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Multiscale Modelling of Blast-Induced TBI Mechanobiology - From Body to Neuron to Molecule

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ABSTRACT

Blast induced traumatic brain injury (bTBI) has become a signature wound of the recent military operations and is becoming a significant factor of recent civilian blast explosion events. In spite of significant clinical and preclinical research on TBI, current understanding of injury mechanisms is limited and little is known about the short-term and long-term outcomes. Mathematical models of bTBI may provide capabilities to study brain injury mechanisms, perhaps accelerate the development of neuroprotective strategies and aid in the development of improved personal protective equipment. The paper presents a novel multiscale simulation framework that couples the body/brain scale biomechanics with micro-scale mechanobiology to study the effects of 'primary' micro-damage to neuro-axonal structures with the 'secondary' injury and repair mechanisms. Our results show that oligodendrocyte myelinating processes distribute strains among neighbour axons and cause their off-axis deformations. Similar effects have been observed at the finer scale for the Tau-Microtubule interaction. The need for coupled modelling of primary injury biomechanics, secondary injury mechanobiology and model based assessment of injury severity scores is discussed. A novel integrated computational and experimental approach is described coupling micro-scale injury criteria for the primary micro-mechanical damage to brain tissue/cells as well as to investigate various secondary injury mechanisms.

Keywords: Blast wave; Mechanobiology military medicine; Multiscale modelling; Traumatic brain injury

1. INTRODUCTION

Blast events accounted for nearly 70 per cent of injuries in wounded service members in both Iraq and Afghanistan, and are the main cause of traumatic brain injury (TBI)[1-2]. Most cases of blast neurotrauma are mild (concussion) and are difficult to diagnose[3]. Mild TBI (mTBI) may cause a variety of heterogeneous symptoms including: concentration problems, blurred vision, irritability, headaches, sleep disorders and depression. Some individuals develop chronic states known as the post-traumatic stress disorder (PTSD) and chronic traumatic encephalopathy (CTE)[4-5].

Compared to impact-related injury, the mechanisms involved in blast injury are much less understood. Primary concussive blast injuries may be caused by the direct transmission of the blast wave across the cranium and the brain, by the impact of blast ejecta on the body (e.g., shrapnel and debris) and by the individual striking an object (e.g., a fall against ground or vehicle). Protection against blast wave TBI is particularly challenging because, in spite of the protective helmet, a significant part of the soldier's head is still exposed to the blast. In spite of its importance and many years of research, current understanding of the primary (biomechanics) and secondary (neurobiology) brain injury mechanisms is limited and the neurobiology of secondary injury and repair mechanisms remain elusive. A better understanding of blast wave TBI can be achieved with complementary experimental-computational modelling approach. However, computational modelling of neurotrauma poses significant challenges as it involves several physical and biomedical disciplines as well as a range of spatial and temporal scales[6-7].

Most computational models of blast TBI confine their focus to modelling macroscopic biomechanics of the brain, often ignoring the presence of the elastic skull, flexibility of the neck and head movements, effects of vascular and cerebral fluids and responses of the rest of the body[8-12]. Predicted intracranial pressures and stress/strain fields are the typical end points. Multiscale models, coupling the body/brain scale biomechanics with micro-scale mechanobiology can link the effects of 'primary' micro-damage to neuro-axonal structures with the 'secondary' injury and repair mechanisms[6,13-16]. The main challenges are to develop multiscale anatomical geometry models of the brain with 'embedded' microstructures, to calculate loadings to these microstructures using macro-scale results and to 'bridge' the millisecond long primary injury to very long time secondary injury models.

