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Master Thesis

CONNECTING DIFFUSION TENSOR INFORMATION WITH MECHANICAL ANISOTROPY OF A HYPER-VISCOELASTIC CONSTITUTIVE MODEL FOR BRAIN TISSUE

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This study aims to test the mechanical behavior of a hyper-viscoelastic fiber-reinforced material for brain tissue which accounts for anisotropic features of the brain thereby exploiting DT imaging. The degree of anisotropy of axonal fibers and their orientation are integrated into an existing finite element head model; subsequently, calculations of tissue loads and deformation patterns are performed in order to identify possible relationships between a particular deformation in a tissue and an injury in the same. Through the use of LS – DYNA®, a concussive impact between two football players is simulated (NFL Case Study 57H2) and the biomechanics of the struck player’s head is analyzed. Mechanical measures such as principal strain, strain rate and anisotropic equivalent strain are computed and a correlation between internal microscopic structure and macroscopic mechanical properties is investigated.

Results of the research show that especially white matter mechanical behavior is dependent on the primary orientation and the angular distribution of axonal fibers. The inclusion of anisotropy into a constitutive model for brain tissue has a significant effect on the predicted injury locations when tissue-level measures such as maximum principal strain or anisotropic equivalent strain are used as injury criteria. Indeed this study confirms that the coupling method DT imaging – FE model is an innovative and promising possibility to improve bio-fidelity of head finite element simulations.
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INTRODUCTION

1.1 Diffuse Axonal Injury (DAI) and Concussion in Brain Injury

Traumatic Brain Injury (TBI) occurs when an external force, like a mechanical insult or a sudden trauma, produces damage to the brain. Causes may include falls, motor vehicle accidents and collisions in sports \cite{1}; as a matter of fact TBI can result when the head suddenly and violently hits an object or when an object pierces the skull and enters brain tissue disrupting its normal function. The seriousness of the injury may vary from mild, moderate or severe, depending on the extent of the damage to the brain. Symptoms of mild TBI are generally brief changes in mental status or consciousness. Instead, a person with a moderate or severe TBI experiences an extended period of unconsciousness or amnesia after the injury and may present symptoms as permanent headache, repeated vomiting or nausea, restlessness or agitation \cite{2}.

In addition, according to their clinical appearance, brain injury types can be also categorized in focal and diffuse injury \cite{3} meaning that a focal injury occurs in a specific location while a diffuse injury involves a more widespread area. Focal injuries are commonly associated with mechanical static loads (\(>200\ ms\)) or dynamic loads (\(<200\ ms\)) in which the head strikes or is struck by an object; in this case strain waves through the cranium and the brain, and in some cases even skull fracture, are induced. On the other hand, diffuse injuries are more often found in acceleration-deceleration injuries in which the mechanical load is transmitted from the body to the head (non-contact dynamic load). Different hypotheses exist but, getting down to the details, the head does not necessarily contact anything but brain tissue is damaged because tissues marked by different density are accelerated at different rates. Frequent causes of diffuse injuries are rotational forces: indeed, in case of a rotational acceleration of the skull, the rotation of the brain is delayed because of inertia; as a consequence, deviatoric stresses occur within the brain. Two common and serious mechanisms in ensuing brain damage are concussion and Diffuse Axonal Injury. Concussion, called as well as mild traumatic brain injury (MTBI) or minor head trauma, is a type of TBI in which the head and brain move rapidly back and forth generally due to a bump, blow or jolt to the head. Mechanical forces generate linear, rotational, or angular brain displacement, or a combination of these types of motion \cite{4}. This movement may change the way brain normally works involving temporary impairment of neurological function that are usually not life-threatening. Symptoms may be caused primarily by temporary biochemical changes in neurons, taking place for example at their cell membranes and synapses \cite{5}; anyway,
in most cases, neurological function heals by itself within time. Due to this fact health care professionals use to describe a concussion as a mild brain injury. Even so, its effects must be not underestimated because of the seriousness and long-term consequences. Another common mechanism which takes place subsequently to a closed head injury, such as when the head is hit by a solid object, is Diffuse Axonal Injury (DAI). DAI is one of the most devastating type of TBI and it involves a massive loss of neuronal function towards the central area of the brain with extensive lesions in white matter tracts. The injury mechanism is characterized by axonal stretching, disruption and eventual separation of nerve and it basically consists of two main steps: firstly the axon is highly stretched due to mechanical trauma forces and secondly the axon is torn at the site of stretch. The tearing does not happen immediately but it is due to secondary biochemical cascades causing physical axon disruption and proteolytic degradation of the cytoskeleton.

DAI is a diffuse brain injury meaning that the damage occurs over a widespread area. When a diffuse axonal injury takes place it results in massive disruption of millions of neurons interconnecting all the various distinct functional areas of the brain and it has a devastating effect on overall neurological function. The outcome is an immediate loss of consciousness of the injured person with over 90% of patients remaining in a persistent vegetative state. For those who regain consciousness there is in general few hope of neurological functions improvement. Due to brain vulnerability, diffuse axonal injury, which is the most severe of traumatic brain injuries, is a common cause of death or permanent disability worldwide. To provide a quantitative view, in the United States recent data collected by the Center of Disease Control and Prevention (2010) shows that approximately 1.7 million people suffer a traumatic brain injury annually involving 1,365,000 emergency department treatments, 275,000 hospitalizations and 52,000 deaths. Besides, TBI is a contributing factor to a third of all injury-related deaths with a total estimated direct and indirect medical cost of 76.5 billion dollars.

From data estimations it results that DAI takes place in almost half of traumatic brain lesions and is the second cause of death by TBI. Therefore diffuse axonal injuries, and in general all traumatic brain injuries related to neurological function loss, are a crucial and severe public health problem involving also deep social and economic aspects. In this sense, the elaboration of new health technologies, such as new brain injury criteria used to assess the probability of TBI and DAI as a result of a mechanical insult, may support medical servants in diagnosis, treatments and prevention strategies leading to the reduction of the incidence and gravity of brain injuries. Final aim of developing new technologies is helping disease or injury prevention in a whole population.

1.2 The Role of Brain Anisotropy in the Axonal Injury Mechanism

DAI is the most devastating traumatic brain injury and it consists of an elongation mechanism and axons injury resulting from acceleration-deceleration dynamic loads applied to the head. When it comes to consider more in detail the mechanism of axonal injury, it is not possible to correctly analyze it without examining the complexity of brain tissue in which multiple length scales and different materials are involved. The global mechanical forces at head level are indeed
responsible for local physiological impairment of brain cells leading, finally, to brain malfunctioning\[13\].

The key to better understand the axonal injury mechanism lies therefore in anisotropy properties of the brain and, getting down to specifics, in varying densities and stiffness of brain tissue. White matter (brainstem and central brain structures) is sure enough characterized by a greater density than gray matter (cerebral hemispheres); when mechanical loads are transmitted from the body to the head, tissues of different density are accelerated at different rates and lower density tissues move more rapidly than those of greater density. Due to different inertial characteristics, as the brain rotates during acceleration-deceleration events, different velocities are generated. This difference causes elongation of neuronal axons which connect between the gray and white matter and finally it leads to neuronal axons shearing with all its devastating consequences. Considering this mechanism, it can be therefore assumed that there is a strong relation between deformation and injury at axonal level \[14\] and that the density gap plays an important role in DAIs formation and localization. Consequently, it becomes also clear why DAI lesions are mostly concentrated in the white matter or in the gray-white matter interface where different density properties can be found: according to various epidemiological studies \[15\], common places to find axonal injuries are indeed frontal and temporal lobe white matter, corpus callosum (bridge between the cerebral hemispheres) or corticomedullary junction (gray-white matter interface).

Since a relation between axon strain and injury cannot be neglected \[14\], it is interesting to analyze more in detail anisotropy properties from a mechanical point of view: in this sense it can be claimed that the presence of heterogeneous materials inside brain tissue ensues also to heterogeneities in the mechanical properties of the same. As a matter of fact, results of finite element simulations \[13\] which use loading conditions representative for TBI show that applying a strain at tissue level generates tissue deformations resulting into high axonal strains of white-gray matter interface. During brain impacts these strains can even become higher than the applied tissue strain and maximum values of deformation are typically reached when the principal loading direction is aligned with the main axonal orientation or near a stiff inclusion \[13\]. Axons deviating from the main axonal direction can have a logarithmic strain of about 2.5 times the maximum logarithmic strain of the axons in the principal direction over the complete range of loading directions \[13\]. For anisotropic brain tissue with a relatively stiff inclusion, the relative logarithmic strain increase is above 60%.

Analyzing all these data, an important influence on axonal strain due to cellular level heterogeneities and anisotropy properties of brain tissue can be established. The role of anisotropy in the axonal injury mechanism is undeniably crucial since brain tissue is shown to have a clear orientation and location-dependent sensitivity to mechanical loads \[13\]. Therefore, in order to predict and to assess more accurately DAI, these effects should be taken into account in the elaboration of new health technologies and the identification of adequate intra-cerebral mechanical parameters acting as DAI prediction metric represents an important and generally accepted strategy to address brain injury. A series of various mechanical measurements have already been proposed in literature as DAI metric and they are typically expressed in terms of pressure, shearing stresses, maximal principal strain or invariants of the strain tensor. However, the parameter which seems to be the most interesting due to a really strong potential as a measure for DAI prediction and location \[16\] is axonal elongation. Addressing axonal deformation within the brain during head impact can therefore improve understanding of DAI mechanism since elements sustaining maximum axonal strain are located where this injury is typically
observed. Finally, considering the correlation between axonal structural anisotropy and mechanical response \[^{17}\] , information of micro-scale axonal main distribution obtained from DT imaging can be coupled with a finite element head model mechanical analysis. Final aim is to improve axonal elongation computation.

1.3 Diffusion Tensor MR Imaging and Head Trauma Finite Element Simulation for Improving Injury Prediction

Traumatic brain injury mechanisms are difficult to study experimentally due to the variety of impact conditions involved: as a matter of fact, translational or rotational forces, as well as acceleration-deceleration loads, may be used to produce an injury and several different methods to generate pressure pulses useful in percussion experiments have been already presented in literature, with a broad range in impact pressure patterns \[^{18}\] . In addition, difficulties in experimental studies concern also ethical issues related to the use of human cadavers and animals. Due to the high human cost, living men obviously cannot be employed to perform experiments but, considering the usage of human cadavers or animals, benefits and costs of research still must be balanced \[^{19}\] . Independently from the ethical debate, valid experimental data must anyway be extrapolated to living man and, to this effect, mathematical modeling appears to be a valuable tool for analyzing the complex geometrical and mechanical properties of human structures in the study of trauma. As a matter of fact, mathematical models can be used to predict response to injury-producing conditions, they can provide acknowledgment about situations that cannot be simulated experimentally and they can make accessible information that cannot be measured in surrogate and animal experiments.

In this sense, finite element modeling appears to be the most appropriate technique through which human head impact tolerance can be studied. Thanks to the accurate representation of the anatomically specific geometry and the capability to take in account physical and geometrical nonlinearities, a representative finite element human head model would allow valid calculations of tissue loads and deformation patterns of the brain, identifying possible relationships between a particular deformation in a tissue and an injury in the same. With the help of the FE head model, biomechanics of axonal injuries may be studied and gained insights by simulating the injuries really experienced in a crash environment; mechanical parameters such as pressure, shearing stresses, maximal principal strain or invariants of the strain tensor can be extracted and they can be used in order to perform axonal elongation calculation.

As a matter of fact, the identification of suitable intra-cerebral mechanical parameters acting as injury prediction metric represents a crucial strategy to address traumatic brain injury. Since elements sustaining maximum axonal strain are located where injuries are typically observed \[^{21}\] , the computation of axonal elongation during head impact becomes critical to better understand injury mechanism. The use of head trauma finite element simulations can thus help in predicting and localizing traumatic brain injuries. Moreover, since a correlation between axonal structural anisotropy and mechanical response can be established \[^{17}\] , any additional information of micro-scale axonal distribution may be greatly useful in order to enhance axonal strain calculations and, consequently, to better address brain injuries.
To this effect, Diffusion Tensor Imaging (DTI) can be an interesting tool to utilize in association with FE head simulations. As a matter of fact, thanks to directional measurements of water diffusion in soft tissue, DTI can provide information on microscopic details about tissue architecture, either normal or in a diseased state. The theoretical assumption made in this type of imaging is that molecular diffusion is less restricted along fiber bundles than in other directions and, thus, its computation may be used to detect the direction of main axon fiber tracts running through the voxel. Given the high fiber anisotropy in nervous system, DTI can finally map axonal pathways providing main axonal orientation within the brain [20]. This important information can then be coupled with a finite element head model mechanical analysis resulting in an improvement of axonal strain computation, thanks to the extra information of micro-scale axonal distribution obtained by imaging [21].

In addition, there are also further advantages provided by DTI which contribute to make this approach successful for TBI localization and prediction: firstly imaging employment results in a precision enhancement of axonal elongation calculation due to the fact that axonal distribution information is obtained at a remarkably detailed level if compared to mechanical parameters extracted by FE simulations (DTI resolution is typically further more refined than current FE head model meshes).

Secondly, anisotropy measurements can be extracted from diffusion tensor computation [20]; since axonal injuries are typically detected where brain tissue expresses the highest level of anisotropy, these parameters can provide quantitative values to study TBI offering clearly great potential in injuries prediction and localization. Above all, Fractional Anisotropy (FA) appears to be the most appropriate quantity through which brain tissue distribution can be studied [21]: namely it is a scalar value between zero and one which describes the degree of anisotropy of water molecules diffusion process; zero value means that diffusion is equally restricted in all directions while one value signifies that diffusion occurs only along one axis and it is fully restricted along all other directions. Performing DTI calculations, a fractional anisotropy brain map can be obtained displaying axonal orientation data in a summarized and straightforward format. This additional information can finally be used to enhance axonal elongation computing[21].

In the end, the fact that DTI is a non-invasive tool to gather biological knowledge cannot be ignored. This means that data collection from living human is allowed and, since the body is not invaded or cut open as during surgical investigations, a variety of physiological and pathological conditions can be studied concerning little human cost. Consequently it can be claimed that coupling DTI and FEHM mechanical analysis could be a successful approach for improving traumatic brain injury prediction.
Chapter 2

DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is a recently developed MRI technique that can delineate macroscopic axonal organization in nervous system tissues. It uses water molecules motion as a probe to infer the neuroanatomy of tissues, providing structural information which is usually not visible with other MR imaging techniques. TBI effects can thus be better detected and, moreover, the understanding of axonal injury mechanism can be improved considering fiber tracts contribution to the anisotropic behavior of the brain. In this chapter, the basic principle of DTI methodologies is introduced, including diffusion tensor analysis and anisotropy measures.

2.1 Principle of Diffusivity and Diffusion Anisotropy

Human tissues are mainly composed of liquid components and are subtly regulated by an innumerable quantity of processes where water diffusion plays an essential role, such as transport of enzymes, metabolic substrates and metabolites. Measures of water mobility can thus be a valid instrument for describing tissue substructure and it becomes essential analyzing laws which govern diffusion phenomenon. Physically, diffusion consists of particles translational motion self-propelled by thermal energy and it results in their random movement from regions of higher concentration to regions of lower concentration. The transport of particles suspended in a fluid or gas is often referred to as Brownian motion and, in a homogenous barrier-free medium with n dimensions, it obeys to Einstein relation

\[ r^2 = 2nD\tau \quad n = 1,2,3 \]  

(2.1)

where \( r \) is the mean displacement of the molecules, \( \tau \) is referred to diffusion time and \( D \) is a scalar proportionality constant known as the diffusion coefficient. This coefficient is directly proportional to diffusing particle kinetic energy (namely on its temperature in Kelvin \( T \)) and inversely proportional to particle radius \( r_p \) and medium viscosity \( \eta \), according to Einstein-Stokes relation

\[ D = \frac{kT}{6\pi r_p \eta} \]  

(2.2)

in which \( k \) is Boltzmann’s constant \[22\].
For instance, considering pure water at body temperature (37°C), the coefficient $D$ assumes a value of $3 \times 10^{-9} \text{ m}^2/\text{s}$ meaning that in 50 ms water displacement is about 0.03 mm; anyway, due to the presence of obstacles like cell bodies or other biological organized structures, this value is noticeably reduced when it comes to consider diffusion in human tissues. As a matter of fact, in brain tissue water diffusion is still related to cells structural organization: when water molecules flow, axonal membranes and myelin sheaths hinder the motion and, if it occurs, the diffusion runs mainly parallel to axonal direction [23].

Assuming anyway that water molecules could diffuse without following a preferential direction induced by impediments, the probability that they could diffuse covering a distance $r = \sqrt{x^2 + y^2 + z^2}$ over a time interval $t$ is described by the following Gaussian distribution

$$P(x,y,z,t) = \frac{1}{\sqrt{(4\pi Dt)^3}} \exp\left(\frac{-1}{2D} \left(\frac{x^2+y^2+z^2}{2Dt}\right)\right)$$

(2.3)

which allows us to obtain the so-called Diffusion Sphere when $x^2 + y^2 + z^2 = 2Dt$ [22].

The interpretation of equation 2.3 appears then clear: in free diffusion, 99.7 % of water molecules have a displacement minor or equal to $3\sqrt{2D\Delta t}$ and lie inside the diffusion sphere whose center represents null displacement (Figure 2.1).

As said before, the previous relationships well describe water molecules diffusion in a homogenous barrier-free medium. In this situation the coefficient $D$ assumes the same value in all directions and the displacement due to Brownian motion is directionally independent. Therefore a preferential direction of flowing does not exist and diffusion is said to be isotropic. This is the case of gray matter which is characterized by a low level of cells organization leading to a measured apparent diffusivity largely independent of the orientations of the tissue [23].

Instead, in white matter, where the level of organization is high due to axonal alignment, the diffusivity assumes different values depending on the orientation of the tissue and in particular it is higher along fiber direction. Diffusion is thus said to be anisotropic. To describe diffusion

![Figure 2.1 - Gaussian Diffusion Sphere for a homogenous barrier-free medium with 3 dimensions. The curve on the right represents the probability as function of the radial distance $r = \sqrt{x^2 + y^2 + z^2}$.](image-url)
process in an anisotropic medium more than a single scalar is needed; as a matter of fact, the three dimensional space is sampled into a diffusion tensor which characterizes the orientation-dependent water mobility

\[
D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}
\] (2.4)

and equation 2.3 becomes

\[
P(r, t) = \frac{1}{\sqrt{(4\pi|D|t)^3}} \exp\left(\frac{-r^2 D^{-1}r}{2t}\right)
\] (2.5)

which allows us to obtain the so-called Diffusion Ellipsoid (Figure 2.2). Looking at the picture it becomes clear that the probability of diffusion is not the same in all directions and, moreover, it is strictly related to tissue anisotropy properties. This phenomenon is exploited in diffusion tensor imaging (DTI) in order to reconstruct axonal organization of brain tissue (for detailed theory about DT imaging see following paragraphs 2.2 and 2.3).

