THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

in

MACHINE AND VEHICLE SYSTEMS

Traumatic Brain Injuries: Animal Experiments and Numerical Simulations to Support the Development of a Brain Injury Criterion

JACOBO ANTONA-MAKOSHI

Division of Vehicle Safety
Department of Applied Mechanics
CHALMERS UNIVERSITY OF TECHNOLOGY
Gothenburg, Sweden, 2016

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JACOBO ANTONA-MAKOSHI

ISBN 978-91-628-9848-9 (Print)

ISBN 978-91-628-9849-6 (PDF)

Doktorsavhandlingar vid Chalmers tekniska högskola

ISSN: 0346-718X

Department of Applied Mechanics

Chalmers University of Technology

SE-412 96 Gothenburg

Sweden

Telephone +46(0)31 7721000

Printed by Chalmers Reproservice

Gothenburg, Sweden, 2016

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Abstract

Traumatic Brain Injuries (TBIs) account for about half of the 1 300 000 annual traffic related deaths and the 50 000 000 injuries worldwide. The burden of TBI is ethically unacceptable and economically unsustainable. Recognising the efforts and achievements in reducing TBI conducted by the vehicle industry, research institutions and academy worldwide, the problem still call for additional research that lead to prevention of TBI. The main aim of this thesis is to develop a brain injury criterion and associated injury thresholds that can be used with crash test dummies in the design of safer cars.

The craniocervical motion that produces diffuse brain injuries in experimental settings with animals was investigated by introducing finite element (FE) models of the animals. One rat and one monkey brain FE model were developed from medical images of the animals and validated using experimental data. The validated rat model was applied to simulate sagittal head rotational acceleration experiments with rats. Sequential analysis of the trauma progression indicated that acute subdural haematoma occurred at an early stage of the trauma, while diffuse axonal injury likely occurred at a later stage. The validated monkey model was applied to simulate past head impact experiments with primates that typically produced concussion symptoms. The analysis revealed large brainstem strains supporting the hypothesis that concussions are produced due to mechanical loading of the brainstem. These results also indicate the need to incorporate the craniocervical motion in human FE models and physical test devices in the development of countermeasures for concussive injury prevention.

A method to make primate brain injury experimental data applicable for humans was also investigated. The monkey FE model was used to simulate 43 primate head impact experiments. Brain tissue injury risk curves that relate probability of injury, obtained in the experiments, with brain strains estimated in the simulations were developed. By assuming comparable mechanical properties of the brain tissues in monkeys and humans, these risk curves were applied to estimate injury risk in 76 impacts simulated with a human head-neck FE model which was also developed and validated for the purpose of this investigation. Overall, the investigated method proved to be technically feasible and to provide biomechanically justifiable means to related craniocervical kinematics and brain strains. This method accounts for contact phenomena typical from vehicle crash like head impacts, which past scaling techniques did not.

Finally, new conceptual global brain injury criterion and injury risk functions that have the potential to predict the risk of diffuse brain injuries, were developed. The concept, denoted as Brain Injury Threshold Surface (BITS), establishes equal brain injury risk surfaces as a function of time-dependent and combined translational and rotational head kinematics typical in head impacts in car crashes. BITS appeared to explain the variance seen in both concussion from the monkey experiments and brain strains levels from the simulations with the monkey and the human brain FE models. Although evaluations of the new criteria and associated risk surfaces are pending, these have the potential to guide the development of superior restraints which would reduce the number and severity of brain injuries in future traffic accidents.

Keywords: traffic safety, traumatic brain injuries, concussions, animal experiments, finite element method.

List of Appended Papers

Paper I

Antona-Makoshi, J., Davidsson, J., Risling, M., Ejima, S., Ono, K., 2014. Validation of Local Brain Kinematics of a Novel Rat Brain Finite Element Model under Rotational Acceleration, International Journal of Automotive Engineering, Vol.5, No.1, pp.31-37.

Division of work between authors: Antona-Makoshi designed the study and conducted the modelling. Davidsson supervised the study and conducted the experiments. Antona-Makoshi supported Davidsson with the preparation and execution of the experiments. Risling provided environments for experimental training and medical images. Antona-Makoshi wrote the paper. Davidsson provided active support in writing the paper. Ejima, Risling and Ono supervised, provided scientific guidance and reviewed the paper.

Paper II

Antona-Makoshi, J., Eliasson, E., Davidsson, J., Ejima, S., Ono, K. 2015. Effect of Aging on Brain Injury Prediction in Rotational Head Trauma—A Parameter Study with a Rat Finite Element Model. Traffic Injury Prevention, Vol.16, No sup1, pp. S91-S99.

Division of work between authors: Antona-Makoshi and Eliasson planned the study together under the supervision of Davidsson and Ejima. Simulation work was conducted by Eliasson under the guidance of Antona-Makoshi. Antona-Makoshi led the writing of the paper with the support of Eliasson. Davidsson provided experimental data, scientific guidance and active support in writing the paper. Ejima and Ono supervised, provided scientific guidance and reviewed the paper.

Paper III

Antona-Makoshi, J., Davidsson, J., Ejima, S., & Ono, K. 2012. Reanalysis of Monkey Head Concussion Experiment Data using a Novel Monkey Finite Element Model to Develop Brain Tissue Injury Reference Values. IRCOBI Conference, Dublin, Republic of Ireland.

Division of work between authors: Antona-Makoshi conducted the literature review, experimental data re-organisation and analysis, modelling and wrote the paper. Davidsson supervised on a daily basis and provided active support in writing the paper. Ejima and Ono supervised, provided scientific guidance and reviewed the paper.

Paper IV

Antona-Makoshi, J., Davidsson, J., Ejima, S., Ono, K., Brolin, K., Anata, K., 2013. Correlation of Global Head Kinematics and Brain Tissue Injury Predictors to Experimental Concussion Derived from Monkey Head Trauma Experiments. IRCOBI Conference, Gothenburg, Sweden.

Division of work between authors: Antona-Makoshi conducted the literature review, experimental data re-organisation and analysis, and modelling. Anata provided support with the experimental data analysis. Antona-Makoshi wrote the paper. Davidsson and Brolin provided scientific guidance and active support in writing the paper. Ejima and Ono supervised, provided scientific guidance and reviewed the paper.

Paper V

Antona-Makoshi, J., Davidsson, J., Ejima, S., Ono, K., 2016. Development of a Comprehensive Injury Criterion for Moderate and Mild Traumatic Brain Injuries. International Journal of Automotive Engineering, Vol.7, No.2, pp. 69-75.

Division of work between authors: Antona-Makoshi conducted the literature review, experimental data re-organisation and analysis, and modelling. Antona-Makoshi wrote the paper. Davidsson provided scientific guidance and active support in writing the paper. Ejima and Ono supervised, provided scientific guidance and reviewed the paper.

Paper VI

Antona-Makoshi, J., Holcombe, S., Ono, K., Davidsson, J., 2016. Development of a Brain Injury Criterion and Associated Thresholds. In preparation for Journal submission.

Division of work between authors: Antona-Makoshi and Davidsson planned the study together. Antona-Makoshi conducted the literature review, the modelling, and wrote the paper. Holcombe performed the programming to process the data analysis, provided scientific guidance and reviewed the paper. Ono supervised and provided scientific guidance. Davidsson provided scientific guidance and active support in writing the paper.

Preface

The work presented in this thesis was carried out at the Japan Automobile Research Institute, Department of Safety Research and at the Injury Prevention Group, at the Vehicle Safety Division, Department of Applied Mechanics at Chalmers University of Technology under the supervision of Associate Professor Johan Davidsson and Professor Karin Brolin from 2011 to 2016. The research was funded by the Japan Automobile Research Institute Advanced Research Program and by Chalmers Area of Advance, Transport.

Acknowlegements

To Eri, Nina, Koto ... and those to come (?): This thesis has been conducted in parallel to the construction of this family. It has taken away a lot of precious time of the, so far, happiest period of my life. Eri, I admire your strength and generosity during the challenging pregnancies, deliveries and care of our kids. Not a day goes by without me thinking about how fortunate I am for having you all. I love you.

To Johan Davidsson: Being a good PhD supervisor is an extremely difficult task, but you have succeeded and in a way that always kept my motivation high. You have also been the key person that boosted my interest in both science and education. You have my deepest respect and lifetime appreciation. Thank you.

To Susumu Ejima: This thesis started the day I let my frustrations go... and threw them at you. My personal and professional integration in Japan has been, by far, my most challenging undertaking. You played a major role to make a success of it. You have been my educator, my colleague, my boss and my friend during the most critical years of this thesis. Thank you.

To Koshiro Ono: I remember the day you came to my desk with a bunch of old and dusty documents. Those documents contained what is, in my humble opinion, the most valuable experimental data set in the history of impact biomechanics research. Your legacy is in good hands. Especial acknowledgement for that email you sent me when I was at high risk of derailing (2012/03/17). Thank you.

To Karin Brolin, Mats Svensson and Mårten Risling: For your valuable supervision and guidance at different stages of this thesis and your always encouraging words. Thank you.

To Kozo Watanabe: None of the wonderful things that have happened to me since 2008, including this thesis, would have been possible without your unconditional support. For any reason, I felt you treated me as you would have your own son. I hope you feel proud of me as a father would. Thank you.

To my colleagues at JARI: Former president Toshio Kobayashi, Minoru Sakurai, Kunio Yamazaki, Takeshi Harigae, and Atsuhiro Konosu for giving me the freedom I needed to develop my scientific curiosity. Yoshihiro Yamamoto for generosity taking the majority of the 'dirty work', allowing me to concentrate on this thesis. Hisashi Imanaga, Koji Mikami and Ryohei Honma for those countless refreshing coffee breaks and nomikai. Thank you.

To Sven Holcombe: I am not sure if I ever told you, but I am convinced that your frustrating experiences in Japan were crucial for my success. I enjoyed our technical and philosophical talks related to this thesis, but I have enjoy the rest of our talks even more. Also, congratulations for the news you gave me a few days before printing this thesis. I can’t wait until the date we can all meet up. Cheers mate.

To Orlando Sanchez and Sébastien Vauclair: The first year of this thesis we spent together in Gothenburg was as wonderful as our times as students at Chalmers. I am happy to know that life keeps on giving me chances to meet you from time to time. Thank you friends.

A mis padres y hermanos: Gracias por apoyarme en todo lo que he hecho en mi vida. Las circunstancias me ha llevado muy lejos de vostros, pero nunca he dejado de percibir vuestro apoyo. Espero que estéis orgullosos de mi. Os quiero.

Nomenclature

α	Rotational/Angular Acceleration
ω	Rotational/Angular Velocity
2D	Two-dimensional
3D	Three-dimensional
AIS	Abbreviated Injury Scale
ATD	Anthropomorphic Test Device
BrIC	Brain Rotational Injury Criterion
BITS	Brain Injury Threshold Surface
CSDM	Cumulative Strain Damage Measure
CSF	Cerebro Spinal Fluid
CG	Centre of Gravity
CNS	Central Nervous System
CR	Centre of Rotation
CT	Computed Tomography
DAI	Diffuse Axonal Injury
FE	Finite Element
FMVSS	Federal Motor Vehicle Safety Standards
GAMBIT	Generalised Acceleration Model for Brain Injury Threshold
Global NCAP	Global New Car Assessment Program
HIC	Head Injury Criterion
HIP	Head Injury Power
JARI	Japan Automobile Research Institute
KTH	Kungliga Tekniska Högskolan
MPS	Maximum Principal Strain
MRI	Magnetic Resonance Imaging
MS	Milliseconds
M/S	Meter per second
NHP	Non-Human Primate
NHTSA	National Highway Traffic Safety Administration, USA
PMHS	Post Mortem Human Subject
RIC	Rotational Injury Criterion
RMDM	Relative Motion Damage Measurement
RVCI	Rotational Velocity Criterion Index
SDH	Sub-Dural Haematoma
SIMon	Simulated Injury Monitor
SUFEHM	Strasbourg University Finite Element Head Model
TBI	Traumatic Brain Injury
THUMS	Total Human Model for Safety, developed by Toyota Motor Corporation in cooperation with Toyota Central R&D Labs Inc.
VMS	Von Mises Stress
WHO	World Health Organization
WSU	Wayne State University, USA
WSTC	Wayne State Tolerance Curve

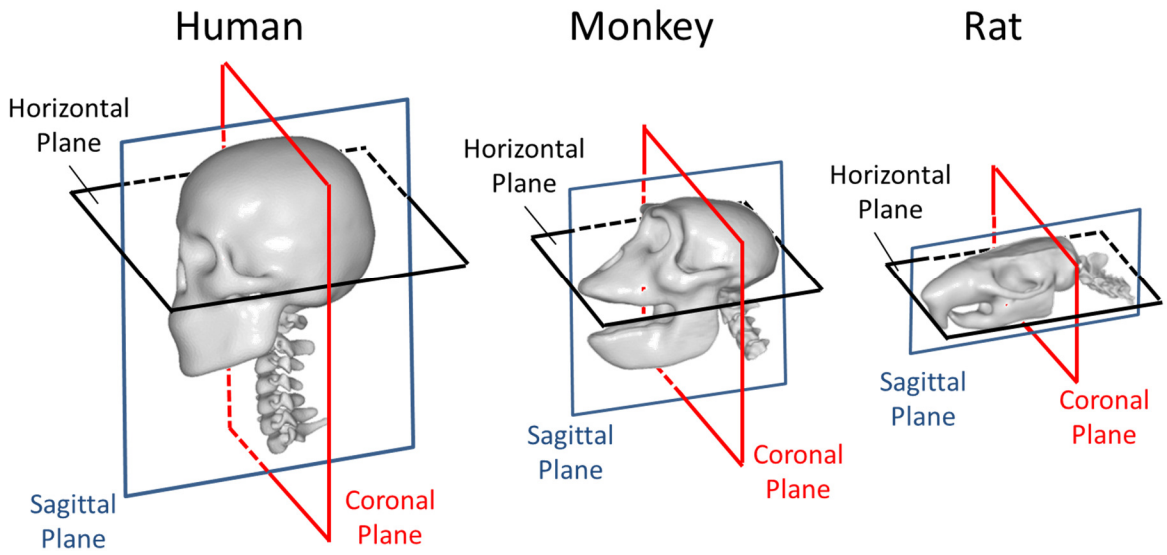

Figure 0.1: Head anatomical planes for Human (left), Monkey (middle), and Rat (right).

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1. Introduction

Traumatic Brain Injuries (TBIs) account for about half of the 1 300 000 annual traffic related deaths and the 50 000 000 traffic related injuries worldwide (World Health Organization 2013). Vehicle occupants comprise the largest group of road traffic deaths by road user type in high-income countries. Pedestrian and other vulnerable road users' deaths are predominant in low and mid-income countries (World Health Organization 2013). TBIs are the main cause of death and severe injuries amongst most vehicle crash types and population groups, being children, young adults and the elderly who are at higher risks than mature adults (Bruns & Hauser 2003; Bener et al. 2010). Other activities add to the high frequency of TBIs; 60% of all deaths in hospitals among children and young adults in the western world are a consequence of TBI (Melvin & Yoganandan 2015), 1 400 000 emergency department treatments per year in the US (Faul et al. 2010) and 1 000 000 hospital admissions annually in the European region (Deck & Willinger 2008). TBIs produce a total estimated annual medical cost in the US of USD 76.5 billion (Faul et al. 2010). Comprehensive estimations of social costs per body region injured in vehicle crashes in the US, including medical costs, emergency services, lost work wages and loss of quality of life, among others, point at TBIs as the second most costly injury after spinal cord injuries (Zaloshnja et al. 2004). Concussions are the most common moderate-to-serious type of TBI in motor vehicle crashes (Viano & Parenteau 2015). These injuries may occur at relatively low crash severities (Addendum) and their consequences are often irreversible, causing sequelae, long term pain and disability (Iverson et al. 2005). Acute subdural haematomas (ASDHs), diffuse axonal injuries (DAIs) and brainstem injuries are three of the most common types of severe and fatal brain injuries (Gennarelli & Thibault 1982; Sawauchi et al. 2007, Addendum). These types of injuries occur in traffic less frequently than concussions and at higher collision speeds, but their consequences are often devastating (Addendum). Despite the ever-improving vehicle occupant protection (European Comission 2012; NHTSA 2012), prevention strategies of traffic related TBIs must still be assigned top priority.

Vehicle industry utilises Anthropomorphic Test Devices (ATDs) and mathematical models of these ATDs and of humans to evaluate safety of new products in crash tests and simulated crashes. These evaluation methods require injury criteria and injury risk functions that relate measurements from the physical tests or simulated crashes with the risk of injuries in humans. Depending on the tools utilised and the injuries studied, such measurements can vary from global level (i.e. head acceleration obtained with accelerometers installed in ATDs) to tissue level (i.e. brain tissue strains estimated using mathematical models of the brain). Hence, the effectiveness of improvements introduced in new vehicles in reducing risk of injuries in traffic accidents is directly, and to a large extent, conditioned by the injury criteria and injury risk functions utilised. These must differentiate injurious from non-injurious conditions at loading conditions of interest (Kent 2002, Mendoza-Vazquez 2014). The Head Injury Criterion (HIC) (Gadd 1966, Versace 1971), currently the only head injury criterion in use in vehicle regulations such as the Federal Motor Vehicle Safety Standards 208 (FMVSS208) and in the Global New Car Assessment Program (Global NCAP), predominantly calculates the risk of skull fracture from the resultant translational head acceleration over time. The HIC has been used extensively over several decades and contributed to a substantial reduction of vehicle collision related head injuries. However, since there is no consistent relation between linear skull fractures and neural injuries (Gennarelli 1980; Cooper 1982; Chapon et al. 1983; Melvin & Yoganandan 2015), the effectiveness of HIC in reducing TBIs is questioned. The HIC is also criticised for not considering important factors such as impact direction, area of contact, stiffness of the impacting surface, and head rotational kinematics induced by oblique impacts or when the torso is restrained (McElhaney 2005). In addition, HIC was originally developed for severe head injuries and it may not be suitable for prediction of moderate and mild TBIs, which predominantly occur in the absence of skull fractures (Got et al. 1983; Gennarelli et al. 1987). Several past and currently ongoing research projects have opted for the development of rotational brain

injury criteria that are complementary to the HIC. Despite these efforts, there is no consensus on the combination of criteria suitable for skull and brain injury assessments with ATDs. In other words, criteria that can be used with ATDs and mathematical models of humans in all types of crash testing, that also account for rotational head kinematics and that can predict mild, moderate and severe TBIs should be made available.

Injury data from tests with Post Mortem Human Subjects (PMHSs) can be paired with data from reconstructions of these tests with ATDs (Davidsson et al. 2014) or mathematical models of the human (Mendoza-Vazquez 2014) for the development of injury risk functions using statistical methods. One advantage of this approach is that the risk function is valid for the ATD or the mathematical model of the human which are also to be used in tests carried out to support product development. Hence, differences between the ATD or the mathematical model of the human and the human surrogate (the PMHSs) are compensated for. However, since most TBIs cannot be diagnosed in PMHSs, TBI criteria and risk functions cannot be developed with this methodology. An alternative is to pair real-world event data with reconstructions using ATDs or mathematical models of the human. Such alternative requires non-invasive instrumentation of humans to capture head kinematic data from real-world events in which they are at risk of suffering head impacts, such as in motorsports (Melvin et al. 1998) and contact sports, such as American football (Rowson et al. 2012) or ice hockey (Zuckerman et al. 2015). However, this methodology has its limitations due to lack of accuracy of the measurements of the head kinematics due to uncoupling between the instrumented helmet and the head of the player. In addition, this method introduces difficulties in isolating effects of impact direction on injury risk and thereby limiting the opportunity to understand the head-neck kinematics producing the injuries. Further, the method commonly lack measurements of vital signs immediately after the impact and the diagnosis methods used are non-invasive. Another alternative to the PMHS method that has been used extensively in the past for the development of brain injury risk functions is to scale experimental animal data.

Utilising living non-human primates as human surrogates, when investigating brain injury mechanisms and tolerance, was common in research practice in the past (Ommaya & Hirsch 1971; Abel et al. 1978; Ono et al. 1980; Gennarelli et al. 1982). Some of the experimental series contributed to the development of the HIC, in combination with PMHS and volunteer tests comprising military volunteers (Snyder 1971). Despite their high research value, the ethical controversy put all work using primates to a sudden halt in the early 1980s. Since then, non-primate animals such as miniature pigs (Fievisohn et al. 2014), sheep (Anderson et al. 2003), ferrets (Ueno et al. 1995) and rats (Marmarou et al. 1994; Davidsson et al. 2009; Davidsson & Risling 2011; Stemper et al. 2015) have become preferred surrogates for humans in TBI biomechanics research.

One important scientific concern when utilising animals as surrogates for humans in the development of brain injury risk functions is the need for scaling the data prior to use with ATDs. The scaling methods used in the past (Holbourn 1943; Ommaya et al. 1967; Stalnaker et al. 1973; Ono et al. 1980) were based on assumptions that have been scarcely validated and heavily criticised (Ommaya 1985; Margulies & Thibault 1992; McElhaney 2005; Davidsson et al. 2009; Rowson et al. 2012). The most commonly adopted scaling method was based on the similarity principles between species; Holbourn (1943) stated that the level of rotational acceleration required to produce injury in brains with similar properties and shapes is inversely proportional to the ⅔ power of the masses of the brain. The scaling by Holbourn requires that the brain acts as an elastic medium, and that the brain tissue is homogeneous and isotropic in nature. These requirements are not fulfilled since it is well established that brain tissue behaves as a non-linear (Bilston et al. 1997), viscoelastic (Arbogast & Margulies 1998; Darvish & Crandall 2001; Prange & Margulies 2002), anisotropic (Shuck & Advani 1972; Arbogast & Margulies 1998) and inhomogeneous material (Gefen et al. 2003; Elkin et al. 2010; Elkin et al. 2011; Elkin & Morrison 2013). The scaling suggested by Holbourn also requires that animal and human brains are geometrically similar, which they to some degree are for primates but not for rodents, sheep, or swine. Since the Holbourn

scaling method has been based on scarcely validated and heavily criticised assumptions, other scaling techniques should be adopted.

Recent efforts have attempted to improve past scaling in the development of brain injury criterion at tissue level by applying scaled animal head kinematics data to a special type of mathematical model of the human head, a Finite Element Model (FE model) of the human head. Thereafter, tissue brain injury risk functions were developed by combining tissue strain data from the FE model of the human head with injury data from the animal tests (Takhounts et al. 2013). This method does, however, not allow establishing correlation between the animal head-neck kinematics and the injuries produced; predicted brain strains are not expected to be identical in the animal and the human head when scaled head kinematics are applied to the two FE models. A better approach to overcome this limitation is to reconstruct the experiments using FE models of the animal specimens. By using this approach, controlled TBI experiments can be simulated and functions be constructed that relate the internal mechanical parameters and the risk of brain injuries (Ueno et al. 1995; Anderson 2004; Fijalkowski et al. 2009; Ren et al. 2015). The constructed tissue risk functions may then, under the assumption that animal and human brain tissue are similar in stiffness and have similar injury probability for a given deformation of the brain tissue, be used in FE models of humans. This would provide a link between deformation fields inside the brains of animals and humans and thus may be more physically/biomechanically justifiable (Takhounts et al. 2013). Such human FE models and injury risk functions can then support the development of a global level injury criterion that can be used with ATDs. These ATDs can then be used in the development and evaluation of superior vehicle restraints and contribute to the prevention of TBIs.

2. Aims

This thesis contributes to the ultimate goal of reducing traffic accident related Concussion and Diffuse Axonal Injuries. The main aim is to develop a conceptual brain injury criterion and associated injury thresholds that can be used with ATDs in the design process of safer cars.

More specifically the aims were:

- To investigate the head, neck and brain kinematics that produce TBIs in the experimental setting with animals by introducing FE models of the animals.
- To investigate different methods to scale animal data to humans.
- To develop a conceptual new global brain injury criterion and associated injury thresholds with the potential of, when properly applied, reducing the amount and severity of TBIs in traffic accidents.

3. Brain Injuries

This chapter includes a review of the classification of brain injuries that occur in traffic accidents, the mechanism responsible for these injuries, and their proportions. Brain injuries are commonly ranked according to the Abbreviated Injury Scale (AIS), which is an anatomically based and consensus derived scoring system that classifies an individual injury by body region according to its relative severity on a 6 point scale (Gennarelli & Wodzin 2006). Table 1 summarises examples of brain injuries from the AIS 2005, which provides different classification according to head internal organs (Brain) injuries and concussive injuries.

Table 1. AIS classified Brain Injuries (Association for the Advancement of Automotive Medicine 2005)

AIS	*Severity*	*Internal Organs - Brain*	*Concussive Injury*
0	No injury	-	-
1	Minor	-	Mild Concussion (No LOC)
2	Moderate	Cerebellum and Cerebrum (SAH)	Moderate Concussion (LOC <1 hour)
3	Serious	Cerebellum and Cerebrum (contusion, haematoma, laceration, penetration, swelling, …)	Severe Concussion (LOC 1-6 hours)
4	Severe	Cerebrum (DAI confined to white matter)	Mild DAI (LOC 6-24 hours)
5	Critical	Cerebrum (DAI involving corpus callosum) Brainstem (compression, contusion, haemorrhage, …)	Moderate DAI (LOC >24 hours without brainstem signs) Severe DAI (LOC >24 hours with brainstem signs)
6	Maximal	Brainstem (laceration, penetrating, transection, …)	

SAH: Sub-arachnoid haemorrhage, LOC: Loss of Consciousness, DAI: Diffuse Axonal Injury

3.1. Classification of Brain Injuries

Traffic related primary TBIs result from mechanical energy transferred to the brain from physical forces that act directly on the head or are transmitted through the head-neck complex (Nahum and Melvin 2012). This mechanical energy produces deformations of the brain, its neurons, its supporting structures or its vasculature beyond tolerable levels which result in the injuries. The acute changes induced by the primary injuries may alter gene expression which triggers regulation of both harmful and beneficial factors following the initial brain trauma (Rostami 2012). Such a process is usually defined as a cascade of biochemical reactions that may follow and evolve into secondary injuries.

Closed head are those brain injuries in which the skull and dura mater remain intact.

Focal brain injuries are those that occur in a specific location of the brain volume. Examples of such are vasculature injuries that may result in haemorrhages in all regions of the brain. Other examples are focal lesions to the brain parenchyma referred to as contusions and lacerations. Diffuse brain injuries comprise Concussion and DAI which are usually spread out throughout different brain regions.

This thesis focuses primarily on the prediction of primary, closed head and diffuse TBIs. A secondary focus of the thesis is on the prediction of primary, closed head and focal TBIs

3.2. Diffuse Brain Injuries

Concussions and DAI, which appear to the less and more severe ends of a continuous spectrum of brain dysfunction characterised by increasing amounts of axonal damage throughout the brain and the brainstem. Diffuse injuries range from the mildest form of concussion, which is not associated with loss of consciousness, to classical (cerebral) concussion with transient disturbance of consciousness, to DAI

with prolonged loss of consciousness of varying duration (Gennarelli et al. 1987; Gennarelli et al. 2003). Diffuse brain Injuries are associated with mechanical disruption of axons that is produced when brain tissue is subjected to strains above a recoverable limit (Galbraith et al. 1993; Bain & Meaney 2000; Anderson et al. 2003). Diffuse brain injuries are usually produced by head impacts that produce abrupt head motions, typically of combined translational and angular nature (Ono et al. 1980; Newman et al. 2000; Anderson et al. 2003; King et al. 2003).

The term concussion is controversial; its definitions have evolved over time, and past and present diagnosis of concussions in clinical setting differ (Gennarelli & Wodzin 2006; Carroll et al. 2010). Concussions have historically been defined based on symptoms. Past definitions of concussion (classical concussion or cerebral concussion) required symptoms such as loss of corneal reflex, apnoea, bradycardia or loss of consciousness prolonged for varying periods of time. Currently, a concussion (often called mild Traumatic Brain Injury) is diagnosed when the patient appears to be confused but loss of consciousness or amnesia is not required. In addition pathological findings in standard imaging are not expected. While the symptoms following concussions are relatively well established, its pathology is not fully understood; and diffuse and gross tissue lesions are absent. The detailed injury mechanism responsible for concussion is still to be determined whereas some information on the pathology is available; injuries to afferents of the cortex and normal cellular activity disruption in the reticular activating system in the brainstem (Jefferson 1944; Adelstein 1978; Ropper & Gorson 2007; Pearce 2008). The immediate effects include neuronal swelling, inflammation, axonal disruption, as well as metabolic and autonomic changes. Pathophysiological changes that occur following a concussion have been described as a multilayered neuro-metabolic cascade whereby affected cells typically recover, although under certain circumstances they might degenerate and die (Giza & Hovda 2001).

