MECHANICAL PROPERTIES OF THE BRAIN-SKULL INTERFACE

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ABSTRACT

Knowledge of the mechanical properties of the brain-skull interface is important for surgery simulation and injury biomechanics. However, these properties are known only to a limited extent. The goal of this study is to determine the mechanical properties of the brain-skull interface which will lead to the provision of boundary conditions for modelling the brain to predict brain shift during surgery. The most straightforward way to determine the mechanical properties of the brain-skull interface would be to conduct experiments on interface samples. However, the complex anatomical structure of this interface poses difficulties in extracting the interface samples without damaging tissues that form the interface. To overcome this problem, in-situ indentation experiments of the brain were conducted to determine the mechanical properties of the brain-skull interface, and the macroscopic mechanical properties of the brain-skull interface were obtained from the results of these experiments. To the best of my knowledge, this is the first ever analysis of this kind. In this study, the results of in-situ brain indentation experiments are presented and the interface’s mechanical properties were derived by complementing analysis of the results of these experiments with brain modelling using non-linear Finite Element (FE) procedures.

Firstly, in-situ brain indentation experiment was conducted and the reaction forces on the indentor were measured. To determine the deformation field within the brain, X-ray opaque markers were implanted inside the brain and two mobile C-arms were used to capture their displacements during in-situ indentation experiments. Subsequently, a cylindrical sample of brain tissue was extracted and uniaxial compression test was conducted to determine the subject specific mechanical properties of the cylindrical tissue sample. The calibration of the X-ray image intensifiers was
done to correct any distortion present in the images and the displacement of the markers were obtained from the X-ray images. Finally, a nonlinear model of the *in-situ* indentation experiment was created in the FE solver ABAQUS™ and the properties of the brain-skull interface models were derived so that the calculated indentor reaction forces matched those measured experimentally. To verify the brain deformation, the 3D displacements of those X-ray opaque markers were also obtained from the nodal displacements predicted by the FE model of *in-situ* indentation experiment. By representing the brain-skull interface as linear springs having stiffness 11.45 \( \frac{\text{Nm}}{\text{mm}^2} \), the developed FE Model of *in-situ* indentation experiment accurately predicted the force-displacement relationship of the indentor and 3D displacements of the implanted X-ray opaque markers that represent the local deformation of the brain during the experiment.
He grants wisdom to whom He pleases; and he to whom wisdom is granted receives indeed a benefit overflowing; but none will grasp the Message but men of understanding

- The Holy Quran: Chapter 2, Verse: 269
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1.1 Motivation

Recent developments in robotics technology, especially the emergence of automatic surgical tools and robots have motivated the latest interest in brain tissue biomechanics for surgical simulation, computer-integrated surgery and image-guided therapy, and as a supporting tool for diagnosis and prognosis of brain disease (Miller & Chinzei, 1997, Miller & Chinzei, 2002, Miller, 2002, Miller, 2011). Biomechanical models have been applied to predict craniotomy (surgical removal of part of the skull to expose the brain) induced brain shift (Miller et al., 2000, Miller et al., 2010). A number of studies reported the brain shift to be on the order of 20 mm or more (Dorward et al., 1998, Hartkens et al., 2003, Miga et al., 2003, Maurer et al., 1998, Nabavi et al., 2001, Sun et al., 2005b). To predict the brain shift a biomechanical model must take into account factors such as the mechanical properties of the brain tissue, intraoperative conditions and external loads such as the presence of surgical instruments and appropriate boundary conditions. For many decades the mechanical properties of the brain tissue have been investigated. A substantial amount of important data has been reported for different types of species (for instance, primate: Metz et al., 1970, porcine:
Brands et al., 2000, Miller & Chinzei, 1997, Miller & Chinzei, 2002, Prange & Margulies, 2002, Hrapko et al., 2006, human: Estes & McElhaney, 1970, Donnelly & Medige, 1997, Prange et al., 2000, bovine: Bilston et al., 1997, Bilston et al., 2001) and under different type of loading scenarios. For instance, stress relaxation: Galford & McElhaney, 1970, Arbogast et al., 1997; constant strain rate test: Miller & Chinzei, 1997, Velardi et al., 2006; dynamic frequency sweep experiment: Fallenstein et al., 1969, Arbogast & Margulies, 1998. However, testing isolated brain tissues alone is not sufficient for the development of a biomechanical model of human brain. The model should also define boundary conditions for modelling the brain. Despite the research progress in the area of brain tissue biomechanics, knowledge of the mechanical properties of the brain-skull interface that determines the boundary conditions for the modelling of the brain is very limited due to the complexity of the brain-skull interface (Jin, 2009, Jin et al., 2011). Consequently, the brain-skull interface models used in the literature are “best guesses” and their relation to reality is unclear (Miller, 2011). Previously, the brain-skull interface has been modelled as either a tied, frictionless or frictional sliding contact, with or without brain-skull separation (Hu et al., 2007, Ji et al., 2004, Ji & Margulies, 2007, Miga et al., 2000, Wittek & Omori, 2003, Wittek et al., 2005, Wittek et al., 2007). Hence, there is no consensus about the model of the brain-skull interface. Although investigations to determine the mechanical properties of pia-arachnoid complex (PAC) or pia alone have been conducted previously (Jin et al., 2006, Jin et al., 2007, Jin, 2009), the overall mechanical properties of the brain-skull interface are still unknown. An experimental investigation to determine the overall mechanical characteristics of the brain-skull interface has not been achieved thus far. The objectives of this study were to experimentally determine the material properties of the brain-skull interface and model the brain-skull interface using the experimental and modelling data.
1.2 Anatomy of the Brain-Skull Interface

The human brain is one of the most important organs of the human body and it is well protected by a thick skull and surrounded by three concentric, membranous layers known as the meninges:

- Dura Mater
- Pia Mater
- Arachnoid mater

The brain-skull interface containing these meninges separates the brain from the skull. Their function is to provide a protective coating to the brain and also contributes towards the formation of blood-brain barrier. Knowledge of the anatomy of these meninges has evolved over time and its understanding is fundamental for investigating their mechanical properties.

1.2.1 Dura Mater

The dura mater is the outermost layer of the brain-skull interface (see Figure 1.1). Continuous with the dura of the spinal cord, it becomes continuous with the periosteum on the inner surface of the skull bone and with the sutural ligaments at the cranial sutures (Patel et al., 2009, Snell, 2010). It is hard to separate the dura from the suture lining with the increment of age. The dura becomes separable from the sutures as they start fusing. The dura also becomes thicker, tougher, and more adherent to the inner surface of the skull with the increment of age (Standring, 2008).
The Dura mater consists of three layers which are skull’s periosteum and meningeal layer and the border (limiting) cells layer. The skull’s periosteum sticks to the inner surface of the skull, with especially strong attachments to the sutures and skull base and contains blood vessels and nerves. On the other hand, the meningeal layer sticks to the endosteal layer (see Figure 1.2) and forms reflections that divide the brain into different freely communicable subdivisions (Greenberg et al., 1994, Snell, 2010).

The most noticeable of these sections are the falx cerebri and the tentorium cerebelli. The falx cerebri is a sickle-shaped, midline reflection that elongates vertically between the two cerebral hemispheres (see Figures 1.3 and 1.4).
Figure 1.2 Lateral view of brain with falx in the middle after removal of endosteal dura mater (Adeeb et al., 2012)

Figure 1.3 Removal of Falx cerebri (Adeeb et al., 2012)
The meningeal layer internally includes a unique layer of fibroblasts that has been named as the dural border cell layer (Nabeshima et al., 1975). In the literature this layer is also referred as the subdural mesothelium, subdural cells, inner dural cell layer, part of the arachnoid, and subdural compartment (Haines et al., 1993). It forms the interface layer between the dura and the arachnoid (Haines et al., 1993, Mack et al., 2009, Nabeshima et al., 1975). It continues internally with the arachnoid and externally with the meningeal dura mater, without causing intervention of the Subdural Space (SS) (Haines, 1991). The SS is a potential place when it pathologically accumulates fluid or blood. It actually refers to a pathologic space created by disruption of the dural border cell layer.

Apart from their separation for forming the dural venous sinuses, there is no distinctive borderline between the meningeal layer and periosteal layer (see Figure 1.5). They can be differentiated through histological analysis by the fact that the meningeal...
layer has fewer fibroblasts and proportionately fewer collagen compared to periosteal layer (Haines et al., 1993).

Figure 1.5 Diagram of meningeal layer (Patel et al., 2009)

### 1.2.2 Pia Mater

The pia mater has not received much attention in the literature when compared to the dura and arachnoid mater. However, its presence as an envelope of the nervous system and direct involvement with the blood vessels gives it a great importance during neurosurgery. The pia mater holds an important anatomic position and significantly contributes towards stabilizing and protects the nervous system (Adeeb et al., 2013a).

The pia is the innermost delicate, highly vascular meningeal layer that envelops surrounding the brain and spinal cord. It consists of a continuous layer of cells that
adheres to the surface of the brain. It covers the gyri, and goes deep into the brain including the fissures and sulci (Adeeb et al., 2013a) (see Figures 1.6, 1.7 and 1.8).

Figure 1.6 View of the base of the brain following removal of arachnoid mater (Adeeb et al., 2013a)

Figure 1.7 Later view of the brain following removal of arachnoid mater (Adeeb et al., 2013a)
Figure 1.8 Sagittal view of medial surface of the brain showing interface between arachnoid and pia mater (arrows) (Adeeb et al., 2013a)

The pia mater stretches from the brain surface into blood vessels in the sub-arachnoid space (SAS) for forming the outer coating (see Figure 1.9).

Figure 1.9 View of the entry of an artery into cortex through pia mater (Patel et al., 2009)
The pia mater is separated from the overlying arachnoid by the SAS and cisterns. The SAS is divided into subdivisions by networks of fine, continuous, sheet-like trabeculae. This network of trabeculae also connects the arachnoid and pia mater.

### 1.2.3 Arachnoid Mater

The arachnoid mater is a delicate and avascular layer that lies in middle of layer of the meninges. It is directly connected with the dura mater from which it can be easily separated along a potential space forming the “SS”. It invests the entire brain (see Figure 1.10).

![Figure 1.10 Later view of the cerebral hemisphere with overlaying arachnoid mater following removal of dura mater (Adeeb et al., 2013b)](image)

It also covers the blood vessels and nerves, which passes through the SAS (Snell, 2010, Standring, 2008). In contrast to the pia, it bridges over the sulci and fissures, except the great longitudinal fissure separating both cranial hemispheres. It is
connected to the pia mater through the CSF filled SAS which is cut across by fine filaments that connect both layers, named arachnoid trabeculae (Greenburg et al., 1994, Patestas et al., 2006, Snell, 2010, Standring, 2008). The SAS varies in thickness and is absent in certain places were the brain and pia are in direct contact with the arachnoid, and where nerves and blood vessels exit the brain. Otherwise, this space is continuous around the brain and with the SAS surrounding the spinal cord.

The arachnoid mater is formed from two different cell layers which are: the arachnoid barrier cells and the arachnoid trabeculae. The arachnoid barrier cell layer is adjacent to the dural border cells of the dura (Alcolado et al., 1988). It consists of densely packed cells that provide the layer with a barrier function to prevent the movement of fluid across it. The arachnoid trabeculae consists a more loosely packed layer of cells that lies deep into the arachnoid barrier cell layer. The cells bridge the SAS and attach to the pia as well as each other and also enclose vessels that traverse the layer.
1.3 Knowledge of the Mechanical Properties of the Brain-Skull Interface and Brain-Skull Interface Modelling: State-of-the-Art

1.3.1 Knowledge of the Mechanical Properties of the Brain-Skull Interface

Modelling of interactions between continua (e.g. soft organs) undergoing deformations is a challenging task. Representing the brain-skull interface remains an unresolved issue in brain modelling.

Several studies have been conducted to investigate the material properties of the meninges for different species. In one study Tunturi (1978) conducted uniaxial stretch experiment to study the mechanical behaviour of the canine spinal pia mater. In that study, the pia mater was dissected from the spinal cord along the longitudinal direction. The increased length was measured after applying an initial load of 1 gram and then at an increment of 5 grams until rupture. The pia mater exhibited a moderately linear elastic response and the maximum load and stretch ratio at rupture were found 41 grams and 1.03, respectively. No detailed information regarding the dimension of the pia specimen was available and the reported results were qualitative.

