Axonal strain as brain injury predictor based on real-world head trauma simulations.

Debasis Sahoo, Caroline Deck, Remy Willinger

Abstract The main objective of this study was to develop a brain injury criterion based on FE computation of axon elongation. To achieve this objective a state-of-the-art finite element head model with enhanced brain and skull material laws, was used for numerical computation of real world head traumas. No less than 109 well-documented traumatic brain injury cases were simulated and axon elongation computed to derive brain injury tolerance curve. Based on statistical analysis of different intracerebral parameters (Von Mises stress, Von Mises strain and axonal strain) it was shown that axonal strain was the appropriate candidate parameter to predict diffuse axonal injury. The proposed brain injury tolerance limit for a 50% risk of diffuse axonal injury has been established at about 15% of axonal strain. Further head kinematics based metric: Head Injury Criterion has also been computed for all head trauma cases to compare its injury prediction capability with the axon strain based metric. This study provides a key step for a realistic injury metric for diffuse axonal injury.

Keywords axon elongation, brain modeling, brain injury tolerance limit, head trauma simulation.

I. INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death and permanent impairment over the last decades [1-2]. In both the severe and mild TBI, diffuse axonal injury (DAI) is the most common pathology [3]. DAI is characterized by dynamic tensile elongation of axonal fibers and consequential fiber rupture [4]. However, the structural signature of this microscopic level injury is not easily captured by conventional medical imaging methods and results difficulty in DAI diagnosis. Hence computational head models on the other hand can be deployed to study the DAI mechanism especially for the definition of brain injury tolerance limit. Several widely recognized FE head models were developed to study the specific aspects of head trauma biomechanics. Based on these models and head-trauma simulations, brain stress and strain were proposed as possible criteria to predict DAI [5-7]. Further studies emphasized that the tensile axonal elongation was the most realistic mechanism of DAI [8-9]. Multiscale computation of axon elongation by using finite element head model in numerical simulation can enlighten the DAI mechanism and help to establish advanced head injury criteria, which was the main objective of this study.

The consequence of axonal injury leads to cognitive and permanent disabilities and fatalities in most of the TBIs. Clinical studies on TBI patients enhanced the understanding of the injury mechanism over years [10-11]. However the diagnosis of DAI is primarily based on neurocognitive assessments due to difficulty in detecting the microscopic injuries through conventional imaging techniques. Finite element head models can incorporate high-fidelity tissue level anatomy with the advent of diffuse tensor imaging (DTI) and proved to be promising for head injury mitigation study and establishing new head injury criteria. It was found that, the water diffusion was anisotropic in brain white matter in which water tends to diffuse predominantly along the long axis of the fibers [12]. This indicates that the hypothesis to model the brain with isotropic material presents important limitations. In this context it is important to consider brain anisotropy and to progress towards brain injury criteria based on the computation of axon elongation as a more appropriate metric to predict DAI. It is possible to extract the information concerning the trajectory of axon fibers within the brain by performing DTI. Chatelin *et al.,* [13] incorporated the DTI data (both fractional anisotropy and fiber orientation) into the post processing of head impact simulations in order to compute the strain in the axon direction, but this study was based on an

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isotropic brain model. Colgan *et al.,* [14] also incorporated anisotropic orientations of axonal fibers into a hyperelastic material of a brain FE model to predict the mechanical response and the effect of anisotropy in case of high rotational TBI. The method utilized for fiber tract generation was an approximation because, only the voxel inside the largest ellipsoid within each element were chosen. Cloots *et al.,* [15] developed a plain strain 2D FE model based on anatomical and pathological observations for axonal injury. The results of this study indicated that cellular level heterogeneities have an important influence on the axonal strain. Wright *et al.,* [16] utilized the same technique as [15] to develop a region specific 2D FE brain model. Kraft *et al.,* [17] performed frontal impact finite element head model (FEHM) simulations by including DTI data into a hyperelastic brain model and predicted that the temporal and occipital regions undergo the highest axonal strain. However, exclusion of viscoelasticity was a limitation to this study. Cloots *et al*. [18] implemented multi scale approach to a FE model and a critical volume element that represents a critical region of the brain tissue for axonal injury was considered for axon strain computation. The brain tractography implemented to the critical volume element was not based on real DTI of human brain. In 2014, Giordano and Kleiven [19] extended the study of [18] and computed the strain in the direction of fiber for 58 American football accident cases and proposed thresholds for axon elongation ranges from 7% to 15% depending on the brain region. The brain tractography was approximated by dividing the entire FA distribution to eight intervals and assigning a maximum FA value to compute axon dispersion parameter for each interval. Also the fiber contribution to the brain tissue stiffness was assumed to be linear and the bulk modulus was reduced several orders to prevent volumetric locking of the elements during the FE simulation (from experimental 2.1GPa to 50MPa). Regardless of various limitations, all the above studies point to the importance of the implementation of anisotropy in FE brain models and to focus on axon elongation. Hence FEHMs involving enhanced constitutive law based on recent in vivo experiments and taking into account fiber anisotropy is indeed of great importance to the field of head trauma biomechanics.