Concussions commonly occur without skull fractures (Got et al. 1983; Gennarelli et al. 1987). Concussions are the most common moderate-to-serious TBIs in motor vehicle crashes (Viano & Parenteau 2015) accounting for 60% of all AIS2+ injuries to the head (Table 8 in Addendum). The injury risk approximately increases linearly with crash severity for collision velocity changes below 35 km/h (Figure 16 in Addendum). DAI occur in traffic less frequently than concussions and at higher collision speeds (with a velocity change of 56 km/h or above), but their consequences are often devastating. Fifty percent of the DAI cases suffer moderate to severe deficits, 21% of the cases have vegetative survival, and 7% are fatal (Gennarelli & Thibault 1982; Melvin & Yoganandan 2015).

3.3. Focal Brain Injuries

Contusions and lacerations are the most frequently found focal brain lesions and consist of heterogeneous areas of necrosis, pulping, infarction, or micro haemorrhages that can occur in different locations of the brain. Contusions may be produced due to direct contact between the cortex and the deforming skull at the site of impact (coup contusions). Contusions can also occur at remote sites from the impact (contrecoup contusions) or by direct contact between the cerebrum and the rough internal surfaces of the skull basal bone. Cerebral contusions are in general more consistently associated with skull fractures than other intracerebral injuries as well as frequently associated with concussion symptoms (Styrke et al. 2007). Cerebral Contusions have been reported as an incidence of 20-30% of severe injuries (Khoshyomn & Tranmer 2004) and up to 89% of the brains CT examined post-mortem. Despite their large incidence, cerebral contusions can heal without medical intervention and are frequently associated with other brain injuries of more clinical relevance. This is not the case for brainstem contusions, which are usually classified as critical and are of high clinical relevance.

Intracranial haemorrhages often comprise life-threatening vasculature related injuries produced by violent motions of the brain inside the skull. Blood may accumulate in different intracranial regions which may increase intracranial pressure. Such increase of pressure may require surgical intervention.

Acute Subdural Haemorrhages (ASDHs) are commonly produced when the brain move relative the skull, the vasculature that bridges the brain's surface to the various dural sinuses is torn (Gennarelli & Thibault 1982) and blood accumulates between the dura mater and the brain. ASDHs are the most common type of focal injuries with an incidence of 5 to 30% among severely head-injured patients. ASDHs can occur in moderate head impacts producing combined translation and rotation head kinematics (Ono et al. 1980). Mortality rates for ASDH range from 30 to 60% (Cooper 1982; Gennarelli & Thibault 1982). Intra Cerebral Haemorrhages and Subarachnoid Haemorrhages are examples of other forms of focal injuries less frequent than ASDH in traffic accidents. Intracerebral haemorrhages are collections of blood within the cerebral parenchyma that develop superficially and extend deeply into the lateral ventricles, into the corpus callosum and the brainstem and can be distinguished from contusions and ASDH by CT scans (Cooper 1982; Melvin & Yoganandan 2015). Intracerebral haemorrhages are commonly associated with temporal bone fractures (Asha'ari et al. 2012).

4. Review of Brain Injury Experiments and Accident Studies

Methods that allow the establishment of injury thresholds can roughly be divided into three main categories: experiments with volunteers, reconstruction of accidents, and experiments with animals. The latter are the main focus of this thesis and are hence reviewed thoroughly in this section.

4.1. Volunteer Experiments and Accident Reconstructions

Snyder (1971) summarised a number of free-fall and sled tests with military volunteers conducted at the Aeronautical Research Laboratory base in New Mexico, USA. These data provided evidence of brain injury tolerance decreasing with increasing pulse durations, supporting the need to account for the duration of the injurious events in the development of preventive strategies. Ewing et al. (1975) subjected volunteers to rotational head accelerations in the sagittal plane up to 2.7 krad/s^2 and durations over 20 ms without finding any adverse effects in the volunteers. Currently, strict restrictions apply for the usage of volunteers in impact biomechanics research, hence the need for alternative research methodologies. An alternative data source for the establishment of injury thresholds and risk functions is real-life events, such as motor sports car crashes and contact sports, in which the participants are at risk of suffering head impacts. Instrumentation has largely been applied to helmets of American football players to capture head kinematics during no-concussive and concussive hits. This type of data have been used to propose concussion thresholds (Rowson et al. 2009, 2012). However, this use of such a data source has a number of limitations; lack of accuracy of the accelerometer measurements due to uncoupling between the instrumented helmets and the head of the players, difficulties in isolating directional effects of impact, limiting the opportunity to understand the craniocervical kinematics that produce the injuries, and study groups limited to young and fit athletes. In addition, while practicing sports, the players are under high cardiorespiratory activity. The influence accelerated breathing and high pulse may have on the brain conditions and physiology needs to be clarified. Most of these limitations can be complemented with animal testing.

4.2. Animal Experiments

Successful animal brain injury models should produce the injury type that is the object of the study in an isolated, controlled and repeatable manner. The injury type and severity should be representative of those seen in the clinical setting. A large number of models have been developed and used for the clarification of the injury mechanisms and to develop improved injury diagnosis methods and treatment methods. However, the biomechanical response has been characterised in very few models. Such characterisation is a requirement for the development of brain injury criteria and associated risk functions using data from reconstruction of the experiments using computational models of the animal. In this chapter animal TBI models developed for biomechanics research are reviewed. Emphasis is given to those models that have been successfully utilised to generate consistent and large data sets of graded injury severity and considered suitable for reconstructions using FE models of the experimental set-up. Special focus is on concussion and DAI models as these are of high clinical relevance in motor vehicle crashes (Viano & Parenteau 2015, Addendum).

Early experimental animal research studies focused on understanding the mechanisms and establishing thresholds for whiplash-type brain and neck injuries. Ommaya et al. (1966; 1971) reported a series of experiments in which injuries were produced in primates by either direct impact to the occipital zone of the head or by hyper-extension head loading caused by impact to the base of a mobile chair carrying the seated animal. In total, 42 squirrel monkeys (brain mass 20-27 gr.), 83 Rhesus monkeys

(brain mass 70-100 gr.) and 11 Chimpanzees (350-500 gr.) were utilised for these experiments. Cerebral concussions were scored according to loss of coordinated response to external stimuli, duration of apnoea and bradycardia. Displacement of the head and body was recorded by cinematography at 3,000 to 5,000 frames per second and values for rotational acceleration were calculated from displacement data obtained from film analysis. Rotational accelerations ranging from 20 to 1,000 krad/s^2 with durations from 1 to 12 ms were estimated (Ommaya et al. 1967). By comparing the results from the direct head impact experiments with the head acceleration experiments, it was shown that higher levels of angular motion were required to produce cerebral concussion in the head acceleration experiments (whiplash). Hence, suggesting that approximately half of the potential for brain injury during impact to the unprotected movable head is directly proportional to the amount of head rotation. The remaining risk of brain injury was attributed to the contact phenomena of the impact. The experiments by Ommaya et al. laid the foundation for contemporary experimental works and highlighted the importance of the methods used to load the head in the experiments.

Based on the method used to load the head, experimental brain injury models can be classified as impact models or acceleration models. The objective with impact models is to reproduce head impacts to a structure while the objective with acceleration models is to produce the head response without skull bone deformations. Figure 1 illustrates examples of acceleration models for primates (Gennarelli et al. 1972) and for rats (Davidsson et al. 2009) and impact models for primates (Ono et al. 1980) and for rats (Marmarou et al. 1994).

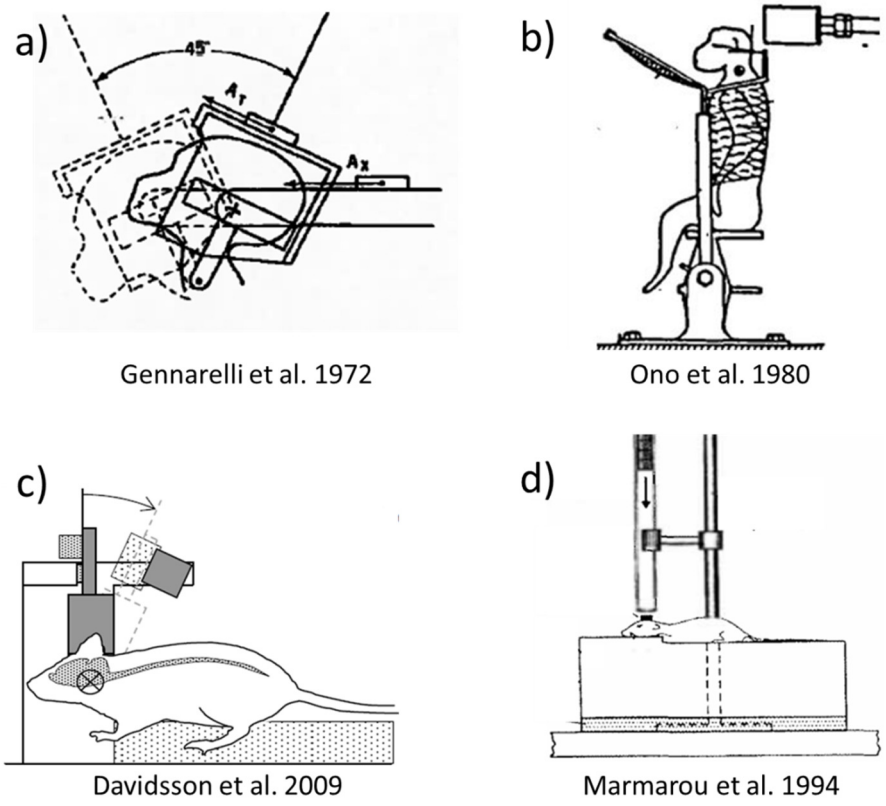


Figure 1. Schematic illustrations of acceleration models (a and c) and impact models (b and d) designed for primates and rats.

4.2.1. Head Acceleration Models

Gennarelli et al. (1971; 1972) conducted a series of experiments in which accelerations in the sagittal plane were induced to the head of squirrel monkeys. A test apparatus consisting of a cylindrical cam

attached to the periphery of a flywheel (HAD-II) was utilised to impose controlled accelerations to a helmet tightly fastened to the head of the animals. The translational acceleration and both components of the rotational acceleration (tangential and radial) were measured at the head centre of gravity. The imposed loading followed a biphasic pulse consisting of varying acceleration-duration followed by varying deceleration-duration with a separation time interval of 3 ms. Both phases of the pulses were approximately triangular in shape. In one series of experiments, 12 specimens were subjected to predominantly translational acceleration-deceleration loading with peak accelerations ranging from 665 g to 1,230 g and peak deceleration values of approximately one-half of these values. In another series of experiments, 13 specimens were subjected to predominantly rotational acceleration-deceleration loading with peak positive tangential accelerations at the head centre of gravity ranging from 348 g to 1,025 g and the centre of rotation located at the base of the neck. In these experiments the deceleration magnitudes were nearly the same as the acceleration magnitudes. Typical duration of the acceleration and the deceleration pulses were 1.8 and 3.3 ms, respectively. Brain pathology occurred in both series, but with a greater frequency and severity in the group of animals predominantly exposed to rotational head loading. Subdural haematoma was produced in the frontal region in half of the animals predominantly subjected to translational acceleration loading. More extensive haematomas, including in the temporal regions were found in all animals exposed to rotational loading. Predominant translational loading did not produce concussion while predominant rotational loading produced concussion lasting from 2 to 12 minutes.

Abel et al. (1978) extended the Gennarelli et al. (1972) work with a series of experiments with larger sized primates focused on producing subdural haematomas and cerebral concussions. The original test HAD-II apparatus was substituted by a HYGE pneumatic actuator coupled to a cam-linkage mechanism that allowed delivering controlled accelerations-decelerations to the head of larger sized species. Forty rhesus monkeys were exposed to single biphasic rotational acceleration-deceleration trauma in the sagittal plane. Peak rotational accelerations ranged from 18 to 120 krad/s^2. Peak values of the tangential component of the rotational accelerations at the centre of gravity of the head ranged up to 1,300 g. Although typical acceleration-deceleration pulses from this new device had similar separation time intervals (4ms) as the HAD-II device, peak acceleration magnitudes were lower than peak deceleration magnitudes. Acceleration and deceleration pulses had approximate durations of 6 and 3.5 ms, respectively. Physiological and neurological data recorded included electrocardiogram, electroencephalogram, systemic arterial pressure, intracranial pressure, respiration and corneal reflex. The post trauma symptoms were evaluated using the Experimental Trauma Score (ETS). This score was defined by the researchers involved in the experiments and was based on simple but objective physiological, behavioural and neurological variables as follows. An animal with ETS 0 was one in whom no physiological, behavioural or neurological changes were noted following the test. In ETS 1, blood pressure or heart rate were the only variables that changed. ETS 2 included a brief period of apnoea in addition to blood pressure or heart rate changes but the animal was conscious. ETS 3 involved a very brief duration of unconsciousness followed by complete neurological recovery. ETS 4 involved unconsciousness from the time of impact which remained for 5-15 minutes. Most animals in this category exhibited prolonged behavioural abnormality including timidity, and disinterest in their environment, but ate and drank normally. ETS 5 implied neurological death (never recovering from unconsciousness) within 6 hours from the trauma. ETS 6 was applied to cases in which extremely high head accelerations produced brainstem laceration and instantaneous death. According to this scale, the term cerebral concussion typically referred to at the time of the experiments would correspond with ETS grades ranging from 3 to 6. The pathological injury outcome was analysed in relation to the ETS grade scored at the experiments. Cases of ETS grade 2 or lower showed little abnormality in the form of occasional cortical contusions in the frontal lobes. SAH and ASDH could be observed for ETS 3 and higher. Brainstem haemorrhage was only reported in fatal levels of ETS. ASDH occurrence was shown to correlate well with the onset of tangential head accelerations occurring at values of 700 g. This study

pioneered in establishing graded correlation between physiological symptoms immediately after impact and macroscopic brain pathology.

Gennarelli et al. 1982 conducted experiments with 23 rhesus monkey and 22 baboon specimens aiming at the generation of graded DAI and their accompanying neurological deficits. The head of the rhesus specimens was subjected to a single biphasic rotational acceleration-deceleration, by rotating it through a 60 degree arc, in the sagittal plane, the coronal plane, or a 45 degree oblique plane between these two planes. The peak deceleration was approximately three times the peak acceleration and ranged from 70 krad/s^2 to 180 krad/s^2. The duration of these decelerations ranged from 6 and 9 ms, with a tendency for shorter durations to correspond with higher peaks and longer durations with lower peaks (Gennarelli et al. 1987). Neurological assessment was conducted in the 45 animals. Cerebral concussion, characterised by unconsciousness that lasted less than 15 minutes followed by good recovery, occurred in 15 cases, the majority of them from the sagittal group. Mild and moderate levels of prolonged coma (unconsciousness lasting between 15 minutes and 6 hours) occurred in 10 of the animals. Severe prolonged traumatic coma (more than 6 hours) was produced in 13 cases, all of them from the coronal loading group. Four of these animals never recovered from coma. The remaining ten awakened from coma but never recovered enough function to eat or drink. Neuropathology analysis was conducted in 26 of the 45 tested specimens. DAI was evaluated microscopically and the output was graded 1 to 3 according to its extent. DAI grade 1 was scored when axonal damage was confined to the white matter of the cerebral hemispheres. DAI grade 2 when tissue tears (characterised by axonal and small vascular damage) in the corpus callosum or the central brain area in addition to the cerebral hemispheres were found. DAI grade 3 included axonal damage in the brainstem in addition to the axonal damage found in grade 2. Overall, it was concluded that as duration of coma increased from concussion to prolonged traumatic coma, the incidence and the severity of DAI increased. Intensity of axonal damage was found to be proportional to lesions in the corpus callosum, and axonal damage produced by coronal head acceleration was a major cause of prolonged traumatic coma and its sequelae.

Smith et al. (1997; 2000) developed a head acceleration model to explore potential anatomical origins of posttraumatic coma. The HAD-II device was utilised to study DAI in miniature pigs (brain mass 80 to 90 gr.) by applying pulses of varying duration. Anaesthetised specimens were subjected to head rotational acceleration in the coronal plane (transverse to the brainstem) and compared to specimens subjected to similar rotational acceleration levels applied in the horizontal plane (circumferential to the brainstem). Peak decelerations applied were approximately three times the peak accelerations and ranged from 60 krad/s^2 to 180 krad/s^2 with durations between 4 and 6 ms. Immediate prolonged coma, assessed by changes in EEG (slowing down of alpha rhythm in the frontal and parietal regions and intermittent rhythmic high amplitude delta and theta activity in all regions), was consistently produced by head horizontal plane rotation, but not by head coronal plane rotation. Immuno-histochemical examination of the injured brains revealed that DAI was produced by head rotation in both planes in all animals. However, extensive axonal damage in the brainstem was found in the pigs injured via head horizontal plane rotation. No relationship was found between coma and the extent of axonal damage in other brain regions. In these animals, the severity of coma was found to correlate with both the extent of axonal damage in the brainstem and the applied loading conditions. The study suggested head loading directional dependence in producing DAIs in the brainstem. These observations may however be affected by the characteristic neck anatomy of the pigs that does not rotate in the coronal plane. In addition, interpreting the implications for humans is difficult due to differences in head and neck orientation between bipeds and quadrupeds (Margulies & Coats 2012).

Davidsson et al. (2009; 2011) developed a model in which the head of rats (brain mass 1.7 to 2 gr.) is exposed to biphasic rotational acceleration-deceleration in the sagittal plane. The model has been extensively utilised for behavioural and pathological studies and has been successful in producing graded DAI with no obvious signs of contusions, intra-cerebral haemorrhages and skull fractures. Prior to

trauma, a curved aluminium plate is glued to the skull after removing skin and periosteum from the cranial vaults and bones. This plate is secured to a bar that rotates around a horizontal axis perpendicular to the sagittal plane of the animal. The trauma is produced when a solid brass weight hits a polyurethane bumper on the bar which subjects the animal's head to an extension motion. Applied acceleration can be varied up to 2 Mrad/s^2 while the duration remains at about 0.4 ms. The acceleration is followed by deceleration with a magnitude of roughly one-fourth of the acceleration magnitude and 0.5 ms duration. Both pulses are approximately triangular shaped with a separation between them of approximately 1 ms. After the trauma, the animals have been utilised for behavioural studies (Rostami et al. 2012) or sacrificed at different times post trauma for pathological studies (Davidsson et al. 2009; Davidsson & Risling 2011). Presence of haematoma is assessed macroscopically. Detection of injured axons and decaying axons is carried out by through tissue staining followed by inspection with confocal microscopes. The overall findings using this model can be summarised as follows: producing graded DAIs in the corpus callosum, the border between the corpus callosum and cortex and in tracts in the brainstem with no obvious signs of contusions, haemorrhages and skull fractures (Davidsson & Risling 2011), initiation of inflammatory responses (Risling et al. 2011), limited behavioural changes (Rostami et al. 2012) and changes to a large number of genes (Davidsson & Risling 2011). Predominantly head rotational acceleration-deceleration experiments in the sagittal plane conducted with this model have shown a threshold of 1 Mrad/s^2 above which DAI is likely to occur in young adult rats (Davidsson et al. 2009; Davidsson & Risling 2011). Similarly, for COX2 presence and S100 concentrations at >0.9 Mrad/s^2, the number of stained cells in the cortex and hippocampus as well as the concentration increased (Davidsson et al. 2009). Subdural bleedings typically occurred in animals exposed to severe trauma. Overall, this rotational trauma model produces graded axonal injury, in a repeatable and controlled manner with a limited amount other types of TBIs and as such is useful in the study of injury biomechanics, diagnostics, and treatment strategies following DAIs (Davidsson & Risling 2011).

4.2.2. Head Impact Models

Ono et al. 1980; Kanda et al. 1981; Sakai et al. 1982 and Kikuchi et al. 1982 conducted a large series of head impact experiments with primates at the Japan Automobile Research Institute (JARI). The experiments were conducted under the auspices of the Ministry of Transportation of Japan through grants-in-aid of the Automobile Bureau Safety section and with the involvement of major academic institutions in Japan. The large majority of the specimens utilised throughout the series were Rhesus monkeys or Japanese monkeys (phylogenetically similar) although a limited amount of squirrel monkeys, baboons and chimpanzees were included in these studies. The motion of the head and torso of the specimens was captured by high speed cameras at 2,000 or 4,000 frames per second. Physiological measures such as respiration, blood pressure, electrocardiogram and electroencephalogram were recorded prior, during and after the impacts. Neurological measures including corneal and light reflex, response to painful stimuli, and eye movement were measured from 10 seconds after the impact. Pathological analysis included macroscopic examination and microscopic observation of formalin-fixed brain tissue samples prepared shortly after death or sacrifice of the animals following the tests. The severity of any concussion was evaluated according to symptoms (persistent loss of corneal reflex, cessation of respiration and blood pressure disturbances) immediately after impact, according to definitions in use at the time of the experiments (Committee on Terminology in Neurotraumatology of the World Federation of Neurological Society 1979). The experiments comprised a total of 89 specimens and 193 impacts delivered with different apparatus and variety of loading conditions. Figure 2 summarises the experiments; the name of each group, the number of impacts and number of specimens in each group, the target injury severity level, schematic illustrations of the specimens and the techniques used to deliver the impacts, and the main characteristic head kinematics producing the impacts.

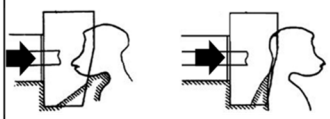
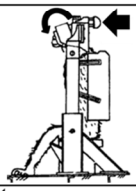
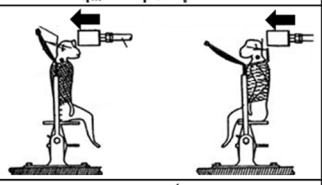
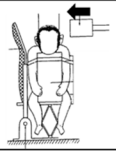
Group	# Tests / Specim.	Impact method	Injury severity	Illustration of test apparatus	Acceleration
A	27 / 27	Broad mask	Severe to fatal		Translation
B	18 / 18	Rotating case	Severe to fatal		Predominant rotation
C	73 / 21	Padded impactor	Mild to severe		Rotation + translation
D	75 / 23	Padded impactor	Mild to severe		Rotation + translation

Figure 2. Summary of JARI primate head impact experiments carried out 1976 to 1978 (Ono et al. 1980; Kanda et al. 1981; Sakai et al. 1982 and Kikuchi et al. 1982)

Ono et al. 1980 presented the first three groups of impacts (A, B and C) consisting of sagittal head impacts with different loading conditions. Group A consisted of single fatal impacts to 27 specimens (21 frontal and 6 occipital). The impacts were delivered over a broad area of contact through a plaster mask fitted to the head which produced high levels of virtually pure translational motion of the head. The head was measured in plane accelerations using four linear accelerometers mounted on the skull. Average resultant translational accelerations of the head ranged from 240 to 1,100 g with the duration of these accelerations ranging from 3 to 18 ms. All the 27 cases scored concussion, 13 survived the impact, 7 received SAH and only 1 skull fracture was reported. Noticeably, no contusion was produced in this group. Group B comprised of 18 animals subjected to a single occipital impact to the device that constrained the head. This device rotated with respect of a horizontal axis approximately passing through the base of the cervical spine. Head translational and rotational accelerations in group B (and groups C and D) were measured with a nine accelerometer system mounted on the skull. Average resultant head translational accelerations ranged from 500 to 800 g with the duration of these accelerations of 1 to 5 ms. Average resultant rotational accelerations were in the range of 50 to 290 krad/s^2 with durations equivalent to those of the translational accelerations. All the 18 cases in this group scored concussion, 12 survived the impact, 11 received SAH, 12 contusion, and 6 skull fractures. Group C comprised a series of comparatively milder padded impacts in which subjects were impacted repeatedly with increasing impact severity conditions until concussion was produced. A total of 73 impacts were delivered to the frontal or occipital part of the head of the 21 specimens. The impacts produced average resultant head translational accelerations ranging between 140 to 500 g with durations from 1 to 14 ms. Resultant rotational accelerations ranged from 6 to 120 krad/s^2. Skull fractures were found in 4 of the 21 specimens. SAH was found in 10 of the specimens, SDH in 6 and contusion in 6. Brainstem injuries accompanied by deep-seated haemorrhage was found in 5 specimens. Additional detailed analysis of the outcome of this group after excluding the cases with skull fracture (Kanda et al. 1981) revealed frequent haemorrhages and circulatory disturbances in the midbrain, pons and medulla oblongata, suggesting that

non-fatal brainstem lesions in the absence of skull fractures were associated with the development of concussion symptoms.

Sakai et al. (1982) and Kikuchi et al. (1982) separately presented a group of coronal impacts (group D). The animals in this group were subjected to similar loading and experimental methods as Group C, but with the impacts being delivered to the temporal region of the head. A total of 75 impacts of increasing severity until concussion, were delivered to the head of 23 specimens. Velocities of the impactor ranged from 10 to 27 m/s. Average resultant head translational accelerations ranged from 70 to 1,310 g with durations of these accelerations ranging from 2 to 43 ms. Skull fractures were found in 6 of the 23 specimens. These fractures were accompanied by massive brain injuries that terminated the specimen within 15 minutes. Brain pathology was found in 18 of the specimens, including 9 specimens with SAH, 5 with SDH, and 4 with brainstem haemorrhages. Sakai et al. (1982) compared the outcome of these lateral impacts and the sagittal impacts by Ono et al. (1980). This comparison revealed, contrary to the experiments with the acceleration-deceleration device reported in Gennarelli et al. (1982), that the tolerance for concussion and severe pathological brain injuries was higher for lateral impacts than that of sagittal impacts.

The overall key findings of the JARI primate head trauma impact series could be summarised as follows; impacts delivered to the front, rear or lateral region of the head of primates with three different experimental models produced single phase head acceleration events. The resultant head accelerations were either translational (Group A), predominantly rotational (Group B) or a combination of these (Groups C and D) with variable durations and severities. Concussion symptoms were produced as a result of all used impact directions, regardless of the experimental method utilised to deliver the impact. High levels of primarily head translational acceleration produced fatal concussion and SAH brain injuries without skull fractures. ASH was produced in all groups, with higher rates when the heads were exposed to predominantly rotation accelerations (Group B). SDHs were produced only when the impact was delivered using a padded impactor surface (Groups C and D). This device resulted in combined translational-rotational head acceleration. Tolerance to lateral impacts was higher than those that produced head accelerations in the sagittal plane. A conservative curve that defined the threshold for concussion as a function of head translational acceleration in the sagittal plane and duration of the acceleration was drawn (Ono et al. 1980).

Marmarou et al. (1994) and Abd-Elfattah Foda and Marmarou (1994) developed a weight drop rat head injury model. The model allows a weight to fall onto a metallic disc fixed to the top part of the intact skull of the animal which is supported by a foam bed. The disc and the foam bed were utilised to mitigate the risk of skull fracture. A total of 161 anaesthetised adult rats were subjected to injurious impacts. The severity of the impact was controlled by varying the mass of the weight and the drop height. A first group, consisting of 54 rats, was designed to establish the impact conditions that would produce severe injuries with a mortality rate of approximately 50% and reduced risk of skull fractures. These conditions were established in a test with a 450 gr weight falling from a 2 m height resulted in a mortality rate of 44% with a low incidence (12.5%) of skull fractures. Mathematical analysis with lumped mass models estimated that this mass-height combination resulted in a head acceleration of 900 g and brain compression of 0.28 mm. In a second group of impacts, comprising 107 animals, the mass of the weight was set to 450 gr and the drop height was adjusted to either 1 m or 2 m. This group aimed at producing brain injuries of different severities and at determining the primary cause of death. Some specimens were mechanically ventilated and others were allowed to breathe spontaneously. Pathological studies using light and electron microscopy were also performed at 1, 6, 24, or 72 hours, or 10 days after the experiment. Severe impacts were typically followed by apnoea, convulsions, and moderate hypertension. The surviving rats developed decortication flexion deformity of the forelimbs, with behavioural depression and loss of muscle tone. No fatalities occurred with the 1 m level injury, while 59% mortality was seen with the 2 m level injury. However, the pathological changes observed in both groups were

similar. The mortality rate decreased markedly in animals mechanically ventilated during the impact. Hence, the main cause of death was attributed to central respiratory depression. Gross pathological examination did not reveal supratentorial focal brain lesions. Petechial haemorrhages were noticed in the brainstem at the 2 m level injury. Microscopically, the model produced a graded widespread injury of the neurons, axons, and microvasculature. Neuronal injury was mainly observed bilaterally in the cerebral cortex. The trauma resulted in massive DAIs that involved the corpus callosum, internal capsule, optic tracts, cerebral and cerebellar peduncles, and the long tracts in the brainstem. This model was capable of producing DAIs in rats with low incidence of skull fracture and controlled mortality. These injuries were produced by a head impact that produced nearly pure translational head motion.