Ozawa et al. (2004) studied the elastic modulus of the rabbit spinal pia mater. The spinal cord was subjected to loading in the transverse direction and the difference in length along the stretch direction, with and without pia mater, was measured. A Maxwell material model was built to simulate the pia and parenchyma of the spinal cord.
and the authors concluded that the pia mater and spinal parenchyma make a significant contribution towards the load bearing capacity of the spinal cord. Aimedieu and Grebe (2004) conducted quasi-static uniaxial tensile experiments to in study the tensile stiffness of the bovine PAC. Based on the force-displacement relationship, they found a stiffness value of 0.024 and 0.19 N/mm for the toe region and the subsequent linear region, respectively. However, the elastic modulus of PAC was not investigated.

Reina et al. (Reina et al., 2004) used scanning electron microscopy to investigate the material properties of human spinal pia mater and reported the isotropic mechanical behaviour of the pia mater. Runza et al. (1999) studied the fibers of the human spinal arachnoid mater and reported that no directional preferences were found to support either the isotropy or anisotropy of the PAC in the intracranial region. In another study Mao et al. (2006) reported that PAC plays a very important role under dynamic cortical deformation (DCD) test. Kimpara et al. (2006) conducted uniaxial tension experiment to investigate the mechanical properties of porcine spinal pia at varying strain rates. In his experiment samples of spinal pia mater were dissected from pig and their thickness were ranged from 0.13 mm to 0.27 mm. After conducting experiment the elastic modulus, ultimate stress, and ultimate strain at three regions were determined measured at varying strain rates (see Tables 1.1, 1.2 and 1.3). Furthermore, the regional and strain rate dependency was reported.

Table 1.1 Experimental results for denticulate ligament from Kimpara et al. (Kimpara et al., 2006)

<table>
<thead>
<tr>
<th>Strain Rate (s⁻¹)</th>
<th>Young’s Modulus (MPa)</th>
<th>Ultimate Strain (%)</th>
<th>Ultimate Stress (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>26.5</td>
<td>46.6</td>
<td>8.1</td>
</tr>
<tr>
<td>0.05</td>
<td>30.6</td>
<td>48.9</td>
<td>8.9</td>
</tr>
<tr>
<td>0.5</td>
<td>63.9</td>
<td>40.5</td>
<td>18.7</td>
</tr>
</tbody>
</table>
Table 1.2 Experimental results for posterior median septum from Kimpara et al. (Kimpara et al., 2006)

<table>
<thead>
<tr>
<th>Strain Rate (s^{-1})</th>
<th>Young's Modulus (MPa)</th>
<th>Ultimate Strain (%)</th>
<th>Ultimate Stress (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>21.7</td>
<td>33.0</td>
<td>4.8</td>
</tr>
<tr>
<td>0.05</td>
<td>25.4</td>
<td>37.6</td>
<td>6.6</td>
</tr>
<tr>
<td>0.5</td>
<td>39.3</td>
<td>34.4</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Table 1.3 Experimental results for posterolateral sulcus from Kimpara et al. (Kimpara et al., 2006)

<table>
<thead>
<tr>
<th>Strain Rate (s^{-1})</th>
<th>Young's Modulus (MPa)</th>
<th>Ultimate Strain (%)</th>
<th>Ultimate Stress (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>10.8</td>
<td>30.4</td>
<td>1.3</td>
</tr>
<tr>
<td>0.05</td>
<td>12.4</td>
<td>31.4</td>
<td>1.4</td>
</tr>
<tr>
<td>0.5</td>
<td>13.2</td>
<td>28.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Jin et al. (2006, 2007, 2009) investigated the mechanical behaviour of bovine PAC at varying strain rates under normal traction, tensile loading and shear loading. They reported the Young’s modulus of PAC under normal traction and tangent tension at various strain-rates. The results from his study are shown in Table 1.4.

Table 1.4 Young’s moduli of PAC from Jin’s study (Jin et al., 2006, Jin et al., 2007, Jin, 2009)

<table>
<thead>
<tr>
<th>Strain Rate (s^{-1})</th>
<th>Under Tangent Tension</th>
<th>Young’s Modulus (MPa)</th>
<th>Under Normal Traction</th>
<th>Young’s Modulus (MPa)</th>
<th>Strain Rate (s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.056</td>
<td>6.75</td>
<td>0.36</td>
<td>30.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.59</td>
<td>7.52</td>
<td>2</td>
<td>31.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.74</td>
<td>10.78</td>
<td>20.5</td>
<td>35.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95.9</td>
<td>40.19</td>
<td>116.3</td>
<td>59.81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As summarised in this section, only a limited numbers of studies have been carried out to investigate the mechanical properties of the PAC (or pia alone) in different species. All of these studies focused on the mechanical properties of the
meninges individually rather than the entire brain-skull interface. Nevertheless, experimental investigation to determine the overall mechanical properties of the brain-skull interface has not yet achieved. So, there is no clear consensus about the representation of the brain-skull interface (Bandak & Eppinger, 1994, Kleiven & Hardy, 2002, Miller et al., 1998, Ruan et al., 1994, Takhounts et al., 2003, Zhang et al., 2001b). In previous studies the brain-skull interface has been modelled based on simplified assumptions. For instance as either a tied, frictionless or frictional sliding contact, with or without brain-skull separation (Hagemann et al., 1999, Hu et al., 2007, Ji et al., 2004, Ji & Margulies, 2007, Joldes et al., 2009, Miga et al., 2000, Wittek et al., 2003, Wittek et al., 2005, Wittek et al., 2007, Wittek et al., 2009). A brief review of biomechanical models used to represent the brain-skull interface for application brain injury biomechanics and biomechanics for medicine is given in the following section.

1.3.2 Biomechanical Models of the Brain-Skull Interface

Models for Application in Injury Biomechanics

Biomechanical models of human brain have been developed by the researchers over the past four decades to study brain injuries. These models emerged from a simple spherical shell and fluid models with linear elastic material properties to complex, 3D models with detailed anatomical features and viscoelastic, non-linear properties. Apart from the brain and the skull these models also require sufficient information about the mechanical properties of the brain-skull interface. Therefore, investigation of the mechanical properties of the brain-skull interface holds great interest for research in brain injury biomechanics as it plays an important role for determining the boundary conditions for modelling the brain.
Chapter 1: Introduction

The first biomechanical model (Anzelius, 1943) of head was introduced as spherical liquid mass. In that model the pressure was analysed due to impact and the author found that the positive pressure occurred close to the impact whereas the negative pressure occurred at the counter coup location. The model was limited to simple geometry, boundary conditions and homogeneous mechanical properties. Slattenschek and Tauffkirchen (Slattenschek & Tauffkirchen, 1970) developed a translational lumped-parameter model consisting two masses connected by a spring and a damper in parallel. This model was also used by Brinn et al. (see Brinn et al., 1970) and Stalnaker et al. (Stalnaker et al., 1971) to study head injuries. In some other studies (Firoozbakhsh et al., 1975, Bycroft, 1973, Liu et al., 1975, Ljung, 1975) the researchers tried to understand the impact on head or brain under pure rotational loads using simple biomechanical models.

The first 3D biomechanical model of brain to investigate head injury was developed by Ward and Thompson (1975). The model included a 3D overview of the cerebrum, cerebellum, brain stem, ventricles, falx cerebri and tentorium cerebelli and linear elastic material property was assigned to the brain. The authors presented the importance of modelling the tentorium and falx cerebri by comparing cadaver head impact test results with and without the membranes. This model was revised later where a meshed skull and new material properties were introduced (Nahum et al., 1977) and it was validated by comparing the model response with cadaver head impact test data. In that study the measured and computed pressures were compared at five different locations in the brain. Good agreement was observed except opposite the impact site, where computed stress was higher than the measured negative pressure. Ward et al. (Ward et al., 1980) revised the model again to simulate cadaver impact tests and real
aerospace accidents. The authors varied the poisson’s ratio of the brain according to impact duration to simulate the pressure release mechanisms. The results showed that serious injuries occur at pressures more than 34 psi (234 KPa). In another study (1982) the same authors reviewed the applications and limitations of the available biomechanical models of the brain during that period. The authors pointed out the deficiencies in various early models and came to conclusion with three recommendations for the models which are: (i) simulation of the opening in the base of the skull should be conducted and the foramen magnum should be performed as tissue and fluids move through the opening, (ii) The model should include the falx and tentorium to partition the cranial cavity and provide support for the brain, and (iii) finally the brain must not be modelled as incompressible.

Khalil et al. (1982) also presented a critical review of various current biomechanical models of brain to that date and reported several important features that compromised the accuracy of those models. The authors described the following limitations of the models: (i) no relative motion was allowed between the brain and skull, (ii) variation of fluid compressibility do not correspond to the experimental values, (iii) too much lower resonant frequencies in comparison with the experimental values and (iv) the input acceleration is not much similar to that of head impact. In conclusion, they recommended investigating the boundary conditions for the brain modelling depending on the impact. Troseille et al. (1992) developed an experimental protocol for cadaver testing and measurement of the acceleration and intracranial pressure to include them in the biomechanical model of brain. The authors also discussed the influence of the material properties of brain, tentorium and cerebrospinal fluid in biomechanical modelling of the brain.
Chapter 1: Introduction

Ruan et al. (1993) developed a 3D biomechanical model of the brain and it was validated with the comparison of its response using cadaver head impact experimental data. The model included the scalp, a three-layered skull, cerebrospinal fluid, dura mater, falx cerebri, and the brain. Zhou et al. (1995) developed a more detailed 3D human brain model which included the scalp, skull, dura, falx tentorium, pia, cerebrospinal fluid, venous sinuses, ventricles, cerebrum (white and gray matter), cerebellum, brain stem, and parasagittal bridging veins. The authors investigated the importance of inclusion of the white and gray matter, ventricles and bridging veins in the model. Initially the model was validated by comparing with the experimental cadaver impact tests of Nahum et al. (1977) and additionally the author run a sagittal plane rotation simulation using a rotational impulse from an animal test which was conducted by Abel et al. (1978). The results showed the influence of including the ventricles in the model for the prediction of higher shear stresses in the corpus callosum and brain stem. Bandak et al. (1994) conducted a study of strain in brain under impulsive loadings. The authors investigated the reasons behind deformation based brain injury and came out with an idea of a Cumulative Strain Damage Measure (CSDM), based on the partial volume of the brain that has experienced a specific level of stretch. The authors also pointed out that this measure can be a possible predictor for Diffuse Axonal Injury (DAI) that results from head impact.

Turquier et al. (1996) performed a validation study of a 3D biomechanical model of the brain against cadaver impact experiments. In this study they tried to find the basis of assumptions used for modelling of the brain. The model consisted of a rigid, enclosed skull, falx, tentorium, subarachnoid space, cerebrum, cerebellum and brain stem associated with the corpus callosum. Although the model corresponded to the
cadaver impact experimental data but it showed significant oscillations and a symmetrical coup and contrecoup pressure during the simulation. The model was simulated using both linear elastic and viscoelastic material properties for the brain and while using the viscoelastic property it was found that, it reduced the oscillations but the subarachnoid space Young’s modulus effects the vibrations very highly. Furthermore, when the model was simulated using mechanical properties of the brain proposed by Ruan et al. (1993) the better agreement with cadaver impact experimental data was found. Based on the findings of this study Kang et al. (1997) introduced a new 3D model. The new model included the skull, falx, tentorium, subarachnoid space, scalp, cerebrum, cerebellum, and brain stem and has more realistic geometry and refined mesh comparing with the previous model. It was validated against the cadaver impact tests of Nahum et al. (1977).

Claessens et al. (1997) developed two types of a 3D head model. The first model included homogeneous structure of the brain and the brain-skull interface was modelled as being coupled whereas the second model included falx cerebri, tentorium, cerebrum, cerebellum and brainstem and a contact algorithm was introduced to represent the brain-skull interface. Again the models were validated against the cadaver impact tests conducted by Nahum et al. (1977). Better results were obtained using the second model for the impact simulation. The authors reported that the results were influenced by inclusion of the tentorium and falx cerebri in the model. The authors also discussed the importance of allowing relative motion between the skull and brain in the model.

