. Consequently, the growth rate becomes zero and growth arrests. Instead, as long as $c_n > c_0$, the cell phase is allowed to grow and the proliferation is proportional to the difference between the actual nutrients concentration and the hypoxia threshold. Moreover, in (3.48), we have that growth depends on the fraction of cells that is already present - which is reasonable since cell population grows by duplication; finally, we have a factor $(1 - \phi_s)$, whose presence is explained by the necessity to decrease the proliferation rate as the cellular phase approaches saturation and fills all the available space: this accounts for the phenomenon of contact inhibition. A possible alternative formulation for Γ_s , if we want to reproduce growth interruption before complete saturation, consists in the introduction of a volumetric fraction threshold ϕ_{max} :

$$\Gamma_{\rm s} = \nu \phi_{\rm s} (\phi_{\rm max} - \phi_{\rm s}) (c_n - c_0)_+ \,. \tag{3.49}$$

More complex relations including explicitly the role of stresses may be considered: we limit to mention the one proposed by Mascheroni et al. [102, 103], that adapted to our framework reads

$$\Gamma_{\rm s} = \nu \phi_{\rm s} (\phi_{\rm max} - \phi_{\rm s}) \left(c_n - c_0 \right)_+ \left(1 - \delta_1 \frac{(\Sigma)_+}{(\Sigma)_+ \delta_2} \right), \tag{3.50}$$

where $\delta_1 < 1, \delta_2$ are positive constants that account for the role of mechanical stress on cell proliferation, and Σ is an appropriate measure of stress. For instance, to reproduce growth inhibition due to compression, one can take as stress measure the isotropic part of the Cauchy stress, namely [102]:

$$\Sigma = -\frac{1}{3}\operatorname{tr}(\mathbb{T}_{s}). \tag{3.51}$$

3.2.6 The Complete Eulerian Model

In the following, we collect together the equations governing the evolution of the system developed in the previous sections. To gather the equations for both the tumour and the healthy domain in a unified Eulerian formulation of the model, we introduce a level-set function φ such that $\varphi(t) > 0$ in $\Omega_t(t)$ and $\varphi(t) < 0$ in $\Omega_h(t)$. The introduction of such a function allows to employ an Heaviside function $H(\varphi(t))$ to distinguish between the tumour and the healthy region.

The set of equations in the domain $\Omega = \Omega_t(t) \cup \Omega_h(t)$, composed by the union of the tumour region and the healthy region, is then:

$$\partial_t \phi_{\rm s} + \nabla \cdot (\phi_{\rm s} \mathbf{v}_{\rm s}) = \Gamma_{\rm s} H(\varphi(t)), \qquad (3.52a)$$

$$\partial_t \phi_\ell + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \Gamma_\ell H(\varphi(t)) = -\Gamma_\mathrm{s} H(\varphi(t)), \qquad (3.52\mathrm{b})$$

$$\phi_{\ell} + \phi_{\rm s} = 1 \,, \tag{3.52c}$$

$$-\nabla p + \nabla \cdot \mathbb{T}_{s} = \mathbf{0}, \qquad (3.52d)$$

$$\mathbf{v}_{\ell} = \mathbf{v}_{s} - \frac{\mathbb{K}(\phi_{\ell})}{\mu \phi_{\ell}} \nabla p , \qquad (3.52e)$$

$$\dot{\mathbf{F}}_{\mathrm{s}} \mathbf{F}_{\mathrm{s}}^{-1} = \nabla \mathbf{v}_{\mathrm{s}} \,, \tag{3.52f}$$

$$\frac{\dot{g}}{g} = \frac{1}{3} \frac{\Gamma_{\rm s}}{\phi_{\rm s}} H(\varphi(t)) , \qquad (3.52g)$$

$$\partial_t c_n + \mathbf{v}_\ell \cdot \nabla c_n = \frac{1}{\phi_\ell} \nabla \cdot (\phi_\ell \mathbb{D} \nabla c_n) + \left[-\zeta \phi_{\mathrm{s}} c_n + S_n (1 - c_n)\right] H(\varphi(t)), \qquad (3.52\mathrm{h})$$

$$\partial_t \varphi + \mathbf{v}_{\rm s} \cdot \nabla \varphi = 0, \tag{3.52i}$$

where

$$\mathbb{F}_{e} = \mathbb{F}_{s} \mathbb{F}_{g}^{-1}, \qquad (3.53a)$$

$$\mathbb{F}_{g} = g\mathbb{I}, \qquad (3.53b)$$

$$\widehat{\mathcal{W}}_{\rm sn}(\mathbb{C}_{\rm e}) = \left[\frac{1}{2}\mu_{\rm 1t}\left(\mathrm{I}_{\mathbb{C}_{\rm e}} - 3\right) + \frac{1}{2}\mu_{\rm 2t}\left(\mathrm{II}_{\mathbb{C}_{\rm e}} - 3\right)\right]H(\varphi(t)) +$$
(3.53c)

+
$$\left[\frac{1}{2}\mu_{1h}\left(I_{\mathbb{C}_{e}}-3\right)+\frac{1}{2}\mu_{2h}\left(II_{\mathbb{C}_{e}}-3\right)\right]\left[1-H(\varphi(t))\right],$$
 (3.53d)

$$\mathbb{T}_{s} = 2J_{e}^{-1}\mathbb{F}_{e}\frac{\partial\widehat{\mathcal{W}}_{sn}}{\partial\mathbb{C}_{e}}\mathbb{F}_{e}^{T}, \qquad (3.53e)$$

$$\mathbb{K}(\phi_{\ell}) = K(\phi_{\ell})\mathbb{A}, \qquad K(\phi_{\ell}) = \frac{\phi_{\ell}^2}{1 - \phi_{\ell}}K_0$$
(3.53f)

$$\Gamma_{\rm s} = \nu \phi_{\rm s} (\phi_{\rm max} - \phi_{\rm s}) (c_n - c_0)_+ .$$
(3.53g)

(3.53h)

We note that the system is closed, since it features 21 scalar unknowns (the volumetric fractions ϕ_s and ϕ_ℓ , the nine components of the deformation gradient \mathbb{F}_s , the three components of the velocities \mathbf{v}_s and \mathbf{v}_ℓ , the scalar fields g, p and c_n , the function φ) and (3.52)-(3.53) constitute a set of 21 scalar equations. Once the system has been solved, the displacement field can be retrieved through the relation:

$$\mathbb{F}_{s} = \mathbb{I} + \operatorname{Grad} \mathbf{u}, \tag{3.54}$$

where Grad \mathbf{u} is defined as in (2.12).

The material interface between the tumour and the healthy tissue, $\partial \Omega_t(t)$, moves with the tumour cells, with velocity $\mathbf{v}_s|_{\partial \Omega_t}$. In particular, we have to guarantee the continuity of the displacement, stress and flux at the interface, so we have the following interface conditions to be satisfied on the two sides of the boundary:

$$\mathbf{v}_{\mathrm{s}}|_{\Omega_{\mathrm{t}}} \cdot \mathbf{n} = \mathbf{v}_{\mathrm{s}}|_{\Omega_{\mathrm{h}}} \cdot \mathbf{n} \,, \tag{3.55a}$$

$$\left[\phi_{\ell}\left(\mathbf{v}_{\ell}-\mathbf{v}_{s}\right)\right]|_{\Omega_{t}}\cdot\mathbf{n}=\left[\phi_{\ell}\left(\mathbf{v}_{\ell}-\mathbf{v}_{s}\right)\right]|_{\Omega_{h}}\cdot\mathbf{n},$$
(3.55b)

$$p|_{\Omega_{\rm t}} = p|_{\Omega_{\rm h}} , \qquad (3.55c)$$

$$\mathbb{T}_{\mathbf{s}}|_{\Omega_{\mathbf{t}}}\mathbf{n} = \mathbb{T}_{\mathbf{s}}|_{\Omega_{\mathbf{h}}}\mathbf{n}\,,\tag{3.55d}$$

$$c_n|_{\Omega_{\rm t}} = c_n|_{\Omega_{\rm h}} \,, \tag{3.55e}$$

$$\left[\phi_{\ell}c_{n}(\mathbf{v}_{\ell}-\mathbf{v}_{s})-\phi_{\ell}\mathbb{D}\nabla c_{n}\right]|_{\Omega_{t}}\cdot\mathbf{n}=\left[\phi_{\ell}c_{n}(\mathbf{v}_{\ell}-\mathbf{v}_{s})-\phi_{\ell}\mathbb{D}\nabla c_{n}\right]|_{\Omega_{h}}\cdot\mathbf{n},$$
(3.55f)

where **n** denotes the unit normal vector to $\partial \Omega_t(t)$ pointing outwards. We emphasize that the continuity of the effective stress \mathbb{T}_s (3.55d) stems from the continuity across the interface of the total stress \mathbb{T} combined with the assumption (3.55c) that requests the continuity of the pressure across the surface [102]. In fact, the saturation condition in our case implies that $\mathbb{T} = -p\mathbb{I} + \mathbb{T}_s$, which in turn implies the interface condition

$$\left[-p\mathbb{I} + \mathbb{T}_{s}\right]|_{\Omega_{t}}\mathbf{n} = \left[-p\mathbb{I} + \mathbb{T}_{s}\right]|_{\Omega_{h}}\mathbf{n}.$$
(3.56)

Hence, accounting for (3.55c), we obtain the continuity of the effective stress across the separating surface.

3.2.7 Lagrangian Formulation of the Model

The purpose of this section is to rewrite the set of equations (3.52) using a Lagrangian description of motion, where the quantities of interest are considered in terms of material coordinates. In the following, we will denote by Ω_t^* the reference configuration of the tumour, i.e. the configuration at t = 0; more generally, we will use a superscript * to denote any material element. With this notation, we recall from Theorem 1 that if we consider dV and $d\Sigma$ to be, respectively, a volume element and a surface element in the current configuration, we have

$$dV = J_{\rm s} \, dV^* \,, \tag{3.57a}$$

$$d\mathbf{\Sigma} = J_{\rm s} \mathbb{F}_{\rm s}^{-T} d\mathbf{\Sigma}^*. \tag{3.57b}$$

Moreover, from now on we will use the symbols ∇ and ∇ to denote the spatial gradient and spatial divergence, respectively, while Grad and Div will refer to the material gradient and divergence.

Integrating equation (3.52a) over the tumour domain $\Omega_t(t)$, we have:

$$\int_{\Omega_{t(t)}} \left[\partial_t \phi_s + \nabla \cdot (\phi_s \mathbf{v}_s) \right] dV = \int_{\Omega_{t(t)}} \Gamma_s dV.$$
(3.58)

Using Reynolds' transport theorem 2 and recalling that the material interface $\partial \Omega_t$ moves with the tumour cells, we obtain

$$\frac{d}{dt} \int_{\Omega_{t(t)}} \phi_{s} \, dV = \int_{\Omega_{t(t)}} \Gamma_{s} \, dV. \tag{3.59}$$

By (3.57), we write the global balance equation in the reference configuration as

$$\frac{d}{dt} \int_{\Omega_{t^*}} \phi_{\rm s} J_{\rm s} \, dV^* = \int_{\Omega_{t^*}} \Gamma_{\rm s} J_{\rm s} \, dV^*, \qquad (3.60)$$

which locally becomes

$$\dot{\overline{J_s\phi_s}} = J_s\Gamma_s. \tag{3.61}$$

As regards equation (3.52b), the same integration over the tumour domain leads to

$$\int_{\Omega_{t(t)}} \left[\partial_t \phi_\ell + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) \right] \, dV = - \int_{\Omega_{t(t)}} \Gamma_s \, dV. \tag{3.62}$$

However, since the interface does not move with the fluid, in this case we have to make use of the generalized Reynolds' transport theorem 3, which gives

$$\frac{d}{dt} \int_{\Omega_{t(t)}} \phi_{\ell} \, dV - \int_{\partial \Omega_{t(t)}} \phi_{\ell} (\mathbf{v}_{s} - \mathbf{v}_{\ell}) \cdot d\mathbf{\Sigma} = -\int_{\Omega_{t(t)}} \Gamma_{s} \, dV.$$
(3.63)

Hence, (3.57) yields

$$\frac{d}{dt} \int_{\Omega_{t}^{*}} \phi_{\ell} J_{s} \, dV^{*} - \int_{\partial \Omega_{t}^{*}} \phi_{\ell} (\mathbf{v}_{s} - \mathbf{v}_{\ell}) \cdot J_{s} \mathbb{F}_{s}^{-T} d\mathbf{\Sigma}^{*} = -\int_{\Omega_{t}^{*}} \Gamma_{s} J_{s} \, dV^{*}.$$
(3.64)

Using the divergence theorem, we obtain

$$\frac{d}{dt} \int_{\Omega_{t}^{*}} \phi_{\ell} J_{s} \, dV^{*} - \int_{\Omega_{t}^{*}} \operatorname{Div} \left[J_{s} \phi_{\ell} \mathbb{F}_{s}^{-1} (\mathbf{v}_{s} - \mathbf{v}_{\ell}) \right] \, dV^{*} = -\int_{\Omega_{t}^{*}} \Gamma_{s} J_{s} \, dV^{*}. \tag{3.65}$$

The final local balance then reads

$$\overline{J_{s}\phi_{\ell}} + \operatorname{Div}\left[J_{s}\phi_{\ell}\mathbb{F}_{s}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{s})\right] = -\Gamma_{s}J_{s}.$$
(3.66)

As regards the momentum balance of the solid phase, if we set $\mathbb{T} = -p\mathbb{I} + \mathbb{T}_s$ to be the Cauchy stress tensor of the mixture and integrate (3.52d) over the tumour domain, we obtain

$$\int_{\Omega_{t(t)}} \nabla \cdot \mathbb{T} \, dV = \mathbf{0}. \tag{3.67}$$

Using the divergence theorem and (3.57) to write the integral on the reference configuration, we have

$$\int_{\partial \Omega_t^*} J_s \mathbb{T} \mathbb{F}_s^{-T} \, d\mathbf{\Sigma}^* = \mathbf{0}.$$
(3.68)

Recalling the definition of the first Piola-Kirchhoff stress tensor $\mathbb{P} = J_s \mathbb{T} \mathbb{F}_s^{-T}$ and using again the divergence theorem, we obtain

$$\int_{\Omega_t^*} \operatorname{Div} \mathbb{P} \, dV^* = \mathbf{0},\tag{3.69}$$

which locally becomes

$$\operatorname{Div} \mathbb{P} = \mathbf{0}. \tag{3.70}$$

Finally, we rewrite (3.52e) using the Lagrangian formulation as

$$\mathbf{v}_{\ell} = \mathbf{v}_{\mathrm{s}} - \frac{\mathbb{K}}{\mu \phi_{\ell}} (\mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} p).$$
(3.71)

In fact, if we write Darcy's Law in integral form

$$\int_{S} \phi_{\ell}(\mathbf{v}_{\ell} - \mathbf{v}_{s}) \cdot d\mathbf{\Sigma} = -\int_{S} \frac{\mathbb{K}}{\mu} \nabla p \cdot d\mathbf{\Sigma}$$
(3.72)

and move the integrals to the reference configuration, we get

$$\int_{S^*} \left[\frac{\mathbb{K}}{\mu} \mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} p + \phi_{\ell} (\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}}) \right] \cdot J_{\mathrm{s}} \mathbb{F}_{\mathrm{s}}^{-T} d\mathbf{\Sigma}^* = \mathbf{0}.$$
(3.73)

If all the involved quantities are supposed to be regular, we have the local form

$$J_{\mathrm{s}}\mathbb{F}_{\mathrm{s}}^{-1}\frac{\mathbb{K}}{\mu}\mathbb{F}_{\mathrm{s}}^{-T}\operatorname{Grad} p + \phi_{\ell}J_{\mathrm{s}}\mathbb{F}_{\mathrm{s}}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}}) = \mathbf{0}, \qquad (3.74)$$

which is equivalent to

$$\mathbb{F}_{\mathrm{s}}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}}) = -\frac{1}{\mu\phi_{\ell}} \mathbb{F}_{\mathrm{s}}^{-1} \mathbb{K} \mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} p.$$
(3.75)

Multiplying both sides by \mathbb{F}_{s} we obtain

$$\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}} = -\frac{\mathbb{K}}{\mu \phi_{\ell}} \mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} p, \qquad (3.76)$$

which is precisely (3.71).