Anderson et al. (2003) conducted a series of head impact experiments with sheep. The study aimed at the production of axonal injury while measuring head impact dynamics and the subsequent kinematics of the head. Eleven anaesthetised specimens were instrumented to measure physiological and biomechanical data. Each animal was subjected to a single controlled impact delivered to the left temporal region of the skull. Respiration rate, blood pressure, heart rate, electro-cardiogram, and intracranial pressure were monitored throughout the duration of the experiment for physiological assessment. A nine accelerometer array was secured to the skull with screws. A modified captive bolt gun, mounted on a rigid frame, was used to deliver the impact to the sheep head. The gun was modified to measure striker velocity and impact force. The striker had a mass of 395 g, and presented a spherical contact surface on impact. The impact force was measured using a force transducer placed between the body of the striker and the tip of the striker. Following a 4 hour survival period after the trauma, the animal was terminated. The brains were collected and formaldehyde fixed for a period of two weeks. Thereafter, immunochemical analysis was conducted for the detection of injured axons through tissue staining followed by inspection with light microscopes. Three coronal sections from each brain were examined in detail. Resulting impact forces varied between 5 and 7.4 kN over a duration of approximately 2 to 3 ms. Head translational accelerations ranged from 700 to 1,800 g. Impact velocities varied between 23 and 45 m/s. Rotational head accelerations ranged from 81 to 227 krad/s^2. Skull fractures occurred in 8 of the 11 experiments. Five of these fractures were of depressed type. Gross pathology revealed cerebral contusions adjacent to the site of the impact on the skull, SAH at the site of impact and sometimes in the contrecoup site. In the most severe cases, fractures caused extensive SAH and lacerations in the cortex in addition to contusions adjacent to the impact site. Microscopic pathology of the brains revealed that all animals sustained widespread axonal injury in several regions of the brain. These regions commonly included the thalamus, hippocampus, margins of the lateral ventricles, digitate cortical white matter and the corpus callosum. The anterior section usually exhibited less axonal injury than the medial and posterior sections and the left (impact) hemisphere in all cases. Overall it was concluded that the distribution of axonal injury in the sheep brain was related to the severity of the impact to the head and that this distribution was not independent from skull fractures.

Fievisohn et al. (2014; 2015) recently developed two novel injury devices to characterise impact-induced traumatic brain injury with mini pigs. Eleven animals were exposed in each device. The first model imparts pure translational acceleration to the head by means of a drop tower. Translational head accelerations with this model ranged from 27 to 70 g. The second model produced combined translational-rotational acceleration of the head using a compound drop pendulum. Translational accelerations ranging from 40 to 96 g and rotational accelerations from 1 to 3.8 krad/s^2 were produced with this model. The objective of the study was to evaluate the neuropathology associated with two injury devices. Proton magnetic resonance spectroscopy was utilised to quantify metabolic changes and immunohistology was utilised to evaluate axonal damage. The results revealed that both input modes led to similar neurofilament damage, which indicates axonal disruption. The results revealed that the two models produced similar metabolic changes, mainly in the inflammatory response and myelin disruption, but also several differences in brain metabolites, suggesting distinct underlying mechanisms.

Hence, the study indicates that neuropathological changes in the brain following trauma may be unique to isolated translation and combined translation-rotation of the head.

4.3. Summary

Historical experimental tests series in which a large number of primate specimens were used to study TBI from closed head trauma have been reviewed. The experiments conducted in the US focused on biphasic rotational head acceleration trauma. The experiments conducted in Japan mainly focused on single event head impact type trauma with a moderate deceleration phase (Figure 3). Early 1980s testing with primates was put to a halt and the research community shifted to smaller and less controversial animal species (Chapter 9). Since then, several non-primate models have proved successful in generating graded brain injuries well characterised for biomechanical studies. These models are being utilised to generate data way beyond the techniques used in the past primate experiments, including behavioural studies (Rostami et al. 2012), bio-markers (Rostami 2012), several types of immunohistology (Marmarou et al. 1994; Davidsson et al. 2009; Davidsson & Risling 2011; Risling et al. 2011), advanced imaging (Fievisohn et al. 2014). These and other animal experiments developed current knowledge of the pathophysiology of TBI and of the global head kinematics producing these injuries.

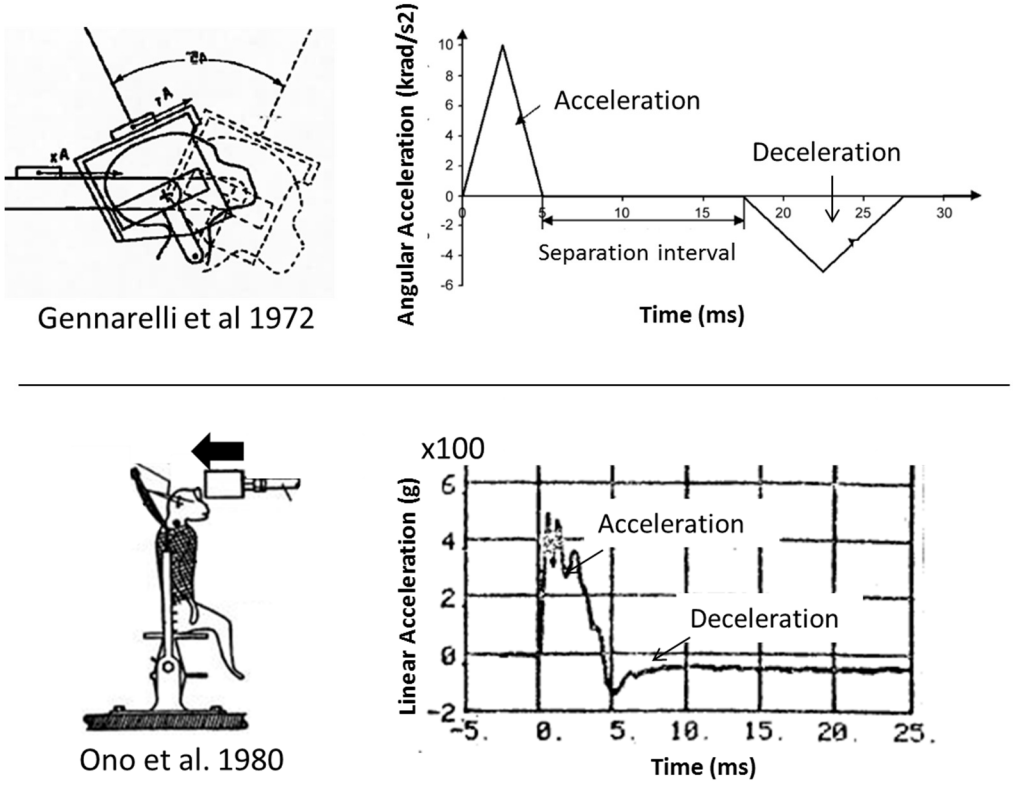


Figure 3. Above: Illustration of the rotational acceleration device and scheme of a typical biphasic rotational acceleration-deceleration produced with a separation interval between the acceleration and the deceleration phases (i.e. Gennarelli et al. 1972). Below: Illustration of head impact device and representative translational acceleration curve showing acceleration followed by a gentle deceleration and without separation interval (Ono et al. 1980).

Rotational acceleration models do not involve impact and therefore may not reproduce the scenarios clinically relevant for traffic accidents, as illustrated by McLean (1995). The McLean study investigated over 400 motor vehicle accidents and concluded that no case of head injury without indication of impact to the head could be found. Data from head impact models could, if properly reproduced using a FE model of experimental setup, enable the development of criteria and associated thresholds for specific

injuries relevant in traffic accidents. In addition, improving the applicability of the animal data to humans, which is one of the aims of this thesis, will most likely be more difficult for non-primate animals than for primate animals. The reason for this is the fact that differences in brain size, brain geometry, relative dimensions and location of important structures within the brain, tissue properties, the amount of folding of the cerebrum, etc. are larger between smaller animal species and humans than between non-human primates and humans. Hence, the head impact experiments carried out at JARI (Ono et al. 1980; Kanda et al. 1981; Sakai et al. 1982 and Kikuchi et al. 1982) were considered the most appropriate for the development of tissue and global level brain injury criterion and associated thresholds for concussions relevant for traffic accidents. Nevertheless, an attempt was carried out in this thesis to use data from sagittal plane rotational trauma experiments carried out with rats (Davidsson et al. 2009) to develop a risk function for DAIs.

The contribution of the magnitude of head angular motion to the development of diffuse brain injuries has been demonstrated with head acceleration models in primates (Gennarelli et al. 1971; 1972; Abel et al. 1978; Gennarelli et al. 1982), in swine (Smith et al. 1997; 2000) and in rats (Davidsson et al. 2009; 2011). Combined translational-rotational motion of the head produced by impact experiments to unconstrained heads has been shown to produce diffuse brain injuries often involving the brainstem in primates (Groups C and D in the JARI experiments by Ono et al. 1980 and Sakai et al. 1982) sheep (Anderson et al. 2003) and swine (combined input injury device by Fievisohn et al. 2014). Head impact induced pure translational head motion has been shown to produce concussion symptoms and subarachnoid haematoma in the absence of contusions and skull fractures with primates (Group A in Ono et al. 1980). Comparable pure translational models have also produced DAIs of different severity and spread as detected by immunohistochemistry with swine (translational-input injury device by Fievisohn et al. 2014) and rats (Abd-Elfattah Foda & Marmarou 1994; Marmarou et al. 1994). Evidence of increasing injury risks with increasing pulse durations has been established for both head acceleration and head impact primate models (Ommaya & Gennarelli 1974; Ono et al. 1980). This decrease of injury tolerance with increasing pulse durations is consistent with that observed in free-falls of military human volunteers (Snyder 1971). Finally, the review of animal experiments suggests that the direction of head acceleration may influence injury outcome (Gennarelli et al. 1982; Smith et al. 2000). However, evidence of this is scarce and the results in these studies appear to be contradictory to another study with primates (Sakai et al. 1982). In addition, these results were obtained using primates and swine, and may not be valid for humans as the neck and brain anatomy differ between the species (Margulies & Coats 2012).

5. Review of Brain Finite Element Modelling

The FE method is a computer-based numerical technique for approximate calculation of the behaviour of solid deformable and rigid structures (Hallquist 2006). The structures are broken down into many small continuous compatible elements called meshing. Six equations are solved to calculate the motion and deformation of each element for several time steps; from time zero to a predefined termination time. Three of them are the equilibrium equations according to the fundamentals of physics defined by Newton's Law. The other three equations require strain/stress relations which are a function of the defined material properties. The latter are preferably defined based on tissue experiments (McElhaney 2005). The time step utilised to solve the equations is calculated based on size, mass and material properties of each element. The smallest time step needs to be small enough to ensure a stable numerical solution and, at the same time, be large enough so it can be handled by the available computational resources.

TBIs result from mechanical energy transferred to the brain from physical forces that act directly on the head or are transmitted through the head-neck complex (Melvin & Yoganandan 2015). The direction, type, rapidity, and magnitude of head motions determine the strains in the brain. A particular set of input variables will produce a particular and unique strain field/time profile, which will result in clinically apparent symptoms and pathological alterations (Gennarelli 2015). Most symptoms are commonly observable right after trauma while pathologies and some symptoms develop over time as these are part of a biological process. While brain FE models currently cannot simulate these processes they are applied under the assumption that injurious biological processes are triggered when the brain tissue reaches a certain level of deformation.

To estimate the deformation level/strain fields that produce the injuries in the brain, it is common to apply external loads to the FE model equalling measures from real world events or experiments with animals that led to injuries. The correlation between the estimated stresses/strains sustained by the brain tissue and the injury outcome in the real world events or experiments can be determined. Axonal damage, characteristic of diffuse brain injuries, is produced when brain tissue is subjected to strain (Galbraith et al. 1993; Bain & Meaney 2000; Anderson et al. 2003). Subdural haematomas are produced when violent motions of the brain inside the skull tear the vasculature between the brain cortex and the skull (Gennarelli & Thibault 1982). Therefore, brain tissue strain (or stress) and brain-skull relative motion measurements can be considered as reasonable indicators to investigate brain injury risks. All this provides human and animal brain FE models with a great potential to complement TBI experimental and accidental research.

A scheme of the development process for contemporary brain FE models and a brief review of state-of-the-art human and animal brain FE models of relevance for this thesis are presented in this chapter.

5.1. Development of Brain Finite Element Models

The first step to build a brain FE model is to obtain and digitise the geometry of the head of the volunteer, patient, or specimen to be modelled. Based on this geometry, a mesh is constructed. Thereafter, material models and properties are assigned to each component of the models. Finally, the interaction between different regions of the model need to be defined based on contact algorithms.

Geometry considered to have sufficient accuracy for brain FE models can currently be obtained from medical images from volunteers (Gayzik et al. 2011) or animals (Anderson 2004; Baumgarter et al. 2009) by means of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). These imaging techniques generate stacks of 2 dimensional digital images of the brain and its surrounding

structures. The stacks can be processed to develop 3 dimensional surfaces or volume geometries suitable for FE meshing.

The mesh is generated by discretising the digital surfaces or volumes previously obtained. A good mesh should have a reasonably small size to ensure numerical accuracy and meet the target requirements. The mesh type, density and quality must be driven by the requirements of the physical problems to be solved with the model. Depending on the role that each component may play during a simulated head loading event, different meshing strategies may be adopted. For example, the pia mater that surrounds and protects the brain (Appendix A) can be modelled with quadrangular membrane elements that share nodes with the brain surface. Another example is brain parenchyma, which frequently undergoes large deformations and is typically modelled with hexahedral solid elements. These types of elements are more time consuming to develop than tetrahedral elements, but are more reliable in estimating deformation of soft tissues such as the brain (Miller et al. 2009).

The choice of brain tissue material model and properties is a critical step since it significantly influences the tissue responses predicted by the brain model. Brain tissue behaves as a non-linear (Bilston et al. 1997; Takhounts, Crandall, et al. 2003), viscoelastic (Arbogast & Margulies 1998; Darvish & Crandall 2001; Prange & Margulies 2002), anisotropic (Shuck & Advani 1972; Arbogast & Margulies 1998) and inhomogeneous material (Gefen et al. 2003; Elkin et al. 2010). In addition, the bulk modulus of brain tissue is much larger than the shear modulus (Donnelly & Medige 1997). Hence, brain tissue can be considered nearly incompressible and its behaviour is largely dependent on shear moduli (McElhaney et al. 1976). Complex material models are required to account for all the characteristics mentioned above. However, in practice, linear viscoelastic or hyperelastic-viscoelastic (to account for rate effect) models defined by two or more shear moduli terms, the short (G_0) and the long term modulus (G_1), and relaxation times (τ) are implemented in brain FE models. Shear moduli values reported in the literature present a large variability span across testing methods and species utilised (Chatelin et al. 2010). Comparative studies between animal and human brain tissue properties tested under similar conditions are rare. McElhaney et al. (1976) conducted compression tests with cylindrical samples from human and primate brain tissue. They concluded that there were no significant differences and that G_0 and G_1 approximate values could be established in 10 and 3 kPa, respectively. Takhounts, Crandall, et al. 2003 compared bovine brain tissue with human brain tissue under comparable testing conditions. The study concluded that the human tissue was somewhat stiffer than the bovine, although these differences were not significant. Other studies seem to suggest that small animal species may have softer properties than humans. G_0 and G_1 moduli of 450 Pa and 30 Pa have been estimated from shear strain dynamic testing of porcine brain tissue (Shen et al. 2006). Furthermore, indentation tests with rat brain tissue samples have provided some of the softest brain tissue properties in the literature (Elkin et al. 2011; Elkin & Morrison 2013). However, no study in which a direct comparison between rodent and human brain tissue under similar testing conditions has been found.

Contact algorithms define the way FE solvers treat the interaction between different neighbouring parts of the model which mesh is not continue. The approach adopted to model the interface between the skull and the brain cortex surface in brain FE models is critical due to its influence on the brain motion and brain tissue strains predicted with the models (Kleiven & Hardy 2002). The most commonly used approach is the Tied contact method which imposes constraint to any relative motion between the brain surface and the skull. This technique has been shown to over constrain brain motion but is still utilised due to its simplicity (Kimpara et al. 2006; Takhounts et al. 2008; Mao et al. 2013). Sliding-only contact options, which allow tangential motion between the brain surface and the skull while transferring loads in tension, may be a better alternative to model relative brain-skull motion (Kleiven 2002; Kleiven & Hardy 2002). However, this option presents some technical limitations associated to the software ability to prevent small penetrations between the brain surface and the cerebrospinal fluid (CSF) elements (Kleiven 2002). Another possible alternative to the tied contacts may be to model the CSF with

solid elements (susequently denoted CSF-solid) that share nodes with the brain cortex surface and the inner skull (Willinger et al. 1995; Zhou et al. 1995). In this case, the properties assigned to the CSF exert control of the brain-skull relative motion, which can occur in both surface tangential and normal directions. Similarly to the skull-brain interface, the methods utilised to model the ventricular spaces within the central part of the brain may also influence the predicted brain strains (Chapter 7.1). Hence, considerations similar to those presented for skull-brain interaction may also be required when modelling ventricular spaces.

5.2. Brain Finite Element Models

A number of human and animal brain FE models have been developed in the last few decades. Kleiven (2002) reviewed in large detail most models available at that time and developed his own human model. Some of the reviewed models have evolved during the last few years and some new have been developed since then. State-of-the-art human and animal brain FE models are reviewed in this section. For details on previous versions or older brain FE models, the readers are referred to Kleiven 2002.

5.2.1. Human Models

The human brain FE models and their main characteristics included in this review, are summarised in Table 2. The Global Human Body Model Consortium (GHBMC) brain FE model (Mao et al. 2013) is considered a thoroughly validated evolution from former models developed at the Wayne State University (Zhou et al. 1995; Al-Bsharat et al. 1999; Zhang et al. 2001). The GHBMC model was developed from CT and MRI images taken from a volunteer and it is to date the model with the highest anatomical detail and finest mesh. The Kungliga Tekniska Högskolan (KTH) model was initially developed based on anatomical data from the Visible Human Project (Ackerman 1998), a source of digitised medical images and photographs of a PMHS. The anatomical detail of the KTH model is relatively simple (Kleiven & von Holst 2001; Kleiven & Hardy 2002; Kleiven 2007; Giordano & Kleiven 2014). The Total Human Model for Safety (THUMS) model was also based on the Visible Human Project (Ackerman 1998). The geometry of THUMS is slightly more detailed than in the KTH model, and was developed and validated together with a model of the neck (Kimpara et al. 2006). The Simulated Injury Monitor (SIMon) model is a simplified brain model with a rigid skull developed from a set of CT scans (Takhounts et al. 2008). The SIMon was developed by the NHTSA for automotive safety applications and is supplied with a tool that enables easy processing of head kinematic data from ATDs. The Strasbourg University Finite Element Head Model (SUFEHM) (Willinger et al. 1995; Deck & Willinger 2008; Sahoo et al. 2014) was developed from medical images of a volunteer at the University of Luis Pasteur and is the model with the simplest anatomical detail (Willinger et al. 1995). The brain in all the reviewed models is built of mainly hexahedral solid elements. Brain tissue material models are either linear viscoelastic (THUMS, SIMon, GHBMC) or hyperelastic-viscoelastic (KTH, SUFEHM). The properties assigned to these materials from the stiffest (SUFEHM) with G_0=49 kPa and G_1=16 kPa to the softest (SIMon) with G_0=1.6 kPa and G_1=0.9 kPa. The GHBMC, SIMon and THUMS incorporate tied contact skull-brain interface. The KTH and the SUFEHM models were assigned sliding-only and CSF-solid techniques, respectively. Despite the large variability of mesh size between models, mesh convergence has been ensured in the models with coarser meshing (Kleiven 2007; Deck & Willinger 2008). Recently, the most updated versions of the KTH (Giordano & Kleiven 2014) and the SUFEHM models (Sahoo et al. 2014) incorporate fractional anisotropy, which enables the investigation of more advanced brain tissue criteria such as strain along the direction of the axons within the brain tissue. These enhancements may improve the prediction of regional brain strain values. The latter may correlate better with some types of brain injury than do other global head or current local brain tissue metrics (Giordano & Kleiven 2014).

Despite the large differences between human brain FE models, the level of validation that can be achieved with these models is limited by the availability of experimental data. In the past, brain models used to be validated with intracranial pressure data measured from PMHS head impact tests (Nahum et al. 1977; Trosseille et al. 1992). However, this method proved insufficient for models that are to be applied for research of brain injury types in which brain tissue strains may be the predominant injury mechanism (Bradshaw et al. 2001), such as diffuse brain injuries. Currently, models are validated with data obtained from series of experiments with PMHSs in which the motion of opaque markers in the brain at head impacts were recorded by means of high-speed x-ray (Al-Bsharat et al. 1999; Hardy et al. 2001; Hardy et al. 2007). Although not a direct measurement of brain tissue strains, this approach is believed to provide a better insight of the reliability of predicting tissue strains with the brain FE models. The human brain models included in this review have been, to different extents and level of accuracy, validated with local brain motion data (Al-Bsharat et al. 1999; Hardy et al. 2001; Hardy et al. 2007). The most recent version of the KTH model (Giordano & Kleiven 2014) has also been validated against strain data estimated from the motion data by Hardy et al. (2007).

Table 2. Summary of recently developed or updated Human brain FE models.

Model name and main reference	Geometry source	Number of brain solid elements	Brain tissue material model and properties	Skull-brain interface	Validation
KTH Kleiven 2002	Visible Human Data	7 128	Hyperelastic and viscoelastic G_0=12.5kPa/ G_1=1kPa	Sliding-only	Pressure Brain motion Strain
THUMS Kimpara et al 2006	Visible Human Data	24 000	Linear viscoelastic G_0=12kPa/G_1=6kPa	Tied	Pressure Brain motion
SIMon Takhounts et al 2008	CT	40 708	Linear viscoelastic G_0=1.6kPa/ G_1=0.9kPa	Tied	Pressure Brain motion
SUFEHM Deck & Willinger 2008	MRI	5 320	Hyperelastic and viscoelastic G_0=49kPa/ G_1=16kPa	CSF-solid	Pressure Brain motion
GHBMC Mao et al 2013	MRI & CT	211 000	Linear viscoelastic G_0=6kPa/ G_1=1.2kPa	Tied	Pressure Brain motion

G_0 = Short term shear modulus; G_1 = Long term shear modulus

Applications of human brain FE models are multiple. One example is the investigation of injury causation mechanisms by detailed reconstruction and simulation of traffic accidents that have resulted in TBIs. The accidents are simulated with the brain FE models and the results from the simulations are compared with the type, extent and location of the brain injuries based on the medical records of the patients (Kleiven 2007; Deck & Willinger 2008; Fahlstedt et al. 2012). Such an approach, although limited by the uncertainties inherent to accident reconstructions, can support the clarification of the head kinematics that produced the injuries. Furthermore, if applied to a sufficient number of cases, it can also provide means of evaluation of the reliability of brain injury criteria (Deck & Willinger 2008). Another application of human brain FE models is the development of brain injury criteria and associated thresholds by matching reconstructions of real world head impact events through simulations of these events with human brain FE models. This method has been applied to series of concussive and non-concussive head sport impacts. The head kinematics were measured from the head impacts and applied to the rigid skull of the FE models (Kleiven 2007; Kimpara & Iwamoto 2012). The underlying assumption of this simulation technique is that the effect of the impact event such as skull deformation on injury risk may be neglected. This assumption may apply for concussions, since they usually occur without skull fractures, suggesting small skull deformation. A limitation of this method is that concussions are usually diagnosed based on symptoms at different times following the impact and standard imaging is usually normal. Hence, the correlation between the results from the simulations and the concussions are made based on a limited understanding of the head kinematics causing the injuries.

A further example of the application of human brain FE models is the evaluation of the ability of global brain injury criteria to correlate with brain tissue strains in loading scenarios from crash tests with ATDs and PMHSs in which more severe brain injuries such as DAI may occur (Takhounts et al. 2013; Gabler et al. 2015; Yanaoka et al. 2015). Since the loads were applied to rigid models of the skull in these studies, this method tends to oversee that the injuries, the object of this study, commonly occur in combination with skull fractures or skull bone deformations. In addition, since TBIs cannot be diagnosed with ATDs or PMHS, this method will require a complementary methodology to establish injury thresholds (Takhounts et al. 2013).

5.2.2. Animal Models

In order to improve the understanding of the relation between animal head kinematics and the injuries produced, animal experiments can be simulated with FE models of the specimens. Contrary to human models, animal brain FE models are not thoroughly validated and their application is limited to investigations of specific injury mechanisms or to develop local tissue injury risk functions. Examples of these models and applications are presented in Table 3. Anderson (2004) developed a sheep brain FE model to simulate the dynamics of skull and brain during sheep closed head impacts experiments (Anderson et al. 2003). Validation was attempted by comparing pressure measurements in the simulations with those measured from the experiments. A number of rat brain FE models have also been developed. Mao et al. (2006) developed an anatomically detailed rat brain FE model. The cortical motion of the model was partially validated with in-vivo indentation test data. The validated model was utilised to simulate controlled open head cortical impact experiments and to investigate mechanisms for contusions. Baumgarter et al. (2009) developed a rat brain FE model from MRI and CT images for investigations of DAI from rotational acceleration-deceleration experiments (Davidsson et al. 2009). The model has been enhanced by incorporating brain region dependent tissue properties (Finan et al. 2012) and validated against brain-skull motion experimental data obtained in Paper I in the current thesis (Ren et al. 2015). The validated FE model has been utilised to simulate the rotational acceleration-deceleration experiments (Davidsson et al. 2009) and to develop brain tissue injury risk curves that relate DAI risk from the experiments with tissue strain criteria from the simulations.

Table 3. Summary of recently developed Animal brain FE models

Species and reference	Geometry source	Number and type of elements	Brain tissue material type and properties	Skull-brain interface	Application
Sheep Anderson 2004	MRI & CT	2 912 Sol 2 723 Sh	Linear viscoelastic G_0=49 kPa, G_1=16.7 kPa	Sliding-only	Development of local tissue injury risk curves DAI in sheep
Rat Mao et al. 2006	Rat brain Atlas	255 700 Sol	Linear viscoelastic G_0=1.7 kPa, G_1=0.5 kPa	Automatic surface to surface	Investigation of contusion mechanisms in dynamic cortical indentation
Rat Ren et al. 2014	MRI & CT	156 656 Sol 12 881 Sh	Linear viscoelastic G_0=1.3 kPa, G_1=0.4 kPa	CSF-solid	Development of local tissue injury risk curves for DAI in rats

Sol = Solids; Sh = Shells; G_0 = Short term shear modulus; G_1 = Long term shear modulus;

5.3. Summary

Medical imaging technology, advances in meshing techniques as well as software and hardware development have boosted the development and application of detailed brain FE models. Human brain FE models are technically mature tools with multiple research and industrial applications. The achievable level of full scale brain motion validation in all models is limited by a reduced set of local

brain motion experiments conducted with cadavers (Hardy et al. 2001; Hardy et al. 2007). As human brain FE models become more accurate, the models are adapted to predict regional brain deformations in response to complex head motions such as those seen in traffic accidents. Animal brain FE models are usually less validated than human models and their applications are limited to reduced sets of experiments. However, in combination with controlled experimental models and improved invasive and non-invasive injury diagnosis techniques, the animal brain FE model may enable the development of injury risk functions that can be used to predict brain injuries at the tissue level.