Miller et al. (1998) conducted injury-experiments using miniature pigs and developed two types of a 2D plane strain model which can be used in conjunction with the experimental data for analysis of DAI. The authors proposed two different ways to
model the brain-skull interface. The first model represented the subarachnoid space (CSF) nearly incompressible solid having low shear modulus and the second model introduced a sliding frictional interface between the brain and the skull to allow the relative motion between them. Al-Bsharat et al. (1999) developed one of the most detailed 3D biomechanical models of the brain. It was a modified version of the model developed by Zhou et al. (1995). The improvement in this model was done in terms of the quality of the mesh and additionally the skull was modelled as a three-layered solid. Different linear viscoelastic material properties were assigned to the gray and white matter whereas CSF remained as a low shear modulus solid. And a sliding interface was introduced to simulate the interaction between the CSF and pia mater. Lately, a more realistic 3D head model was developed based on digital CT and MRI data obtained from the Visible Human Project Data set (Krabbel et al., 1996). It included a more detail geometry of the skull and brain.
Figure 1.11 Brain Injury models: (a) Brain Injury model by Classens et al. (Classens et al., 1997) (b) brain model by Willinger et al. (1992) (c) Brain model by Kleiven et al. (2003) (d) Wayne State University brain injury model (Zhang L. et al., 1999)

A summary of the literature review for the brain-skull interface model used in the developed 2D and 3D biomechanical for human and animals brain are given in Tables 1.5 and 1.6 respectively.
Table 1.5 Summary of the brain-skull interface model used in 2D biomechanical models of human and animal brain based on the study by Kleiven (2002)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Brain-Skull Interface</th>
<th>Model of Geometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueno et al., 1989</td>
<td>Tied nodes</td>
<td>Sagittal Human</td>
</tr>
<tr>
<td>Ueno et al., 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng et al., 1990</td>
<td>Both tied and sliding were</td>
<td>Coronal Half Cylindrical</td>
</tr>
<tr>
<td></td>
<td>studied</td>
<td></td>
</tr>
<tr>
<td>Ruan et al., 1991</td>
<td>CSF modelled as a solid</td>
<td>Coronal Human</td>
</tr>
<tr>
<td>Willinger et al., 1992</td>
<td>CSF modelled as a solid</td>
<td>Sagittal Human</td>
</tr>
<tr>
<td>Chu et al., 1994</td>
<td>Tied nodes</td>
<td>Parasagittal Human</td>
</tr>
<tr>
<td>Kuijpers et al., 1995</td>
<td>Both tied and sliding were</td>
<td>Parasagittal Human</td>
</tr>
<tr>
<td></td>
<td>studied</td>
<td></td>
</tr>
<tr>
<td>Zhou et al., 1994</td>
<td>Tied nodes</td>
<td>Coronal Porcine</td>
</tr>
<tr>
<td>Al-Bsharat et al., 1997</td>
<td>Sliding</td>
<td></td>
</tr>
<tr>
<td>Miller et al., 1998</td>
<td>Both CSF modelled as a solid</td>
<td>Axial Mini. Pig</td>
</tr>
<tr>
<td>Miller et al., 1999</td>
<td>and sliding cont. were studied</td>
<td></td>
</tr>
<tr>
<td>Prange et al., 1999</td>
<td>Sliding with friction</td>
<td>Coronal Human</td>
</tr>
</tbody>
</table>
Table 1.6 Summary of the brain-skull interface model used in 3D biomechanical models of human and animal brain based on the study by Kleiven (2002)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Brain-Skull Interface</th>
<th>Model of Geometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiMasi et al., 1991</td>
<td>Ranging from sliding to fixed</td>
<td>3D Human</td>
</tr>
<tr>
<td>DiMasi et al., 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bandak et al., 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruan et al., 1994</td>
<td>CSF modelled as a solid</td>
<td>3D Human</td>
</tr>
<tr>
<td>Ruan et al., 1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruan &amp; Prasad, 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruan &amp; Prasad, 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bandak et al., 1995</td>
<td>Common nodes</td>
<td>3D Human</td>
</tr>
<tr>
<td>Kumaresan et al., 1995</td>
<td>CSF modelled as a solid</td>
<td>3D Human</td>
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<td>3D Human</td>
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<td>Willinger et al., 1999</td>
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<tr>
<td>Turquier et al., 1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueno et al., 1995</td>
<td>Interface gap.</td>
<td>3D Ferret</td>
</tr>
<tr>
<td>Zhou et al., 1995</td>
<td>Ranging from tied nodes to sliding without separation</td>
<td>3D Human</td>
</tr>
<tr>
<td>Zhou et al., 1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Bsharat et al., 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claessens et al., 1997</td>
<td>Ranging from sliding to fixed</td>
<td>3D Human</td>
</tr>
<tr>
<td>Huang et al., 1999</td>
<td>Common nodes</td>
<td>3D Human</td>
</tr>
<tr>
<td>Huang et al., 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shugar, 1977</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al., 2001a</td>
<td>Tied interface</td>
<td>3D Human</td>
</tr>
<tr>
<td>Zhang et al., 2001b</td>
<td>Sliding without separation</td>
<td></td>
</tr>
</tbody>
</table>

Hardy et al. (2001) investigated the relative motion between the brain and the skull using a FE model where they used no-slip boundary conditions between the brain and skull. Wittek and Omori (2003) conducted a parametric study of the effects of the
boundary conditions for modelling the brain on a FE model of human head under angular acceleration. They considered three situations for representing the brain-skull interface: (1) the brain is rigidly attached to the skull; (2) there is frictionless sliding contact between brain and skull and no separation between them and (3) modelling the CSF as a layer of solid elements with fluid like properties. Ji et al. (2004) studied the relative displacement at the brain-skull boundary for the human head where they used free interfacial conditions between the brain and the skull. In another study the same author (Ji & Margulies, 2007) proposed a sliding (with or without friction) boundary condition between the brain stem and the skull in FE models of the human head. Recently, Ji et al. (2007) introduced a contact algorithm to define the brain-skull contact based on force displacement method (FDM). In another recent study a FE model for PAC has been developed (Ma et al., 2008) based on previous studies conducted by Jin et al. (2006, 2007) to investigate the mechanical properties of the PAC.

Models for Application in Biomechanics for Medicine

In the previous studies the brain-skull interface models used for application in surgical simulation are based on simplified assumptions due to limited knowledge of the mechanical properties of the interface. For instance Takizawa et al. (1994) developed a brain model where they used a fixed connection between the cerebral hemisphere and the skull to represent the brain-skull interface. Kyriacou and Davatzikos (1999) used a no slip-boundary condition between the brain and the skull in their study e.g. the dura mater is fixedly attached to the skull and there is no movement between the brain and dura mater at the contact surface. In another study Hagemann et al. (1999, 2002) coupled elastic and fluid models to model behaviour of the brain tissue and the CSF.
Miller and Chinzei (1997) introduced a non-linear viscoelastic model of brain tissue and proposed the boundary conditions (2000) for modelling the brain to predict brain shift during neurosurgery. The authors used boundary conditions such as the upper half surface of the brain has a frictionless sliding contact with the skull; there is a gap between the brain and skull and the bottom surface of the brain was fixed. In some other studies a frictionless sliding contact between brain and the skull was used to represent the brain-skull interface (Skrinjar et al., 2002, Hu et al., 2007, Wittek et al., 2007). Wittek et al. (2007) developed a fully non-linear FE model to model large deformation during surgery. The authors used three different boundary conditions for modelling the brain in their study: (1) no gap between the brain and the skull and the loading was defined on the nodes of the exposed brain surface only, (2) a gap between the brain and the skull and the loading was defined not only on the nodes of the exposed brain surface only and (3) there is gap between the brain and the skull for brain motion within the cranial cavity and the loading was defined not only on the nodes of the exposed brain surface but also on some limited number of nodes located on the unexposed brain surface. In some other studies the boundary conditions for modelling of the brain have been applied such that all surface nodes of the brain except those at the craniotomy and brainstem were fixed in the direction normal to the skull, thus allowing a tangential movement (Lunn et al., 2005, Lunn et al., 2006, Miga, 1998, Platenik et al., 2002, Sun et al., 2005a). Lately, Ji et al. (2009) proposed an algorithm to define the brain–skull contact by incorporating it into an inversion estimation scheme for the deformation field using the steepest gradient descent (SGD) framework.
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1.4 Aims and Overview of the Study

As summarised in the previous section a limited numbers of studies have been carried out to investigate the mechanical properties of the different types of meninges separately such as the PAC (or pia alone). However, in order to develop a biomechanical model of the human brain, the mechanical properties of the entire brain-skull interface that provides the boundary conditions for modelling the brain are of more importance. The goal of this study is to determine the mechanical properties of the brain-skull interface which will lead to the provision of boundary conditions for use when modelling the brain to predict brain shift during surgery. The most straightforward way to determine the mechanical properties of the brain-skull interface would be to conduct experiments on interface samples. However, the complex anatomical structure of this interface poses difficulties in extracting the interface samples without damaging tissues that form the interface (Haines et al., 1993). To overcome this problem, in-situ indentation experiments of the brain were conducted to determine the mechanical properties of the brain-skull interface, and the macroscopic mechanical properties of the brain-skull interface were derived from the results of these experiments (Mazumder et al., 2012, Mazumder et al., 2013). My methodology to determine the mechanical properties of the brain-skull interface is shown in Figure 1.12.
Chapter 1: Introduction

Figure 1.12 Methodology to determine the mechanical properties of the brain-skull interface

To the best of my knowledge, this is the first analysis of this kind. When conducting in-situ indentation of the sheep brain, the reaction force on the indentor was measured. To determine the brain deformation X-ray opaque markers were inserted into the brain. After the indentation, a cylindrical sample of brain tissue was extracted and subjected to uniaxial compression test to determine the subject-specific mechanical properties. A model of the in-situ brain indentation was built in ABAQUS™/Standard finite element solver. In the model, the mechanical properties of the brain tissue were assigned to match those obtained from the uniaxial compression test. To verify deformation field within the brain, the experimentally determined displacements of the implanted X-ray opaque markers in the brain were compared with their calculated displacement within the model. The properties of the brain-skull interface were derived
so that the calculated indentor reaction force and deformations within the brain matched those measured experimentally. This allowed identification of the overall mechanical properties of the brain-skull interface.

1.5 Overview of the Thesis

This thesis is organised as follows: in Chapter 2 a detailed description of the experiments to determine the mechanical properties of the brain-skull interface is presented. The theory of camera calibration is revisited. It also includes the steps to determine the displacements of the X-ray opaque markers implanted inside the brain. In Chapter 3 the modelling of the brain-skull interface is described. The loading and the boundary conditions associated with the modelling of the uniaxial compression test of cylindrical samples and in-situ brain indentation experiments are also addressed. The chapter is concluded with a brief description of proposed mechanical properties of the brain-skull interface. In Chapter 4 the experimental results from the uniaxial compression experiments of cylindrical samples and in-situ brain indentation experiments are presented. Additionally, the calculated indentor reaction force and deformations within the brain determined from the modelling are compared with those measured experimentally. The Chapter 5 includes the discussion part of the thesis. Finally the thesis is concluded in Chapter 6 by making conclusion and directions for future research.
EXPERIMENTS TO DETERMINE
THE MECHANICAL PROPERTIES OF
THE BRAIN-SKULL INTERFACE†

2.1 Determining the Mechanical Responses of the Brain–Skull Interface and Adjacent Brain Tissue: In-Situ Brain Indentation

To determine the mechanical behaviour of the brain-skull interface, in-situ indentation experiments of sheep brain were conducted. The experiments were performed at the Royal Perth Hospital of Western Australia. Four in-situ brain indentation experiments were conducted. The subject-specific materials properties for the specimens used for in-situ indentation experiments were determined through uniaxial compression experiments using cylindrical samples of brain tissue (see Section 2.1.3). The specimen preparation, experimental setup and experiment protocol for in-situ indentation experiments are given in following section.