![Figure 2.2 - Gaussian Diffusion Ellipsoid for an anisotropic medium with three dimensions. Ellipsoid axes are functions of diffusion tensor D and instant of observation t.](image)

**2.2 MRI Diffusion Signal**

The effective anisotropic diffusion tensor \( D \) can be estimated from a series of diffusion weighted images which are peculiar magnetic resonance images capable of detecting the diffusion motion of water molecules thanks to the relationship existing between the signal intensity and the applied magnetic field gradient sequence \[24]. Specifically, in diffusion weighted imaging (DWI)
the signal of a biological tissue is determined by the mean distance a hydrogen molecule moves per unit time based on random microscopic translational motion; the signal loss produced by the translational molecular movement increases with the speed at which the molecules move through a magnetic gradient field and, moreover, the direction and the amount of diffusion weighting can be controlled by the operator modifying the direction and the strength of the gradient field applied. The numerical parameter that quantifies water motion is the diffusion constant $D$ and usually varies with the direction of diffusion (apart from the isotropic case). To define uniquely the shape and the orientation of the diffusion ellipsoid at least six non-collinear diffusion measurements are required from which the diffusion tensor $D$ can be reconstructed.

### 2.2.1 Stejskal - Tanner Sequence

Diffusion weighted images are typically acquired with an echo planar imaging technique [25]. The spin-echo sequence which allows obtaining a MRI signal related to the diffusion coefficient $D$ is known as Stejskal-Tanner sequence and is composed of a pair of gradient pulses delivered between the excitation pulse and signal collection in order to sensitize the sequence to diffusion effects. Particularly, in Stejskal-Tanner pattern a bipolar gradient pulse is provided: firstly a $90^\circ$ radio frequency pulse is applied then, with a time interval of $T_E/2$ (half echo time), a second $180^\circ$ refocusing pulse is supplied, characterized by the same magnitude but opposite direction. After the time $T_E$, a FID echo (Free Induction Decay echo) produced by spins affected by local magnetic field alterations appears. If diffusion motion occurs, a spin phase shift proportional to the distance which the molecules move through the magnetic gradient field is produced and, consequently, a loss of FID signal is obtained. Quantitatively the phase shift of the magnetic moment generated by applying a gradient pulse of magnitude $G$ along a direction, for instance $x$ direction, is function of spin position $x_i$ along the same direction and it can be mathematically described as

$$
\Phi_i = \int_0^\tau \gamma G x_i \, dt
$$  \hspace{1cm} \text{(2.6)}

where $\tau$ is the duration of the applied gradient and $\gamma$ represents the gyromagnetic ratio. Considering that during the time interval $\Delta t$ which elapses between the pair of applied gradient pulses the spin diffuses from the initial position $x_1$ to the final position $x_2$, the phase shift results

$$
\Delta \Phi = \Phi_1 - \Phi_2 = \gamma \Delta t G (x_1 - x_2)
$$  \hspace{1cm} \text{(2.7)}

leading to a clear loss of spin total magnetization. The obtained FID signal loss is thus proportional to diffusion motion of water molecules in a tissue. Moreover, Stejskal-Tanner sequence distinctive features are two strong symmetric gradient lobes placed symmetrically on either side of the $180^\circ$ refocusing pulse (colored areas in Figure
2.3). As dephasing is proportional to the time during which the gradients are switched on and the strength of the applied gradient field, these gradients have the essential purpose of enhancing spin phase shift thereby accelerating intra-voxel diffusion motion. They finally produce a set of FID echo (echo planar imaging, single shot-EPI) which permits to reduce artifact effects of cardiac activity, CSF pulsing or body motion [25].

As a result, the signal attenuation depends on the strength and duration of the gradient pulses \((G, \delta)\), their spacing \((\Delta t)\) and the diffusion constant along the direction of the gradient field \((D)\):

\[
S = S_o \exp\left(-\frac{(y\delta G)^2(\Delta t - \frac{\delta}{3})D}{3}ight)
\]  

(2.8)

where \(S_o\) represents the signal without the application of the gradient \(G\) and \(y\) is the gyromagnetic ratio. Generally, \(G\) is greater than or equal to 10 \(mT/m\) and, considering the time relationship \(\delta \ll \Delta t\), diffusion gradient duration becomes negligible allowing to rewrite equation 2.8 as following

\[
S = S_o \exp\left(-\frac{(y\delta G)^2\Delta tD}{3}\right)
\]  

(2.9)

The amount of diffusion weighting achieved with a given gradient pulse pair and inversion pulse sandwich is denoted by the b-value \((s/mm^2)\). This factor expresses the signal loss to be expected from a given pulse sequence for a given diffusion constant.

\[
b = (y\delta G)^2\Delta t
\]  

(2.10)

Diffusion constants in biological tissues can be measured by repeated scanning with different \(b\)-values but otherwise identical imaging parameters, in particular unchanged gradient direction. The measured diffusion constants are represented by the apparent diffusion coefficient (ADC) which is distinct from the constant of unobstructed diffusion in pure water.

Images whose gray-scale values represent the mean ADCs of the corresponding voxels are known as ADC maps and, particularly, an area of reduced mobility of the water molecules, that is bright on a diffusion weighted image, will appear dark on the corresponding ADC map (small diffusion constant).

Diffusion constants for different directions can instead be measured by changing the direction of the gradient field. Such measurements provide detailed information on the local geometry of the microscopic structures that restrict water diffusion. Based on the measurement of the diffusion constants in six selected directions the entire geometry can be calculated by using the formalism of three-dimensional tensors. This version of diffusion imaging is called diffusion tensor imaging or DTI.

A more accurate geometric model of the structures that hinder diffusion in a voxel can be generated when additional diffusion constants for other directions are measured.
2.2.2 Effects of Eddy Currents and B-Value

Diffusion tensor imaging is inherently a low-resolution and a low SNR imaging technique. As a matter of fact, diffusion images are highly sensitive to all kinds of movements and resolution problems may be exacerbated by $B_0$ magnetic field susceptibility effects and eddy current-induced distortions (Figure 2.4).

In echo-planar imaging, diffusion gradient pulses are typically large and must be applied for short intervals in order to reduce non-diffusion motion sensitivity ($\delta \ll \Delta t$); to this effect, the so-called eddy current phenomenon may manifest itself when a finite amount of residual magnetic field lingers after turning off the diffusion gradient pulse, overlapping FID signal detection. If the residual magnetic field affects signal detection, the resulting imaging is affected too and undesirable image distortions are generated. Common effects of eddy currents are geometric distortions such as blurring of the boundaries between gray and white matter tissues, misregistration between individual diffusion weighted images and, consequently, miscalculation of diffusion tensors.

However, recent advancements in hardware quality of MRI scanners have made it possible to limit this type of distortion which has currently become less problematic for image acquisition; eddy-current compensation schemes are applied and, in addition, eddy current effects caused by diffusion gradient pulses may be suppressed using appropriate pulse sequences. For instance, one of the most widely used approaches is the so-called double-echo sequence: in this technique...
the lingering gradient is eliminated thereby applying consecutively positive and negative magnetic gradients \[27\]. Parallel imaging and segmented k-space sampling are as well broadly used methods. They both allow a substantial shortening of echo train length and echo spacing while retaining the robustness to motion, finally resulting in a substantial reduction of \(B_0\) susceptibility artifacts \[20\].

Lastly, since eddy-current-induced distortions are mostly linear and global, they can also be corrected in post-processing implementing a post-acquisition image procedure to register the diffusion images to reference images \[28\]. Anyway, independently on which type of correction is performed, since DTI is inherently a noise-sensitive and artifact-prone technique, image quality and robustness must be assured.

From image quality point of view, another important parameter that must be considered in diffusion tensor imaging is the so-called b-value. The majority of DTI studies nowadays use b-values in the range of 700–1000 \(s/mm^2\) leading to 30–50% signal reduction, if mean diffusivity of normal white matter is assumed to be around 0.8 to 1 \(\times 10^{-3} \ mm^2/s\).

However, the determination of the optimum b-value \[29\] is a complex issue due to this coefficient relation to many imaging parameters such as diffusion weighting, image signal to noise ratio (SNR) and acquisition time. According to equation 2.10, it can be demonstrated that the higher b-value the more accurately signal attenuation can be measured (due to higher SNR) while the smaller is the b-value the shorter the echo time is achieved. Therefore it is clear that a compromise between shortening of echo train length and retaining the robustness to motion must be agreed and a balance between increasing and decreasing b-value must be reached.

In addition, other factors are affected by b-value quantities such as eddy current and motion artifacts; in general a smaller b-value produces fewer artifacts.

In an isotropic context, b-value also allows us to compute the apparent diffusion coefficient (ADC) directly from equation 2.9 and 2.10:

\[
\ln \left( \frac{S}{S_0} \right) = -Db
\]  \hspace{1cm} (2.11)

Hypothesizing that inside a voxel different diffusion times belonging to different biological microstructures are short enough to exclude exchanging phenomena between voxels, apparent diffusion coefficient can be substituted to \(D\) and measured signal loss becomes

\[
\ln \left( \frac{S}{S_0} \right) = -ADCb
\]  \hspace{1cm} (2.12)

where the only unknown value is the apparent coefficient \(ADC\), determinable acquiring at least two measures of the signal \(S\) (in practice more measures are used).

Images whose gray-scale values represent the mean \(ADCs\) of the corresponding voxels are known as \(ADC\) maps and are really useful to localize cerebral ischemia or tumors.
2.3 Diffusion Tensor Computation

One of the most unique features of diffusion measurement by DTI is that it detects water motion only along the applied gradient axis. The main assumption made in this type of imaging is that, whenever there is ordered structures such as axonal tracts in nervous tissue or protein filaments in muscle, water tends to diffuse along these structures. Therefore determining the way water diffuse it is possible to obtain precious information about the object in analysis. However, when diffusion motion has directionality, transport cannot be described using a single diffusion measurement or by a single diffusion constant. To characterize the process more elaborate diffusion measurement and data processing are needed.

One such method, called precisely diffusion tensor imaging, was introduced in the early 1990s and it is based on the mathematical concept of tensors. The formalism provides an approximation of the mean diffusion of water molecules in all directions in an ellipsoid whose three main axes may differ in length due to differences in diffusion along the axes. Properties of the 3D ellipsoid are defined by six parameters consisting of three lengths for the longest, shortest and middle axes perpendicular to each other (called eigenvalues $\lambda_1, \lambda_2, \lambda_3$) and their orientations (eigenvectors $v_1, v_2, v_3$). Because six parameters are required to define uniquely an ellipsoid, at least six measurements along six arbitrary axes are needed to determine uniquely the diffusion tensor. However, more measurements can be performed in order to better define the ellipsoid shape under the existence of measurement errors.

To keep track of the parameters, diffusion tensor formalism uses a $3 \times 3$ tensor $D$ that is related to them by a diagonalization procedure:

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \rightarrow \lambda_1, \lambda_2, \lambda_3, v_1, v_2, v_3$$

(2.13)
This diffusion tensor is symmetric and contains six independent values reflecting diffusion ellipsoid independent parameters. As a matter of fact, the shape (eigenvalues) and the orientation (eigenvectors) of the ellipsoid cannot be measured directly in experiments and, consequently, a mathematical assumption is required: in practice, the extent of diffusion, which is equivalent of lengths of the ellipsoid, is quantified along various directions and then related to diffusion tensor parameters [24].

Mathematically, equation 2.9 can be used only for isotropic diffusion or if diffusion is considered along a single axis. A more complete expression, correct for anisotropic media, is the following:

\[
\ln \left( \frac{S}{S_0} \right) = -\int_0^t \gamma^2 \left[ \int_0^{t'} G(t'') dt'' \right] \cdot D \cdot \left[ \int_0^{t'} G(t'') dt'' \right] dt'
\] (2.14)

which can be more easily rewritten in the compact form

\[
\frac{S}{S_0} = \exp -\sqrt{bD}\sqrt{b}^r
\] (2.15)

\[
\sqrt{b} = \gamma G \sqrt{\Delta t - \frac{\delta}{3}}
\] (2.16)

In these formulae \(\sqrt{b}\) and \(G\) are vectors containing information of both gradient strength and orientation. Expanding expression 2.15 in matrices gives

\[
\ln \left( \frac{S}{S_0} \right) = -\left[ \sqrt{b_x} \quad \sqrt{b_y} \quad \sqrt{b_z} \right] \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \left[ \sqrt{b_x} \quad \sqrt{b_y} \quad \sqrt{b_z} \right]
\] (2.17)

and due to the symmetry of diffusion tensor

\[
-\ln \left( \frac{S}{S_0} \right) = D_{xx}b_x + D_{yy}b_y + D_{zz}b_z + 2D_{xy}\sqrt{b_x}\sqrt{b_y} + 2D_{xz}\sqrt{b_x}\sqrt{b_z} + 2D_{yz}\sqrt{b_y}\sqrt{b_z}
\] (2.18)

which in compact form becomes
Using six measurements along six arbitrary axes and the least diffusion weighted image $S_0$, it is possible to obtain a system of equations which, once solved for each pixel, provides an estimation of the six unknown values $D_{ij}$. Therefore at least six measurements with different gradient directions are needed to uniquely determine the diffusion tensor $[32]$. 

\[
\tilde{b} = \begin{bmatrix} b_x & b_y & b_z & \sqrt{b_x} & \sqrt{b_y} & \sqrt{b_z} \end{bmatrix} \quad (2.19 \ a)
\]

\[
\bar{D} = [D_{xx} \ D_{yy} \ D_{zz} \ 2D_{xy} \ 2D_{xz} \ 2D_{yz}]^T \quad (2.19 \ b)
\]

\[
-ln\left(\frac{S}{S_0}\right) = \tilde{b} \cdot \bar{D} \quad (2.19 \ c)
\]

Lastly, diffusion ellipsoid parameters $(\lambda_1, \lambda_2, \lambda_3, \mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3)$ are estimated thereby diagonalizing the tensor $\bar{D}$; eigenvalues and eigenvectors are computed and, consequently, diffusion ellipsoid shape and orientation are determined. This calculation must clearly be repeated for each voxel since a diffusion tensor can be obtained for each pixel in DT images. In practical situations, it is possible to arbitrarily choose gradient orientations. In general, it is convenient to choose them in order to uniformly sample three-dimensional space with the purpose to obtain the more possible uniform space resolution. Three-dimensional space sampling orientations are then specified into a matrix whose rows correspond to space unit vectors defining sampling direction $\mathbf{B}$. In fact more than six measurements using different gradient directions are often performed in experiments in order to improve image SNR and resolution to better define the ellipsoid shape under the existence of measurement errors $[33]$. In this case the system $2.20$ is over-determined therefore a fitting technique is preferred to solving it. Since equations are equivalent to simple linear equations $(y = \text{const} - ax)$, linear least-square fitting is used to solve the system:

\[
\begin{bmatrix}
\ln (S_1) \\
\ln (S_2) \\
\ln (S_3) \\
\ln (S_4) \\
\ln (S_5) \\
\ln (S_6)
\end{bmatrix} = \ln(S_0) - \begin{bmatrix}
\tilde{b}_1 \\
\tilde{b}_2 \\
\tilde{b}_3 \\
\tilde{b}_4 \\
\tilde{b}_5 \\
\tilde{b}_6
\end{bmatrix} \cdot \bar{D} \quad (2.20)
\]

Thanks to the symmetry of $\bar{D}$ it is finally possible to reconstruct the $3 \times 3$ diffusion tensor $\mathbf{D}$. 

16
2.4 Diffusion Anisotropy Measures

Once the diffusion tensor is estimated, different indices can be computed to extract anisotropy information. Thanks to them it is then possible to infer structural organization of human tissues delineating anatomy of biological structures at a voxel level.

The diffusion tensor is inherently a real, symmetric, positive definite second order tensor from which diffusion ellipsoid shape and orientation can be determined \[33\]. The first information that can be derived is thus the numerical value of eigenvalues and eigenvectors \( \lambda_1, \lambda_2, \lambda_3, v_1, v_2, v_3 \) where \( \lambda_i \) is the \( i \)-th eigenvalue and \( v_i \) the corresponding eigenvector. Moreover, it is assumed that \( \lambda_1 > \lambda_2 > \lambda_3 \) which means considering \( \lambda_1 \) as the greatest diffusion value along a fiber axis denoted by the direction unit vector \( v_1 \) \[34\]. Since \( D \) is symmetric and positive definite \[35\] its eigenvectors are orthogonal and they can be considered as principal direction axes of a system of principal direction coordinates (Figure 2.6).

\[
D = \begin{bmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{bmatrix} = \begin{bmatrix} v_1 & v_2 & v_3 \end{bmatrix} \begin{bmatrix}
\lambda_1 & 0 & 0 \\
0 & \lambda_2 & 0 \\
0 & 0 & \lambda_3
\end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} \quad (2.22)
\]

As previously said, the diffusion tensor is typically assumed to be positive definite. Despite this, noise in the measurements, physiologic fluctuations or large image misregistration may cause the estimated eigenvalues of the tensor to be negative, thereby violating this assumption. Negative eigenvalues occur predominately in regions of high anisotropy and, since comparison
and interpretation of them influences the accuracy of the extracted anisotropy information, they must be corrected in order to infer properly structural organization of tissues in DTI analysis. Literature offers several numbers of correction methods [36] that can be used in such a situation; generally constrained algebraic techniques are performed: for instance, a pre-estimation method replaces the measured diffusion weighted signals that are greater than the reference (measured non-diffusion-weighted) signal with the reference signal. In a post-estimation method, instead, the negative eigenvalues are replaced with zero. Anyway, the most widely used is also a post-estimation technique that replaces the negative eigenvalues with their absolute values [36]. Once the shape and the orientation of the diffusion ellipsoid are determined for each pixel, a number of rotationally invariant scalar parameters can be inferred. The mean diffusivity (MD) exemplifies the mean diffusion in a voxel and can be computed thereby averaging the elements on the diagonal of the diffusion tensor or, equally, its eigenvalues ($\bar{\lambda}$). MD value is thus defined as following:

$$MD = \frac{D_{xx} + D_{yy} + D_{zz}}{3} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = \bar{\lambda} \quad (2.23)$$

The apparent diffusion coefficient (ADC), instead, represents the mean diffusion coefficient of different biological microstructures inside a voxel and can be calculated along any direction $e$ simply projecting the diffusion tensor to that direction:

$$ADC_e = e^T \cdot D \cdot e = \lambda_1 (e \cdot v_1)^2 + \lambda_2 (e \cdot v_2)^2 + \lambda_3 (e \cdot v_3)^2 \quad (2.24)$$

Even if the previous indices carry interesting information about diffusion, they are not specific for anisotropic processes because they average out the shape and the orientation of the diffusion ellipsoid; therefore they are not really useful when it comes to delineate anatomy of biological anisotropic tissues. More specific indices have been proposed in literature to characterize anisotropic diffusion such as relative anisotropy (RA), fractional anisotropy (FA) and volume ratio (VR). These indices combine information carried by eigenvalues to obtain invariant scalar parameters which describe the degree of diffusion anisotropy by using a measurement of difference among eigenvalues [37]. Specifically, relative anisotropy index (RA) represents the

Figure 2.6 – Diffusion ellipsoid: $\lambda_i$ is the $i$-th eigenvalue and $\mathbf{v}_i$ the corresponding eigenvector. $\lambda_1$ represents the greatest diffusion value along a fiber axis denoted by the direction unit vector $\mathbf{v}_1$. 
ratio of anisotropic part of the diffusion tensor to its isotropic part and it is defined as a normalized standard deviation according to:

\[
RA = \sqrt{\frac{1}{2} \left( \frac{\lambda_1^2 - \lambda_2^2)^2 + (\lambda_2^2 - \lambda_3^2)^2 + (\lambda_3^2 - \lambda_1^2)^2}{\lambda_1 + \lambda_2 + \lambda_3} \right)}
\]

Fractional anisotropy (FA), alternatively, measures the magnitude fraction of the diffusion tensor attributed to anisotropic diffusion process; therefore it represents the degree of anisotropy of structures in a voxel and its normalized expression of the eigenvalues is defined as the following:

\[
FA = \sqrt{\frac{\lambda_1^2 - \lambda_2^2)^2 + (\lambda_2^2 - \lambda_3^2)^2 + (\lambda_3^2 - \lambda_1^2)^2}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}
\]

If diffusion is isotropic, namely \(\lambda_1 = \lambda_2 = \lambda_3\), this index becomes zero. Instead, for perfect anisotropic condition (\(\lambda_1 \gg \lambda_2 = \lambda_3 = 0\)) fractional anisotropy becomes one. The rest of the values lie in a range of \(0 \div 1\) with larger numbers indicating higher diffusion anisotropy features (Figure 2.7).