In this thesis one rat, one monkey and one human brain FE model have been developed from CT and MRI images of the corresponding specimens (Chapter 7.1). Brain tissue linear viscoelastic properties in line with some current state-of-the-art brain FE models were utilised. Emerging advanced brain tissue modelling techniques that consider anisotropy were not studied in this thesis (Giordano & Kleiven 2014; Sahoo et al. 2014). Sliding-only and CSF-solid skull-brain interaction modelling techniques were also investigated and implemented in the models. These investigations and implementations were supported with a limited set of original experiments conducted with rats to validate local brain motion in the rat model. The skull of the rat FE model was modelled as rigid and the model was utilised to simulate head sagittal rotational acceleration-deceleration experiments with rats. The monkey and the human models, which were intended for simulations of head impact events, were developed together with a complete model of the skull, neck and surrounding soft tissues. The monkey and the human brain FE models were combined to investigate improved methods to make animal experimental data applicable for humans, and to support the development of brain injury criteria and associated risk functions.

6. Review of Brain Injury Criteria, Thresholds and Risk Functions

Current vehicle safety regulations such as the FMVSS use ATDs for the evaluation of safety through crash tests. In addition to the physical ATDs, the vehicle industry uses mathematical models of the ATDs and of humans to develop and evaluate the performance of new products in both crash tests and simulated crashes. Regardless of the tools used, safety evaluations require injury criteria and injury risk functions that relate measurements from the physical tests or simulated crashes with risk of injuries in humans. Depending on the tools utilised and the injuries studied, such measurements can vary from tissue level (i.e. brain tissue strain estimated using FE models) to global level (i.e. head accelerations measured with sensors installed in ATDs). Tissue criteria rely on the capacity of brain FE models to predict proper tissue response and that the parameter chosen to describe the response correlates to risk of injury. Global brain injury criteria stand on the premise that there is a relationship between head kinematics and brain tissue responses and that this can predict the risk of a certain brain injury (Newman 2015).

A number of studies have suggested brain injury thresholds for humans based on a single parameter describing brain tissue strains or head kinematics. Within these, angular head motion has received especial attention due to its well established contribution in producing brain injuries in experiments with animals (Ommaya et al. 1967; Margulies & Thibault 1992; Davidsson et al. 2009). However, the same animal studies have also suggested that a single metric such as peak rotational acceleration may not fully characterise the diffuse brain injury spectrum, from concussion to severe DAI (Newman 1986; Yoganandan et al. 2008). Hence, global criteria that include variables such as time histories of translational and rotational head motion parameters have also been proposed and are currently under evaluation. A review of local and global brain injury criteria with simple or multiple variables, as well as their associated thresholds and risk functions is provided in this section.

6.1. Local Tissue Injury Criteria and Associated Injury Risk

Human and animal brain FE models have been utilised to develop local tissue injury criteria and associated risks. Zhang et al. (2004) utilised the Wayne State University human brain model to reconstruct football impacts and proposed shear stress in the brainstem to be the best injury predictor for concussions. Kleiven (2007) utilised the KTH human brain model to simulate series of concussive and non-concussive head impacts in American football and developed injury risk curves. Among others, strain in grey matter and corpus callosum, as well as stress at the brainstem were identified as some of the significant predictors for concussion. By applying logistic regression to each of the identified parameters, injury risk functions were calculated and thresholds suggested. For example, 50% probability of concussion was associated with a 26% strain in the grey matter and a 21% strain in the corpus callosum. Takhounts et al. (2003; 2008; 2013) developed the Cumulative Strain Damage Measurement (CSDM) which is a local tissue criterion that calculates the cumulative volume of brain tissue experiencing tensile strains over a predefined critical level. Based on reconstructions of scaled animal experimental data processed with the SIMon human brain FE model, a CSDM of 0.425 was associated with a 30% probability of DAI/AIS4+ injury (Takhounts et al. 2013).

Anderson (2004) simulated sheep head impact experiments (Anderson et al. 2003) with a sheep brain FE model. DAI risk curves were developed by comparing the results from the simulations with the amount and distribution of DAIs observed following the experiments. To quantify the amount and distribution of damaged axons, a grading system defined by the researchers involved was used in conjunction with a 4-mm grid placed over brain sections. The indicated level of stress that corresponded to approximately 10-20% risk of an intermediate level of axonal injury severity and distribution was

approximately 20 kPa. Lamy et al. (2013), reconstructed sagittal head rotational acceleration-deceleration experiments with rats (Davidsson et al. 2009) using an FE model of the animals, estimated brain tissue first principal strain at 3.9 and 4.7% thresholds for DAIs as detected with immunochemistry. The Anderson (2004) and the Lamy et al. (2013) studies did however not explain how the proposed thresholds relate to humans.

6.2. The Head Injury Criterion

The Wayne State Tolerance Curve (WSTC) (Lissner et al. 1960; Patrick 1965; Gurdjian et al. 1966) is recognised as the earliest global head tolerance criterion (Prasad 1999). The WSTC indicates a relationship between the average head anterior-posterior translational acceleration and its duration. Based on the clinical observation that concussion is present in 80% of patients with simple linear skull fractures (Melvin & Yoganandan 2015), it was assumed that by measuring the tolerance of the skull to fracture loads, one effectively infers the tolerance to brain injury. Lissner et al. (1960) presented the earliest version of the WSTC, which was hand-drawn from eight measurement data points from embalmed cadaver head drop impact tests that produced durations from 1 to 6 ms (Figure 4). Thereafter, Gurdjian et al. (1966) added data points from open head fluid percussion experiments with dogs of 6 to 20 ms duration and from human volunteer sled test data points and the curve was extended to include durations of up to 22 ms (Figure 5). The WSTC accounts for similar injury severity in head impacts; a given average acceleration at a particular pulse duration which lies below the curve is considered to cause at most a cerebral concussion without permanent sequelae while any point which lies above the curve is considered to be dangerous to life (Schmitt et al. 2014). Gadd (1966) noticed that representing the WSTC in a log-log axis, provided a line with a slope of 2.5 that fitted the experimental data (including cadaveric, animal and volunteer data) reasonably well. Based on this observation, the Severity Index (SI) was proposed (Gadd 1966). One problem found with the SI was that the head acceleration duration had to be arbitrarily terminated. To account for this issue, the SI was modified by Versace (1971) into the Head Injury Criterion (HIC, Equation 1). The HIC was adopted in the FMVSS208 regulation in 1974 and is to date the only global head injury criterion widely utilised for vehicle safety evaluation.

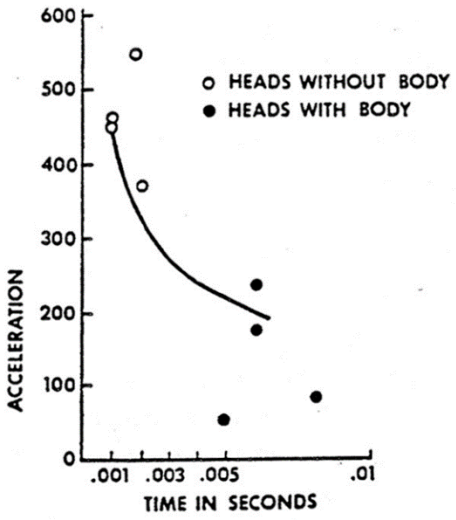


Figure 4. Original WSTC (Lissner et al. 1960, reprinted from McElhaney et al. 1976)

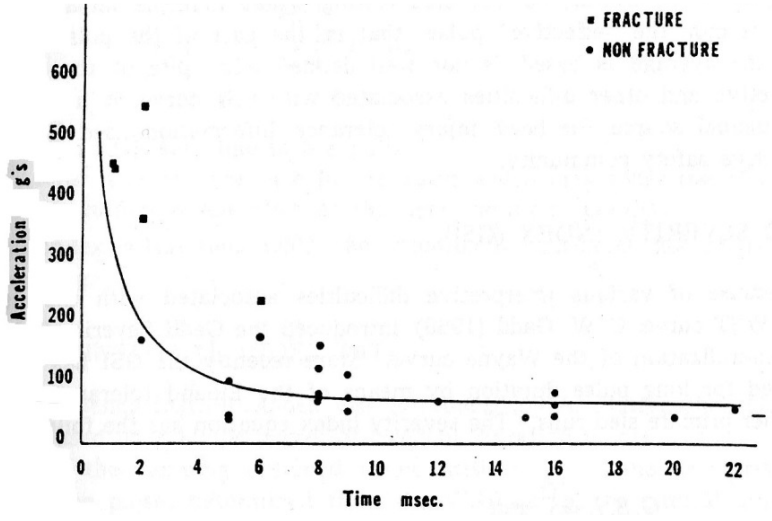


Figure 5. Original data from WSU including all data points, fracture and non-fracture, with first published tolerance curve by Gurdjian et al. 1966 superimposed on the plotted points (reprinted from McElhaney et al. 1976)

$$\mathrm{HIC} = \left\{\left[\frac{1}{t2-t1}\int_{t1}^{t2} a(t)dt\right]^{2.5}(t2-t1)\right\}_{\max} \qquad \text{(Equation 1)}$$

Currently, HIC_{15} and HIC_{36} (with integration time intervals of 15 and 36 ms, respectively) are used with skull fracture probabilities of 31% at HIC_{15} = 700 and 48% at HIC_{36} = 1000 (Eppinger et al. 1999). An AIS 4+ head injury risk curve based on HIC_{15} was developed by Prasad and Mertz (1985). Curves for other levels of AIS were developed by NHTSA based on the AIS 4+ curve developed by Prasad and Mertz (NHTSA, 2000)

The WSTC and the HIC are criticised for not considering factors that are important to brain injury. Such factors include the impact direction and area of contact, stiffness of the impacting surface, and rotational accelerations of the head induced by oblique impacts or when the torso is restrained (Newman 1986; McElhaney 2005). The effectiveness of HIC in reducing TBI is questioned due to the lack of a consistent relationship between linear skull fractures and neural injuries (Gennarelli 1980; Cooper 1982; Chapon et al. 1983; Nahum & Melvin 2012). In addition, the HIC was developed from test data that generated severe head injuries and it may not be suitable for prediction of moderate and milder forms of TBI, which predominantly occur in the absence of skull fractures (Got et al. 1983; Gennarelli et al. 1987, Addendum). Within all the limitations attributed to HIC, not accounting for rotational head motion has received the most attention, leading to a number of proposals for injury criteria that explicitly account for head rotational kinematics variables.

6.3. Rotational Acceleration Thresholds

Ewing et al. (1975) subjected military volunteers restrained with a 4-point belt to frontal sled decelerations. These produced head rotational accelerations in the sagittal plane of up to 2.7 krad/s^2 and durations longer than 20 ms without any adverse effects on the volunteers. Löwenhielm (1975) proposed a tolerance value in the sagittal plane of 4.5 krad/s^2 for gliding contusions based on bridging vein rupture produced by head impact tests with PMHSs. Pellman et al. (2004) suggested a 50% risk of concussion for head rotational acceleration peaks of 5.5 krad/s^2 obtained from head impact measurements taken through instrumented helmets in American football games. A similar methodology was followed by Rowson et al. (2012) to suggest a slightly higher threshold of 6.4 krad/s^2.

Table 4. Suggested rotational acceleration thresholds (in krad/s^2)

AIS	Ewing 1975	Löwenheim 1975	Ommaya 1984	Davidsson 2009	Margulies 1992	Pellman 2004	Rowson 2012	Gennarelli 2003	Injury type (example, AIS 2005)
Plane	Sagittal	Sagittal	Sagittal	Sagittal	Coronal	All	All	All	
0	<2.7								No injury
1			<1.7					3	mild concussion; No LOC
2			1.7			5.5	6.4	4.5	Brief LOC; Skull fracture
3		4.5	3					8	LOC 1-6 hours, contusion
4			3.9	10	9			12	DAI
5			4.5					14.5	DAI in corpus callosum and brainstem

LOC = Loss of consciousness; DAI = Diffuse Axonal Injury

Animal experiments are commonly utilised to estimate brain injury thresholds. Ommaya (1967) proposed cerebral concussion thresholds as a function of head rotational acceleration using primates and, in a successive study, as a function of both head rotational acceleration and rotational velocity change (Ommaya et al 1971). The data were scaled to be applicable for humans by applying scaling as suggested by Holbourn (1943). In Ommaya (1984) relationships between brain injuries at different AIS levels and

peak head sagittal rotational acceleration were established for angular velocities above 30 rad/s (Table 4). Margulies and Thibault (1992) suggested a DAI specific threshold of 9 krad/s^2 for rotation in the coronal plane. This threshold was obtained from impacts to the head of PMHSs and data from experiments in which baboons were subjected to rotational head acceleration-deceleration with acceleration peaks ranging from 7 krad/s^2 to 20 krad/s^2 (Gennarelli et al. 1982). Davidsson et al. (2009) estimated the sagittal head rotational acceleration threshold for DAI in humans to be 10 krad/s^2 for a pulse duration of 4 ms. This estimate was based on extrapolated results from rotational acceleration-deceleration experiments with rats. Gennarelli et al. (2003) proposed several rotational acceleration thresholds for diffuse brain injuries ranging from mild concussion to severe DAI. The proposed values were based on a review of the existing literature, including the scaled DAI (AIS4) data from primate experiments (Margulies & Thibault 1992) and American football concussion (AIS2) data (Newman et al. 2000). The thresholds for these two types of injury were plotted versus their corresponding AIS level and a linear fit was assumed to extrapolate the two data points to all AIS levels of diffuse brain injuries.

Several studies have suggested that contusion, concussion and DAI thresholds are a function of some measures of acceleration level and duration (Gurdjian et al. 1966; Ommaya et al. 1967; Ono et al. 1980). Hence, it has been suggested that diffuse brain injuries cannot be captured by a single metric of head kinematics (Yoganandan et al. 2008). An example to illustrate this is presented in Figure 6 which shows experimental data points from concussed and non-concussed primate head impact experiments represented in an acceleration amplitude vs duration plot (Ommaya et al. 1967). The figure shows that, as the duration of the event increased, the threshold for concussion decreased. Hence, suggesting the need of accounting for the duration of the events in the development of brain injury criteria.

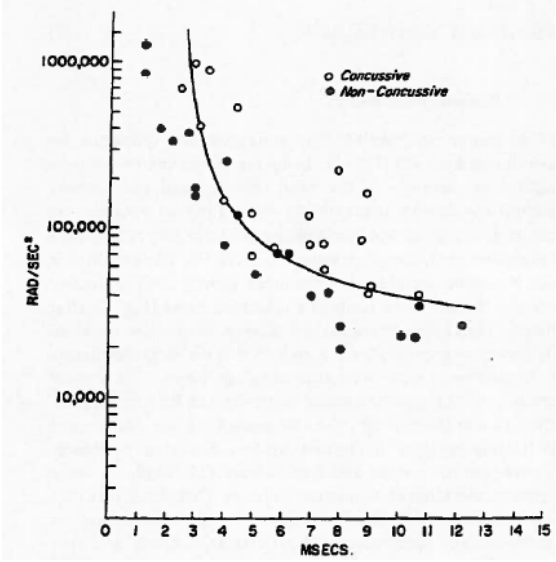


Figure 6. Tolerance curve for rotational acceleration amplitude versus duration for concussed and non-concussed primates (Ommaya 1967)

6.4. Global Injury Criteria and Associated Injury Risks based on Rotational Head Motion

Global brain injury criteria that explicitly account for angular head motion variables are summarised in Table 5. When available, their associated thresholds or risk functions are referenced in the table. Some of these criteria account for angular head motion only and are meant to be combined with the HIC for head injury evaluation. Others combine both translational and rotational accelerations as an attempt to capture the kinematics typical in head impacts.

The Generalized Acceleration Model for Brain Injury Threshold (GAMBIT) combines resultant head translational and rotational acceleration peaks to establish thresholds for severe head injuries (Newman 1986). PMHS head impact data that produced skull fractures and primate head impact tests data that produced prolonged (more than 6 hours) unconsciousness and DAI (Gennarelli et al. 1972) were used in the development of GAMBIT. The method used to scale the animal data to be applicable for humans was not clarified. GAMBIT = 1 corresponds with a 50% risk of AIS 3+ injuries with critical translational and rotational acceleration critical values of 250 g and 10 krad/s^2, respectively. Subsequent work including American football head impacts reconstructed with helmeted ATDs was conducted and concussion/AIS2 injury risk curves for GAMBIT were proposed (Newman et al. 2000). At the time of developing the GAMBIT, the need of accounting for directional and time dependency was suggested, but not taken into account since the data and tools available at the time were insufficient to develop thresholds that accounted for these characteristics. The Head Injury Power (HIP) is meant to account for directional dependent translational and rotational effects as well as durations (Newman et al. 2000). HIP stands on the hypothesis that the maximum rates of translational and rotational energy are the controlling mechanism in brain injuries induced by head impacts. Direction dependency is assigned by weighting the corresponding direction component with the corresponding moment of inertia of the head. Due to lack of human data, mass and moments of inertia from an ATD head were applied to the equation. HIP was developed from the same reconstructions of helmeted head impacts as the GAMBIT and a concussion AIS 2 injury risk curve was also developed (Newman et al. 2000). According to this risk curve, a HIP of 12.5 kW corresponds to a risk of concussion of 50%. Kleiven (2007) proposed, based on reconstructions of head impacts from American football with the KTH brain model, a linear combination of HIC_{36} and the peak change in rotational velocity. The proposed criteria was denoted KLC. The choice of rotational velocity instead of rotational acceleration was supported by previous experimental work with PMHSs (Hardy et al. 2001) which suggested that peak change in rotational velocity could better capture brain motion than peak rotational acceleration. Kimpara and Iwamoto (2012) applied a similar methodology to reconstruct football impacts with the THUMS model and developed two injury criteria; the Power Rotational Head Injury Criterion (PRHIC) and the Rotational Injury Criterion (RIC). PRHIC was an adaptation of the HIP in which only the rotational terms are considered. RIC is an adaptation of the HIC in which rotational accelerations are considered instead of the translational.

Recently, the Brain rotational Injury Criterion (BrIC) has been proposed (Takhounts et al. 2013). BrIC is based on peak rotational velocity in three directions (head x-, y- and z-) and does not account for time dependency. It is intended to be used together with HIC. Large amount of test and simulation data were used in the development of BrIC, which consisted of several steps. First, a total of 67 experimental animal injury data including rhesus monkeys, baboons, and miniature pigs were selected (Abel et al.1978, Stalnaker et al. 1977, Meaney et al. 1993). These data were predominantly comprised of rotational acceleration-deceleration experiments that produced DAIs. The injuries from the animal tests were assumed to correspond with AIS 4+ injury in humans. The head motion data from the animal experiments were scaled in amplitude and time, to account for size differences between the animal and humans (Takhounts et al. 2003), and applied to the rigid skulls of two different human brain FE models; the SIMon and the GHBMC. Injury risk curves that relate the tissue strain measurements from the simulations (MPS and CSDM) with a probability of AIS 4+ were constructed. Thereafter, AIS 1+, 2+, 3+ and 5+ were scaled from the AIS 4+ curve using the ratios between corresponding risk curves for HIC at 50% risk. Second, 190 tests in which pendulum impacts were delivered to the head of different ATDs at various impact angles and energies were reconstructed using the two different human brain FE models. Linear correlation analysis was conducted between the peak values of head kinematic metrics from the tests and peak MPS and CSDM values from the simulations. From this analysis, it was concluded that the resultant rotational velocity was the best correlation to the strain measures. Hence, the BrIC criterion based on peak resultant rotational velocity was proposed. Third, head motion data

from 223 full vehicle NCAP and offset frontal crash tests conducted with 7 different ATDs were collected from the NHTSA database and processed with SIMon and GHBMC. The kinematics and tissue data were added to the pendulum impact test data set and analysed. It was found that the best linear fit between the kinematics data and the MPS/CSDM from the simulations was provided by a critical resultant rotational velocity ω_{cr}= of 54 rad/s. Such value was suggested to correspond with a 50% risk of DAI/AIS4+ injuries according to the risk curve previously developed from the scaled and processed animal data. However, as detailed analysis progressed, it was noticed that when the human brain FE models were exercised with the same prescribed rotational motion in different directions, different critical values of maximum angular velocity was achieved. This was interpreted as a need to separate direction components and a modified BrIC formulation with three directional terms was proposed (Table 5). Finally, the critical rotational velocity values for each direction were calculated from the complete data set and established in ω_{xcr} =66, ω_{ycr}=56, and ω_{zcr}=42 rad/s. These critical values imply that, when BrIC is calculated, more weight is placed on rotation around the z-axis (head horizontal plane), followed by the y-axis (head coronal plane) and x-axis (head coronal plane) for a given and equal amplitude of rotational velocity.

Table 5. Global Head injury criteria including rotational head motion variables

Criterion and reference	***Injuries***	***Equation***	***Risk functions***
GAMBIT Newman 1986	Severe head injuries Concussions	$\mathrm{GAMBIT} = \left[\left(\frac{a_{max}}{a_{cr}}\right)^2 + \left(\frac{\alpha_{max}}{\alpha_{cr}}\right)^2\right]^{\frac{1}{2}}$	$\mathrm{p(AIS2)} = \frac{1}{1+e^{6.777-17.26GAMBIT}}$
HIP Newman 2000	Concussions	$\mathrm{HIP} = \sum_{i=1}^{3} ma_i \int a_i dt + \sum_{i=1}^{3} I_i \alpha_i \int \alpha_i dt$	$\mathrm{p(AIS2)} = \frac{1}{1+e^{4.682-0.003655HIP}}$
KLC Kleiven 2007	Concussions	$\mathrm{KLC} = 0.004718\omega_{Res} + 0.000224\mathrm{HIC}$	-
RIC Kimpara 2012	Concussions	$\mathrm{RIC} = \left\{\left[\frac{1}{t2-t1}\int_{t1}^{t2} \alpha(t)dt\right]^{2.5} (t2-t1)\right\}_{max}$	$\mathrm{p(AIS2)} = \frac{1}{1+e^{7.036-0.000000679RIC}}$
BrIC Takhounts 2013	DAIs/AIS4+	$\mathrm{BrIC} = \sqrt{\left(\frac{\omega_x}{\omega_{xcr}}\right)^2 + \left(\frac{\omega_y}{\omega_{ycr}}\right)^2 + \left(\frac{\omega_z}{\omega_{zcr}}\right)^2}$	$\mathrm{p(AIS4)} = 1 - \frac{1}{e^{-\left(\frac{\mathrm{BRIC}}{1.204}\right)^{2.84}}}$
RVCI Yanaoka 2015	DAIs/AIS4+	$\mathrm{RVCI} = \sqrt{Rx\left(\int_{t1}^{t2} \alpha_x dt\right)^2 + Ry\left(\int_{t1}^{t2} \alpha_y dt\right)^2 + Rz\left(\int_{t1}^{t2} \alpha_z dt\right)^2}$	-

a(t): Translational acceleration; a_{max}: Maximum translational acceleration; a_{cr}: Critical translational acceleration; a_i: Directional translational acceleration; $\alpha(t)$: Rotational acceleration; α_{max}: Maximum rotational acceleration; α_{cr}: Critical rotational acceleration; α_i: Directional rotational acceleration; ω_{max}: Maximum rotational velocity; ω_{cr}: Critical rotational velocity; m: head mass; I_{ii}= Directional dependent head moment of inertia

The BrIC is currently under evaluation (Gabler et al. 2015; Mueller et al. 2015; Panzer et al. 2015; Yanaoka et al. 2015). Panzer et al. (2015) conducted an assessment of BrIC by processing a large amount of crash data with the GHBMC brain FE model. The data included the pendulum and vehicle crash test data used to develop the BrIC and two additional data sets; car-to-pedestrian PMHS and ATD tests and ATD data from small and moderate overlap frontal crash tests provided by the Insurance Institute for Highway Safety in the US (Panzer et al. 2015). The results indicated that BrIC may provide better correlation to brain strains than HIC, RIC, GAMBIT and HIP under the simulated conditions. The results also identified over-prediction of injury risks by BrIC in car-to-pedestrian crashes and potential issues

for events where the head is loaded for a long time. Yanaoka et al. (2015) utilised the GHBMC model to process ATD data from the NHTSA tests database, and complemented it with large amounts of simulated occupant car crashes and car-to-pedestrian impacts with multibody models. The study evaluated BrIC, RIC and HIP and proposed a new criterion that was denoted Rotational Velocity Change Index (RVCI) (Table 5). The RVCI accounts for direction and time dependent head rotational velocity and aims at establishing correlation with strain data for both occupant and pedestrian impacts. The results identified the same problems of over prediction of injury risks in car-to-pedestrian impact as Panzer et al. (2015). It was also shown that BrIC provided better correlation to strains than RIC and HIP but lower than the RVCI proposed by the authors. The authors did not mention how to establish injury thresholds for the proposed criterion. Finally, Mueller et al. (2015) compared the BrIC and the HIC values measured in small and moderate overlap vehicle frontal crash tests. The results showed a high correlation between HIC and BrIC. When the predictions were compared to brain injury risks observed in real-world crashes, with similar vehicle damage as obtained in the crash tests, it was noted that BrIC predicted higher brain injury risks than those obtained in real-world crashes. The authors questioned the method utilised in Takhounts et al. (2013) to scale the animal data prior to its use in the development of the BrIC.

6.5. Methods to apply Animal Data to Humans

Holbourn (1943, 1956) suggested that the level of rotational acceleration required to produce injury in brains with similar properties and shapes could be scaled with an inversely proportional relation to the ⅔ power of the masses of the brains. Holbourn's crude scaling requires that the brain acts as an elastic medium, the brain tissue is homogeneous and isotropic in nature (Ommaya et al. 1967). These requirements are not fulfilled since it is well established that brain tissue behaves as a non-linear (Bilston et al. 1997), viscoelastic (Arbogast & Margulies 1998; Darvish & Crandall 2001; Prange & Margulies 2002), anisotropic (Shuck & Advani 1972; Arbogast & Margulies 1998), and inhomogeneous material (Elkin et al. 2010; 2011). Margulies et al. (1990) conducted work to verify Holbourn's equation based on brain-like (gel) physical models of primates and humans. Such models were used to deduct relationships between shear strain and rotational acceleration for different shapes and sizes, and to suggest angular velocity and acceleration thresholds for DAI in humans. Ommaya et al. (1967) applied Holbourn's scaling for a preliminary estimation of rotational acceleration across several primate species but admitted that the rotational thresholds should be considered reliable for the Rhesus, sketchy for the chimpanzee, and completely speculative for humans. Still, Holbourn's approach is used to extrapolate thresholds from any animal species for humans.

Recent efforts have attempted to improve past scaling in the development of BrIC. Takhounts, Eppinger, et al. (2003) applied an equal stress/equal velocity relationship to scale head kinematics motion data from experiments with primate and swine to the size of humans and applied the scaled data to human brain FE models. This methodology allows scaling of kinematic data including head translational, head rotational, and duration of the acceleration. The latter is important, since it is well established that acceleration thresholds for short durations are higher than for long duration impacts (Versace 1971; Ono et al. 1980; Ommaya 1985). This method does however not allow establishing correlation between the animal head-neck kinematics and the injuries produced; predicted brain strains are not expected to be identical in the animal and the human head when scaled head kinematics are applied to the two FE models. In addition, the effect that the impact phenomena have on injury risk is not accounted for despite its contribution to concussions (Ommaya et al. 1967), contusions (Ono et al. 1980) and DAI (Anderson et al. 2003).

An approach to improve the Takhounts method may be to reconstruct the experiments using FE models of the animal specimens and transfer the data to humans via simulations conducted with human FE models. Mendis (1992) developed a baboon brain FE model to study brain strain during rotational acceleration of the head, and correlated the strains calculated in the simulations with axonal injury grade

from three selected experiments by Gennarelli et al. (1987). Thereafter, the geometry of the baboon model was scaled to a human brain size model and exercised this model to determine the loading conditions that would produce similar brain strains as in the baboon model. The work by Mendis (1992) was technically limited and reduced to only three selected experiments, but was pioneering in proposing a method to establish local brain tissue equivalence from primates to humans using FE models of the animal and human-like brains. Such an approach can be applied to simulate larger series of experiments and to construct functions that relate the internal mechanical parameters, or tissue criteria, from the simulations with the risk of brain injuries from the experiments (Ueno et al. 1995; Anderson 2004; Fijalkowski et al. 2009; Ren et al. 2015). These functions may then, under the assumption that animal and human brain tissue is similar in stiffness and has the similar injury probability for a given deformation of the brain tissue, be used in human FE models. This would provide a link between deformation fields inside the brains of animals and humans and thus may be more physically/biomechanically justifiable as recognised by Takhounts et al. (2013). Since the human brain is at large a scaled-up primate brain in its cellular composition (Herculano-Houzel 2009, 2012) and the mechanical properties of primate and human brain tissue are similar (Galford & McElhaney 1970), the main assumptions are fulfilled.