Concerning the nutrients, we start from the balance equation

$$\frac{\partial}{\partial t}(\phi_{\ell}c_n) + \nabla \cdot (\phi_{\ell}c_n\mathbf{v}_{\ell}) = \nabla \cdot (\phi_{\ell}\mathbb{D}\nabla c_n) + \Gamma_{\ell}c_n + G_n$$
(3.77)

and we integrate it over the tumour domain recalling the closed mixture assumption, obtaining:

$$\int_{\Omega_{t(t)}} \left[\partial_t(\phi_\ell c_n) + \nabla \cdot (\phi_\ell c_n \mathbf{v}_\ell) \right] dV = \int_{\Omega_{t(t)}} \nabla \cdot (\phi_\ell \mathbb{D} \nabla c_n) dV - \int_{\Omega_{t(t)}} (\Gamma_s c_n - G_n) dV. \quad (3.78)$$

Using Reynolds transport theorem and Gauss theorem, we have

$$\frac{d}{dt} \int_{\Omega_{t(t)}} \phi_{\ell} c_n \, dV - \int_{\partial \Omega_{t(t)}} \phi_{\ell} c_n (\mathbf{v}_s - \mathbf{v}_{\ell}) \cdot d\mathbf{\Sigma} = \int_{\partial \Omega_{t(t)}} \phi_{\ell} \mathbb{D} \nabla c_n \cdot d\mathbf{\Sigma} + \int_{\Omega_{t(t)}} (\Gamma_s c_n - G_n) \, dV.$$
(3.79)

If we rewrite the integrals on the reference configuration, the balance becomes:

$$\frac{d}{dt} \int_{\Omega_{t}^{*}} \phi_{\ell} c_{n} J_{s} dV^{*} - \int_{\partial \Omega_{t}^{*}} \phi_{\ell} [c_{n} (\mathbf{v}_{s} - \mathbf{v}_{\ell}) + \mathbb{D}\mathbb{F}_{s}^{-T} \operatorname{Grad} c_{n}] \cdot J_{s} \mathbb{F}_{s}^{-T} d\mathbf{\Sigma}^{*} = -\int_{\Omega_{t}^{*}} (\Gamma_{s} c_{n} J_{s} - G_{n} J_{s}) dV^{*}, \qquad (3.80)$$

so that its local version is

$$\overline{J_{s}\phi_{\ell}c_{n}} - \operatorname{Div}[J_{s}\phi_{\ell}c_{n}\mathbb{F}_{s}^{-1}(\mathbf{v}_{s}-\mathbf{v}_{\ell})] - \operatorname{Div}[J_{s}\phi_{\ell}\mathbb{F}_{s}^{-1}\mathbb{D}\mathbb{F}_{s}^{-T}\operatorname{Grad}c_{n}] = -\Gamma_{s}c_{n}J_{s} + G_{n}J_{s}.$$
 (3.81)

Recalling the mass balance of the fluid phase (3.66), (3.81) can be rephrased as

$$J_{s}\phi_{\ell}\dot{c_{n}} + J_{s}\phi_{\ell}\mathbb{F}_{s}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{s}) \cdot \operatorname{Grad} c_{n} - \operatorname{Div}[J_{s}\phi_{\ell}\mathbb{F}_{s}^{-1}\mathbb{D}\mathbb{F}_{s}^{-T}\operatorname{Grad} c_{n}] = G_{n}J_{s}, \qquad (3.82)$$

which finally becomes

$$\dot{c_n} + \mathbb{F}_{\mathrm{s}}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}}) \cdot \operatorname{Grad} c_n - \frac{1}{J_{\mathrm{s}}\phi_{\ell}} \operatorname{Div}[J_{\mathrm{s}}\phi_{\ell}\mathbb{F}_{\mathrm{s}}^{-1}\mathbb{D}\mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} c_n] = \frac{G_n}{\phi_{\ell}}.$$
(3.83)

To close the mathematical problem, we need to prescribe a constitutive equation for the elastic component of the first Piola-Kirchhoff stress tensor \mathbb{P}_s . Recalling its definition and doing

some calculation, we obtain:

$$\mathbb{P}_{\mathrm{s}} = J_{\mathrm{s}} \mathbb{T}_{\mathrm{s}} \mathbb{F}_{\mathrm{s}}^{-T} \tag{3.84}$$

$$=2J_{\rm s}J_{\rm e}^{-1}\left(\mathbb{F}_{\rm e}\frac{\partial\widehat{\mathcal{W}}_{\rm sn}}{\partial\mathbb{C}_{\rm e}}\mathbb{F}_{\rm e}^{T}\right)\mathbb{F}_{\rm s}^{-T}$$
(3.85)

$$= 2J_{\rm g}J_{\rm e}J_{\rm e}^{-1}\,\mathbb{F}_{\rm e}\frac{\partial\widehat{\mathcal{W}}_{\rm sn}}{\partial\mathbb{C}_{\rm e}}\mathbb{F}_{\rm e}^{T}(\mathbb{F}_{\rm e}\mathbb{F}_{\rm g})^{-T}$$
(3.86)

$$=2J_{\rm g}\mathbb{F}_{\rm e}\frac{\partial\widehat{\mathcal{W}}_{\rm sn}}{\partial\mathbb{C}_{\rm e}}\left((\mathbb{F}_{\rm e}\mathbb{F}_{\rm g})^{-1}\mathbb{F}_{\rm e}\right)^{T}$$
(3.87)

$$=2J_{\rm g}\mathbb{F}_{\rm e}\frac{\partial\widehat{\mathcal{W}}_{\rm sn}}{\partial\mathbb{C}_{\rm e}}\mathbb{F}_{\rm g}^{-T}$$
(3.88)

$$=2J_{g}\mathbb{F}_{s}\mathbb{F}_{g}^{-1}\frac{\partial\widehat{\mathcal{W}}_{sn}}{\partial\mathbb{C}_{e}}\mathbb{F}_{g}^{-T},$$
(3.89)

where in the last passage we highlighted the meaning of the first Piola tensor and the formal analogy with (3.26).

3.2.8 The Complete Lagrangian Model

To sum up, the set of equations in Lagrangian form in the tumour reference domain Ω^*_t is:

$$\dot{\overline{J}_{s}\phi_{s}} = J_{s}\Gamma_{s}, \qquad (3.90a)$$

$$\frac{\dot{J}_{s}\phi_{\ell}}{J_{s}\phi_{\ell}} + \operatorname{Div}\left[J_{s}\phi_{\ell}\mathbb{F}_{s}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{s})\right] = -J_{s}\Gamma_{s}, \qquad (3.90b)$$

$$\phi_{\rm s} + \phi_{\ell} = 1, \qquad (3.90c)$$

$$\operatorname{Div} \mathbb{P} = \mathbf{0} \,, \tag{3.90d}$$

$$\mathbf{v}_{\ell} = \mathbf{v}_{\mathrm{s}} - \frac{\mathbb{K}(\phi_{\ell})}{\mu \phi_{\ell}} (\mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} p), \qquad (3.90e)$$

$$\dot{g} = \frac{g}{3} \frac{\Gamma_{\rm s}}{\phi_{\rm s}} \,, \tag{3.90f}$$

$$\dot{c_n} + \mathbb{F}_{\mathrm{s}}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}}) \cdot \operatorname{Grad} c_n - \frac{1}{J_{\mathrm{s}}\phi_{\ell}} \operatorname{Div}[J_{\mathrm{s}}\phi_{\ell}\mathbb{F}_{\mathrm{s}}^{-1}\mathbb{D}\mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} c_n] = \frac{G_n}{\phi_{\ell}}, \qquad (3.90g)$$

where

$$\mathbb{F}_{e} = \mathbb{F}_{s} \mathbb{F}_{g}^{-1}, \qquad (3.91a)$$

$$\mathbb{F}_{g} = g\mathbb{I}, \quad J_{g} = \det \mathbb{F}_{g}, \qquad (3.91b)$$

$$\widehat{\mathcal{W}}_{\rm sn}(\mathbb{C}_{\rm e}) = \frac{1}{2} \mu_{\rm 1t} \left(I_{\mathbb{C}_{\rm e}} - 3 \right) + \frac{1}{2} \mu_{\rm 2t} \left(II_{\mathbb{C}_{\rm e}} - 3 \right) \,, \tag{3.91c}$$

$$\mathbb{P} = -p\mathbb{I} + \mathbb{P}_{s}, \qquad \mathbb{P}_{s} = 2J_{g}\mathbb{F}_{e}\frac{\partial\widehat{\mathcal{W}}_{sn}}{\partial\mathbb{C}_{e}}\mathbb{F}_{g}^{-T}$$
(3.91d)

$$\mathbb{K}(\phi_{\ell}) = K(\phi_{\ell})\mathbb{A}, \qquad K(\phi_{\ell}) = \frac{\phi_{\ell}^2}{1 - \phi_{\ell}}K_0$$
(3.91e)

$$\Gamma_{\rm s} = \nu \phi_{\rm s} (\phi_{\rm max} - \phi_{\rm s}) (c_n - c_0)_+ , \qquad (3.91f)$$

$$G_n = -\zeta \phi_\ell \phi_{\rm s} c_n + S_n \phi_\ell (1 - c_n) \,. \tag{3.91g}$$

A similar reasoning can be employed to derive the Lagrangian equations in the healthy tissue reference domain $\Omega_{\rm h}^*$, recalling that in this region we do not consider proliferation and we assume that production and consumption of nutrients are balanced. Eventually, we are lead to the following set of equations in the healthy domain:

$$\overline{J_{\rm s}\phi_{\rm s}} = 0\,,\tag{3.92a}$$

$$\overline{J_{s}\phi_{\ell}} + \operatorname{Div}\left[J_{s}\phi_{\ell}\mathbb{F}_{s}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{s})\right] = 0, \qquad (3.92b)$$

$$\phi_{\rm s} + \phi_{\ell} = 1 \,, \tag{3.92c}$$

$$\operatorname{Div} \mathbb{P} = \mathbf{0}, \qquad (3.92d)$$

$$\mathbf{v}_{\ell} = \mathbf{v}_{\mathrm{s}} - \frac{\mathbb{K}(\phi_{\ell})}{\mu \phi_{\ell}} (\mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} p), \qquad (3.92e)$$

$$\dot{g} = 0, \qquad (3.92f)$$

$$\dot{c_n} + \mathbb{F}_{\mathrm{s}}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{\mathrm{s}}) \cdot \operatorname{Grad} c_n - \frac{1}{J_{\mathrm{s}}\phi_{\ell}} \operatorname{Div}[J_{\mathrm{s}}\phi_{\ell}\mathbb{F}_{\mathrm{s}}^{-1}\mathbb{D}\mathbb{F}_{\mathrm{s}}^{-T} \operatorname{Grad} c_n] = 0.$$
(3.92g)

The set of constitutive assumptions (3.91) still holds, provided that in the healthy region we assume $\mathbb{F}_{g} = \mathbb{I}$, since there is no growth there, and possibly change the material parameters by considering μ_{1h} and μ_{2h} . Then, the effective unknowns of the problem are the volumetric fractions ϕ_{s} and ϕ_{ℓ} , the scalar fields g, c_{n} and p, the displacement field of the solid phase \mathbf{u}_{s} and the fluid velocity \mathbf{v}_{ℓ} .