In addition, FA scalar values can be used as a gray-scale quantity for the corresponding voxels in an image with the purpose of obtaining the so-called FA maps (Figure 2.8). In neuroscience these maps are really convenient to analyze brain white matter since it is markedly anisotropic. Compared to \(T_1\) and \(T_2\) magnetic resonance images, gray and white matter have a greater contrast in FA maps due to the difference of axonal fiber density; therefore, diagnosis of pathological conditions or altered states becomes easier [38]. Another interesting index to analyze anisotropy of tissues is the Volume Ratio (VR) which represents the ratio of the diffusion ellipsoid volume to the volume of the sphere constructed by using the mean eigenvalue as radius. Its formulation is expressed as follows:

\[
VR = \frac{\lambda_1 \lambda_2 \lambda_3}{(\frac{\lambda_1 + \lambda_2 + \lambda_3}{3})^3}
\]

As for fractional anisotropy, VR values lie in a range of \(0 \div 1\) but in this case larger numbers indicating lower diffusion anisotropy features. As a matter of fact, if diffusion is perfectly isotropic (\(\lambda_1 = \lambda_2 = \lambda_3\)) the diffusion ellipsoid and the sphere constructed using the mean eigenvalue have the same volume; therefore volume ratio becomes one.
On the other hand, when diffusion is perfectly anisotropic (\( \lambda_1 \gg \lambda_2 = \lambda_3 = 0 \)) this index becomes zero.

Lastly, for concluding, a really useful tool to delineate anisotropy and, consequently, improve the understanding of anisotropic features of biological structures at voxel resolution is the color orientation map (Figure 2.9). Specifically, it is a RGB image which is obtained by connecting \( \mathbf{v}_1 \) values to fractional anisotropy quantities: for each voxel the x-coordinate is multiplied by the corresponding FA value and is associated to the red component of the image; at the same time y-coordinates are multiplied by FA quantities and related to the green component of the colored map. Finally, each \( z \) -coordinate is still multiplied by fractional anisotropy and associated to the blue component of the RGB image. In the end an interesting colored image that shows orientation features is obtained. Since it is really difficult to visualize 3D vectors, in this way the information is easily converted to a color space and a color-coded map is generated [39].
Figure 2.8 – Fractional anisotropy map on a 231 x 183 grid. The boundary between gray and white matter lies around a value of 0.2: for FA > 0.2 white matter is found otherwise for FA < 0.2 gray matter is detected.

Figure 2.9 – Color orientation map on a 231 x 183 grid. For each voxel the principal eigenvector is multiplied by the corresponding FA value and is associated to the red, green and blue component of the image (R(x), G(y), B(z)); a colored image that shows orientation features is obtained.
Chapter 3

HEAD TRAUMA FINITE ELEMENT MODEL

The head is one of the most vulnerable parts of the human body. When subjected to an impact, it is exposed to high inertial and contact forces which may cause brain tissue to deform beyond recoverable limits finally resulting in traumatic brain injury. For the time being, knowledge of the mechanism through which an impact load results into an injury is still incomplete. To these effects, mathematical models provide an interesting and powerful tool for analyzing the mechanics of head impacts where the complex geometry and variation of mechanical properties of human tissues during a trauma can be effectively studied [40].

In particular, finite element modeling appears to be the most appropriate method to achieve this goal: as a matter of fact, finite element models can predict body response to injury-producing conditions, provide acknowledgment about situations that cannot be simulated experimentally and make accessible information that cannot be measured in surrogate and animal experiments. With the help of a FE head model, mechanical parameters such as pressure, shearing stresses, maximal principal strain or invariants of the strain tensor can be computed and they can be used as injury prediction metrics [41].

The purpose of the following chapter is presenting the head trauma finite element model used in this study thereby providing a description of the geometry and material properties of its components; moreover, interface and loading conditions applied to the model are described and NFL Case Study number 57H2 [41] is introduced.

3.1 Geometry and Components of the Model

The finite element model used in this study was developed at the Royal Institute of Technology (KTH) in Stockholm by Kleiven (2002) under LS-DYNA® software [42] and it is a parameterized and detailed 3D model of the head significantly valuable for looking into the effects of impact loads. As shown in Figure 3.1, the KTH finite element head model includes the scalp, the skull, the brain, the meninges, the cerebrospinal fluid (CSF), eleven pairs of the largest parasagittal bridging veins and a simple neck with the extension of the spinal cord and the dura mater. Since the differentiation between gray and white matter and the inclusion of the ventricles are necessary to match regions of high shear stress to locations of DAlS [43], separate representation of gray and white matter is implemented; moreover, the model handles the inclusion of the ventricles.

All parametrical choices concerning the geometry of the head are based on a detailed analysis of previous studies [42] including as well data taken from computer tomography images, Visual Human Database, and anatomical books.
According to this analysis, volume ratio of white matter to gray matter is chosen to be 0.5 while the volume of the corpus callosum is equal to 16.4 ml, a slightly larger value with respect to the reported average of 13.4 ml for healthy male and female adults proposed in previous literature [44]. The volume of the thalamus, instead, is chosen to be 12.5 ml in agreement with the reported literature value of 11.6 ml [45] and the brainstem and midbrain are modeled as structures with a volume of 29 ml, matching closely the average estimate of 28 ml measured in experiments involving healthy adult individuals [46]. The geometry is a feature of an adult human head with a total mass of 4.52 Kg and the principal mass moments of inertia are adopted in order to correspond to the ones representing an average man.

As previously said, the 3D morphology of the model is constructed combining information extracted by a male and a female human cadaver CT, MR and sliced color images with geometric data available through the Visible Human Database (National Institute of Health). Points on the boundaries of the different tissues are determined and used to identify lines and surfaces that define the geometry of the scalp, skull, dura mater, brain tissue etc. In this way a realistic skull thickness variation, extending from the thick and porous frontal bone to the thin temporal bones, is achieved [47] (Figure 3.2).

Subsequently, a finite element mesh is created: using LS–DYNA ® software, the inner and outer layer of compact bone of the skull, facial bones, and scalp are modeled by four-node shell elements; the diploë layer of the cranium and the tissues of the cerebrum, cerebellum and spinal cord are defined by eight-node brick elements. Finally, the dura mater, tentorium and falx are represented by four-node membrane elements.

Overall, the FE head model presents a mesh made up with 16906 nodes, 11158 eight-node brick elements, 10165 four-node shell and membrane elements and 22 two-node truss elements (Figure 3.1). A total of 7,128 hexahedral elements are specifically dedicated to the brain: among these less than 4 % is characterized by an internal angle larger than 140° (the

![Figure 3.1 - Finite element model of the human head. On the left outer components of the model are shown; on the right an inner view of the model is provided in order to highlight inner brain structure geometry. [image from <<Predictors for Traumatic Brain Injuries Evaluated through Accident Reconstructions >> Kleiven, S. (2007). 51st Stapp Car Crash Journal, 81-114.]]
maximum reached angle corresponds to 150° or smaller than 40° (the minimum reached angle corresponds to 30°) while the Jacobian is mostly larger than 0.5; this assure balance between anatomical accuracy of results and stability during calculations. In addition, the mesh density is parameterized and a convergence analysis is performed with the purpose of obtaining sufficient mesh resolution.

From a computational point of view, the mean running time for a typical simulation of 40 ms is about 6 hours, using a single processor PC operating at 4.0 GHz, which represents a reasonable duration time allowing results to be obtained relatively rapidly. Of course, this feature is a desirable characteristic for parametric studies as well as for development tool usage of the model and contributes to make it a valuable tool for biomechanical simulations. Moreover, the finite element model developed by Kleiven has a robust and broad validation in previous studies including several relative motion experiments, intra-cerebral acceleration experiments, skull fracture experiments and intra-cranial pressure experiments. Validation consists in simulating different types of impacts and testing if the model can reproduce experimental results with good agreement: the FE model used in this study generates results in line with post-mortem human subject experimental data covering four impact directions (frontal, occipital, lateral and axial), short and long durational impacts (2 – 150 ms), high and low severity (sub-concussive to lethal) and both penetrating and non-penetrating injuries.

![Figure 3.2 – Scheme for creating a 3D FE-mesh from 2D images. The picture shows how points on the boundaries of different tissues are determined and used to identify lines and surfaces defining the geometry of the model. Image from <<Predictors for Traumatic Brain Injuries Evaluated through Accident Reconstructions >> Kleiven, S. (2007). 51st Stapp Car Crash Journal, 81-114.]

### 3.2 Material Properties

From a biomechanical point of view, head injuries can be described as tissue material failure marked by some form of stress, strain or deformation. Through a finite element analysis a
measure of these mechanical values across and within the different tissues can be obtained, providing a link between the external mechanical quantities and the internal injuries \[41\]. Common to all mechanical analysis of materials and their behavior in structural components is the need for constitutive models that connect the states of stress and strain of an element. Clearly, in a simulation of a head trauma, biological materials are involved and therefore their constitutive relations must be specified for each component of the model. The peculiarity of this kind of simulation lies in the fact that biological materials most of the times do not follow the constitutive relations for common engineering materials. They are often anisotropic, inhomogeneous, nonlinear and viscoelastic. In addition a great variability between different individuals must be taken in account. As consequence, identifying a constitutive relation able to describe accurately the behavior of tissue during an impact is a hard issue. Since FE head model originally developed by Kleiven is broadly validated \[42\], in this study its constitutive laws are used except for brain tissue where the original model is extended with anisotropic tissue behavior. A summary of the properties used for the head model is given in Table 3.1.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Young’s Modulus [MPa]</th>
<th>Density [Kg/dm³]</th>
<th>Poisson’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer Compact Bone</td>
<td>15000</td>
<td>2.00</td>
<td>0.22</td>
</tr>
<tr>
<td>Inner Compact Bone</td>
<td>15000</td>
<td>2.00</td>
<td>0.22</td>
</tr>
<tr>
<td>Porous Bone</td>
<td>1000</td>
<td>1.30</td>
<td>0.24</td>
</tr>
<tr>
<td>Neck Bone</td>
<td>1000</td>
<td>1.30</td>
<td>0.24</td>
</tr>
<tr>
<td>Brain</td>
<td>HGO material</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cerebrospinal Fluid</td>
<td>$K = 2.1 \text{ GPa}$</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Sinuses</td>
<td>$K = 2.1 \text{ GPa}$</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Dura Mater</td>
<td>31.5</td>
<td>1.13</td>
<td>0.45</td>
</tr>
<tr>
<td>Falx</td>
<td>31.5</td>
<td>1.13</td>
<td>0.45</td>
</tr>
<tr>
<td>Tentorium</td>
<td>31.5</td>
<td>1.13</td>
<td>0.45</td>
</tr>
<tr>
<td>Pia Mater</td>
<td>11.5</td>
<td>1.13</td>
<td>0.45</td>
</tr>
<tr>
<td>Scalp</td>
<td>Viscoelastic</td>
<td>1.13</td>
<td>0.42</td>
</tr>
<tr>
<td>Bridging Veins</td>
<td>$EA = 1.9 \text{ N}$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.1 – A summary of the properties of the head model components used in this study. The capital letter $K$ represents the Bulk Modulus while $EA$ means Force/Unit strain.

### 3.2.1 Scalp Modeling

The scalp is defined as the soft tissue that covers the cranial vault. It develops in the body area bordered by the face anteriorly and the neck to the sides and posteriorly and it is, generally, 5 to 7 mm thick \[51\]. Anatomically, it consists of five layers with the first three bound together as a single unit (Figure 3.2): they are respectively the hair-bearing skin (or cutaneous layer), the superficial fascia (connective tissue layer), the epicranial aponeurosis, the loose areolar tissue and the pericranium. The latter one is the periosteum of the skull bones \[51\].
From a mechanical viewpoint, only a small number of fresh human scalp samples have been tested but material behavior is clearly demonstrated to be viscoelastic [52][53]; as a matter of fact, in previous studies [52] response in compression of the scalp is shown to be almost elastic until strains of 30–40% are applied while larger strains generate a concave stress-strain curve typically detected in soft biological tissues. Moreover, several relaxation tests performed in tension on monkey scalp specimens indicate a clear viscoelastic stress relaxation behavior [53]. As consequence, according to literature, scalp mechanical behavior is assumed to be adequately described by linear viscoelastic theories and in the FE model used in this study a viscoelastic constitutive law is chosen for scalp modeling.

More in detail, material density is assumed to be 1.13 Kg/dm$^3$ while its Poisson's ratio is defined as 0.42; these values are chosen in agreement with Kleiven's FE model [41].

### 3.2.2 Skull Modeling

The skull is defined as a bone complex, localized in the head, which plays the role of supporting facial structures and forming a cavity to contain the brain. It consists of 22 different bones that are joined together by immovable joints formed by bony ossification (sutures).

A typical anatomical classification divides the skull in 8 cranial and 14 facial bones whose illustration can be found in Figure 3.2. The eight plate-like cranial bones form the human cranium whose base is constituted by an irregular plate of bone containing depressions, ridges and small holes (foramen) allowing the passage of blood vessels and nerves. The largest hole, called foramen magnum, is instead the transition area between the spinal cord and the brainstem.

From a mechanical point of view, several experiments have been performed on human skulls in order to determine their mechanical behavior [54]. Frontal, parietal and occipital structures investigated in these studies show two well-defined shells of compact bone with a separation core of spongy bone (diploë) in between. Since the cortical grain structure of the compact bone is randomly oriented, inner and outer layers are demonstrated to have transversely isotropic behavior where the isotropy is expressed in the tangential direction of the skull; on the other hand, the spongy bone shows a broad variability in mechanical response due to its quite diversified structure with marrow spaces lying in a range of 3 mm down to microscopic size [42].

Anyway, a clear difference in behavior for tangential and radial compression can be established and elastic mechanical behavior can be assumed also for porous bone.

According to the literature, the FE model used in this study applies a linearly elastic constitutive law for skull modeling. More in detail, different properties are chosen for compact and porous bone: a rigid body formulation is specified in LS – DYN™ code where compact bone density is assumed to be 2.00 Kg/dm$^3$ and porous bone density is defined as 1.3 Kg/dm$^3$. Young's modulus is equal to 15 GPa for inner and outer layer of the skull while a value of 1 GPa is chosen for the diploë. Finally Poisson's ratio of the compact bone is defined as 0.22 and the porous bone is characterized by a Poisson's ratio of 0.24; all these values are in agreement with Kleiven's FE model [41] and are considered to be reliable since Kleiven provided a broad and robust validation of his model.
3.2.2 Meninges Modeling

The meninges are defined as the system of membranes which envelopes the brain in order to protect it against blows and shocks to the head. They consist primarily of connective tissue and, entering the brain and emerging from the skull, they form as well part of blood vessel walls and sheaths of nerves. Meninges are composed of three layers: respectively from the outer to the inner dura mater, arachnoid mater and pia mater can be found (Figure 3.1).

The dura mater is a strong, thick, and dense membrane. It is composed of dense fibrous tissue and its inner surface is mostly adherent or close to the inner layer of compact bone of the skull, serving as a covering for the brain. Beneath the dura mater the arachnoid mater is found; it is a thin, transparent membrane composed of fibrous tissue. The arachnoid does not follow the convolutions of the surface of the brain and therefore it looks like a loosely fitting sac closely attached to the dura. The pia mater is the membrane that firmly adheres to the surface of the
brain and spinal cord. It is a thin, very delicate and fibrous covering rich in blood vessels. Adhesion between meningeal membranes is prevented by the presence of spaces filled with fluids that act as lubricants; between dura and arachnoid mater a very thin subdural space and a small amount of lubricant are found. Instead a relatively large gap, called the subarachnoid space, separates the arachnoid from the pia mater and is filled with cerebrospinal fluid (CSF), a lymphlike fluid which provides a protective cushion against shock waves to the head. As a further protection, arachnoid trabeculations help to anchor the brain to prevent excessive motion in case of sudden acceleration or deceleration. From a mechanical viewpoint, assigning a constitutive law to meninges is a really hard issue. As a matter of fact, only few mechanical tests have been performed on human meningeal tissues and literature reports information only about dura mater biomechanics.

In previous studies testing the mechanical response of dura mater in uniaxial tension at low and high strain rates, the membrane shows a non-linear stress-strain response which is characteristic of collagenous soft tissues. Polarized light microscopy reveals that the structural entities of spinal dura are aligned in the axial direction while cranial dura do not demonstrate a preferential alignment. Young’s modulus can be determined using tensile testing and is shown to vary in the range of $41 - 55$ MPa. Moreover, the results indicate that a small amount of initial stain occurs with no load. This phenomenon can be explained considering the fibrousness of the tissue: at the beginning fibers just straightens out not taking any load during small deformations. Only the more compliant connective tissue is loaded.

According to the literature, the FE model used in this study applies different constitutive law for modeling different layers of meninges. More in detail, dura mater, falx and tentorium are assigned an isotropic constitutive law characterized by a density of $1.13 \, kg/dm^3$, a Young’s modulus of $31.5 \, GPa$ and a Poisson’s ratio of 0.45; pia mater, instead, is defined using the fabric material formulation in LS-DYNA®. This formulation is especially developed for layered orthotropic materials and is valid for membrane elements only. In the FE model used in this study an isotropic behavior is assigned to the material invoking the special membrane element formulation of LS-DYNA® which is more suited to the deformation experienced by fabrics under large deformation. A density of $1.13 \, kg/dm^3$, Young’s modulus of $11.5 \, GPa$ and Poisson’s ratio of 0.45 are chosen as constitutive parameters.

About CSF and other lubricants located among the membranes, an elastic isotropic fluid formulation is utilized and the constitutive law of the material is marked by density equal to $1.00 \, kg/dm^3$ and bulk modulus of $2.1 \, GPa$. With the fluid option, fluid-like behavior is obtained where the bulk modulus $K$ and pressure rate $p$ are given by:

$$ K = \frac{E}{3(1-2\nu)} \quad (3.1) $$

$$ p = -K\dot{\varepsilon}_{ii} \quad (3.2) $$

All these values are taken from KTH original FE model.
3.2.4 Brain Modeling

The brain is the most complex organ of the human central nervous system. It is mainly composed of a network of neurons, blood vessels, glial cells and other supportive tissues functionally arranged in four major components: cerebrum, diencephalon, cerebellum and brain stem. The latter structure is connected to the spinal cord through the foramen magnum (for more detail see Figure 3.3).