Because of ethical reasons experimental neurotrauma is typically studied using either animal models or in vitro brain cell/tissue cultures. The results of those injury studies are directly 'extrapolated' to humans, assuming that the primary neuro-damage mechanisms and neuropathology outcomes are similar as in humans[17-18]. To facilitate this extrapolation,

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various brain injury criteria have been developed that correlate the macroscopic mechanical insult parameters, such as overpressure, force, impulse, acceleration with experimentally observed neuropathology parameters, such as cognitive, cell death, intracranial pressure, white matter kurtosis, and others. However, direct use of animal experimental outcomes to humans is questionable as it is not clear how to reproduce (scale down) the mechanical loads seen in humans, in small animals, or *in vitro* and how the resultant neuro injury/repair pathways may be different in animals and humans[18-20]. Complementary multiscale models of TBI in animal models and in human may be able to correlate brain injury mechanisms in animals and in humans as well as provide a foundation for the development of brain tissue specific injury criteria. Dissimilar anthropometry and anatomy of animal and human heads/brains makes it difficult to apply macroscopic (head-scale) injury criteria such as head injury criteria (HIC) or brain rotational injury criteria (BrIC)[21] in humans. However, it is generally accepted that the cell-level structural and biological features are preserved. We propose that a new generation of brain tissue/cellular scale injury criteria should be developed.

Multiscale modelling is emerging as a platform for personalised and predictive in medicine and biology including brain injury[13-16]. It can be used not only for better understanding of the relation between macroscopic brain biomechanics and neuro-mechano-biology of injury but also as a tool for the development of novel injury criteria needed for injury scaling to humans. Conventionally, computational TBI has been conducted either at the macroscale modelling of head/brain biomechanics [e.g. 11] or at the scale of individual neuro-axonal structures[22-25]. To date, however, the rigorous link between the two scales has not been fully demonstrated. In our previous publications we have described a multiscale modelling framework for TBI based on computational biomechanics/biology (CoBi) tools and presented computational models of both macro-scale modelling of brain injury biomechanics[26-27] as well as micro-scale modelling of mechano-biology of synaptic injury[28]. Here, we present further developments to both high-fidelity and reduced order FEM macro-scale models TBI as well as formulation and example simulation results of micro/molecular scales neuro-mechano-biology of axonal and synaptic injury. The axonal injury micro-mechanics model can be used as a starting point for the molecular scale modelling the secondary neurobiology effects such as Tau phosphorylation and aggregation, disassembly of microtubule networks, blockage of intra-axonal transport, formation of axonal varicosities, beading and retraction balls. We also propose a novel formulation of dynamic brain injury criteria based on microscopic injury mechanobiology.

2. METHODS

2.1 Multiscale Modelling Framework of TBI

The overall architecture and functionality of CoBi multiscale framework for modelling blast-wave TBI and macro-micro scale injury biomechanics has been presented before[6,14]. In this paper we have further improved the model by incorporating the micro-to-nano mechanobiology of brain microstructures including: axonal, synaptic and microvascular injury. Figure 1 presents the overall architecture of CoBi multiscale framework for modelling blast-wave TBI in humans and animal models.

The framework enables one-way coupling between multiple scales, i.e., blast/debris loading on the human body are used as initial conditions for the whole body/head biodynamics and for intracranial biomechanics models; these models in turn provide boundary conditions for micro-scale simulations of