For the sake of a more compact notation, in the following we set

$$\mathbf{w}_{\ell s}^* := \mathbb{F}_{\mathbf{s}}^{-1}(\mathbf{v}_{\ell} - \mathbf{v}_{\mathbf{s}}), \tag{3.93}$$

$$\mathbb{K}^* := J_{\mathbf{s}} \mathbb{F}_{\mathbf{s}}^{-1} \mathbb{K} \mathbb{F}_{\mathbf{s}}^{-T}, \tag{3.94}$$

$$\mathbb{D}^* := J_{\mathrm{s}} \mathbb{F}_{\mathrm{s}}^{-1} \mathbb{D} \mathbb{F}_{\mathrm{s}}^{-T}.$$
(3.95)

Then, denoting by $H_{\Omega_t^*}$ the indicator function of the tumour reference domain, the complete

Lagrangian model in the domain $\Omega^* = \Omega^*_t \cup \Omega^*_h$ becomes:

$$\overline{J_{\rm s}\phi_{\rm s}} = J_{\rm s}\Gamma_{\rm s}H_{\Omega_{\rm t}^*}\,,\tag{3.96a}$$

$$\overline{J_{\mathrm{s}}\phi_{\ell}} + \mathrm{Div}\left[J_{\mathrm{s}}\phi_{\ell}\mathbf{w}_{\ell\mathrm{s}}^*\right] = -J_{\mathrm{s}}\Gamma_{\mathrm{s}}H_{\Omega_{\mathrm{t}}^*}, \qquad (3.96\mathrm{b})$$

$$\phi_{\rm s} + \phi_{\ell} = 1 \,, \tag{3.96c}$$

$$\operatorname{Div} \mathbb{P} = \mathbf{0}, \qquad (3.96d)$$

$$J_{\mathbf{s}}\phi_{\ell}\mathbf{w}_{\ell\mathbf{s}}^{*} = -\frac{1}{\mu}\mathbb{K}^{*}\operatorname{Grad} p, \qquad (3.96e)$$

$$\dot{g} = \frac{g}{3} \frac{\Gamma_{\rm s}}{\phi_{\rm s}} H_{\Omega_{\rm t}^*} , \qquad (3.96f)$$

 $J_{s}\phi_{\ell}\dot{c}_{n} + J_{s}\phi_{\ell}\mathbf{w}_{\ell s}^{*} \cdot \operatorname{Grad} c_{n} - \operatorname{Div}[\phi_{\ell}\mathbb{D}^{*}\operatorname{Grad} c_{n}] = J_{s}G_{n}, \qquad (3.96g)$

$$\mathbb{P}_{s} = 2J_{g}\mathbb{F}_{s}\mathbb{F}_{g}^{-1}\frac{\partial\widehat{\mathcal{W}}_{sn}}{\partial\mathbb{C}_{e}}\mathbb{F}_{g}^{-T}, \qquad (3.96h)$$

$$\Gamma_{\rm s} = \nu \phi_{\rm s} (\phi_{\rm max} - \phi_{\rm s}) (c_n - c_0)_+ , \qquad (3.96i)$$

$$G_n = \left[-\zeta \phi_\ell \phi_{\rm s} c_n + S_n \phi_\ell (1 - c_n)\right] H_{\Omega_{\rm t}^*} \,. \tag{3.96j}$$

As for the Eulerian case, we need to provide appropriate conditions at the interface between the tumour and the host tissue. We recall that for a general balance equation in Lagrangian form

$$\overline{\psi J} = bJ - \operatorname{Div} \Phi_*, \tag{3.97}$$

where ψ is the quantity of interest, J is the determinant of the deformation gradient tensor and Φ_* is the Piola transform of the vector field Φ :

$$\mathbf{\Phi}_* = J \mathbb{F}^{-1} \mathbf{\Phi},$$

the boundary conditions are written as

$$\llbracket \psi J \, \mathbf{v}_{\Sigma_*} \cdot \mathbf{N} - \mathbf{\Phi}_* \cdot \mathbf{N} \rrbracket = 0, \tag{3.98}$$

where $\llbracket \cdot \rrbracket$ denotes the jump across the interface Σ_* , **N** is the unit normal vector directed outwards and

$$\mathbf{v}_{\Sigma_*} \cdot \mathbf{N} = (\mathbf{v}_{\Sigma} - \mathbf{v}) \cdot \mathbb{F}^{-T} \mathbf{N}.$$

Applying this general formula to (3.90) and considering N to be the unit normal field pointing outward the tumour reference domain, we obtain the following set of boundary conditions:

$$\left[\!\left[\mathbf{v}_{s} \cdot \frac{\mathbb{F}_{s}^{-T} \mathbf{N}}{\left[\mathbb{F}_{s}^{-T} \mathbf{N}\right]}\right]\!\right]_{\partial\Omega} = 0, \qquad (3.99a)$$

$$\llbracket \phi_{\ell} J_{\mathbf{s}} \mathbb{F}_{\mathbf{s}}^{-1} (\mathbf{v}_{\mathbf{s}} - \mathbf{v}_{\ell}) \cdot \mathbf{N} \rrbracket |_{\partial \Omega} = 0, \qquad (3.99b)$$

$$\llbracket (-J_{\mathrm{s}}p\mathbb{F}_{\mathrm{s}}^{-T} + \mathbb{P}_{\mathrm{s}})\mathbf{N} \rrbracket|_{\partial\Omega} = \mathbf{0}, \qquad (3.99c)$$

$$\llbracket p \rrbracket|_{\partial\Omega} = \mathbf{0} \,, \tag{3.99d}$$

$$\llbracket c_n \rrbracket|_{\partial\Omega} = \mathbf{0}\,,\tag{3.99e}$$

$$[\![J_{\mathbf{s}}\phi_{\ell}c_{n}\mathbb{F}_{\mathbf{s}}^{-1}(\mathbf{v}_{\mathbf{s}}-\mathbf{v}_{\ell})\cdot\mathbf{N}+J_{\mathbf{s}}\phi_{\ell}\mathbb{F}_{\mathbf{s}}^{-1}\mathbb{D}\mathbb{F}_{\mathbf{s}}^{-T}\operatorname{Grad}c_{n}\cdot\mathbf{N}]\!]|_{\partial\Omega}=0.$$
(3.99f)

Given that $[\![-J_s \mathbb{F}_s^{-T} \mathbf{N}]\!]|_{\partial\Omega} = \mathbf{0}$, it is possible to rephrase the previous set of interface conditions as

 $[\![J_{\mathbf{s}}\mathbb{F}_{\mathbf{s}}^{-1}\mathbf{v}_{\mathbf{s}}\cdot\mathbf{N}]\!]_{\partial\Omega} = 0, \qquad (3.100a)$

 $[\![\mathbb{K}^* \operatorname{Grad} p \cdot \mathbf{N}]\!]|_{\partial\Omega} = 0, \qquad (3.100b)$

$$\mathbb{P}_{s}\mathbf{N}]|_{\partial\Omega} = \mathbf{0}, \qquad (3.100c)$$

$$\llbracket p \rrbracket|_{\partial\Omega} = \mathbf{0}, \tag{3.100d}$$
$$\llbracket c_n \rrbracket|_{\partial\Omega} = \mathbf{0}, \tag{3.100e}$$

$$c_n ||_{\partial\Omega} = \mathbf{0} \,, \tag{3.100e}$$

$$\llbracket J_{\mathbf{s}}\phi_{\ell}c_{n}\mathbb{F}_{\mathbf{s}}^{-1}(\mathbf{v}_{\mathbf{s}}-\mathbf{v}_{\ell})\cdot\mathbf{N}+J_{\mathbf{s}}\phi_{\ell}\mathbb{F}_{\mathbf{s}}^{-1}\mathbb{D}\mathbb{F}_{\mathbf{s}}^{-T}\operatorname{Grad}c_{n}\cdot\mathbf{N} \rrbracket|_{\partial\Omega}=0.$$
(3.100f)

3.3 Parameters Estimation

The last passage to complete the mathematical model and focus on its numerical implementation consists in assessing the values of the parameters that appear in the system. This is both a challenging and delicate task: since our goal is to simulate tumour progression and its mechanical impact, the choice of the parameters is crucial to have a realistic and reliable outcome. At the same time, when working in the field of mathematical biology, accurate estimations of the parameters are often difficult to obtain. In this section, we review the literature so as to assign a value, or at least a range of values, to the parameters introduced in our model.

First of all, we deal with the material parameters μ_{1t} and μ_{2t} that appear in the Mooney-Rivlin energy density. Mihai et al. [60] proposed various constitutive elastic models specific for brain tissue: among them, they also consider a Mooney-Rivlin-type energy, for which they propose as values for the material parameters $\mu_{1t} = -3.5899$ kPa and $\mu_{2t} = 5.5218$ kPa. Since we will be working with units of the order of millimeters, we convert them into MPa, resulting in $\mu_{1t} = -3.5899 \cdot 10^{-3}$ MPa and $\mu_{2t} = 5.5218 \cdot 10^{-3}$ MPa.

As regards the parameters involved in the growth rate Γ_s proposed in Equations (3.48) and (3.49), we estimate them as done in other recent works on Glioblastoma [1, 2]. In particular, the cell proliferation constant ν is taken as the inverse of typical doubling times for *in vitro* glioma cells, that vary from 24 to 48 hours: then, a range 0.5 - 1 day⁻¹ can be considered appropriate for ν [113]. Since proliferation depends significantly on nutrients availability, also smaller values seem however admissible [1]: for this reason, in the following we will consider the minimum value inside the mentioned interval, i.e. $\nu = 0.5 \text{ day}^{-1}$. The hypoxia threshold c_0 is estimated in the literature as ranging from 0.15 to 0.5 [121, 113, 118]: we will mainly consider the former in simulations, as done by Gerlee and Anderson [121]. Moreover, we need to estimate the nutrients consumption rate ζ and the nutrients supply rate S_n appearing in (3.46): as far as the former is concerned, following the approach by Colombo et al. [1], it can be estimated indirectly through biological measurements of the oxygen diffusion coefficient in the human brain D_n and the distance covered by an oxygen molecule before it is uptake by a cancer cell l_n . The mean value for D_n reported in the literature is $D_n = 10^{-5} \text{ cm}^2/\text{day} = 86.4 \text{ mm}^2/\text{day} [1, 113]$, while l_n is estimated to be about $l_n = 100 \mu \text{m} = 10^{-1} \text{ mm} [113]$. Hence, we can take a value of $\zeta = D_n/l_n^2 = 8640 \ 1/day$. The parameter S_n is instead quite difficult to estimate: as done in [1, 2] we refer to the value of 10^4 1/day proposed in [109]. Finally, as mean diffusion coefficient of the nutrients, we consider the same D_n previously mentioned, recalling that we consider oxygen as the main source of nourishment for the cells.

We still need to give an estimate of ϕ_{sn} , that is, the cell volumetric fraction in the natural state: as we proved in (3.36), with our assumption on growth process it is a constant, so we can

assume that it is given from the outset. Different values appear in the literature: Colombo et al. [1] and Agosti et al. [2] in their model for Glioblastoma considered a value of $\phi_{\rm sn} = 0.39$, which they derived as the complementary value of the extra-cellular space studied in [122] and amounting at up to 61%. Differently, in their tumour growth model, Mascheroni et al [102] employed a quite high value of $\phi_{\rm sn} = 0.8$. In order to avoid overestimation or underestimation, we decide to take as reference the value proposed by Giverso et al. [48], which is $\phi_{\rm sn} = 0.5$.

Finally, it remains to estimate the value K_0 which appears in the permeability tensor expression: for simplicity, as it is often done in the literature, we prefer to estimate the ratio $k := K_0/\mu$, where μ is the dynamic viscosity of the fluid phase; given its definition and the spatial and temporal scale we employ in our model, such a ratio has units $\text{mm}^2/(\text{MPa} \cdot \text{day})$. Values found in the literature cover quite a wide range: for instance, Mascheroni et al. [102] consider a value $k = 4.875 \cdot 10^{-13} \text{ m}^2/(\text{Pa} \cdot \text{s})$; a conversion to our framework results in a value of $k = 5.5 \cdot 10^2 \text{ mm}^2/(\text{MPa} \cdot \text{day})$. Moreover, in their dimensional analysis, Giverso et al. [48] consider a range of $10^{-15} - 10^{-13} \text{ m}^2/(\text{Pa} \cdot \text{s})$, which corresponds to an interval of $10^0 - 10^2 \text{ mm}^2/(\text{MPa} \cdot \text{day})$ in our case, consistent with the aforementioned value. For this reason, in our simulations we will consider an estimation of $k = 5.5 \cdot 10^2 \text{ mm}^2/(\text{MPa} \cdot \text{day})$.

We report the complete list of all the used parameters, along with their description, their values and the main references in which they can be found, in Table 3.1.

Parameter	Description	Value	Ref.
$\mu_{1 ext{t}}$	Mooney-Rivlin material parameter	$-3.5899 \cdot 10^{-3} \text{ MPa}$	[60]
$\mu_{2\mathrm{t}}$	Mooney-Rivlin material parameter	$5.5218 \cdot 10^{-3} \text{ MPa}$	[60]
ν	Cell proliferation constant	$0.5 \rm{day}^{-1}$	[113]
c_0	Hypoxia threshold	0.15	[121]
ζ	Nutrients consumption rate	8640 day^{-1}	[113]
S_n	Nutrients supply rate	$10^4 \rm day^{-1}$	[1]
$\phi_{ m sn}$	Cell volume fraction in the natural state	0.5	[48]
ϕ_{\max}	Maximum cell volume fraction	0.8	-
D_n	Mean nutrients diffusion coefficient	$86.4 \text{ mm}^2 \text{ day}^{-1}$	[113]
k	Hydraulic conductivity	$5.5 \cdot 10^2 \text{ mm}^2 \text{ MPa}^{-1} \text{ day}^{-1}$	[102]

Table 3.1: Values of model parameters.

To complete the parameters overview, we need to provide a definition for the diffusion tensor \mathbb{D} and for the tensor of preferential directions \mathbb{A} , as defined in [1, 2, 3]. Since we consider oxygen as the main nutrients source, the components of \mathbb{D} can be inferred from DTI imaging data, following the procedure summarized in Sections 1.3 and 4.2. Concerning \mathbb{A} , its construction is done using DTI data modified as described in [34, 2, 3]; in particular, it is assumed that the tensor \mathbb{A} has the same eigenvectors of the diffusion tensor, but increased anisotropy along the preferential directions, a control parameter r is introduced: given λ_1 , λ_2 , λ_3 the descending order eigenvalues of \mathbb{D} and \mathbf{e}_1 , \mathbf{e}_2 , \mathbf{e}_3 the corresponding eigenvectors, \mathbb{A} is defined as

$$\widehat{\mathbb{A}} = a_1(r)\lambda_1 \mathbf{e}_1 \otimes \mathbf{e}_1 + a_2(r)\lambda_2 \mathbf{e}_2 \otimes \mathbf{e}_2 + a_3(r)\lambda_3 \mathbf{e}_3 \otimes \mathbf{e}_3,$$
(3.101a)

$$\mathbb{A} = \frac{1}{\widehat{\mathbb{A}}_{av}} \widehat{\mathbb{A}}, \qquad \widehat{\mathbb{A}}_{av} = \frac{1}{3} \operatorname{tr}(\widehat{\mathbb{A}}).$$
(3.101b)

In the previous expressions, r is the tuning parameter of anisotropy and $a_i(r)$ are functions of r

defined by

$$\begin{pmatrix} a_1(r) \\ a_2(r) \\ a_3(r) \end{pmatrix} = \begin{pmatrix} r & r & 1 \\ 1 & r & 1 \\ 1 & 1 & 1 \end{pmatrix} \begin{pmatrix} c_l \\ c_p \\ c_s \end{pmatrix} ,$$
 (3.102)

where the coefficients c_l , c_p , c_s are the anisotropy indices introduced in (1.9). The case r = 1 corresponds to no increase in anisotropy, while r > 1 enhances anisotropy according to the indices, as given by (3.102).

Chapter 4

Numerical Implementation

Once we have developed our mechanical model for Glioblastoma growth, it is customary to derive an appropriate weak formulation of the involved equations, in order to solve them numerically and simulate tumour progression. To this end, we manipulate the Lagrangian model to obtain a weak formulation, which is then discretized in time and space for the subsequent implementation. Boundary and initial conditions are also discussed and prescribed. Finally, we explain how the brain meshes that we will employ for our simulations have been obtained from patient-specific data, allowing to account for a realistic geometry.