† Parts of this chapter appear in a paper (Mazumder et al., 2013) published in ACTA of Bioengineering and Biomechanics journal and in a paper (Mazumder et al., 2012) presented in 10th International Symposium Computer Methods in Biomechanics and Biomedical Engineering, Berlin, Germany.
2.1.1 Specimen Preparation

Fresh sheep heads were collected from a local abattoir immediately after slaughtering. The sheep head was kept at a constant temperature of 4°C in a refrigerator. This was done to avoid the specimen from getting frozen which might alter the mechanical properties of the brain. The dissection started within eight hours post mortem and one hour prior to the experiment. A vibrating circular saw was used to make a 4cm x 2cm rectangular opening into the skull above the left hemisphere of the brain. A small cube of cortex close to its surface was removed using a scalpel. Four X-ray opaque reference markers, each having 1 mm diameter, were then placed at the four corners of the craniotomy area on the surface of the brain. These markers were used to determine the location of the indentor during the experiment. Immediately after that five X-ray opaque (spherical steel ball) markers (diameter 0.5 mm) were inserted in close proximity to the area of indentation. This was done by using a stainless steel cannula having 0.6 mm diameter. The markers were held in the tip of cannula by wax and then inserted into the brain by pushing a metal wire through the cannula. These markers were tracked by two OEC 9800 series mobile C-arms to determine the brain deformation. A detail description of the mobile C-arms is given in section 2.1.4. The two mobile C-arms were positioned so that the imaging planes were orthogonal to each other to obtain 3D coordinates of the X-ray opaque markers. A Computed Tomography (CT) scan of the whole head was taken after the preparation of the specimen preparation. It was later used for generating the 3D model of the sheep brain.
2.1.2 Testing Apparatus

A 5948 Micro Tester Testing System was used in a horizontal configuration for the *in-situ* indentation experiments. It was utilized for the experiments of the brain because of its versatility for vertical and horizontal indentation application. The Micro Tester 5948 consists of a universal displacement actuator platform with a displacement control of 20 nm (Instron Documentation of 5948 Micro Tester, 2010). The portable and light features of the device allowed it to be moved easily and be quickly automatically recalibrated. A special rectangular Perspex tray was used to constrain the sheep skull for tracking the markers implanted inside the brain during the experiment. An L-shaped indenter was used to indent the brain *in-situ* in the craniotomy area. The schematic diagram for the experiment and experimental set up is shown in Figure 2.1. The 5948 Micro Tester and the L-shaped indenter are shown in Figure 2.2.
Figure 2.1: (a) Schematic diagram of *in-situ* sheep brain indentation (b) Experiment set up for *in-situ* brain indentation (see Mazumder et al., 2012, Mazumder et al., 2013)
Figure 2.2: (a) L-shaped indentor (b) Micro Tester 5948 (Instron Documentation of 5948 Micro Tester, 2010)
Chapter 2: Experiments to Determine the Mechanical Properties of the Brain-Skull Interface

2.1.3 Experimental Protocol

The loading speed of the indenter was kept constant at 12 mm/min. The distance to maximum compression was 4.8 mm (the indenter displacement was measured from start of the contact between the indenter and the brain tissue until the indenter reached the maximum point of indentation). The primary focus was to get the force-displacement relationship of the in-situ indentation of the brain close to the surface of the brain. Only one loading cycle was used for each specimen. To ensure a no-slip boundary condition, sand paper was attached on the face of the L-shaped indenter. The contact was confirmed through a load reading from the micro tester. Movement of the L-shaped indenter was stopped automatically by the micro tester when it reached 4.8 mm and then it turned back automatically to its initial position.

It should be noted that although plans were made to conduct four experiments, unfortunately it was not possible to conduct all of them. The 3rd experiment was called off prior to the start of the experiment due to the emergency arrival of a patient in the hospital, while the specimen was prepared and the experimental set up was arranged. Furthermore, after conducting the 1st experiment, the mobile C-arms were damaged due to a hardware issue and therefore, X-ray images were not available. Due to this the location of the reference markers was not available. As a result, the location on the indenter while conducting the in-situ brain indentation was unknown. So, it was not possible to build the FE modelling of the in-situ brain indentation experiment for the 1st experiment. During the 2nd experiment the indenter hit the skull during the in-situ experiment. So, it was not possible to determine the mechanical properties of the brain-skull interface from the results obtained from the experiment and hence, the modelling of in-situ indentation test for this experiment was not built as well. The modelling of in-
The in-situ indentation experiment shown in this study for in-situ indentation is based on information available for the 4th and final experiment only. Although modelling of all four in-situ indentation experiments was not available due to circumstances beyond my control but the determination of subject-specific material properties of cylindrical samples by using uniaxial compression experiments (for the subjects used in three in-situ indentation experiments) was conducted. The results from these subject-specific uniaxial compression tests are shown in Chapter 4.

Additionally, five in-situ brain indentation trial experiments were conducted prior to conduction of four main experiments. The same protocols and methodology were followed to conduct these trials for in-situ indentation test. The main experimental results as well as the results from these trials are shown in Figure 4.1. The trials were conducted to check the repeatability of the in-situ indentation experiments.

### 2.2 Determining Deformations of the Brain Tissues Using X-ray Opaque Markers

During specimen preparation for the in-situ indentation experiment, five X-ray opaque markers were implanted within the brain to calculate the brain deformation. The displacements of the markers during in-situ indentation experiment were determined from the X-ray images captured by the two mobile C-arms.
2.2.1 X-ray Image Intensifier System

Use of X-ray imaging systems, such as mobile C-arms are very common for surgical navigation and motion tracking of surgical instruments (Acosta et al., 2004, Hofstetter et al., 2000, Hott, 2004). Hing et al. (Hing et al., 2007) used two mobile C-arms for tracking X-ray opaque markers to determine the deformation of the soft tissue during needle insertion. In this study a similar approach was used to determine the deformation of the brain during the in-situ indentation experiments. Two OEC 9900 series mobile C-arms were used to image the indentor and X-ray opaque markers inside of the brain. The mobile C-arm used in this study is shown in Figure 2.3.

![Figure 2.3 OEC 9900 Series Mobile C-arm](image)

The OEC 9900 series mobile C-arm by OEC Medical Systems Inc. has a 12 inch. tri-mode image intensifier. The whole system consists of image intensifiers and two sources. The two mobile C-arms were positioned so that the imaging planes were
orthogonal to each other and the images were captured at a rate of 2 frames per second and with a resolution of 1024x1024 pixels.

### 2.2.2 Calibration of the Mobile C-Arms

In this study the deformation of the brain tissue was determined by tracking the 3D motion of X-ray markers implanted inside the brain. Figure 2.4 shows X-ray images of the brain tissue taken by the two mobile C-arms. The indentor as well as the X-ray opaque markers can be seen in those images.

![Figure 2.4 Sagittal view of the X-ray images of in-situ brain indentation taken by the two mobile C-arms (0.5 mm diameter X-ray opaque markers are indicated with red circles and 1 mm diameter X-ray opaque markers are enclosed with blue circles)](image-url)
Figure 2.5 Axial view of the X-ray images of \textit{in-situ} brain indentation taken by the two mobile C-arms (0.5 mm diameter X-ray opaque markers are indicated with red circles and 1 mm diameter X-ray opaque markers are enclosed with blue circles)

To calculate the displacements of the X-ray opaque markers, the camera parameters of the mobile C-arms were needed to be determined through calibration. The most straightforward approach is to approximate the projection geometry of an X-ray image intensifier by the pinhole camera model (Zhang, 1999, Zhang, 2000). Several studies (Heikkil & Silven, 1997, Tsai, 1987, Zhang, 1999, Zhang, 2000) are available regarding the methods for calibrating the pinhole camera model. In this study, the pinhole camera model was used to calibrate the two mobile C-arms. The camera calibration toolbox (Bouguet, 2009) for MATLAB (The Math Works, Natick, MA,
USA) was used to perform the calibration for two mobile C-arms. Similar calibration materials and procedure were used in Ma et al. (Ma et al., 2008).

### Pinhole Camera Model

The pinhole camera model uses the mathematical relationship to project the image from 3D reference plane to the image plane by a pinhole camera such that no lenses are used to focus light as aperture. In the literature this point in 3D reference frame is defined as the optical (or lens or camera) centre.

Light from a point passes along a single straight path through a pinhole onto the image plane. Figure 2.5 shows the geometry of the pinhole camera where the target image is upside-down on the image plane (Fleet & Hertzmann, 2006).

![Figure 2.6 Geometry of a pinhole camera (Celic & Erden, 2012)](image)

### Geometrical and Mathematical Relations of the Pinhole Camera

The point C in Figure 2.6 is the origin of 3D orthogonal coordinate system and also the position of the pinhole camera aperture as well. X, Y, Z are referred as three
axes of the 3D orthogonal coordinate system. The Z axis corresponds to the direction of the field of view of the camera and it is defined as the optical axis or principal axis.

Figure 2.7 Geometry of the pinhole camera with coordinates (Celic & Erden, 2012)

The image plane is positioned as parallel to X and Y axes and at a distance from the point C where the 3D world is projected through the aperture of the pinhole camera. The distance between target image plane and the camera centre is equivalent to the focal length \( f \) of the pinhole camera. The image plane is perpendicular to the Z axis.

The point \( P \) is referred as the principal point where the image plane intersects the optical axis and the coordinates of the principal point are given by \((u_0, v_0)\). The point \( m_1 \) is the projection of the point \( m \) in the real world through the red projection line. Furthermore, the image plane intersects the red projection line at point \( m_1 \).

Moreover, a 2D coordinate system on the image plane can be seen in the figure 2.8, with origin positioned at point \( P \) and with axes \( u \) and \( v \) which are parallel to \( X \) and \( Y \) axes respectively. The coordinates of point \( m_1 \) in this coordinate system is \((u, v)\).
As the next step we have to define the relationship between the coordinates of $m_1$ ($u, v$) and coordinates of point $m$ ($x, y, z$) according to camera reference frame. An equation can be obtained from the Figure 2.7.

$$u = f \frac{x}{z} \quad \text{and} \quad v = f \frac{y}{z} \quad \text{(2.1)}$$

Figure 2.8 Geometry of a pinhole camera as seen from the X axis (Celic & Erden, 2012)

Central Projection by Using Homogenous Coordinates

If the world and image points are described as homogenous vectors, then central projection can be defined as a linear mapping between their homogenous coordinates. It can be expressed in terms of matrix multiplication.

$$\begin{pmatrix} u \\ v \\ 1 \end{pmatrix} \sim \begin{pmatrix} fX \\ fy \\ fz \end{pmatrix} = \begin{bmatrix} f & 0 & 0 & 0 \\ 0 & f & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix} \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix} \quad \text{(2.2)}$$

In practice, the origin of coordinates in the image plane does not coincide with the point $P$. So, the equation 2.2 can be modified to equation 2.3 in the following:
where \( k \) is equivalent to the camera calibration matrix. In equation (2.5), if we replace \( m_1 \) as \((u, v, 1)^T\) and \( m \) as \((X, Y, Z, 1)^T\) and the camera is assumed to be positioned at the origin of Euclidian coordinate system with the principal axis of the camera directing straight down the Z-axis, then this coordinate system can be called the camera reference frame (Hartley & Zisserman, 2003).

**Intrinsic Pinhole Camera Calibration Parameters**

**Focal Length:** The focal length of an optical system can be defined as a measure of the system’s capacity to converge or diverge light. For an optical system in air, it is the distance over which initially collimated rays are brought to a focus. An optical system having a shorter focal length has greater optical power compared to the one with a long focal length. The shorter focal length allows the system to bend the light rays more strongly and bring them to a focus in a shorter distance.

Longer focal length (lower optical power) contributes towards higher magnification and narrower angle of view, while the shorter focal length (higher optical power) renders a wider angle of view.

The calibration toolbox stores the focal length in pixels in a 2D vector expressed as \( f_c \), the first row of the matrix corresponds to the focal length on \( u \) direction whereas
the second row of the matrix corresponds to the focal length on \( v \) direction. The aspect ratio is equivalent to \( f_c(1)/f_c(2) \) and it is equal to 1 if the CCD sensor array is square. But generally the camera sensor array generally is not square. So, the toolbox uses two different focal lengths. The \( k \) matrix in equation 2.4 must be updated as shown in the following:

\[
k = \begin{bmatrix}
  f_c(1) & 0 & u_0 \\
  0 & f_c(2) & v_0 \\
  0 & 0 & 1
\end{bmatrix}
\]  

(2.6)

*Principle Point:* The principal point coordinates corresponds to the centre of coordinates on the image plane (also the sensor plane), \( P (u_0, v_0) \) and they are stored as a 2D vector. First row of the vector describes the pixel coordinates along the \( u \) direction and the second row of the vector demonstrates the pixel coordinate on \( v \) direction.

*Skew Coefficient:* The skew coefficient gives the angle between the \( u \) and \( v \) pixel axes. The optimal value of the skew coefficient is \( 90^\circ \) and in the calibration toolbox it is expressed as \( \alpha_c \). Considering the skew coefficient \( \alpha_c \) the \( k \) matrix in equation 2.6 can be updated as in the following:

\[
k = \begin{bmatrix}
  f_c(1) & \alpha_c & u_0 \\
  0 & f_c(2) & v_0 \\
  0 & 0 & 1
\end{bmatrix}
\]  

(2.7)

*Distortions:* The calibration toolbox stores the image distortion coefficients \( K_c \) (radial and tangential distortions) as a 5x1 vector.