The cerebrum accounts for more than the 80% of the total brain mass and it is in turn divided into two cerebral hemispheres that are joined by means of the corpus callosum (a sheaf of axons highly packed); the cerebrum performs complex functions like interpreting touch, vision and hearing, as well as speech, reasoning, emotions, learning, and fine control of movement. The diencephalon is formed by the thalamus, hypothalamus and epithalamus and it represents the first sorting center of the sensory system. The cerebellum is located under the cerebrum and its function is to coordinate muscle movements, maintain posture and balance. The brainstem includes the midbrain, pons and medulla. It performs many automatic functions such as breathing, heart rate, body temperature, wake and sleep cycles and digestion.

A typical classification of brain tissue divides it into gray and white matter according to the color assumed by the brain areas. Gray matter contains most of the neuron cell bodies concentrated in locations on the surface of the brain and deep within the organ; the white matter, instead, is mainly formed by the axons that connect different parts of the nervous system to each other. The white appearance of the fresh tissue is caused by lipid in the myelin sheaths of the axons.

From the standpoint of engineering material, brain tissue is often likened to a soft gel. More than thirty years of research into the mechanical properties of the brain and brain tissue confirm this statement, with reported values of the bulk modulus around $2.1 \text{ GPa}$ and a shear modulus roughly $10^5$ times smaller than the previous one. Therefore, it can be claimed that the deformation depends on the shear modulus only and mechanical tests are mainly performed in shear or torsion. Several different constitutive laws have been proposed as suitable for description of brain deformation, including isotropic viscoelastic, anisotropic hyperelastic and anisotropic hyper-viscoelastic formulations. Overall, the gray matter regions of the brain, which primarily contain neural cell bodies, are retained to be
macroscopically isotropic since a preferential direction in mechanical response cannot be seen. White matter, instead, shows anisotropic nature because of its organized arrangement of neural axons and experimental studies demonstrate that the material stiffness is directionally dependent, especially at large strains \[66\]. In most of the studies performed, white matter is modeled as an anisotropic non-linear material described by a hyperelastic strain energy function. The use of the hyperelastic model implies that no significant mechanical damage occurs in the tissue for strain less than 50% \[67\]. Finally, the effect of the viscoelasticity has as well been investigated: a typical stress-strain curve for brain tissue in simple shear shows that the stiffness of the material increased with the strain, resulting in a concave stress-strain curve. Moreover, it is demonstrated that stiffness increases also with strain rate and stress relaxation phenomena are typically observed when the specimen is deformed a given amount \[63\]. Since it is reasonable to consider anisotropic hyper-viscoelastic characteristics for a constitutive model of the brain tissue, the FE model of the head used in this study assign a hyper-viscoelastic fiber-reinforced anisotropic material model to the brain, according to the formulation proposed by Gasser, Ogden and Holzapfel (GOH) for modeling arterial layers with distributed collagen fiber orientations \[68\]. This choice is justified by the excellent and promising features Gasser-Ogden-Holzapfel formulation provides if it is applied to brain tissue; in their study, GOH propose a new material model capable to integrate information on tissue composition accounting for the internal load carrying mechanisms of the individual constituents. They developed an interesting framework that is particularly suitable for characterizing the dispersion of the collagen fiber orientation in a continuum sense: in particular, a scalar structure parameter representing the diversity of the collagen arrangement enters the hyperelastic formulation. This concept of dispersion of orientation can also be interestingly applied to brain tissue; as a matter of fact, different brain regions are characterized by different microstructure and even those that appear clearly anisotropic may profoundly differ in organization of neural axons, leading to different anisotropy properties of the tissue. Arterial layer collagen fiber reinforcement can be likened to axonal fiber reinforcement of the brain and the dispersion of the former can be compared to the dispersion of the latter. The GOH constitutive formulation thus allows to model brain areas marked by different anisotropic nature considering both the anisotropic hyper-viscoelastic behavior and the correlation between the internal structure and the macroscopic mechanical properties. Moreover, studies of traumatic brain injuries performed recently by Rudy Cloots \[69\] demonstrate the capability of this constitutive formulation to truthfully describe mechanical behavior of brain tissue.

In the FE model developed for the current study several user defined material are assigned to different parts of the brain. Utilizing Cloots’ executable \[69\] which implements the Gasser-Ogden-Holzapfel model in \(LS-DYNA\), nine user materials characterized by different dispersion of axonal fibers are defined. According to the GOH formulation, the hyperelastic strain energy potential for each material is

\[
W = \frac{G}{2}(I_1 - 3) + K \left(\frac{J^2}{4} - \frac{1}{2} \ln J\right) + \frac{k_1}{2k_2} \sum_{\alpha=1}^{N} (\exp^{k_2(k_{\alpha})^2} - 1)
\] (3.3)
where
\[
\tilde{E}_\alpha = k(I_1 - 3) + (1 - 3k)(I_{4\alpha} - 1)
\]  \hspace{1cm} (3.4)

In the previous formulation \(W\) represents the strain energy per unit of reference volume, \(G\) is the shear modulus, \(I_1\) denotes the first invariant of the isochoric part of the Cauchy-Green strain tensor, \(K\) defines the bulk modulus, \(J\) is equal to the determinant of the deformation gradient and represents the volume ratio, \(k_1\) and \(k_2\) are parameters related to the fiber stiffness and \(N\) is the number of fiber families. Finally, the strain-like quantity \(\tilde{E}_\alpha\) numerically characterizes the deformation of the fibers being function of \(I_{4\alpha} = \tilde{\mathbf{C}} : \mathbf{n}_{\alpha 0} \mathbf{n}_{\alpha 0}\) (where \(\tilde{\mathbf{C}}\) is the isochoric part of the Cauchy-Green strain tensor and \(\mathbf{n}_{\alpha 0}\) is the fiber direction unit vector in the undeformed configuration) and \(k\). The latter parameter is essential in the material formulation since it represents the dispersion of the fiber direction: values of \(k\) lie in a range of \(0 \div 1/3\) with a value of zero meaning perfectly aligned fibers (namely full transverse anisotropy) and a value of \(1/3\) meaning randomly distributed fibers (i.e. isotropy). It is therefore clear that \(k\) is related to the degree of anisotropy of the material which certainly has a significant influence on the mechanical response.

An important assumption of the Gasser-Ogden-Holzapfel model is that fibers contribute their mechanical strength only in tension and not in compression \(^{[68]}\); by means of the Macaulay brackets \(\langle \cdot \rangle, \langle \tilde{E}_\alpha \rangle\) becomes zeros if \(\tilde{E}_\alpha\) is negative.

As said before, in the FE model used in this study nine different user defined materials are created thereby varying the value of the degree of anisotropy \(k\). By exploiting diffusion tensor techniques and fractional anisotropy calculations, a value of the anisotropy degree (\(FA\)) is computed for each element and it is then incorporated in the model (more details of the procedure are provided into Chapter 4); brain geometry of the original head developed by Kleiven is therefore redefined sorting elements which belong to the brain into nine different groups according to the following relational table:

<table>
<thead>
<tr>
<th>FA range</th>
<th>(k) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 ÷ 0.2</td>
<td>0.3333</td>
</tr>
<tr>
<td>0.2 ÷ 0.3</td>
<td>0.2732</td>
</tr>
<tr>
<td>0.3 ÷ 0.4</td>
<td>0.2500</td>
</tr>
<tr>
<td>0.4 ÷ 0.5</td>
<td>0.2273</td>
</tr>
<tr>
<td>0.5 ÷ 0.6</td>
<td>0.2000</td>
</tr>
<tr>
<td>0.6 ÷ 0.7</td>
<td>0.1667</td>
</tr>
<tr>
<td>0.7 ÷ 0.8</td>
<td>0.1282</td>
</tr>
<tr>
<td>0.8 ÷ 0.9</td>
<td>0.0769</td>
</tr>
<tr>
<td>0.9 ÷ 1.0</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Table 3.2 - Relational table for correlating fractional anisotropy values to corresponding dispersion orientation parameter in the GOH model.
The previous illustrated relationship (Table 3.2) is a new proposed correlation between the anisotropy degree and the dispersion fiber parameter in the GOH material model, to the best knowledge of the author, never used before in mechanical simulations. It finds its mathematical justification in literature and experimental studies of fractional anisotropy distribution on the whole brain; moreover, it is derived using the same theoretical assumptions which are the bases of the Gasser-Ogden-Holzapfel material model. According to previous literature, gray matter is characterized by a low degree of anisotropy and FA values are found to vary in a range of $0 \div 0.2$; since the behavior of this tissue is extensively assumed to be isotropic, in this study a value of $k = 1/3$ is assigned to GOH dispersion orientation parameter for each element of the FE model marked by a FA value lying in that range (Table 3.2).

For greater values of fractional anisotropy, instead, the following mathematical relation is assumed to exist:

$$ FA = \sqrt{\frac{1 - 2k}{k^{-2}} \left( \frac{1 - 2k}{k^{-2}} - 1 \right)^2 + \frac{2}{k^{-2}}} $$

It can be easily demonstrated that, accordingly to the theory, for $k = 1/3$ the correspondent fractional anisotropy value is $FA = 0$ which represents a perfectly isotropic condition; for $k = 0$, instead, the correspondent fractional anisotropy value is $FA = 1$ which stands for a perfectly transversely anisotropic situation. Equation 3.5 can be as well graphically expressed as seen in Figure 3.4.

![Relationship between kappa and FA](image)

*Figure 3.4 – Graph of the analytical relationship between fractional anisotropy and dispersion orientation parameter in the GOH model. In the figure, fractional anisotropy is shortened in to FA while mechanical parameter $k$ is called kappa. The relationship is clearly quadratic within the existence range of parameters.*
This quadratic relationship is derived using the same theory assumption for fiber alignment made by Gasser, Ogden and Holzapfel in their paper \cite{68}. Looking at the mathematics behind the material model, they introduce a symmetric generalized structure tensor of second order defined as 

\[ H = a_{ij} \mathbf{e}_i \otimes \mathbf{e}_j \]

which is an alternative measure of the fiber distribution. Then, they assume that the orientation of the fibers is distributed with rotational symmetry about a mean referential direction (taken as \( \mathbf{e}_1 \)) so that the fibers contribute a transversely isotropic character to the overall response of the material. In this way the general orientation density function \( \rho(M(\theta, \Phi)) \) depends only on \( \theta \) as \( \rho(\theta) \) and the off-diagonal coefficients of \( H \) vanish while the diagonal terms remaining are given by \( a_{22} = a_{33} = k \) and \( a_{11} = 1 - 2k \). Consequently, the structure tensor becomes

\[ H = k I + (1 - 3k) a_0 \otimes a_0 \quad (3.6) \]

and being

\[ a_0 = [1 \ 0 \ 0] \quad (3.7) \]

the structure tensor can be rewritten as

\[ H = \begin{bmatrix} 1 - 2k & 0 & 0 \\ 0 & k & 0 \\ 0 & 0 & k \end{bmatrix} \quad (3.8) \]

The new proposed idea here is to associate this structure tensor to the diffusion tensor obtained from DT imaging with the purpose to identify a correlation between the parameters which characterize the two tensors. As a matter of fact, fractional anisotropy is an index capable of measuring the degree of anisotropy of a structure exactly as the mechanical dispersion parameter \( k \) does, due to the fact that both \( H \) and \( D \) are related to the fiber distribution in a material.

After the necessary process of diagonalization to extract fractional anisotropy from the diffusion tensor, \( D \) becomes:

\[ D = \begin{bmatrix} d_{xx} & d_{xy} & d_{xz} \\ d_{yx} & d_{yy} & d_{yz} \\ d_{zx} & d_{zy} & d_{zz} \end{bmatrix} = \begin{bmatrix} \mathbf{v}_1 & \mathbf{v}_2 & \mathbf{v}_3 \end{bmatrix} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \begin{bmatrix} \mathbf{v}_1 \\ \mathbf{v}_2 \\ \mathbf{v}_3 \end{bmatrix} \quad (3.9) \]

where \( \lambda_i \) is the \( i \)-th eigenvalue and \( \mathbf{v}_i \) the corresponding eigenvector.

Since \( D \) is symmetric and positive definite, its eigenvectors are orthogonal and they can be considered as axes of a system of principal direction coordinates. If \( a_0 = [1 \ 0 \ 0] \) and all the other assumptions made by Gasser, Ogden and Holzapfel hold true, it corresponds to \( \lambda_1 \) being the greatest eigenvalue and the direction identified by \( \mathbf{v}_1 \) (main eigenvector) being \( a_0 \).
Moreover, $\lambda_2 = \lambda_3$ since the behavior of the material is assumed to be transversely isotropic. Considering $FA$ definition:

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

(3.10)

when $\lambda_2 = \lambda_3$ it reduces to

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

(3.11)

Then, in order to relate $k$ to $\lambda_i$, the spatial representation through ellipsoid of the tensors is invoked; when $k = 1/3$ the structural tensor becomes

$$H = \begin{bmatrix}
\frac{1}{3} & 0 & 0 \\
0 & \frac{1}{3} & 0 \\
0 & 0 & \frac{1}{3}
\end{bmatrix}$$

(3.12)

which in spatial ellipsoid representation corresponds to a sphere (Figure 3.5). Instead, a $k$ value of 0 makes the ellipsoid collapsed into a line (Figure 3.5). In general, when $k$ is a value covered between 0 and 1/3, the eccentricity of the ellipsoid is related to the ratio $(1 - 2k)/k$.

Considering the diagonalized $D$ tensor, instead, if diffusion is isotropic ($\lambda_1 = \lambda_2 = \lambda_3$), fractional anisotropy becomes zero and the diffusion tensor can be spatially represented by a sphere. For perfect anisotropic conditions ($\lambda_1 \gg \lambda_2 = \lambda_3 = 0$) fractional anisotropy becomes one and the diffusion ellipsoid collapses into a line. In general, values of fractional anisotropy lie in a range of $0 \div 1$ and the ellipsoid eccentricity is related to the ratio $\lambda_3/\lambda_2$.

![Figure 3.5 - Structure tensor $H$ represented for different values of $k$ parameter. From the left to the right, the passage from a perfectly isotropic condition to a perfectly transversely anisotropic is illustrated.](image)
Therefore, utilizing the same spatial ellipsoid representation, a correlation between $D$ and $H$ can be established. Specifically, the idea beneath this association is that in order to have the same degree of anisotropy, the two ellipsoids must have the same eccentricity. As consequence:

$$\frac{\lambda_1}{\lambda_2} = \frac{1 - 2k}{k}$$

(3.13)

Considering again the FA definition:

$$FA = \frac{\sqrt{\lambda_1 - \lambda_2}}{\sqrt{\lambda_1^2 + 2\lambda_2^2}}$$

(3.14a)

$$FA = \frac{\sqrt{\lambda_1 - 1}}{\sqrt{\lambda_1^2 + 2}}$$

(3.14b)

$$FA = \frac{\sqrt{(1 - 2k - 1)^2}}{\sqrt{(\frac{1 - 2k}{k})^2 + 2}}$$

(3.14c)

Finally the range of fractional anisotropy is discretized into nine increments and for each interval the maximum value of $FA$ is chosen to compute the corresponding $k$, according to equation 3.5. The choice of selecting the maximum value of the interval is justified by the fact that $\lambda_2 = \lambda_3$ is an assumption: when the equality is not respected a lower value of $FA$ is obtained and generally fibres are more randomly distributed after averaging.

Coming back to material definition in $LS - DYNA \circledR$, other mechanical parameters of the axonal tissue, necessary to completely define the $GOH$ formalism, are obtain from the analysis of the studies of Cloots $^{[69]}$: firstly it seems reliable that the fiber contribution to the stiffness is assumed to be linear therefore a value close to zero is assigned to $k_2$ ($k_2 \rightarrow 0$); secondly viscoelasticity is considered by adding six viscoelastic modes whose relaxation parameters and time correspondent time constants are reported in Table 3.3; thirdly a value of 1214 Pa is chosen for the shear modulus $G$ while a quantity of 11590 Pa is assigned to the mechanical parameter $k_1$ in respect of the ratio of 0.105 experimentally identified by Ning et al $^{[71]}$. Finally, particular attention must be paid to the value chosen for the bulk modulus $K$: even though it is known to be around 2.1 $GPa$, a lower value of 50 $MPa$ is used in this study in order to prevent volumetric locking of the elements. Since it is still much greater than the shear modulus and the brain has an incompressible behavior, the same pressure and strain response are found when lowering $K$ a couple of orders of magnitude. Therefore choosing a lower value for the bulk
modulus is allowed, especially with the purpose of ensuring numerical stability for all calculations.

<table>
<thead>
<tr>
<th>Relaxation parameters of the viscoelastic modes for brain tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_1$ for $\tau_1 = 10^{-6} s$</td>
</tr>
<tr>
<td>$M_2$ for $\tau_2 = 10^{-5} s$</td>
</tr>
<tr>
<td>$M_3$ for $\tau_3 = 10^{-4} s$</td>
</tr>
<tr>
<td>$M_4$ for $\tau_4 = 10^{-3} s$</td>
</tr>
<tr>
<td>$M_5$ for $\tau_5 = 10^{-2} s$</td>
</tr>
<tr>
<td>$M_6$ for $\tau_6 = 10^{-1} s$</td>
</tr>
</tbody>
</table>

*Table 3.3 - Summary of viscoelastic material properties of the brain tissue in the head model. The volumetric behavior is assumed to be independent of time.*

### 3.3 Interface Conditions

Contact treatment forms an essential part of large deformation head impact simulations that are typically performed when an axonal injury process wants to be investigated. Accurate modeling of contact interfaces between bodies is crucial to the prediction capability of the finite element model and must therefore be carefully planned in a simulation.

In this study, considering the anatomy and physiology of the human head components, the interface between the dura mater and the skull is modeled with a tied-surface to surface contact formulation in LS$-$Dyna®, where the contact is defined by identifying what locations (segment sets) are to be checked for potential penetration of a slave node through a master segment. Since a tied contact type is chosen, slave nodes are constrained to move with the master surface and, at the beginning of the simulation, the nearest master segment for each slave node is located based on an orthogonal projection. Using an established criterion (considering also an offset) the distance between the slave node and the master segment is deemed: if the slave node is calculated to be too close to the master segment, it is automatically moved to the master surface (Figure 3.7). In the present study, dura mater-skull interface is characterized by a viscous damping coefficient in percent of critical defined as 50.00; this mechanical parameter is in agreement with the value originally chosen by Kleiven [41] for his finite element model.

To define meninges-brain interface in LS$-$Dyna®, instead, a sliding only contact definition is preferred, since the presence of the cerebrospinal fluid between the meningeal membranes and the brain is not negligible when large rotational loads are induced on the head. As a matter of fact, a sliding interface do not allow any separation in the radial direction but only sliding in the tangential direction and transfer of tension and compression in the radial direction are allowed (Figure 3.6). This choice is justified by the fact that a fluid structure interface experiences a vacuum when inertia forces create tension in brain regions opposite impact.
Consequently, meninges-brain interface is marked by a static coefficient of friction equal to 0.2, a dynamic frictional coefficient of 0.2 and a viscous damping coefficient in percent of critical defined as 50.00; all these mechanical parameters are in agreement with the values originally chosen by Kleiven [41] for his finite element model.