In the current study a state-of-the-art finite element head model with enhanced brain and skull material laws, was used for numerical computation of real world head traumas. 109 well-documented TBI cases were simulated and axon elongation computed to derive brain injury tolerance curve. Different intracerebral parameters (Von Mises stress, Von Mises strain and axonal strain) were computed and statistical analyses were performed to identify the most suitable metric to predict DAI. This study provides a realistic way to use axon elongation to develop a new brain injury metric.

II. METHODS

This section describes briefly the enhanced finite element head model used for the computation of axon elongation under real world head trauma. A description of the head trauma database and the statistical method applied for the extraction of brain injury tolerance is proposed as well.

Presentation of improved head FEM

The Strasbourg University Finite Element head model was recently enhanced in terms of new constitutive material laws for brain and skull as reported in detail in [20-21] under LS-DYNA platform. The main anatomical features of this FEM include the scalp, skull, membranes, brain, brainstem and cerebrospinal fluid (CSF). The head model presents a continuous mesh that was made up of 13,208 elements, including 1,797 shell elements for the skull and 5,320 brick elements for the brain. The total mass of the head model was 4.7 kg. A detailed presentation of different parts of the FE head model is shown in

Fig. 1. The skull model was improved by using an appropriate composite material model by taking fracture into account as it is essential to ensure a realistic skull model response for the computation of brain loading. The skull was modeled with three-layered composite shell representing the inner table, diploe and outer table of human cranial bone. The finite element skull model was validated against experimental data from 15 PHMS experiments and the skull internal energy was the best candidate parameter to predict skull failure. The proposed tolerance limit for a 50% risk of skull fracture was 448mJ of skull internal energy. More information about the constitutive law implemented under LS-DYNA is available in [21].

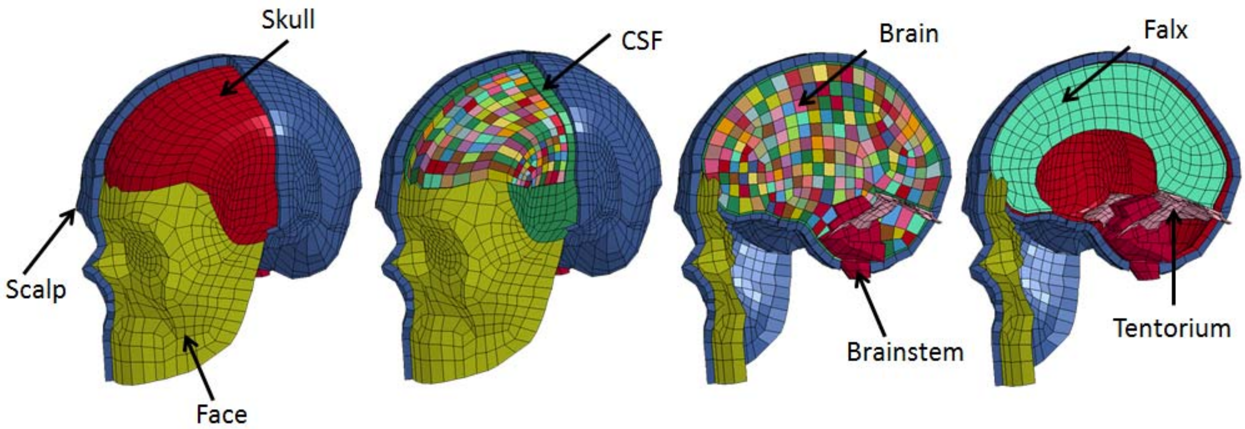

Fig. 1. Detailed human head FE model [20-21]

The brain model was improved by implementing anisotropy based on fractional anisotropy and fiber orientation extracted from medical imaging (DTI) into the brain FE model in order to mimic the main axon bundles [20][22]. More details about the brain material modeling are reported in [20]. The mechanical behavior of the brain model has been extensively validated for brain pressure and local motion of brain relative to skull against experimental data from [23-26] at different impact locations in accordance with experiments. The maximum difference of peak pressure was under 5% between simulation and experimental data. Further details of this validation study can be found in [20].

Accident Database

An important step in the current study is the presentation of the head trauma database which will be used for the simulation of the head impacts and from which brain injury criteria will be derived. The accident database used consists of 109 cases collected from different existing accident databases and involving pedestrian, motorsport, American football player and motorcycle accidents. In each database, the accident report consists of the final position of the pedestrian and vehicle after the accident, skid marks on the road and vehicle, type of vehicle, vehicle speed, impact position of the pedestrian on the vehicle and the condition of the road at the scene. The medical report includes the victim's age, gender, height, weight and details of injuries sustained by the victims. For each of these accidents the head impact conditions were investigated in partnership with a number of institutions as briefly exposed here after:

- Six motor sport accidents were collected from Formula 1 accidents (FIA) as reported in [27].
- A total of 11 well-documented motorcycle accident cases were collected from European cooperation in science and technology (COST 327) accident databases [28].
- Twenty-two American football impact events were collected from the reconstruction study reported by [29-30].
- Seventy pedestrian accident cases including 15 well-documented pedestrian accidents collected from in-depth Investigation of the Vehicle Accidents in Changsha, China (IVAC) database [31], 28 pedestrian accidents from the "German In-depth Accident Study" (GIDAS) database [7][32], 7 pedestrian accidents from the "Centre for Automotive Safety Research" in Adelaide, South Australia database [33] and finally 12 pedestrian accidents collected from the Tsinghua accident database plus 8 cases collected from the Crash Injury Research (CIREN) accident database [34].