Figure 7 illustrates the flow of data in the three different approaches to make animal data applicable to humans denoted as Injury thresholds crude scaling (Holbourn 1943), Head kinematics scaling (Takhounts et al. 2013) and Local brain tissue equivalence approach.

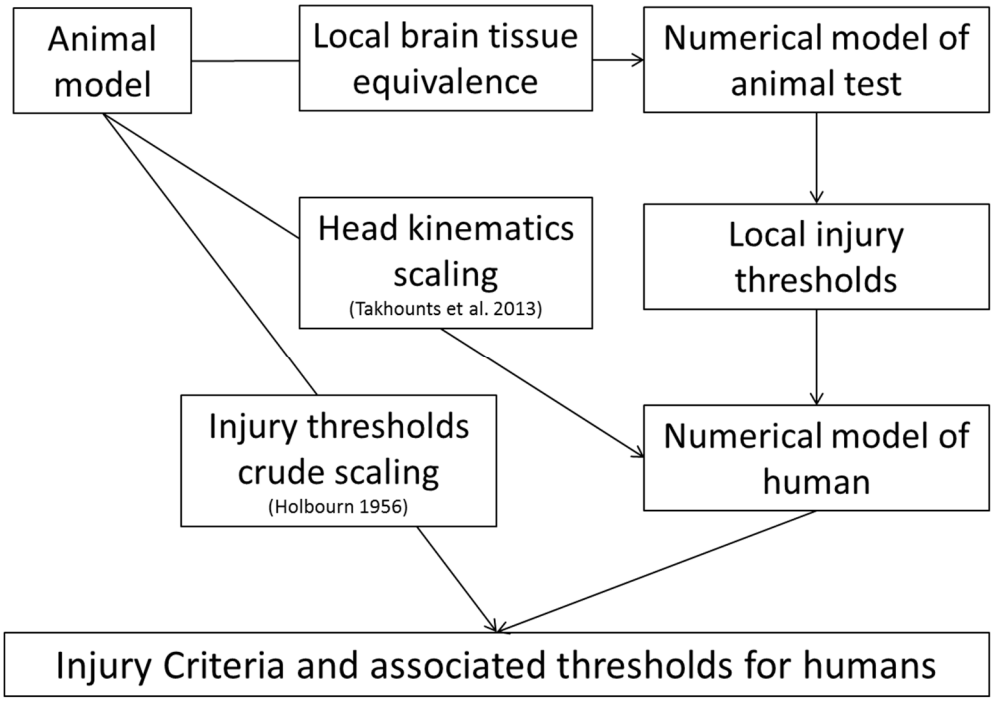


Figure 7. Flow of data in different approaches to make animal experimental brain injury data applicable to develop injury criteria and thresholds for humans.

6.6. Summary

The HIC (Gadd 1966, Versace 1971), currently the only head injury criterion in use in vehicle regulations and safety assessment programmes, predominantly calculates the risk of skull fracture from the resultant translational head acceleration over time. The HIC has been used extensively over several decades and contributed to a substantial reduction of vehicle collision related head injuries. However, since there is no consistent relation between linear skull fractures and neural injuries (Gennarelli 1980; Cooper 1982;

Chapon et al. 1983; Melvin & Yoganandan 2015), the effectiveness of HIC in reducing TBI is questioned. The HIC was originally developed for severe head injuries and it may not be suitable for prediction of moderate and mild TBIs, which predominantly occur in the absence of skull fractures (Got et al. 1983; Gennarelli et al. 1987), or for prediction of severer TBIs which mechanisms are not related to those that produce skull fractures.

Recently, Takhounts et al. (2013) and Yanaoka et al. (2015) have opted for the development of the BrIC and the RVCI, criteria designed to complement the HIC in the evaluation of severe DAI/AIS4+ injuries. The combination of HIC and BrIC is a reasonable approach from a current regulation and safety assessment programme perspective, since current vehicles and restraint systems that have proved safe have been optimised through high energy crash tests using HIC. However, HIC in combination with rotational-only criteria (BrIC, RVCI) may not account for a large number of the concussions that occur at low energy traffic accidents (Addendum). It may also be limited in its ability to predict mechanisms that cause Concussions and DAIs in the absence of skull fractures and without rotational head motion (Group A in Ono et al. 1980; Marmarou et al. 1994; Fievisohn 2015). Nevertheless, independently of its possible combination with HIC, BrIC provides a certain level of improvement with respect to past injury criteria (HIC, GAMBIT, HIP, and RIC) in terms of correlation to strain measures from simulations with brain FE models (Takhounts et al. 2013; Panzer et al. 2015; Yanaoka et al. 2015). At the same time, possible issues that may arise from not incorporating duration effects (Yanaoka et al. 2015) or from the possible utilisation of BrIC in loading environments which it has not been designed for, such as car-to-pedestrian impacts, have also been raised (Panzer et al. 2015; Yanaoka et al. 2015). In addition, the methodology utilised in the development of BrIC to scale animal experimental data to establish injury risks for humans may have led to misleading injury risk estimations (Mueller et al. 2015). Of especial concern is the method utilised in the development of BrIC to extrapolate the curves obtained from DAI/AIS4+ injuries to all levels of AIS injury levels which lack any scientific basis. In other words, more reliable methods to make animal experimental data applicable for humans are needed as is criteria that can be used with ATDs able to predict mild, moderate and severe TBIs not necessarily associated with skull fractures.

In this thesis, an enhanced methodology to make animal experimental data applicable for humans has been investigated and applied to develop a new global injury criterion and associated thresholds for humans (Figure 7). A large series of monkey head impact experiments were simulated with a monkey brain FE model. Injury risk curves were developed that relate local brain tissue strains from the simulations to physiological changes measured at the experiments. These curves were used, together with series of head impacts simulated with a human brain FE model, to support the development of a new global injury criterion and associated thresholds for humans.

7. Summaries of Appended Papers

In this thesis TBI data from experiments with rats (Davidsson et al. 2009; 2011) and monkeys (Ono et al. 1980) were re-analysed and simulated with newly developed and partially validated FE models of the animals' brains. In addition, a human brain FE model was developed and validated using PMHS experimental data from the literature. The rat brain FE model was developed and validated (Paper I), later enhanced and applied for research on the effect of ageing on brain injury risk (Paper II). The monkey brain FE model was utilised in case-by-case simulations of 43 head impact experiments with monkeys (Papers III and IV). The results from these simulations were combined with 76 impacts simulated with the human brain FE model and utilised to develop a new conceptual global brain injury criterion and associated thresholds for humans (Papers V and VI). All simulations in this thesis were conducted in LS-DYNA FE code (LSTC Inc., Livermore, CA, USA). In this chapter, the rat, the monkey and the human brain models developed are presented in detail together with a summary of the papers included in this thesis. The full papers are appended at the end of this thesis.

7.1. Method – Brain Finite Element Models

The rat brain FE model presented in Papers I and II was intended for simulations of sagittal head rotational acceleration-deceleration trauma experiments with rats (Davidsson et al. 2009; 2011). These experiments did not involve impact to the skull and the trauma never produced skull fractures. Hence, the skull was assigned rigid properties and the rotational head accelerations measured in the experiments were imposed to the skull of the model to simulate the experimental loading conditions. The model was developed in two versions as presented in Paper I and Paper II, respectively. The model in Paper I consisted of a total of 147,036 elements, including 79,469 solids and 67,567 shells. The lateral ventricular spaces were modelled and left empty. The skull-brain interface was modelled with a sliding-only contact approach. The model in Paper II consisted of 190,526 elements, including 131,746 solids and 58,780 shells. Both the ventricular and the layer of CSF between the skull and the brain were filled with solid elements that shared nodes with the surrounding regions. These elements were assigned material properties according to a hypoelastic material model with a bulk modulus of 2.1 GPa (ρ=1,000 kg/m^3, υ=0.49999). The implications of different ventricle modelling techniques are exemplified in Appendix B. Figure 8 compares a coronal section in each model version (Paper I on the left and Paper II on the right). Details of the modelled components and how these related to each other are provided in column 3 and 4 in Table 6

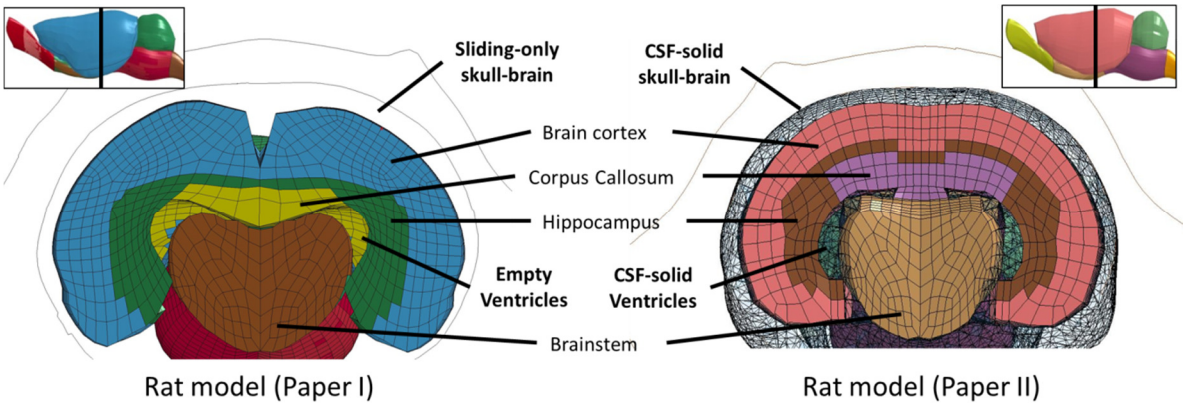


Figure 8. Coronal section of rat brain FE model in Paper I (left) and Paper II (right)

Table 6. Summary of properties of the brain FE models developed in this thesis

Model component		*Rat model (Paper I)*	*Rat model (Paper II)*	*Monkey model (Papers III, IV and V)*	*Human model (Paper VI)*
Outer Skin	El type Mat mod Mat prop	Not modelled	Not modelled	Quad memb t=1 Null -	Quad memb t=1 Null -
Scalp	El type Mat mod Mat prop	Not modelled	Not modelled	Tetra Fu Chang foam Scalp (McElhaney)	Hexa Fu Chang foam Scalp (McElhaney)
Scalp-Skull	Interface	Not modelled	Not modelled	Tied	Shared nodes
Skull outer table	El type Mat mod Mat prop	Quad shell Rigid -	Quad shell Rigid -	Quad shell Null -	Quad shell Piece-wise linear plastic E=6.48 GPa
Skull diploe	El type Mat mod Mat prop	Not modelled	Not modelled	Hexa Piece-wise linear plastic E=6.48 GPa (McElhaney)	Hexa Isotropic Elastic Plastic E=40 MPa
Skull inner table	El type Mat mod Mat prop	Quad shell Rigid -	Quad shell Rigid -	Quad shell Null -	Quad shell Piece-wise linear plastic E=6.48 GPa
Dura mater	El type Mat mod Mat prop	Not modelled	Not modelled	Quad shell t=0.5 Elastic E=40 MPa (Melvin)	Quad shell t=1 Elastic E=40 MPa (Melvin)
Skull-Dura	Interface	Not modelled	Not modelled	Tied	Tied
Arachnoid mater	El type Mat mod Mat prop	Not modelled	Not modelled	Quad membrane t=0.5 Elastic E=12.5 MPa (Jin)	Not modelled
Pia mater	El type Mat mod Mat prop	Quad memb t=0.1 Elastic E=40 MPa (Zhang)	Quad memb t=0.1 Elastic E=30 MPa (Kimpara)	Quad memb t=0.5 Elastic E=12.5 MPa (Jin)	Quad memb t=1 Elastic E=12.5 MPa (Jin)
CSF	El type Mat mod Mat prop	Not modelled	Tetra Elastic Fluid K=2.1 GPa	Hexa Elastic Fluid K = 2.1 GPa	Tetra Elastic Fluid K = 2.1 GPa
Skull-Brain	Interface	Sliding-only	CSF-solid	Sliding-only	CSF-solid
Brain	El type Mat mod Mat prop	Hexa General viscoelast Rat tissue (Elkin)	Hexa General viscoelast Rat tissue (Elkin)	Hexa Brain Linear Viscoelast G_0=10.3 KPa, G_1=3.7 KPa (McElhaney)	Hexa Brain Linear Viscoelas G_0=1.6 KPa, G_1=0.9 KPa (Takhounts)
Falx	El type Mat mod Mat prop	Not modelled	Not modelled	Hexa Elastic E=12.5 MPa	Hexa Elastic E=12.5 MPa
Brain-Falx	Interface	Not modelled	Not modelled	Sliding-only	CSF-solid
Tentorium	El type Mat mod Mat prop	Not modelled	Not modelled	Quad memb t=1 Elastic E=12.5 MPa	Quad memb t=1 Elastic E=12.5 MPa
Brain-Tento	Interface	Not modelled	Not modelled	Surface to surface	Surface to surface

El=Element, Mat=Material, t=thickness in mm, ρ= density, υ= Poisson's ratio

The monkey brain FE model presented in Papers III, IV and V was intended for simulations of sagittal head padded impact experiments with monkeys (Group C in Ono et al. 1980). In the experiments, neck hyperextension motion and brainstem pathology were produced by the impacts. Hence, a complete model of the head and neck-complex was developed. The model consisted of 356,567 elements, including 258,447 solid and 98,120 shell elements. Figure 9 shows images of different modelled brain regions (left) as well as the falx and the tentorium (right). Figure 10 shows a coronal section of the model and a close up of this section with details of the different structures. A simplified approach was adopted to model the ventricles; these were filled with brain tissue elements. The space between the brainstem and the internal surfaces of the cerebral hemispheres was minimised and a tied contact was defined between the upper brainstem surface and the surfaces surrounding the adjacent hemispheres. The brain-skull interface was modelled with a sliding-only approach similarly to past studies with human brain FE models (Zhang et al. 2001; Kleiven 2002). Details of the modelled components and how these related to each other are provided in column 5 in Table 6. The possible influence of the approaches adopted to model the ventricles and the brain-skull interface is further evaluated in Appendices B and C.

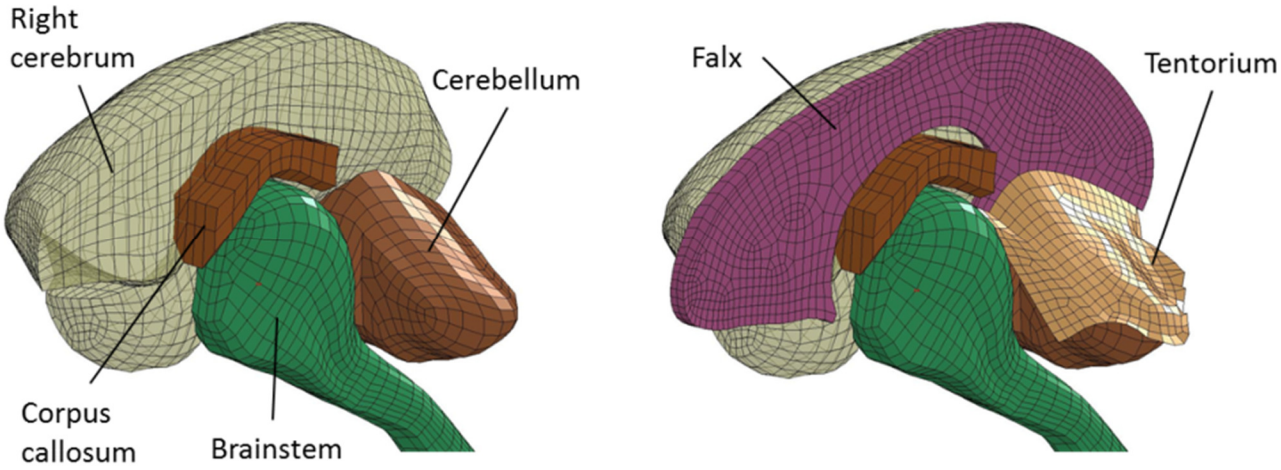


Figure 9. Monkey brain FE model (Papers III, IV and V): Brain regions, falx and tentorium

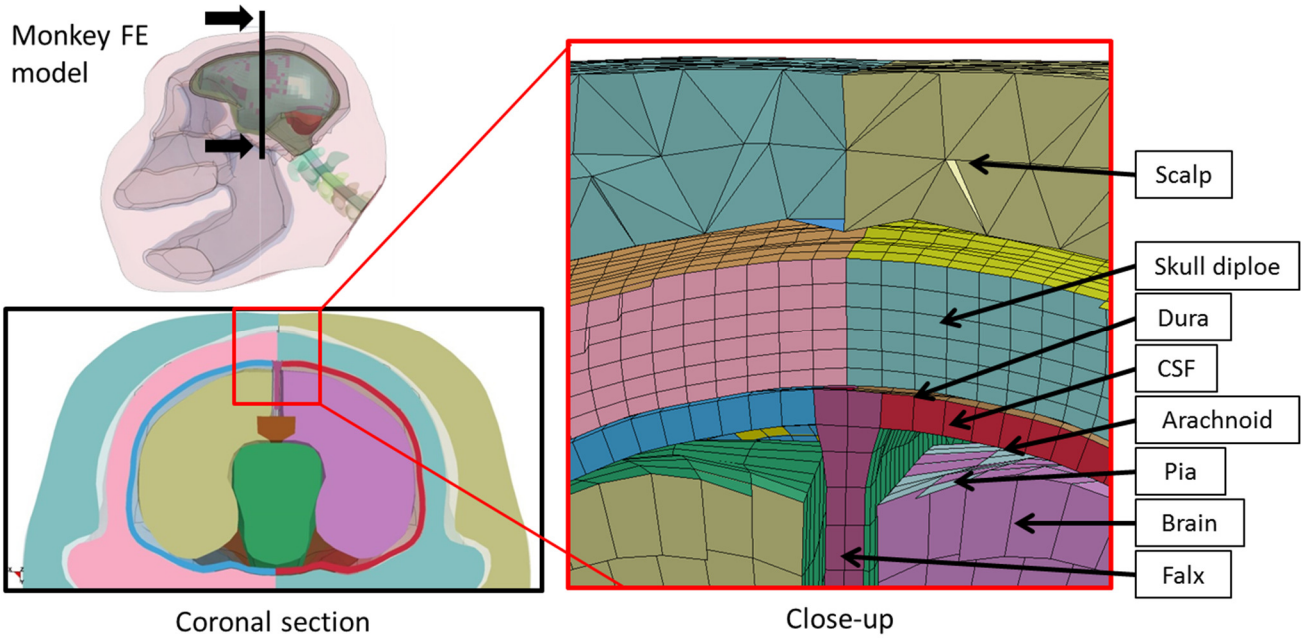


Figure 10. Monkey brain FE model (Papers III, IV and V): Coronal section and close up

The human brain FE model presented in Paper VI was intended for simulations of head impacts under a wide range of impact conditions representative of those occurring in real-world car crashes. Hence, a complete model of the head neck complex was built. The final model consists of a total of 345,557 elements, including 291,948 solids and 53,609 shells. The brain regions, falx and tentorium were modelled similarly to the monkey model. Figure 11 shows images of these brain regions (left), as well as the falx and the tentorium (right). Figure 12 shows a coronal section of the human model with details of the different structures included. Both the ventricular and the brain-skull spaces were filled with CSF-solid elements that shared nodes with the surrounding regions. Details of the modelled components and how these related to each other are provided in column 6 in Table 6.

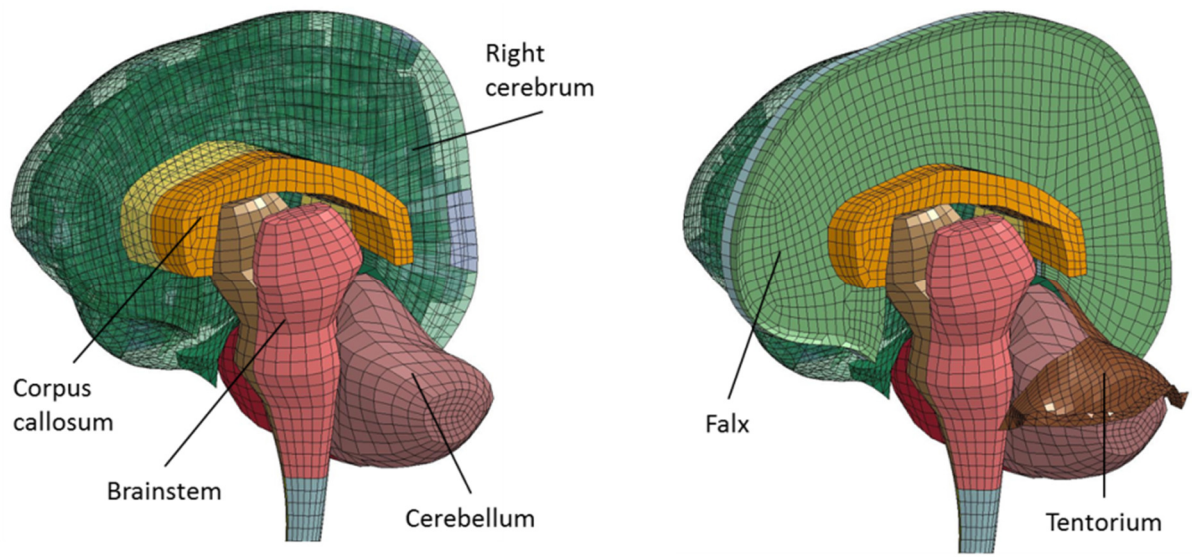


Figure 11. Human brain FE model (Paper VI): Brain regions, falx and tentorium

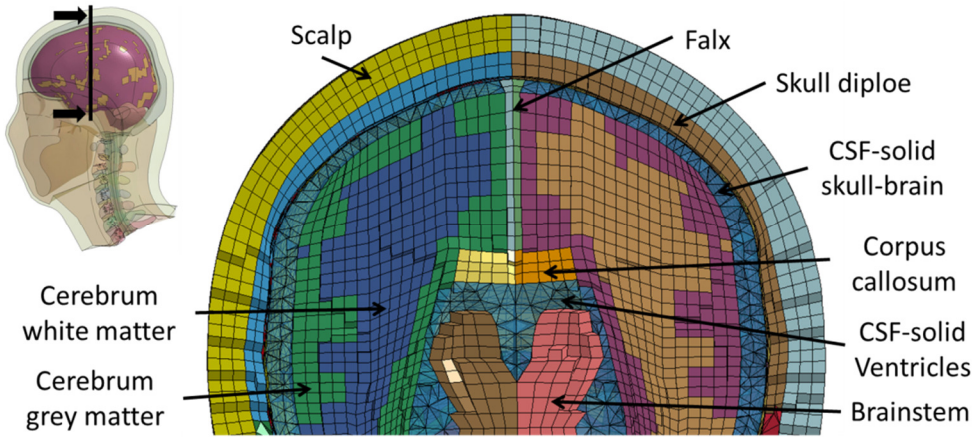


Figure 12. Human brain FE model (Paper VI): Coronal section

7.2. Papers I and II

Papers I and II investigated craniocervical and brain kinematics that produce DAI and often subdural haematoma in rotational acceleration head trauma experiments with rats (Figure 13). The rat brain FE model was developed and the local motion of the brain was validated against a new series of experiments with rats designed to study relative motion between the brain and the skull. Rotational head acceleration-deceleration experiments by Davidsson et al. (2009; 2011) were simulated to assess the capacity of the model to predict high-strain concentrations in brain regions commonly exhibiting axonal injuries following rotational trauma. For this, peak strain distribution patterns from the simulations were compared with schemes of the axonal injuries detected in the experiments. Further, brain volume and region specific brain material properties were implemented into the model to account for aging. Three age-dependent models were established, Young Adult, Mature Adult and Old Age, that were used in parametric studies to investigate possible effects of age related intracranial changes on the risk of DAI and ASDH under rotational head loading (Paper II).

The simulation results showed high strain concentration in the brainstem and in the border between the corpus callosum and cortex, which was consistent with the regions in which DAI was found in the experiments (Figure 13). Sequential analysis of the simulated trauma progression (Paper II) indicated that ASDH develop at an early stage of the trauma, while DAI develop at a later stage. Tissue stiffening from Young Adult to Mature Adult rats resulted in lower strain amplitudes in the brain while larger brain volumes exhibited intermediate level strains; especially towards the rear of the brain. Such observations were consistent with the results obtained in experiments with Young Adult and Mature Adult rats. When brain tissue softening and brain atrophy were introduced in the model, to account for aging, DAI and ASDH injury risk indicators increased.

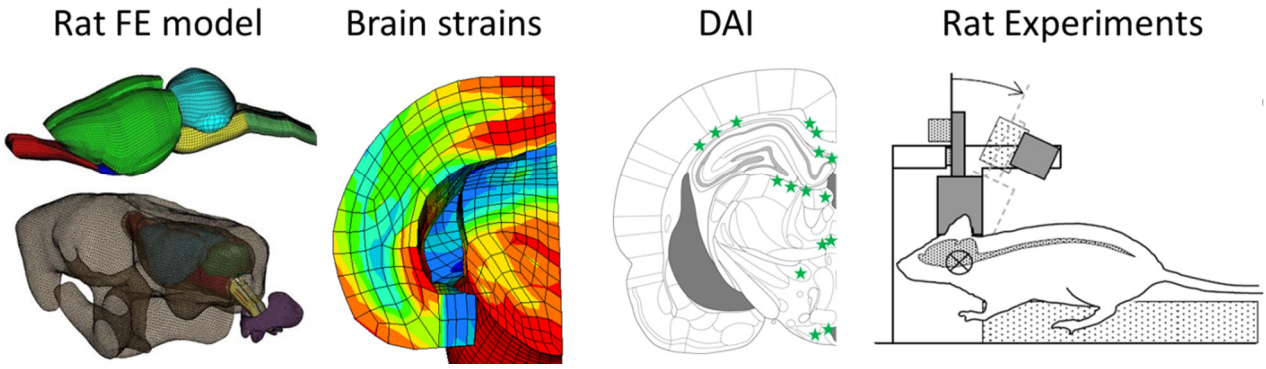


Figure 13. From left to right: Images of the rat brain FE model, brain strains fringe plots from a simulated rotational experiment (Paper II), a scheme with DAI locations from the experiments, and a schematic of the experiments with rats

To conclude, the detailed rat brain FE models predicted high brain tissue strains in locations known to exhibit DAI following experiments. They also suggest that injury type and age specific reduction strategies in the development of superior restraint systems for elderly may be possible, motivating further studies on isolated brain injury types and age-dependency in brain trauma.

7.3. Papers III and IV

The aim of Papers III and IV was two-fold: to investigate the injury mechanism that produced concussion symptoms and some degree of pathology in the experimental setting with primates; to provide brain tissue injury risk curves to support the development of injury criteria and thresholds indented to be used in test with ATDs. The monkey brain FE model was developed and partially validated according to experimental data from the literature. The validated model was utilised to simulate a series of 19 frontal and 24 occipital non-fatal head impact experiments selected from the past monkey head trauma experiments (Ono et al. 1980). The impacts were delivered to the head through a padded piston, with impact velocity, maximum impact stroke and padding rubber properties set for each test, which resulted in combined rotation and translation of the head. The 19 occipital impacts selected for simulation were delivered to 7 specimens who suffered 9 concussions (Paper III) and the 24 frontal impacts also selected for simulations were delivered to 8 specimens who suffered 10 concussions (Paper IV). Records of concussion, evaluated according to changes in physiological functions such as loss of corneal reflex, and changes in respiration and cardiovascular patterns during and immediately after the impacts were matched with the simulation results. Finally, risk functions for concussion as a function of simulated brain tissue responses were developed.