Considering the projection of point \( m \) on the camera reference frame and taking \( X_n \) as the normalized (pinhole) image projection the distorted coordinates \( X_d \) can be calculated using the equations 2.8 and 2.9, which is shown in equation 2.10.
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\[ A = \begin{bmatrix} X/Z \\ Y/Z \end{bmatrix} = \begin{bmatrix} u_n \\ v_n \end{bmatrix} \]  \hspace{1cm} (2.8)

\[ r^2 = u_n^2 + v_n^2 \]  \hspace{1cm} (2.9)

In equation 2.10 \( X_d \) is the distorted coordinates and it is determined from the undistorted image coordinates \( X_n \) and the tangential distortion vector \( dx \) (calculated from the equation 2.11 (Heikkil & Silven, 1997).

\[ X_d = \begin{bmatrix} X_d(1) \\ X_d(2) \end{bmatrix} = (1 + K_c(1)r^2 + K_c(2)r^4 + K_c(5)r^6)X_n + dx \]  \hspace{1cm} (2.10)

\[ dx = \begin{bmatrix} 2K_c(3)u_n v_n + K_c(4)(r^2 + 2u_n^2) \\ K_c(3)(r^2 + 2v_n^2) + 2K_c(4)u_n v_n \end{bmatrix} \]  \hspace{1cm} (2.11)

In equation 2.10 \( K_c \) vectors includes of both tangential and radial distortion coefficients. So, the final pixel coordinates of the projection of point \( m \) can be expressed using in the following formula:

\[ u = f_c(1)(X_d(1) + \alpha_c * X_d(2)) + c_c(1) \]  \hspace{1cm} (2.12)

\[ v = K_c(2)X_d(2) + c_c(2) \]  \hspace{1cm} (2.13)

A linear relationship exists between the pixel coordinates of the projection of point \( m \) and distorted coordinate vector.

\[ \begin{bmatrix} u \\ v \\ 1 \end{bmatrix} = k \begin{bmatrix} X_d(1) \\ X_d(2) \\ 1 \end{bmatrix} \]  \hspace{1cm} (2.14)

Based on the equations 2.12, 2.13 and 2.14, the camera calibration matrix \( K \) can be defined as in the following:
Chapter 2: Experiments to Determine the Mechanical Properties of the Brain-Skull Interface

Extrinsic Pinhole Camera Calibration Parameters

The extrinsic parameters are associated with the camera’s location and the orientation of it with the world reference frame (see Figure 2.8). Rotations and translations vectors are used to define the extrinsic parameters and give the relationship between the world reference frame \((X_{world}, Y_{world}, Z_{world})^T\) the camera reference frame coordinates \((X, Y, Z)^T\).

![Diagram of camera coordinates](image)

Figure 2.9 Rotation and translation from world coordinates to camera coordinates (Celic & Erden 2012)

\[
\begin{bmatrix}
\hat{u} \\
v \\
1
\end{bmatrix} = k_{3 \times 3}(\hat{w}R_{3 \times 3} \hat{w}O_{3 \times 1})_{3 \times 4} \begin{bmatrix} w_m \\ 1 \end{bmatrix} = k \begin{bmatrix} r_1 & r_2 & r_3 & t \end{bmatrix}
\]

(2.16)

\(\hat{w}R_{3 \times 3}\) and \(\hat{w}O_{3 \times 1}\) in equation 2.16 are called the rotation matrix and the translation matrix respectively. They define the translation and rotation of the

\[
k = \begin{bmatrix} f_c(1) & \alpha_c f_c(1) & u_0 \\ 0 & f_c(2) & v_0 \\ 0 & 0 & 1 \end{bmatrix}
\]

(2.15)
coordinates from the world reference frame to the camera reference frame. The projection of the point \( m \) on the camera reference frame can be expressed in the following formula:

\[
m_1 = P m
\]

(2.17)

where \( P \) is the projection matrix that equals at the same time and includes both the intrinsic \((k)\) and the extrinsic parameters \((R, O)\).

The projection matrix \( P \) consists of 11 parameters (see Figure 2.9) five out of them are intrinsic, three of them are rotation and the rest three are translation parameters.

![Figure 2.10 Rotation with Euler Angles (Celik & Erden 2012)](image)

\[
R = \begin{pmatrix}
\cos k & \sin k & 0 \\
-sin k & \cos k & 0 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
\cos \phi & 0 & \sin \phi \\
0 & 1 & 0 \\
-sin \phi & 0 & \cos \phi
\end{pmatrix}
\begin{pmatrix}
1 & 0 & 0 \\
0 & \cos \omega & \sin \omega \\
0 & -sin \omega & \cos \omega
\end{pmatrix}
\]

(2.18)

\[
R = \begin{pmatrix}
\cos k \cos \phi & \sin k \cos \omega - \cos k \sin \phi \sin \omega & \sin k \sin \omega + \cos k \sin \phi \cos \omega \\
-sin k \cos \phi & \cos k \cos \omega + \sin k \sin \phi \sin \omega & \sin k \sin \omega - \sin k \sin \phi \cos \omega \\
-sin \phi & -cos \phi \sin \omega & \cos \phi \cos \omega
\end{pmatrix}
\]

(2.19)
Finally, the relationship between the world-coordinates \( (X_{\text{world}}, Y_{\text{world}}, Z_{\text{world}}) \) and the image coordinates \((u,v)\) can be expressed using the following equation:

\[
\begin{bmatrix}
  u \\
  v \\
  1
\end{bmatrix} = k
\begin{bmatrix}
  0 & 0 & 0 & T_x \\
  0 & R & 0 & T_y \\
  0 & 0 & 0 & T_z 
\end{bmatrix}
\begin{bmatrix}
  X_{\text{world}} \\
  Y_{\text{world}} \\
  Z_{\text{world}} \\
  1
\end{bmatrix}
\]

(2.20)

After conducting calibration the following camera parameters were found for the two mobile C-arms as listed in Table 2.1 below.

<table>
<thead>
<tr>
<th>Mobile C-arms</th>
<th>Camera Parameters (pixel)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \alpha_u )</td>
</tr>
<tr>
<td>C-arm 1</td>
<td>6949.26111</td>
</tr>
<tr>
<td>C-arm 2</td>
<td>8149.60104</td>
</tr>
</tbody>
</table>

The estimated average, maximum and standard deviation of re-projection error indicating the accuracy of determining the 3D position of an object point (i.e. control point or a marker) from the X-ray images are provided in Table 2.2. The maximum uncertainty in determining the marker positions was determined to be 0.65 mm (4.7 pixels).

<table>
<thead>
<tr>
<th>Mobile C-arms</th>
<th>In pixel</th>
<th>In Millimeters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average error</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>C-arm 1</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>C-arm 2</td>
<td>1.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>
2.2.3 Distortion Correction of X-ray Images

To accurately determine the displacements of the markers implanted inside the brain from the captured X-ray images, it is essential to remove the geometric distortion from the images. For an X-ray image intensifier system there are three types of distortions which are radial distortion, tangential distortion and spiral distortion (see Figure 2.11). The radial distortion is caused by X-ray image intensifier through projection of a flat surface into the input sulphur screen of the intensifier system whereas the spiral distortion is caused by deflection of the electrons due to earth’s magnetic field (Gronenschild, 1997, Gronenschild, 1999) (see Figure 2.10). The CCD camera used to capture the intensified images introduces the tangential distortion (see Figure 2.11) as well as some radial distortion due to the imperfection of the lens elements (Heikkil & Sliven, 1997, Hartley & Zisserman, 2003, Weng et al., 1992).

Figure 2.11 Different types of geometrical distortions for X-ray Image Intensifier system: (a) radial distortion (b) tangential distortion and (c) spiral distortion (see Ma et al., 2009)

In this study, the spiral distortion was found to be negligible in the X-ray images (see Figure 2.11) captured during the in-situ indentation experiments. Consequently,
only the radial and tangential distortions were taken into consideration during this study. The distortion coefficients for this study were determined by using the camera calibration toolbox for MATLAB developed by Boughet (2009). The tangential and radial distortions are modelled using this toolbox. The control points were taken from captured X-ray images of a chess board pattern calibration grid from mobile C-arms, taken at 15 different orientations. Figure 2.11 shows the chess board pattern calibration grid and captured X-ray image of the pattern by a mobile C-arm. From the picture it can be easily seen that the spiral distortions are negligible in the captured X-ray images.

The estimated tangential and radial distortions for the two mobile C-arms are listed in Table 2.3.

<table>
<thead>
<tr>
<th>Mobile C-arms</th>
<th>Distortion Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$k_1$</td>
</tr>
<tr>
<td>C-arm 1</td>
<td>-3.17041</td>
</tr>
<tr>
<td>C-arm 2</td>
<td>-8.60631</td>
</tr>
</tbody>
</table>
2.2.4. Determination of Marker Displacements from X-Ray Images

Movement of the markers was tracked along the X-ray image sequences using codes implemented in MATLAB. Firstly, the image boundaries were removed to choose the region of interest for the movement of the markers. A gray scale morphological filter was used to detect the markers from the X-ray images. The marker positions were detected in the image by performing a Top Hat Transform (Solomon et al., 2011). Then a morphological structuring element was used to locate the markers in the image. Subsequently, thresholding was used to extract the marker location and the location of the markers was estimated as their centroid. After that, the location of the markers was represented as the centroid (blobs). Between two consecutive frames the tracking code only looked at the nearest neighbour location of a particular marker to track and update the position of the marker. It was mentioned earlier in section 2.1.1 that, four X-ray opaque reference markers (1 mm diameter) placed on the surface of the brain in the area of the craniotomy. These markers were visible in the CT images and X-ray images and used to determine the initial location of the indentor during \textit{in-situ} indentation experiments. The indentor location was estimated by performing registration of the two co-ordinate systems.

Figure 2.12 shows the detected markers for a given frame of the X-ray images during the $4^\text{th}$ \textit{in-situ} indentation experiment. Triangulation functions of the camera calibration toolbox for MATLAB (Bouguet, 2009) were used to calculate 3D position of the X-ray opaque markers from the captured X-ray images by the two mobile C arms.
Figure 2.13 Three X-ray opaque markers (red rectangle box) extracted from the X-ray images by using grey scale morphological filtering at a given frame: (a) axial view (b) sagittal view
2.3 Determining Subject-Specific Constitutive Properties of the Brain Tissue: Uniaxial Compression of the Brain Tissue Samples

The human brain is the most complex organ human body. The main structures of the brain consist of cerebral hemispheres, diencephalon, brain stem and cerebellum. The brain tissue itself consists of white matter and gray matter, the former mainly made of myelinated nerve fibres the latter predominantly cellular components.

Ommaya (1968) suggested the brain as a “soft, yielding structure, not as stiff as gel or as plastic as a paste”. Walsh and Schettini (1984) and Sahay et al. (1992) measured the induced changes in intra-cranial pressure to establish elastic parameters of the brain tissue. Estes and McElhaney (1970) and Galford and McElhaney (1970) conducted experiments to determine the mechanical properties of the brain tissue. The strain rates used in those studies were applicable for head injury modelling and much higher than those relevant to surgical procedure. Using these experimental results, Pamidi and Advani (1978) and Mendis et al. (1995) proposed a non-linear constitutive model for human brain tissue. However, the proposed models using high strain rates were relevant to the impact and injury scenarios. Later, Guillaume et al. (1997) investigated the brain response to hypergravity and Donnelly and Medige (1997) conducted experiment to determine the mechanical properties of the brain tissue in shear. Again, high strain rates were used in those studies by limiting their application modelling and surgical procedure.

Miller and Chinzei (1995a, 1995b) investigated the mechanical properties of the brain which were relevant to surgical simulation. Since then a number of experimental
Chapter 2: Experiments to Determine the Mechanical Properties of the Brain-Skull Interface

Studies have been carried out to determine the mechanical properties of brain tissue (Bliston et al., 1997, Cheng & Bliston, 2007, Gefen & Margulies, 2004, Miller & Chinzei, 1997, Miller & Chinzei, 2002, Miller et al., 2000, Prange & Margulies, 2002, Velardi et al., 2006). The researchers conducted their experiments under conditions for specific applications which are summarized in Table 2.4.

Table 2.4 List of recent experiments to determine the mechanical properties of brain tissue (Based on the study by Couper & Albermani, 2006).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Species</th>
<th>Preparation</th>
<th>Experimental Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller &amp; Chinzei, 1997</td>
<td>Porcine</td>
<td>Obtained at termination and tissue samples were tested at approximately 12 hours post mortem</td>
<td>Unconfined constant rate compression No preconditioning</td>
</tr>
<tr>
<td>Miller et al., 2000</td>
<td>Porcine</td>
<td>Fresh under anaesthesia and in-vivo tissue indentation</td>
<td>In-vivo constant rate indentation</td>
</tr>
<tr>
<td>Bilston et al., 2001</td>
<td>Bovine</td>
<td>Obtained at termination and samples were tested approximately within 8 hours post mortem</td>
<td>Oscillatory shear, Shear relaxation, constant strain rate</td>
</tr>
<tr>
<td>Prange &amp; Margulies, 2002</td>
<td>Porcine</td>
<td>Obtained at termination and samples were tested at approximately 5 hours post mortem</td>
<td>Shear stress relaxation Preconditioned</td>
</tr>
<tr>
<td>Miller &amp; Chinzei, 2002</td>
<td>Porcine</td>
<td>Obtained at termination and samples were tested at approximately 12 hours post mortem</td>
<td>Confined constant rate tension</td>
</tr>
<tr>
<td>Gefen &amp; Margulies, 2004</td>
<td>Porcine</td>
<td>Fresh under anaesthesia and in-vivo tissue indentation</td>
<td>In-vivo indentation</td>
</tr>
<tr>
<td>Velardi et al., 2006</td>
<td>Porcine</td>
<td>Obtained from termination and samples were tested within 5-6 hours post mortem</td>
<td>Constant rate tensile No preconditioning</td>
</tr>
<tr>
<td>Cheng &amp; Bilston, 2007</td>
<td>Bovine</td>
<td>Obtained from termination and sample were tested immediately</td>
<td>Unconfined constant rate compression Preconditioned</td>
</tr>
</tbody>
</table>

The major factors affecting this wide range of different experiments to determine the mechanical properties of the brain tissue are due to a number of reasons such as experimental protocol, specimen preparation, post-mortem duration, in-vivo and
in-vitro difference (Gefen & Margulies, 2004) regional dependence and age respect (Gefen et al., 2003, Prange & Margulies, 2002).