**CONTACT_SLIDINGONLY**

*Figure 3.6 – Schematic illustration of the sliding only contact used to model the interface between the meninges and the brain. This type of contact allows only sliding in the tangential direction and transfer of tension and compression in the radial direction.*

**CONTACT_TIED_SURFACE_TO_SURFACE**

*Figure 3.7 – Schematic illustration of the tied surface to surface contact used to model the interface between the skull and the dura mater. This type of contact constrains slave nodes to move with the master surface.*

### 3.3 Loading Conditions: NFL Case Study number 57H2

The finite element head model is imposed the kinematics based on a reconstruction of a sport accident really happened in the American National Football League (NFL) where a loss of consciousness is involved [41]; the purpose of this simulation is to investigate the mechanical behavior of the head during the impact and compare obtained results with tissue loads and
deformation patterns of the brain found in previous studies in which the same loading conditions are applied \cite{41} \cite{69}. The final goal is to study the correlation between internal microscopic structure and macroscopic mechanical properties in soft biological tissue accounting for the anisotropic behavior of brain.

In the simulation of the brain response using head kinematics from the NFL reconstruction, the skull is assumed to be rigid while the head is subjected to translational and angular accelerations according to the kinematics obtained from laboratory testing. A summary of the applied loading acceleration conditions is illustrated in Figure 3.9.

The reconstruction of the kinematics of the sport accident which happened in the American Football League was performed same years ago by a research team funded by the NFL \cite{72} \cite{73} with the purpose of investigating the mechanics of several concussion cases. Video recordings of the game were analyzed and the initial head kinematics was determined. To reconstruct

Figure 3.9 - Head model loading conditions based on the reconstruction of a struck sport player. On the top a sequence of images taken from the simulation respectively at 0, 20 and 40 ms is shown. On the bottom translational and angular accelerations are illustrated.
head to head collision, two helmeted dummies equipped with nine linear accelerometers were impacted towards each other and resulting linear and angular accelerations were measured. The relative velocity of impacting players was instead inferred by a frame-by-frame analysis of the video taken of the accident. Finally, the struck player was represented as stationary while the whole relative velocity determined from video analysis was applied to the striking player. In this way dummy heads were impacted similarly to the real trauma incident [73][74].

The case study chosen in the current simulation is the number 57H2 of the 58 cases collected by the NFL research program where the acronym H2 stands for head number two and means that the struck player, namely the injured, is considered. Specifically this case is selected due to the high accelerations present in the lateral and axial direction, the loss of consciousness involved (often related to brainstem injury) and the possibility to compare results obtained in different studies modeling brain tissue behavior with different constitutive laws.

From a computational point of view, in *LS – DYNA*, loading conditions are applied to the head imposing translational and rotational velocities to a specific node locate at the head center of gravity (exactly node ID 31200 constrained to the skull); this procedure involves the use of six *DEFINE_CURVE cards where x, y and z translational and rotational velocities (3x2) are specified as functions of time (Figure 3.9). Then the kinematics of the accident is imposed thereby utilizing the *LS – DYNA* function * BOUNDARY _ PRESCRIBED _ MOTION _ NODE that applies to node 31200 the correspondent load curve for each of the six velocity components.
APPLICATION OF DT IMAGING TO DERIVE BRAIN ANISOTROPIC FEATURES

Computational models are often used as tools to study traumatic brain injury \[40\][41][42]; the in-vivo mechanical response of neural tissue during impact loading of the head is analyzed and measures of injury based on mechanical parameters are computed. However, the reliability of such models depends on the incorporation of an appropriate level of structural detail and the accurate representation of the material behavior. Since a strong correlation between internal microscopic structure and macroscopic mechanical properties is established for brain tissue and several brain regions show a marked anisotropy, constitutive equations must account for the information of axonal orientation within the brain. In the current study, the anisotropic orientation of neural tissue is incorporated into a hyper-viscoelastic material model for the brain tissue thereby exploiting diffusion tensor techniques; finally, an explicit dynamic FE analysis is performed. In this chapter the application of diffusion tensor imaging to derive brain anisotropic features is discussed providing a detailed description of the coupling method used to connect orientation information to the finite element model.

4.1 Diffusion Tensor and Anisotropy Calculations

The axonal fiber orientation information for this work is determined through the use of diffusion tensor imaging (theoretical details are provided in Chapter 2). According to the literature \[30\], it is assumed that for brain tissue a main diffusion direction corresponding to the axonal fiber direction can be detected while the degree of anisotropy for a neural fiber is described by the fractional anisotropy value.

To assess axonal orientation within the brain, a DICOM dataset with a matrix size of $116 \times 92 \times 42$ and a spatial resolution of $2 \times 2 \times 3.6 \ mm$ is used; imaging data refers to a healthy subject and was acquired using a Siemens Tim Trio scanner operating at $3.0 \ T$ with a time echo of 91.4 $ms$ and a repetition time of 5200 $ms$. In order to better define the diffusion ellipsoid shape under the existence of measurement errors \[32\], thirty measurements along thirty arbitrary axes were performed and a b-value equal to 1000 $s/mm^2$ was used. In the current study, the principal orientation field and the fractional anisotropy values are extracted thereby processing the previously described image dataset in MATLAB; to this effect a diffusion tensor and FA calculation code is developed and a 4D volume ($9 \times 116 \times 92 \times 42$) which contains diffusion tensor for each pixel plus a 3D Volume ($116 \times 92 \times 42$) defining fractional anisotropy are computed. Some results are illustrated in Figure 4.1.
Specifically, the program starts loading all the necessary diffusion frameworks for tensor computation (diffusion-weighted volume, b-value and gradient directions) and continues requiring a brain mask in order to identify pixels which belong to the brain thus bypassing calculations on the background. This mask is defined as a 3D logical volume containing for each voxel a value equal to 1 if the area belongs to the brain and must be taken in account for calculation, otherwise a value of 0 is assigned to the voxel. In the current work, the brain mask is loaded as a NIFTI image and it is obtained using 3D SLICER free software package where the segmentation editor is used.

Subsequently, the code computes the diffusion tensor. According to equation 2.21, least squares technique is applied and the diffusion tensor is determined for each voxel; its eigenvectors and eigenvalues are computed with the special attention of setting a correction procedure if the assumption of positive-definitiveness of the diffusion tensor is violated [36]. Finally, the fractional anisotropy index is extracted (equation 2.26) and the program ends saving the 4D tensor field and the 3D anisotropy map which represent brain tissue orientation information in

![Image](image-url)

*Figure 4.1 – Results of diffusion tensor and fractional anisotropy calculations for an axial slice of the brain. On the top left principal direction vector field is illustrated: lines represent the direction of axonal fibers in a two-dimensional space. On the bottom left a detail of the vector field is shown. On the top right a fractional anisotropy map is visualized.*
the geometry of the DICOM dataset. The code is found to be efficient and fast, since it processes about 450,000 pixel and produces results in less than three minutes.

Here a diffusion image dataset which refers to a single healthy subject is utilized. A recommendation should be to acquire imaging data on a high number of volunteers in order to obtain statistically robust mean diffusion properties. As a matter of fact, because of biological tissue variability, data acquired on a single subject may affect global results. In this case, however, fractional anisotropy distribution in the whole brain is found to be in line with literature values \[70\] (Figure 4.2), therefore diffusion tensor and anisotropy calculations are assumed to be correct. An average value of 0.23 for the whole brain is detected which is close to the 0.22 mean value found for over 20 healthy volunteers in previous study \[70\]. Moreover, as proposed in the literature, a superposition of two theoretical Gaussian curves can be done (Figure 4.3) and gray matter distribution can be sorted from white matter trend. In conclusion, the computed diffusion information seems promising.

\[70\]

**Figure 4.2** – Fractional anisotropy distribution in the whole brain. According to previous studies, an average value of 0.23 is found with a standard deviation equal to 0.16

**Figure 4.3** – Fractional anisotropy distribution in the whole brain. According to previous study two theoretical Gaussian curves representing gray (in red) and white matter distribution (in green) can be fitted.
4.2 Mesh Morphing to Apply Orientation

Once the location and orientation of the tensor information and the fractional anisotropy is computed, brain tissue anisotropic features in the geometry of the image dataset are obtained. However, the geometry of the FE head model differs from the previous one since different brains are involved and DTI resolution is typically further more refined than a FE head model mesh. Axonal distribution information is obtained at a remarkably detailed level if compared to the volume occupied by the elements of the current head model; therefore, in order to implement anisotropic features in the material constitutive law, a coupling technique connecting the two different geometries is required.

The protocol used in the current work to morph meshes and apply orientation to FE model scale is summarized below in Figure 4.3. Briefly, the FE head model is first subjected to a mesh voxelization and then a co-registration between the DTI mask and the obtained voxelized FE brain mask is performed. In particular, the two logical 3D volumes are fitted using imaging and numerical external geometries with an affine registration procedure: a spatial transformation aligning the DTI scale to FE geometry is determined and it is subsequently applied to previously computed FA map and tensor field volume.

In this way, a 3D map of axonal fiber directions and diffusion anisotropy at FE model scale and resolution is produced.

Figure 4.4 – Description of the global protocol for diffusion information mapping at FE model resolution. A co-registration between the DTI brain and the FE brain is performed using imaging and numerical external geometries with an affine registration procedure.
4.2.1 FEHM Mesh Voxelization

Voxelization is defined as the conversion of mesh objects from their continuous geometric representation into a set of voxels. In mapping diffusion information at FE model resolution, the procedure of voxelization represents the first step and it is required because of the definition of the head model geometry through nodes and elements. In order to apply affine registration, a set of voxels defining brain shape is first needed and, consequently, the mesh must be voxelized to produce a 3D image.

In the current work a MATLAB voxelization routine written by Adam H. Aitkenhead from the Christie NHS Foundation Trust (2010) is used and a bounded logical grid representing the brain shape is obtained. The function, called VOXELIZE, is capable of converting STL format into a voxel model and requires as input parameters the filename of the STL file and the desired number of voxels in the output grid respectively in x, y and z directions. It produces as output a 3D logical volume of the voxelized data (a value of 1 is assigned if the voxel is detected as inside the mesh while a value of 0 is for voxels located outside the mesh) and a list of the x, y and z coordinates of voxel centers. Specifically, the VOXELIZE routine works by passing rays in a direction through each pixel of the orthogonal plane and by finding the locations where the rays cross the mesh. Since the ray-tracing option ‘xyz’ is set, the mesh is ray-traced in each of the x, y and z directions, with the overall outcoming obtained as a combination of each direction results. This gives the most reliable result at the expense of computation time. In this work, the STL file defining brain model geometry is obtained thereby importing nodes and elements from LS–Dyna® to Altair HyperMesh® where hexahedral elements are split into triangular. The original surface and volume definition is thus converted into a new one in which a raw unstructured triangulated surface is described by triangles faces and vertices (ordered by the right-hand rule), maintaining the same three dimensional coordinate system (Figure 4.5 ). This file is subsequently read in MATLAB and used as VOXELIZE input.

Dimensions of the grid are instead chosen in order to obtain as output an iso-voxel model with a spatial resolution of $1 \times 1 \times 1 \ mm$; as a matter of fact, a $1 \ mm$ resolution is considered to be detailed enough to make sure that important features are not lost and, in the meantime, coarse enough to avoid spatial inefficiency. In numerical terms this means choosing 140 voxels in the x direction, 168 voxels in the y direction and 128 voxels in the z direction for an overall number of 3,010,560 voxels with a volume of 1 mm$^3$ each.

![Figure 4.5 – Visualization of the STL file defining the geometry of the brain; the format can be exported by Altair HyperMesh®. Coordinates are expressed in meters.](image)
As termination of the function, the logical output grid containing the brain shape is produced and it is saved as a NIFTI format 3D volume for further manipulations. Coordinates of the voxels centers are also provided. 2D projections of voxelized data are illustrated in Figure 4.6; the FE brain mask in axial, coronal and sagittal planes can be seen.

![Figure 4.6 - Visualization of the 2D voxelized data projections; images are obtained thereby summing values of the brain mask voxels along a specific direction. On the left x-z projection is provided, in the center x-y projection is found; on the right y-z projection is viewable.](image)

### 4.2.2 Fast Affine Registration

Image registration consists of a sequence of geometric operations that transform different sets of data into one coordinate system. In general, a fixed (or reference) image is detected and a moving image is forced into alignment with it and thereby spatially transforming it until the best match is found [75].

In this study, registration of volumes is required to align the DTI of the brain and the voxelized grid with the purpose of producing a 3D map of axonal fiber directions and diffusion anisotropy at FE model resolution. To this effect, an affine registration method is chosen: as a matter of fact, despite of its limited number of parameters, affine registration results in a physically plausible application and, as a consequence, it is considered to be sufficiently accurate for mapping DTI and FE geometries. Twelve parameters defining the spatial transformation are detected and the diffusion tensor field and fractional anisotropy map are resampled through the usage of the 3D SLICER 3.6.3 software package for registering and resampling.

Specifically, with the purpose of identifying the best affine transformation, the fast affine registration module of SLICER is chosen. This command line module implements a registration algorithm based on Mattes’ mutual information registration metric and affine transformation which is often used to align images of different subjects [76]. A voxelized output grid is chosen as the fixed image to register the moving image against; this means that the calculated transform maps a spatial position within the fixed image to a spatial position within the moving image. The moving image to register to the fixed image is consequently diffusion imaging brain mask and, since no initial transformation is specified, than one is created that centers the two datasets.

As termination of SLICER module, the transform that aligns the fixed and moving image is calculated and produced as output. It maps positions in the fixed coordinate frame to the moving
coordinate frame and allows the passage between the two geometries. In addition, an output volume resampling the moving image to the fixed image coordinate frame is as well generated and used to investigate visually the quality of the registration. Finally, in order to quantify the algorithm performance numerically, a registration error is defined as the ratio of the number of non-zero voxels in the punctual difference between the voxelized grid and DTI brain mask to the total number of pixel in the volume:

\[
error = \frac{\#(OUTPUTgrid - brain mask)}{TOT} \times 100 \%
\]  \hspace{1cm} (4.1)

As the volumes are logical ones, their difference contains a value of 0 for all voxels that are equal in both FE and DTI mask, a value of 1 for all voxels within the brain in the voxelized output grid but considered outside DTI volume and, finally, a value of −1 for all voxels belonging only to imaging brain. Counting the number of non-zero voxels over the total number of voxels in the difference dataset corresponds thus to quantify the registration error. In the current work, several registration parameters are tuned for investigating their impact on algorithm performances and coefficients that give the smallest registration error are chosen. A summary of tuning parameters results is provided in Table 4.1; a value of 30 is chosen for the histogram bins, that represent the number of bins used to generate the joint probability function in the mutual information algorithm; generally values of 30 to 100 are advised but in this case the parameter must be kept low otherwise the registration fails. This can be explain considering that if the number of bins is too large the estimated probability density functions will be a field of impulses and will inhibit reliable registration estimation.

Spatial samples coefficient is instead assigned a value equal to 999,999 which is the maximum allowed: the Mattes’ mutual information metric uses this number of samples for stochastic sampling of the images. Obviously larger values yield more accurate probability density functions and consequently improve registration quality.

Again, the number of iterations to run (Iteration Number) is set to 2000, since it is sufficient for convergence, and the transform scaling (namely the relative scaling between rotation and translation parameters) is defined as 50 (0.5 degree). The latter parameter is used to weight the transform parameters and their effect on the registration objective function. With these parameters the registration error is esteemed to be equal to 6.6832%. Result of registration can be visually checked in Figure 4.7 while the computed affine transformation is represented as matrix in equation 4.2.

\[
T = \begin{bmatrix}
1.0197700 & -0.0331933 & 0.0157712 & 0.971214 \\
0.0163382 & 0.9409400 & 0.2481160 & -21.690900 \\
0.0006967 & -0.2657690 & 1.1068700 & -1.833410 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]  \hspace{1cm} (4.2)
### FAST AFFINE REGISTRATION PARAMETERS

- **Histogram Bins**: 30
- **Spatial Samples**: 999.999
- **Iterations**: 2000
- **Translation scaling**: 50
- **Registration error**: 6.6832 %

### VARIATION OF Translation scaling

- **Histogram Bins**: 30
- **Spatial Samples**: 999.999
- **Iterations**: 2000

  - **Translation scaling**: 40 ----> registration error = 6.7163 %
  - **Translation scaling**: 49 ----> registration error = 6.6838 %
  - **Translation scaling**: 50 ----> registration error = 6.6832 %
  - **Translation scaling**: 53 ----> registration error = 6.6843 %
  - **Translation scaling**: 55 ----> registration error = 6.7162 %
  - **Translation scaling**: 100 ----> registration error = 6.8214 %

### VARIATION OF Histogram Bins

- **Spatial Samples**: 999.999
- **Iterations**: 2000
- **Translation scaling**: 50

  - **Histogram Bins**: 25 ----> registration error = 6.6843 %
  - **Histogram Bins**: 28 ----> registration error = 6.6835 %
  - **Histogram Bins**: 30 ----> registration error = 6.6832 %
  - **Histogram Bins**: 35 ----> registration error = 6.6996 %
  - **Histogram Bins**: 40,50,80 ----> REGISTRATION FAILED

---

Table 4.1 – Summary of parameters tuning results for fast affine registration run in 3D SLICER 3.6.2; the voxelized output grid is assumed to be the fix image while the DTI brain mask is considered as the moving image. Registration error is calculated according to equation 4.1.
Figure 4.7 – Results of affine registration. DTI brain mask is mapped to FE brain scale. A small amount of error is visible. On the top left an axial view of slice 65 is provided. On the bottom left a detail of the sagittal view of slice 73 is illustrated. On the top right a coronal view of slice 85 is visualized.

4.2.3 DTI Volume Resampling

Once the affine transformation aligning the DTI scale to FE geometry is determined and the coupling of the two different geometries is addressed, a 3D map of axonal fiber directions and diffusion anisotropy at FE model scale can be produced. To this effect, the resampling module of 3D SLICER is used and the affine transformation is applied to the diffusion tensor field and to the fractional anisotropy map.

Specifically, for the FA volume (that is scalar), the resample Scalar/Vector/DWI module of 3D SLICER is utilized. It implements image and vector-image resampling through the use of Insight Toolkit (ITK) transforms and it supports any transform that is implemented in ITK (rigid, affine, non-rigid). It can also handle diffusion weighted MRI image resampling. Attention must be paid to the fact that the spatial transformation is performed in spatial coordinates, and not at pixel or grid level. Consequently, it is crucial to ensure that image spacing is properly set on the images involved. In the current work an image resolution of $2 \times 2 \times 3.6 \text{ mm}$ is defined for the fractional anisotropy map while an image resolution of $1 \times 1 \times 1 \text{ mm}$ characterizes the FE geometry. Spatial transformation is performed without errors due to spatial inefficiency.

Fractional anisotropy is chosen as input (namely the volume to resample) set as the reference volume for the voxelized output grid. This means that the FE geometry is used to set sampling parameters such as origin, spacing, orientation and dimensions. Subsequently, the transforming node is loaded directly from SLICER and the linear interpolator is chosen. The interpolator is
required since the mapping from one space to the other will often require evaluation of the intensity of the image at non-grid positions. Finally, the resampling module is run and a diffusion anisotropy map at finite element scale is obtained. Results of resampling can be seen below in Figure 4.8.