The simulation results showed high strain concentration in the dorsal part of the brainstem, close to the skull foramen magnum, which coincided with the locations in which brainstem pathology was reported in few of the experiments (Figure 14). Risk functions for concussion as a function of strains in the brainstem were developed. These functions, assuming similar brain tissue mechanical properties and tissues injury thresholds between primates and humans, can be used to relate brain tissue strains and risk of injury in studies with human brain FE models.

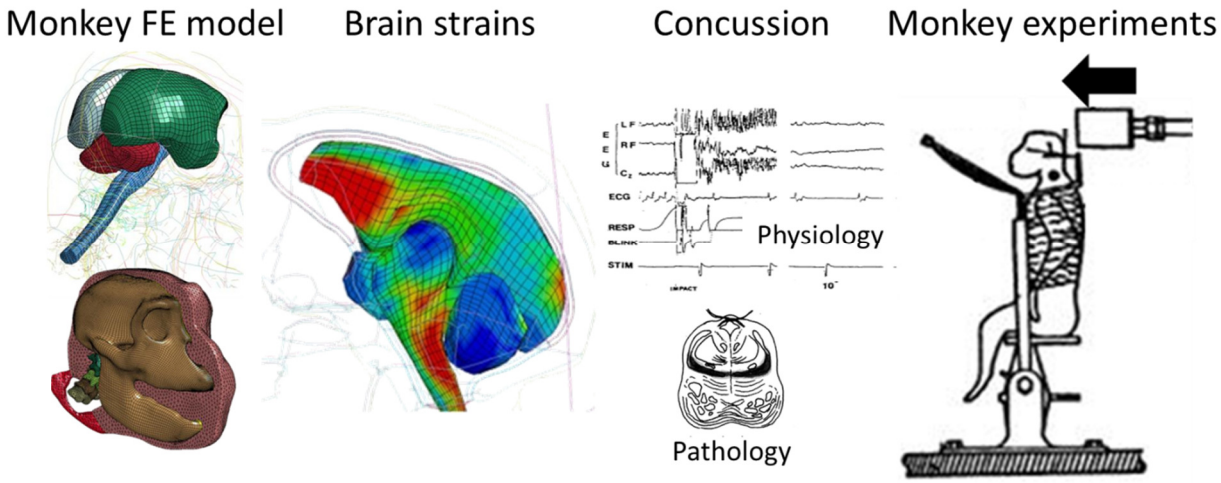


Figure 14. From left to right, monkey brain FE model images, brain strain fringe plots from a simulated occipital impact experiment, concussion like physiological changes and brainstem pathology from the experiments and illustration of the experimental model

The findings presented in these papers support the hypothesis suggested at the time of the experiments whereof brainstem trauma was responsible for the concussion symptoms (Kanda et al. 1981). The findings also highlight the importance of considering the craniocervical motion in the investigation of concussion mechanisms and in the development of injury criteria for concussions. In addition, the risk functions proposed can be used to support the development of a global brain injury criterion for usage with ATDs.

7.4. Papers V and VI

The aim of Papers V and VI was to develop a conceptual global brain injury criterion and associated injury thresholds with the potential of, when properly applied, reducing the amount and severity of diffuse brain injuries in traffic accidents. The developed concept, denoted as Brain Injury Threshold Surface (BITS), establishes equal brain injury risk surfaces as a function of resultant head rotational acceleration, resultant head translational acceleration, and the duration of this acceleration. Combinations of head kinematics and impact durations that lie above or below a surface are expected to produce higher or lower brain strains, respectively.

In Paper V, the BITS concept was developed using the head kinematics, occurrence of concussion, and brainstem strain data from the 43 head impact experiments simulated with the monkey brain FE model (Papers III and IV). The data were represented in a 3D Cartesian space with resultant rotational acceleration, resultant translational acceleration, and duration as axis. BITSs were optimised to the injury occurrence data from the experiments and to the strain data from the simulations by using the Accuracy method (Fawcett 2006). The resulting BITSs appeared to explain the variance seen in both the injury and simulation data (Figure 15, left).

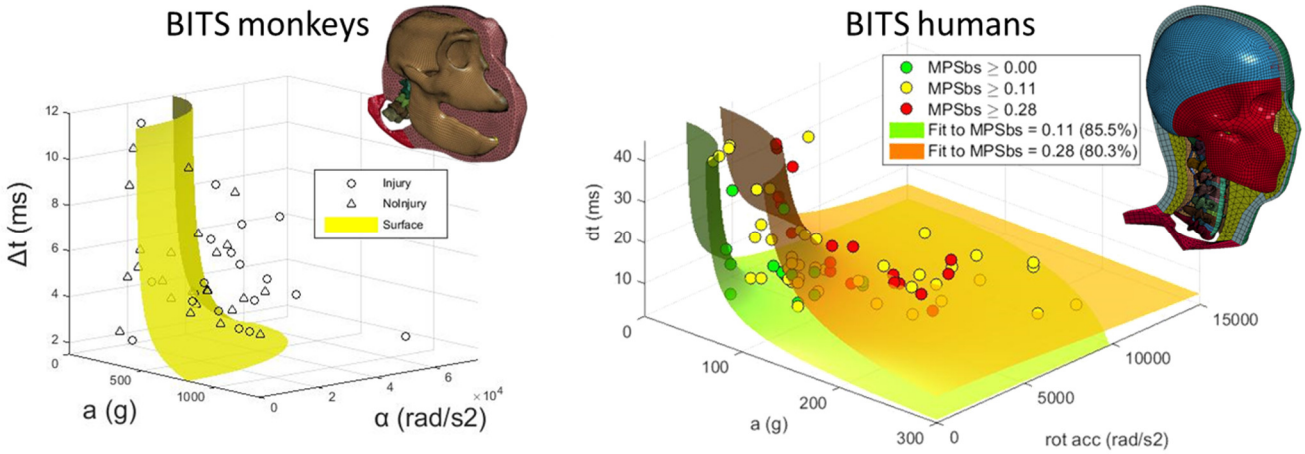


Figure 15. Injury data points and BITS for monkeys (left) and strain data points and BITS for two levels of MPS in the brainstem for humans (right).

In Paper VI, the BITS concept was adapted to humans using data from 76 head impacts simulated with the validated human brain FE model. The impacts were simulated under impact conditions likely to occur and produce diffuse brain injuries in car crashes. BITSs were fitted to different brainstem strain levels from the simulated impacts (Figure 15, right). Each surface was assigned an injury risk level according to brain strain injury risk curves previously developed from the monkey data (Paper IV).

In conclusion, a new global brain injury criterion was proposed. The criterion, denoted as BITS, establishes concussion injury thresholds as a function of time-dependent combined translational-rotational acceleration. BITS appeared to explain the variance seen in concussion from the monkey experiments as well as the brain strain levels from the simulations with both the monkey and the human brain FE models. The proposed injury risk surfaces are intended to be utilised with ATDs and HBMs to estimate the risks of brain injury during the design process of superior protective systems for humans.

8. Addendum: Brainstem Injuries in Motor Vehicle Crashes

This addendum was authored by Jacobo Antona-Makoshi and Johan Davidsson. Accident data for the analysis were provided by Chantal Parenteau and David Viano.

8.1. Introduction

The brainstem plays a vital role in maintaining life by controlling important motor nuclei such as the cardiovascular and the respiratory centres. Anatomically, it is the deepest and lowest part of the brain; it connects to the diencephalon above and the spinal cord below. Primary lesions include direct superficial contusion, DAI, primary capillary haemorrhage, and Ponto-medullary rent. Severe brainstem injuries, at AIS 4 and AIS 5, typically involve tearing in the brainstem area and may occur sometimes without any other type of brain injury noted (Adelstein 1978). The injury mechanism responsible for these severe brainstem injuries appears to be craniocervical hyperextension, usually because the face impacts with a part of the car. Some researchers feel that the severe brainstem injuries are caused by rotational acceleration of the head. Several studies have suggested that primary brainstem injuries occur following a direct impact of the brainstem against the tentorial free edge (Oppenheimer 1968; Clifton et al. 1981). DAI is a severe form of acute diffuse brain injury with poor long term outcome. There is evidence that DAIs are found in the white matter in several brain regions including the brainstem. In severe forms of DAI it is also common to observe haemorrhagic lesions in the brainstem (Gean & Marsh 1994). Traffic accident data have shown that when critical and fatal brain injuries occur, the brainstem is commonly involved in side impacts (Sunnevång et al. 2015), in frontal and side impacts (Yoganandan et al. 2009), in small and moderate offset frontal impacts (Mueller et al. 2015) and in rollover crashes (Mattos et al. 2013).

It has been suggested that less violent brainstem traumas produce the loss of consciousness often seen in concussion, typically graded an AIS 2 or AIS 3 injury, because of the involvement of the reticular activation formation of the brainstem and diencephalon (Jefferson 1944; Powiertowski & Choróbski 1967; Adelstein 1978; Ropper & Gorson 2007; Pearce 2008). It is thought that the normal cellular activities in the reticular activating system are disrupted by the trauma but concussion is also thought to be a milder type of diffuse axonal injury, because axons may be injured to a minor extent due to stretching. Several other theories of concussion with loss of consciousness have been suggested in the past, e.g. the vascular, reticular, centripetal, pontine cholinergic and convulsive hypotheses. The latter implies that loss of consciousness is not due to malfunction of the brainstem reticular activating system but rather due to functional deafferentation of the cortex as a consequence of diffuse mechanically-induced depolarisation and synchronised discharge of cortical neurons (Shaw 2002). Researchers have found that in several of the comatose patients the primary injuries to the brainstem were always part of more diffuse hemispheric brain damage (Adams et al. 1977). Interestingly, concussions with loss of consciousness are rare if the head is exposed to translational acceleration, severe enough to produce cortical contusions and subdural haematomas, without rotational acceleration (Ommaya & Gennarelli 1974).

Despite awareness that the brainstem has very vital functions and is an integrated part of the brain, and in addition is commonly injured, several brain injury criteria intended for traffic safety improvements and in helmet evaluation have been developed without properly taking the craniocervical kinematics into account. One reason for being that the biomechanics of concussion is still unknown and that craniocervical kinematic motion is less monitored in sports and is commonly rather unknown in traffic accidents. Another reason is that it has not received as much attention in accidentology studies.

There is no descriptive study available that allows placing brainstem injuries in context with other types of brain injuries in traffic accidents as a function of crash severity. Hence, in this addendum National Automotive Sampling System - Crashworthiness Data System (NASS-CDS) are used to estimate the incidence and risk of brainstem injuries in motor vehicle crashes and compare them to other types of brain injuries considering crash type, crash severity and belt usage.

NASS-CDS is a stratified sample of crashes that are prospectively selected for in-depth investigation. Most of the vehicles are towed from the scene because of damage. The data includes information based on crash investigation teams, vehicle registration, medical records, police reports and interviews. The data was extrapolated to US national estimates using weighting factors.

Viano and Parenteau (2015) recently estimated the annual incidence and risk of brain injuries and severe head injuries by crash type, severity and seatbelt use in motor vehicle crashes from the NASS-CDS database. Their study did not specifically look into brainstem injuries.

8.2. Method

The method used in this addendum was identical to that of Viano and Parenteau (2015) with the exception that NASS-CDS data from two additional years was included; data from 1994-2013 was analysed to study head injuries in non-ejected occupants by crash type and belt use. Another exception was that the analysis included brainstem injuries. This study included all crashes and occupants aged 15 years and above. Only light vehicles with model year 1994+ were included in the study.

The crash types were defined as follows:

- Front: Vehicles involved in frontal impacts where the greatest damage was to the front (general area of damage in the front, GAD1 = F). Collisions in which a rollover occurred were excluded from the sample (Rollover ≤0).
- Side: Vehicles involved in side impacts where the greatest damage was to the left or right side (GAD1= L or R). Collisions in which a rollover occurred were excluded from the sample (Rollover ≤0).
- Rear: Vehicles involved in rear impacts where the greatest damage was to the rear (GAD1=B). Collisions in which a rollover occurred were excluded from the sample (Rollover ≤0).
- Rollover: Vehicles involved in rollover were those with a rollover >0.
- Other: Vehicles involved in other impacts where the greatest damage was to the top or undercarriage (GAD1=U or T). Collisions in which a rollover occurred were excluded from the sample (Rollover ≤0).
- Unknown: Vehicles involved in impacts with unknown damage information

The belt use was defined as follows:

It was defined by the variables manual belt use (MANUSE) and automatic belt use (ABELTUSE):

- Belted: if MANUSE = 4:
- Unbelted: if year < 110 and ((MANUSE <= 1) and (1 > ABELTUSE or ABELTUSE = 2)) and if year>109 and (0 <= MANUSE <= 1);

Injury severity were defined as follows:

Injury severity of the occupant was assessed using the Maximum Abbreviated Injury Scale (MAIS) and the “TREATMNT” variable. MAIS represents the assessment of life-threatening injuries at the time of first medical evaluation and not long-term consequences. It ranges from MAIS 0 to 9, where MAIS 9 is an injury with unknown severity. MAIS 4-6 represents a severe-to-unsurvivable injury. Fatality was also used to determine if the occupant died of injuries in the accident. The variable “TREATMNT” was

used to define fatality, which is TREATMNT = 1. Because fatalities can occur at any MAIS level, severely injured occupants were defined as those with MAIS 4-6 or fatality. The shorthand notation for this is MAIS 4+F.

Head injuries were classified as:

- Concussion was classified as moderate-to-serious injury (AIS 2-3) to the brain (region90 = 1, struspec = (0, 2, 4, 6, 8, 10) when strutype = 6)
- DAI was classified as severe-to-critical injury (AIS 4-5) to the brain and the brainstem (region90 = 1, struspec = (0, 2, 4, 6, 8, 10) when strutype = 6 and struspec = (2, 4, 6) when strutype = 4)
- AIS 4+ head injury was classified as severe-to-maximum injury (AIS 4-6) to the head (region90 = 1).
- Brainstem injury was classified as critical-to-maximum (AIS 5-6) to the head (region90 = 1 and struspec = 2 when strutype =4)

8.3. Results

Table 7 present all injuries sustained in each of the analysed crash types. Out of the 2 079 821 occupants involved in a motor vehicle crash 5 443 ± 955 occupants sustained an AIS 4+ head injury and 872 ± 133 a brainstem injury annually.

Table 7. Annual Head injury counts and risks by belt use and crash type

	Front	***Side***	***Rear***	***Rollover***	***All***
Occupants involved in a tow away motor vehicle crash	893 104	399 607	132 209	151 199	2 079 821
Occupants assigned an AIS value (MAIS 0+F)	862 166	384 414	125 762	142 706	1 975 617
Uninjured occupants (MAIS 0)	486 498	222 629	70 592	56 202	1 175 852
Occupants with at least one minor or moderate injury (MAIS 1-2)	357 628	151 826	54 592	79 625	759 781
Occupants with at least one serious injury (MAIS 3)	13 296	5 461	246	4 129	25 879
Occupants with at least one severe to fatal injury (MAIS 4+F)	4 744	4 498	332	2 749	14 104
Occupants with at least one skull fracture (AIS 2+)	1 058	913	73	638	3 126
Occupants with at least one severe to maximum head injury (AIS 4+ head)	1 507	2 045	199	1 041	5 443
Occupants with concussions (AIS 2-3)	14 143	7 519	2 240	7 140	34 680
Occupants with DAI (AIS 4-5)	250	517	44	288	1 244
Occupants with brainstem injuries (AIS 5-6)	264	296	49	136	872
Total number of brainstem injuries (AIS 5-6)	286	334	53	144	961

The injury risk was determined by dividing the number of occupants with a particular injury by the number of occupants with known injury status (MAIS 0+F). These risks are provided in Table 8. The risk for severe head injury (AIS 4+) was highest in rollovers (0.73% ± 0.16%) and slightest in rear impacts (0.16% ± 0.05%). Similarly, the risk of concussion, DAI and severe brainstem injuries were highest in rollovers while these risks were lowest in frontal impacts.

Out of the occupants with known seatbelt usage 1 489 700 were belted and 360 824 were unbelted in the impact. Risk for head injury for the belted and unbelted occupants is given in Table 9 and Table 10, respectively. Seatbelt use was effective in preventing all types of brain injuries, irrespective of the impact type. Seatbelt use was most effective in preventing DAI at 87% with a 0.223% ± 0.094% risk when unbelted and 0.0289% ± 0.005% when restrained. The seatbelt was the most effective, for any impact type, in preventing brainstem injuries in rear-end impacts (94%), DAI in frontal impacts, side impacts and rollovers (92%) and AIS 4+ head injury in rear-end impacts (92%).

Table 8. Rate of head injuries per occupant assigned an AIS value (%)

	Front	*Side*	*Rear*	*Rollover*	*All*
Occupants with at least one severe to maximum head injury (AIS 4+ head)	0.18	0.53	0.16	0.73	0.28
Occupants with concussions (AIS 2-3)	1.64	1.96	1.78	5.00	1.76
Occupants with DAI (AIS 4-5)	0.03	0.13	0.03	0.20	0.06
Occupants with brainstem injuries	0.03	0.08	0.04	0.10	0.04

Table 9. Head injury risks and crash type for belted occupants

	Front	*Side*	*Rear*	*Rollover*	*All*
Occupants with at least one severe to maximum head injury (AIS 4+ head)	0.10	0.32	0.09	0.41	0.17
Occupants with concussions (AIS 2-3)	0.94	1.62	1.58	3.66	1.28
Occupants with DAI (AIS 4-5)	0.01	0.06	0.03	0.07	0.03
Occupants with brainstem injuries (AIS 5-6)	0.02	0.06	0.02	0.05	0.03

Table 10. Head injury risks and crash type for unbelted occupants

	Front	*Side*	*Rear*	*Rollover*	*All*
Occupants with at least one severe to maximum head injury (AIS 4+ head)	0.63	2.34	1.02	2.23	0.74
Occupants with concussions (AIS 2-3)	3.87	4.93	4.58	11.63	3.26
Occupants with DAI (AIS 4-5)	0.14	0.76	0.13	0.83	0.22
Occupants with brainstem injuries (AIS 5-6)	0.11	0.22	0.31	0.31	0.11

Figure 16 presents head injury risks as a function of impact severity (delta V). The data clearly show that for substantial risk of DAI and brainstem injuries, impact severity must be rather high while risk of concussion is substantial also at low velocities.

8.4. Discussion and Conclusions

Recently, Viano and Parenteau (2015) investigated the annual incidence of vehicle occupant brain injuries in tow-away motor vehicle crashes using 1994-2011 NASS-CDS data. The study quantified, for the first time, a risk of 1.64% for concussions classified as moderate-to-serious brain injury (AIS2-3). The same study also estimated a 0.063% risk for DAI classified as severe-to-critical injury (AIS 4-5). In this addendum, the study by Viano and Parenteau (2015) has been updated and extended to include brainstem injuries classified as critical-to-fatal (AIS 5-6). The study found the risk of brainstem injuries to be 0.05% and therefore to be rather low compared to concussions and other brain injuries. However, the injury frequency/risk is a function of impact severity.

Concussions are the most common moderate-to-serious TBIs in motor vehicle crashes (Viano & Parenteau 2015) accounting for 60% of all AIS2+ injuries to the head. The injury risk approximately increases linearly with collision severity for collisions velocity changes below 35 km/h (Figure 16). This is different compared to other head AIS2+ injuries; for these injuries the risk was low (<1%) at velocity changes below 25 km/h. Hence an injury criterion useful for restraint performance assessments in low to moderate severity crash tests ought first and foremost to predict concussions. Therefore, the injury criterion for these severities should preferably capture the craniocervical kinematics, as these have been suggested responsible for concussions.

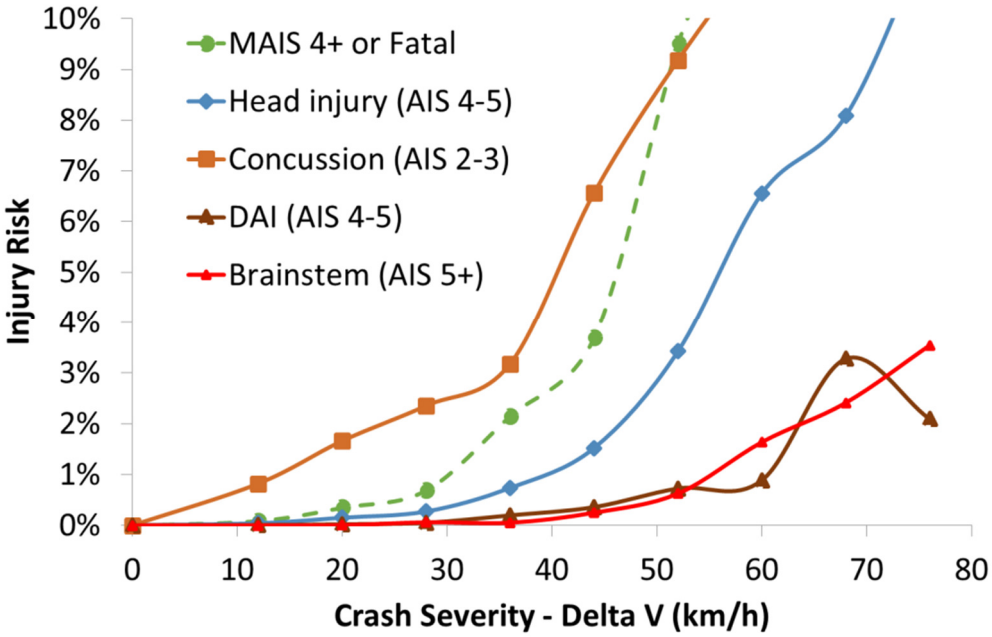


Figure 16. Injury risk by impact severity and injury type in non-ejected vehicle occupants (zero risk plotted at zero delta V)

For collisions with a velocity change of 56 km/h or above there were 27 036 reported AIS 4+ head injuries in the NASS-CDC data. Approximately 27% of these were DAI or brainstem injuries. Hence, a head injury criterion that is to be used in severe test conditions, similar to those currently used in regulatory or NCAP tests, should, based on the knowledge that DAI are frequently observed in the brainstem, predict both cephalic injuries as well as brainstem injuries. Based on this reasoning proper craniocervical kinematics should be modelled when this criterion is developed and when it is in use.

Seatbelt use was associated with lower risk of head injuries for all collision types and studied head injury categories. Although belt usage significantly reduces brainstem injury risk, from 0.108% ± 0.020% for unbelted occupants to 0.029% ± 0.005% for belted occupants, severe brainstem injuries still occur. Mueller et al. (2015) identified a subset of small and moderate offset collisions that produced brainstem injuries. In these collisions it appeared that the governing injury mechanisms may have included head to A-pillar contact, or head to central console impacts following poor belt retention in far side collisions.

9. Ethical Considerations

In this thesis, rat specimens have been utilised to obtain CT and MRI images for FE model development. In addition, new rotational head trauma experiments were conducted to generate model validation data (Papers I and II). These imaging studies and experiments were performed at the Neuroscience Department of the Karolinska Institute, Sweden, in accordance with the Swedish National Guidelines for Animal Experiments and under the approval of the Animal Care and Use Ethics Committee in Stockholm, Sweden [doc. N143/09]. In addition, CT and MRI images were obtained from anaesthetised primate specimens at the Primate Research Institute of the Kyoto University (KUPRI), Japan. These images were obtained for the development of the monkey FE model (Papers III to V). The experiments were reviewed and approved by the Animal Welfare and Animal Care Committee ethics panel of the KUPRI [Permission 2011-134, 7 June, 2011].

All other head trauma data that were re-analysed and reconstructed using FE animal head models in this thesis were conducted in the past. The experiments with primates were carried out at the JARI from 1976 to 1978 as part of a research programme under the auspice of the Ministry of Transportation of Japan. Support was granted by the Automobile Bureau Safety section. The experiments were carried out with the involvement of several major academic institutions in Japan, such as Jikei University School of Medicine, University of Tokyo, Tokyo Women's Medical College and Nihon University. The experiments followed animal care regulations in effect at that time. However, the ethical guidelines were reviewed and additional primate experiments have not been carried out at JARI since then. At the start of this thesis, the researchers involved discussed if the utilisation of these data in new studies is ethical. The researchers found no evidence for the need to obtain additional ethical permission for use of the experimental data. The arguments concerning the presence of any ethical controversy that could potentially arise from the utilisation of the primate experimental data are presented below. These arguments were discussed with a member of the Chalmers University Research Ethics Committee, who supported the rationale and decisions adopted by the author of this thesis.

In most liberal democratic societies, two main theories, the Consequentialist (Utilitarianism) and the Deontologist (from the Greek Duty), are currently used to approach any social ethical questions in general and research ethical questions in particular (Peach 1995). The Consequentialist theory analyses a problem by focusing on the consequence of an action. For example, in the case of the trauma experiments comprising living primates, the action would be to carry out the experiments. While the consequences would be two: 1) the death of a limited amount of specimens and 2) obtaining valuable data that can, when properly utilised, save human lives and improve the lives of human beings. The Deontological theory analyses ethical issues from the perspective of what humans must do independently of the output of results. For example, the duty of a physician is to save lives. Hence, killing humans for research purposes is not ethically acceptable no matter what the utility of the results is. From a Consequentialistic perspective, there is no doubt about the important role that the historical primate experiments have played in establishing important knowledge. Examples of this knowledge are the improved understanding of the brain injury mechanisms (Chapter 0) and data that was used to establish head injury criteria (Chapter 6). Besides the utility of the results, researchers have the duty to adapt their research to the needs of society. When comparing the value of human and animal life, the majority of society admits differences between humans and animals. However, the sensitivity of society with respect to animal species is changing towards a more humanised perception of animals, which directly affects what is considered ethically acceptable. This perception is especially strong for non-human primates. Hence, from a Deontologist perspective, the past experimental methods in which non-human primates were subjected to injurious head impacts for the goal of reducing brain injuries in accidents cannot be considered an ethically acceptable research method in modern society. Since the only negative consequence identified in the experiments was the suffering and death of specimens, by following the

same rationale, the research method proposed in this thesis will not impose any additional suffering or deaths. Hence, using a computer simulation based method to re-analyse the experiments performed in the past can thereby be considered an ethically acceptable research methodology. Moreover, the re-analysis of the experimental data conducted in this thesis was carried out to contribute to the reduction of brain injuries, and hence to a safer society.

10. General Discussion

The main goal of this thesis was to develop a closed head impact criterion and associated thresholds that will, when properly applied, reduce TBI in traffic accidents. Focus has been on the development of a closed head impact criterion for use with ATDs. In order to achieve this main goal, several intermediate objectives have been addressed; definition of the study approach, clarification of the governing global injury mechanisms, definition of injury criteria that account for such mechanisms, and establishment of associated thresholds.

10.1. Study Approach

Initially, the means by which the brain injury criterion and thresholds for humans were to be developed within this thesis were defined. A decision was made at an early stage to include animal experimental injury data in the development. This called for the use of novel techniques to make the animal data applicable for humans. It was also decided that the main focus would be on diffuse brain injuries; particularly including concussions as they represent the most common type of moderate-to-serious type of brain injury, but with the potential to include DAIs as well as they represent a relevant type of severe-to-critical injury (Addendum). A scheme of the overall study approach is presented in Figure 17 and a description of the steps undertaken follows:

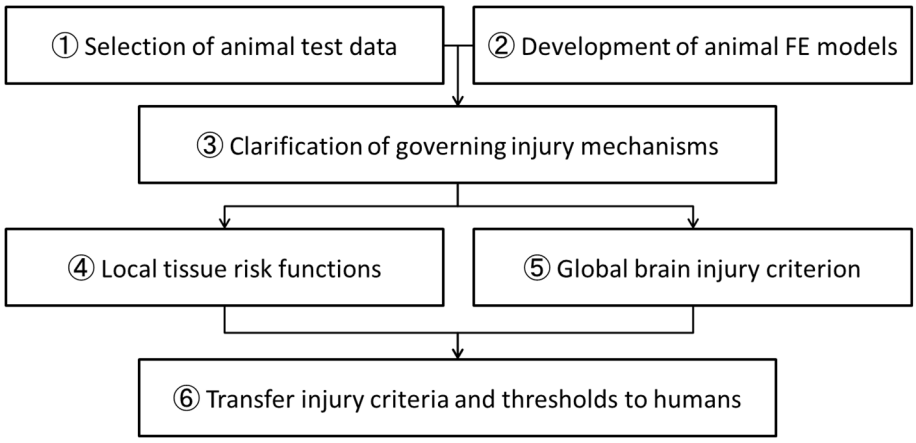


Figure 17. Scheme of the study approach to develop a global brain injury criterion for humans

1. Selection of animal test data potentially applicable for humans; head rotational acceleration experiments with rats that mainly produced DAI pathology (Davidsson et al. 2009; 2011) and a sub-set of head impacts experiments with monkeys that produced concussion symptoms (Ono et al. 1980) were selected for this study (Chapter 4.3).
2. Development of animal brain FE models for reproduction of the animal tests; medical images of rat and primate specimens were obtained and utilised to build and partially validate detailed brain FE models of the animals (Chapter 7.1).
3. Clarification of the governing global injury mechanisms in the animal experiments; the rat and the monkey experiments were simulated with brain FE models of the corresponding animals. Injury data from the experiments were combined with head-neck motion and brain strain data from the simulations. Additionally, a sub-study focused on studying the effects of ageing on injury prediction was conducted with the rat FE model for future integration of ageing in brain injury criteria development (Paper II).
4. Development of local tissue risk curves that predict diffuse brain injuries; the curves were developed based on 43 of the monkey head impact experiments and simulations of these experiments with the

monkey brain FE model. The curves relate the probability of developing concussion symptoms with a measure of brain tissue strains (Paper IV).