4.1 Weak Formulation of the Lagrangian Model

In this section we derive a weak formulation of the Lagrangian model proposed before, which will be used to implement a finite element algorithm. We recall that, in general, the weak form of a time-independent differential problem reads:

find
$$u \in V$$
 : $a(u, v) = F(v) \quad \forall v \in V,$ (4.1)

where V is a proper functional space, a is a bilinear form and F is a functional. Analogously, the weak form of a time-dependent differential problem can be written generally as

find
$$u(t) \in V$$
 : $\left(\frac{\partial u}{\partial t}(t), v\right) + a(u(t), v) = F(v) \quad \forall v \in V.$ (4.2)

Before going further, we summarize and simplify the Lagrangian model (3.96) through some algebraic manipulation. First of all, we sum the first two equations of (3.96): using the saturation condition and the closed mixture assumption, and substituting (3.96e), we obtain

$$\dot{J}_{\rm s} = {\rm Div}\left[\frac{\mathbb{K}^*}{\mu}\,{\rm Grad}\,p\right].$$
(4.3)

Then, recalling the definition of ϕ_{sn} (3.29) and the fact that it is a constant quantity, we can rewrite the first equation of the model (3.96a) as a simple identity:

$$J_{\rm s}\phi_{\rm s} = J_{\rm g}\phi_{\rm sn} \qquad \Rightarrow \qquad \phi_{\rm s} = \frac{J_{\rm g}}{J_{\rm s}}\phi_{\rm sn}.$$
 (4.4)

As regards the equation for the first Piola-Kirchhoff stress tensor $\mathbb{P}(3.96d)$, we remember that

$$\mathbb{P} = J_{\mathrm{s}} \mathbb{T} \mathbb{F}_{\mathrm{s}}^{-T} = -J_{\mathrm{s}} p \mathbb{F}_{\mathrm{s}}^{-T} + \mathbb{P}_{\mathrm{s}}, \qquad (4.5)$$

where \mathbb{P}_{s} is the constitutive elastic part of the first Piola-Kirchhoff stress tensor. It follows that $\operatorname{Div} \mathbb{P} = \mathbf{0}$ becomes

$$\operatorname{Div}\left[-J_{\mathrm{s}}p\mathbb{F}_{\mathrm{s}}^{-T}+\mathbb{P}_{\mathrm{s}}\right]=\mathbf{0}.$$
(4.6)

Finally, we can reformulate the equation for the nutrients (3.96g) using Darcy's Law in the reference configuration as follows:

$$J_{s}\phi_{\ell}\dot{c}_{n} - \frac{\mathbb{K}^{*}}{\mu}\operatorname{Grad} p \cdot \operatorname{Grad} c_{n} - \operatorname{Div} \left[\phi_{\ell}\mathbb{D}^{*}\operatorname{Grad} c_{n}\right] = J_{s}G_{n}.$$
(4.7)

To sum up, the equations we have to solve in the reference domain $\Omega^* = \Omega^*_t \cup \Omega^*_h$ are:

$$\dot{J}_{\rm s} = {\rm Div}\left[\frac{\mathbb{K}^*}{\mu}\,{\rm Grad}\,p\right], \qquad J_{\rm s} = \det\mathbb{F}_{\rm s}\,,$$

$$(4.8a)$$

$$J_{\rm s}\phi_{\rm s} = J_{\rm g}\phi_{\rm sn}\,,\tag{4.8b}$$

$$\mathbb{F}_{s} = \mathbb{I} + \operatorname{Grad} \mathbf{u}_{s} \,, \tag{4.8c}$$

$$\phi_{\rm s} + \phi_{\ell} = 1 \,, \tag{4.8d}$$

$$\operatorname{Div}\left[-J_{\mathrm{s}}p\mathbb{F}_{\mathrm{s}}^{-T}+\mathbb{P}_{\mathrm{s}}\right]=\mathbf{0}\,,\tag{4.8e}$$

$$\dot{g} = g \frac{\Gamma_{\rm s}}{3\phi_{\rm s}} H_{\Omega_{\rm t}^*} \,, \tag{4.8f}$$

$$J_{s}\phi_{\ell}\dot{c}_{n} - \frac{\mathbb{K}^{*}}{\mu}\operatorname{Grad} p \cdot \operatorname{Grad} c_{n} - \operatorname{Div}\left[\phi_{\ell}\mathbb{D}^{*}\operatorname{Grad} c_{n}\right] = J_{s}G_{n}, \qquad (4.8g)$$

recalling that we take $J_{\rm g} = 1$ and $\dot{J}_{\rm g} = 0$ in the healthy region $\Omega_{\rm h}^*$.

The system of equations (4.8) allows to determine all the unknown fields, namely, the displacement field $\mathbf{u}_{s}(\mathbf{X},t)$ and the scalar fields $p(\mathbf{X},t)$, $\phi_{s}(\mathbf{X},t)$, $\phi_{\ell}(\mathbf{X},t)$, g(t) and $c_{n}(\mathbf{X},t)$, $\forall \mathbf{X} \in \Omega^* = \Omega^*_{\mathbf{t}} \cup \Omega^*_{\mathbf{h}}$ and $\forall t \in (0,T)$, provided that proper initial and boundary conditions are prescribed. To this end, since in our simulations for Glioblastoma growth in the brain we will deal with the cranial skull as the boundary of our domain, we consider the following set of boundary conditions:

$$\mathbf{u}_{\rm s} = \mathbf{0} \qquad \text{on} \qquad \partial \Omega_{\rm h}^* \setminus \partial \Omega_{\rm t}^*, \forall t \in (0, T)$$
(4.9a)

$$p = 0 \quad \text{on} \quad \partial \Omega_{h}^{*} \setminus \partial \Omega_{t}^{*}, \forall t \in (0, T)$$

$$(4.9b)$$

$$c_{h} = 1 \quad \text{on} \quad \partial \Omega^{*} \setminus \partial \Omega^{*} \forall t \in (0, T)$$

$$(4.9c)$$

$$c_n = 1 \quad \text{on} \quad \partial \Omega_{\mathbf{h}}^* \setminus \partial \Omega_{\mathbf{t}}^*, \forall t \in (0, T)$$

$$(4.9c)$$

$$\text{Grad} \ n \cdot \mathbf{N} = 0 \quad \text{on} \quad \partial \Omega_{\mathbf{h}}^* \setminus \partial \Omega_{\mathbf{t}}^*, \forall t \in (0, T)$$

$$(4.9d)$$

$$\mathbb{K}^{*} \operatorname{Grad} p \cdot \mathbf{N} = 0 \qquad \text{on} \qquad \partial \Omega_{h}^{*} \setminus \partial \Omega_{t}^{*}, \forall t \in (0, T)$$

$$\mathbb{P}\mathbf{N} = \mathbf{0} \qquad \text{on} \qquad \partial \Omega_{h}^{*} \setminus \partial \Omega_{t}^{*}, \forall t \in (0, T)$$

$$(4.9d)$$

$$\mathbb{P}\mathbf{N} = \mathbf{0} \qquad \text{on} \qquad \partial \Omega_{h}^{*} \setminus \partial \Omega_{t}^{*}, \forall t \in (0, T)$$

$$(4.9e)$$

$$\mathbb{D}^* \operatorname{Grad} c : \mathbf{N} = 0 \qquad \text{on} \qquad \partial \Omega^* \setminus \partial \Omega^* \quad \forall t \in (0, T)$$
(1.50)

In detail, we impose a null Dirichlet boundary condition for the displacement \mathbf{u}_{s} and for the pressure p, while we consider a null Neumann condition for the normal fluxes \mathbb{K}^* Grad $p \cdot \mathbf{N}$,

 \mathbb{D}^* Grad $c_n \cdot \mathbf{N}$ and for the normal stress $\mathbb{P}\mathbf{N}$ at the boundary of the cranial skull. As regards the nutrients concentration, we suppose that the brain boundary is sufficiently far from the tumour: we can then assume that on the boundary the oxygen concentration is maintained constant at the physiological value of 1 by the vasculature.

Concerning initial conditions, at the beginning of the GBM growth process it is reasonable to assume that the displacement and the pressure are equal to zero; meanwhile, we take the scalar field g related to the growth component of the deformation gradient as equal to 1 everywhere in the domain at t = 0. We also assume that the volumetric fraction of the cell phase is initially equal to the constant volumetric fraction in the natural state $\phi_{\rm sn}$. Finally, in order to obtain the initial nutrients concentration $c_n^0(\mathbf{X})$, we solve the steady version of the nutrients governing equation (4.8g), neglecting advection:

$$-\operatorname{Div}\left[\phi_{\ell}\mathbb{D}^{*}\operatorname{Grad}c_{n}\right] = J_{s}G_{n}.$$
(4.10)



Figure 4.1: Initial distribution of nutrients concentration $c_n^0(\mathbf{X})$, obtained by solving the stationary equation (4.10).

To sum up, we have the following set of initial conditions:

$$\mathbf{u}_{s}(\mathbf{X}, 0) = \mathbf{0} \qquad \forall \mathbf{X} \in \Omega^{*}$$

$$p(\mathbf{X}, 0) = 0 \qquad \forall \mathbf{X} \in \Omega^{*}$$

$$(4.11a)$$

$$(4.11b)$$

$$g(\mathbf{X}, 0) = 1 \qquad \forall \, \mathbf{X} \in \Omega^* \tag{4.11c}$$

$$\phi_{\rm s}(\mathbf{X}, 0) = \phi_{\rm sn} \qquad \forall \, \mathbf{X} \in \Omega^* \tag{4.11d}$$

$$c_n(\mathbf{X}, 0) = c_n^0(\mathbf{X}) \qquad \forall \mathbf{X} \in \Omega^*.$$
(4.11e)

We are now ready to derive a weak formulation of the Lagrangian model, which will allow us to solve it numerically using the finite element method. We first write the weak form in each domain Ω_t^* and Ω_h^* , separately and then we extend the weak form to the whole domain $\Omega^* = \Omega_t^* \cup \Omega_h^*$. First of all, we multiply each side of (4.8a) by a test function $q_t \in H^1(\Omega_t^*)$ and integrate the whole equation over the Lagrangian tumour domain:

$$\int_{\Omega_{t}^{*}} \dot{J}_{s} q_{t} \, dV^{*} = \int_{\Omega_{t}^{*}} \operatorname{Div}\left[\frac{\mathbb{K}^{*}}{\mu} \operatorname{Grad} p\right] q_{t} \, dV^{*}.$$

$$(4.12)$$

If we integrate by parts the second order derivatives, we obtain

$$\int_{\Omega_{t}^{*}} \dot{J}_{s} q_{t} \, dV^{*} = -\int_{\Omega_{t}^{*}} \operatorname{Grad} q_{t} \cdot \frac{\mathbb{K}^{*}}{\mu} \operatorname{Grad} p \, dV^{*} + \int_{\partial\Omega_{t}^{*}} \frac{q_{t}}{\mu} \mathbb{K}^{*} \operatorname{Grad} p \cdot \mathbf{N} \, d\Sigma^{*}.$$
(4.13)

Similarly, in the healthy domain, we take $q_{\rm h} \in H^1(\Omega_{\rm h}^*)$ and we obtain

$$\int_{\Omega_{\rm h}^*} \dot{J}_{\rm s} q_{\rm h} \, dV^* = -\int_{\Omega_{\rm h}^*} \operatorname{Grad} q_{\rm h} \cdot \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \, dV^* + \int_{\partial\Omega_{\rm h}^*} \frac{q_{\rm h}}{\mu} \mathbb{K}^* \operatorname{Grad} p \cdot \mathbf{N} \, d\Sigma^*, \tag{4.14}$$

where $\partial \Omega_h^* = \partial \Omega_t^* \cup \partial \Omega_h^{out}$ is the boundary of the healthy domain that is composed by the interface with the tumour $\partial \Omega_t^*$ and by the external boundary corresponding to the cranial skull $\partial \Omega_h^{out}$. Since on $\partial \Omega_h^{out}$ we impose the null Neumann condition (4.9d), we have

$$\int_{\Omega_{\rm h}^*} \dot{J}_{\rm s} q_{\rm h} \, dV^* = -\int_{\Omega_{\rm h}^*} \operatorname{Grad} q_{\rm h} \cdot \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \, dV^* - \int_{\partial\Omega_{\rm t}^*} \frac{q_{\rm h}}{\mu} \mathbb{K}^* \operatorname{Grad} p \cdot \mathbf{N} \, d\Sigma^*, \tag{4.15}$$

where **N** is the normal vector to the interface pointing outwards of the tumour domain Ω_t^* . Thus, summing up (4.13) and (4.15) and taking $q \in H^1(\Omega^* \setminus \partial \Omega_t^*)$ we obtain

$$\int_{\Omega^*} \dot{J}_{\mathrm{s}} q \, dV^* = -\int_{\Omega^*} \operatorname{Grad} q \cdot \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \, dV^* - \int_{\partial\Omega^*_{\mathrm{t}}} \left[\!\!\!\left[\frac{q}{\mu} \mathbb{K}^* \operatorname{Grad} p\right]\!\!\!\right] \cdot \mathbf{N} \, d\Sigma^*, \tag{4.16}$$

that thanks to the interface condition (3.100b) can be rephrased as

J

$$\int_{\Omega^*} \dot{J}_{\mathrm{s}} q \, dV^* = -\int_{\Omega^*} \operatorname{Grad} q \cdot \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \, dV^* - \int_{\partial\Omega^*_{\mathrm{t}}} \mu^{-1} \mathbb{K}^* \operatorname{Grad} p \, [\![q]\!] \cdot \mathbf{N} \, d\Sigma^*, \tag{4.17}$$

so that if we take $q \in H^1(\Omega^*)$ the jump across the boundary $\partial \Omega_t^*$ vanishes. Generally speaking, if we consider a sharp interface between the tumour and the host tissue, the last term on the right-hand side of (4.17) is not supposed to vanish. As a matter of fact, the field J_s may be discontinuous and the test function q cannot be taken directly in $H^1(\Omega^*)$. However, the implementation of a weak formulation with jumps and discontinuities is not trivial: for the sake of simplicity, in a first version of our model we will take $q \in H^1(\Omega^*)$, assuming that the interface between tumour and surrounding tissue is not exactly sharp, but rather described by a steep mollification of the indicator function $H_{\Omega_t^*}$ of the tumour reference domain. This assumption ensures that all quantities are continuous and allows to rephrase the weak formulation of the first equation as

$$\int_{\Omega^*} \dot{J}_{\rm s}(\mathbf{u}_{\rm s}) \, q \, dV^* = -\int_{\Omega^*} \operatorname{Grad} q \cdot \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \, dV^*, \tag{4.18}$$

for all test functions $q \in H^1(\Omega^*)$. If we introduce a discretization of the time derivative using the implicit Euler method, we have

$$\int_{\Omega^*} \frac{J_{\rm s}^{k+1}(\mathbf{u}_{\rm s}^{k+1}) - J_{\rm s}^k(\mathbf{u}_{\rm s}^k)}{\Delta t} q \ dV^* = -\int_{\Omega^*} \operatorname{Grad} q \cdot \frac{(\mathbb{K}^*)^{k+1}}{\mu} \operatorname{Grad}(p^{k+1}) \, dV^*, \tag{4.19}$$

where, given N time steps on the interval (0,T), $\Delta t := T/N$ is the time step, and we have used a superscript k to denote the value of a quantity at time $t_k = k\Delta t$. For the sake of a lighter notation, from now on we will drop the superscript k + 1 to denote the value of a quantity of interest at the next time step. Then, in order to write the weak formulation properly, we multiply both sides by Δt , isolating on the right-hand side all terms that involve only the test functions:

$$\int_{\Omega^*} J_{\mathbf{s}}(\mathbf{u}_{\mathbf{s}}) \ q \ dV^* + \Delta t \int_{\Omega^*} \operatorname{Grad} q \cdot \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \ dV^* = \int_{\Omega^*} J_{\mathbf{s}}^k(\mathbf{u}_{\mathbf{s}}^k) \ q \ dV^*.$$
(4.20)