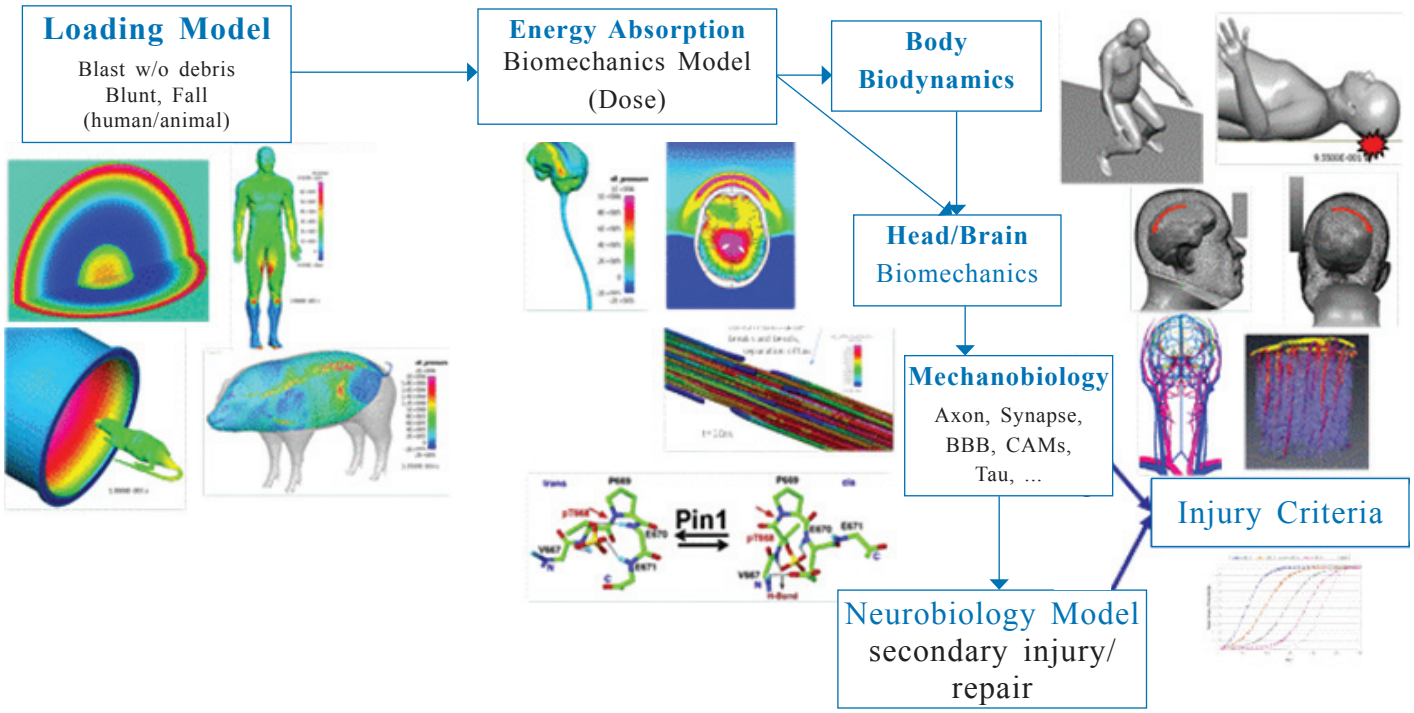

Figure 1. A computational framework for multiscale modeling of TBI.

neuro-axonal structures in brain regions most susceptible for injury; and the latter models are used for detailed modelling of subcellular molecular mechanobiology and for electro-biochemistry of injury and repair pathways. The following sections present modelling details for each of those scales with the focus on the white matter axonal injury.

2.2 Macro-scale FEM Biomechanics Models

High fidelity anatomical geometry of the whole human body, with detailed resolution of the brain, is used for multiscale simulations modelling of blast TBI. Figure 2 presents the anatomical geometry model used for blast wave loads (skin mesh), for whole-body biodynamics (articulated joint-segmented body), whole body/brain biomechanics (3D FEM mesh model) and a reduced order fast running model of head/brain biomechanics. Because the duration of the blast-human interaction is very short (a few milliseconds) and the induced human body motion is small (a few centimeters) we assume one-way (explicit) coupling of blast wave gas dynamics and biomechanical analyses (rigid body is assumed). A triangulated human skin mesh is used to record time/space resolved pressure loads on the skin obtained from CFD simulations[6,14,27]. These load data can be used for both reduced order models of human body biodynamics and for FEM injury biomechanics simulations.

High fidelity FEM biomechanics modelling of the human body and brain with large deformations is conducted using hexahedral (brick) mesh which, in comparison with tetrahedral, supports larger deformations without element tangling and provides better accuracy and numerical stability. We used CoBi FEM based hexahedral meshing tool to automatically generate whole human body FEM model for the Zygote body human anatomy with high resolution in the face, skull, and brain (Fig. 2). The whole body FEM mesh involves ~2.5 10^6 hexahedra (typical mesh size of 2 mm) to resolve pressure, and shear waves in the brain, lungs, skeleton and other organs. The human body model can be equipped with the protective armor such as helmet, vests, boots, etc. Explicit FEM solver with reduced integration brick elements and homogenised material properties, Table 1, used for high-fidelity biomechanics simulations. The CSF layer between the skull and the brain is not explicitly modelled. Instead the entire space beneath the skull is modelled with an isotropic viscoelastic material, taking into account of the shear resistance provided by the arachnoid trabeculae and the large blood vessels in the subarachnoid space. The lungs are modelled because of the sound speed being much slower in the lung than in other body tissues. All materials other than skeleton, brain and lungs are modelled as soft tissues.