The 70 pedestrian accident cases were reconstructed in previous studies by using MADYMO software. From this multi-body replication of the pedestrian kinematics, the information about the velocity of the head just before the impact, impact location and orientation of the head were obtained. The methodology of these pedestrian kinematic reconstructions are reported in [7][31-36].

Concerning the motorcyclist accidents, American football player impacts and FIA cases, the 3D head acceleration fields were recorded during experimentations which have been done in the COST project [28] for motorcyclists cases, by [27] and [30] for FIA cases and American football player accident cases respectively. For all these experimental accident reconstructions (39 cases), the 6 accelerations versus time curves (3 linear and 3 rotational accelerations), recorded at the center of gravity of the dummy were transferred to Strasbourg

University and considered as input for the numerical simulation of the head trauma.

Finally the 109 head trauma cases were divided into two groups i.e. with (27%) and without DAI (73%). The distribution of pedestrian head impact locations on the vehicle windscreen for all 70 pedestrian cases is illustrated in

Fig. 2. The different markers represent the injury severity sustained by the victims according to the Abbreviated Injury Scale (AIS).

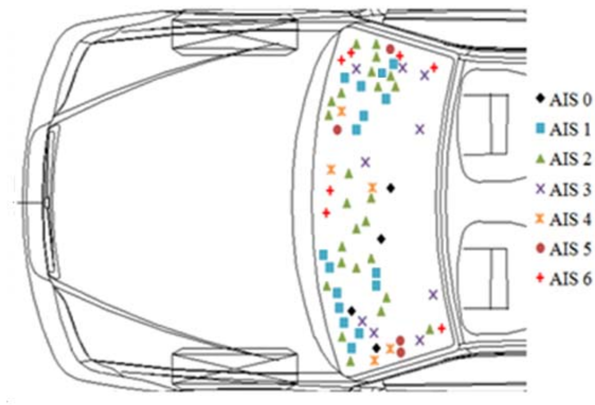

Fig. 2. Distribution of pedestrian impact locations on vehicle windscreen for the 70 well-documented pedestrian accident cases.

Head trauma Simulations and Statistical Analysis

The methodology for accident reconstruction is composed of several steps, as described in

Fig. 3. The foremost step is to develop a well-documented database as exposed previously. The next step is to get the victim kinematics. The accident cases were divided into two categories: pedestrian accident cases in which there was a direct head impact against the windscreen and the others accidents cases (motor sports, American football and formula one accident) for which the experimental 6 head acceleration fields were implemented at the center of gravity of the head. For these latter cases the skull was assumed to be rigid which is acceptable as only helmeted victims are in this group and none of them presented any skull fracture.

For the simulation of the 70 pedestrian head impacts, a realistic FE windscreen model was used as all of the victims impacted the head against the windscreen as shown in

Fig. 2. The finite element windscreen model used in the current study was developed and validated by [37]. Proposed was a 3-layer composite model (double-layered glass and PBV-tied model) with mechanical properties reported in [37]. Validation of the windscreen model was performed by comparing the numerical and experimental accelerations at the center of gravity of the headform under controlled experimental impacts as well as glass crack patterns. The head finite element model was propelled against the windscreen model at the same location observed on the accident's scene. The loading condition was the relative head position and the initial velocity between the head and the windscreen at the time just prior to the impact as computed from the victim kinematic simulation. For the cases which did not require windscreen the loading condition was obtained by implementation of the 6 head accelerations curves (3 linear and 3 angular accelerations). A total of 39 cases were reconstructed by this method.

For the 109 head trauma simulations, brain Von Mises stress, brain Von Mises strain and axonal strain were computed. The Von Mises stress and Von Mises strain were extracted from the simulation results by LS-DYNA post processing tool. For axon strain calculation, a dedicated Python program was used to extract the Green – St-Venant strain tensor (also called the Green-Lagrangian strain tensor) for each brain element (5,320 brick elements) from the LS-DYNA output data. Then these strain tensors are oriented along the main anisotropy direction $\vec{l}_{el}$ of each element to calculate the axonal strains during the total time duration of the simulation for each element. The axonal strain, noted ϵ_{axon}, is calculated based on the Eq 1.

$$\epsilon_{axon} = (\overline{\epsilon} \times \vec{l}_{el}) \cdot \vec{l}_{el} \quad (1)$$

where $\vec{l}_{el}$ is the axonal orientation vector per element and $\overline{\epsilon}$ the strain tensor per element.