As far as equation (4.8e) is concerned, we multiply it by a vector test function $q_t \in H^1(\Omega_t^*)$ and integrate over the tumour reference domain:

$$\int_{\Omega_{\rm t}^*} \operatorname{Div}\left[-J_{\rm s} p \mathbb{F}_{\rm s}^{-T} + \mathbb{P}_{\rm s}\right] \cdot \boldsymbol{q}_{\rm t} \, dV^* = 0.$$
(4.21)

Using tensor integration by parts, we get

$$-\int_{\Omega_{t}^{*}} \left(-J_{s} p \mathbb{F}_{s}^{-T} + \mathbb{P}_{s}\right) : \operatorname{Grad} \boldsymbol{q}_{t} \, dV^{*} + \int_{\partial \Omega_{t}^{*}} \left(-J_{s} p \mathbb{F}_{s}^{-T} + \mathbb{P}_{s}\right) \mathbf{N} \cdot \boldsymbol{q}_{t} \, d\Sigma^{*} = 0.$$
(4.22)

If we do the same in the healthy domain, taking $q_{\rm h} \in H^1(\Omega_{\rm h}^*)$ the result is

$$-\int_{\Omega_{\rm h}^*} \left(-J_{\rm s} p \mathbb{F}_{\rm s}^{-T} + \mathbb{P}_{\rm s} \right) : \operatorname{Grad} \boldsymbol{q}_{\rm h} \, dV^* - \int_{\partial \Omega_{\rm t}^*} \left(-J_{\rm s} p \mathbb{F}_{\rm s}^{-T} + \mathbb{P}_{\rm s} \right) \mathbf{N} \cdot \boldsymbol{q}_{\rm h} \, d\Sigma^* = 0, \tag{4.23}$$

since we have assumed that on the outer boundary of the healthy domain, i.e. the cranial skull, the null Neumann condition (4.9e) holds. It follows that, summing the two equations (4.22), (4.23) and being $q \in H^1(\Omega^* \setminus \partial \Omega_t^*)$, the weak formulation on the whole domain is

$$-\int_{\Omega^*} \left(-J_{\mathrm{s}} p \mathbb{F}_{\mathrm{s}}^{-T} + \mathbb{P}_{\mathrm{s}} \right) : \operatorname{Grad} \boldsymbol{q} \, dV^* - \int_{\partial \Omega^*_{\mathrm{t}}} \left[\left(-J_{\mathrm{s}} p \mathbb{F}_{\mathrm{s}}^{-T} + \mathbb{P}_{\mathrm{s}} \right) \mathbf{N} \cdot \boldsymbol{q} \right] d\Sigma^* = 0.$$
(4.24)

With the same assumptions as before, if we choose $q \in H^1(\Omega^*)$, the jump vanishes and we obtain

$$-\int_{\Omega^*} \left(-J_{\mathrm{s}} p \mathbb{F}_{\mathrm{s}}^{-T} + \mathbb{P}_{\mathrm{s}} \right) : \operatorname{Grad} \boldsymbol{q} \, dV^* = 0.$$

$$(4.25)$$

We further observe that the variational problems (4.17) and (4.25) are nonlinear and coupled: in view of the numerical implementation, it is convenient to rewrite them into a single nonlinear variational problem by summing the two weak forms. Doing that, we obtain the following variational problem for the displacement and the pressure: find $(\mathbf{u}_{s}, p) \in H^{1}(\Omega^{*}) \times H^{1}(\Omega^{*})$ such that

$$(J_{\rm s}(\mathbf{u}_{\rm s}), q_p) + \Delta t \ \left(\operatorname{Grad} q_p, \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p\right) - (\mathbb{P}(\mathbf{u}_{\rm s}, p), \operatorname{Grad} \boldsymbol{q}_u) = \left(J_{\rm s}^k(\mathbf{u}_{\rm s}^k), q_p\right), \tag{4.26}$$

for all $(\boldsymbol{q}_u, q_p) \in \boldsymbol{H}^1(\Omega^*) \times H^1(\Omega^*)$, where (\cdot, \cdot) denotes the standard scalar product in $L^2(\Omega^*)$.

The last partial differential equation for which we need a weak formulation is the one for the nutrients (4.8g). Multiplied by a test function $q_t \in H^1(\Omega_t^*)$ it becomes:

$$\int_{\Omega_{t}^{*}} J_{s} \phi_{\ell} \dot{c}_{n} q_{t} dV^{*} - \int_{\Omega_{t}^{*}} \frac{\mathbb{K}^{*}}{\mu} \operatorname{Grad} p \cdot \operatorname{Grad} c_{n} q_{t} dV^{*} - \int_{\Omega_{t}^{*}} \operatorname{Div}[\phi_{\ell} \mathbb{D}^{*} \operatorname{Grad} c_{n}] q_{t} dV^{*} = \int_{\Omega_{t}^{*}} J_{s} G_{n} q_{t} dV^{*}.$$

Integrating by parts, we obtain

$$\int_{\Omega_{t}^{*}} \left(J_{s} \phi_{\ell} \dot{c}_{n} - \frac{\mathbb{K}^{*}}{\mu} \operatorname{Grad} p \cdot \operatorname{Grad} c_{n} \right) q_{t} dV^{*} + \int_{\Omega_{t}^{*}} \phi_{\ell} \operatorname{Grad} q_{t} \cdot \mathbb{D}^{*} \operatorname{Grad} c_{n} dV^{*} + \int_{\partial\Omega_{t}^{*}} q_{t} \phi_{\ell} \mathbb{D}^{*} \operatorname{Grad} c_{n} \cdot \mathbf{N} d\Sigma^{*} = \int_{\Omega_{t}^{*}} J_{s} G_{n} q_{t} dV^{*}.$$

Following the same approach on the healthy domain and summing the equations, for $q \in H^1(\Omega^* \setminus \partial \Omega^*_t)$ one has

$$\int_{\Omega^*} \left(J_{\mathbf{s}} \phi_{\ell} \dot{c}_n - \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \cdot \operatorname{Grad} c_n \right) q \, dV^* + \int_{\Omega^*} \phi_{\ell} \operatorname{Grad} q \cdot \mathbb{D}^* \operatorname{Grad} c_n \, dV^* + \int_{\partial\Omega^*_t} \left[q \, \phi_{\ell} \mathbb{D}^* \operatorname{Grad} c_n \right] \cdot \mathbf{N} d\Sigma^* = \int_{\Omega^*} J_{\mathbf{s}} G_n \, q \, dV^*,$$

recalling the null Neumann condition on the flux (4.9f). Also in this case, by taking $q \in H^1(\Omega^*)$ and recalling the interface condition, the previous formulation becomes

$$\int_{\Omega^*} \left(J_{\mathbf{s}} \phi_\ell \dot{c}_n - \frac{\mathbb{K}^*}{\mu} \operatorname{Grad} p \cdot \operatorname{Grad} c_n \right) q \, dV^* + \int_{\Omega^*} \phi_\ell \operatorname{Grad} q \cdot \mathbb{D}^* \operatorname{Grad} c_n \, dV^* = \int_{\Omega^*} J_{\mathbf{s}} G_n \, q \, dV^*.$$

It is now mandatory to introduce a time discretization of the previous equation: we do that by invoking again the implicit Euler method, which leads to

$$\begin{split} \int_{\Omega^*} \left[J_{\mathbf{s}}^{k+1} \; \frac{c_n^{k+1} - c_n^k}{\Delta t} - \frac{(\mathbb{K}^*)^{k+1}}{\mu \phi_{\ell}^{k+1}} \operatorname{Grad}(p^{k+1}) \cdot \operatorname{Grad}(c_n^{k+1}) \right] q \; dV^* + \\ &+ \int_{\Omega^*} \operatorname{Grad} q \cdot (\mathbb{D}^*)^{k+1} \operatorname{Grad}(c_n^{k+1}) \; dV^* = \int_{\Omega^*} J_{\mathbf{s}}^{k+1} \; \frac{G_n^{k+1}}{\phi_{\ell}^{k+1}} \; q \; dV^*. \end{split}$$

Multiplying by Δt , reordering the terms and dropping the superscript k + 1 we arrive at

$$\int_{\Omega^*} \left[J_{\mathrm{s}} c_n \, q - \Delta t \frac{\mathbb{K}^*}{\mu \phi_\ell} \operatorname{Grad} p \cdot \operatorname{Grad} c_n \, q + \Delta t \operatorname{Grad} q \cdot \mathbb{D}^* \operatorname{Grad} c_n \right] dV^* = \qquad (4.27)$$
$$= \int_{\Omega^*} \left(J_{\mathrm{s}} c_n^k + \Delta t \, J_{\mathrm{s}} \, \frac{G_n}{\phi_\ell} \right) \, q \, dV^*,$$

for all $q \in H^1(\Omega^*)$. We stress that, given the displacement \mathbf{u}_s and the pressure p obtained by solving (4.26), (4.27) is a linear variational problem to be solved with respect to the unknown c_n .

4.2 Mesh Preparation

The computational brain mesh and the meshes containing the values of \mathbb{D} and \mathbb{A} have been constructed from DTI and MRI data, collected from patients of the Istituto Neurologico Carlo Besta in Milan and kindly processed and provided by Dr. Abramo Agosti (MOX, Politecnico di Milano). Without going into detail, since mesh building from imaging data is not the focus of this work, in our simulations we have employed already existing brain meshes of patients affected by

Glioblastoma Multiforme, constructed as done in [1, 2, 3]. In the following, we briefly summarize the process and refer the reader to the cited papers for a more detailed description.

The first step consists in the segmentation of MRI imaging, i.e. the partitioning of several grey-scale images in order to label the different regions of the brain and the tumorous zone. This can be done using specific software packages, such as *Slicer3D*. Once the segmentation has been performed, the computational 3D brain mesh can be constructed from the segmented images using dedicated Python libraries (VTMK and TetGen): they are able to build a three-dimensional tetrahedral mesh and to provide smoothing and refinement where needed. In particular, the grid is refined in the brain area around the growing cancer, in order to provide a better solution in the interested zone without increasing too much the computational cost. The external surface of the mesh and a slice highlighting the refined tumour area are reported in Figure 4.2: the mesh is composed by 230842 tetrahedral cells and 39357 points.



(a) External brain mesh.

(b) Refinement in the tumour zone.

Figure 4.2: External computational brain mesh and refinement. The tetrahedral mesh is conveniently refined in the tumour zone.

To include diffusion and preferential directions information into the mesh, data from DTI imaging are employed. First of all, the six images coming from DTI medical exams need to be aligned with the ones from MRI, since in general they are not. This is done thanks to automated tools [1, 2]: once all the images are aligned, one can create six different meshes, in which a diffusion value for the coefficient D_{ij} is assigned to each cell. Doing so, diffusion data can be integrated into the computational mesh built upon MRI data: a Z-normal slice of each DTI mesh, representing an independent component of \mathbb{D} , is reported in Table 4.1. Using an analogous procedure, six meshes containing the values of the six independent components of the tensor \mathbb{A} are constructed: an example is shown in Table 4.2.



Table 4.1: Components of the diffusion tensor \mathbb{D} reconstructed from DTI imaging data of a patient, sliced with Z-normal planes. The highest values for diffusion coefficients are attained in the cerebrospinal fluid and are coloured in red.


Table 4.2: Components of the preferential directions tensor A reconstructed from DTI imaging data of a patient, sliced with Z-normal planes. In this case, white matter has the highest values.

4.3 Implementation of the Problem

To perform simulations and solve our equations numerically, we still need to introduce a spatially discrete formulation of the continuous variational problems (4.26) and (4.27), as well as of the other equations involved in the model. We make use of linear tetrahedron \mathbb{P}_1 elements, so we introduce the following finite element spaces:

$$\boldsymbol{V}_h := \{ \boldsymbol{q}_h \in \left[C^0(\overline{\Omega^*}) \right]^3 : \boldsymbol{q}_h |_K \in \left[\mathbb{P}_1(K) \right]^3 \quad \forall K \in \mathcal{T}_h \} \subset \boldsymbol{H^1}(\Omega^*) , \qquad (4.28)$$

$$W_h := \{q_h \in C^0(\overline{\Omega^*}) : q_h|_K \in \mathbb{P}_1(K) \ \forall K \in \mathcal{T}_h\} \subset H^1(\Omega^*),$$
(4.29)

where \mathcal{T}_h is a conforming decomposition of the domain Ω^* into tetrahedra K. Then, we are able to define our fully discrete variational problem as follows: for $k = 1, \ldots, N$, given $(\mathbf{u}_h^k, p_h^k, c_h^k) \in \mathbf{V}_h \times W_h \times W_h$ find $(\mathbf{u}_h, p_h, c_h) \in \mathbf{V}_h \times W_h \times W_h$ such that $\forall (\mathbf{v}_h, w_h, q_h) \in \mathbf{V}_h \times W_h \times W_h$

$$\left(J_{\mathbf{s}}(\mathbf{u}_{h}), w_{h}\right) + \Delta t \left(\operatorname{Grad} w_{h}, \frac{\mathbb{K}^{*}}{\mu} \operatorname{Grad} p_{h}\right) - \left(\mathbb{P}(\mathbf{u}_{h}, p_{h}), \operatorname{Grad} \boldsymbol{v}_{h}\right) = \left(J_{\mathbf{s}}^{k}(\mathbf{u}_{h}^{k}), w_{h}\right), \quad (4.30)$$

$$\left(J_{s}(\mathbf{u}_{h})c_{h},q_{h}\right) - \Delta t\left(\frac{\mathbb{K}^{*}}{\mu\phi_{\ell}}\operatorname{Grad}p_{h}\cdot\operatorname{Grad}c_{h},q_{h}\right) + \Delta t\left(\operatorname{Grad}q_{h},\mathbb{D}^{*}\operatorname{Grad}c_{h}\right) =$$
(4.31)

$$= \left(J_{s}(\mathbf{u}_{h})c_{h}^{k}, q_{h} \right) + \Delta t \left(J_{s}(\mathbf{u}_{h}) \frac{G_{n}(c_{h})}{\phi_{\ell}}, q_{h} \right)$$

where we have dropped the unnecessary subscripts in order to have a lighter notation and we have denoted by (\cdot, \cdot) the standard scalar product on $L^2(\Omega^*)$. We remark that, since we are working in a Lagrangian configuration, also the tensors $\mathbb{K}^* = J_s \mathbb{F}_s^{-1} \mathbb{K} \mathbb{F}_s^{-T}$ and $\mathbb{D}^* := J_s \mathbb{F}_s^{-1} \mathbb{D} \mathbb{F}_s^{-T}$ depend on \mathbf{u}_h .