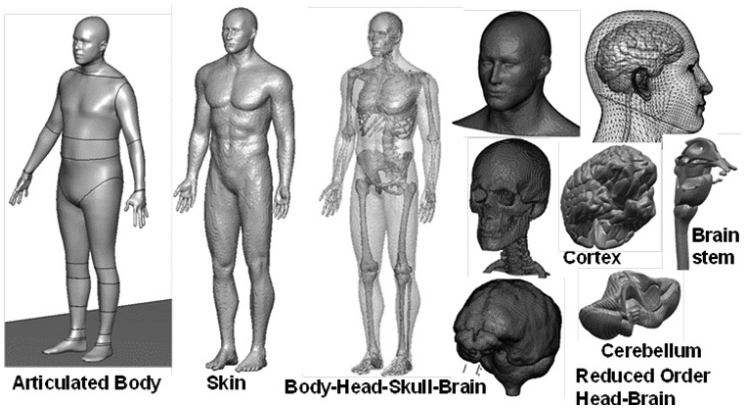

Figure 2. High-fidelity and reduced-order human anatomical geometry models.

Table 1. Mechanical properties used in human FE model

Tissue	Material	Elastic constants	Density (Kg/m^3)
Skeleton	Linear elastic	E = 5GPa, ν = 0.3	1100
Brain, spinal cord	Viscoelastic	K = 2.19 GPa, G0 = 49 KPa, G1 = 33 KPa, τ = 6 ms	1000
Lung	Linear elastic	E = 50 Kpa, ν =0.3	100
Soft tissue	Linear elastic	E = 80 MPa, ν=0.4	1000

To enable very fast and robust head/brain biomechanics simulations (few minutes) we have developed a reduced order model the head/brain to simulate the brain response to blast, ballistic, impact and inertial loads. The brain model is subdivided into three interacting anatomical regions as shown in Fig. 2: cortex, cerebellum and the brain stem. There appears to be sufficient experimental and animal evidence showing that, although TBI is associated with the widespread damage to the brain, the brainstem may be especially susceptible to the effects of neurotrauma[29]. Because of its relatively slender structure, the brainstem is modelled using composite beam elements. Both the cerebrum and the cerebellum are modelled as the rigid bodies. The cerebrum is rigidly connected with the top of brain stem, while the cerebellum is rigidly connected with the pons of brainstem. The bottom of brain stem, which is near the foramen magnum, is assumed to be rigidly connected to the rest of head. The masses and moments of inertia for rigid bodies are obtained from a 3D FEM model.

2.3 Micro-mechanics of Axonal Structures

The brain functional impairment in TBI cannot be studied without accounting for mechanical damage to brain microstructures, such as axons, synapses or the blood brain barrier (BBB). Here we present micro- and molecular-level responses of the white matter axonal structures to blast loads (for the synaptic injury model see[32]). The predicted macro-scale brain mechanical strains at selected brain locations are used to simulate the micro-mechanical response of the local axonal fiber bundles. In the CNS white matter axonal fibers are 'wrapped' up with layers of the myelin sheets projected from proximal oligodendrocytes (ODCs). The mechanical link between axons and ODC projections may contribute to the axonal deformation and injury, e.g., generation of varicosities, disassembly of microtubule-Tau structures, separation of myelin sheets from axonal membranes and potentially shearing of ODC projections. Such a primary axonal damage will have consequences in secondary neurobiology injury and repair pathways. Figure 3 presents the geometrical model of the three axons and two ODCs with several processes. Viscoelastic beam elements are used to model axons, ODCs and processes. The junctions among them are enforced by the kinematic continuity conditions. The