5. Development of a conceptual global brain injury criterion and thresholds; the concept, denoted Brain Injury Threshold Surface (BITS), incorporates three head kinematic variable terms: peak rotational resultant acceleration, peak translational resultant acceleration, and duration of this acceleration. BITSs were initially developed based on the monkey data to investigate their potential to capture both the injury data from the monkey experiments and the brain tissue strain data from the simulations (Paper V).
6. Transfer the new global brain injury criterion and threshold to be applicable for humans; a detailed human head-neck FE model was developed from medical images and validated with data from the literature. The human model was used to simulate 76 head impacts likely to occur and produce diffuse brain injuries in vehicle crashes. Head kinematics and brain tissue strain data from these simulated impacts were extracted and applied to develop BITSs for humans (Paper VI). Finally, each of these BITSs was assigned a probability of concussion injury according to the tissue risk curves previously developed from the monkey data (Paper IV).

One of the strengths of the approach adopted in this study is that it allowed the combination of animal tests with FE models of the specimens. This combination provided means to understand the head, neck and brain kinematics that produced injuries in the experiments (Chapters 7.2, 7.3, and 10.4), which were later considered in the development of injury criteria (Chapter 10.5). Overall, the basis for the study approach is the assumptions that brain tissue mechanical properties are similar and that equivalent level of tissue strain is associated to injury severity levels across the two species. The first assumption is supported by a study in which monkey and human brain tissue samples were subjected to dynamic compression, concluding that there were no significant differences between the two species (McElhaney et al. 1976). The second assumption has also been suggested in several studies that attempted making injury data applicable to humans based on experiments with monkeys (Margulies & Thibault 1992; Mendis 1992; Takhounts et al. 2013). However, no comparative studies could be found in which rat and human brain tissue mechanical properties have been obtained under comparable testing conditions. Hence, it was decided to withhold the utilisation of rat experimental data during the development of the brain injury criterion for humans and limit the methodology to apply the animal data for humans to the monkey data.

10.2. Monkey Experimental Data and Applicability for humans

A sub-group of the JARI monkey head impact experiments (Group C in Ono et al. 1980) was considered appropriate for the development of tissue and global level brain injury criteria and associated thresholds for diffuse brain injuries relevant for traffic accidents and primarily targeted in this thesis (Chapter 4.3, Addendum). The choice of data was based on the technique used to induce trauma in the experiments, impacts to the unrestrained head, which likely resemble head impact conditions that produce most brain injuries in traffic accidents (McLean 1995; Yoganandan et al. 2009). It was also based on the severity and type of injuries produced in the experiments, moderate-to-serious concussions, which account for 60% of all AIS2+ injuries to the head in motor vehicle crashes (Viano & Parenteau 2015, Addendum).

The impacts induced combined translational-rotational motion of the head causing concussions. The severity of a concussion was evaluated by measuring changes in vital functions such as corneal reflex, cessation of respiration and blood pressure changes in accordance with an existing definition at the time of the experiments (Committee on Terminology in Neurotraumatology of the World Federation of Neurological Society 1979). Besides the symptoms, a reduced number of cases scored gross pathology including contusions SAH and ASDH as detected at autopsy. The animal experiments were reproduced using FE models of the animal and brain injury criteria that predict the brain injuries were developed for

monkeys and humans. Therefore the injury criteria and thresholds proposed in Papers III to VI primarily predict concussion symptoms as scored at the time of the experiments.

Concussions have historically been defined based on symptoms, their definitions have evolved over time, and past and present diagnosis of concussions differ (Gennarelli & Wodzin 2006; Carroll et al. 2010). Past definitions (classical concussion or cerebral concussion) required symptoms such as loss of corneal reflex, apnoea, bradycardia or loss of consciousness prolonged for varying periods of time, and historically diagnosed regardless of or in combination with pathological findings. Currently, a concussion is diagnosed when the patient appears to be confused, although loss of consciousness or amnesia is not required and pathological findings in standard imaging are not expected. In addition, the definitions of concussion are still subject to debate in both sports and traffic safety related fields (McCrory 2001; Gennarelli 2015), and the concussions often reported in sports may not necessarily represent the same mechanisms and severities as those occurring in traffic accidents. In other words, the concussions reported in the JARI experiments, and hence in the development of injury criteria in this thesis, may not accurately match what would currently be diagnosed as mild concussion. On one hand, the occurrence of pathology in few of the selected cases suggests that the majority of the monkey experimental injury data utilised in this thesis would be representative of *Internal organs (Brain)* AIS levels ranging from 1 to 3 (Table 1). On the other hand, the experiments did not produce loss of consciousness of durations long enough to be considered as *Concussive* AIS3 or higher (Table 1). Hence, the injury risk curves developed in this thesis represent a form of concussive injury with limited risk of pathology that, using the most modern coding, approximate an AIS2 level head injury. These risk curves provide an opportunity to complement current understanding of the governing mechanisms that produce mostly mild concussions in sports, with a form of concussions associated to a slightly higher severity, and of more relevance than other brain injury criteria, i.e. the HIC, for traffic accidents (Addendum).

In order to refine this study and extend it to other injury types and severities, further work is required. The monkey brain FE model and methodology applied in this thesis can be applied to other groups of monkey experiments carried out in the past at JARI (Figure 2). The methodology can also be applied to head acceleration-deceleration experiments reviewed in Chapter 4.2.1 (Abel et al. 1978; Gennarelli et al. 1982). These experiments were essential in establishing a graded correlation between physiological symptoms immediately after impacts and brain pathology. Such correlation will enable the expansion of the current study to more severe forms of diffuse brain injuries including severe and critical DAIs. Summing up all the historical experiments on monkeys reported in the literature, several hundreds of impacts are already available. A joint research effort between institutions may contribute to the development of truly comprehensive brain injury criteria and associated risk functions with the potential to include not only diffuse brain injuries, but also contusions, ASDH, SAH and brainstem injuries, all of them highly relevant for traffic injuries (Addendum).

10.3. Animal Brain Finite Element Models

Existing animal brain FE models were reviewed (Chapter 5.2.2) and new models of a rat and a monkey have been developed (Chapter 7.1). One important limitation identified in all animal brain FE models is the paucity of experimental data for validation of the models. Past FE models have, at best, attempted validation on intracranial pressure measured at head impacts (Anderson 2004). Therefore, in this thesis, effort was made to generate a limited set of experiments with rats (Paper I). The experiments generated brain-skull motion data that were utilised to partially validate the motion of the brain cortex with respect to the skull in the rat FE model (Paper I and Paper II). The rat brain FE model developed in Paper I, which includes a skull-brain interface modelled with sliding-only contact and ventricular spaces left empty, provided brain-skull relative motion in agreement with the experiments. However, tissue strains were found to be affected by how the ventricles were modelled (Appendix B). The model developed in Paper II, which includes a skull-brain interface and ventricles filled with solid CSF elements, provided

reasonable brain cortex motion and, in addition, prevented strain concentrations around the ventricles (Appendix B). This modelling approach also provided facilitated modelling of cases with reduced brain volume (Appendix C), and enhanced the model's ability to predict high strains in the regions where DAIs were commonly found following the experiments (Paper II). The fact that models with comparable levels of brain cortex motion led to different tissue strain predictions in the central parts of the brain highlighted two possible issues. First, the experimental method applied to measure the brain cortex motion was insufficient for capturing the motion of the entire brain, which calls for additional experimental work that allows enhanced model validation. Second, models validated against brain motion data only, if not accompanied by adequate modelling practices, may not provide reliable brain tissue strain predictions. When additional validation data is made available and the rat brain FE model in this thesis has been enhanced, the model can support further investigations to make experimental data with rats applicable for humans. It can also be applied in a number of studies such as, for example, investigations of improved brain-skull interface simulation techniques (Klug et al. 2013), incorporation of brain tissue properties that account for brain tissue property changes and accumulated damage due to repetitive mild trauma (Gabler et al. 2013), or validation of emerging advanced brain tissue modelling techniques (Giordano & Kleiven 2014; Sahoo et al. 2014).

In contrast to the rat brain FE model, the monkey brain FE model in Papers III to V was developed using a pragmatic approach. It was known from an early stage that new primate experimental data were not expected to be generated in this thesis, and that experimental data for model validation was scarce and the level of detail of location of injuries reported in past experiments was limited. These limitations with the data were also considered in the development of the monkey FE model. Despite limited validation of the brain motion, the sub-studies undertaken to evaluate the adequacy of the approaches adopted to model the brain-skull interface (sliding-only) and the ventricles (tied-contact) (Chapter 7.1, Appendix B, and Appendix C), showed that the monkey model was numerically robust. Therefore the model was considered suitable for simulations of single event head impacts (Papers III to V). Nevertheless, for future studies additional model validation should be considered. Experiments to obtain model validation data at sub-injurious levels with living monkeys such as those recently conducted with human volunteers (Sabet et al. 2008) or with naturally deceased monkeys at higher impact levels may be considered in the future.

10.4. Governing Global Injury Mechanisms

The combination of animal tests and mathematical modelling of the tests provided a better means to understand the craniocervical and brain kinematics that produced injuries in the experiments. Due to significant differences between the head rotational acceleration models and the head impact models they are discussed separately.

10.4.1. Head Rotational Acceleration-Deceleration

In the head rotational acceleration-deceleration simulations conducted with the rat FE model (Paper II), the largest brain-skull relative displacements occurred at rotational acceleration, while high strains in the brain cortex and brainstem occurred both during acceleration and deceleration, but with higher values immediately after the deceleration (Figure 18). At the initial loading stage, when the head was subjected to extension, the brain lagged behind the skull due to inertia and viscoelasticity. This produced a relative motion between the upper surface of the brain cortex and the inner skull, triggering a raise in a RMDM (ASDH risk indicator) and MPS values (DAI risk indicator) in the forebrain and the brainstem until reaching peaks shortly after the rotational acceleration peak was reached. Thereafter, the skull was subjected to deceleration, while the brain cortex and the brainstem were still travelling rearwards. When the internal regions of the brain eventually caught up with the utmost brain regions and the skull, the generated momentum for the internal regions produced a second raise the largest MPS as the skull was

subjected to flexion. The combined analysis indicated that ASDH, that frequently were observed following experimental trauma may have been caused at the onset acceleration, while DAI, commonly observed in the corpus callosum and its borders and in the brainstem, may have been produced by either the onset acceleration or more likely as a consequence of the combination of the onset acceleration and the deceleration (Figure 18). These findings are consistent with two studies in which the complete pulses from past monkey head rotational acceleration-deceleration experiments (Abel et al. 1978; Gennarelli et al. 1982) were applied to the skull of simplified brain FE models for the clarification of ASDH (Lee et al. 1987) and DAI mechanisms (Yoganandan et al. 2008). Lee et al. (1987) found that at onset acceleration the maximum strains occurred in the brain cortex surface elements in regions to which bridging veins are attached, which suggests that ASDH was produced by the onset acceleration. Yoganandan et al. (2008) showed that rotational acceleration-deceleration pulses with a certain separation time between them produce two peak strains. The first of these strain peaks is related to the acceleration pulse and the second strain peak will depended on the difference in amplitude between the acceleration and the deceleration peaks, and the separation in time between them.

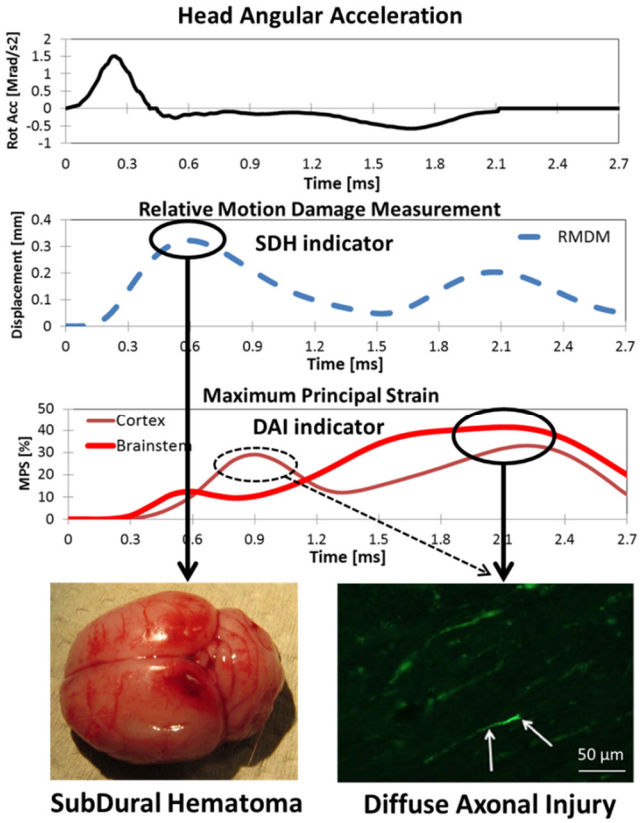


Figure 18 Governing Injury mechanisms in rotational head acceleration-deceleration with rats
Head rotational acceleration (top graph), RMDM as indicator of ASDH risk (middle graph), and MPS as indicator of DAI risk from representative elements of the brain cortex and the brainstem (bottom graph)

In summary, head rotational acceleration-deceleration experiments with animals can induce injuries in association with both the head onset acceleration and the rebound deceleration. In traffic accidents the highest rotational acceleration is expected to occur when the head of an occupant makes contact with an airbag or other structures (McLean 1995; Yoganandan et al. 2009). Sometimes the peak acceleration is preceded by a rather high rotational acceleration due to neck loads induced on the head (Viano et al. 1986). Brain injury criteria should at least include the acceleration during the head contact but preferably all accelerations that contribute to injury risk. In the development of the brain injury criterion proposed in this thesis (BITS), focus was on the main event and for this single-event impacts were utilised.

10.4.2.Head impacts

Analysis of past monkey experiments were carried out by physicians (Kanda et al. 1981). That analysis was focused on concussion, based on measured physiological changes, such as circulatory disturbances, and their possible correlation to pathological observations. The latter included studies of haemorrhages and contusions in the brain tissue. Based on the presence of pathology in the brainstem, Kanda hypothesised that the changes taking place in these regions were responsible for the concussions. This hypothesis is supported by a large number of animal experimental studies (Jefferson 1944; Powiertowski & Choróbski 1967; Adelstein 1978; Ropper & Gorson 2007; Pearce 2008) and by the simulation work presented in this thesis, for both occipital (Paper III) and frontal (Paper IV) impacts; the simulations conducted with the monkey FE model provided the highest strains at sites where contusions and SAHs were reported in the experiments (Ono et al. 1980). It is noticed at this point that the brainstem loading mechanisms suggested may not be captured by criteria that have been developed with human brain FE models without consideration of craniocervical motion and that only account for rotational motion (BrIC, RVCI, RIC in Table 5). Furthermore based on the simulations, it was understood that the frontal and occipital impact experiments were of a different nature in terms of efficacy of the impact, as well as in terms of craniocervical kinematics produced by the impacts. Frontal impacts produced higher peak rotational accelerations while occipital impacts produced higher peak translational accelerations. However, in both frontal and occipital impacts, the craniocervical kinematics led to compression of the tissues located in the dorsal brainstem region; especially in a region close to the foramen magnum (Figure 19). Hence, the simulations provided results that supported grouping frontal and occipital impacts in the development of a conceptual global injury criteria (Paper V) and that a single criterion can be used to assess injury risks using an ATD in collisions when head kinematics to the sagittal plane are limited. This new knowledge was applied when transferring the BITS for monkeys to humans via a human FE model (Paper VI) although the understanding of craniocervical kinematics and their relation to brainstem injury risk in side collisions are currently unknown.

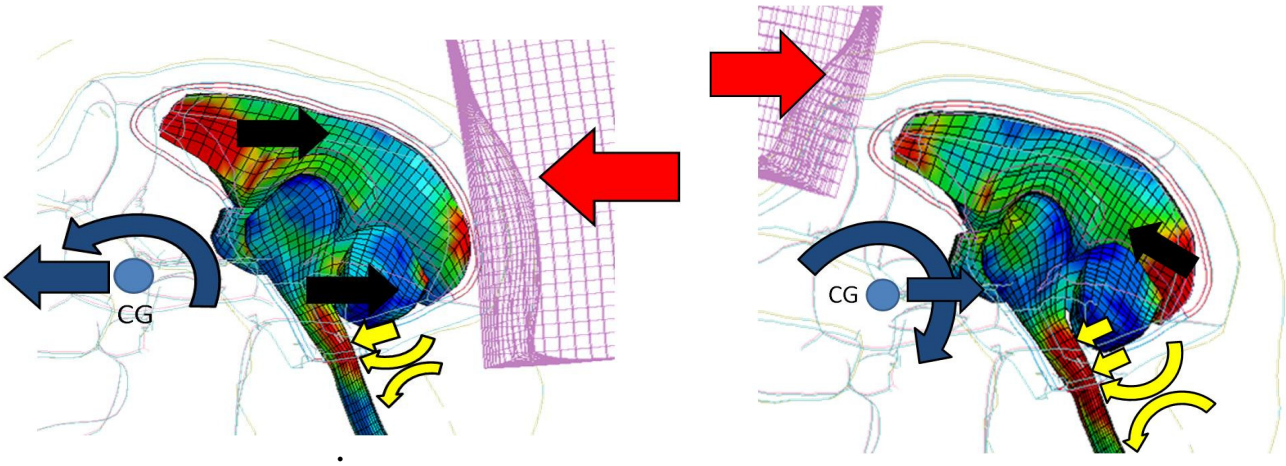


Figure 19. Governing Injury mechanisms in occipital (left) and frontal (right) head impacts with monkeys. The illustrations show fringe plots of the MPS in the brain from the simulations (red colour indicates MPS above 0.18). Red arrows indicate location and direction of the impact. Blue arrows represent translational and rotational accelerations around the centre of gravity of the head. Black arrows indicate the motion of the brain inside the brain cavity relative to the skull. Yellow arrows illustrate the mechanism that produces the increase of strains in the brainstem.

10.5. Development of Brain Injury Criteria

The need for developing criteria that can be used with ATDs able to predict predominantly mild and moderate diffuse brain injuries caused by head impacts in traffic accidents and not necessarily associated

with skull fractures was identified (Addendum and Chapter 6.6). Consequently, a new conceptual global brain injury criterion, referred to as Brain Injury Threshold Surface (BITS), that accounts for time-dependent combined translational and rotational head acceleration was developed (Paper V and Paper VI). Equation 1 presents a BITS generic equation where a_{max} is the peak translational head resultant acceleration, ΔT the duration of this acceleration, and α_{max} the peak rotational resultant acceleration. The a_{cr} , α_{cr} , and Δ_{cr} referred to as critical values, are positive constants with the same units as their corresponding variables. In the development of BITS, a number of decisions had to be made. The rationales and data that support the proposed concept, its current status, and the required future work are discussed in this section.

$$\text{BITS} = \left(\frac{a_{max}}{a_{cr}}\right)^2 + \left(\frac{\alpha_{max}}{\alpha_{cr}}\right)^2 - \left(\frac{\Delta_{cr}}{\Delta T}\right)^2 \qquad \text{(Eq. 1)}$$

10.5.1. Translational vs Rotational Acceleration

BITS incorporates peak translational acceleration and peak rotational acceleration in the same way as the GAMBIT (Newman 1986). Most TBIs in traffic are produced by head impacts (McLean 1995; Yoganandan et al. 2009) that produce combined translational-rotational head kinematics (Newman et al. 2000; King et al. 2003; Melvin & Yoganandan 2015). Head impacts delivered to unconstrained heads of animals that produced combined translational-rotational head kinematics have been shown to cause diffuse brain injuries often involving the brainstem in primates (groups C and D in the JARI experiments by Ono et al. 1980; Sakai et al. 1982) and in sheep (Anderson et al. 2003) and in swine (combined input injury device by Fievisohn et al. 2014). In addition, a number of numerical studies with human brain FE models have suggested that the use of either translation or rotation may underestimate the risks (DiMasi et al. 1995; Ueno et al. 1995; Kleiven 2002). In the development of the BITS it was shown that, when the three terms of the equation were considered, as much as 95% of the strains predicted by the FE animal model and 72% of the concussions observed in the original experiments could be correctly classified (Table 3 in Paper V). When the rotational acceleration term was removed from the equation, these percentages decreased to 91% and 67%, respectively. Similarly, when the translational acceleration term was removed from the original equation, the initial values were reduced to 80% and 70%. The contribution of both translational and rotational components to explain the variance in the occurrence of injury is also illustrated in Figure 20. This figure shows the 43 data points from the simulated monkey head impact experiments (Papers III to V) in a peak translational acceleration vs peak rotational acceleration plot. Drawing lines according to the first two terms of the BITS (or the GAMBIT), it is possible to establish thresholds above which the majority of impacts produced injuries and below which the majority of impacts did not produce injuries. This addresses the potential benefit of incorporating both translational and rotational terms in injury criteria as has been done in the GAMBIT and the BITS, for instance.

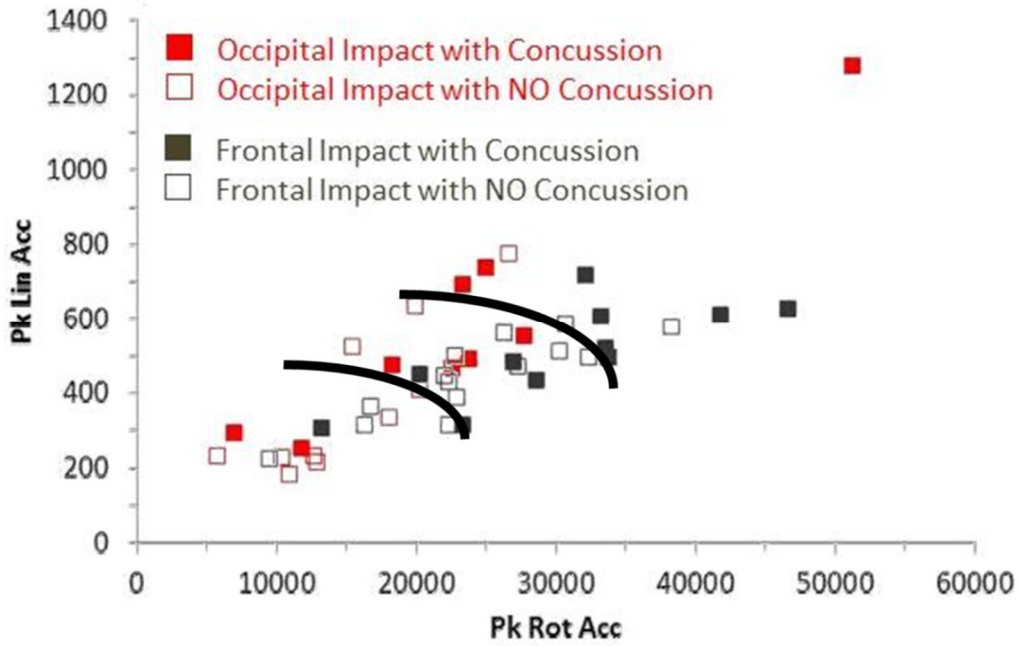


Figure 20. Peak translational acceleration (in g) versus peak rotational acceleration (rad/s^2) from the monkey sagittal head impact simulations in Papers III to V.

10.5.2. Rotational acceleration vs Rotational velocity

A large number of studies have established peak rotational acceleration thresholds for different injury types and severities. These studies were mainly based on primate experimental injury data or reconstructed head impacts in football games (summarised in Table 4). Recently, Hardy et al. (2001; 2007) pointed out the importance of angular velocity in describing brain-skull motion in PMHS experiments. Peak angular velocity has shown better correlation with tissue strains than peak rotational acceleration when applying purely rotational impulses (Kleiven 2006) and when processing data from pendulum impacts to ATD heads (Takhounts et al. 2013) with human brain FE models. Recent simulation work by Gabler et al. (2015) and Panzer et al. (2015) supports the use of peak rotational velocity only for short duration impacts, the use of peak rotational acceleration for long duration impacts, and the need for at least two of three parameters (acceleration, velocity and time) for events of moderate duration. The rationale stands on a review of theoretical considerations with a 1 degree of freedom vibration system (von Gierke 1964) and is consistent with results obtained in past monkey head impact experiments (Ommaya & Hirsch 1971). These experiments showed that, to better capture the variance in the concussions produced in the primates, rotational acceleration and rotational velocity could be combined. The BITS incorporates peak rotational acceleration and time, and hence has the potential to capture brain response at moderate and long duration impacts of interest in traffic accidents, as suggested by Gabler et al. (2015) and Panzer et al. (2015). For lower duration events, which are typically associated to hard contacts that may deform the skull causing increased risks of other types of injuries such as contusions, the BITS incorporates the translational acceleration term in its equation.

10.5.3. Duration vs No Duration

Tolerance levels for several types of TBIs decrease as pulse duration increases. This has been observed in animal experiments that produced concussions (Gurdjian et al. 1966; Ommaya et al. 1967; Ono et al. 1980), ASDHs (Gennarelli & Thibault 1982 later revised by Lee et al. 1987 and Melvin & Yoganandan 2015), contusions (Ono et al. 1980) and DAI (Gennarelli et al. 1982; Margulies & Thibault 1992). The decrease is also consistent with that observed in free-falls of military human volunteers (Snyder 1971). Moreover, such decreases have been shown to be asymptotic (Figure 5 and Figure 6). The BITS

incorporates a second order term duration in order to address the duration dependency and the asymptotic behaviour of this dependency. The results in Table 3 in Paper V showed only a marginal decrease (2%) of correct classification of both predicted brain tissue strains and predicted risk of concussion when the duration term was suppressed from the BITS equation. This marginal gain can be explained by the small range of duration of the head impact in the experimental data used in the study (from 2.4 to 11.7 ms). When the same comparison was applied to the human head impact simulation data in Paper VI, which included head impact durations ranging from 4 to 44 ms, the benefit of including the duration term became more evident (Table 2 in Paper VI). Hence, the inclusion of duration in the BITS will enhance its usefulness over criteria that do not include duration, e.g. the GAMBIT.