In the current study Head injury criterion (HIC) is also evaluated for all the 109 head trauma cases. HIC is a head kinematics based injury criteria widely used to access head injury. The Head Injury Criterion (HIC) was related to the work of Gadd [38] to develop the Gadd severity index GSI [39] by using the Wayne State Tolerance Curve (WSTC). Versace et al. [40] proposed a version of the HIC based on the study of correlation of WSTC and GSI. In 1972, the National Highway Traffic Safety Administration (NHTSA) [41] defined the current version of HIC as described in Eq 2.

$$HIC = \max_{(t_1,t_2)} \left\{ (t_2 - t_1) \left[\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} a(t)dt \right]^{2.5} \right\} \quad (2)$$

where a [$m.s^{-2}$] is the resultant linear acceleration measured at the center of gravity of the Hybrid III dummy head. t_1 and t_2 [ms] are chosen in order to maximize the HIC value. The maximum time duration ($t_2 - t_1$) was set as 36 ms at first, however, current standards use 15 ms [41] and corresponding HIC_{15} was used in the current study. A HIC_{15} of 700 was estimated as a 5% risk of AIS4+ head injury. For adult pedestrians, a HIC value of 1,000 within a time window of 15 ms has been proposed as an injury tolerance level for severe head injuries [42].

In order to define the best suitable parameter to predict DAI, statistical analysis was carried out for the mechanical parameters calculated numerically. The aim of the statistical analysis is to provide a means of assessing the capability of a number of variables to predict brain injury.

Binary logistical regression was used for this assessment and carried out using the version 18.0 release of the statistical software package (SPSS). This method involved fitting of a regression model between possible brain injury metrics (x= Von Mises stress, Von Mises strain, brain axon elongation and HIC). With this method, the probability of brain injury (DAI) is defined as in Eq 3.

$$P(x) = \frac{e^{a+bx}}{1+e^{a+bx}} \quad (3)$$

where a and b are two parameters calculated by regression.

The candidate parameters (Von Mises stress, Von Mises strain, axon elongation and HIC value) were then compared using the Nagelkerke R^2 statistic (where the limits for this measure are 0 for a poor fit and 1 for a good fit) to determine which head injury metric provides the best correlation with the occurrence of brain injury.