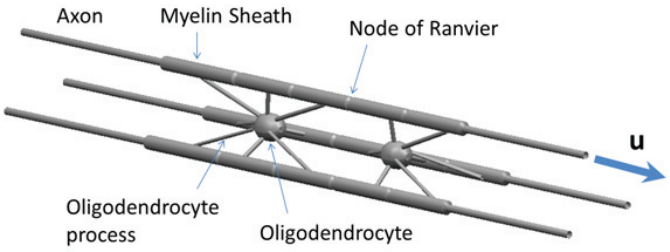

Figure 3. Axon-ODC structure for modelling axonal damage due to sudden stretch.

total length of model is 1.2 mm. The geometrical and material parameters for the myelinated axon model are provided in Tables 2 and 3. The length of the node of Ranvier is very small compared to the internodal length and is represented as a shared node in the FEM beam model.

Table 2. Geometrical parameters of FEM model[2]

Parameter	Value (μm)
Axon diameter	1
Myelin diameter	2
Oligodendrocyte diameter	5
Process diameter	0.5
Length of the node of Ranvier	1
Internodal length	100

Table 3. Material parameters of axon[1]

Material	Young's Modulus (kPa)
Axon	9.5
Myelin	2.0
Oligodendrocyte	2.0
Oligodendrocyte process	2.0

2.4 Nano Scale Modelling of Tau-Microtubule Interaction

Axonal cytoplasm is filled with axially arranged Tau-Microtubule (MT) network responsible for both structural stability and function such as axonal transport. The spacing between MTs is maintained by Tau proteins that promote MT polymerisation, bundling and stabilisation in axons. Since MTs can support both the axial and transverse loadings we use an array of viscoelastic beams to model axonal MTs, Fig. 4. Due to its predominantly axial response, Tau proteins are modelled by the bar element with the rate-dependent mechanical properties. Two different material models are used:

(a) The classic Kelvin model with the constant Young's modulus E and the viscosity η, $\sigma = E\varepsilon + \eta\dot{\varepsilon}$ and

(b) A simple but more accurate model in which the experiment-based force-elongation curves at different loading rates are directly used.

In addition, the presence of the cytoplasm, which is assumed as a stationary viscous fluid, is represented by tangential and normal drag forces on the MT and MAP tau elements. The drag coefficients on MT and Tau (C_n, C_t) by the surrounding fluid are:

$$F_n^{drag} = -C_n(l_e d)v_n, \quad F_t^{drag} = -C_t(l_e \pi d)v_t$$

in which l_e and d, are the length and the diameter of the element cross-section respectively, and v_n, v_t are normal and tangential velocities of the element, respectively.

The material properties for MT are: G∞ = 1 GPa, G1 = 2 GPa, τ = 1 ns, ρ = 1000 Kg/m^3 and for Tau: E = 5 MPa, η = 0.05 Pa*s and ρ = 1000 Kg/m^3. In dynamic simulations of MT failure, critical strain criteria were enforced for elements; upon reaching this critical strain, elements were debonded from its neighbours. The critical strain for MTs was set at 0.5 and for Tau cross-links to 1.0 on based on experimental measurements of the rupture strain[30]. The Tau criterion represents the length at which the Tau protein dimers can no longer maintain a bridge between neighbouring MTs

2.5 Models of Mechanobiology of Neuro-axonal Injury

Primary mechanical damage to axonal microtubule-Tau structures may initiate a cascade of secondary biochemical signalling cascades of injury and repair involving Tau protein (Tauopathies) as well as demyelination, cytoskeletal remodelling, fluid and electrolyte shifts causing local axonal swelling, and other[22,31-32]. It has been documented that repetitive mTBI, a major risk factors for the CTE, may cause the development of neurofibrillary tangles made of hyper-phosphorylated Tau, also a hallmark of the Alzheimer's disease. A computational model of Tau neuropathology could include several elements:

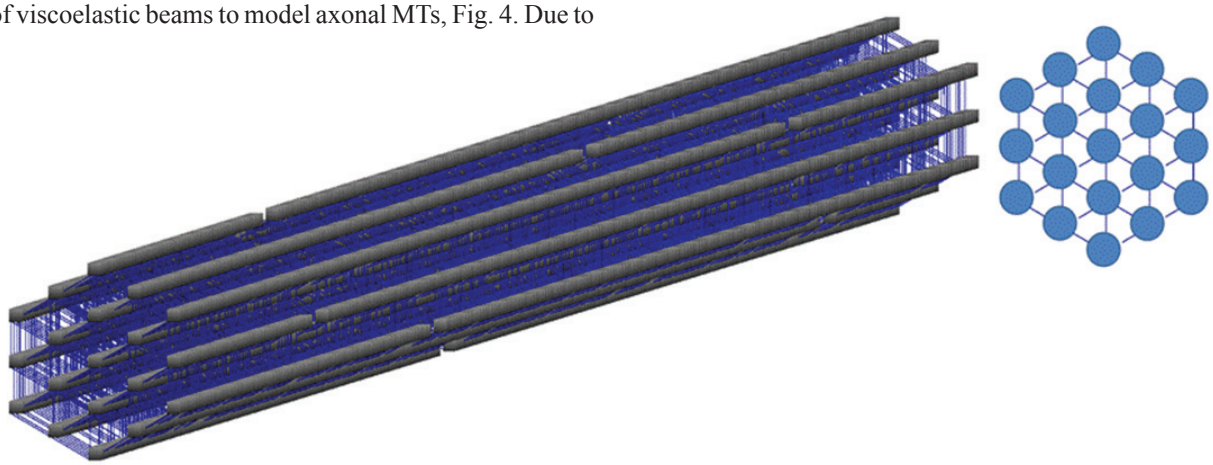

Figure 4. Model setup for axonal microtubules cross-linked with Tau proteins.

- Mechanical separation of Tau from MTs, loss of MT array spacing and MT remodelling,
- Kinetics of disassociated Tau phosphorylation balanced by action of both kinases and phosphatases,
- Kinetics of Tau isomerisation and Pin1 catalysed trans (physiological) to cis (toxic) isoform,
- Cis-Tau aggregation and its retrograde axonal transport toward, and accumulation in, the somato-dendritic compartment.

Such a model is being developed, but it requires experimental test data for parameter calibration and model validation.

3. RESULTS

The blast induced primary mechanical brain injury may involve several time-sequenced mechanical loads. The initial load in the first few milliseconds is caused by the compression/tension stresses in the brain, followed by the shear waves extending up to hundreds of milliseconds, still followed by inertial head rotation/acceleration and the corresponding brain movement. The last event, seconds after the primary blast may be caused by head impact on hard objects. Here we present simulation results from the first and third events. Figure 5(a) shows several instances of the pressure loads on a human body obtained from CFD simulations of a blast wave impacting the body from the front. The moving shock front diffracts on human body surface, and reflects around concave regions (eye socket, lower neck, and groin). The blast pressure reaches the face and the chest first since they are closer to the explosive. The high pressure on the lower leg is caused by the ground reflection. The predicted pressure loads from the blast model, previously validated[27], have been used to simulate the high-fidelity 3D biomechanics of the skull/brain as well as the rest of the body. Figure 5(b) shows the intracranial pressers at three selected times within the first millisecond post blast impact. As seen from Fig. 5(b), the intracranial pressure wave at 0.6ms reflects from the posterior cranial wall. Figure 6 presents intracranial pressure profiles at three locations within the brain (fm-front, mm-middle and rm-rear location). Significant pressure oscillations can be observed in the 5 ms duration due to multiple wave reflections within the cranium.