In order to resample the diffusion tensor field, instead, the resample DTI module of SLICER must be used. It implements diffusion tensor image resampling through the use of ITK transforms. As the previous module, it supports any transform that is implemented in ITK (rigid, affine, non-rigid). Once again, resampling is performed in space coordinates, not in pixel or grid coordinates; therefore attention must be paid to the space definition and it is crucial to ensure that image spacing is properly set on the images involved. In the current work an image resolution of $2 \times 2 \times 3.6 \ mm$ is defined for fractional diffusion tensor field while an image resolution of $1 \times 1 \times 1 \ mm$ characterizes FE geometry. No errors occur due to spatial inefficiency (too small voxels).
As input volume, $DTI$ volume is chosen while the voxelized output grid works as reference. This means that the $FE$ geometry is used to set sampling parameters such as origin, spacing, orientation and dimensions. Subsequently, the transforming matrix is loaded from $SLICER$ and the linear interpolator is chosen. The main difference with the previous resampling method is that an appropriate reorientation of the diffusion tensor is performed. As a matter of fact, the orientational information that this image contains must be handled appropriately when it is transformed spatially during image registration, otherwise it can be affected by resampling. When a transformation is applied to a $DT - MR$ image, it is expected the shape of regions in the image to change but the underlying tissue microstructure in those regions does not. Only the orientation of the tissue microstructure can change. Thus, preserving the size and shape of the $DTs$ in the image, which reflect the properties of the tissue microstructure, is essential but in the meantime $DTs$ must be reoriented in a way consistent with the reorientation of the tissue caused by the transformation.

To this effect, in $SLICER$ $DTI$ resampling module the option for using the preservation of principle direction ($PPD$) is checked; the choice of this specific algorithm is based on its reliability in preserving the principal direction of the $DT$ which is shown to be the most effective \cite{77}. As a matter of fact, $PPD$ algorithm is capable to take into account shearing, stretching and rigid rotation adopting the assumption that the directionality of the tissue structure corresponds
to the direction of the eigenvectors of the DT. As consequence, anatomical accuracy of the transformed image is secured.

To conclude, the DTI resampling module is run and a diffusion tensor field is obtained at FE resolution. Some results are shown in Figure 4.9. A specific part of the brain, i.e. the corpus callosum, is zoomed in to properly visualize the first eigenvector direction after image registration. A correct uniaxial lateral orientation is shown meaning that preservation of principal direction effectively keeps orientation information intact.

4.3 Diffusion Information Mapping at FE Model Resolution

After FA and DTI volume resampling, diffusion information is obtained at head model scale. As a matter of fact, in order to transform such volumes a voxelized output grid is used as spacing source and its geometry is referred to set origin, orientation and dimensions of the resampled output. However, since the aim of mesh morphing is incorporating the anisotropic features of neural tissue into a hyper-viscoelastic material model for the brain, a further step is necessary to convert voxel information into a format readable in LS – DYNA® which works with elements and nodes numbering.

To this effect, maintaining the same three dimensional coordinate system, voxel diffusion characteristics are processed to extract the degree of anisotropy and the principal orientation for each element belonging to the brain of the FE model; once element anisotropic information is addressed, it is finally incorporated into LS – DYNA® generating a new material and a new element formulation for the brain. In next paragraphs, a description of the computerized procedure to convert diffusion information at voxel resolution into the finite element model can be found.

4.3.1 Computerized Protocol to Select DTI Voxels for each Element

To implement information from the three dimensional diffusion image to the FEM, the next step consists of identifying and selecting all DTI voxels belonging to each brain element of the model; final purpose is to average their anisotropic properties extracting as consequence mean element anisotropy information that can be used to formulate material behavior in LS – DYNA®. Because of the great number of brain elements, a computerized protocol is here developed and MATLAB help is utilized to assess the objective.

In the current work, after registration, the DTI of the brain consists of regular plan-parallel voxels with 1 by 1 mm size. Information about coordinates of voxel centers is accessible thanks to the output of the VOXELIZE function (see paragraph 4.2.1) which produces a 3D logical volume of data (a value of 1 is assigned if the voxel is detected as inside the mesh while a value of 0 is for voxels located outside the mesh) and a list of the x, y and z coordinates of voxel centers. Since the voxelized grid is used as spacing source to set origin, orientation and dimensions of the resampled volumes, after the registration coordinates of its centers correspond to coordinates of resampled volumes centers. Moreover, an eight-node element in
LS – DYNAP® is defined through its eight nodes which are in turn defined by an identification number and their x, y and z coordinates in a three dimensional Cartesian system. Considering spatial coordinates is therefore possible to determine a relationship between voxels and brain elements and, particularly, a voxel can be established to be whether inside or outside an element. Selection procedure consists instead in determining this spatial correlation.

To this effect, a MATLAB code is developed in this study. It interprets an eight-node brick element of LS – DYNAP® as a convex polyhedron with eight vertices (nodes) and determines if a point in space belongs or not to it through the use of the MATLAB function INHULL. Specifically, as first, a list of all brain elements is created: from LS – DYNAP® k-file the script loads all the information necessary to characterize an element and it stores them into ELEM.mat and NODES.mat data file. Subsequently, for format convenience, this information is assigned to a list of structures in which each component represents an element by the means of four parameters: elID, partID, coordNodes and centroid. They are respectively the element ID used in LS – DYNAP® code to define the element, the part ID used in LS – DYNAP® code to define the part which the element belongs to, an 8 x 3 matrix containing for each row x, y and z coordinates of the eight nodes describing the element and a 1 x 3 vector with x, y and z coordinates of the element centroid.

Once the element MATLAB format is ready, the script continues with determining voxel centers belonging: it scrolls all the element list and, for each element, it calls the function INHULL with the purpose of determines which points of the DTI volume are inside and which points are outside the element. As a matter of fact, this function is a helping script written by John D’Errico (Eastman Kodak) that works testing if a set of points are inside a convex hull. For each element, the 8 x 3 matrix of nodal coordinates is given as input and the set of center voxel points is tested. As output a logical array is produced which i – th row contains the value 1 if the i – th point belongs to the hull or 0 otherwise. In this way, voxels belonging is easily addressed. In particular it must be noticed that only voxel center is tested: this means that a voxel is considered inside an element if its center fits the polyhedron; otherwise the voxel does not belong to the element.

In conclusion the program terminates storing into ELEM_LIST[i] a N x 3 matrix of x, y and z coordinates of all voxels centers inside the element; N represents the number of voxel found and it clearly depends on the element in analysis. Specifically, a high number of voxels is obtained for elements with big volumes while a low number is associated to small elements.

4.3.2 Averaging Procedure

Final step to determine the anisotropy degree and the main orientation of each element is to investigate diffusion information for the corresponding selected voxels and apply an averaging procedure in order to extract mean element features. Because of the great number of brain elements, a computerized protocol is developed here and MATLAB is utilized to complete the objective.

Specifically, the script utilizes the ELEM_LIST.mat and DATA.mat data files and calculates the resulting fractional anisotropy value and principal direction vector for each element as the mean values of all selected voxels. DATA.mat contains all the information necessary for calculations and it is loaded before running the code. Once again, the element list is scrolled and the N x 3 matrix representing x, y and z coordinates of all voxels centers inside the element is
extracted. For each voxel, the Euclidean distance between the center of the element and the center of the voxel is computed: this operation is necessary to determine weights for the weighted averaging procedure. As a matter of fact, in order to reinforce the influence of the diffusion parameters close to the center of the element, these are weighted by accounting for the distance $D$ between the center of the element and the center of the voxel. Finally, weighted averaging of values is performed using the following formulas:

$$\langle T \rangle_{\text{elem}} = \frac{\sum_{i=1}^{N} T_i e^{-D_i}}{\sum_{i=1}^{N} e^{-D_i}}$$  \hspace{1cm} (4.3)$$

$$\langle FA \rangle_{\text{elem}} = \frac{\sum_{i=1}^{N} FA_i e^{-D_i}}{\sum_{i=1}^{N} e^{-D_i}}$$  \hspace{1cm} (4.4)$$

In equation 4.3 and 4.4, $N$ refers to the number of selected voxels for one finite element and $FA_i$, $T_i$, $D_i$ respectively to the $FA$ value, the diffusion tensor and the distance to the center of the element for each selected voxel.

Once element diffusion information is calculated, eigenvectors of the mean diffusion tensor are extracted. They are necessary to determine the local system of coordinates of the material in $LS - DYNA$® and will be further processed. For concluding, the script stores mean diffusion values as structure parameters into the element list where $fa$ represents the fractional anisotropy value of the element, $firstEvec$ the principal eigenvector, $secondEvec$ the second eigenvector and $thirdEvec$ the third eigenvector of the element. The script terminates producing as output $ELEM\_LIST$ and save it as a $MATLAB$ data file with the same name.

Results of the averaging procedure can be seen in Figure 4.10 and 4.11; the distribution of the mean degree of anisotropy is plotted for the whole brain and for corpus callosum. For the principal direction, instead, a histogram is realized representing the distribution of the angles formed between the lateral direction (x-direction) and the principal eigenvector orientation.

By comparing experimental data with theoretical knowledge it can be concluded that the averaging procedure does not heavily affect the diffusion features. As a matter of fact, during the averaging process part of the anisotropic properties are lost and this may represent a problem for the accuracy of the analysis. In the current study, mean diffusion values are shown to be in line with what predicted by the theory. For fractional anisotropy a mean value of 0.23 is obtained with a standard deviation of 0.12 which is really close to the 0.22 mean value with a standard deviation of 0.09 found in previous studies [70]. Moreover, brain regions such as white matter, corpus callosum or brain stem, which are well-known to have anisotropic features, show a marked degree of anisotropy. For the accuracy of the principal direction, instead, the corpus callosum is investigated; from the theory it is known that it has uniaxial lateral orientation: looking at angle distribution, lateral orientation is still found to be the main direction meaning that principal direction features are not extremely affected during the averaging.
FRACTIONAL ANISOTROPY DISTRIBUTION
WHOLE BRAIN

Mean FA value = 0.23
Max FA value = 0.84
Min FA value = 0
Standard deviation = 0.12

CORPUS CALLOSUM
WHITE MATTER
BRAIN STEM

Figure 4.10 – Fractional Anisotropy distribution after averaging procedure. On the bottom brain details are shown.

Table 4.2 – Summary of fractional anisotropy distribution in brain regions.
Figure 4.11 – Distribution of the angles formed between lateral direction (x-direction) and principal eigenvector orientation in the Corpus Callosum. After the averaging procedure, lateral orientation is still found to be the main direction.
Chapter 5

SIMULATION OF A CONCUSSIVE IMPACT

Finite element modeling appears to be the most appropriate technique through which human head tolerance to impact can be studied. Thanks to the accurate representation of the anatomically specific geometry and the capability to take into account physical and geometrical nonlinearities, a representative finite element model of the human head would allow valid calculations of tissue loads and deformation patterns of the brain, identifying possible relationships between a particular deformation in a tissue and an injury in the same. In this chapter a practical application of finite element modeling is described. Through the use of LS – DYNA®, a concussive impact between two football players is simulated and the biomechanics of the struck player’s head is analyzed. The final purpose of the simulation is to test the mechanical behavior of a hyper-viscoelastic fiber-reinforced material for brain tissue which accounts for anisotropy features of the brain thereby exploiting DT imaging. In particular, the next paragraphs depict material and element formulations in LS – DYNA® including a brief description of the simulation protocol.

5.1 Description of Material and Elements Keyword Input

In the current work LS – DYNA® software is used to study in-vivo mechanical response of neural tissue during impact loading of the head.

From a computational point of view, the program works through the specification of a keyword input file that provides a flexible and logically organized database where all finite element problem features must be given. The keywords can be entered in an arbitrary order in the input file however, for clarity in this work, the following block structure is chosen: first a section for redefining LS – DYNA® default, setting output parameters and controls is found; secondly, material and geometry characteristics of the final element analysis are specified. Finally, there is a section for defining loads and boundary conditions of the problem.

Since this study is centered on the formulation of a new material which accounts for anisotropic features of the brain, the following paragraphs are focused on material definition including elements, parts and sections based on anisotropic properties of the brain.

5.1.1 Redefinition of Elements, Parts and Sections Depending on FA Value

Because the KTH finite element head model has a broad validation [42], the current constitutive laws are used to define the material of the components in the input file, with the exception of

57
brain tissue where the original material model is modified and extended accounting for anisotropic behavior. To this effect, Gasser-Ogden-Holzapfel hyper-viscoelastic fiber-reinforced anisotropic model is utilized and its formulation is supplied to the program by the means of a user subroutine. The custom executable which includes the material subroutine has been written by Rudy Cloots (2011) during his doctoral studies at Eindhoven University of Technology and it is invoked in the keyword input deck using *MAT_USER_DEFINED_MATERIAL_MODELS command with appropriate input parameters. Since this study aims to incorporate anisotropic features in the brain tissue material formulation, nine different GOH user defined materials are created thereby varying the value of the degree of anisotropy $k$ and redefining the brain finite elements based on fractional anisotropy. Table 5.1 specifies the correlation between fractional anisotropy and fiber dispersion orientation $k$. For more theoretical details see Chapter 3 (paragraph 3.2.4).

<table>
<thead>
<tr>
<th>FA range</th>
<th>$k$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 ÷ 0.2</td>
<td>0.3333</td>
</tr>
<tr>
<td>0.2 ÷ 0.3</td>
<td>0.2732</td>
</tr>
<tr>
<td>0.3 ÷ 0.4</td>
<td>0.2500</td>
</tr>
<tr>
<td>0.4 ÷ 0.5</td>
<td>0.2273</td>
</tr>
<tr>
<td>0.5 ÷ 0.6</td>
<td>0.2000</td>
</tr>
<tr>
<td>0.6 ÷ 0.7</td>
<td>0.1667</td>
</tr>
<tr>
<td>0.7 ÷ 0.8</td>
<td>0.1282</td>
</tr>
<tr>
<td>0.8 ÷ 0.9</td>
<td>0.0769</td>
</tr>
<tr>
<td>0.9 ÷ 1.0</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

*Table 5.1 – Relational table for correlating fractional anisotropy values to corresponding dispersion orientation parameter in the GOH model.*

As a consequence, brain regions are not any longer distinguished depending on their anatomy but nine different groups are created on the base of the degree of anisotropy of the material. Specifically, neural tissue is in general assumed to have GOH hyper-viscoelastic anisotropic behavior but a distinction is made among regions marked by different anisotropy properties. This sorting choice is justified by the assumption that the GOH material formulation allows to consider both the hyper-viscoelastic behavior and the correlation between the internal structure and the macroscopic mechanical properties. The final purpose is to enhance the reliability of the FE head model.

Since elements, parts and sections are closely related in LS − DYNA®, redefinition of elements leads to a redefinition of parts and sections into the keyword input deck. In particular, every user defined material is related to a part which in turn is related to a section. Finally, an element is related to a material by the means of a part (Figure 5.1).
In the current work, nine different user defined materials are created thereby varying the value of the degree of anisotropy $k$, therefore nine different parts are created in turn representing the anisotropic characteristics of these materials. The identification number $5000i$ is used to label the $i$th group of brain elements where 0 corresponds to isotropic group and 8 to the most anisotropic group. All groups are referred to the same section (50) that contains information to define element formulation and integration rules. Specifically, all brain elements are considered to be solid eight-node elements (as in the original head model) while a constant stress solid element integration rule with hourglass control is chosen. This choice is not the best possible but it is obliged by the material formulation contained in the executable.

Results of parts, sections and elements redefinition are shown in Figure 5.2; as it can be seen, brain components are not any longer divided into anatomical regions (cerebellum, corpus callosum, etc) but they are sorted depending on their degree of anisotropy. This separation looks quite fragmentary however, according to theoretical knowledge, most anisotropic parts are still shown to be located on the inner parts of the brain such as the corpus callosum, the brain stem and the white matter.

### 5.1.2 Application of DTI Orientations to Brain Components

Constitutive modeling of soft tissues is an important and challenging area in biomechanics. Accurate constitutive models are necessary to reliably reproduce tissue behavior and, in particular, there is the need to establish the mechanical-functional parameters required to reproduce their functions.

To this effect, in this work, brain tissue constitutive modeling integrates critical information on tissue structure with the purpose of elucidating the underlying mechanism of tissue mechanical behavior. As a matter of fact, several studies demonstrate that the sensitivity of brain tissue to a mechanical load is orientation-dependent; therefore, avoiding ambiguities in material
Isotropic component of the brain (0<FA<0.2)

Anisotropic component of the brain (0.2<FA<0.3)

Anisotropic component of the brain (0.3<FA<0.4)

Anisotropic component of the brain (0.4<FA<0.5)

Anisotropic component of the brain (0.5<FA<0.6)

Anisotropic component of the brain (0.6<FA<0.7)

Figure 5.2 - Results of parts, sections and elements redefinition. The separation looks quite fragmentary. Most anisotropic part are shown to be inner part of the brain.
characterization is possible when fiber orientation is modeled, since it offers insight into the function, structure, and mechanics of the components.

As said before, Rudy Cloots has developed a GOH model subroutine for LS - DYN@ software \[^{[69]}\]: it implements the mechanical behavior of a hyper-viscoelastic fiber-reinforced anisotropic material according to the formulation proposed by Gasser, Ogden and Holzapfel \[^{[68]}\]; anyway, even if his research show promising results, only specific regions of the brain are assigned anisotropic behavior with only one direction specified for the entire material formulation. In particular, the corpus callosum is considered to be anisotropic with uniaxial lateral orientation while brainstem is modeled as transversally anisotropic component oriented in the inferior-superior direction.

In the current study, Cloots' work is extended: the anisotropy degree of brain regions is determined thanks to fractional anisotropy calculation and it is accounted for all eight-node elements representing the brain (more details are provided into paragraph 5.1.1). Moreover, local fiber orientation is introduced into the constitutive model thereby specifying directions element-wise with *ELEMENT_SOLID_ORTHO* keyword in the LS - DYN@ input deck. As a matter of fact, the ORTHO option allows to define three dimensional solid element (8-noded hexahedrons in this case) through the part ID and the section ID plus a local coordinate system suitable for anisotropic materials. To this effect, in the input deck two additional cards are specified for all brain elements characterized by anisotropic behavior. Two local directions are defined: vector *a*, that represents the principal local orientation of the material (its *x, y* and *z* components are assigned a numerical value in the card) and vector *d*, representing a vector in the plane of material vectors *a* and *b*. Specifically, local axes are computed as follows:

\[
\begin{align*}
    c &= a \times d \quad (5.1a) \\
    b &= c \times a \quad (5.1b)
\end{align*}
\]

where *a* is the *x*-local direction, *b* represents the *y*-local direction and *c* is defined as *z*-local direction. The geometry of the local system is shown in Figure 5.3.

![Figure 5.3 - Options for determining principal material axes. This choice corresponds to AOPT = 2.0 in the input deck.](image)
In the current study, considering brain tissue diffusion characteristics, it is assumed that a principal fiber direction can be identified for each element \((\lambda_1 > \lambda_2 > \lambda_3)\) which in turn means assuming that diffusion occurs mainly along the fiber axis denoted by the direction unit vector \(\mathbf{v}_1\). Since the diffusion tensor is symmetric and positive definite \([35]\) its eigenvectors are orthogonal and they are considered as principal direction axes of a system of principal direction coordinates. Vectors \(\mathbf{a}\) and \(\mathbf{d}\) are therefore chosen as respectively corresponding to \(\mathbf{v}_1\) and \(\mathbf{v}_2\); in this way \(\mathbf{v}_1\) represents \(x\)-local direction, \(\mathbf{v}_2\) is the local \(y\)-direction and \(\mathbf{v}_3\) is defined as the local \(z\)-direction.

