

THESIS FOR THE DEGREE OF LICENTIATE OF ENGINEERING

In

MACHINE AND VEHICLE SYSTEMS

**Reanalysis of primate head impact experiments
to clarify mild traumatic brain injury kinematics
and thresholds**

by

JACOBO ANTONA-MAKOSHI



Vehicle Safety Division
Department of Applied Mechanics
CHALMERS UNIVERSITY OF TECHNOLOGY
Gothenburg, Sweden, 2013

**Reanalysis of primate head impact experiments
to clarify mild traumatic brain injury kinematics
and thresholds**

JACOBO ANTONA-MAKOSHI

© JACOBO ANTONA-MAKOSHI, 2013

THESIS FOR LICENTIATE OF ENGINEERING no 2013:18
ISSN 1652-8565

Department of Applied Mechanics
Chalmers University of Technology
SE-412 96 Gothenburg
Sweden
Telephone +46 (0)31 772 1000

Printed by Bibliotekets reproservice, Chalmers University of Technology
Göteborg, Sweden, September, 2013

ABSTRACT

Fatalities and severe injuries due to road traffic accidents still represent a serious health and economic issue in today's society. Brain injuries are the most common severe injuries and these injuries account for more than half of the 1.3 million traffic related deaths annually worldwide. However, improved accident avoidance systems are predicted to mitigate and reduce future accident severity. Thus, the number of traffic related deaths and severe injuries would be reduced and therefore a focus shift towards long-term disabling injuries is expected. One of the most common of such injuries is mild traumatic brain injury.

To develop effective countermeasures aimed at reducing traumatic brain injuries, it is essential to understand head-neck and brain kinematics at impacts to be taken into account in the development of injury criteria and the establishment of thresholds. With this purpose, experiments comprising animals, used as human surrogates, are deemed essential and historically, head impact experiments on non-human primates have been carried out. Some of these experimental results have been scaled to suit humans and were used in the development of the head injury criterion, currently in use in the FMVSS 208 US regulation for motor vehicles.

This head injury criterion has been used for decades, but is still criticised for not considering many 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 induced by oblique impacts or when the torso is restrained. Therefore, alternative or complementary criteria that consider rotational acceleration of the head have been proposed in combination with brain tissue injury criteria, for human head finite element models. The finite element models are currently undergoing validation with reconstructions of real-life sports and traffic accidents, as well as scaled animal injury data. Unfortunately, the accuracy of the methods used to capture head kinematics and detailed brain injury location and severity from real-life events has limitations. The existing criteria also fail to capture the head-neck kinematics that causes the brain injuries. Moreover, the methods used to scale animal data to humans are not reliable.

The ultimate goal of this study is to generate knowledge that contributes to the development of MTBI criteria and associated limits that will, when properly applied, reduce the number of moderate brain injuries due to closed head impacts. This thesis aims at proposing improved criteria that account for the head-neck and brain kinematics that occur during brain trauma and to provide thresholds for concussions. This will be facilitated by numerical reconstruction of past head trauma experiments using primates.

By re-analysing the existing primate trauma experiments, using a finite element model of these specimens, the reliability of global head injury criteria available in literature was evaluated. This was done by simulating and analysing sub-sets of frontal and occipital primate head impacts; selected from large series of trauma experiments previously conducted at the Japan Automobile Research Institute. Based on the simulation results, the brain injury kinematics hypothesised when the former experiments were analysed is supported: concussions occur due to physical stress to the brainstem. Based on these findings, brain tissue injury thresholds were also proposed. Assuming that tissue thresholds are the same for non-human primates and humans, these results can be used to interpret results obtained with human finite element models without scaling.

In the future, these results are expected to be used as references for virtual safety assessment and to provide the basis for further development of protective strategies for humans.

LIST OF APPENDED PAPERS

PAPER I: 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. In Proceedings of the International Research Council on the Biomechanics of Injury conference, Dublin, Republic of Ireland.

Division of work between authors: Antona-Makoshi conducted the literature review, experimental data re-organisation and analysis, and modelling tasks. 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 II: Antona-Makoshi, J., Davidsson, J., Ejima, S., Ono, K., Brodin, K., Anata, K., (2013). Correlation of global head kinematics and brain tissue injury predictors to experimental concussion derived from monkey head trauma experiments. In Proceedings of the International Research Council on the Biomechanics of Injury conference, Gothenburg, Sweden.

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

Conference Presentations of the Present Work:

IRCOBI Conference 2012, Dublin, Republic of Ireland

40th International Workshop on Human Subjects for Biomechanical Research 2012, Savannah (GA), USA

49th Japan Traffic Science Conference 2013, Tokyo, Japan

IRCOBI Conference 2013, Gothenburg, Sweden

ABBREVIATIONS

AIS	Abbreviated Injury Scale
CSF	Cerebro Spinal Fluid
CT	Computed Tomography
DAI	Diffuse Axonal Injuries
DBI	Diffuse Brain Injuries
TBI	Traumatic Brain Injuries
GAMBIT	Generalized Acceleration Model for Brain Injury Threshold
HIC	Head Injury Criterion
JARI	Japan Automobile Research Institute
KTH	Kungliga Tekniska Högskolan, Sweden (Royal institute of Technology in English)
MPS	Maximum Principal Strain
MRI	Magnetic Resonance Imaging
Ms	Miliseconds
MTBIs	Mild Traumatic Brain Injuries
NHP	Non-human primate
NHTSA	National Highway Traffic Safety Administration, US
SDH	Sub-Dural Hematoma
SIMon	Simulated Injury Monitor
THUMS	Total Human Model for Safety
VMS	Von Mises Stress
WHO	World Health Organization
WSU	Wayne State University

ABSTRACT

LIST OF APPENDED PAPERS

ABBREVIATIONS

1.BACKGROUND	1
1.1.Head injuries	1
1.1.1.Mild traumatic brain injuries	1
1.2.The human brain	1
1.3.Head injury criteria and thresholds for humans	2
1.4.Scaling of animal injury data to humans	4
1.5.Finite element modelling to understand brain injuries	6
1.6.Brain tissue mechanical properties	6
1.7.Experiments to understand brain injuries.....	7
1.7.1.Human volunteers, PMHSs, sports and real life crashes	7
1.7.2.Non-human primate animal experiments	8
2.AIMS	10
2.1.Ultimate goal and long term plan	10
2.2.Aims.....	11
3.MATERIALS AND METHODS	11
3.1.Head trauma experimental data	11
3.2.Medical images	12
4.SUMMARY OF PAPERS.....	12
4.1.Paper I	12
4.2.Paper II	13
5.ETHICAL CONSIDERATIONS	15
6.GENERAL DISCUSSION	16

6.1.Kinematics of brain injuries.....	16
6.2.Global head injury criteria.....	17
6.3.Brain tissue injury criteria	18
7.LIMITATIONS	19
8.FUTURE WORK	20
9.CONCLUSIONS	20
10.ACKNOWLEDGEMENTS	21
11.REFERENCES	21
PAPERSI-II	

1. BACKGROUND

The background and the focus of this thesis are presented in this chapter. An introduction of the problem of head injuries (1.1) is followed by an explanation of the Finite Element (FE) method (1.2) and the experiments (1.3) in which this study supports advancing the understanding of brain injuries from an impact biomechanics perspective.

1.1. Head injuries

Head injuries account for about half of the 1.3 million annual deaths and the 50 million traffic related injuries worldwide, estimated by the World Health Organization (WHO, 2013). The majority of head injuries are Traumatic Brain Injuries (TBIs), which result from mechanical energy to the head from external physical forces (WHO, 2004). TBIs represent 60% of all deaths in hospitals among children and young adults in the western world (Melvin et al., 1993) and comprise 1 million hospital admissions annually in the European region (Deck et al., 2008). About 40% of the TBI patients were admitted to hospitals for non-focal injuries (Wismans et al., 2000), referred to as Distributed Brain Injuries (DBIs). Between 70 and 90% of TBIs that receive treatment fall into the group of Mild Traumatic Brain Injuries (MTBIs) (Cassidy et al., 2004), often referred to as concussions in the literature.

1.1.1. Mild traumatic brain injuries

The Spectrum of MTBIs varies from fully recoverable (transient) to Structural Damage (permanent) (Iverson et al., 2005). Besides traffic accidents, sports and falls represent a large number of MTBIs. Although MTBIs can be associated with skull fractures, they commonly occur without fractures (Gennarelli et al., 1987, Got et al., 1983). Consequences of MTBIs are often irreversible, causing sequelae, long term pain and disability (Iverson et al., 2005).

Due to underreporting and lack of a widely accepted consistent definition, the economic costs of MTBIs are difficult to quantify, although estimates suggest them to be as high as the costs of moderate and severe TBI (Krauss et al., 2005). The estimates include direct costs such as hospital admissions, and indirect costs such as loss of earnings, sequelae, and early retirement (Borg et al., 2004).

Fatal and severe traffic related TBIs still demand further attention. Since improved accident avoidance systems are expected to mitigate and reduce accident severity, the potential for increased focus on long-term disabling injuries, of which MTBIs are a major issue, has been made possible. In addition, countermeasures for the prevention and mitigation of MTBIs are expected to indirectly provide additional protection against more severe injuries.

1.2. The human brain

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. Figure 1 shows a diagram of a human brain.

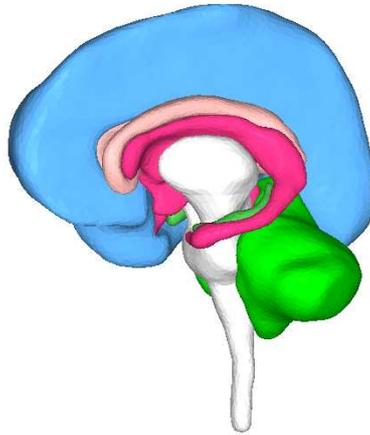


Fig. 1. Image of an oblique view diagram of a human brain. The image shows right cerebral hemisphere (blue), corpus callosum (pink), ventricles (purple), cerebellum (green) and brainstem (white). Left cerebral hemisphere is omitted from the image for visibility.

The human brain can be divided into four major parts: the cerebrum, diencephalon, brainstem and cerebellum:

The cerebrum is the largest and most complex part of the central nervous system. It consists of two cerebral hemispheres which outermost layer is a convoluted mantle of grey matter called the cerebral cortex. This cortex is about 2-4 mm thick and contains approximately 40% of brain mass. The cerebrum enables humans to perceive, communicate, remember, understand, appreciate and initiate voluntary movements. The two hemispheres are connected through the corpus callosum, which facilitates interhemispheric communication.

The diencephalon is a deep portion of the brain that connects the cerebrum with the brainstem. Apart from controlling most of the endocrine system, the diencephalon regulates body temperature, water balance, sleep-wake patterns, food intake and behavioural responses associated with emotion.