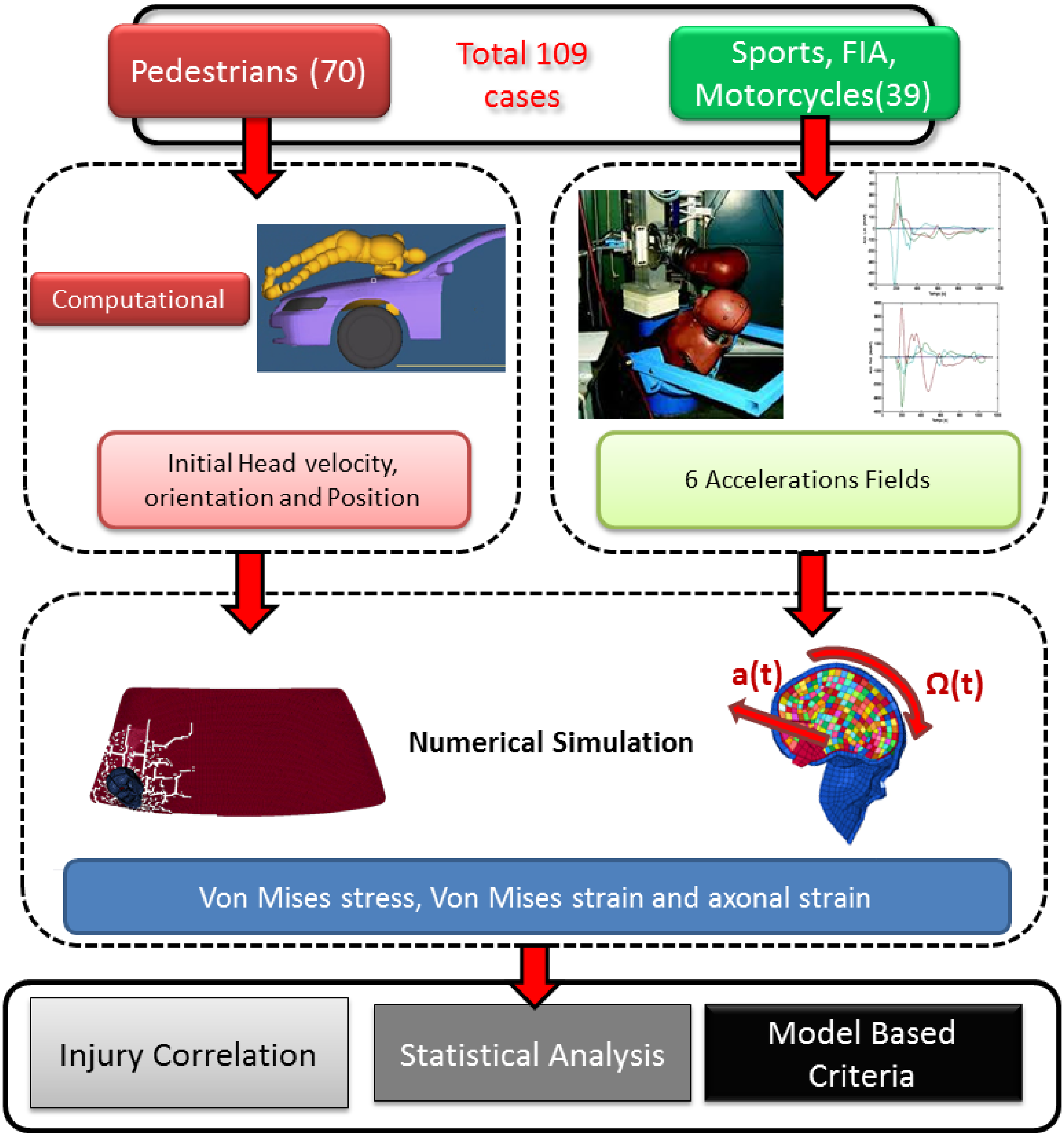

Fig. 3. Methodology for numerical head trauma simulation. Pedestrian cases are driven by head orientation and initial velocity and the other cases are driven by the 6D acceleration curves

III. RESULTS

Head trauma simulations of 109 well-documented accident cases were performed by using an advanced FEHM under LS-DYNA platform. The results in terms of maximum of brain Von Mises stress, brain Von Mises strain and axonal strain with occurrence or not of brain injury are shown in Fig. 4, Fig. 5 and Fig. 6. The white columns represent the cases without DAI and the black columns represent the cases with DAI. The min-max range for Von Mises stress, Von Mises strain and axonal strain are 21-205 kPa, 0.006-2.47 and 0.02-0.43 respectively. It appears from Fig. 6 that axon elongation presents low overlap of injured/non-injured cases. This observation will now be objectively confirmed by the statistical analysis.

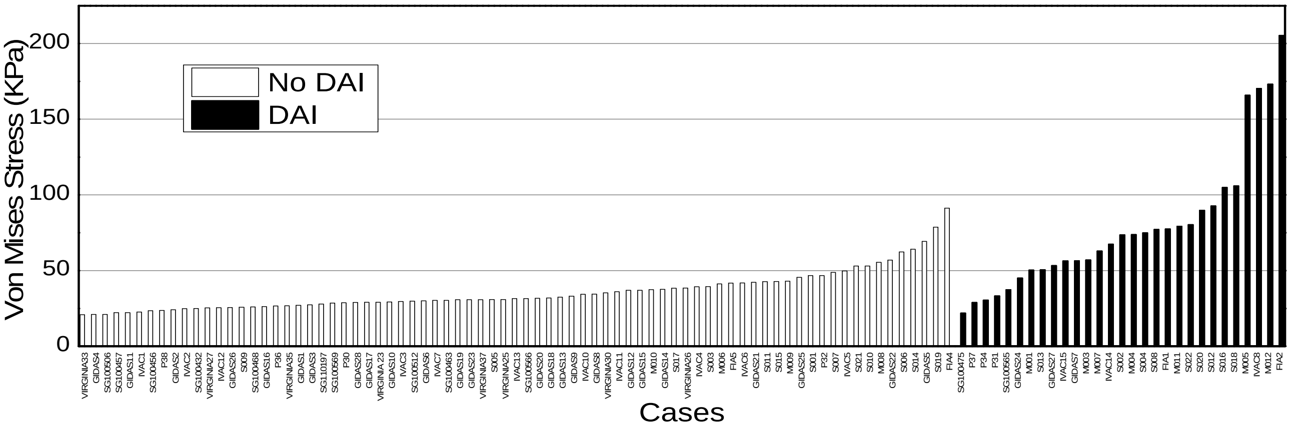

Fig. 4. Von Mises Stress calculated for all the accident cases reconstructed using an advanced FEHM