From a computational point of view, information on eigenvectors is extracted by the element list data file \((\text{firstVec}, \text{secondVec})\) and it is implemented in \(LS – DYNAN \) automatically printing component values into the keywords input deck. By the means of an example, the specification of element 1156 is provided.

\[
\begin{align*}
* \text{ELEMENT\_SOLID\_ORTHO} \\
$\# \ eid & pid & n1 & n2 & n3 & n4 & n5 & n6 & n7 & n8 \\
1156 & 50001 & 2607 & 2640 & 2646 & 2606 & 2601 & 2625 & 2630 & 2602 \\
$\# \ a1 & a2 & a3 \\
-0.88226 & 0.31752 & 0.34755 \\
$\# \ d1 & d2 & d3 \\
0.40670 & 0.88591 & 0.22305
\end{align*}
\]

In conclusion, fiber orientation is included into the material model for brain tissue and the underlying mechanism of tissue mechanical behavior is elucidated.

### 5.2 Simulation Protocol

In the current work the \(LS – DYNAN \) software is used to study in-vivo mechanical response of brain tissue. The finite element head model is imposed the kinematics based on a reconstruction of a sport accident from the American National Football League \((NFL)\) and the mechanical behavior of the head during the impact is investigated. Tissue loads and deformation patterns are analyzed in particular looking at maximum principal strain and anisotropic equivalent strain measure \([69]\). The final goal is to study the correlation between internal microscopic structure and macroscopic mechanical properties in soft biological tissue accounting the anisotropic behavior of brain.

#### 5.2.1 Test A

In Test A, the finite element head model is imposed the kinematic, boundary and loading conditions based on case study 57H2 (more details are found in Chapter 3). The sport accident which occurred in the American National Football League is reconstructed and the behavior of brain tissue during impact is investigated.
The GOH hyper-viscoelastic material model is utilized and parts, sections and materials are rearranged based on fractional anisotropy values. In this simulation the principal directions are not specified in *ELEMENT_SOLID ORTHO* keyword: this choice is done with the purpose of highlighting and better analyzing the relationship between the anisotropy degree \((FA)\) and the dispersion fiber parameter in the GOH material model \((k)\). To the best knowledge of the author, this correlation has never been used before in mechanical simulations and lacks experimental validation. The idea beneath the test is thus to examine the mechanical behavior of GOH components for varying \(k\) values.

### 5.2.2 Test B

In Test \(B\), once again, the finite element head model is imposed the kinematic, boundary and loading conditions based on case study 57H2 (more details are found in Chapter 3). The sport accident really happened in the American National Football League is reconstructed and the behavior of brain tissue during the impact is investigated. The GOH hyper-viscoelastic material model is utilized and parts, sections and materials are completely rearranged considering both the degree of anisotropy of brain tissue and its principal direction. In *ELEMENT_SOLID ORTHO* a local system of coordinates is defined (more details are provided in paragraph 5.1.2) which accounts for the anisotropy of the element. Finally, anisotropic equivalent strain measure is computed.

### 5.3 Simulation Results

In the current study, the anisotropic orientation of neural tissue is incorporated into a hyper-viscoelastic material model for brain tissue thereby exploiting diffusion tensor techniques; subsequently explicit \(FE\) analyses are performed and the in-vivo mechanical response of neural tissue during impact loading of the head is analyzed. This paragraph displays obtained results focusing attention on maximum principal strain and anisotropic equivalent strain measures. Tissue loads and deformation patterns are investigated: the final purpose is to study the correlation between internal microscopic structure and macroscopic mechanical properties in brain tissue.

#### 5.3.1 Stress and Strain Analysis

At the beginning of the analysis, Test \(A\) is performed. The finite element head model is imposed the kinematics of Case Study 57H2 and the behavior of brain tissue during the impact is investigated. Since the main purpose of the simulation is analyzing the relationship between the anisotropy degree \((FA)\) and the dispersion fiber parameter in the GOH material model \((k)\), attention is focused on mechanical behavior of GOH components for varying \(k\) values.
All anisotropic brain regions are given only one global direction: in this test, the lateral orientation is arbitrarily chosen and this choice is justified by the kinematics of the impact. As a matter of fact, the struck head is mostly accelerated in the lateral direction; considering fibers oriented along the same orientation allows better examining fiber stiffness contribution to the mechanics of the material.

Results of the simulation are displayed in Figure 5.4, 5.5, 5.6, 5.7 and 5.8. Firstly, internal energies of GOH materials are investigated (Figure 5.4). Attention on these energies is paid since in LS – DYNAmics® they are computed based on the six components of stress and strain (tensorial values). Specifically, the calculation is done incrementally for each element considering stress, incremental strain and volume as follows:

$$E_{int}^{(n+1)} = E_{int}^{(n)} + \sum \text{stress} \times \text{incremental strain} \times \text{volume}$$  \hspace{1cm} (5.2)

where the sum is performed over all six directions of tensors \((x, y, z, xy, yz, xz)\). The internal energies of all the elements in a material is then summed to give the total internal energy. Studying these energies therefore allow examining variation in stresses and strains of materials depending on fiber dispersion \((k)\).

Figure 5.4 depicts, as theoretically expected, different behavior of GOH components internal energies: in particular, the energies are plotted against time and the identification number 5000\(i\) is used to label the \(i – th\) group of brain elements where 0 corresponds to isotropic features and 8 to the most anisotropic features. As it can be seen from the graph, the curve shape is, in general, the same for all the nine materials with a peak at about 6 ms and, subsequently, a slow increasing of energies in time. A reduction in magnitude can be instead noticed with increasing fiber stiffness contribution \((k \rightarrow 0)\). This reduction is due to variation in volume of the components (the model contains a larger number of element for materials with less anisotropic characteristics) but also to a smaller incremental strains of GOH components.

Considering the first three curves, that contain approximately the same volume of elements, it can be shown that a higher transversely anisotropy leads to smaller incremental strains into the material. This can be easily explained taking into account fiber contribution to the stiffness of the structure: the more fibers are aligned to lateral direction, the more they will resist the deformation in the same orientation and, meanwhile, the deformation will be slower. At the end, this behavior results into smaller magnitude for internal energies.

About stresses, instead, no significant variation is identified; moreover, comparing the GOH material with the original hyper-viscoelastic model used by Kleiven, similar maximum principal stresses can be noticed: in the original simulation a peak of 55.318 kPa is reached at about 0.075 s while in Test \(A\) the maximum value of stresses is 58.922 kPa and it is obtained at about 0.075 s. Figure 5.5 and 5.6 show the similar time history of maximum principal stress respectively in the original and the new FE model.

Finally, again for Test \(A\), principal strain of the GOH materials is investigated. An average of strain characteristics of all elements into a group is performed and plotted. Figure 5.7 depicts, as theoretically expected, different behavior of GOH components maximum principal strain when varying \(k\): in particular, the curves are plotted against time and the identification number 5000\(i\)
Figure 5.4 – Behavior of GOH components internal energies. The energies are plotted against time and the identification number 5000i is used to label the i-th group of brain elements where 0 corresponds to isotropic features and 8 to the most anisotropic features.

Figure 5.5 – Maximum Principal stress in the original KTH FE model. The stress is plotted against time and its higher value is identified at node 7179.
Figure 5.6 – Maximum Principal stress in the FE model used in the current study. The stress is plotted against time and its higher value is identified at node 7274.

Figure 5.7 – Behavior of GOH components principal strain (Green St Venant). The strains are plotted against time and the identification number 5000i is used to label the i-th group of brain elements where 0 corresponds to isotropic features and 7 to the most anisotropic features.
is used to label the $i - \text{th}$ group of brain elements where 0 corresponds to isotropic features and 8 to the most anisotropic features. As it can be seen from the graph, the curve shape is, in general, the same for all the nine materials with two peaks clearly visible at about 12 ms and 25 ms. Deformation reaches macroscopic levels with values over 30% confirming for this particular situation that injurious loads may occur and brain tissue is a vulnerable part for injury. A reduction in magnitude with the increasing of fiber stiffness contribution ($k \to 0$) can instead be noticed in the graph. This reduction is due to fiber alignment which improves the stiffness of the structure: the more fibers that are aligned, the more they will resist deformation and, meanwhile, the deformation will be earlier in time (peaks tend to move to the left). All the mechanism leads to a consequent reduction of strains that can clearly be detected in Figure 5.7. It is interesting also analyzing the anatomical position of elements where maximum principal strains occur: particularly, they are located in element 4748 for material 50000, element 1161 for material 50001, element 1193 for material 50002, element 4910 for material 50003, element 4514 for material 50004, element 4050 for material 50005, element 4384 for material 50006 and element 1506 for material 50007. Figure 5.8 provides a graphical view of their location.

Figure 5.8 – On the left, localization of GOH brain elements where maximum principal strain (Green St Venant) occurs. The strains are located into midbrain for poorly anisotropic materials (4748, 1161, 1193), into white matter for averagely anisotropic materials (4514, 4050, 4384) and into corpus callosum for highly anisotropic materials (1506, 5070). Below, maximum principal strain of a sagittal cross section of the head model at 14 ms. Higher deformation occurs around the brain stem.
According to theoretical expectations, strains are higher where the brain tissue anisotropy is more pronounced: elements highlight in Figure 5.8 belong to midbrain for less anisotropic materials (4748, 1161, 1193), to white matter for medium anisotropic materials (4514, 4050, 4384) and to corpus callosum for highly anisotropic materials (1506).

In addition, Figure 5.8 provides a strain field for the head model in which it is clear that elevated strain levels, up to 0.30, occur, especially around the brainstem. A sagittal cross section of the brain is illustrated and the brainstem is clearly presented as a vulnerable part for injuries. This is in agreement with the loading conditions applied to the head model: as a matter of fact, NFL Case Study 57H2 involves loss of consciousness which is often related to brainstem injury. Once the analysis of fiber stiffness contribution is concluded, Test B is performed. The finite element head model is imposed the kinematics of Case Study 57H2 and the behavior of brain tissue during impact is investigated. Since the purpose of this simulation is to improve material modeling accounting for anisotropic features of the brain, the GOH hyper-viscoelastic model is utilized and parts, sections and materials are completely rearranged considering both the degree of anisotropy and principal directions. The prediction capability of the finite element model is finally investigated; simulation results are shown in Figure 5.9, 5.10, 5.11 and 5.12.

Firstly, maximum principal stresses are investigated. Since Test A shows no significant variation in stresses (might be insensitive to the shear stiffness and fiber stiffness), this analysis aims to identify whether specification of local orientation affects load patterns or not. As it can be seen from Figure 5.9, the incorporation of axonal fiber direction into GOH material model produces only slight modification of maximum principal stresses. In the original simulation performed by Kleiven a peak of 55.318 kPa is reached at about 0.075 s, in Test A the maximum value of stresses is 58.922 kPa and it is obtained at about 0.075 s while in Test B a peak of 51.464 kPa is detected at about 0.075 s; the shape of the curve remains the same in all the three cases. The slight magnitude reduction of maximum principal stresses is considered not to be significant for affecting mechanical behavior of the head; moreover, this decreasing can be easily explained when considering the incorporation of axonal local directions in brain tissue: as a matter of fact, in Test A all the elements are arbitrarily assigned one direction (x-lateral) while in Test B diffusion tensor information is incorporated into the model and a more random distribution of axonal fibers can be found. This means that stresses are as well more randomly distributed along all the directions, leading into a reduction of maximum principal stresses in favor of others principal stresses.

![Figure 5.9 – Maximum Principal stress in the FE model used in the current study (Test B). The stress is plotted against time and its higher value is identified at element 4817.](image-url)
Figure 5.10, instead, depicts maximum principal strain for this simulation. An average of strain characteristics inside an element for each brain element is performed and plotted. As it can be seen from the graph, the curve shape is the same as the one obtained in Test A. Two peaks are clearly visible at about 14 ms and 27 ms but they appear later in time with respect to the previous study. Deformation reaches macroscopic levels and a maximum value of 0.3275 is found, higher than the maximum strain identified in Test A. However strain values confirm for this particular situation that injurious loads may occur. Comparing Figure 5.10 and 5.7, it can be demonstrated that stiffness properties for the brain especially affect the strains in the tissue. As a matter of fact, stiff properties (Test A) produce lower peak values of maximal principal strain which occur also earlier in time. These differences are crucial for a FE model of the human head designed to predict traumatic brain injuries, therefore a reliable incorporation of axonal orientation into the model is essential to better understand traumatic injury mechanisms.

To highlight deformations of brain tissue, figure 5.11 illustrates a strain field for the head model. Looking at the picture, it is clear that elevated strain levels (up to 0.30) occur, especially around the brainstem. A sagittal cross section of the brain is shown and the brainstem is clearly presented as a vulnerable part for injuries. Once again, this is in agreement with the loading conditions applied to the head model: as a matter of fact, NFL Case Study 57H2 involves loss of consciousness which is often related to brainstem injury. In addition, the insertion of axonal directions into brain material model is shown to affect strains in the tissues. When Figure 5.11 is compared to Figure 5.8, a general more extended deformation can be noticed with white matter particularly involved into the process.

*Figure 5.10 – Behavior of GOH components principal strain (Green St Venant). The strain is plotted against time and it occur at element 4901 (white matter).*
Finally, maximum strain rate of brain tissue is investigated since it has been suggested as an injury predictor in previous studies [41][78]. An average of strain rate characteristics inside an element for each brain element is extracted and plotted in Figure 5.12. Looking at the graph, a peak is clearly visible at about 18 ms when the strain velocity reaches 70 s\(^{-1}\). Time history of the curve shows that, at the beginning, deformation rate rapidly increases until a value of 30 s\(^{-1}\) is obtained; then, after a period settled around that value, the curve presents a peak meaning that the strain rate rapidly increases again (70 s\(^{-1}\)). In the end, an almost constant strain rate of 30 s\(^{-1}\) can be found.

In previous studies [78], strain rate has been hypothesized to be a key biomechanical parameter to explain the cause of brain injury and concussion. Focusing on brain reaction to complex inputs of translational and rotational acceleration, tolerance levels are estimated to be 46 s\(^{-1}\) for a 25% probability of MTBI, 60 s\(^{-1}\) for a 50% probability of MTBI and 80 s\(^{-1}\) for a 75% probability of MTBI. Considering maximum strain rate in Test B, a probability of concussion higher than 50% can thus be found. This is in agreement with the loading conditions applied to the head model: as a matter of fact, NFL Case Study 57H2 involves loss of consciousness which is often related to traumatic brain injuries.
5.3.2 Comparison between Isotropic and Anisotropic Brain Constitutive Models

Simulations $A$ and $B$ aim to test the mechanical behavior of the GOH hyper-viscoelastic fiber-reinforced material that accounts for anisotropic features of the brain. The finite element head model is imposed the kinematics of Case Study 57H2 and the response of brain tissue during the impact is investigated. Since the current work is an extension of previous studies performed by Kleiven and Cloots, it is worth to compare results obtained utilizing the same head model and imposing the same loading condition to the problem (Case Study 57H2) but assigning different properties to brain tissue. As a matter of fact, in Kleiven's work [41] brain is considered as an isotropic material while Cloots [69] takes into account anisotropy for only specific regions of the brain that are assigned only one direction for the entire material formulation. The current study, instead, considers the degree of anisotropy for all brain regions and the local fiber orientation is introduced into the constitutive model thereby specifying directions element-wise.

In this paragraph, maximum principal strain, deformation field and maximum strain rate are therefore analyzed for the three cases; results are presented in Figure 5.13, 5.14 and 5.15. The correlation between internal microscopic structure and macroscopic mechanical properties in brain tissue is investigated.

Figure 5.13 shows a comparison between maximum principal strains computed for the three different simulations. As it can be seen from the curves, maximum absolute values of the strains are similar in all cases (up to 0.3) but the shape of the curves and their time history vary when anisotropic features are accounted for brain tissue. In case of isotropic features maximum deformation is reached earlier in time and the graph presents only one peak: principal strains firstly increase until the maximum is obtained, then decrease. Considering anisotropic features for the brain, instead, the results obtained in Test $B$ are close to what was calculated by Cloots: two peaks are clearly visible in the curves and they are localized at about 14 ms and 27 ms. Deformations reach macroscopic levels, confirming for Case Study 57H2 that injurious loads may occur. However, beyond the shape of the graph, the localization of maximum strains must also be considered: while in Cloots' study deformations mainly affect the brain stem and midbrain, in Test $B$ the maximum strains are found to be in the frontal white matter, meaning that accounting for anisotropy for the whole brain is crucial to determining reliable axonal stretching in neural tissue. Strains first increase, subsequently decrease and finally increase again, subjecting axons to higher loads than in the isotropic condition. Interesting is also considering where the highest deformation is located in Kleiven's simulation: key points are situated around the gray matter while from theoretical knowledge it is known that more anisotropic parts are generally subjected to higher deformations.

To highlight deformations of brain tissue, figure 5.14 illustrates a comparison among strain fields for the head model obtained in the three different simulations. Looking at the picture, it is clear that elevated strain levels (up to 0.30) occur in every case, especially around the brainstem. On the top left, a sagittal cross section of the brain is shown for Test $B$ and the brainstem is clearly presented as a vulnerable part for injuries. This is in agreement with the loading conditions applied to the head model: as a matter of fact, NFL Case Study 57H2 involves loss of consciousness which is often related to brainstem injury. On the bottom left, a sagittal cross section of the brain is depicted for Cloots's simulation: highest deformations are still shown to be around the brainstem but they involve smaller area. This means that the insertion of anisotropy degree and axonal directions into all brain material affect strains in the
tissues. On the top right, Kleiven’s results are illustrated: a sagittal cross section of the brain is reported and smaller deformations can be noticed for the isotropic case. Accounting for anisotropy, a general more extended deformation can be found with white matter particularly involved into the process.

Figure 5.13 – Maximum principal strain for brain tissue in Test B, Kleiven et al. and Cloots et al. (blue, red and green lines); curves are plotted against time while strain is adimesional.

Figure 5.14 - Maximum principal strain of a sagittal cross section of the head model at 14 ms. On the top left (A), Test B results are presented; on the top right (B) Kleiven's results are shown; on the bottom left (C) Cloots' results are illustrated. Higher deformation (up to 0.3) occurs around the brain stem.
Finally, maximum strain rate of brain tissue is as well investigated because in previous studies [41][78] it is demonstrated that it can be used as an injury predictor. A comparison among rates for Test B, Kleiven et al. and Cloots et al. studies can be seen in Figure 5.15. Looking at the graph, maximum absolute values of strain rate are similar in all cases (up to 60 s⁻¹) but the shape of the curves and their time history vary when anisotropic features are accounted for brain tissue. In case of isotropic features maximum strain velocity is reached earlier in time and with a lower magnitude. Considering anisotropic features for the brain, instead, the results obtained in Test B are really close to what calculated by Cloots: a peak is clearly visible in the graphs at about 18 ms when the strain velocity reaches 70 s⁻¹. Time history of the curve shows that, at the beginning, deformation rate rapidly increases until a value of 30 s⁻¹ is obtained; then, after a period settled around that value, the curve presents a peak meaning that the strain rate rapidly increases again (70 s⁻¹). In the end, an almost constant strain rate of 30 s⁻¹ can be found. Beyond the shape of the graph, the localization of maximum strains must also be considered: in both Cloots’ study and Test B maximum principal strain is found to be in the gray matter. This is theoretically in agreement with Kleiven’s finding [41] that, when using the strain rate as a predictor for traumatic brain injuries, the area with the best correlation is the gray matter. Considering maximum principal strains, viscoelastic properties mainly affect the shape of the curves. Accounting for anisotropy of all brain is thus not crucial to reliable determining velocities of deformation.