The brainstem connects to the diencephalon above and the spinal cord below. It consists of three segments: midbrain, pons and medulla oblongata. Important motor nuclei are found in the medulla oblongata such as the cardiovascular centre and the respiratory centre. Hence, the brainstem plays a vital role in maintaining life.

The second largest part of the brain is the cerebellum. The cerebellum processes inputs from the cerebral cortex, the brainstem, and sensory receptors to provide the precise timing and appropriate patterns of skeletal muscle contraction needed for the coordinated movements in our day-to-day life. Cerebellar activity occurs subconsciously.

The distribution of grey and white matter relates to the structure of the nerve cell. Many 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 color (grey matter).

Within the brain are four cavities filled with Cerebro Spinal Fluid (CSF). These cavities form the ventricular system. The two lateral ventricles are located in the cerebrum whilst the third and fourth ventricles are located in the diencephalon and behind the pons, respectively. The CSF is a water-like fluid produced primarily in the lateral ventricles. Besides serving as a cushion for the brain within the rigid skull, the CSF helps to maintain a suitable environment for the nervous tissue.

1.3. Head injury criteria and thresholds for humans

A number of head and brain injury criteria have been developed in the past, some of which were originally intended to predict skull fractures. However, since some of these were thought to closely correlate with brain injury

as well, the following section summarises existing head and traumatic brain injury criteria independent of the type of head injury it is intended to predict.

Global head injury criteria, together with Anthropomorphic Test Devices (ATDs), are used to assess safety in consumer products such as vehicles or helmets. Within the existing criteria, the Head Injury Criterion (HIC) (Gadd et al., 1966, Versace et al., 1971, NHTSA, 1972) is the most widely used for head injury assessment in regulation and consumer tests. HIC was designed by combining skull fracture thresholds from head impacts in Post Mortem Human Subjects (PMHSs), scaled non-human primate head impact data, and human volunteer sled test data. HIC is calculated based on the linear acceleration head centre of gravity and the duration of the acceleration. Figure 2 shows a HIC equation where $a(t)$ is the head linear acceleration and t_1 and t_2 correspond with initial and final acceleration times, respectively.

$$\text{HIC} = \left\{ \left[\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} a(t) dt \right]^{2.5} (t_2 - t_1) \right\}_{\max}$$

Fig. 2. HIC equation

HIC has been shown to correlate to skull fractures and severe concussions for impacts of 15ms or less duration (Prasad et al., 1985). A HIC of 1,000 is well correlated to a risk of AIS3+ injury of 53% (NHTSA, 1995). Still, the HIC is criticised for not considering factors that are important to brain injury. Such additional factors include the impact direction and area of contact, stiffness of the impacting surface, and rotational accelerations induced by oblique impacts or when the torso is restrained (Gennarelli et al., 1982, Newman 1986, McElhaney, 2005). Therefore, alternative or complementary criteria that consider rotational acceleration of the head, such as the Generalized Acceleration Model for Brain Injury Threshold (GAMBIT) (Newman, 1986), the Brain Rotational Injury Criterion (BRIC) (Takhounts et al., 2011) and the Rotational Injury Criterion (RIC) (Kimpapa et al., 2012) have been proposed. Table II in Paper II summarises the equations of HIC and some of the alternatives for global head injury criteria in the literature.

GAMBIT combines head linear and rotational acceleration peaks to establish thresholds for severe injuries. Such thresholds were established based on critical head linear acceleration (a_{cr}) of 250g and a rotational acceleration (α_{cr}) of 10 krad/s² estimated from PMHS head impact data that produced skull fractures and from experiments with non-human primates that produced prolonged (more than 6 hours) unconsciousness and neuropathologic findings of Diffuse Axonal Injuries (DAI) (Gennarelli et al, 1972). BRIC critical values, obtained from vehicle crash tests comprising Hybrid III dummies and processed with a human FE model, were established at $\alpha_{cr} = 39.7$ krad/s² and critical rotational velocity (ω_{cr}) of 46.41 rad/s² for DAI/AIS4+ injuries.

Besides the above mentioned criteria, a number of studies have proposed rotational acceleration peak thresholds for different AIS levels, concussion/MTBI and/or DAI. Although concussion/MTBI is usually regarded as the clinical precursor of DAI and the overlap of these two types of injuries is not well established, DAIs are usually considered to occur at higher trauma severity than concussion/MTBIs.

Ommaya et al. (1984) established a relationship between different AIS levels and peak sagittal plane rotational acceleration of the head. For rotational velocities above 30 rad/s a tolerance level for AIS2 was established in 1.7 krad/s², AIS3 in 3 krad/s², AIS4 in 3.9 krad/s² and AIS5 in 4.5 krad/s². Margulies et al. (1992) suggested 9 krad/s² for DAI in coronal impacts by extrapolating primate data (Gennarelli et al., 1982). Davidsson et al. (2009) estimated human thresholds of 10 krad/s² for a pulse duration of 4 ms for DAI in the sagittal plane from extrapolated rat head rearward rotational experimental data.

The above mentioned studies focused on establishing thresholds for moderate to severe injuries. However, few works are available to establish thresholds for MTBI. Ewing et al. (1975) subjected volunteers to head accelerations in the sagittal plane of up to 2.7 krad/s², without any adverse effects on the volunteers. Recently, Rowson et al. (2012) suggested a 50% risk of concussion for head rotational acceleration peaks of 6.4 krad/s² obtained from head

impact measurements taken through instrumented helmets in football games. A similar methodology was followed by Pellman et al, (2003) to suggest a lower threshold of 5.5 krad/s² associated to a 50% risk of concussion.

Local brain tissue injury criteria can be used with FE models of human and animal brains. This opens the potential for virtual safety assessment methodologies that incorporate brain injury mechanisms at tissue level.

Based on the simulation of a series of concussive and non-concussive head impacts in American football, Kleiven (2007) identified, among others, strain in grey matter and corpus callosum, as well as strain rate in grey matter stress at the brainstem as some of the significant predictors for concussion. By applying logistic regression to each of the identified parameters, injury risk curves were calculated and thresholds suggested. For example, 50% probability of concussion was associated with a 26% strain in the grey matter, a 21% strain in the corpus callosum, and a 48.5 s⁻¹ strain rate in the gray matter. Following a similar methodology, Zhang et al., (2004) proposed a shear stress in the brainstem of 7.8 kPa as the best injury predictor.

Based on simulations of rotational rat head trauma experiments Lamy et al., (2013) estimated brain tissue first principal strain at 3.9 and 4.7% thresholds for MTBI/DAI for two different immuno-pathologic methodologies used to define the injuries. However, the study did not explain how the proposed thresholds relate to humans.

Besides simple measures of stress, strain or strain rate in the brain FE models, more complex criteria have been proposed. An example of this is the Cumulative Strain Damage Measurement (CSDM) (Takhounts et al., 2003, 2011) 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 real life human impacts and scaled animal experimental data with a human FE model, a CSDM of 0.425 was associated with a 30% probability of DAI/AIS4+ injury (Takhounts et al., 2011).

A hybrid approach has evolved in which brain injury risk is assessed in two steps; first physical measurements from ATDs are collected, then these measurements serve as boundary conditions in identical head trauma simulations using human FE models of the head. This approach establishes a relationship between global head injury criteria measurable with physical testing (BRIC) and injury risk based on brain tissue mechanics (CSDM).

1.4. Scaling of animal injury data to humans

Head impact experiments on non-human primates, used as human surrogates, have been carried out in the past. The purpose of these studies was to understand head and neck kinematics that produce brain injuries, and to establish injury thresholds. These thresholds were scaled to apply to humans supported by similarity principles between species. However, the scaling methodologies used (Holbourn 1943, Stalnaker et al. 1973, Ono et al 1980, Ommaya et al 1985), were based on assumptions that have been scarcely validated and heavily criticised (Ommaya et al., 1985, Margulies et al., 1992, McElhaney, 2005, Davidsson et al., 2009, Rowson et al., 2012) for presenting many scientific limitations.

Global dimensional scaling: Holbourn (1943, 1956) stated that the level of rotational acceleration required to produce injury in brains with similar properties and shapes is inversely proportional to the ²/₃ power of the masses of the brain. That statement was made on the basis of physical reasoning alone, and is likely based on the fact that the surface area and the cross-sectional area of body forms scaled by isometry are proportional to the 0.67 power of the body volume. Figure 3 shows Holbourn's equation where $\ddot{\theta}_p$ is the head rotational acceleration threshold for primates, $\ddot{\theta}_h$ is the head rotational acceleration threshold for humans, M_h is the brain mass in humans, and M_p the brain mass in primates.

$$\ddot{\theta}_p = \ddot{\theta}_h \left(\frac{M_h}{M_p} \right)^{\frac{2}{3}}$$

Fig. 3. Holbourn's equation.

According to Ommaya et al. (1967), the assumptions by Holbourn can be defined as follows:

- The brain acts as an elastic medium
- Brain tissue is homogeneous and isotropic in nature
- Density of brain tissue in monkey and human is equal
- Monkey and human brains are geometrically similar, through one scale factor
- The skull is very stiff, such that deformations of the skull do not contribute heavily to the strains in the enclosed brain
- Stiffness factors of the contained brains in monkey and human are equal

Some of these statements are questionable since it is well established that brain tissue behaves as a non-linear (Bilston et al., 2001), viscoelastic (McElhaney et al., 1976, Arbogast et al., 1997, Darvish et al., 2001, Prange et al., 2002), anisotropic (Shuck et al., 1972, Arbogast et al., 1998), and inhomogeneous material (Gefen et al., 2012, Elkin et al., 2010-2011). In addition, the assumption that deformation of the skull does not contribute to the strains in the enclosed brain is contrary to some studies. Ono et al (1980), based on non-human primate impacts, pointed out the need to consider skull deformations at the site of impact to clarify contusions and Andersson et al. (2004) indicated, based on impact experiments on sheep, that the severity of axonal injury is not independent from skull deformations and fractures.

Ommaya et al. (1985), wrote with regards to rotational thresholds scaled using Holbourn's approach: "It should be re-emphasised that this information is considered to be reliable for the Rhesus, sketchy for the chimpanzee, and completely speculative for man." Still, Holbourn's approach is the most commonly used to extrapolate thresholds from any animal species for humans. Margulies et al. (1985) conducted work to verify Holbourn's equation based on brain-like (gel) physical models of monkeys and humans. Such models were used to deduct relationships between shear strain and rotational acceleration for different shapes and sizes, and to suggest rotational thresholds for DAI in humans. Thibault et al. (1998) reviewed the scaling approach for the purpose of scaling injury thresholds from human adults to children, and concluded based on a modified Holbourn's equation in which a term to compensate for the differences in tissue properties between adults and infants was included.