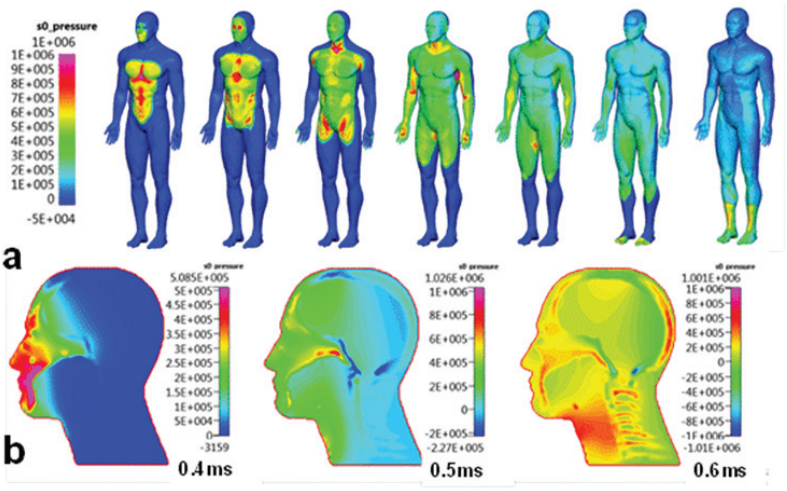

Figure 5. (a) Time instances of blast loadings on human body and (b) Pressure propagation across the brain.

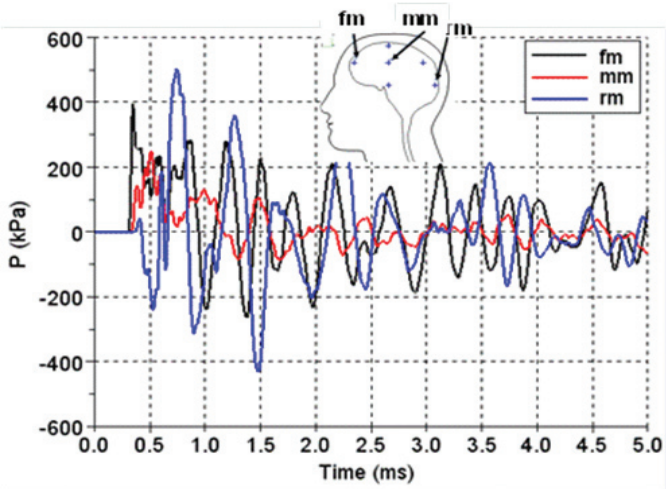

Figure 6. Time histories of the intracranial pressure at three monitoring points (front, middle, rear).

Several phenomena observed in the experimental tests[33-34] can be reproduced in our simulations:

(i) There is about 0.1 ms time delay of pressure onset between coup (location fm) and contrecoup (location rm) sites
(ii) The frontal location experiences compression (coup) while the posterior brain is in tension (contrecoup)
(iii) The positive peak pressure in the contrecoup site is higher than the coup site
(iv) In the contrecoup site, three positive peaks are gradually weakening
(v) Three negative pressure dips over the cavitation limit of -100 kPa.

High-fidelity FEM simulations of brain biomechanics during head acceleration and rotation require fully coupled fluid-structures interaction and long simulation times. A novel, fast running reduced order model of head/brain biodynamics during head impact and inertial acceleration/rotation loads. The model predicts the interaction between the brain and the skull and interaction between three brain structures: cortex, cerebellum and the brainstem. In our simulations, the head-impacts a stationary block with an initial velocity of 10 m/s. The total number of equations to be solved in this model is about 200 and the computational time is less than one minute to simulate the head response with time duration of 5 ms. Figure 7 presents deformation fields in the brain and in the brainstem caused by a head front impact on a rigid wall. From our simulations we observed that at early stage (<0.7 ms), the cerebrum moves forward and collides with the front part of the skull. The cerebrum then rebounds and rolls backward. At 2.7 ms, the brain experiences the second collision and contacts with the backside of skull before moving forward again. The cerebrum moves relative to the skull. There is also a relative motion between the cerebrum and the cerebellum. The cerebrum may come in contact with the cerebellum during the event. As shown in Fig. 7, the brainstem experiences the stretch and bending partly because of the movement of cerebrum (attached at the top of the brainstem) and cerebellum (connected