Once we have obtained the discrete formulation of the partial differential equations, the last step is to introduce a proper discretization of the other equations involved, namely the ordinary differential equation for g (4.8f), the saturation condition (4.8d) and the relation (4.8b).

Regarding (4.8f), it can be easily discretized in time using the implicit Euler method. Then, we have

$$\frac{g^{k+1} - g^k}{\Delta t} = g^{k+1} \frac{\Gamma_s^{k+1}}{3 \phi_s^{k+1}} H_{\Omega_t^*}, \qquad (4.32)$$

which can be immediately rephrased as

$$g^{k+1} = g^k \left(1 - \Delta t \, \frac{\Gamma_s^{k+1}}{3 \, \phi_s^{k+1}} H_{\Omega_t^*} \right)^{-1}.$$
(4.33)

Equation (4.8b) is simply discretized as follows:

$$J_{\rm s}^{k+1}\phi_{\rm s}^{k+1} = J_{\rm g}^{k+1}\phi_{\rm sn} \qquad \Rightarrow \qquad \phi_{\rm s}^{k+1} = \frac{J_{\rm g}^{k+1}}{J_{\rm s}^{k+1}}\phi_{\rm sn}. \tag{4.34}$$

Once we have computed ϕ_s^{k+1} , we can derive ϕ_{ℓ}^{k+1} using the saturation condition (4.8d):

$$\phi_{\ell}^{k+1} = 1 - \phi_{\rm s}^{k+1}.\tag{4.35}$$

Given the discretized form of all the necessary equations, we are now able to run numerical simulations of the model. To this end, we implemented our code using an open source computing software for solving partial differential equations called FEniCS [123, 124, 125]. Such a software provides a high-level Python and C++ interface for solving PDEs through the finite element method: in particular, FEniCS code is attractive since it remains very close to the mathematical formulation, allowing the user to write down a program which closely resembles the variational form of equations. For instance, in FEniCS it is possible to choose the finite element of interest, define function spaces for test and trial functions, import external meshes easily ad define a variational problem with just a few lines of code. It also comes with built-in classes specifically dedicated to the resolution of nonlinear variational problems, which in our case is an important feature. In Appendix A we report and comment in detail the Python codes we implemented and used for our numerical simulations.

Chapter 5

Numerical Simulations

In this chapter, we employ the previously derived discrete formulation of our model to implement it through the finite element solver FEniCS. We firstly simulate Glioblastoma progression on a simplified cubic geometry, both with an isotropic and artificially anisotropic setting, to test the code and its features. Then, we move to the real brain mesh whose construction was explained in the previous chapter, since our main goal is to investigate the mechanical deformation of brain tissue.

5.1 Simulations on a Simplified Geometry

Firstly, we test our numerical code on a simplified geometry, in order to evaluate its reliability and accuracy. Hence, we simulate GBM growth on a cubic geometry, with side length of 10 mm and a spherical proliferation region placed at the center of the cube, with a radius of approximately 1.5 mm. As we discussed, the tumour region is separated from the healthy tissue by a steep mollification of the indicator function: in order to guarantee a better outcome while containing the computational cost as much as possible, we refine the mesh along the boundary of the tumour in the Lagrangian reference domain, as shown in Figures 5.1a and 5.1b. After that, we take into account the parameters values reported in Table 3.1. For the first simulations, we consider both the host tissue and the tumour as identical from the mechanical viewpoint, so we do not distinguish the elastic parameters in the two regions: we consider all the domain as composed by general brain tissue, with Mooney-Rivlin parameters μ_{1t} and μ_{2t} as reported in Table 3.1. Eventually, to investigate the role of tumour growth in a softer host tissue, we perform a simulation taking μ_{1h} , μ_{2h} as material parameters in the healthy region, while keeping μ_{1t} , μ_{2t} in the tumour region.

We also choose a time step $\Delta t = 0.1$ days, which is nearly equal to 2 hours and a half. Initial and boundary conditions are imposed as described in (4.9) and (4.11): first of all, we run two simulations on the cubic mesh, one with isotropic diffusion and permeability and another with artificial anisotropy, in order to better observe its effect on growth.

In the isotropic case, both the diffusion tensor and the permeability tensor are multiples of the identity tensor: specifically, we take $\mathbb{D} = D_n \mathbb{I}$ and $\mu^{-1} \mathbb{K} = k\mathbb{I}$, where D_n and k are estimated as in Table 3.1. We first solve the stationary problem for the nutrients, and then the other equations in the model (4.30), (4.31), (4.33) and (4.34): in this situation, we expect to find results that reflect the isotropic growth of the tumour, putting in evidence the fact that no preferential directions for diffusion and fluid motion are identified.

Indeed, as shown in Figure 5.1 and Figure 5.2, in this case the tumour is expanding isotropically: during growth, it maintains a spherical shape, which induces a uniform displacement along all directions. Moreover, looking at Figure 5.1, the deformation due to the growing GBM is evident: the displacement in the surrounding tissue amounts at 0.11 mm in magnitude after 16.5 days of cancer progression. The average velocity of tumour expansion then amounts at 0.0068 mm/day: this value is consistently smaller than the ones found in the literature. For instance, the diffuse interface model proposed in [1] predicted a velocity of 0.068 mm/day, which is an order of magnitude greater than ours [3]. It is also smaller than the maximum expansion velocity reported in the literature, which is around 0.09 mm/day [126]. In Figure 5.2 we report the distribution of the other variables involved in our model: they all mirror the isotropic evolution of the tumour as expected. More specifically, we have a reduced concentration of nutrients in the diseased region at the center of the cube, since the tumour is consuming oxygen and other nutrients to sustain its own proliferation (Fig. 5.2a); at the same time, the presence of an incremented cell volume in the tumour core (Fig. 5.2d) provokes a decrease in fluid pressure (Fig. 5.2b). Finally, the scalar field q that governs the deformations due to GBM growth is greater than 1 inside the tumour region and equal to 1 outside, as expected. A little irregularity appears along the boundary of the tumour, due to the choice of a steep mollification of the indicator function.

As regards the anisotropic simulation, we employ the same parameters and time step as in the isotropic case, though varying the diffusion tensor and the permeability tensor. We do not consider real data obtained from DTI imaging yet: instead, we impose a forced anisotropy along the Z-axis, taking the tensor of preferential directions as $\mathbb{A} = \text{diag}(0.1, 0.1, 2.8)$. Therefore, we have $\mathbb{D} = D_n \mathbb{A}$ and $\mu^{-1} \mathbb{K} = k \mathbb{A}$: consequently, in this simulation we expect to observe enhanced diffusion, fluid motion and displacement induced by GBM proliferation along the Z-direction.

This is indeed the case, as one can observe through the comparison between variables in the isotropic and anisotropic setting, reported in Tables 5.1, 5.2, 5.3 and 5.4. The presence of anisotropy in diffusion and conductivity causes the tumour to grow preferentially along the Z direction: as we can see in Table 5.1, in the isotropic case there is a uniform induced displacement in a circular region around the growing Glioblastoma, while the introduction of anisotropy forces GBM to acquire a more elongated shape. As a consequence, the displacement is greater along the preferential direction (about 0.13 mm) and reduced on the other two directions (about 0.007 mm each). Furthermore, anisotropy in diffusion and fluid motion is evident as shown in Tables 5.2 and 5.4: nutrients concentration and fluid pressure maintain a more compact shape in the XY-plane, while they show a clear preferential direction along the Z-axis.

At this point, having observed a relevant difference in GBM growth due to anisotropy in both diffusion and permeability, we decide to run two more simulations in order to investigate which variable gave the most consistent contribution to anisotropic proliferation. Hence, we firstly perform a simulation in which diffusion is anisotropic while the permeability tensor is isotropic, then we consider an isotropic \mathbb{D} and an anisotropic K: results are shown in Table 5.5. We clearly see that anisotropy in growth mainly stems from anisotropy in permeability, while the contribution of diffusion is almost negligible, though we observe anisotropy in nutrients distribution. This is not surprising, since in our model the relative velocity of the solid phase, which coincides with the velocity of the tumour material interface, is proportional to the pressure gradient through the tensor K: as a consequence, setting anisotropy in the permeability tensor causes GBM to identify a preferential direction for growth.

Simulations performed so far on the cubic geometry assumed that the healthy and the cancerous tissue were mechanically identical. Hence, we lastly decide to investigate the effect of a softer host tissue: we suppose that the material outside the tumour region is hyperelastic, but with Mooney-Rivlin parameters that are half the ones of the proliferating GBM. The displacement



(e) Y-component of the displacement.

(f) Z-component of the displacement.

Figure 5.1: Magnitude and components of displacement in the isotropic cubical case. The results are shown after a time t = 16.5 days and clipped along the YZ-plane. All the plots have spatial units of millimeters.



Figure 5.2: Plot of the other variables of the model in the isotropic cubical case. The results are shown after a time t = 16.5 days and clipped along the YZ-plane.



Table 5.1: Comparison between displacement magnitude and components in the isotropic case and in the anisotropic case, at time t = 16.5 days, in the YZ-plane. The difference is evident in the Z-direction, since diffusion and hydraulic conductivity are enhanced along the Z-axis.



Table 5.2: Comparison between nutrients concentration and fluid pressure in the isotropic case and in the anisotropic case, at time t = 16.5 days, in the YZ-plane. The difference is evident in the Z-direction, since diffusion and hydraulic conductivity are enhanced along the Z-axis.



Table 5.3: Comparison between displacement magnitude and components in the isotropic case and in the anisotropic case, at time t = 16.5 days, in the XY-plane. Since diffusion and conductivity are enhanced along the Z-axis, we observe a consequent reduction in displacement along the other two directions.



Table 5.4: Comparison between nutrients concentration and fluid pressure in the isotropic case and in the anisotropic case, at time t = 16.5 days, in the XY-plane. Since diffusion and conductivity are enhanced along the Z-axis, we observe a consequent reduction in concentration and pressure along the other two directions.



Table 5.5: Comparison between variables with only anisotropic diffusion and only anisotropic permeability, at time t = 16.5 days, in the YZ-plane. Anisotropy in the deformation subsequent to growth is mainly due to the anisotropic contribution of tensor K.

plots are reported in Figure 5.3 for an isotropic simulation: indeed, after 11 days of progression, in the case with softer host tissue we observe a greater displacement (about 0.12 mm) than in the other case (about 0.086 mm). These values correspond to an average expansion velocity along the preferential direction of 0.011 mm/day: though still smaller than the values found in the literature, in this case the difference is less pronounced, and our velocity has the same order of magnitude as other works [3]. This result clearly shows the relevance of elasticity in the mechanical impact of Glioblastoma growth: furthermore, it underlines the importance of an accurate choice of the material parameters for brain tissue, in order to obtain a reliable quantification.



Figure 5.3: Displacement magnitude after t = 11 days with (a) different elastic parameters in the host and tumour tissue and (b) identical elastic parameters. In the case with softer host tissue, we observe a consistently greater displacement around the growing tumour.

5.2 Simulations on the Brain

After having tested our code on a simplified case, we shift to GBM simulations on a realistic brain geometry, obtained from DTI and MRI data. Preparation of the mesh have been described in Section 4.2: here, we present the results of numerical tests of our model, in order to gain insight into the mechanical impact of a growing tumour inside the brain. Differently from the cubical case, the diffusion tensor and the permeability tensor have been constructed through medical data, so as to build a realistic geometry. Moreover, we take an indicator function of the tumour region bigger than the simplified situation, so as to represent real dimensions of the GBM.

In Figure 5.4 the final configuration of the tumour inside the brain mesh after a simulation of t = 90 days is shown, while in Tables 5.6 and 5.7 we report the plots of the different variables involved in our model. As we can observe, the growing mass indeed provokes a displacement in the surrounding tissue, whose maximum value can be quantified in about 0.14 mm in magnitude after three months. In this case, the average tumour expansion velocity amounts at 0.002 mm/day: as in the cubic case, this value is significantly smaller than the ones present in the literature. The behaviour of all the other variables is in agreement with tumour proliferation: we have a negative pressure in the tumour zone, where the volumetric fraction of the cell phase ϕ_s increases and the concentration of nutrients c_n decreases, as expected.



Figure 5.4: Tumour region (in red) inside the brain mesh after 90 days of growth.

In order to highlight the displacement induced by the growing GBM, in Figure 5.5 we show the tumour mass surrounded by the ring representing the magnitude of \mathbf{u}_{s} , along three different planes and with three different sections.

Concerning anisotropy, if we observe the different colour scales in Tables 5.6 and 5.7, we can verify that the displacement magnitude is not the same along the three cutting planes: in particular, the maximum attained value for $||\mathbf{u}_{s}||$ ranges from 0.092 mm in the XY-plane to 0.14 mm in the XZ-plane. This is a first sign of anisotropy: as a matter of fact, if we analyze the displacement vector components at different times, we can observe that the displacement along X remains almost isotropic during the whole simulation, while growth along Y and Z turns out to be practically isotropic until the first month, after which it shows a slight anisotropy. In Table 5.8 we collect the observed maximum and minimum values of the components of the displacement vector, proving what we have just discussed.



Table 5.6: Comparison between variables during GBM growth in the brain, clipped along three different planes, at time t = 90 days. After three months, the maximum displacement induced by the tumour is around 0.14 mm in the XZ-plane, while the minimum amounts at 0.092 mm in the XY-plane.



Table 5.7: Comparison between variables during GBM growth in the brain, clipped along three different planes, at time t = 90 days.

Days	Х	Y	Z
5 days	0.044 mm	0.043 mm	0.047 mm
	- 0.050 mm	- 0.045 mm	-0.048 mm
30 days	0.089 mm	0.086 mm	0.095 mm
	-0.097 mm	-0.096 mm	- 0.100 mm
60 days	0.093 mm	0.090 mm	0.097 mm
	-0.100 mm	-0.110 mm	-0.110 mm
90 days	0.094 mm	0.091 mm	0.099 mm
	-0.100 mm	-0.120 mm	-0.120 mm

Table 5.8: Maximum and minimum displacement values along each direction at t = 5, 30, 60, 90 days.



Figure 5.5: Displacement magnitude plots on (a)-(c) three different planes and (d)-(f) three different sections with highlighted tumour mass, after 90 days of growth.