10.5.4.Direction

At this stage in the development, the BITS does not incorporate directional components, i.e. the criterion does not scale accelerations in different directions differently. Several injury criteria have opted for the incorporation of direction dependency (BrIC, HIP, RVCI). The review of animal experiments (Chapter 4.3) suggests that the direction of head acceleration may influence injury outcome (Gennarelli et al. 1987). The Gennarelli et al (1987) study suggested that primate tolerance to rotational acceleration-deceleration was lower in the coronal plane than in the sagittal. These results were contradictory to another study in which tolerance to head impacts was lower in the sagittal plane than in the coronal (Sakai et al. 1982). Directional dependency has also been investigated based on simulations with human brain FE models (Kleiven 2006) and in analysis of concussion impacts in football (Rowson et al. 2012). Kleiven (2006) exercised a human brain FE model by imposing rotational accelerations in different head directions and concluded that higher brain strains were produced when rotation was applied on the coronal plane, which would be consistent with the Gennarelli et al. (1987) experiments with monkeys. In a later study, Kleiven (2007) simulated 58 concussive and non-concussive football head impacts and conducted logistic regression analysis for different combinations of rotational and head kinematics. Significance tests of the regression analysis revealed that some of the significance test scores improved when directional kinematics was included, while some others did not (Kleiven 2007). Rowson et al. (2012) selected groups of head impacts that had produced concussions and in which head accelerations were either primarily sagittal plane rotation or primarily coronal plane rotation. Both groups had similar average translational and rotational accelerations but sagittal impacts were over-represented (33 cases) in the sample when compared to coronal impacts (7 cases). This suggests that, in football impacts of comparable severities, sagittal impacts may produce concussions more frequently than coronal impacts. This would then be consistent with the Sakai et al. (1982) primate experiments. In other words, more work is required to clarify the contribution of directional effects on injuries and the need and possible incorporation of direction dependency in the BITS. Using the monkey brain FE model to simulate the sagittal and the coronal monkey head acceleration-deceleration by Gennarelli et al. (1987) and the JARI coronal head impact experiments by Sakai et al. (1982) may provide further insights into the reasons for contradictory results between the two studies. If simulations of the JARI coronal impacts reveal brainstem loading mechanisms that can be grouped with sagittal impacts (as has been shown in frontal and occipital impacts Figure 19), it may be possible to reconstruct the coronal impacts and include these in the brain tissue injury risk curves, and therefore bypass the need to incorporate directional components in the BITS. In case different governing mechanisms are identified, the BITS may need to be modified to incorporate direction dependence.

10.5.5.Transferring the BITS thresholds to humans

The BITS concept, developed using a monkey FE model and data from past monkey experiments, was transferred to humans in Paper VI. A human FE-model was subjected to a large number of impacts and the results were used to establish surfaces in the three dimensional space; the parameters were

translational acceleration, rotational acceleration and pulse duration, for which the strain was constant. Tissue injury risk curves developed in Paper IV were used to convert these surfaces to risk of injury. To allow for this transfer to be carried out consistently, ideally these two models should be developed under the same modelling principles and using identical models of the materials reproduced by the model. This was partially achieved in terms of brain anatomical detail and modelling, but brain tissue mechanical properties differed between models (Chapter 7.1).

The monkey brain FE model was assigned brain tissue mechanical properties in the order of 10 kPa as obtained from a series of monkey brain tissue dynamic compression tests (McElhaney et al. 1976). This model was utilised to simulate the monkey head impact experiments and to develop injury risk curves that relate the risk of developing concussion symptoms in the experiments with MPS in the brainstem in the simulations (Paper IV). According to the curves developed, MPS of 0.23 represents a 50% risk of concussion. These values are in accordance with two works in which head impacts in football games had been reconstructed with human brain FE models with brain tissue stiffness comparable to that of the monkey brain FE model (Kleiven 2007) or stiffer (Zhang et al. 2004). The human brain FE model developed in Paper VI was initially planned to incorporate brain tissue mechanical properties in the same range as those that were used in the monkey brain FE model since the brain tissue compression tests has shown similar responses between both species (McElhaney et al. 1976). However, as the model development work progressed it was understood that the brain tissue material properties selected were stiffer when compared to a number of other sources of brain tissue mechanical properties (Chatelin et al. 2010). The first attempt to validate the new human brain model using brain motion data from experiments with PMHSs (Hardy et al. 2001) confirmed that human brain tissue is softer than previously reported. Hence, it was decided to implement softer brain tissue properties into the human model, in the order of 1.6 kPa, to be consistent with different experimental brain tissue mechanical property studies (Arbogast & Margulies 1997) and other human FE models (Takounts et al. 2008). The human model with softer properties was finally validated with the brain motion data (Hardy et al. 2001, 2007) and utilised to simulate 76 head impacts with loading conditions likely to occur in car crashes (Paper VI). The fact that the brain tissue properties used in the human model were dissimilar to those used in the monkey model is a limitation that needs to be considered. Future work will include a reduction of monkey brain tissue stiffness to ensure consistency with the human brain FE model and development of new brain tissue injury risk curves to tune the human thresholds. Until that work is conducted, the human thresholds proposed in Paper VI should be considered as preliminary values.

10.6. Limitations and Future Work

The road map that has been utilised to guide the research presented in this thesis is illustrated in Figure 21. The map includes reconstructions of real-world accident data, using physical and virtual models, applying scaling methods and animal research. The activities addressed within this thesis are highlighted with a red rectangle. These activities presented a number of limitations which are presented below. Required future work to account for these limitations and to provide continuation to the research conducted in this thesis is also presented.

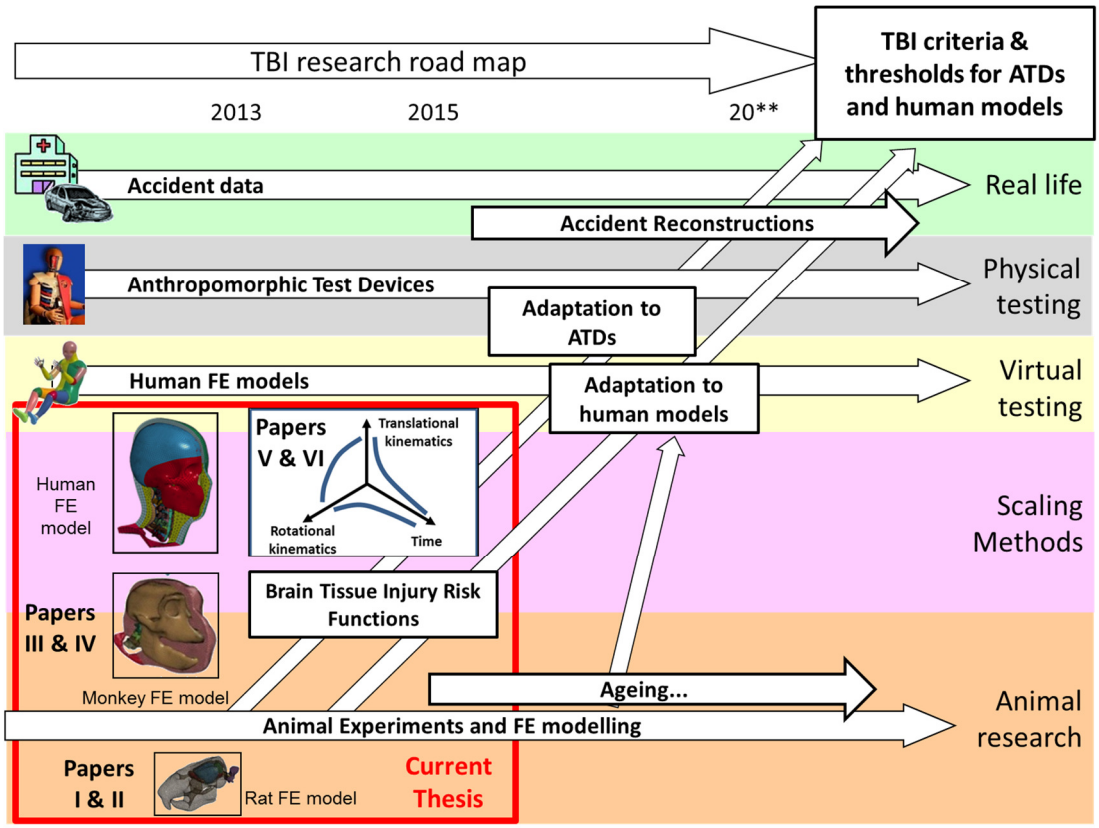


Figure 21. Road map for brain injury research including:

The validation of the brain FE models developed in this thesis is limited, especially the validation of the monkey model; the motion of the brain relative to the skull, which affects the overall brain motion inside the skull, is not validated. This relative motion possibly influence the results presented in paper III and IV to some degree. Refinement of the monkey model to incorporate brain tissue properties that match those used in state of the art human brain FE models (which brain motion relative the skull has been validated using data from PMHS tests) and to enhance the brain-skull interface modelling is ongoing. Experiments to obtain brain motion data at sub-injurious levels with living monkeys or with naturally deceased monkeys at higher impact levels may be considered in the future.

In the monkey experiments used in this study, some of the animals were subjected to subsequent impacts. However, in the statistical analysis presented in Papers III and IV each impact was assumed to be an independent variable. Since repeated impacts may affect the injury thresholds of the specimens, the assumption taken may be affecting the results. Nevertheless, if the results have been affected, they would be inclined to be affected towards more conservative thresholds as has been assumed that the injury thresholds of specimens subjected to multiple impacts would be the same as had they not been subjected to impacts previously. Further work to compensate for previous impacts in statistical analysis is needed in order to mitigate this limitation.

Concussions represent the most common type of mild and moderate TBI in traffic crashes. Although there is an agreement on the symptoms observed in concussed individuals, there is no general agreement on how to quantify these symptoms. This study is based on a specific technique to evaluate concussion based on changes in physiological measurements caused by a specific method of delivering the impact to the head, in this case direct padded impacts, and should not be confused with other techniques. Care must be taken when applying the conclusions from this work to other loading conditions, or other types and severities of injuries and scoring systems. Furthermore, the detailed injury mechanisms that trigger concussion symptoms are yet to be clarified. In this thesis any brainstem strains are assumed to be responsible for the symptoms used in the correlation study between strain measures and symptoms. However, the assumption remains to be verified. Further experimental research at trauma and at the

tissue level is required to clarify the detailed mechanisms for concussion and the validity of the assumptions used to match tissue data from simulations with the injuries.

Concussions and DAI are considered to be the less and more severe ends of a continuous spectrum of diffuse brain injuries. BITS as developed in this thesis is mostly predictive of concussions and less of DAI. The monkey brain FE model and the methodology proposed to make the experimental injury data applicable to humans can be applied to incorporate simulations of experiments which focused on DAI (Gennarelli et al. 1982). Such an expansion will allow adapt BITS for prediction of more severe forms of diffuse brain injuries.

The effect of ageing on brain injury prediction has been studied with the rat brain FE model and experiments in Paper II. The study approach adopted in this study to develop a brain injury criterion and associated thresholds from animal tests stands on a series of monkey head trauma impacts conducted in the past with adult monkey specimens. Other complementary approaches based on collection and reconstructions of Sports head impact data are limited to young athletes and cannot be applied to studies on the effect of ageing. In other words, neither the past monkey experiments nor the currently used approach to collect and reconstruct sports impacts allow the incorporation of ageing into the development. Additional experiments with rats and simulations with the rat brain FE model may contribute to fill this gap and support the incorporation of ageing in the development of injury criteria and thresholds.

A method to make animal experimental data applicable to humans has been proposed. The method combines animal experiments with simulations of the experiments with FE models of the animals, and stands on the assumption that brain tissue material properties and injury thresholds are similar for the studied species. Evidence that supports the assumption for monkey and human brain tissue was found (McElhaney 1976), but not for rodent and human brain tissue. In order to allow the transfer of data from rats to humans, further experimental work is required. Future testing with rats should include: comparative studies on rat and human brain tissue mechanical properties, incorporation of physiological measurements during and following trauma tests that allow comparing the duration of symptoms. In addition it would be beneficial to use injury scoring techniques so that the new injury data would be comparable to past primate injury data as well as comparable to state of the art injury scoring techniques used for humans.

In the development process of BITS, a human FE model has been utilised and preliminary thresholds for concussion have been suggested. BITS targets at being applied in crash tests with ATDs. These ATDs are designed for specific testing conditions and the craniocervical kinematics response to impacts may differ between ATDs. Hence, evaluation of the applicability of BITS for different ATDs needs to be conducted. This evaluation has not yet been conducted.

11. Contributions

This thesis contributes to traffic safety and the reduction of brain injuries. The brain injury biomechanics have been studied using mathematical models with particular focus on diffuse brain injuries and the development of their injury criteria and associated thresholds for concussion for future use with ATDs.

A rat brain FE model was developed and validated with original experimental data. The model was utilised to show means to simulate aging in human brain FE models. Both the mathematical model and the experimental data have attracted the interest of several other academic institutions. The experimental data has been used in validation of FE models developed by the University of Strasbourg (Ren et al. 2014). By making the developed brain FE model and validation data available for other researchers, additional knowledge will be generated that may contribute to a reduction of brain injuries.

A monkey brain FE model was developed, partially validated and utilised to simulate monkey head impact experiments for the development of a conceptual brain injury criterion and associated injury thresholds. The model can also be used in the reconstructions of other past experiments, e.g. those reported in Gennarelli et al. (1982) or additional sub-sets from the JARI primate head impact experiments including coronal impacts (Kikuchi et al. 1982; Sakai et al. 1982) or higher severity impacts (Ono et al. 1980) than those selected for this thesis.

A human brain FE model was developed, validated and utilised in this thesis for the transfer of the conceptual brain injury criteria and injury risk curve to be valid for humans. The model is currently in use for numerical reconstructions of accident data collected by JARI. This model, as many others, may become an important tool for research and applications and as such, further contribute to the reduction of brain injuries.

Brain tissue strain injury risk curves were constructed from reconstructions of past animal experiments with known symptoms and pathology and with the absence of skull fractures using the developed monkey brain FE model. Under certain assumptions, these risk curves can be used with human brain FE models to estimate risks for concussion injuries. Since the applicability of these curves is dependent on the brain tissue material model used in the monkey brain FE model, the use of these curves is somewhat restricted. On the other hand, the brain tissue material model used with the monkey model can be adapted to match those used with other human brain FE models and provide human model specific curves.

A new conceptual brain injury criteria and injury threshold (surface) to be used with ATDs that has the potential to predict the risk of diffuse brain injuries, have been developed. Although additional evaluation of these using real-world data is pending, these can be considered for use in restraint evaluations.

12. Conclusions

In this thesis, the craniocervical and brain kinematics that produce brain injuries in the experimental setting with animals was investigated by introducing FE models of the animals. One rat and one monkey brain FE models were developed from medical images of the animals. The rat brain FE model incorporated region specific material properties from tissue experimental data from the literature and was validated against full scale experiments with rats specifically designed to study relative motion between the brain and the skull. The validated rat model was applied to simulate sagittal plane head rotational acceleration-deceleration experiments with rats to improve the understanding of the trauma. In addition, the model was utilised in a study focused on the effect of ageing on brain injury prediction. The monkey FE model was partially validated using experimental data from the literature, and utilised to simulate series of sagittal head impact experiments conducted in the past to develop tissue strain injury risk functions.

The rat FE model predicted high-strain concentrations in brain regions commonly exhibiting axonal injuries following experimental rotational trauma. Sequential analysis of the trauma progression indicated that ASDH occurred at an early stage of the trauma, while DAI occurred at a later stage. When reduced brain volume and tissue stiffness were introduced in the model, to simulate an older population, the ASDH and DAI risks were elevated, respectively. These findings, if applicable to humans, suggest that injury type and age-specific reduction strategies in the development of superior restraint systems may be possible with the support of age-specific brain FE models.

In reconstructions, using the monkey brain FE model, of sagittal plane head impact experiments carried out in the past with monkeys large brainstem strains were predicted. The obtained results support the hypothesis that concussions are frequently produced due to mechanical loading of the brainstem. Hence, craniocervical motion must be incorporated in human FE models and ATDs when used in the development of countermeasures targeting a reduction in concussions.

A method to improve the applicability of animal brain injury experimental data to humans was investigated. The method uses simulations of the experiments with FE models of the animals and develops injury risk curves at tissue level. These curves relate probability of injury, as obtained from the animal experiments with simulated brain strains. By assuming comparable brain tissue mechanical properties between species, these curves can be applied in human brain FE models to estimate probability of injuries in humans. In this thesis, brain tissue injury risk curves were constructed from reconstructions of 43 primate head impact experiments that typically produced concussion symptoms. These curves were later used to estimate injury risk from brain strain data from 76 impacts simulated with a human brain FE model that was developed and validated for the purpose of this investigation. Overall, the method investigated proved to be technically feasible, to provide biomechanically justifiable means to related head kinematics and brain strains, and to account for contact phenomena typical from vehicle crash like head impacts.

A conceptual new global brain injury criterion and associated thresholds to be used with ATDs that have the potential to predict the risk of diffuse brain injuries in traffic crashes have been developed. The concept, denoted as Brain Injury Threshold Surface (BITS), establishes equal brain injury risk second-order surfaces as a function of time-dependent and combined translational-rotational kinematics of the head typical from head impacts in car crashes. BITS appeared to explain the variance seen in concussion from the monkey experiments as well as the brain strain levels from the simulations with the monkey and the human brain FE models. Although additional evaluation of the new criterion and risk curves is pending, e.g. extending of the studies to other types and severities of injuries, adapting to different ATDs, and reconstructing real world accidents with known injury outcome, these have the potential, when

properly applied, to guide the development of superior restraints that reduce the number and severity of brain injuries in future traffic accidents.

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Appendix A: Human Brain Anatomy and Physiology

The human brain is the main organ of the central nervous system (CNS). It is located in the head and protected by the skull. The weight of an adult human brain is approximately 1.4 kg. It consists of 78% water, 11% lipids, 8% protein and small amounts of other substances. The human brain is divided into four major parts: cerebrum, diencephalon, brainstem and cerebellum. The cerebrum is the largest and most complex part of the CNS. It consists of two cerebral hemispheres which outermost layer is called the cerebral cortex which is mainly composed by grey matter. The cerebrum enables perceiving, communicating, memorising, understanding, and initiating voluntary movements. The two hemispheres are connected through the corpus callosum, which facilitates communication between hemispheres. The diencephalon, located in the central part of the brain, connects the cerebrum with the brainstem. It controls the endocrine system, regulates water balance, body temperature, sleep-wake patterns, food intake and behavioural responses associated with emotion. The brainstem consists of three segments, midbrain, pons and medulla oblongata, and connects to the diencephalon above and the spinal cord below. The brainstem plays a vital role in maintaining life since it controls important motor nuclei such as the cardiovascular and the respiratory centres. The cerebellum is the second largest part of the brain. It processes information from the cerebral cortex, the brainstem, and sensory receptors to provide skeletal muscle contraction needed for the coordinated movements in our day-to-day life. Cerebellar activity occurs subconsciously.

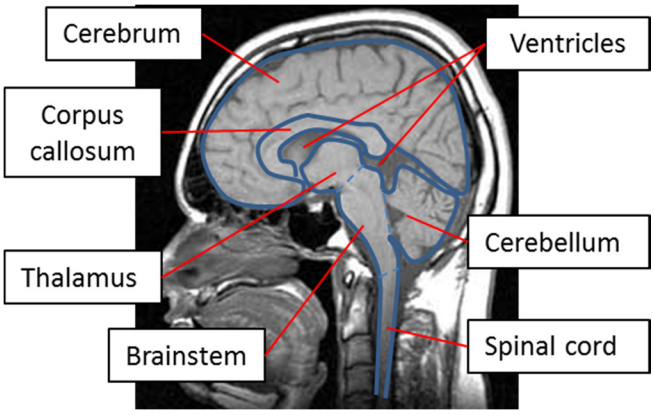


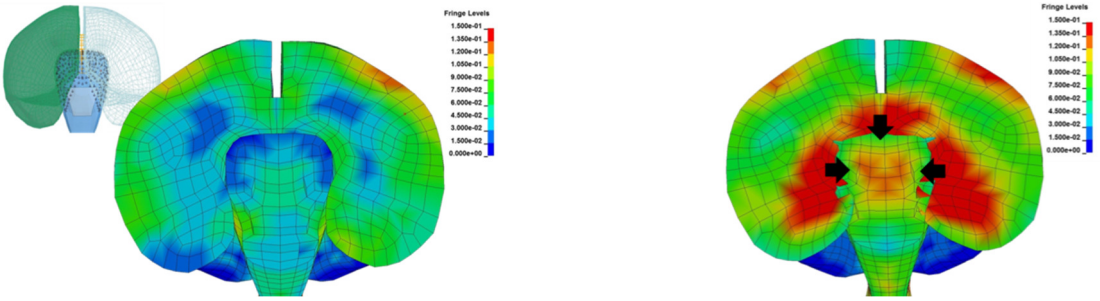
Figure A22. Sagittal plane view of a human brain MRI

The adult male human brain contains about 86 billion neurons, 19% of which are located in the brain cortex (Herculano-Houzel 2009). A neuron (or nerve cell) processes and transmits information through electro-chemical signals. Neurons consist of a cell body, dendrites and an axon. The axons are surrounded by a myelin sheath, which is white in colour; consequently those parts that contain many myelinated axons appear white (white matter). The parts that contain concentrations of nerve cell bodies embedded in a network of nerve processes are grey in colour (grey matter).

The brain is surrounded and protected by three membranes called meninges: pia mater, arachnoid mater and dura mater. The meninges protect the brain and contribute to ensuring that the nervous tissue environment is suitable. The dura mater is the outermost membrane and is attached to the internal part of the skull. The pia mater is the innermost layer; it is large vascularised, attaches to the cerebral cortex and follows its contour. The arachnoid mater is located between the dura and the pia mater and it is crossed by the bridging veins. The space between the pia mater and the arachnoid is filled with the CSF, a water-like fluid that serves as a cushion for the brain. Besides the sub-arachnoid space, within the brain there are four cavities filled with the fluid. These cavities form the ventricular system. The two lateral ventricles are located in the cerebrum while the third and fourth ventricles are located in the diencephalon and behind the pons, respectively.

Appendix B: Ventricles Modelling

Different ventricles modelling approaches were investigated and applied to the models in this thesis. Figure B23 compares strain fringe plots of a coronal section from a simulation of an occipital impact with the monkey brain FE model. The left image shows the monkey brain FE model with a tied-contact between the upper part of the brainstem and the surrounding structures as utilised in Papers III to V. On the right image, the same simulation with the tied-contact released is shown. When the contact is removed, the internal parts of the cerebrum hemispheres tend to implode (black arrows), producing large element distortions. This suggests that, if the ventricles were modelled without imposing any constraint to deformation of the central parts of the brain, the model could have induced artifacts. The tied-contact avoids such distortions, hence suggesting that the modelling approach adopted for the ventricles in the monkey brain FE model may be an acceptable simplification solution for ventricle modelling.



Tied-contact between brainstem and cerebrum
(Papers III, IV and V)

Released tied-contact
(for comparison in this Appendix)

Figure B23. Simplified ventricles modelling approach utilised in the monkey brain FE model

Figure B24 compares a coronal section from the rat brain FE models presented in Paper I and Paper II, respectively. Strain fringe plots from a simulation of a sagittal head rotational acceleration event with both versions of the model are also shown. The left image, the rat brain FE model with empty ventricles (Paper I) and the right image, a similar simulation with the rat brain FE model with CSF-solid elements filling the ventricles is shown. When the ventricles are left empty, the internal parts of the cerebrum hemispheres tend to implode (black arrows), producing large element distortions in a similar way as shown when releasing the tied-contact in the monkey model (Figure B23). This was also solved by filling the ventricles with CSF-solid elements.

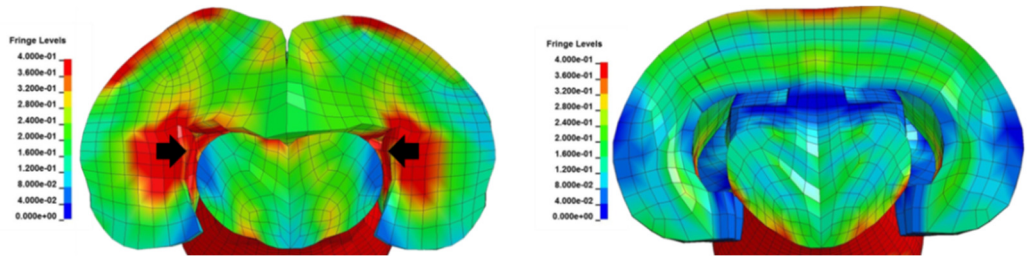


Figure B24. Comparison of ventricles modelling approaches with rat brain FE model: Empty ventricles Paper I (left) and CSF-solid Paper II (right)

In summary, when the ventricular space was modelled in detail but left empty (Paper I), brain distortions may be induced in the central parts of the brain. This could be solved by restricting relative motion through a tied contact between the brainstem surface and the surrounding structures (monkey brain FE model in Papers III to V) or by filling the ventricles with CSF-solid elements (rat brain FE model in Paper II and human brain FE model in Paper VI). Either of these approaches prevented excessive distortion of the surroundings of the ventricles.

Appendix C: Brain-skull interface modelling

Different brain-skull interface modelling approaches were investigated and applied to the models in this thesis. A sub-study with simplified spherical brain FE models and a rigid skull was conducted to compare two different skull-brain interface modelling approaches and their robustness with reduced brain volume models; sliding-only contact (CONTACT AUTOMATIC ONE WAY SURFACE TO SURFACE TIEBREAK option 4) allows for relative motion in tangential direction to the contact surface while constraining motion in the normal direction and CSF-solid which allows a certain level of motion of the brain surface in both tangential and normal directions. The same rotational acceleration-deceleration pulse (Paper I) was imposed to the skulls of the four different models shown in Figure C25. The dimensions and properties of the models were similar to the rat brain FE model presented in Paper I and II. The acceleration is applied to the skull and with respect a centre of rotation (CR) located outside the skull in a similar way as in the rat experiments simulations. The change in length between a surface node and the closest node on the skull were extracted from the simulations.

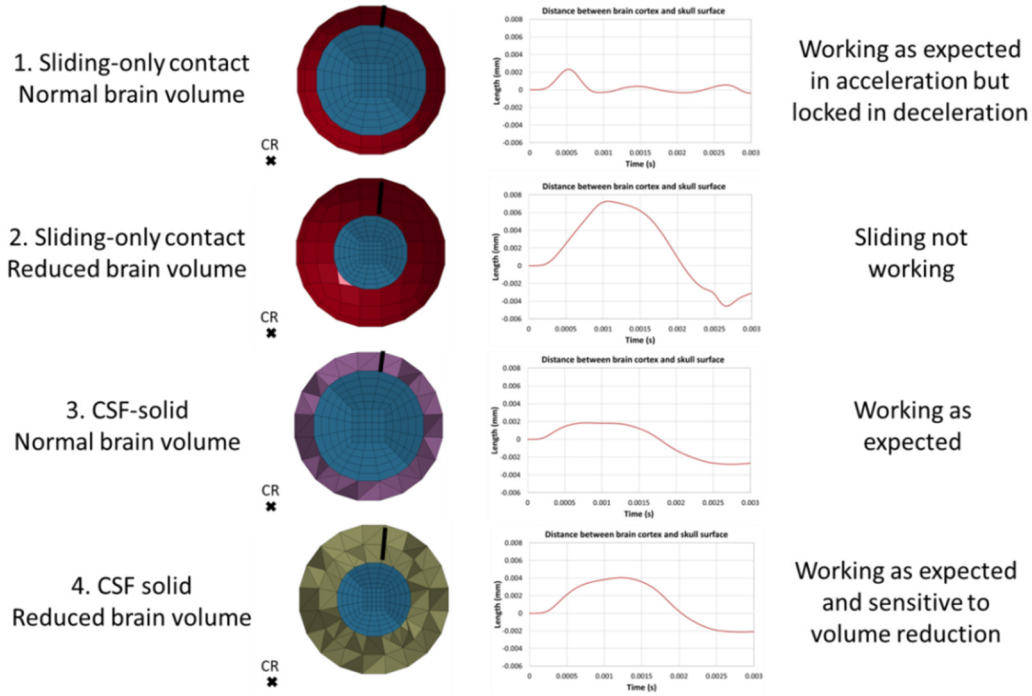


Figure C25. Comparison of sliding-only and CSF solid approaches under skull rotational acceleration-deceleration with both normal and reduced brain volumes

The results showed that Sliding-only contact with normal brain volume allowed relative motion at the rotational acceleration. However, as the skull loading progressed, the contact locked, prohibiting further relative motion between the nodes (Case 1). When the volume was reduced (Case 2), the motion between the brain and the skull was not constrained, indicating failure of the contact. This could not be solved by increasing contact distance parameters. The simulation with CSF-solid and normal brain volume (Case 3) provided a certain level of motion in both the loading and unloading phases. In addition, the reduced brain volume (Case 4) worked as expected and showed sensitivity to volume changes. It was concluded that, for simulations of single-event impacts, either option would provide acceptable brain-skull relative motion. Sliding-only option was applied to the monkey model for simulations in Papers III to V. It was also understood that, for simulations of rotational acceleration-deceleration events and age related brain volume changes, CSF-solid approach may be a better option. Therefore, this approach was implemented in the rat brain FE model in Paper II and the human model in Paper VI.