Other studies, proposed improved dimensional scaling in combination with FE calculations. Mendis (1992) built a baboon FE model to study brain strain during rotational acceleration of the head, and to correlate the strains calculated in the simulations with axonal injury grade from primate experiments (Gennarelli et al., 1987). Although the model and the methodology were limited, the work by Mendis was pioneering in suggesting a scaling methodology from non-human primates to humans using FE models. Takhounts et al. (2003) applied an equal stress/equal velocity method to define equivalent conditions at tissue level to scale experimental conditions from animal experiments to a human model. In this case the experimental kinematic loading conditions were scaled in amplitude and time to satisfy the equal stress/velocity scaling relationship. This methodology allows scaling of kinematic loading conditions including head linear, head rotational, and duration of the acceleration. The latter is important, since it has been established that acceleration thresholds for short durations are higher than for longer duration impacts (NHTSA 1972, Ono et al., 1980, Ommaya et al., 1985, Genarelli et al., 1987). The counterpart of this method is that, once the kinematics loading conditions are scaled, the brain tissue patterns from the simulations cannot be matched with the location of the injuries produced in the experiments.

Global adimensional scaling has also been utilised to extrapolate non-human primate data to humans. Stalnaker et al. (1973) used adimensional scaling which, based on Buckingham's theorem, provide a method for computing sets of dimensionless parameters from the given variables. Buckingham's theorem provides a way of generating sets of dimensionless parameters, without identifying the most 'physically meaningful'. Head linear acceleration, pulse duration, velocity of impact, average skull radius, and average skull thickness were some of the variables used by Stalnaker et al. (1973) and Ono et al. (1980) to determine human thresholds for TBI.

1.5. Finite element modelling to understand brain injuries

Axonal damage is produced when brain tissue is subjected to strain (Galbraith et al., 1993, Meaney et al., 1999, Anderson et al., 2000). Therefore, brain tissue strain (or stress) is suitable as a reference indicator in computational studies, providing the FE method with potential for DBI research.

The FE method is a computer-based numerical technique for the approximate calculation of the behaviour of solid structures (Hallquist, 1998). The structure is broken down into many small continuous compatible elements (called meshing). Six equations are used to calculate the motion and deformation in time of each element. Three of them are the equilibrium equations according to the fundamentals of physics (Newton's Law). The other three equations require strain/stress relations (material properties) which are defined based on tissue experiments (McElhaney, 2005). FE models cannot simulate biological processes similar to brain injury. Instead, they are used under the assumption that injurious biological processes are triggered when the brain tissue reaches a certain level of strain (or stress). Then, by applying external loads equalling measures from real life events that led to injuries, the mechanical process can be simulated and the correlation between the stress/strain sustained by the brain model in the simulations and the injury output in the experiments can be analysed.

Based on this background, human brain FE models have been developed and are extensively used for brain injury research purposes. Examples of state-of-the-art models include the Wayne State University (WSU) model (Zhang et al., 2004), the KTH model (Kleiven, 2007), the THUMS model (Kimpura et al., 2008), and the SIMon model (Takhounts et al., 2003). These models largely differ in the geometrical accuracy of the organs, tissue modelling, computational power requirements and validation level achieved. The latter is limited in all human models due to the lack of human data to validate the models with. The state-of-the-art brain model validation level has been defined in a series of PMHS experiments (Hardy et al., 2001) in which the motion of opaque markers in the brain at head impacts were recorded by means of high-speed x-ray.

Due to the lack of model access, it is difficult to conduct objective comparisons across models. The WSU model is recognised for having high geometrical accuracy while SIMon is recognised for its proved usability when establishing thresholds for dummy physical testing. The WSU, KTH, SIMon and the THUMS models have been utilised to simulate real life accidents and to suggest possible ongoing mechanisms during impacts by establishing correlation between the simulations and medical records of the patients involved in accidents. Current developments in injury diagnosis through medical imaging are opening new possibilities to locate and quantify brain injuries. Such developments will become crucial for enhancing the level of human models and to improve their potential as injury prediction tools.

Animal experimental data compensates for the lack of laboratory controlled human experimental data when establishing injury thresholds for FE models. The SIMon model made use of scaled kinematics in head injuries from animal experiments. However, this methodology does not allow establishing correlation between the injury mechanisms and the injury locations. To overcome this limitation, and to improve the understanding of the relation between animal head kinematics and the injuries produced, experiments are conducted and simulated with FE models of the specimens. In literature, a large number of animal models following this methodology are found using different animal species and models such as sheep (Anderson et al., 2004), swine (Meaney et al., 2003), ferrets (Ueno et al., 1999), and rats (Mao et al., 2006, Baumgartner et al 2009, Fijalkowski et al., 2009).

1.6. Brain tissue mechanical properties

Brain tissue material properties need to be defined in order to simulate a brain response to external forces in head FE models. Brain tissue behaves as a non-linear (Bilston et al., 2001), viscoelastic (McElhaney et al., 1976, Arbogast et al., 1997, Darvish et al., 2001, Prange et al., 2002), anisotropic (Shuck et al., 1972, Arbogast et al., 1998) and inhomogeneous material (Gefen et al., 2012, Elkin et al., 2010-2011). Brain tissue is also considered as an incompressible material (McElhaney, 1976), which implies that deformation is dominated by shear properties.

Complex material models are required to account for all the characteristics mentioned above. However, in practice, linear viscoelastic models defined by two or more shear moduli terms and relaxation times are implemented in brain FE models. When analysing different experiments in terms of such shear moduli, values reported in literature present large variability (Chatelin et al., 2010). Some of the lowest values reported for short (G_0) and long term modulus (G_1) of 450 and 30 Pa, respectively, were published by Shen et al. (2006) based on data obtained from shear strain dynamic testing of porcine brain tissue. McElhane et al. (1976) obtained properties within the highest values of G_0 of 10 kPa and G_1 of 3kPa from human and macaque brain tissue in compression.

In addition to the simplifications required for modelling, the material properties implemented in FE models are biased towards stiff values, some of them beyond the experimental data from the literature. This is likely due to the possible influence of soft properties in compromising the robustness of the model, due to numerical instability at simulated high speed impacts. The WSU model (Zhang et al., 2004) ($G_0 = 34-58$ kPa, $G_1 = 6-8$ kPa) or, to a lesser degree, the THUMS model (Kimpura et al., 2007) ($G_0 = 12-23$ kPa, $G_1 = 6$ kPa) are two examples of models with tissue properties beyond the published experimental data. The brain tissue models implemented in the SIMon (Takhounts et al., 2003) ($G_0 = 10$ kPa, $G_1 = 5$ kPa) and the KTH model (Kleiven et al., 2007) ($G_0 = 12.5$ kPa, $G_1 = 1$ kPa) fall within the range of properties reported in literature.

1.7. Experiments to understand brain injuries

Experimental work that allows studying kinematics of the brain during impacts and to establish injury thresholds, can be roughly divided into two main categories: human volunteer experiments and reconstruction of accidents, experiments with animals. The latter can be split in experiments with non-human primates and with non-primate subjects. Currently, due to ethical controversy of primate research (later discussed in this thesis), non-primate animal subject experiments are conducted. However, most of such studies predominantly focus on fundamental TBI pathology, rather than understanding kinematics and establishing injury thresholds. Due to the scaling potential still being limited, the non-primate category is outside the scope of this thesis.

1.7.1. Human volunteers, PMHSs, sports and real life crashes

Due to ethical reasons, the use of human volunteers for injury research is restricted to sub-injurious experimental conditions. Snyder (1970) summarised a number of free-fall and sled tests with volunteers conducted at the Aeronautical Research Laboratory base in New Mexico (USA). These data provided, amongst others, evidence of tolerance decreasing with increasing pulse durations. In a different study, Ewing et al. (1975) subjected volunteers to head accelerations in the saggital plane up to 2.7 krad/s^2 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.

One possible alternative is the usage of PMHSs for brain injury research. PMHSs have the potential to provide valuable data to establish thresholds for skull fractures, but are limited for TBI research since they cannot provide biological responses to impacts. Another option is to use instrumentation to measure head loading conditions in real-life events, such as in car crashes and sports, in which human volunteers are at risk of suffering head impacts. Instrumentation has mainly been applied to capture head kinematic data from American football players (Duma et al., 2005, Rowson et al., 2009) who often suffer concussion/MTBI. The methodology provides an extraordinary opportunity to obtain data useful for establishing thresholds. However, this methodology has its limitations; a 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 direction limiting the opportunity to understand

the head-neck kinematics that produce the injuries, and a lack of measurements of vital signs during and directly after the impacts, to name a few.

1.7.2. Non-human primate animal experiments

Using living non-human primates as human surrogates, when investigating human brain injury tolerance were common in research practice in the past. Some of the experimental series contributed to the development of the HIC, in conjunction with PMHS testing and volunteer tests comprising military volunteers. Stalnaker et al., (1973, 1977) conducted series of occipital and lateral impacts delivered to the head of macaque and baboon specimens with a rigid impactor. The impacts produced failure of the saggital sinus, hemorrhaging in the brainstem and slight subdural and subarachnoid hemorrhages. Genarelli et al., (1982), conducted series of non-impact rotational acceleration-deceleration tests on specimens of different species. In the experiments, a range of head peak rotational accelerations of 7 to 20 krad/s² were produced. DAI output was graded from 0 to 3, depending on the amount of DAI and its location. Intensity of axonal damage was found to be proportional to lesions in the corpus callosum. Ommaya et al., (1984) conducted a large series of direct impacts and whiplash injuries induced by non-impact head rotation. Based on these experiments, concussion thresholds were established as a function of rotational acceleration and velocity of the head.

One more series of experiments was conducted at JARI, Japan. This series consisted of four main groups with different impact set-ups and injury levels. The specimens used were mainly macaques. The first three groups (A, B and C) represented saggital impacts of different nature and severity (Ono et al., 1980, Kanda et al., 1981). A fourth group of coronal impacts was carried out and presented separately (Sakai et al., 1982, Kikuchi et al., 1982). Figure 4 summarises the groups used in the JARI head trauma experiments, as well as a sketch of the experimental set-ups for each of the groups.

JARI head trauma experiments (1976-1982)

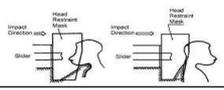
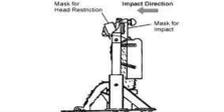
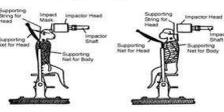
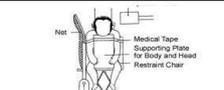
Group	# Tests / Specim.	Impact Area	Level	Impact Direction	Accel.
A	27 / 27	Broad	Fatal		Translation
B	21 / 21	Broad	Fatal		Rotation + translation
C	73 / 21	Narrow	Mild		Rotation + translation
D	30 / 8	Narrow	Mild		Rotation + translation

Fig. 4. Scheme summarising JARI head trauma experiment groups.

The most important outcome from the experiments conducted in Japan was the JARI Human Tolerance Curve which defines human tolerance for concussion. It was also found that concussion was the limiting injury and its thresholds were far lower than the thresholds for fracture.