Main Outcomes and Future Developments

The main purpose of this work is to make a step forward in Glioblastoma Multiforme growth modeling, by proposing a first version of a mechanical model able to account for hyperelastic deformations of brain tissue. Using the well-established framework of Continuum Mechanics and mixture theory, we focused on the development of a mathematical model for GBM growth, including a proper constitutive equation to reproduce the nonlinear elastic behaviour of brain tissue shown by many experiments. In particular, we modelled the brain as a saturated biphasic mixture, comprising a solid phase of cells and a fluid phase. The tumour region is identified and separated from the healthy surrounding tissue by a material interface, which is described by a continuous mollification of an indicator function. With these assumptions, we obtained a Lagrangian model including seven equations, accompanied by the constitutive definition of the hyperelastic energy and by the multiplicative decomposition of the deformation gradient, to distinguish the elastic contribution from the inelastic one due to growth.

After model derivation, the following step consisted in its numerical implementation using the finite element method. Therefore, we derived a weak formulation of our model, so as to solve all the involved equations numerically. The discretized version of the model was then implemented using a Python code: we focused on the development of a finite element algorithm, which was implemented by means of the open source computing library FEniCS. We firstly tested our code on a simplified cubic geometry, both in isotropic and anisotropic conditions, in order to check its reliability. Then, we performed a first simulation on a brain geometry to verify the outcome of our model when applied to a realistic setting: we included medical data from DTI and MRI into the computational mesh, to account for real diffusion patterns and for anisotropy of the fibers inside the brain.

From our simulations, we observed how the growth of a tumour inside the brain has a mechanical impact on the surrounding healthy tissue, causing a deformation and a subsequent displacement quantified in about 0.14 mm after 90 days. Even though the displacements turn out to be very small, it is worth to remark that they cannot be neglected. For instance, when the tumour mass is removed by surgery, the rearrangement of brain tissues strongly depends on deformations and stresses inside the brain, that can be described and quantified only using a mechanical model of this kind. Hence, it is important to have a model providing a complete and realistic mechanical description.

However, our results still show some consistent limitations that need to be addressed in future research developments. First of all, it should be appropriate to overcome the choice of a continuous indicator function for the tumour region: to this end, numerical techniques like the Extended Finite Element Method could be applied to the present model, allowing to treat the fields as discontinuous functions on the two different domains. Even if Glioblastoma infiltration into the surrounding tissues partially justifies its description using an interface that is not totally sharp, it would be more realistic to distinguish the tumour region from the healthy region without any mollification. Moreover, the inclusion of an anisotropic growth tensor should be evaluated: the problem of modeling preferential directions for growth is still quite complicated and not thoroughly addressed in the literature. Indeed, the intrinsic anisotropy of brain tissue might be better modelled if deformations caused by growth are treated through an anisotropic tensor, in addition to the already anisotropic choices made for the diffusion tensor and for the permeability tensor. In our work, we overcame this issue by imposing anisotropy on the growth process in an indirect way, but in a future development we would like to treat growth as directly anisotropic.

Other possible improvements of the proposed model concern the simulation of therapies and resection, highlighting for instance deformations and displacements that happen after surgical removal of Glioblastoma tumour mass; with regard to this, plastic reorganization could be included in the model, to reproduce the mechanical behaviour of the brain as much realistically as possible. In particular, it would be important to describe the reorganization of the brain fibers around the tumour during growth and after resection.

Finally, multiscale modeling could be employed to determine how changes at the cellular level influence tumour evolution at the macroscopic scale.

Appendix A

Code Documentation

In the following, we report the complete Python code that has been used for numerical simulations of the model. After importing the libraries *DOLFIN* and *FEniCS*, we define all the useful kinematic variables that appear in the variational formulations (lines 1-116). Then, we introduce the tumour indicator function as a Python *Expression*, refining the mesh in the cubic case so as to better solve the problem along the tumour boundary (lines 119-153).

Before setting down the variational problems, we employ a C++ code for the evaluation of DTI data and the construction of the diffusion tensor (lines 160-243) and the tensor of preferential directions (lines 248-329), obtained from patient-specific data. We then define the finite elements using linear continuous Lagrange basis, the parameters, the model variables, initial and boundary conditions (lines 346-469).