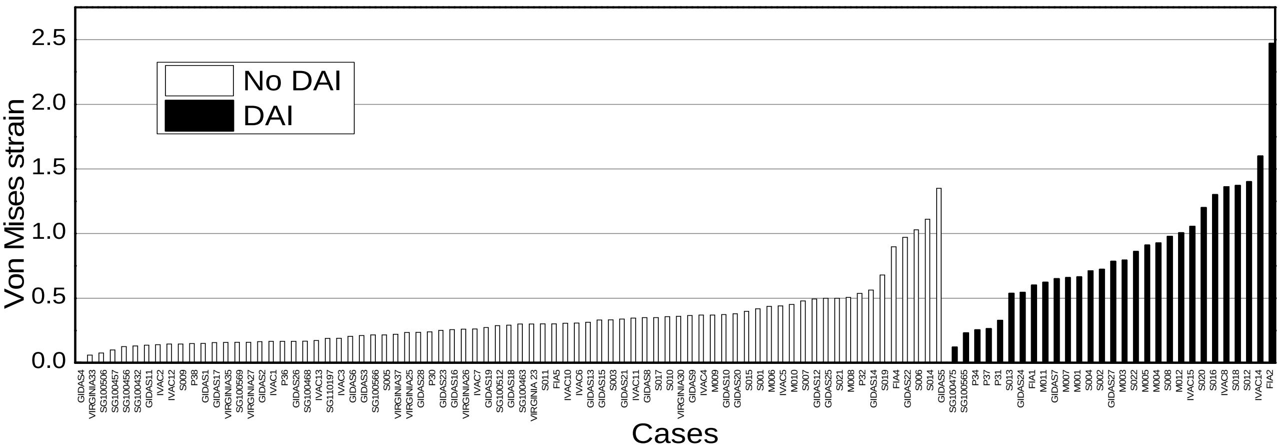

Fig. 5. Von Mises Strain calculated for all the accident cases reconstructed using an advanced FEHM

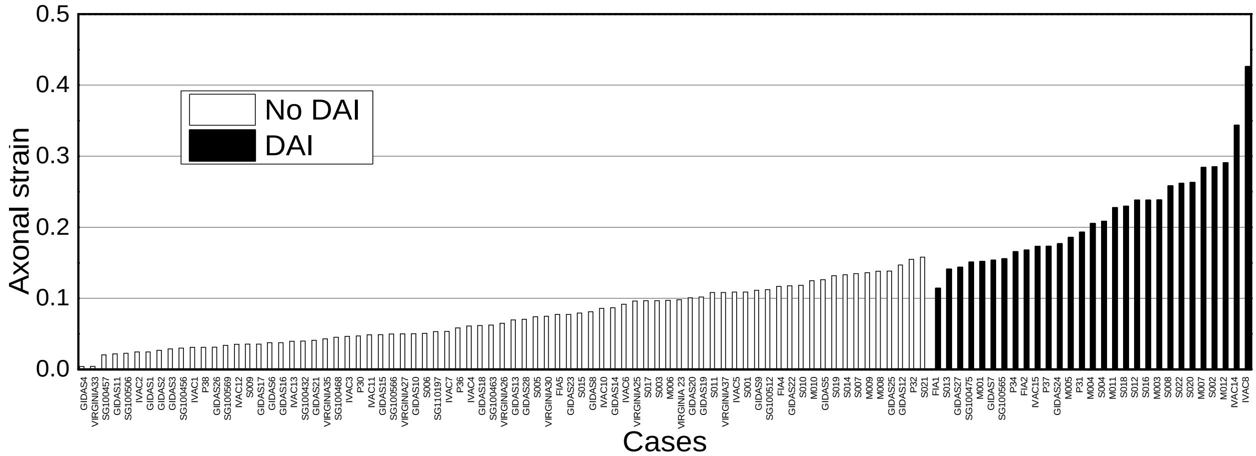

Fig. 6. Axonal strain calculated for all the accident cases reconstructed using an advanced FEHM

The HIC was also calculated for 109 head trauma cases as shown in Fig. 7. The maximum time duration (t_2- t_1) was set as 15ms and corresponding HIC_{15} was computed according to Eq.2. It is observed from Fig. 7 that there is a considerable overlap of injured/non-injured cases by taking in to account HIC for predicting DAI.

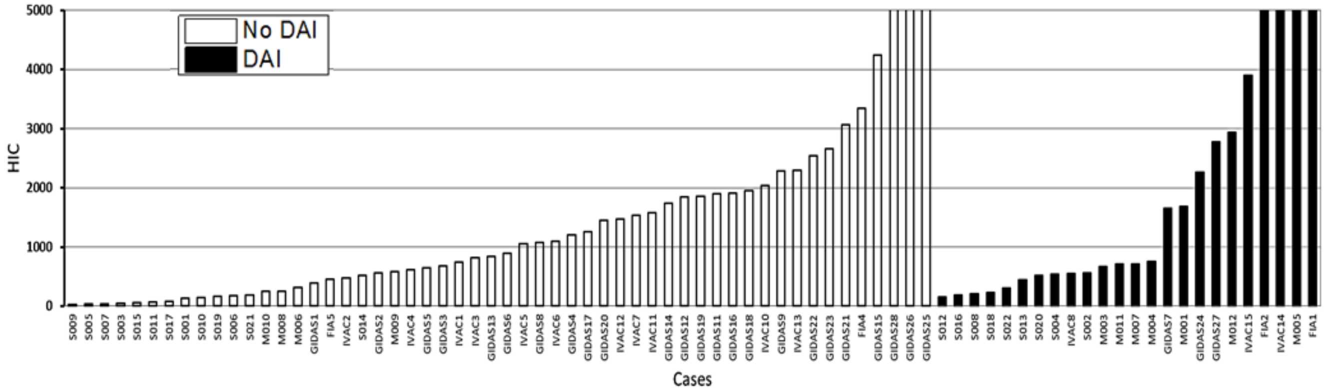

Fig. 7. HIC value calculated for all the head trauma accident cases.