Comparative anatomy. The most commonly used specimens in the experiments were *Macaca mulatta* (Rhesus monkey) and *Macaca fuscata* (Japanese macaque). Phylogenetically, these species are closely related to each other. They differ slightly in size, but have similar head shape and dimensions. Neuroscientists and physiologists consider these two as one species; therefore for the purpose of this thesis, they have been grouped together and are considered as one single macaque species.

The anatomical brain regions are the same in macaques and humans and they are positioned in a similar layout. Both species have a relatively large cerebrum with a convoluted cerebral cortex. The brainstem grows vertically from the centre of the cerebrum and connects with the spine, while the cerebellum is located in the posterior part of the head. Macaque brains have an approximate brain mass of 100 g, a maximum length of 70 mm and a transverse diameter of approximately 50 mm. Human brains weigh approximately 1,400 g, have a length of 165 mm and a transverse diameter of 140 mm. Figure 5 shows diagrams of skull-neck (top) and brain (brain) of a human and a macaque.

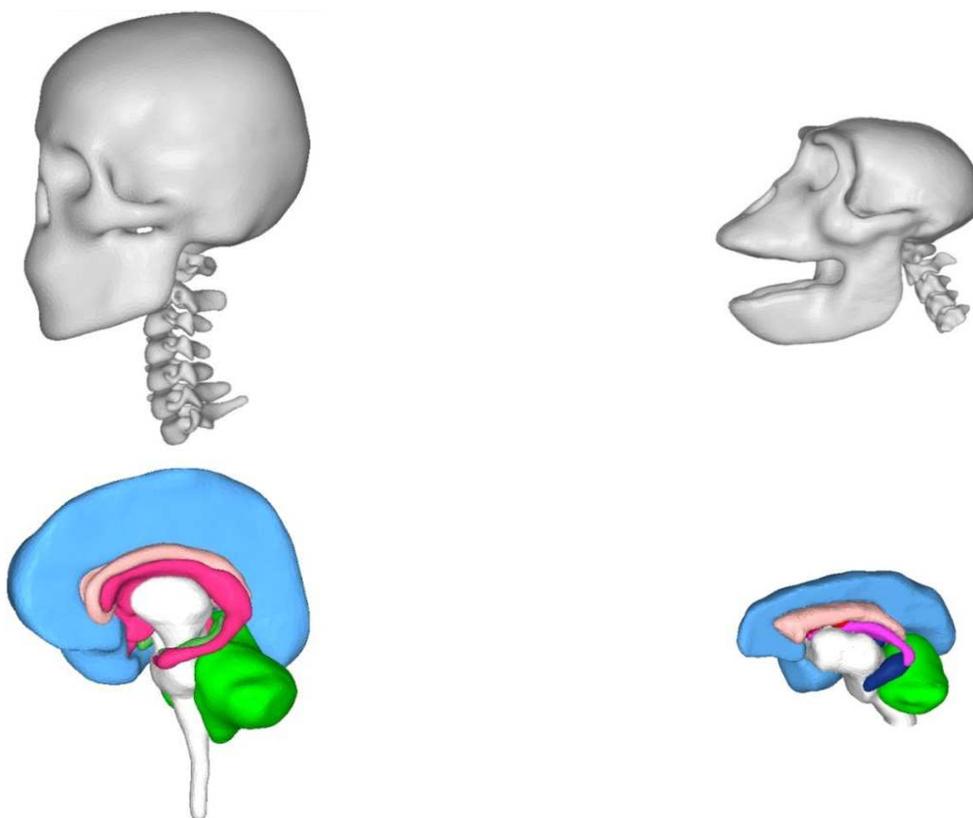


Fig. 5. Top row: diagram of human (left) and macaque (right) skull-neck geometry. Bottom row: human brain (left) and macaque brain (right). Corresponding regions are represented in the same colour. In both cases, left cerebrum is omitted in the images for visibility reasons.

Skull bone structure differs between humans and macaques. This is consensus within the primatologist community and was mentioned as a factor that may affect the difference in response to impacts between macaques and humans (Nusholz et al., 1979, McElhaney et al., 1973). In addition, the thickness of the skull bone and the scalp is less uniform in the macaque than in the human. Such non-uniformity is due to the smaller-sized calvaria and the attachment of the stronger musculature on the external surface of the jaws in macaques. The oversized mandible also affects the thickness of the flesh and musculature covering most of the temporal regions of the macaque's head

(Nishimura, 2011). This may have implications in offering additional natural protection for macaques in side impacts, not present in humans.

2. AIMS

2.1. Ultimate goal and long term plan

The ultimate goal of this study is to generate knowledge that contributes to the development of MTBI criteria and associated limits that will, when properly applied, reduce the number of moderate brain injuries due to closed head impacts.

To achieve this goal, clarification of MTBI mechanisms, definition of injury criteria that account for such mechanisms and establishment of associated thresholds are necessary intermediate objectives. In addition, the injury criteria need to be adapted to be suitable for use in modern ATDs for physical testing in the mid-term. In the longer term, it is expected that criteria for human FE models will be required for virtual testing.

To fulfill these objectives, a number of research activities need to be conducted in parallel. Among others, real-life traffic and sports accident data collection activities, including medical reports and imaging of the injured patients, reconstruction of the accidents using validated human FE models, physical testing with ATDs and experimental activities involving animal experimental data. A sketch of the road map drawn to guide the research presented in this report is shown in Figure 6.

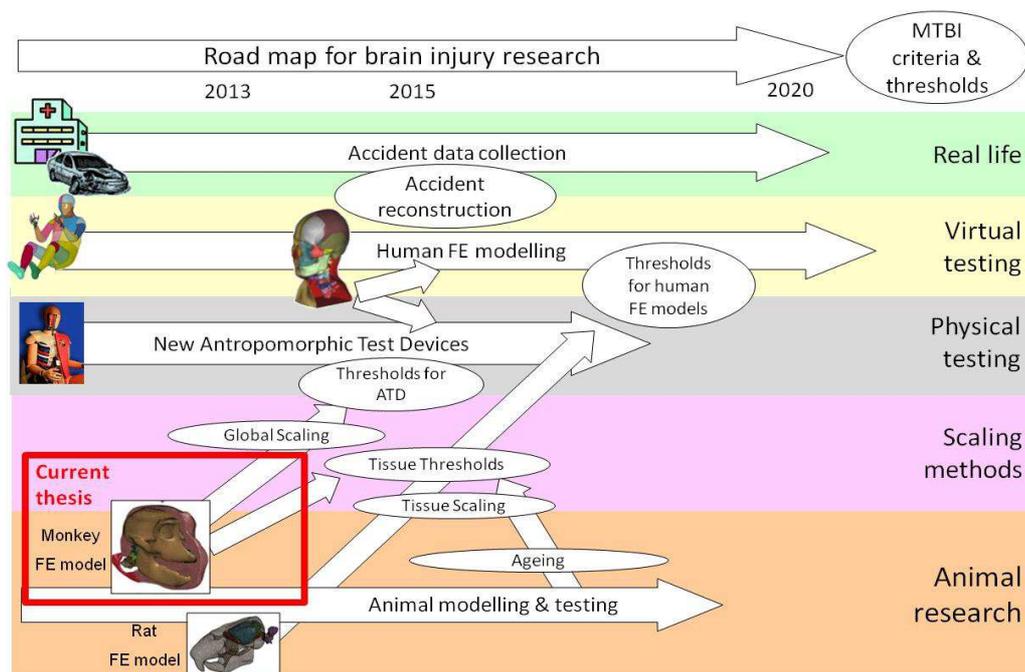


Fig. 6. Road map scheme for brain injury research including: real-life data collection activities, human model development activities, dummy development activities, definition of scaling techniques and animal research

This thesis has focused on animal research activities in which historical non-human primate head trauma experimental data have been re-analysed using an FE model of the specimens, in order to clarify the head-neck kinematics that produced concussions/MTBI in the experiments.

2.2. Aims

This thesis aimed to achieve the following:

- To build and validate a head-neck FE model of a non-human primate
- To improve the understanding of head-neck-brain kinematics that produce concussion/MTBI, by simulating past non-human primate head trauma impact experiments in the saggital plane with the above mentioned model.
- To evaluate the reliability of existing global head injury criteria calculated based on simulations of the head trauma impact experiments in the saggital plane.
- To propose brain tissue injury reference values for concussion/MTBI in humans derived from simulations of the head trauma impact experiments in the saggital plane.

3. MATERIALS AND METHODS

This chapter introduces the materials and methodology used in this thesis. Initially, non-human primate head trauma experimental data (3.1) were re-analysed and two sub-groups of impacts suitable for the simulation work were selected. A head-neck FE model of a non-human primate was then built from medical images (3.2) taken from an anaesthetised specimen. The developed model was tuned and validated based on literature experimental data and used to simulate case-by-case the two sub-groups of head impacts according to the simulation setup described in detail in Papers I and II. Furthermore, the simulations results were processed to extract brain tissue injury measurements such as Von Mises Stress (VMS) and Maximum Principal Strain (MPS) from different regions and to calculate global head injury criteria such as HIC, BRIC, RIC and GAMBIT. Analysis of the correlation between brain tissue measurements, global head injury criteria derived from the simulations and the occurrence of concussion recorded during the experiments, was conducted. Finally, risk curves for concussion as a function of brain tissue measurements were calculated for occipital and frontal impacts separately and together.

Throughout this study, several commercial software programmes were used for the digitisation of a brain atlas (GetData Graph Digitizer, Russia), segmentation of medical images (Simpleware v4.2, Simpleware, UK) and construction of a mesh (Hypermesh v11.0, SimLab and SimLab Kubrix, Altair, US). All simulations were performed with the explicit FE code LS-DYNA (version mpp971s R5.1.1, LSTC, US). Post-processing and analysis were done with LS-Prepost (LSTC, US), Microsoft Excel (Microsoft Corporation, US) and R-statistic (The R Foundation for Statistical Computing, Austria).

3.1. Head trauma experimental data

Two sub-groups of saggital impacts were selected from the JARI non-human primate head trauma experimental database. The selected cases were non-fatal direct impacts that resulted in combined rotational and translational head accelerations. 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. The data selected consisted of a first sub-group of 19 occipital impacts delivered on 7 specimens who suffered 9 concussions (Paper I) and a second sub-group of 24 frontal impacts delivered on 8 specimens who suffered 10 concussions (Paper II). The data available included head linear accelerations, high speed videos, photographs from pathological examinations, and records of symptoms and injuries. Pathological injury scores included Sub-Arachnoid Hemorrhage (SAH), Sub-Dural Hematoma (SDH), and contusions, among others. Concussion was 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. Descriptions of experimental setup, injury scoring methodology, impact conditions and injury output of all cases are included in Papers I and II.