Finally, we construct the variational problems (lines 474-519): in particular, as regards displacement and pressure, we use the built-in class NonlinearVariationalProblem, since our problem is nonlinear. All the equations are solved and the data stored inside the time loop in lines 544-601.

```
import dolfin
1
    from dolfin import *
2
    from fenics import *
3
    import numpy as np
4
5
     #Form compiler options
6
    dolfin.parameters["form_compiler"]["cpp_optimize"] = True
7
    dolfin.parameters["form_compiler"]["representation"] = "uflacs"
8
    dolfin.parameters["form_compiler"]["quadrature_degree"] = 4
9
10
     11
12
     # Renaming grad to Grad because it looks nicer in the reference configuration
^{13}
    from ufl import grad as ufl_grad
14
    def Grad(v):
15
            return ufl_grad(v)
16
17
     # Second order identity tensor
18
19
    def SecondOrderIdentity(u):
            d = u.geometric_dimension()
20
```

```
return variable(Identity(d))
21
22
     # Deformation gradient
23
     def DeformationGradient(u):
^{24}
         I = SecondOrderIdentity(u)
^{25}
^{26}
         return variable(I + Grad(u))
27
^{28}
     # Determinant of the deformation gradient
29
     def Jacobian(u):
         F = DeformationGradient(u)
30
         return variable(det(F))
^{31}
32
     # Right Cauchy-Green tensor
33
     def RightCauchyGreen(u):
^{34}
         F = DeformationGradient(u)
35
         return variable(F.T*F)
36
37
     # Left Cauchy-Green tensor
38
     def LeftCauchyGreen(u):
39
         F = DeformationGradient(u)
40
         return variable(F*F.T)
41
42
     # Invariants of an arbitrary tensor, A
^{43}
     def Invariants(A):
44
         I1 = tr(A)
^{45}
         I2 = 0.5*(tr(A)**2 - tr(A*A))
46
         I3 = det(A)
47
         return [variable(I1), variable(I2), variable(I3)]
^{48}
49
     # Invariants of the (right/left) Cauchy-Green tensor
50
     def CauchyGreenInvariants(u):
51
          C = RightCauchyGreen(u)
52
          [I1, I2, I3] = Invariants(C)
53
          return [variable(I1), variable(I2), variable(I3)]
54
55
     # Isotropic growth tensor in the multiplicative decomposition
56
     def IsotropicGrowthTensor(u, g):
57
              I = SecondOrderIdentity(u)
58
              return variable(g*I)
59
60
     # Elastic part of the deformation gradient
61
     def ElasticPart(u, g):
62
              F = DeformationGradient(u)
63
              F_g = IsotropicGrowthTensor(u, g)
64
65
              return variable(F*inv(F_g))
66
\mathbf{67}
     # Right Cauchy-Green tensor of the elastic part
     def ElasticRCG(u, g):
68
             F_e = ElasticPart(u, g)
69
70
              return variable(F_e.T*F_e)
71
```

```
# Determinant of the growth tensor
72
      def Jg(u, g):
73
              F_g = IsotropicGrowthTensor(u, g)
74
              return variable(det(F_g))
75
76
77
      # Determinant of the elastic part
78
      def Je(u, g):
79
             F_e = ElasticPart(u, g)
              return variable(det(F_e))
80
81
      # First Piola-Kirchhoff stress tensor
82
83
      def Pk(u, p, g):
              J_g = Jg(u, g)
84
              J_e = Je(u, g)
85
              F = DeformationGradient(u)
86
              J = Jacobian(u)
87
              I = SecondOrderIdentity(u)
88
              C_e = ElasticRCG(u, g)
89
              F_g = IsotropicGrowthTensor(u, g)
90
              Ice, IIce, IIIce = Invariants(C_e)
91
92
              mu1 = Constant(-3.59e-03)
93
              mu2 = Constant(5.52e-03)
94
95
96
              #Strain energy: Mooney-Rivlin
97
              psi = (mu1/2)*(Ice - 3) + (mu2/2)*(IIce - 3)
              gamma1 = diff(psi, Ice) + Ice*diff(psi, IIce)
98
99
              gamma2 = -diff(psi, IIce)
100
              P_s = 2*J_g*F_e*(gamma1*I + gamma2*C_e)*inv(F_g).T
101
              return variable(P_s - J*p*inv(F).T)
102
103
      # Pullback of a tensor from the current to the reference
104
      # configuration
105
      def TensorPullback(K0, u):
106
              J = Jacobian(u)
107
              F = DeformationGradient(u)
108
              return variable(J*inv(F)*KO*inv(F).T)
109
110
      # Pullback of a vector field from the current to the reference
111
      # configuration
112
      def VectorPullback(T0, u):
113
              J = Jacobian(u)
114
              F = DeformationGradient(u)
115
116
              return variable(J*inv(F)*T0)
117
118
119
      # ----- Define mesh and tumour indicator function ------#
120
121
      # Cube test simulations
122
      #mesh = BoxMesh(Point(0.0,0.0,0.0), Point(10.0,10.0,10.0), 30, 30, 30)
```

```
{\tt #tumour_indicator} = Expression('0.5 - (1/pi) * atan(50*(pow((x[0]-5),2) + pow((x[1]-5),2) + pow(
123
               \rightarrow pow((x[2]-5),2) - 1.8))', degree=2)
124
              # Brain simulations
125
             mesh= Mesh("brain.xml")
126
              tumour_indicator = Expression('0.5 - (1/pi)*atan(50*( pow((x[0]-190.5),2) + pow((x[1]-294),2) +
127
               \rightarrow pow((x[2]-(-2.5)),2) - 20))', degree=2)
128
129
130
              # --- Code for mesh refinement in the tumour region for the cube case --- #
131
132
             #PT = FiniteElement("Lagrange", mesh.ufl_cell(), 2)
133
             #VT = FunctionSpace(mesh, PT)
134
             #H = interpolate(tumour indicator, VT)
135
136
             #cell markers = MeshFunction("bool", mesh, mesh.topology().dim())
137
             #cell markers.set all(False)
138
              #for cell in cells(mesh):
139
                                #mp = cell.midpoint()
140
                                #if H(mp) > 5e-03:
141
                                                   #cell_markers[cell] = True
142
143
              #mesh = refine(mesh, cell_markers)
144
145
146
              #cell_markers = MeshFunction("bool", mesh, mesh.topology().dim())
147
              #cell_markers.set_all(False)
              #for cell in cells(mesh):
148
              #
                          mp = cell.midpoint()
149
                                  if H(mp) > 1e-02 and H(mp) < 0.99:
              #
150
                                                    cell_markers[cell] = True
              #
151
152
              #mesh = refine(mesh, cell_markers)
153
154
155
156
157
                                  ----- Tensors D and T -----
158
159
              # Code for C++ evaluation of DTI and construction of tensor D
160
             defineMatrix_code_D = """
161
162
             #include <pybind11/pybind11.h>
163
             #include <pybind11/eigen.h>
164
165
             namespace py = pybind11;
166
167
             #include <dolfin/function/Expression.h>
168
             #include <dolfin/mesh/MeshFunction.h>
169
170
171
             class Components_DT_D : public dolfin::Expression
```

```
{
172
      public:
173
174
          // Create expression with 6 components
175
          Components_DT_D() : dolfin::Expression(6) {}
176
177
          // Function for evaluating expression on each cell
178
          void eval(Eigen::Ref<Eigen::VectorXd> values, Eigen::Ref<const Eigen::VectorXd> x, const
179
       → ufc::cell& cell) const override
          {
180
          const uint topDim = cell.topological_dimension;
181
          const uint cell_index = cell.index;
182
          values[0] = (*d11)[cell_index];
183
          values[1] = (*d12)[cell_index];
184
          values[2] = (*d13)[cell_index];
185
          values[3] = (*d22)[cell_index];
186
          values[4] = (*d23)[cell_index];
187
          values[5] = (*d33)[cell_index];
188
          }
189
190
          // The data stored in mesh functions
191
          std::shared_ptr<dolfin::MeshFunction<double> > d11;
192
          std::shared_ptr<dolfin::MeshFunction<double> > d12;
193
194
          std::shared_ptr<dolfin::MeshFunction<double> > d13;
          std::shared_ptr<dolfin::MeshFunction<double> > d22;
195
          std::shared_ptr<dolfin::MeshFunction<double> > d23;
196
          std::shared_ptr<dolfin::MeshFunction<double> > d33;
197
198
      };
199
200
      PYBIND11_MODULE(SIGNATURE, m)
201
      {
202
        py::class_<Components_DT_D, std::shared_ptr<Components_DT_D>, dolfin::Expression>
203
          (m, "Components_DT_D")
204
          .def(py::init<>())
205
          .def_readwrite("d11", &Components_DT_D::d11)
206
          .def_readwrite("d12", &Components_DT_D::d12)
207
          .def_readwrite("d13", &Components_DT_D::d13)
208
               .def_readwrite("d22", &Components_DT_D::d22)
209
              .def_readwrite("d23", &Components_DT_D::d23)
210
              .def_readwrite("d33", &Components_DT_D::d33);
211
212
      7
213
      .....
214
215
216
      # Define DT components expression and matrix
217
      d11 = MeshFunction("double",mesh,"d11S.xml.gz")
218
      d22 = MeshFunction("double",mesh,"d22S.xml.gz")
219
220
      d33 = MeshFunction("double",mesh,"d33S.xml.gz")
221
      d12 = MeshFunction("double",mesh,"d12S.xml.gz")
```

```
d13 = MeshFunction("double",mesh,"d13S.xml.gz")
222
      d23 = MeshFunction("double",mesh,"d23S.xml.gz")
223
224
      d11_file_pvd = File("d11S.pvd","compressed")
225
      d22_file_pvd = File("d22S.pvd","compressed")
226
      d33_file_pvd = File("d33S.pvd","compressed")
227
      d12_file_pvd = File("d12S.pvd","compressed")
228
      d13_file_pvd = File("d13S.pvd","compressed")
229
      d23_file_pvd = File("d23S.pvd","compressed")
230
^{231}
      d11_file_pvd << d11
232
      d22_file_pvd << d22
233
      d33_file_pvd << d33
234
      d12_file_pvd << d12
235
      d13_file_pvd << d13
236
      d23_file_pvd << d23
237
238
239
      d = CompiledExpression(compile_cpp_code(defineMatrix_code_D).Components_DT_D(), d11 = d11, d12 =
240
      \rightarrow d12, d13 = d13, d22 = d22, d23 = d23, d33 = d33, degree=2)
241
      # Diffusion tensor
^{242}
      D0 = as_matrix([ [d[0], d[1], d[2]], [d[1], d[3], d[4]], [d[2], d[4], d[5]] ])
^{243}
244
^{245}
246
      # Code for C++ evaluation of DTI and construction of tensor T
247
      defineMatrix_code_T = """"
^{248}
249
      #include <pybind11/pybind11.h>
250
      #include <pybind11/eigen.h>
251
      namespace py = pybind11;
252
253
      #include <dolfin/function/Expression.h>
254
      #include <dolfin/mesh/MeshFunction.h>
255
256
      class Components_DT_T : public dolfin::Expression
257
      {
258
      public:
259
260
          // Create expression with 6 components
261
          Components_DT_T() : Expression(6) {}
262
263
264
          //\ {\rm Function} for evaluating expression on each cell
265
          void eval(Eigen::Ref<Eigen::VectorXd> values, Eigen::Ref<const Eigen::VectorXd> x, const
       → ufc::cell& cell) const override
266
          {
267
          const uint topDim = cell.topological_dimension;
          const uint cell_index = cell.index;
268
269
          values[0] = (*t11)[cell_index];
270
          values[1] = (*t12)[cell_index];
```

```
values[2] = (*t13)[cell_index];
271
          values[3] = (*t22)[cell_index];
272
          values[4] = (*t23)[cell_index];
273
          values[5] = (*t33)[cell_index];
274
          }
275
276
          // The data stored in mesh functions
277
          std::shared_ptr<dolfin::MeshFunction<double> > t11;
278
          std::shared_ptr<dolfin::MeshFunction<double> > t12;
279
          std::shared_ptr<dolfin::MeshFunction<double> > t13;
280
          std::shared_ptr<dolfin::MeshFunction<double> > t22;
281
          std::shared_ptr<dolfin::MeshFunction<double> > t23;
282
          std::shared_ptr<dolfin::MeshFunction<double> > t33;
283
284
     };
285
286
      PYBIND11_MODULE(SIGNATURE, m)
287
      ſ
288
        py::class_<Components_DT_T, std::shared_ptr<Components_DT_T>, dolfin::Expression>
289
          (m, "Components_DT_T")
290
          .def(py::init<>())
291
          .def_readwrite("t11", &Components_DT_T::t11)
292
          .def_readwrite("t12", &Components_DT_T::t12)
293
          .def_readwrite("t13", &Components_DT_T::t13)
294
               .def_readwrite("t22", &Components_DT_T::t22)
295
               .def_readwrite("t23", &Components_DT_T::t23)
296
              .def_readwrite("t33", &Components_DT_T::t33);
297
      3
298
299
      .....
300
301
      # Define DT components expression and matrix
302
303
      t11 = MeshFunction("double",mesh,"t11S.xml.gz")
304
      t22 = MeshFunction("double",mesh,"t22S.xml.gz")
305
      t33 = MeshFunction("double",mesh,"t33S.xml.gz")
306
      t12 = MeshFunction("double",mesh,"t12S.xml.gz")
307
      t13 = MeshFunction("double",mesh,"t13S.xml.gz")
308
      t23 = MeshFunction("double",mesh,"t23S.xml.gz")
309
310
      t11_file_pvd = File("t11S.pvd","compressed")
311
      t22_file_pvd = File("t22S.pvd","compressed")
312
      t33_file_pvd = File("t33S.pvd","compressed")
313
      t12_file_pvd = File("t12S.pvd","compressed")
314
315
      t13_file_pvd = File("t13S.pvd","compressed")
316
      t23_file_pvd = File("t23S.pvd","compressed")
317
318
      t11_file_pvd << t11
     t22_file_pvd << t22
319
320
     t33_file_pvd << t33
321
     t12_file_pvd << t12
```

```
t13_file_pvd << t13
322
     t23_file_pvd << t23
323
324
325
     tmat = CompiledExpression(compile_cpp_code(defineMatrix_code_T).Components_DT_T(), t11 = t11, t12
326
      \rightarrow = t12, t13 = t13, t22 = t22, t23 = t23, t33 = t33, degree=2)
327
      # Tensor of preferential directions
328
     mat_T = as_matrix([ [tmat[0], tmat[1], tmat[2]], [tmat[1], tmat[3], tmat[4]], [tmat[2],
329
      \rightarrow tmat[4], tmat[5]] ])
330
331
332
333
          ------ Define finite elements and function spaces -----
334
335
336
     P2 = VectorElement("Lagrange", mesh.ufl_cell(), 1) # displacement u
337
     P1 = FiniteElement("Lagrange", mesh.ufl_cell(), 1) # pressure p, growth g, fraction phi_s,
338
     \hookrightarrow concentration c_n
     TH = MixedElement([P2, P1])
339
340
     V = FunctionSpace(mesh, TH)
                                           #(u,p)
341
342
343
     W = FunctionSpace(mesh, P1)
                                                # g, phi_s, c_n
344
345
      # ------ Parameters definition ------ #
346
347
     # Initial and boundary values
^{348}
     c = Constant(1.0)
^{349}
     u0 = Constant((0.0, 0.0, 0.0))
350
     pp = Constant(0.0)
351
     TT = Constant((0.0, 0.0, 0.0))
352
353
     # Simulation time and time step
354
     T = 3e01
                               #30 days
355
     num_steps = 3e02
                               #300 steps
356
     dt = T / num_steps
                               #1e-01 days --> 2,4 hours
357
358
359
     phi_sn = Constant(0.5)
360
                                # day ~-1
     nu = 0.5
361
                              #(mm~4) / (MPa day)
362
     k = Constant(5.5e02)
                                          # Conductivity tensor with DTI data
363
     KO = k*mat_T
364
     \#KO = as_matrix([ [k, 0, 0], [0, k, 0], [0, 0, k] ]) \qquad \# Conductivity tensor isotropic
     cn0 = Constant(0.15)  # Hypoxia Threshold (dimensionless)
365
     zeta = Constant(8640)
                                    # Nutrients consumption rate (1/day)
366
     Sn = Constant(1e04)
                                   # Nutrients supply rate (1/day)
367
368
     #Dn = Constant(86.4)
                                    # Nutrients Diffusion coefficient (mm^2/day)
369
     #D0 = as_matrix([ [Dn, 0, 0], [0, Dn, 0], [0, 0, Dn] ]) # Isotropic diffusion tensor
```

```
phimax = Constant(0.8)
370
371
372
      # ----- Define Dirichlet boundary conditions for u, p, c ------ #
373
374
375
      def boundary(x, on_boundary):
376
            return on_boundary
377
      bcu = DirichletBC(V.sub(0), u0, boundary)
378
      bcp = DirichletBC(V.sub(1), pp, boundary)
379
      bcn = DirichletBC(W, c, boundary)
380
381
      bcs = [bcu, bcp]
382
383
384
      # ----- Define functions for variational problems ----- Define functions #
385
386
      # Incremental displacement and pressure
387
      dup = TrialFunction(V)
388
      (du, dp) = split(dup)
389
390
      # Test functions for displacement and pressure
391
      u_, p_ = TestFunctions(V)
392
393
394
      # Displacement and pressure (current value)
395
      up = Function(V)
      (u, p) = split(up)
396
397
      # Displacement and pressure (previous iteration)
398
      up_prev = Function(V)
399
      (u_prev, p_prev) = split(up_prev)
400
401
      # Functions for scalar field g
402
      g = Function(W)
403
      dg = TrialFunction(W)
404
      q = TestFunction(W)
405
      g_prev = Function(W)
406
407
      # Functions for phi_s
408
      phi_s = Function(W)
409
      dphi = TrialFunction(W)
410
      eta = TestFunction(W)
411
412
      # Functions for c_n
413
414
      cn = Function(W)
415
      dcn = TrialFunction(W)
416
      qcn = TestFunction(W)
417
      cn_prev = Function(W)
418
419
420
      # ----- Define initial conditions ----- #
```

```
421
      # Initial condition for u and p
422
      up_init = Expression( ("0.0", "0.0", "0.0", "0.0"), degree=1)
423
      up_prev = interpolate(up_init, V)
424
425
      # Initial conditions for g and phi_s
426
      g_prev = interpolate(Constant(1.0), W)
427
428
      phi_s = interpolate(Constant(0.5), W)
429
430
431
      # ----- Definition of model variables ------ #
432
433
      # Gamma_s: tumour growth term
434
      cn_g = Expression("cc > c0 ? (cc-c0) : 0", cc = cn_prev, c0 = cn0, degree=1)
435
436
      def Gamma_s(phi_s, cn_g):
437
             return variable(nu*phi_s*(phimax-phi_s)*cn_g)
438
439
      # Gn: source term for nutrients
440
      def Gn_l(phi_s, cn):
441
              return variable(-zeta*phi_s*cn + Sn*(1-cn))
442
443
      Gn = Gn_l(phi_s, dcn)
444
445
446
      # Kinematics
447
      d = len(u)
448
                                            # Identity tensor
     I = SecondOrderIdentity(u)
449
     F = DeformationGradient(u)
                                             # Deformation gradient F_s
450
      C = RightCauchyGreen(u)
                                             # Right Cauchy-Green tensor of F_s
451
452
     F_g = IsotropicGrowthTensor(u, g)
                                                   # Growth part of F_s
453
      F_e = ElasticPart(u, g)
                                                                 # Elastic part of F_s
454
      C_e = ElasticRCG(u, g)
                                                                # Elastic right Cauchy-Green
455
456
457
      Ic, IIc, IIIc = CauchyGreenInvariants(u)
458
      Ice, IIce, IIIce = Invariants(C_e)
                                                             # Invariants of elastic RCG
459
      J = Jacobian(u)
460
      F_k = DeformationGradient(u_prev)
461
     J_k = Jacobian(u_prev)
462
463
      J_g = Jg(u, g)
464
     J_e = Je(u, g)
465
      P = Pk(u, p, g)
466
467
      K_star = TensorPullback(K0, u)
468
     T_star = VectorPullback(TT, u)
469
      D_star = TensorPullback(D0, u)
470
471
```

```
472
473
                            ----- Variational problem for u and p ------ Variational problem for u and p
474
            #
475
           deltat = Constant(dt)
476
           L = J*p_*dx + deltat*inner(Grad(p_), K_star*Grad(p))*dx - inner(P, Grad(u_))*dx - J_k*p_*dx + J_k*p_
477
             \hookrightarrow inner(T_star, u_)*ds
           j = derivative(L, up, dup)
478
           problem = NonlinearVariationalProblem(L, up, bcs, J=j)
479
           solver = NonlinearVariationalSolver(problem)
480
481
           prm = solver.parameters
482
           #info(prm, True)
483
            #prm['newton_solver']['absolute_tolerance'] = 1E-8
484
            #prm['newton solver']['relative tolerance'] = 1E-7
485
            #prm['newton solver']['maximum iterations'] = 25
486
           prm['newton_solver']['relaxation_parameter'] = 1.0
487
488
           prm['newton_solver']['linear_solver'] = 'mumps'
489
            #prm['newton_solver']['linear_solver'] = 'gmres'
490
491
            #prm['newton_solver']['preconditioner'] = 'hypre_amg'
492
            #prm['newton_solver']['krylov_solver']['absolute_tolerance'] = 1E-9
493
            #prm['newton_solver']['krylov_solver']['relative_tolerance'] = 1E-7
494
            #prm['newton_solver']['krylov_solver']['maximum_iterations'] = 1000
495
           prm['newton_solver']['krylov_solver']['monitor_convergence'] = True
496
            #prm['newton_solver']['krylov_solver']['nonzero_initial_guess'] = True
497
            #prm['newton_solver']['krylov_solver']['gmres']['restart'] = 40
498
            #prm['newton_solver']['krylov_solver']['preconditioner']['same_nonzero_pattern'] = True
499
            #prm['newton_solver']['krylov_solver']['preconditioner']['ilu']['fill_level'] = 0
500
501
502
             # ------ Variational problem for nutrients ------ #
503
504
            # Steady state solution to derive initial condition
505
           dcn_staz = TrialFunction(W)
506
           cn_staz = Function(W)
507
           ac_staz = inner(Grad(qcn), D0*Grad(dcn_staz))*dx +
508
             → J_k*tumour_indicator*zeta*phi_s*dcn_staz*qcn*dx + J_k*tumour_indicator*Sn*dcn_staz*qcn*dx
           Lc_staz = J_k*tumour_indicator*Sn*qcn*dx
509
510
511
           solve(ac_staz == Lc_staz, cn_staz, bcn)
512
513
           cn_prev.assign(cn_staz)
514
515
            # Variational problem
516
           Fcn = J*dcn*qcn*dx - deltat*(1/(1-phi_s))*inner(K_star*Grad(p), Grad(dcn))*qcn*dx +
517
             \leftrightarrow deltat*inner(Grad(qcn), D_star*Grad(dcn))*dx - J*cn_prev*qcn*dx -
             \hookrightarrow \quad \texttt{deltat*J*tumour\_indicator*Gn*qcn*dx}
518
           ac = lhs(Fcn)
```

```
Lc = rhs(Fcn)
519
520
521
522
      # ----- Files for data storing ------
523
                                                                     ----- #
      displacement_file = File("u_nutrients.pvd")
524
525
      pressure_file = File("p_nutrients.pvd")
526
     phi_s_file = File("phi_s_nutrients.pvd")
      g_file = File("g_nutrients.pvd")
527
      cn_file = File("cn.pvd")
528
      Js_file = File("Js.pvd")
529
530
      Jp_k = project(J_k, W)
531
532
      t = float(0)
533
      (uu, pp) = up_prev.split()
534
      displacement_file << (uu, t)
535
      pressure_file << (pp, t)</pre>
536
     phi_s_file << (phi_s, t)</pre>
537
      g_file << (g_prev, t)</pre>
538
      cn_file << (cn_prev, t)</pre>
539
      Js_file << (Jp_k, t)</pre>
540
541
542
543
      # ------ Loop for time stepping ------ #
544
545
      n = 1
546
      while(t <= T):</pre>
547
548
              t+= dt
549
              print("Iterazione", n, "-esima", "Tempo", t)
550
551
              TT.t = t
552
553
              # Solution for q
554
              ag = dg*(1-deltat*(Gamma_s(phi_s, cn_g)*tumour_indicator/(3*phi_s)))*q*dx
555
              Lg = g_prev*q*dx
556
              solve(ag == Lg, g)
557
558
              if n % 10 == 0:
559
                      g_file << (g, t)
560
561
562
              g_prev.assign(g)
563
564
565
              # Solution of nonlinear variational problem for u and p
566
              solver.solve()
567
568
              (_u, _p) = up.split()
569
              Jp = project(Jacobian(_u),W)
```

```
570
               if n % 10 == 0:
571
                        displacement_file << (_u, t)
572
                        pressure_file << (_p, t)</pre>
573
                        Js_file << (Jp, t)</pre>
574
575
576
               up_prev.assign(up)
577
578
579
580
               # Solution for phi_s
581
               aphi = J*dphi*eta*dx
582
               Lphi = pow(g, 3)*phi_sn*eta*dx
583
               solve(aphi == Lphi, phi_s)
584
585
               if n % 10 == 0:
586
                        phi_s_file << (phi_s, t)</pre>
587
588
589
590
               # Solution of linear variational problem for cn
591
592
               solve(ac == Lc, cn, bcn)
593
594
               if n % 10 == 0:
595
                        cn_file << (cn, t)</pre>
596
597
               cn_prev.assign(cn)
598
599
600
601
               n = n+1
```

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