The statistical analysis for the 109 simulated head traumas is carried out by using binary logistical regression as exposed in the previous section. The candidate parameters for predicting injuries (DAI) along with their Nagelkerke R^2 value were calculated. It appears that axonal strain presents the highest R^2 value with a value of 0.876 whereas for brain Von Mises stress, brain Von Mises strain and HIC the Nagelkerke R^2 values are 0.502, 0.446 and 0.055 respectively. Hence, axonal strain is the most suitable parameter to predict DAI among the other parameters described in the current study.

Based on this statistical analysis, the injury risk curve for predicting DAI is plotted as shown in Fig. 8. The solid black circles represent the cases for which injury occurred and the white circles are representative of non-injured cases. From this injury risk curve, the critical axon elongation for a 50% risk of DAI is obtained and corresponds to an axon strain of 0.1465.

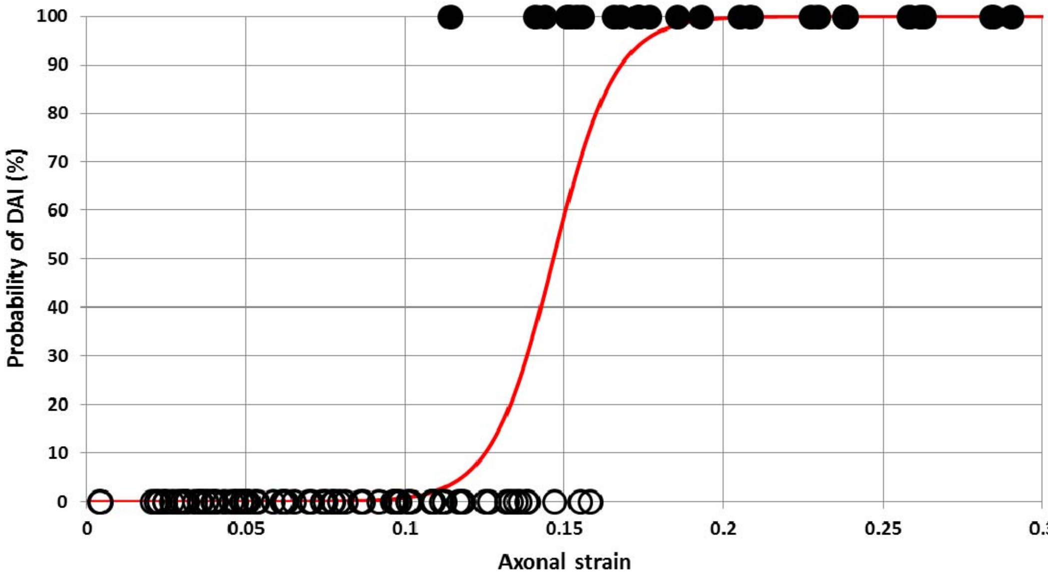

Fig. 8. Injury risk curve to predict probability of DAI by addressing brain axonal strain computed with the advanced human head model. A 50% injury risk is obtained for an axon strain of 14.65%.

IV. DISCUSSION

The main objective of this study was to develop a robust and accurate model based brain injury criterion to predict DAI in case of TBIs in terms of axon elongation. This was achieved via the simulation of 109 well documented real world head traumas. The advanced finite element head model was utilized to perform head impact simulations in accordance with the victim's kinematic analysis outcome. Intracerebral parameter (axonal strain, Von Mises stress and Von Mises strain) and head kinematics based HIC were computed during the simulation to predict DAI. The binary logistic regression method was used for statistical analysis of the correlation between computed parameters and the occurrence of injury.

According to studies by Hynd *et al.,* [43], it was determined that the Nagelkerke R^2 value based on binary logistical regression provides the best statistical assessment over the other measures (Probit regression, Cox regression). The benefits of this method are:

- It provides comparable results to methods such as Probit analysis.
- It is an appropriate analysis for the amount and type of data under investigation.
- It provides a more rigorous assessment of the data as no underlying assumptions are made regarding the outcome of the analysis, i.e. no injury response under zero loads as is assumed in the Modified Maximum Likelihood Method.