During this study, following Miller and Chinzei (Miller & Chinzei, 1997, Miller & Chinzei, 2002) uniaxial compression experiments are conducted using moderate strain rate to determine the mechanical properties of brain tissue. These properties were later assigned to the brain for the modelling of the in-situ indentation experiments.

2.3.1 Tissue Sample Preparation

After the in-situ brain indentation experiment the whole brain was extracted by dissecting the skull using a vibrating circular saw. Then a cylindrical tissue sample was cut from the brain using a hollow stainless steel metal pipe with sharp edge. The diameter of the pipe was 18 mm. The height of the sample was approximately 12 mm. It was possible collect one cylindrical sample from the brain as sheep brains are very small (five times smaller than the volume of the human brain). The cylindrical sample was collected from the other (left) side of the brain to the side where in-situ indentation was performed. Figure 2.13 shows a picture of sheep brain that weighs about 116 grams.
2.3.2 Testing Apparatus

The Micro Tester 5948 system was used in vertical configuration for the uniaxial compression test of the brain tissue (see Figure 2.2).

2.3.3 Experimental Protocol

Following Miller and Chinzei (1997) the constitutive properties of brain tissue were determined through semi-confined uniaxial compression of a tissue sample (see Figure 2.14 a). The cylindrical tissue sample was compressed between two metal plates as shown in Figure 2.14(b). During the experiment sand paper was glued to the surface of both the fixed plate and moving plate to maintain a no-slip boundary condition. The movement of the moving plate started 1 mm from the sample and the maximum compression depth (the moving plate displacement measured from start of the contact between the moving plate and the brain tissue until the moving plate maximum point of
compression) was approximately 3 mm. The diameter of the moving plate was 20 mm and the loading speed was kept constant at 4 mm/min.

Figure 2.15 Uniaxial compression test to determine material constants: (a) Experimental set-up of the semi-confined uniaxial compression test (b) Uniaxial compression of brain tissue in vitro using 5948 Micro Tester (Mazumder et al., 2012, Mazumder et al., 2013)
2.4 Chapter Summary

In this chapter, the methodology to conduct the in-situ brain indentation test and the uniaxial compression test of cylindrical brain is described. The methodology includes in details description of the specimen preparation, apparatus, schematic diagram and experimental protocol. The theory for camera calibration and camera calibration parameters of the MATLAB toolbox (Boughet, 2009) are also explained in section 2.1.3. The camera parameters and the distortion coefficients for the two mobile C-arms are calculated using the toolbox and are shown in Table 2.1 and 2.2 respectively. The results from the in-situ indentation and uniaxial compression experiments are shown in Chapter 4.
Chapter 3: Modelling The Brain-Skull Interface

MODELLING THE BRAIN-SKULL INTERFACE

3.1 Determining the Subject-specific Constitutive Properties of the Brain Tissue: Modelling of Uniaxial Compression of the Brain Tissue Samples

Investigation of determining the mechanical properties of living tissues form a major area of research in biomechanics. In particular, the properties of the muscular–skeletal system, skin, lungs, blood and blood vessels have been investigated (Borowski et al., 1992, Galagher et al., 1982, Mow et al., 1993, Schmid-Schonbein et al., 1986, Fung, 1981).

al., 1997, Nagashima et al., 1987). These investigations require applying the load to brain tissue very quickly and very slowly.

However, the developments in robotics technology, in particular the emergence of automatic surgical tools and robots (Brett et al., 1995) as well as advances in virtual reality techniques (Burdea, 1996) call for closer examination of the mechanical properties of brain tissue at moderate strain rates which are relevant to surgical procedures (Miller, 2002a).

The first papers on investigating the mechanical properties of the brain at moderate loading speeds (relevant to surgical simulation) appeared in 1995 (Miller & Chinzei, 1995a, Miller & Chinzei, 1995b). Since then, several researchers (Bilston et al., 1997, Prange & Margulies 2002, Brands et al., 2004, Miller & Chinzei, 1997) conducted experiments and presented mathematical models of brain tissue mechanical behaviour. The experimental results from those studies showed that the complex mechanical response of brain tissue to external loading such as non-linear stress-strain relationship. Miller et al. (2000, 2002) introduced a number of biomechanical models for brain tissue such as hyperelastic modelling, linear viscoelastic modelling under both tensile and compression conditions and those models can be implemented using commercial FE analysis software such as ABAQUS™.

In this study, following Miller and Chinzei (1997, 2002) the brain tissue constitutive behaviour was modelled using an Ogden-type (Ogden, 1972) Hyperelastic model.

\[ W = \frac{2\mu}{\alpha^2} (\lambda_1^q + \lambda_2^q + \lambda_3^q - 3) \]  

(3.1)
Where \( W \) is the strain energy potential.

\[ \lambda_i (\lambda_1, \lambda_2, \lambda_3) \] are principal stretches. Their values are 1 for no deformation, greater than 1 for extension and smaller than 1 for compression. \( \mu \) is the relaxed shear modulus, and \( \alpha \) is a material coefficient without physical meaning. Following Miller and Chinzei (2002), the value of \( \alpha \) was chosen as –4.7. The density 1000kg/m\(^3\) was chosen for the parenchyma. The constant \( \mu \) of equation 3.1 were varied to obtain a calculated moving plate reaction force-time history close to the relationship measured in the experiments.

The following the simplified assumptions were made while using the model described by Equation 3.1 to determine the subject-specific mechanical properties of the brain:

**Incompressibility**

Very soft tissues are most often assumed as incompressible (Estes & McElhaney, 1970, Miller, 1999, Pamidi & Advani, 1978, Ruan et al., 1994, Sahay et al., 1992, Voo et al., 1996, Walsh & Schettini, 1984). Therefore, in this study the brain tissue was assumed as incompressible material.

**Isotropy**

Very soft tissues do not bear mechanical loads and do not exhibit directional structure. Therefore, they are assumed to have isotropic material properties (Bilston et al., 2001, Farshad et al., 1999, Mendis et al., 1995, Miller, 1999, Miller, 2000, Miller & Chinzei, 2002b, Miller et al., 2000, Nasseri et al., 2002, Walsh & Schettini, 1984). Similarly, in this study, the material properties of the brain were assumed to be isotropic.
During the compression test the top and bottom surfaces of the tissue samples were rigidly constrained in the horizontal direction by using sandpaper. The specific material constants (see equation 3.1) of the cylindrical sample were determined by calibrating non-linear FE model of the uniaxial compression test implemented using the ABAQUS™/ Standard finite element solver (Providence, RI, USA). As compression of the brain tissue sample is a non-linear (in terms of geometry and material behaviour) problem of solid mechanics, the direct equation solver with Full-Newton procedure was used (ABAQUS/CAE User’s manual, 2010). An automatic time increment method was selected with an initial time increment of 0.1 second and the system default displacement based convergence criteria of the ABAQUS™/Standard finite element solver were used.

3.1.1 Finite Element Mesh

The cylindrical brain tissue sample mesh was generated using the Hypermesh™ (Altair Engineering, Troy, Michigan, USA) software package. The surface model for the geometry of the brain tissue sample was generated by Hypermesh™ geometry builder module according to the measured dimensions (height 12 mm, diameter = 14 mm) The volume of the brain tissue sample was discretised by the Hypermesh™ automatic mesh generator with first order hexahedral elements (ABAQUS™/Standard, ABAQUS/CAE User’s manual, 2010) reduced integration, hybrid with linear pressure. As brain tissue is assumed to be incompressible, first order elements with hybrid formulation and linear pressure were used to model the brain tissue sample. The resulting brain tissue sample mesh consists of 9316 nodes and 2025 elements (see Figure 3.1).
3.1.2 Loading and Boundary Conditions

The loading was defined by prescribing the velocity on the nodes of the top surface of the tissue sample. A constant loading speed of 4 mm/min was used during the uniaxial compression of the brain tissue sample. During the experiment the bottom surface of the brain tissue sample was rigidly constrained by using sand paper glued to
the fixed plate. Therefore, the nodes defining the bottom surface of the sample were rigidly constrained in the finite element model (see Figure 3.2). The constant loading speed of 4 mm/min was assigned to the nodes defining the top surface of the sample.

Figure 3.2 The nodes defining bottom surface of the cylindrical brain tissue sample were rigidly constrained in the FE model of the cylindrical brain tissue sample
3.2 Determining the Brain-Skull Interface Mechanical Properties: Modelling \textit{In-Situ} Indentation of the Brain

Modelling \textit{in-situ} indentation of the brain was done using ABAQUS$^{\text{TM}}$/Standard finite element solver. Due to non-linear mechanical behaviour of the brain during \textit{in-situ} indentation experiment, the direct equation solver with Full-Newton procedure was used (ABAQUS/CAE User’s manual, 2010). An automatic time increment method was used in the modelling and the initial time increment was chosen as 0.1 second. The ABAQUS$^{\text{TM}}$/Standard finite element solver default convergence criteria based on displacement were used in the simulation.

3.2.1 Finite Element Mesh

To calculate the deformation of a soft organ during surgical simulation it is essential to include the detailed anatomical features of the organ in the model (Hing et al., 2007, Wittek et al., 2007, Miller et al., 2009). Traditionally, the process of generating patient-specific FE mesh contains numerous independent steps as shown in Figure 3.3. Therein, segmentation and high quality meshing are the most difficult tasks to perform efficiently. Manual segmentation of high-resolution volumetric image is a tedious and irreproducible task (Zhang et al., 2012). After segmentation, FE meshes are built based on extracted surfaces from the segmentation results.
Pre-processing Data

In this study, the geometry of the sheep brain was obtained through CT images. The CT images were acquired on a Toshiba Aquilion 16 CT Scanner in Royal Perth Hospital and the Figure 3.4 shows the Toshiba Aquilion 16 CT Scanner. The resolution of the images was 0.4 mm x 0.4 mm x 0.5 mm.
Segmentation

Image segmentation plays a crucial role in many medical-imaging applications, by automating or facilitating the delineation of anatomical structures and other regions of interest (Pham et al., 2000). In this study, to distinguish the brain parenchyma from the skull and other tissues, the CT images were segmented using 3D SLICER (www.slicer.org), an open source software package for visualization and image analysis developed by Artificial Intelligence Laboratory of Massachusetts Institute of Technology Surgical Planning Laboratory at Brigham and Women’s Hospital, Harvard Medical School.

Initially the sheep brain was segmented using the seed growing algorithm available in 3D SLICER. The automatic segmentation method tends to produce artefacts as different material/ anatomical structure may have the same intensity. Therefore, manual segmentation of each data set was performed on a slice-by-slice basis. The parenchyma was distinguished in the segmentation.

The hardware platform used was an Intel Core i5-750 CPU, 4 × 2.66 GHz, 8 GB RAM, Windows XP Professional ×64 Version, Version 2003, Service Pack 2. The Figures 3.5, 3.6 and 3.7 shows different views (axial, sagittal and coronal) of a segmented slice of the parenchyma. It should be noted that the sheep brain ventricles were found to be significantly small and therefore, they were not included in the segmentation.
Figure 3.5 A segmented slice (axial view) of the sheep head in 3D SLICER

Figure 3.6 A segmented slice (sagittal view) of the sheep head in 3D SLICER
Mesh Generation Using IA-FEMesh

Suitable meshes are required so that computational analysis of anatomical and geometrical information contained within CT scans can be conducted. 3D subject-specific sheep brain meshes were constructed from the segmented CT scan images. The mesh was generated using low-order elements (linear hexahedron). Generally, hexahedral elements are used to model behaviour of almost incompressible continua like brain. In this study, linear tetrahedral elements were not used to avoid volumetric locking (Bathe, 1996). While there are fast and accurate algorithms available for automatic generation of tetrahedral mesh (Viceconti et al., 2004), only few template-based algorithms are available for automatic generation of hexahedral mesh (Owen, 2001, Viceconti & Taddei, 2003). Therefore, IA-FEMesh (a freely available software
toolkit aimed at hexahedral mesh generation developed at the University of Iowa) was used to generate the volume mesh of the sheep brain consisting hexahedral elements only (Magnotta et al., 2008, Grosland et al., 2009). The previous experience from my research group (Wittek et al., 2004, Wittek et al., 2007) indicates that it requires several weeks of work of an experienced analyst to manually generate a patient-specific hexahedral mesh of the brain.