3.2. Medical images

A new set of Computed Tomography (CT) scans and Magnetic Resonance Images (MRI) were obtained from an anaesthetised specimen of *Macaca Fuscata* at the imaging facilities of the Primate Research Institute at Kyoto University (KUPRI). The procedures to care and treat the animal and the purpose of the usage of the images were approved by the Animal Welfare and Animal Care Committee ethics panel of the KUPRI (Permission 2011-134, 7 June, 2011). A Toshiba Asteion 4 (Japan) machine was used to capture the CT scans with 0.5 mm slice thickness and 0.2 mm slice distance. For the MRI, a 0.2 Tesla GE Signa Profile (US) machine was used to capture 1 mm thick slices with 1 mm distance. The images were captured of a 5 years old female specimen with a body mass of 7.9 kg which closely correspond to the average weight of the specimens used in the previously selected trauma experiments.

4. SUMMARY OF PAPERS

In this section, the papers included in this thesis are summarised. In Paper I, an FE model of the head-neck complex of a macaque was built, tuned, validated and used to simulate a subset of occipital mild impacts selected from Ono et al (1980). The paper also includes the analysis of brain tissue injury criteria from the simulations in relation to the reported injuries. In Paper II, the same FE model was used to simulate a subset of frontal mild impacts and to analyse brain tissue injury criteria, global head injury criteria and their relation to the injury outcome.

4.1. Paper I

Paper 1 focuses on the development process of the FE model and its application to simulate, case-by-case, 19 occipital head impacts

Method

An FE model of the head-neck complex of a macaque was generated from the set of CT/MRI images taken from a macaque subject (section 3.2). The final model includes and differentiates between the following regions; skull and scalp, cerebrum, corpus callosum, brainstem, cerebellum, meninges, falx cerebri, tentorium, and the cerebrospinal fluid. Figure 7 shows images of the model and Table I summarises the material models and properties implemented in the model.

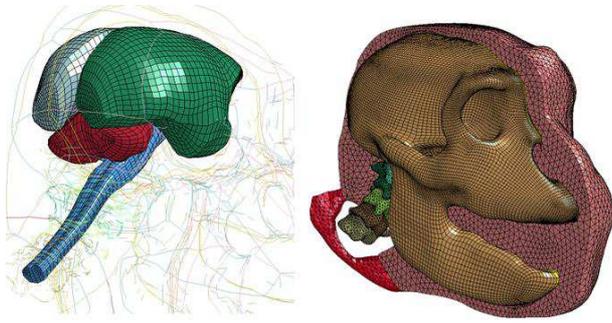


Fig. 7 The Monkey FE model. Images of the brain (left) and the skull, cervical spine and soft tissues (right) where part of the flesh was removed for visibility.

TABLE I
MONKEY FE MODEL MATERIAL PROPERTIES

	Material model	Material properties
Scalp and neck flesh	Fu Chang Foam	Experimental stress-strain curves
Skull bone	Piecewise linear plasticity	$E = 6.48 \text{ GPa}$, $US = 92.4$
Cerebrum, corpus callosum, cerebellum	General viscoelastic	$G_0 = 10300 \text{ Pa}$, $G_1 = 3700 \text{ Pa}$, $\tau = 100 \text{ s}^{-1}$
Brainstem	General viscoelastic	$G_0 = 18540 \text{ Pa}$, $G_1 = 6660 \text{ Pa}$, $\tau = 100 \text{ s}^{-1}$

E =Young Modulus, US =Ultimate strength, G_0 =Short term modulus, G_1 =Long term modulus, τ =decay constant

The model was tuned at tissue level with experimental compression data from coupons of monkey scalp (Galford et al., 1970) and brain tissue (Melvin et al., 1970, McElhaney et al., 1976), and validated at component level against quasi-static skull compression test data by Stalnaker et al., (1977) and for head linear kinematics against full-scale head impact experiments by Ono et al., (1980).

The FE model was used to simulate case-by-case the 19 experimental cases in the selected sub-group of occipital impacts. To define the setup of the simulations, the velocity of the impactor just before the impact, the stiffness of the rubber block, and the maximum stroke of the impactor were set case-by-case according to the recorded data in the experiments (Figure 10 in Paper I). All simulations were run for the entire time period of contact between the head and the impactor and for at least 2 ms more.

The maximum values for the VMS, the MPS and the strain rate were post processed for each of the brain regions separately. A test for significance (Student's *t*-test) was carried out to evaluate the difference in the average values between the group with and the group without concussion. Finally, based on the parameters and regions that presented significant differences, a logistic regression analysis was conducted in order to create risk curves for concussion as a function of brain tissue measurements.

Results

The results indicate that, at a 95% confidence level, the observed mean values obtained for the two groups, i.e., with and without concussion, were significantly different for VMS in the cerebrum, brainstem and corpus callosum, as well as for MPS in the cerebrum and corpus callosum. MPS in the brainstem almost reached significance (94%). For the parameters and regions that presented significant differences between concussion and no concussion, logistic regression analysis were carried out and the probability curve of occurrence of concussion was estimated. From these curves, a MPS of 0.21 in the brainstem was associated with a 50% probability of concussion.

4.2. Paper II

In this study, the monkey head-neck FE model presented in Paper I was used to simulate case-by-case a sub-set of 24 frontal head impacts. In addition to brain tissue criteria, in this paper, global head injury criteria were also

calculated from the simulations, as well as their relationship to tissue criteria. Experimental injury output was also analysed.

Method

The techniques used to define the simulation setup were the same as in Paper I. The FE model was used to simulate the 24 experimental cases in the selected sub-group of frontal impacts. The setup of the simulations was performed as explained in Figure 3 in Paper II. The results from the simulations were processed to extract head translational and rotational accelerations, and peak values for VMS and MPS at the cerebrum and the brainstem. The acceleration curves were used to calculate HIC, GAMBIT, BRIC and RIC for each simulated impact.

Based on the extracted results, first, a *t*-test for significance was carried out to evaluate the relationship between the global head injury criteria and the experimental concussion. Second, brain tissue injury measurements were correlated with occurrence of concussion, and injury risk curves were developed by carrying out a survival analysis to account for censored data (Petitjean et al., 2012). Third, linear regression between the global head injury criteria and the brain tissue injury criteria was conducted followed by the criteria being ranked by magnitude of correlation coefficient. Finally, the simulation results from the occipital cases in Paper I was re-processed to calculate global head injury criteria and the results were compared to the frontal impacts.

Results

According to the injury risk curves obtained by applying survival analysis to the brainstem strain results from the simulation of frontal impacts (Figure 8, left), a 50% probability of concussion for frontal impacts was found to correspond with a MPS of 0.27 in the brainstem. This value was higher than the 0.19 (corrected from 0.21 after applying survival analysis instead of logistic regression) obtained by applying the same methodology for the occipital impacts in Paper I and the 0.23 obtained from combining both groups of impacts. According to a quality index assessment method based on relative size of the 95% confidence interval (Petitjean et al., 2012), the frontal impacts data set provided *Unacceptable* confidence intervals at 50% injury risk, while for occipital and combined impacts, *Fair* confidence intervals were obtained.

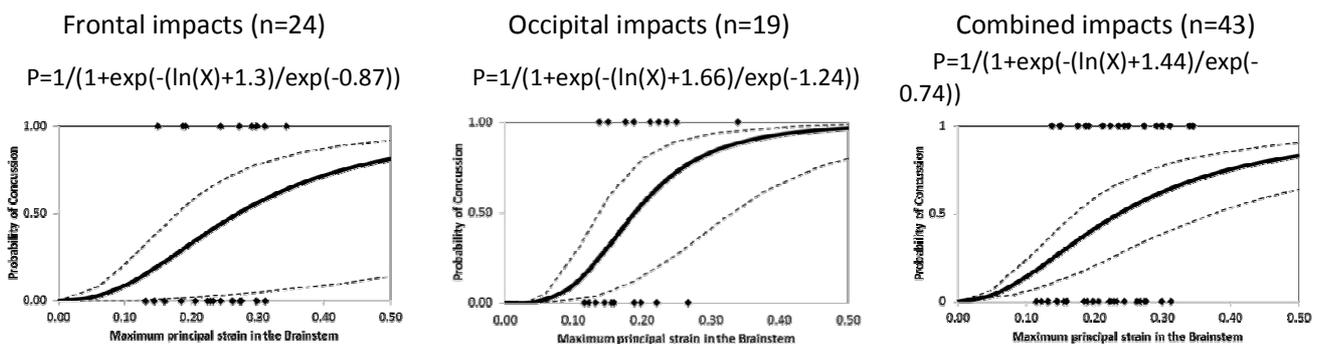


Fig. 8 Probability of concussion (solid line) and 95% confidence intervals (dotted lines) for maximum strain at the brainstem. Curves for frontal impacts (left column) are compared to previous occipital impacts (middle column) and combined impacts together (right column).

Linear correlation coefficients (R^2) defined by applying linear regression to global head injury criteria and brain tissue criteria derived from the simulations of frontal, occipital, and combined impacts revealed that: In frontal impacts, HIC provided the highest correlation to measurements in the cerebrum (0.72 and 0.80 for VMS and MPS, respectively), while GAMBIT had the highest correlation for brainstem measurements (0.82 and 0.81). In occipital

impacts, GAMBIT provided the highest correlation for brainstem measurements (0.91 and 0.92), while BRIC and GAMBIT were equally correlated to cerebrum strains (0.94). When combining the frontal and occipital impacts GAMBIT provided the highest correlation (0.84) to MPS in the brainstem.

5. ETHICAL CONSIDERATIONS

Existing non-human primate head trauma experimental data were re-analysed and used in combination with simulation work in this research project, to improve the understanding of brain injury mechanisms and thresholds. The experiments were conducted in the late 1970's under the auspices of major medical and engineering academic and governmental institutions in the United States and Japan. The experiments followed animal care regulations in effect at that time. However, the ethical controversy put all work to a sudden halt in the early 1980's.

Analysis of the ethical issues in this study was conducted as this research project involved the use of controversial experimental data. For this analysis, two main questions were formulated, analysed and answered:

- Is it ethical, in current society, to carry out non-human primate head trauma experiments for human brain injury research purposes?
- Is it ethical to use existing experimental data, together with computer based technologies to generate new knowledge for human brain injury research purposes?

In current liberal democratic societies, two main theories, the Consequentialist (Utilitarianism) and the Deontologist (from the Greek Duty), are used to approach any social ethical questions in general and research ethical questions in particular (Peach et al., 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, improve the lives of human beings. The Deontological theory analyses ethical issues from the perspective of what humans (researchers or not) 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.

Both approaches were considered and combined to answer the ethical questions. From a utilitarianism perspective, there is no doubt about the high research value to estimate human thresholds obtained from the historical non-human primate experiments. Such data were used as reference for the design of countermeasures to protect humans from head injuries, for example, through different head injury criteria. Some of those criteria are used nowadays to evaluate the safety aspects of consumer goods such as road vehicles or helmets, for example. Besides the utility of the results, researchers have the duty to adapt their research to what society demands from them. When trying to compare the value of human and animal life, the majority of society admits differences between humans and the rest of the animal species. However, the sensitivity of society with respect to animal species is changing towards a 'humanised' perception of animals, which directly affect the evolution of what is considered ethically acceptable. Based on scientific evidences or not, this perception is especially strong when dealing with non-human primates.