Previously reported criteria based on global parameters (HIC, Head impact power (HIP), peak linear/rotational acceleration) have lower Nagelkerke R^2 value (<0.3) compared to the intracerebral parameter's based criteria (Von Mises stress, first principal stress, first principal strain, Von Mises strain) for which the R^2 value is </= 0.5 [6]. With the ease of the FEHM, the criteria based on intracerebral parameters always outsmart the head kinematic based criteria during statistical analysis to predict DAI. In the present study, based on the highest Nagelkerke R^2 value of 0.876, axonal strain presents the best statistical robustness to be the suitable parameter for the prediction of DAI among other parameters presented in this study. The proposed tolerance limit for a 50% risk of DAI is 14.65% of axonal strain. As reported in the literature, the functional deficit occurred at 16% of axonal strain according to the Singh *et al.,* [44] study. Thus, the developed criterion established in the current study is in accordance with this study. Moreover when compared with other investigations [8-9] [45-48] the present axon strain threshold is very close to published data. The proposed axon strain criterion is also compared with studies based on numerical approach by [19] in which the 50% threshold of DAI represent about 13% of axonal strain for the white matter. However, for these authors, the 50% threshold value corresponding to the corpus callosum area is axonal strain of 7.36% which has the best statistical values than the results for white matter [19] indicating less confidence in statistical analysis.

The head kinematics based criteria HIC was computed for all 109 cases and based on statistical analysis the Nagelkerke R^2 value is very low compared to axonal strain R^2 value. It was worth noting that, for some head trauma cases the computed HIC was considerably low, whereas the medical report indicated occurrence of DAI. This was because of the computation of HIC only took into account the linear accelerations and no rotational accelerations were considered which were considerably high in those trauma cases. Thanks to the axonal strain based metric, the FEHM was able to predict the DAI accurately in accordance with medical reports.

Regardless of such promising results, this present study encounters some limitations. One of the shortcomings of this study is the size difference between DTI voxel and finite elements of the brain model. However, it was found only 6 relatively thin elements (0.11 % of the elements) selected individually less than 100 DTI voxels and located close to the membranes. This aspect contributed to validation of the morphological rigid adaptation between DTI and FEM geometry without taking non-rigid transformation into account. Nevertheless further improvements in meshing can enhance the anisotropy data implementation in FEHMs especially for a more accurate axon mesh representation. In this paper a state-of-the-art validated FE head model was used with advanced brain material constitutive laws. The mechanical modelling of human brain modelling is still a challenging task and only limited validation data are available in the literature. Therefore, there are still open questions at in vivo model validation level. Even if there are still limitations related to the brain models, these tools permit reasonable estimation of critical axon strain in case of head traumas. It should be mentioned that the computation if this axon strain threshold is both mesh dependent and constitutive law dependent. A recent attempt published by Giordano et al [19] reported an axon strain of 7% to 15% as a critical value for this brain injury metric. This illustrates that further investigation and harmonization are needed in order to establish unique model based brain injury criteria in terms of axon strain.

However, the precise location of brain injury was not available in the injury description of the reported head trauma cases. In future more detailed cases with injury description concerning DAI location should be reconstructed to demonstrate the ability of this advanced FEHM to get the injury locations.

In the present study brain injury criteria is derived from in vivo human head impacts occurring during real world head trauma. This approach introduces further limitations as real world accident reconstruction is a complicate multi-parametric task. For the numerical simulation of the 109 head traumas, impact conditions were obtained from previous multi-body simulations in order to address the victim's kinematics [7][31-33][35]. The accuracy of the whole accident reconstruction process was thus influenced by the robustness of these multi-body simulations. The MADYMO simulations are meticulously performed by Strasbourg university team which accuracy was reflected in good accordance with the accident database as in [36]. The comparison was made by comparing not only linear fracture patterns but also multiple fracture patterns and also high Nagelkerke R^2 value for skull fracture criteria [36]. The windscreen model was also validated by Peng et al. [37] and used in both studies ([36] and current). The overall simulation chain was progressively proved to be efficient [7][32][36] and assumed to have minimal errors. The confidence of the logistic regression analyses is significantly affected by the sample size. In the current study a total of 109 head trauma cases were simulated, which comprise a considerable sample size if compared to study of [19] (58 cases). Although the current accident database is vast enough to get a good statistical analysis, more number of well documented accident cases concerning DAI can increase the confidence in the criteria. However, given the high correlation between computed axon elongation and the occurrence of brain injury, the results reported in the present study are promising. Moreover the established axon elongation threshold at about 15% is in accordance with the literature. Therefore the present results can be considered as a significant step towards model based criteria for DAI.

V. Conclusions

A state-of-the-art finite element head model with enhanced brain and skull material laws which enable it to compute axon elongation was used for numerical simulation of real world head trauma to develop a robust head injury criterion. A total of 109 well-documented TBI cases were simulated and axon elongations were computed to derive a brain injury tolerance curve. Based on statistical analysis, it was shown that axonal strain was the appropriate candidate parameter to predict DAI. The proposed brain injury tolerance limit for a 50% risk of DAI has been established at 14.65% of axonal strain. The proposed threshold in terms of axonal strain is in accordance with studies reported in literature. Head kinematics based metric (HIC) has also been computed for all head trauma cases to compare its capability to predict brain injury with the axon strain based metric. Results demonstrated very poor correlation of HIC with injury compared to axon strain. It is therefore concluded that the present study provides realistic methods and tools for advanced model based head injury risk assessment and mitigations.

VI. Acknowledgement

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