After segmentation, the digital models of 3D surfaces of the brain and ventricles were created using the Visualization Toolkit (VTK) binary format (Schroeder et al., 2002). Then the 3D geometry of the sheep brain was exported in STL format as triangulated surfaces. These surfaces formed the 3D Volume for the respective mesh definitions in IA-FEMesh. The first step towards generating mesh was to define building block structures for each of the brain surface definitions. The initial building block for the brain was defined by the outer boundary of the brain surface geometry. This block was then subdivided and the block vertices were repositioned closer to the surface to represent the brain surface geometry more accurately (see Figure 3.8).

Figure 3.8 Blocks created for the surface geometry of sheep brain
After defining the entire structure mesh seeding was assigned to the sub divided blocks based on an average element length and the mesh was then projected onto the surface and smoothed to accommodate distorted elements caused by areas of high curvature. The generated mesh of the brain in IA-FEMesh is shown in Figure 3.9.

![Figure 3.9 Generated Volume mesh of the sheep brain in IA-FEMesh](image)

The generated mesh in IA-FEMesh contained some elements having low Jacobian value (less than 1). Following Shepherd et al. (2007) and Ito et al. (2008) hexahedral elements with Jacobian of below 0.2 were regarded as of unacceptably poor quality. Therefore, the mesh quality was improved in Hypermesh™ through correcting of those poor quality elements having low Jacobian. This resulted in a brain mesh consisting of 25644 nodes and 22766 hexahedral elements and the minimum Jacobian value was 0.7. The final generated mesh is shown in Figure 3.10.
Chapter 3: Modelling The Brain-Skull Interface

The indentor and the skull were treated as rigid since they are orders of magnitude stiffer than the brain tissue and only the surfaces of them were included in this model. The skull surface mesh was created in Hypermesh™ by generating a layer of shell elements (3-node shell: S3 and 4-node shell elements: S4) wrapping the external surface of the brain and it consists of 5241 nodes and 5208 shell elements. The indentor surface mesh was also generated in Hypermesh™ using shell elements (3-node shell: S3 and 4-node shell elements: S4) and it consists of 1733 nodes and 3249 shell elements.
3.2.2 Element Formulation and Assignment of Material Properties

For FE discretisation, fully integrated hexahedral elements with hybrid formulation were used to prevent volumetric locking due to incompressibility of the brain tissue. Following Miller and Chinzei (1997) the brain tissue was modelled as a homogenous Ogden-type Hyperelastic material with the constitutive constants determined from the confined compression experiment as mentioned in section 3.1 whereas the skull and indentor were represented as rigid body. The position of the indentor was determined by using four reference markers (diameter 1 mm) placed at the four corners of the craniotomy area on the surface of the brain as mentioned earlier in section 2.1.1. The whole model is shown in Figure 3.13.
3.2.3 Loading and Boundary Conditions

Several previous studies modelled the needle insertion or indentation into soft tissue by applying a loading through prescribed nodal displacements (Hing et al., 2007, Wittek et al., 2008). While this is the simplest approach, the interactions between the soft tissue and the surgical instruments were not included in the model. In order to model the interactions between the indentor and brain tissue, a contact interface model was introduced between the indentor (rigid body) and brain (deformable body). For the contact between the front face of the indentor and the brain, surface to surface hard contact formulations with an augmented Lagrange constraint enforcement were applied (ABAQUS/CAE user’s manual, 2010). A rough contact behaviour (no-slip is allowed once points are in contact) was used to represent the no-slip boundary condition between the brain and indentor during the in-situ indentation experiments.

Figure 3.13 ABAQUS™ model for the in-situ brain indentation experiment
The loading was applied through prescribed motion of the reference point of the indentor mesh and with the constant speed of 12 mm/min. The skull nodes were rigidly constrained during the simulation.

### 3.3 Brain-Skull Interface Model

The objective of this study was to model the interaction of the brain-skull interface rather than replicating the physical structure of the brain-skull interface. Initially, I investigated the contact interaction parameters used in ABAQUS\textsuperscript{TM} (ABAQUS/CAE user’s manual, 2010) and found that while using contact interaction one has to calibrate many complex parameters which present significant difficulties to determine the mechanical properties of the brain-skull interface. Therefore, linear springs were used to represent the brain-skull interface. The brain-skull interface has been modelled using 5240 linear springs (Mazumder et al., 2012, Mazumder et al., 2013). These springs were connected between the brain and the skull to characterize the mechanical properties of the brain-skull interface. To include these linear springs between the brain skull interface axial connector elements in ABAQUS\textsuperscript{TM}/Standard finite element solver were used (ABAQUS/CAE User’s manual, 2010).

### 3.4 Chapter Summary

In this chapter a brief description of the modelling of uniaxial compression of the cylindrical brain tissue samples and \textit{in-situ} brain indentation test are presented.
Necessary pre-processing steps using SLICER 3D and Hypermesh™ to develop the models are also described. Additionally, the parameter selection in ABAQUS™ and the loading and boundary conditions are also reported. The brain-skull interface has been represented as a collection of linear springs by using connector elements in ABAQUS™. Later in Chapter 4 the results from these models are compared with the experimental ones.
In this study, the results of experiments on sheep brain indentation in the area of the brain-skull interface are presented and the information about the interface’s mechanical properties was derived by complementing analysis of the results of these experiments with brain modelling (using non-linear FE procedures). The verification of the finite element model for the brain-skull interface was done in terms of its ability to predict forces acting on the indentor and deformation of the brain due to these forces represented by the displacements of implanted X-ray opaque markers.

During the experiment, the forces acting on the indentor were determined by the load cell. The displacement of the X-ray opaque markers was determined from captured X-ray images by the two mobile C-arms. In the model, the forces acting on indentor were measured from the equations of the continuum mechanics. The displacements of the markers were calculated by using the shape functions of the first order hexahedron elements (Logan, 2001).

† Parts of this chapter appear in a paper (Mazumder et al., 2013) published in ACTA of Bioengineering and Biomechanics journal and in a paper (Mazumder et al., 2012) presented in 10th International Symposium Computer Methods in Biomechanics and Biomedical Engineering, Berlin, Germany.
4.1 Results of Experiments for Determining the Brain-Skull Interface Mechanical Properties

4.1.1 *In-situ* Indentation Experiments

From the *in-situ* indentation experiments the indentor force-displacement relationship was obtained. Figure 4.1 shows the five *in-situ* trial experiment results along with the results obtained from the main 1\textsuperscript{st} and 4\textsuperscript{th} experiment *in-situ* brain indentation experiments. The results from these trials were similar to the 1\textsuperscript{st} and 4\textsuperscript{th} experiments.

![Figure 4.1 Indentation of brain *in-situ*: experimental results for the reaction force-displacement relationship during trial and main experiments](image)

To assess the repeatability of the measurements for the force-displacement relationship, the average force-displacement with standard deviation bars is included in Figure 4.2.
Chapter 4: Results

The average force-displacement magnitude and the standard deviation values are obtained from the results from the five trials and two (1\textsuperscript{st} and 4\textsuperscript{th}) main \textit{in-situ} indentation experiments.

Figure 4.2 Indentation of brain \textit{in-situ}: average experimental results for the reaction force-displacement relationship during trial and main experiments

![Reaction Force vs Displacement Graph](image.png)

Figure 4.3 shows the measured force-displacement relationship from the 2\textsuperscript{nd} \textit{in-situ} indentation experiment. It was mentioned earlier in Section 2.1.3 that, the indentor hit the skull during this experiment. The force-displacement relationship obtained from this experiment is not similar to the results shown in Figure 4.1.
4.1.2 Uniaxial Compression Experiments of Cylindrical Brain Tissue Sample

From the uniaxial compression experiments the moving plate reaction force-time relationship was obtained. The measured reaction force-time relationship from the uniaxial compression test of subject-specific cylindrical samples (for cylindrical samples obtained from 1\textsuperscript{st}, 2\textsuperscript{nd} and 4\textsuperscript{th} \textit{in-situ} indentation experiments) is shown in Figure 4.4.
Chapter 4: Results

4.2 Results of Modelling for Determining the Brain–Skull Interface Mechanical Properties

4.2.1 Uniaxial Compression of Cylindrical Brain Tissue Sample

The comparison between the modelling and experimental force magnitude during uniaxial compression of the cylindrical brain tissue samples (for different subjects used in 1st, 2nd and 4th experiment) is shown in Figures 4.5, 4.6 and 4.7. The subject specific mechanical properties obtained from uniaxial compression tests are listed in table 4.1. For the determined subject-specific material properties, the model accurately predicted moving plate force-time history during the uniaxial compression experiments.
Chapter 4: Results

Figure 4.5 Uniaxial compression of cylindrical brain tissue sample: comparison of modelling and experimental results of the moving plate reaction force-time history (cylindrical sample from 1st indentation *in-situ* indentation experiment)

Figure 4.6 Uniaxial compression of cylindrical brain tissue sample: comparison of modelling and experimental results of the moving plate reaction force-time history (cylindrical sample from 2nd indentation *in-situ* indentation experiment)
Chapter 4: Results

Figure 4.7 Uniaxial compression of cylindrical brain tissue sample: comparison of modelling and experimental results of the moving plate reaction force-time history (cylindrical sample from 4th *in-situ* indentation experiment) (Mazumder et al., 2012, Mazumder et al., 2013)

Table 4.1 Determined subject-specific material properties of the cylindrical brain tissue samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Ogden Type Hyperelastic Material Constants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cylindrical Sample from 1st <em>in-situ</em> indentation experiment</td>
<td>( \mu ) (Pa)</td>
</tr>
<tr>
<td>Cylindrical Sample from 2nd <em>in-situ</em> indentation experiment</td>
<td>480</td>
</tr>
<tr>
<td>Cylindrical Sample from 4th <em>in-situ</em> indentation experiment</td>
<td>720</td>
</tr>
</tbody>
</table>
4.2.2 In-situ Brain Indentation

Figure 4.8 shows the comparison between the calculated and experimentally measured indentor force-displacement relationship during the 4th in-situ brain indentation experiment. By using the subject-specific material properties ($\mu = 720$ Pa and $\alpha = -4.7$) determined in the previous section and the linear springs (overall stiffness $11.45 \text{N/mm}^{-1}$) representing the brain-skull interface, the model of in-situ brain indentation accurately predicted indentor force-displacement relationship during the experiment. For an indentation up to 4.8 mm, the error in the force magnitude is less than 5%.

![Figure 4.8 Indentation of sheep brain in-situ (4th experiment): comparison of modelling and experimental results (Mazumder et al., 2012, Mazumder et al., 2013)](image-url)
4.3 Mechanical Properties of the Brain-Skull Interface: Results and Their Validation

The brain-skull interface was represented using 5240 linear elastic springs (each having 0.3 mm length) connecting the nodes on the outer boundary of the brain model and skull.

Linear springs have been previously used to represent the interface between the brain and skull for investigating brain injury biomechanics. For instance Coats et al. (2012) used spring connectors to represent the pia-arachnoid complex with cerebrospinal fluid and cortical vasculature (PCC) for predicting brain strain and brain-skull displacement and found that using spring connectors to represent the PCC resulted in a better match to brain strain measurements. Feng et al. (2010) used springs to represent the brain-skull interface and investigated the relative brain displacement and deformation during constrained mild frontal head impact. Baghaei et al. (2011) also used springs to model the meningeal layers between the brain and the skull to investigate the brain motion due to blunt head impact.

The interface stiffness (defined as sum of stiffnesses of the springs divided by the interface area) was varied to obtain good agreement between the calculated (using the model summarised in Chapter 3.4) and experimentally measured indentor force-displacement relationship. Such agreement was found to occur for the brain-skull interface stiffness of $11.45 \frac{N\text{mm}^{-1}}{\text{mm}^2}$ (Mazumder et al., 2012, Mazumder et al., 2013).