Hence, from a Deontologist perspective, sacrificing non-human primate animals for the good of humans is not an acceptable research method in current time and social environment. This rationale provides an answer for the first question: Non-human primate head trauma experiments conducted for the purpose of human brain injury research cannot be considered an ethically acceptable research method in modern society. In the case of the second question, the experimental data already exist and are public. Since the only negative consequence identified in the experiments was the death of specimens, by following the same rationale, the research method proposed in this thesis will not damage any specimen. Hence, using a computer simulation based method to simulate and re-analyse the experiments performed in the past can be considered an ethically acceptable research methodology. Moreover,

the re-analysis of the experimental data conducted throughout this research is within the duties of the researchers involved in order to contribute to the reduction of brain injuries, and hence a safer society.

6. GENERAL DISCUSSION

6.1. Kinematics of brain injuries

In the simulations conducted and presented in this study, highest strain concentrations occurred at sites where contusions and subarachnoid hematoma were reported in the experiments (Ono et al., 1980). The analysis of the obtained results and the observed symptoms in the original experiments was performed by physicians (Kanda et al., 1981). Such analysis focused on the concussion output as measured in physiological changes and their possible correlation to pathological observations; including studies of hemorrhages, contusions and circulatory disturbances. Based on the presence of pathology in the brainstem and spinal cord, Kanda hypothesised that the changes taking place in these regions were responsible for the concussions. This hypothesis has been confirmed by the simulation work presented in this thesis, for both occipital (Paper I) and frontal (Paper II) impacts.

Both the occipital and the frontal impacts simulated in this thesis produced combined linear and rotational head accelerations, and, in both cases, the highest strains were found in the contre-coup region of the cerebrum (frontal region for occipital impacts and rear region for frontal impacts) and in the low brainstem. For the occipital impacts, the impacts were delivered through a line that passed close to the centre of gravity of the head, while the frontal impacts were delivered clearly above the centre of gravity. The difference in impact direction relative to the centre of gravity produced comparatively higher linear accelerations and lower rotational accelerations than in frontal impacts in equivalent impact severity conditions. The occipital impacts caused the brain and brainstem to travel backwards relative to the skull cavity against the impact direction. This travel produces contre-coup negative pressures in the frontal part of the cerebrum and compressive forces in the rear part of the lower brainstem, close to the foramen magnum (Figure 9, left). In the frontal impacts, the highest brain tissue strains occurred in the occipital region of the cerebrum and in the rear side of the brainstem between the pons and the foramen magnum. Moreover, in frontal impacts, a comparatively higher rearward rotation of the skull may cause high brainstem strains based on two mechanisms. First, the rearward rotation of the skull induces a direct contact between the lower brainstem and the foramen magnum in a similar way to occipital impacts. Second, the cerebellum is pushed down by the tentorium and thereby compressing the brainstem (Figure 9, right).

As for injury thresholds, the original experiments showed that the head kinematics thresholds for concussion were higher for frontal impacts than for occipital impacts (Ono et al., 1980). Based on these experimental observations, it may be suggested that the specimens used in the experiments were more sensitive to occipital impacts. However, the simulations results from the current study showed that frontal impacts closer resembled a glancing type of impact than the occipital impacts did. In the occipital impacts, the energy was most likely transferred more efficiently to the scalp, the skull and to the brain. This was confirmed in the simulations by calculating the impactor impulse for a frontal impact and an occipital impact with identical impactor conditions, which resulted in higher values for the occipital impact. Hence, in simulated occipital impacts, as delivered in the experiments, more energy is transferred to the head when compared to the frontal impact of the same impact conditions. This indicates that the differences in thresholds seen in the original experiments by (Ono et al., 1980) for frontal and occipital impacts can be explained by differences in the impactor momentum transfer, rather than higher injury thresholds in frontal impacts as compared to occipital impacts. If impacts to the specimens had been delivered in order to transfer the same momentum for frontal and occipital impacts, smaller threshold differences would then have been expected in frontal and occipital impacts.

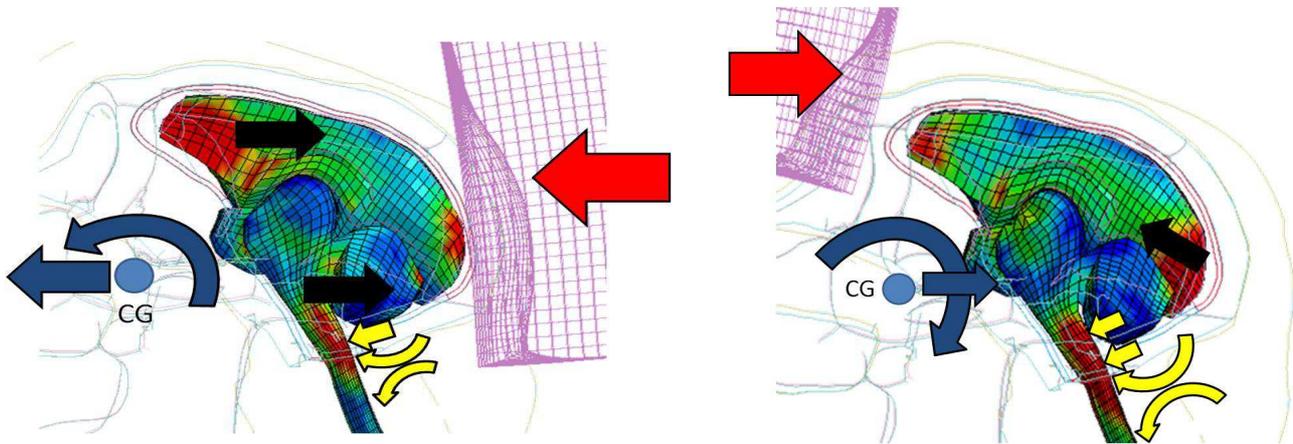


Fig. 9 Illustration of brain MPS in relation to head and brain kinematics in an occipital (left) and a frontal (right) impact under the same impact severity conditions. The illustrations show fringe plots of the MPS in the brain as obtained from the simulations (red color indicates MPS above 0.18). Red arrows indicate location and direction of the impact. Blue arrows represent linear 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.

In summary, from the simulations it was understood that the former frontal and occipital impacts were of a different nature in terms of efficacy of the impact, as well as in terms of head-neck kinematics produced by the impacts (more dominated by rotation in frontal, and linear in occipital). However, in both frontal and occipital impacts, the head-neck kinematics observed led to compressive mechanisms in the rear part of the brainstem close to the skull foramen magnum. Hence, the simulation work supports the potential of grouping frontal and occipital impacts towards the development of protective generalised strategies for sagittal impacts.

6.2. Global head injury criteria

All the global head injury criteria showed significantly higher values for the cases that scored concussion compared to those that did not. GAMBIT showed the highest correlation of brainstem strain values (0.82 for VMS and 0.81 for MPS). It appears that GAMBIT is a good candidate to predict concussion initiated from brainstem injury. However, GAMBIT does not offer the facility to identify the underlying injury causation defined in the simulated non-human primate experiments, since it is limited to global head accelerations without considering the neck (illustrated by a simple example in Figure 10). If the resulting head accelerations from any one of the simulated cases is applied to the skull motion of a head-neck FE model where the vertebrae of the cervical spine is rigidly attached to the skull, the resulting GAMBIT value would be the same, while the brainstem strains would be much lower. In the example presented in Figure 10, the peak MPS is reduced from 0.22 to 0.12 when the relative motion between the head and neck is removed, while the GAMBIT value is 2.2 for both cases.

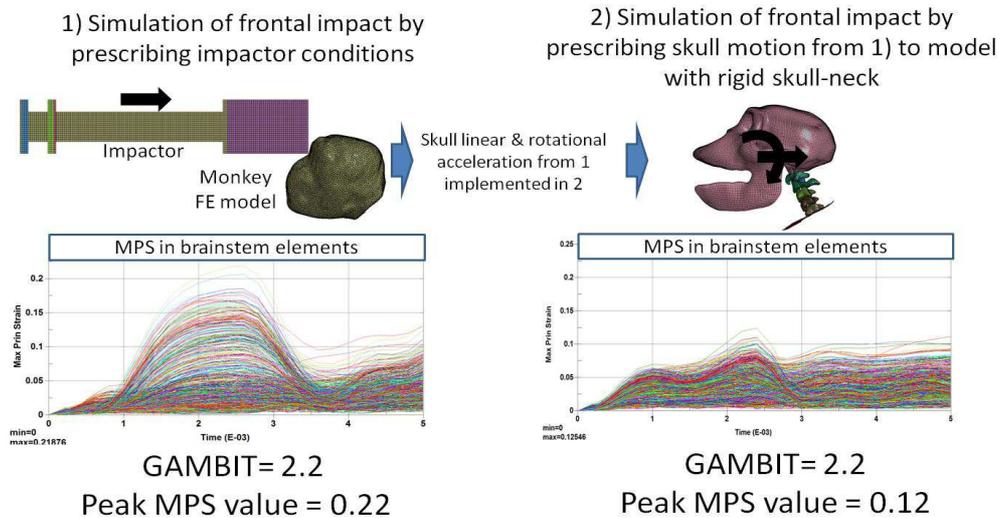


Fig. 10. Illustration of limitations of GAMBIT by comparing a simulation of a frontal impact allowing head-neck motion and a simulation of the same impact with a technique that removes the neck mobility.

The example above is explained based on a simulation technique that removes head-neck relative motion. However, it illustrates how the criteria may fail to capture ongoing head-neck and brain kinematics when used in conjunction with current tools such as ATDs or human FE models that present no biofidelity of the head-neck relative motion. This may have implications such as reducing the effectiveness of the injury criteria when applied for vehicle safety assessment with physical or virtual tools that have no bio-fidelic head-neck relative motion. Examples of this are ATD headforms which have no neck, full scale ATDs that do not have any head-neck relative mobility (Hybrid III), or human head FE models which lack the neck (WSU) or include a neck rigidly attached to the skull (KTH, SIMon). Unless conceptual improvements are introduced to consider the relative head-neck motion, for instance, all currently available criteria should be used carefully and this limitation must be taken into account when applied in physical or virtual testing. Complementary information about the duration of the applied rotational acceleration to the head, or measuring the rotational acceleration of the head with respect to the base of the neck instead of the centre of gravity of the head in full scale dummies, for example, would mitigate the limitation of current global head injury criteria that only consider head acceleration with respect to the centre of gravity of the head.

6.3. Brain tissue injury criteria

When occipital and frontal reconstruction data are combined, the maximum VMS and MPS at the brainstem showed significant differences for the groups with and without concussion. The calculated injury risk curves suggested a probability of 50% for concussion associated with a MPS of 0.19 in occipital impacts, 0.27 in frontal impacts and 0.23 for combined frontal and occipital impacts.