In previous studies [78], anyway, strain rate has been hypothesized to be a key biomechanical parameter to explain the cause of brain injury and concussion. Focusing on brain reaction to complex inputs of translational and rotational acceleration, tolerance levels are estimated to be 46 s⁻¹ for a 25% probability of MTBI, 60 s⁻¹ for a 50% probability of MTBI and 80 s⁻¹ for a 75% probability of MTBI. Considering maximum strain rate in all the cases, a probability of concussion higher than 50% can thus be found. This is in agreement with the loading conditions applied to the head model: as a matter of fact, NFL Case Study 57H2 involves loss of consciousness which is often related to traumatic brain injuries.
5.3.3 Anisotropic Equivalent Strain Measure

All the criteria for injury that have been proposed in previous paragraphs are isotropic and therefore they do not consider brain tissue orientation dependence, probably inhibiting a reliable assessment of injury. To this effect, an anisotropic brain injury criterion which is able to describe the contribution of oriented microstructure is investigated in this paragraph. Anisotropic equivalent strain measure (AESM) has been firstly proposed in Cloots’ research [69] where it is demonstrated that it is capable to account for both the effects of the main axonal direction and of local deviations from this direction. AESM is based on the Liu-Huang-Stout yield criterion and it is modified in terms of strains; its formulation is the following:

\[
\varepsilon_{eq} = \left[ F(\varepsilon_{yy} - \varepsilon_{zz})^2 + G(\varepsilon_{zz} - \varepsilon_{xx})^2 + H(\varepsilon_{xx} - \varepsilon_{yy})^2 \right] + 2L\varepsilon_{yz}^2 + 2L\varepsilon_{zx}^2 + 2L\varepsilon_{xy}^2 \right]^{1/2} + I\varepsilon_{xx}^d + J\varepsilon_{yy}^d + K\varepsilon_{zz}^d
\] (5.3)

in which \(\varepsilon_{ij}\) are the tissue strain component in a Cartesian vector basis and the superscript \(d\) denotes the deviatoric part of the tensor, defined as \(\varepsilon^d = \varepsilon - (1/3)\text{trace}(\varepsilon)I\). The coefficients \(I, J\) and \(K\) refer to the linear terms and are used to describe the difference in the yield strain between uniaxial tension and compression. The parameters of the equivalent strain are determined experimentally [69] from tests in which isochoric uniaxial and biaxial deformations in all loading directions are applied; their values can be found in Table 5.2.

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(F)</td>
<td>0.163</td>
</tr>
<tr>
<td>(G)</td>
<td>-0.056</td>
</tr>
<tr>
<td>(H)</td>
<td>0.163</td>
</tr>
<tr>
<td>(L)</td>
<td>0.119</td>
</tr>
<tr>
<td>(M)</td>
<td>0.051</td>
</tr>
<tr>
<td>(N)</td>
<td>0.119</td>
</tr>
<tr>
<td>(I)</td>
<td>0.000</td>
</tr>
<tr>
<td>(J)</td>
<td>0.707</td>
</tr>
<tr>
<td>(K)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Table 5.2 – Values of the AESM coefficients in equation 5.3. They are obtained from calculations performed in Cloots’ studies where isochoric uniaxial and biaxial deformations in all directions are applied.*

Anisotropic equivalent strain measure represents therefore the maximum axonal strain as a result of the tissue strain components governing the contribution of tissue deformations to
axonal stretching. It is worth to analyze the values assumed in the three previously investigated cases.

To this effect, calculations are performed for brain tissue and specifically for the most anisotropic regions of the brain, according to equation 5.3. Figure 5.16 depicts maximum $AESM$ obtained in the whole brain for Test $B$ (blue line), Cloots’ studies (green line) and Kleiven’s researches (red line). As it can be seen from the graph, maximum absolute values of equivalent strains are lower than maximum values reached by principal strains. This reduction is, on the average, around the 20% and it confirms Cloots’ findings that the maximum principal strain is an over-prediction for the maximum axonal strain in brain tissue. Interestingly, the shape of the curves shows that the highest deformation still occurs at about 14 ms where a peak can be detected (around 0.26) for all the three cases. Time history, instead, varies when anisotropic features are accounted for in brain tissue. As for maximum principal strain, in case of isotropic features maximum deformation is reached earlier in time and smaller values of deformation are detected. On the other hand, considering anisotropic features for the brain, the results obtained in Test $B$ are really close to what calculated by Cloots: a peak is clearly visible in the curves confirming that deformations reach macroscopic levels. Anisotropic equivalent strains firstly increase, subsequently decrease and finally settle around a small constant value. The second peak of the maximum principal strain (27 ms) completely disappears, meaning that, even if principal deformations are high, no significant axonal strains are detected at the brain level.

![Figure 5.16 - Maximum anisotropic equivalent strain measure for brain tissue in Test B, Kleiven et al. and Cloots et al. (blue, red and green lines); curves are plotted against time while AESM is dimensionless.](image-url)
It is also interesting considering which values of deformation are reached in the most anisotropic parts of the brain. The brainstem and corpus callosum are investigated for Cloots and Kleiven’s studies while brain elements with a value of fractional anisotropy higher than 0.6 are considered for Test B. Large strain areas are anyway mainly situated in the white matter, corpus callosum and brainstem.

Figure 5.17 depicts anisotropic equivalent strain results for Test B, Cloots’ studies (green line for brainstem and blue line for corpus callosum) and Kleiven’s researches (green line for brainstem and blue line for corpus callosum). As it can be seen from the graphs, differences between tissue-level strains and axonal strains are evident. Firstly, it is confirmed once again that tissue strain interprets maximum axonal deformation as an over-prediction. In the most anisotropic part of the brain, maximum AESM does not exceed 0.17 while maximum principal strain is higher than 0.25; secondly, different material properties for brain tissue leads to different response of the same in terms of strain and stretching of the axons. Test B shows that, considering elements with fractional anisotropy over 0.6, the maximum axonal strain is obtained at 27 ms when a value of 0.162 is reached. This is in line with Cloots’ results for the brainstem: in this case the graph shows a maximum stretching for axons of 0.11 at about 27 ms. However, reached absolute values and curves shape are different meaning that the incorporation of local axonal directions into the material model affects strains at micro-level. Results of AESM with
Kleiven’s formulation, instead, illustrate a completely different mechanical behavior: deformation for brainstem are depicted to be really smaller if compared to the previous ones; moreover the highest strain (0.08) is reached at about 10 ms which is in agreement with what detected from the analysis of maximum principal strain. This diversification can be explained by the isotropic character of the material utilized in this particular simulation.

Considering anisotropic equivalent strain for the corpus callosum, instead, curves are curiously found to be similar in shape independently whether anisotropy of brain tissue is taken into account or not. In Cloots’s studies, a maximum AESM of 0.11 is obtained for the corpus callosum (10 ms) while in Kleiven’s work a maximum of 0.16 is found for AESM (14 ms). In the isotropic case, however, strains are higher in magnitude and later in time which in general is sign of less stiff properties. This is easily explained when considering Cloots’ usage of fiber-reinforced material for corpus callosum.

For concluding, when the anisotropy of the brain is taken into account, maximum strains are found to be into the brainstem, accordingly to loading conditions of Case Study 57H2. Axonal strains deviate from the maximum principal tissue strains that are predicted into the FE model and, observing the curves, no consistently scaling of tissue strains with maximum axonal deformations can be detected. As a matter of fact, the amount of over-prediction seems to depend on the loading direction with respect to the principal orientation and a dependency on the local heterogeneities at the cellular level can as well be assumed. In the latter case, the introduction of local axonal orientations and fiber distribution into the material model can help to better assess reliable strain levels consequently leading to a better prediction of traumatic brain injury.
Chapter 6

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

6.1 Discussion

This study aims to test the mechanical behavior of a new hyper-viscoelastic fiber-reinforced material for brain tissue which accounts for anisotropic features of the brain thereby exploiting $DT$ imaging. The degree of anisotropy of axonal fibers and their orientation are integrated into an existing finite element head model; subsequently, calculations of tissue loads and deformation patterns are performed in order to identify possible relationships between a particular deformation in a tissue and an injury in the same. Through the use of $LS - DYNA$, a concussive impact between two football players is simulated (NFL Case Study 57H2) and the biomechanics of the struck player’s head is analyzed. Mechanical measures such as principal strain, strain rate and anisotropic equivalent strain are computed and a correlation between internal microscopic structure and macroscopic mechanical properties is investigated.

The results obtained from simulations interestingly show that the incorporation of axonal orientation and the inclusion of fibers dispersion into brain tissue constitutive model affect the degree of injury that is predicted into a computational model of TBI. This can be expected since the reliability of such models depends on an appropriate level of structural detail and the accurate representation of the material behavior.

In particular, Test $A$ demonstrates that the degree of anisotropy of axonal fibers plays a role in the mechanical response of brain material: when the internal energy is considered (Figure 5.4), a higher transversely anisotropy is shown to lead to smaller incremental strains in the fiber direction. This phenomenon can be easily explained taking into account fiber-reinforced contribution to the stiffness of the structure: basically, the more fibers are aligned, the more they will resist to deformation in their orientation and, in the meanwhile, the deformation will be slower. Moreover, to confirm fiber dispersion contribution to mechanical response of brain material, different behavior of GOH components maximum principal strain are detected when varying $k$ (Figure 5.7): as it can be seen from graphs, there is a reduction in magnitude of deformations with the increasing of fiber stiffness contribution ($k \to 0$). Once again, this can be explained considering the alignment of axons: the more they are aligned, the more a stiff mechanical behavior is detectable.

To this effect, the incorporation of axonal fiber dispersion into a constitutive model for brain tissue is crucial to better address reliable strains occurring during an impact and the introduction of fractional anisotropy information into the head model offers a novel approach for assessing it.
Beyond the analysis of fiber stiffness contribution, Test B is in addition performed to study the effects of the incorporation of local axonal orientation into the material constitutive law. Comparing Figure 5.10 and 5.7, it can be claimed that a reliable incorporation of axonal orientation into the model is essential to better understand traumatic injury mechanisms. As a matter of fact, stiffness properties for the brain especially affect the strains in the tissue, which are usually utilized as *TBI* metrics. Mechanical stiffer properties (Test A) are shown to produce lower peak values of maximal principal strain that also occur earlier in time. The local orientation of axonal fibers therefore affects the response of the tissue and, in particular, makes the strains more randomly distributed along all the local directions, leading into an increment of maximum principal strain. This is also confirmed when Figure 5.11 and Figure 5.8 are compared: looking at the cross-sagittal planes of the head in the two cases, a generally more extended deformation can be noticed if the local axonal orientation is taken into account and white matter is shown to be particularly involved in the process.

Since the current work is an extension of previous studies performed by Kleiven and Cloots, results obtained utilizing the same head model and imposing the same loading condition to the problem (Case Study 57) but assigning different properties to brain tissue are compared. Maximum principal strain, deformation field and anisotropic equivalent strain are therefore analyzed for the three cases and, again, the importance of considering the anisotropic features of brain tissue is underlined. Figure 5.13 shows that the shape of the maximum principal strain curves and their time history vary when anisotropic features are accounted for. In case of isotropic features, maximum deformation is reached earlier in time and with low magnitude. Considering anisotropic features for the brain, instead, strains first increase, subsequently decrease and finally increase again, subjecting axons to higher loads than in the isotropic condition. Moreover, in Test B, deformations reach macroscopic levels into the white matter while in Cloots’ study only the brainstem is subjected to high deformational loads. This means that accounting for anisotropy for the whole brain is crucial to reliably determine axonal stretching in neural tissue. Figure 5.14 confirms this finding: it is clear that elevated strain levels occur in every case, especially around the brainstem, but accounting for anisotropy, a more extended deformation can be found with the white matter particularly affected.

Finally, anisotropic equivalent strain measure is investigated. In a previous study, Cloots demonstrates that this measure represents the maximum axonal strain as a result of the tissue strain components. It therefore governs the contribution of tissue deformations to axonal stretching. Calculations of *AESM* are performed for the whole brain first and then specifically for the most anisotropic regions. As it can be seen from Figure 5.16, *AESM* maximum absolute values are lower than the maximum values reached by the principal strains. This reduction is, on average, around 20% and it confirms Cloots’ findings that the maximum principal strain is an over-prediction of the maximum axonal strain in brain tissue. In a study using the same FE head model, but with isotropic viscoelastic material behavior, performed by Kleiven [41], it was shown that loading conditions associated with concussion result in predictions of relatively high strain levels that are on the same level as suggested for DAI [79], even though the mechanical behavior for brain tissue in the model corresponds with the effective shear modulus of approximately 10 kPa at 80 Hz found for brain tissue in vivo by McCracken et al. [80] using magnetic resonance elastography. The lack of correlation between the tissue strain and the diagnosis of concussion in the study by Kleiven might be explained by the overprediction of tissue strains for the interpretation of the maximum axonal strain, which is shown in the current study.
Moreover, a different behavior is detected by varying the brain tissue properties: in case of isotropic features maximum deformation is reached earlier in time and smaller values of deformation are detected. On the other hand, considering anisotropic features for the brain, deformations reach macroscopic levels and anisotropic equivalent strains firstly increase, subsequently decrease and finally settle around a small constant value. In Test B, highest strains are reached into the white matter while in Cloots’ study only the brainstem is subjected to high deformational loads. This finding underlines, once more, that accounting for anisotropy of the whole brain is crucial to reliably determining axonal stretching in neural tissue. To support this, values of AESM reached in the most anisotropic parts of the brain are analyzed. In particular, the brainstem and corpus callosum were investigated by Cloots and Kleiven’s works while brain elements with a value of fractional anisotropy higher than 0.6 are considered for Test B. Figure 5.17 depicts evident differences between tissue-level strains and axonal strains. As it can be seen from the graphs, including diffusion information into the constitutive law of brain tissue leads to higher anisotropic equivalent strain measures; specifically, the highest deformations are localized into the brainstem where a value of 0.162 is reached. Cloots’ results, instead, shows a maximum stretching of the axons of 0.11, which is a considerable reduction in magnitude. Consequently, it can be concluded that the incorporation of local axonal directions and their degree of dispersion into the material model affects the strains at a micro-level.

In an isotropic formulation, results illustrate even a completely different mechanical behavior. Deformation for the brainstem are found to be smaller compared to the previously found while, considering the corpus callosum, anisotropic equivalent strain is instead high. For the corpus callosum, this increase is considered to be due to less stiff material properties. As a matter of fact, in the isotropic case, the strains are higher in magnitude and later in time which in general is sign of more compliant properties. This is easily explained when considering Cloots’ usage of the fiber-reinforced material for the corpus callosum.

When the anisotropy of the brain is taken into account, maximum strains are found to be in the brainstem, according to the loading conditions of Case Study 57H2. Axonal strains deviate from the maximum principal tissue strains that are predicted into the FE model and, observing the curves, no consistent scaling of tissue strains with maximum axonal deformations can be detected. As a matter of fact, the amount of over-prediction seems to depend on the loading direction with respect to the principal orientation and a dependency on the local heterogeneities at the cellular level can be assumed as well. In the latter case, the introduction of local axonal orientations and fiber distribution into the material model can help to better assess reliable strain levels consequently leading to a better prediction of traumatic brain injury. However, even if the results are promising, no AESM tolerance threshold for TBI have been experimentally determined in previous studies; therefore, utilizing anisotropic equivalent strain as a criterion to assess injuries localization into the brain is not possible at the moment. To evaluate the capability of AESM to become a DAI predictor criterion and to determine tolerance threshold for the head, a statistical study should be conducted on a significant number of real word head trauma simulations including a detailed description of DAI location. For the time being, an idea could be utilizing the axonal strain tolerance proposed by Bain and Meaney (2000) [79]. As a matter of fact, according to their analysis, an optimal strain-based threshold for morphological damage to white matter can be considered: it balances the specificity and sensitivity measures, giving a limit strain value of 0.21. Considering the current study, where a strain value of 0.162 is reached for the brainstem, the previous finding of lack of correlation between the tissue strain and the diagnosis of concussion in the study is thus confirmed.
6.2 Conclusion

This research proposes an interesting tool to couple the micro-scale mechanism of damage with the mechanical loading at the macro-scale. Diffusion information, including axonal orientations and the degree of fiber anisotropy, is implemented into a finite element model through the use of diffusion tensor imaging, showing that especially white matter mechanical behavior is dependent on the primary orientation and the angular distribution of axonal fibers. The inclusion of anisotropy into a constitutive model for brain tissue has a significant effect on the predicted injury locations when tissue-level measures such as maximum principal strain or anisotropic equivalent strain are used as injury criteria. In conclusion, this work offers a novel approach for including the anatomical structure of brain tissue into a computational model so that physiologically relevant response can be computed into finite element simulations. The feasibility of implementing anisotropic brain structure information into a brain finite element model is here demonstrated. Indeed this study confirms that the coupling method DT imaging – FE model is an innovative and promising possibility to improve bio-fidelity of head finite element simulations consequently leading to more realistic criteria for TBI.

6.3 Recommendations

The purpose of this work is to test the mechanical behavior of a new hyper-viscoelastic fiber-reinforced material for brain tissue which accounts for anisotropic features of the brain thereby exploiting DT imaging. For using or improving the findings of this research some recommendations are given.

- For mapping diffusion information at FE model resolution, fast affine registration and voxel selection procedure are applied. The main problem of this protocol appears with registration error, meaning that, at the end of the morphing, the DTI and the FE representation of the brain are not perfectly aligned. This misregistration can lead to finite elements selecting no or too few DTI voxels of the brain to be considered as significant. If the affine transformation is not precisely determined, errors in scaling the FEM to the DTI brain shape data can be involved. In this work registration errors is computed to be equal to 6.68% which is considered a reasonable value for errors. However, to improve the registration precision, deformable transformations can be taken into account in future works.

- For mapping the diffusion information at the FE model resolution an averaging procedure is applied. A consequence of applying such a voxel mean calculation is a smoothing of diffusion parameters between elements which can affect the reliability of the FA and principal direction. The main limitation consists in the scaling from DTI voxels to the finite element brain model, which systematically lead to a loss of information. To improve this calculation, locally more refined meshing of the FEM geometry could be used in future studies. Further developments could also consist in investigating mesh resolution influence on diffusion parameters calculation.
In the current study, anisotropic features are implemented into a constitutive model for brain tissue. A new correlation between the GOH $k$ parameter and FA is proposed and theoretically justified; however, there is a lack of experimental data to assure that this correlation really exists. There is a lack of accurate mechanical parameters for brain material, both in terms of heterogeneity and anisotropy. Finding new experimental proof could thus constitute a further development of the proposed method.

The anisotropic equivalent strain measure, proposed by Cloots in previous studies, is here utilized to assess axonal deformations. His parameters $F, G, H, L, M, N, I, J$ and $K$ are used since they are experimentally validated for the brainstem and corpus callosum. However, since in other parts of the brain axons are less aligned, a different relation between the axonal strains and the tissue strains could exist. In this work it is assumed that they can be used for the whole brain tissue.
Bibliography