The brain-skull interface model was verified through comparison between the experimentally measured and predicted 3D displacements of the X-ray opaque markers.
implanted inside the brain. The comparison of the 3D displacements of the markers between the experimentally measured values and predicted modelling values is listed in Table 4.1. As the markers were not located at the vertices of the brain model mesh, the markers movement were computed from the nodal displacement using shape functions of the first order hexahedral element (Logan, 2001).

Table 4.2 Estimated Marker displacements from the 4th in-situ indentation experiment and modelling (Mazumder et al., 2013)

<table>
<thead>
<tr>
<th>Markers</th>
<th>X(mm)</th>
<th>Y(mm)</th>
<th>Z(mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker-1</td>
<td>-0.06</td>
<td>0.61</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>-0.17</td>
<td>1.09</td>
<td>0.82</td>
</tr>
<tr>
<td>Marker-2</td>
<td>0.23</td>
<td>0.41</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>0.46</td>
<td>0.88</td>
<td>1.75</td>
</tr>
<tr>
<td>Marker-3</td>
<td>0.12</td>
<td>0.31</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>0.21</td>
<td>0.61</td>
<td>1.53</td>
</tr>
</tbody>
</table>

The maximum, minimum and average value of the differences between the experimentally measured displacement and predicted marker’s displacement are listed in Table 4.3. The average difference of displacement magnitude was 0.6 mm. The direction of marker movement indicates that the model predicted the brain deformation accurately which is shown in Table 4.2.

Table 4.3 Differences in marker displacements between the 4th in-situ indentation experiment and modelling (Mazumder et al., 2013)

<table>
<thead>
<tr>
<th>Unit (mm)</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displacement in the X direction</td>
<td>0.23</td>
<td>0.08</td>
<td>0.14</td>
</tr>
<tr>
<td>Displacement in the Y direction</td>
<td>0.47</td>
<td>0.29</td>
<td>0.41</td>
</tr>
<tr>
<td>Displacement in the Z direction</td>
<td>0.7</td>
<td>0.28</td>
<td>0.44</td>
</tr>
<tr>
<td>Magnitude</td>
<td>0.8</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

It was possible only to obtain the displacements of three X-ray opaque markers from the images during the 4th in-situ indentation experiment. During the specimen
preparation five markers were inserted during the specimen preparation. But two markers were occluded from the view of the mobile C-arm by the 5948 Micro Tester during the 4th in-situ indentation experiment due to the complex setup of the equipment. Therefore, those markers were not visible in the X-ray images. It should be noted that, inserting markers into brain using cannula is a task requiring manual skills and it was not possible to detect the occlusion of those two markers in real time prior to start of the in-situ indentation experiment considering the complex experimental set up.

4.4 Chapter Summary

From the results presented in Section 4.1, 4.2 and 4.3 it is evident that the developed Finite Element Model for in-situ indentation test accurately predicts the force-displacement relationship of the indentor and 3D displacements of the implanted X-ray opaque markers that represent the local deformation of the brain (see Table 4.2). By using linear springs to represent the brain-skull interface, a good agreement between the calculated and the experimentally measured force-displacement relationship were obtained in a simulation of in-situ brain indentation (see Figure 4.8) and the brain-skull interface stiffness was determined as $11.45 \, \frac{N \, mm^{-1}}{mm^2}$.
DISCUSSION

In this study, the results of experiments on sheep brain indentation in the area of the brain-skull interface are presented and the information about the interface’s mechanical properties are derived by complementing analysis of the results of these experiments with brain modelling (using non-linear FE procedures). This allowed distinguishing between the contribution of the brain tissue and the interface to the reaction force exerted on the indentor. By using linear springs to represent the brain-skull interface, a good agreement between the calculated and the experimentally measured force-displacement relationship were obtained in a simulation of in-situ brain indentation.

It is hypothesised that the minor differences between the experimental and modelling results observed in this study could be attributed to inaccuracies in determining the geometry of the brain. It should be noted that although the inaccuracies in prediction of the brain deformations of an order of 0.6 mm observed in this study may seem large from the perspective of engineering computations in mechanical design, they are highly accurate in the context of computational biomechanics for medicine. Accuracy of image-guided neurosurgery is limited by the resolution of intraoperative magnetic resonance MR images, which is of an order 1 x 1 x 2.5 mm even for state-of-the-art intraoperative MR scanners.
Therefore, the discrepancies between the positions obtained experimentally and those predicted through modelling X-ray marker positions may be considered minor. One possible explanation for this can be the fact that accuracy of determining the brain geometry when constructing computational grids (finite element meshes) is limited by the resolution of available medical image acquisition techniques (in this study the resolution of the CT scan was 0.6 x 0.6 x 0.5). I followed commonly used processes/methods when building the model of a given geometry. The discrete representation of the anatomy of interest is obtained from an intensity image by employing two steps, segmentation and meshing. Segmentation of anatomical features has been investigated in several medical contexts using numerous different approaches (Sonka & Fitzpatrick, 2000). Although, fully automatic image segmentation algorithms are available, yet it is still not possible to apply an automatic image segmentation algorithm with a guaranteed performance in the general case. In most cases during segmentation manual intervention is required, not only demanding the scarcely available time of surgeons but also preventing an automated modelling for FEM. The manual method for segmentation is based on slice-editing. In this study the segmentation of the brain was conducted using 3D SLICER. Firstly, an automatic seed growing algorithm was applied to segment the brain. Then manual corrections were conducted on individual slice of the brain. However, it should be noted that during this process a skilled operator uses a computer mouse, pen, or trackball traces in the region of interest on each slice of the volume and it poses several drawbacks, such as difficulties in obtaining reproducible segmentation results, difficulties in comparing measurements from different operators, and difficulties deducing 3D structure from 2D slices. Unfortunately, there is no commonly accepted method to quantify errors during segmentation process and their effects on the results obtained using finite element
models (such as those I used) that rely no segmentation to determine geometry of the analysed continua.

5.1 Specimen Preparation for In-Situ Indentation Experiments

The specimen (sheep skull) used during in-situ indentation experiments was membranous, tractable, and extremely challenging to be dissected. The applied laboratory techniques to prepare the specimen and insert X-ray opaque markers inside the brain through cannula were difficult. In this study, sheep heads were collected from an abattoir and they were kept at constant temperature of 4°C to avoid the alteration of the mechanical properties of the brain-skull interface. The heads were also placed in an upside down position to avoid loss of CSF and blood from the brain before the specimen preparation. During specimen preparation some part of the brain and the brain-skull interface were removed. The brain lost some CSF and blood through this process which might cause dehydration. To the best of my knowledge, there is no study available in the literature that has investigated the alteration of structural and mechanical property in the brain and meningeal tissue due to dehydration phenomena.

5.2 Determining the Displacement of the X-Ray Opaque Markers from X-Ray Images

In this study, the model for in-situ brain indentation experiment was verified by comparing the predicted displacement of the X-ray opaque markers with those derived from the experiment. It should be noted that implanting markers inside the brain by
using a cannula and a wire was an extremely difficult task. During the specimen preparation five X-ray opaque markers (0.6 mm diameter) were inserted into the brain. They were inserted in the proximity of the area of indentation. But it was not possible to track their position in real time while preparing the specimen. After conducting the experiments, while analysing the X-ray images to determine the marker displacements it was found that two of the markers were occluded by the 5948 Micro Tester during the test due to the complex setup of the equipment (C-arms, 5948 Micro Tester, Perspex tray etc.). As a result it was not possible to track those two markers from the X-ray images.

5.3 Using One Cylindrical Sample to Determine Subject-Specific Mechanical Properties of Brain

In the current study, only one cylindrical sample was used to determine the subject-specific mechanical properties of the brain. During in-situ indentation experiment the left hemisphere of the brain was indented. As a result after in-situ indentation experiment it was not possible to collect tissue from that part of the brain. The tissue sample was collected from the right hemisphere of the brain as it was not damaged during the test. Unfortunately, sheep brain is very small and it was impossible to collect more than one cylindrical sample from the right hemisphere of the brain.

5.4 Experiments to Determine the Mechanical Properties of the Brain-Skull Interface

The results presented here are based on four in-situ indentation experimental
studies. Therefore, one may expect the modelling of all *in-situ* indentation experiments to be built before establishing the modelling of the brain-skull interface. However, this is a first ever experiment of its kind. The preparation and method to conduct the experiment were very challenging. Firstly, the equipment (CT, Mobile C-arms and 5948 Micro Tester) used during the experiments were primarily utilized for the patients in the hospital. As a result the facility was not available on regular basis. Secondly, the appointment for using the facility to conduct the experiments was scheduled one or two months prior to the date of the main experiment. The experiments were scheduled during after-hours periods for once in a month only. Thirdly, the assistance of technicians for operating CT scan, Mobile C-arms, Micro Tester 5948 was required during this after hours period. Such scenarios present significant challenge to conduct the experiments to determine the mechanical properties of the brain-skull interface. Despite this advance planning, the 3rd experiment was called off due to the emergency arrival of a patient. Additionally, the mobile C-arms got damaged due to hardware issue after the conduction of 1st experiment and the X-ray images were unavailable. Due to this the location of the reference markers (used to determine the indentor location during *in-situ* brain indentation experiment) was unknown and therefore the modelling of the 1st *in-situ* brain indentation experiment was not conducted. Furthermore, during the 2nd *in-situ* brain indentation experiment the indentor hit the skull (see Figure 4.3) and the mechanical behaviour of the brain during *in-situ* indentation could not obtained. Consequently, the modelling of the 2nd *in-situ* brain indentation experiment was not done as well. Hence, the modelling of the *in-situ* brain indentation was done for the 4th experiment only. It should be noted that, due to the complexity of the experimental setup of *in-situ* indentation experiments, five *in-situ* sheep brain indentation trials were conducted before conducting the main four experiments using CT and X-ray imaging.
The results from those trials are shown in Figure 4.1.

5.5 Use of Sheep Brain to Determine the Mechanical Properties of the Brain-Skull Interface

In this study sheep brains were selected to determine the mechanical properties of the brain-skull interface as the surrogate of human brain taking into consideration of size and availability. Besides sheep, the previous studies used different species (such as bovine and porcine) to determine the mechanical properties of the meninges (Jin et al., 2006, Jin et al., 2007, Jin, 2009, Tunturi, 1978, Ozawa et al., 2004, Kimpara et al., 2006). However, further information is not available in the literature to correlate the mechanical properties of the brain-skull interface to those of other species. In order to determine the mechanical properties of the human brain-skull interface, similar experiments using human head should be conducted in the future.
CONCLUSIONS

Knowledge of the mechanical properties of the brain-skull interface is required when developing biomechanical models of the brain for applications predicting brain shift during surgery. So far, this knowledge has been rather limited. The focus of this work was to characterize the material behaviour of the brain-skull interface.

Firstly, \textit{in-situ} indentation of sheep brain was conducted and the reaction forces on the indentor were measured. To determine the deformation field within the brain, X-ray opaque markers were implanted inside the brain and two mobile C-arms were used to capture their displacements during \textit{in-situ} indentation experiments. Subsequently, a cylindrical sample of brain was extracted and uniaxial compression test was conducted to determine the subject specific mechanical properties. The calibration of the X-ray image intensifiers were done to correct any distortion present in the images. The 3D coordinates of the markers were triangulated from those images. Finally, a nonlinear Finite Element Model of the \textit{in-situ} indentation experiment was built in the FE solver ABAQUS\textsuperscript{TM} and the properties of the brain-skull interface models were calibrated so that the calculated indentor reaction forces matched those measured experimentally. The 3D displacements of the X-ray opaque markers were obtained from the nodal displacements predicted by the FE model.

It was found that the developed FE Model accurately predicts the force-displacement relationship of the indentor and 3D displacements of the implanted X-ray
opaque markers that indicate the local deformation of the brain (see Table 4.2). By representing the brain-skull interface as linear springs, we obtained good agreement between the calculated and the experimentally measured force-displacement relationship (see Figure 4.8) and the brain-skull interface stiffness was determined as $11.45 \frac{Nm}{mm^2}$.

Accurate material properties of the brain-skull interface will help to develop a biomechanical model of the brain to predict brain shift. The focus of this work was to characterize the material behaviour of the brain-skull interface. Despite some limitations, this study presents the first ever experimentally determined mechanical properties of the brain-skull interface with quantitative assessments of the brain deformation. The results reported in this study will be useful to properly model the brain-skull interface, an important component of the computational model of human brain. Such an improved representation of the in-situ brain-skull interface will lead to an improved prediction for brain shift during neurosurgery. More experimental work is necessary to validate the mechanical properties of the brain-skull interface. One should be careful when extrapolating these results to human brain. Similar experimental and computational investigation should be conducted to correlate the results from this study to human brain.
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