The simulation work in this thesis focused on the mildest impacts within JARI trauma database, below the thresholds for skull fracture. In such range of impact severity, the variability between individuals was very high and the concussion grading system was sensitive to small variations in the measured vital signs. Such variability and the sensitivity of the grading system produced a large overlap between the groups that scored concussion and the groups that did not. This overlap affected the confidence corridors obtained for brain tissue parameters in the simulations, being *unacceptable* for frontal impacts and *fair* for occipital impacts and combined sagittal impacts. Based on the comparative head-neck kinematics and its influence on brain tissue values between frontal and occipital impacts, it has been suggested that frontal and occipital cases may be merged and analysed together.

Hence, the *fair* corridor for MPS in the brainstem obtained from combining impacts is proposed as a brain tissue injury criterion for concussion/MTBI in saggital impacts (Figure 8, right).

The proposed corridor suggests a 50% probability of concussion for a 0.23 MPS in the brainstem. Such reference is in reasonable accordance with the single study found in literature in which a non-human primate FE model was used (Mendis et al., 1992). In that study, the model was a simplified baboon brain which was used to simulate three monkey trauma experimental impacts ranging from (Gennarelli et al., 1978) no injury, moderate to critical DAI, respectively. Due to differences in the experimental methods, the injury types observed, and the lack of brainstem and neck in the baboon FE model, a direct comparison with this study is difficult. Still, the range of values suggested for MPS of 0.17 for the case of no injury, and 0.28 for the case of moderate injury, seem to agree with the MPS of 0.23 derived from the current study.

The brain tissue reference values proposed in this study can be used to interpret results obtained with human FE models without scaling, provided that the human FE model has similar brain tissue properties. To establish such comparison, it is also assumed that similarity principles apply between non-human primates and humans, and that tissue thresholds are the same for non-human primates and humans (McElhaney et al., 1976). Then, the suggested brainstem MPS value of 0.23 for a 50% probability of concussion derived from this work is consistent with a study in the literature in which sports accidents resulting in concussion were reconstructed with the KTH human model (Kleiven et al., 2007) which tissue properties are similar to the monkey FE model presented in this thesis. In the Kleiven's study, MPS of 0.21 and 0.26 in the cerebral cortex and the corpus callosum, respectively, were associated with a 50% probability of concussion. Again, due to the lack of head-neck relative motion in the KTH model, it is not possible to confirm if the brainstem potential damage found and proposed throughout this thesis sustains for human concussive impacts. To confirm this, additional extensive work with improved human head-neck FE models and reconstructions of human accidents with the human FE model is needed. This need will guide the next steps of this research.

7. LIMITATIONS

Concussion is the most common type of TBI. 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 of injuries and scoring systems.

In the non-human primate experiments used in this study, some of the specimens were subjected to subsequent impacts. However, in the statistical analysis presented in Paper I and Paper II, 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.

The level of validation achieved by the primate FE model has limitations. The most important limitation is the lack of validation of the motion of the brain relative to the skull, which affects the overall brain motion inside the skull, and potentially the presented results. Additional simulation based sensitivity analysis is required to clarify how these model related limitations may be affecting the results.

8. FUTURE WORK

A review of concussion/MTBI grading methodologies will be conducted in order to improve the understanding of the severity of the injuries recorded in the past non-human primate experiments with respect to human concussion/MTBI and DAI grading methodologies currently in use in the clinical field for humans, and in the experimental field with non-primate animals.

Throughout this thesis, the influence of linear and rotational components of the head acceleration on the suggested injury kinematics has been discussed, as well as the need to include the relative head-neck motion for MTBI criteria. In addition, the relationship between the head-neck kinematics and the high strains produced in the brainstem was discussed. Further work will be performed to account for these phenomena in the definition of a global head injury criterion that provide injury risk curves as a function of head linear acceleration, head rotational acceleration and impact duration. The concept is illustrated in Figure 11, which represents some of the existing global head injury criteria in a qualitative three dimensional Cartesian space with head rotational acceleration peak, head linear acceleration peak, and acceleration duration as coordinates. Furthermore, it is anticipated that brain injury risk thresholds will be established as hyperboloid convex surfaces with an elliptical base in the Linear acceleration - Rotational acceleration plane, and straight lines or convex downward curves in the acceleration-time planes. Such surfaces will first be developed based on simulation with parameter studies of the monkey FE model. In addition, similar parameter studies will be conducted with a scaled up version of the monkey FE model in order to estimate the surfaces corresponding to human limits, as well as with a human FE model to establish a foundation for comparison across species. As a last step, the surface will be verified based on crash test data with modern dummies and accident reconstructions comprising human body FE models.

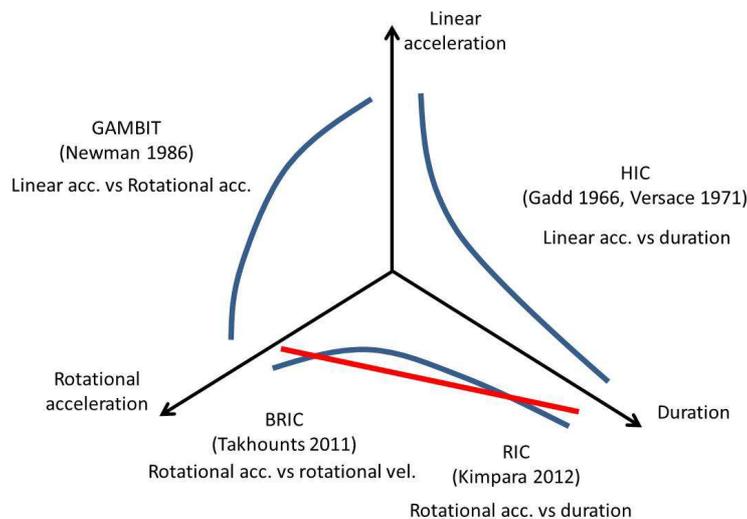


Figure 11. Qualitative illustration of head injury criteria from literature represented in a coordinate system with head linear acceleration, head rotational acceleration and duration as coordinates

9. CONCLUSIONS

An original monkey head-neck FE model has been developed from medical images of a macaque specimen, validated based on literature data, and used to simulate series of non-primate head trauma sagittal impact experiments conducted in the past.

Based on the simulations, it was observed that head-neck kinematics resulting in concussion could not be explained if the brainstem and the neck were not considered. Moreover, both in frontal and occipital impacts, brainstem compressive forces were observed in the rear part of the lower brainstem, which supports the possibility of developing generalised countermeasures for sagittal impacts.

Existing global head injury criteria show good correlation with both injury occurrence and strains in the brainstem. However, these criteria fail to capture the head-neck and brain kinematics as observed in the simulations. Unless conceptual improvements are introduced to consider the relative head-neck motion, for instance, all currently available criteria should be used carefully and this limitation must be taken into account.

Risk functions for concussion as a function of MPS in the brainstem of macaques have been developed. The proposed values, assuming similarity principles between macaques and humans if supported by equal neuronal contents, can be used as reference values for studies with human FE brain models, provided that these have similar brain material properties to the macaque FE model.

10. ACKNOWLEDGEMENTS

I would particularly like to thank:

Toshio Kobayashi, Koshiro Ono, Minoru Sakurai and Susumu Ejima at JARI, Japan, for their contribution to making this project possible, and for their continuous support and guidance.

Johan Davidsson and Karin Brodin at Chalmers, Sweden, for their constructive criticism, guidance and support.

My parents Javier and Kiyoko, and my siblings, Javier, Jorge and Maria, for their support in everything I do.

My beloved wife Eri and daughter Nina for keeping me motivated in everything I do in life.

11. REFERENCES

- Abel, J., Gennarelli, T.A., "Incidence and severity of cerebral concussion in the rhesus monkey following sagittal plane angular acceleration", 22nd Stapp Car Crash Conference, 1978.
- Arbogast, K.B., Margulies, S.S., "Material characterization of the brainstem from oscillatory shear tests", *J. Biomechanics*, 31:801–807, 1998.
- Anderson, R. W., Brown, C. J., Blumbergs, P. C., et al, "Impact mechanics and axonal injury in a sheep model". *Journal of neurotrauma*, Vol 20 (10), 2003
- Antona-Makoshi, J., "Mechanical properties of human brain tissue", Thesis for Masters degree, Chalmers University of Technology, Gothenburg, Sweden, 2007.
- Baumgartner, D., Lamy, M., Willinger, R., et al., "Finite Element Analysis of Traumatic Brain Injuries Mechanisms in the Rat", *Proceedings of the 2009 IRCOBI Conference*, 2009.
- Bilston, L.E., Liu, Z., Phan-Thien, N., "Linear viscoelastic properties of bovine brain tissue in shear: some new experimental data and differential constitutive model", *Biorheology* 38, 2001
- Borg, J., et al. "Non-surgical intervention and cost for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury", *Journal of Rehabilitation Medicine* 36, (2004).
- Cantu, R., "Second-Impact syndrome", *Clinics in Sports Medicine*, Volume 17, Issue 1, 1998.
- Cassidy, J. David, et al. "Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury", *Journal of Rehabilitation Medicine* 36: 28-60, 2004.
- Committee on Terminology in Neurotraumatology (Glossary) of the World Federation of Neurological Society: *Glossary of Neurotraumatology. Acta Neurochir [Suppl]* 25: 14, 1979.

- Chatelin, S., Constantinesco, A., Willinger, R., "Fifty years of brain tissue mechanical testing: From in vitro to in vivo investigations", *Biorheology* 47, 255–276, 2010.
- Darvish, K.K, Crandall, J.R., "Nonlinear viscoelastic effects in oscillatory shear deformation of brain tissue". *Medical Engineering and Physics*, Vol.23. 2001.
- Davidsson J., Risling M., Angeria M., "A New Model and Injury Threshold for Sagittal Plane Rotational Induced Diffuse Axonal Injuries in the Brain", IRCOBI Conference, 2009.
- Davidsson, J. and Risling, M. "A new model to produce sagittal plane rotational induced diffuse axonal injuries", *Frontiers of Neurotrauma*, Vol. 2 (41), 2011.
- Duma, S.M., Manoogian, S.J., Bussone, W.R., et al., "Analysis of real-time head accelerations in collegiate football players", *Clin J Sport Med*, Vol 15, 2005.
- Elkin B. S., Ilankovan A. I., Morrison III B., "A Detailed Viscoelastic Characterization of the P17 and Adult Rat Brain", *Journal of Neurotrauma*, 28(1):1-10, 2011.
- Elkin B. S., Ilankovan A., Morrison III B., "Age-Dependent Regional Mechanical Properties of the Rat Hippocampus and Cortex", *J. Biomechanical Engineering*, 132(1), 2010.
- Erlanger, D., Kutner, K, Barth, J., Barnes, R., "Neuropsychology of sports-related head injury: dementia pugilistica to postconcussion syndrome", *Clin Neuropsychol.* 13,1999.
- Ewing, C. L., et al. "The effect of the initial position of the head and neck on the dynamic response of the human head and neck to-gx impact acceleration", *Naval Aerospace medical research lab detachment Michoud New Orleans, LA-US*, 1975.
- Fijalkowski R. J., Yoganandan N., Zhang J., Pintar F. A., "A Finite Element Model of Region-Specific Response for Mild Diffuse Brain Injury", 53rd Stapp Car Crash Conference, 2009.
- Fredriksson, R., "Priorities and Potential for Pedestrian Protection. Accident data, Experimental tests and Numerical Simulations of Car-to-Pedestrian Impacts", Thesis for doctoral degree (PhD), Karolinska Institute, Sweden, 2011.
- Galbraith, J. A., Thibault, L. E., Matteson, D. R., "Mechanical and Electrical Responses of the Squid Giant Axon to Simple Elongation, *J. Biomech. Eng.* 115, 13, 1993.
- Galford, McElhaney, "A viscoelastic study of scalp, brain, and dura, *Journal of Biomechanics*, Volume 3, Issue 2, 1970.
- Gefen A., Gefen N., Zhu Q., et al., "Age-dependent changes in material properties of the brain and braincase of the rat", *Journal of Neurotrauma*, 20(11), 2003.
- Gennarelli, T.A., Abel, J.M., Adams, H., and Graham, D., "Differential Tolerance of Frontal and Temporal Lobes to Contusion Induced by Angular Acceleration". 23rd Stapp Car Crash Conference, SAE 791022, 1979.
- Gennarelli, T. A., Thibault, L. E., Adams, et al., "Diffuse axonal injury and traumatic coma in the primate", *Annals of Neurology*, 12(6), 564-574, 1982
- Gennarelli, T., Thibault, L., Tomei, et al., "Directional dependence of axonal brain injury due to centroidal and non-centroidal acceleration", 31st Stapp Car Crash Conference, SAE 872197, 1987.
- Got et al., "Morphological and Biomechanical Study of 146 Human Skulls Used in Experimental Impacts, in Relation with the Observed Injuries", 27th Stapp Car Crash Conference, 1983.
- Hallquist, J., LS-DYNA Theoretical Manual 'Livermore Software Technology Corporation' Livermore, Ca, 1998
- Heimer, L., "The Human Brain and Spinal Cord", 2nd edition. Springer-Verlag, 1995.
- Hodgson, V. and Thomas, L., "Acceleration Induced Shear Strains in a Monkey Brain Hemisection", SAE 791023, 1979.
- Holbourn, "Mechanics of Head Injuries", *The Lancet*, p 438-440, 1943.
- Holbourn, Private communication with Dr. Sabina Stritch, 1956
- Ivarsson, "Physical Modeling of Brain and Head Kinematics", Thesis for doctoral degree (PhD), Karolinska Institute, Sweden, 2002
- Iverson, G., "Outcome from mild traumatic brain injury", *Current opinion in Psychiatry* 18.3, 2005.
- Kanda, R., Nakamura, N., Sekino, H., et al. "Experimental head injury in monkeys - concussion and its tolerance level". *Neur. Med. Chir.* 21, 645–656, 1981.
- Kikuchi, A., Ono, K., Nakamura, M., et al., "Human Head Tolerance to Lateral Impact Reduced from Experimental Head Injuries Using Primates", *The Ninth Technical Conference on Experimental Safety Vehicles*, 1982.

- Kleiven, S., Hardy, W., "Correlation of an FE Model of the Human Head with Local Brain Motion – Consequences for Injury Prediction", 46th Stapp Car Crash Conference, 2002.
- Kleiven S., "Predictors for traumatic brain injuries evaluated through accident reconstructions", 51st Stapp Car Crash Conference, 2007.
- Kraus, JF., Chu, LD. "Epidemiology". In Silver JM, McAllister TW, Yudofsky SC. Textbook of Traumatic Brain Injury. American Psychiatric Pub., Inc, 2005
- Kyoto University Primate Research Institute Digital Morphology Museum: [<http://www.pri.kyoto-u.ac.jp/dmm/WebGallery/index.html>], 2013.
- Lamy M., Baumgartner, D., Davidsson, J., Willinger, R., "Traumatic Brain Injury Investigation Using FE Modeling of the Rat and Experimental High Amplitude Rotations in the Sagittal Plane", IRCOBI Conference, 2013.
- Löwenhielm, P., "Mathematical simulation of gliding contusions". J. Biomech., 8(6), 1975
- Mao H., Zhang L., Yang K. H., King A. I., "Application of a Finite Element Model of the Brain to Study Traumatic Brain Injury Mechanisms in the Rat", 50th Stapp Car Crash Conference, 2006.
- Margulies, S., Thibault, L., Gennarelli, T., "A Study of Scaling and Head Injury Criteria Using Physical Model Experiments", IRCOBI conference, 1985
- Margulies, S., Thibault, L., "A proposed tolerance criterion for diffuse axonal injury in man", Journal of Biomechanics, Volume 25, Issue 8, August 1992
- Margulies, S., Prange, M.T, "Regional, directional, and age-dependent properties of the brain undergoing large deformation." Journal of Biomechanical Engineering Vol 124, 2002.
- Marieb, E., "Human Anatomy & Physiology", 5th edition. Benjamin Cummings, Addison Wesley Longman Inc., USA, 2001
- Meaney, D.F., Smith, D., Ross, D.T., and Gennarelli, T.A., "Diffuse axonal injury in the miniature pig: Biomechanical development and injury threshold". ASME Crashworthiness and occupant protection in transportation systems 25: 169-175, 1993.
- Melvin, J., McElhaney, J., and Roberts, V., "Development of a Mechanical Model of the Human Head - Determination of Tissue Properties and Synthetic Substitute Materials", SAE 700903, 1970.
- Melvin, J., Lighthall, W. J. and Ueno, K., "Accidental Injury, Biomechanics and Prevention". Springer-Verlag, New York, USA, 1993.
- McElhaney, Roberts, Hilyard, "Handbook of Human Tolerance". Printed by JARI, Japan, 1976.
- McElhaney, J., "In Search of Head Injury Criteria", John Paul Stapp Memorial Lecture: 49th Stapp Car Crash Conference, 2005.
- Mendis, "Finite Element Model of the Brain to establish Diffuse Axonal Injury Criteria", Ohio State University PhD dissertation, 1992.
- National Center for Injury Prevention and Control, "Report to congress on mild traumatic brain injury in the United States: Steps to prevent a serious public health problem", Atlanta, GA, USA. Centers for Disease Control and Prevention, 2003
- NHTSA Final economic assessment, FMVSS No.201, upper interior head protection. National Highway Traffic Safety Administration, Washington DC, USA, 1995
- Nishimura, T., (Kyoto University Primate Research Institute), Private communications, 2011
- Ommaya, A., "Experimental head injury in the monkey", Head Injury, W.F.Caveness and A.E Walker, Lippincott, Philadelphia, USA, 1966.
- Ommaya, A. K., Yarnell, P., Hirsch, A. E., and Harris, E. H., "Scaling of experimental data on cerebral concussion in sub-human primates to concussion threshold for man", 11th Stapp Car Crash Conference, SAE 670906, 1967.
- Ommaya, A.K., Hirsch, A.E. "Tolerances for cerebral concussion from head impact and whiplash in primates", Journal of Biomechanics, Volume 4, Issue 1, January 1971.
- Ommaya, A., Hirsch, A., "Protection of the brain from Injury during Impact: Experimental Studies in the Biomechanics of Head Injury", AGARD Conference Paper, 1971.

- Ono, K., Kikuchi, A., Nakamura, M., et al., "Human Head Tolerance to Sagittal Impact: Reliable Estimation deduced from Experimental Head Injury using Subhuman Primates and Human Cadaver Skulls", 24th Stapp Car Crash Conference, SAE 801302, 1980.
- Peach, L., "An introduction to ethical theory. Research ethics: Cases and materials", University of Indiana Press, Bloomington, USA, 1995
- Petitjean A, Trosseille X, Praxl N, et al, "Injury Risk Curves for the WorldSID 50th Male Dummy", 56th Stapp Car Crash Conference, 2012.
- Prange M. T., Margulies S. S., "Regional, Directional, and Age-Dependent Properties of the Brain Undergoing Large Deformation", *J. Biomechanical Engineering*, 124:244-252, 2002.
- R Development Core Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Internet: [<http://www.R-project.org>], 2013
- Rowson, S., Brolinson, G., Goforth, M., et al., "Linear and angular head acceleration measurements in collegiate football", *J Biomech Eng*, Vol 131(6), 2009.
- Rowson, S., et al. "Rotational head kinematics in football impacts: an injury risk function for concussion", *Annals of biomedical engineering* 40.1, 2012.
- Sakai et al., "Experimental Head Injury with Lateral Impact Using Monkeys – Dynamic and Pathological Investigation", *Neurologia medico-chirurgica*, Vol 22, No. 7, 1982.
- Shreiber, D. I., Bain, A. C., Meaney, D. F., "In Vivo Thresholds for Mechanical Injury to the Blood-Brain Barrier", 41st Stapp Car Crash Conference, 1997.
- Shuck, L., Advani, S., "Rheological response of human brain tissue in shear", *Journal of Basic Engineering*, Vol. 94. 1972.
- Stalnaker, R., McElhaney, J., "Head Injury Tolerance for Linear Impacts by Mechanical Impedance Methods", *ASME* 1970
- Stalnaker, R., Roberts, McElhaney, J., "Side Impact Tolerance to Blunt Trauma", SAE 730979, 1973
- Stalnaker, R., Benson, J., Melvin, J., "Dynamic and static load response of the head", *IRCOBI Conference*, 1975
- Stalnaker, R., Melvin, J., Nusholtz, G., et al., "Head Impact Response", SAE 770921, 1977.
- Thibault, L. E., Margulies, S., "Age-dependent material properties of the porcine cerebrum effect on pediatric inertial head injury criteria", *Journal of Biomechanics* 31. 1998
- Ueno K., Melvin J. W., Li L., Lighthall J. W., "Development of Tissue Brain Injury Criteria by Finite Element Analysis", *Journal of Neurotrauma*, 12(4):695-706, 1995.
- Viano, D., "Brain Injury Biomechanics in Closed-Head Impact. Studies on Injury Epidemiology, Tolerance Criteria, Biomechanics and Traffic Injury Prevention", Thesis for doctoral degree (PhD), Chalmers University of Technology and Karolinska Institute, Sweden, 1997
- World Health Organization (WHO) "Global Plan for the Decade of Action for Road Safety 2011-2020", March 2010.
- Wismans, J., et al., "Injury bio-mechanics", Course book, Eindhoven Technical University, 2000.
- Zhang L., Yang K. H., Dwarampudi R., et al., "Recent Advances in Brain Injury Research: A New Human Head Model Development and Validation", 45th Stapp Car Crash Conference, 2001.
- Zhang, L., Yang, K., King, A., "A Proposed Injury Threshold for Mild Traumatic Brain Injury", *J. Biomech. Eng.* Vol 126, Issue 2, 2004.