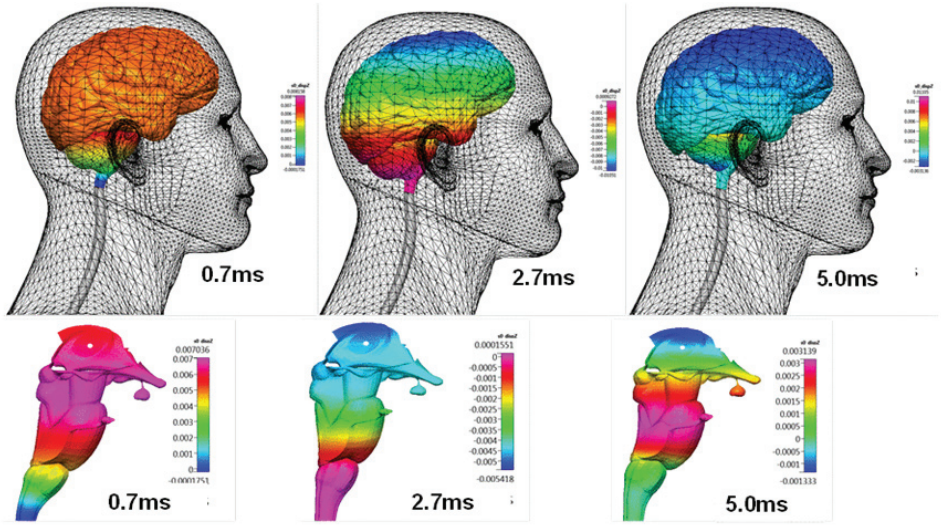

Figure 7. Predicted deformation fields in the brain and in the brainstem at different times after the head impact on a rigid wall.

to the posterior side of the brainstem).

The multiscale simulations of TBI enable micro-scale analysis of mechanical damage of brain microstructures using macroscopic time-dependent strain fields at selected locations in the brain as a loading input. The locations of the maximum strain rates, maximum stress and highest energy absorption in the white matter could be used to study micro-axonal injury. Previously reported simulations of axonal biomechanics assumed either straight or undulated disconnected idealised axonal topologies[23,35-36]. In the present model an idealised initially parallel myelinated axonal fibers interconnected by oligodendrocyte processes is used, Fig. 3. To simulate white matter tension loads a sudden axial movement is prescribed at one end of axon, relative to the surrounding axons. The total time duration is 1 ms and the maximum acceleration of such loading is 100 g. The maximum velocity is 0.5 m/s which corresponds the strain rate of 500/s. At the end of time, the maximum displacement occurred at the loading end of axon is 0.3 mm. The predicted response of strain/deformation pattern in the axon-oligodendrocyte structure at three selected time instances is shown in Fig. 8(a). Since the stiffness of axon is quite low, the axon near the loading end moves axially considerably but the oligodendrocytes have little movement in the first 0.5 ms. After 0.5 ms, the myelinated axons gradually bend because of the extension of connected processes. As expected some compressed processes buckle and lose the load-bearing capacity. At the end of 1 ms, the undulation is clearly seen along two bottom axons without stretching loadings. The numerical results reveal the possible mechanism of impact-induced axon injury including:

- Excessive extension of oligodendrocyte processes result in the demyelination and even breakup of processes
- Varicosity of axon leads to internal damage to cytoskeleton structures such as relatively brittle microtubules (MTs).

When a sudden stretch applied at left ends of three axons, the local bending of axon is much less severe (Fig. 8(b)). This indicates that the non-uniform stretch like shearing loading exacerbates the damage to the axon than the uniform stretching. Further study will be carried out to answer the following question: under the same impact loading, what is the role of material viscosity of axon and oligodendrocyte with respect to the injury severity of axon?

Dynamic deformation of axons cascades down to axonal sub-structures such as myelin adhesion molecules, MTs and associated Tau proteins and other membrane/cytoplasm components. Experimental studies have shown that axons can tolerate large strains under slow loading rates but at high strain rates, typical to TBI, even small strain rates can damage to the Tau-MT structures[22,37]. Computational models of MT and Tau biomechanics have been recently demonstrated with various assumptions[23-24,30,38-39]. Here we present, first ever 3D FEM simulations of biomechanics and microdamage of a bundle of MTs interconnected by a large network of cross-linked Tau dimers. Based on brain-level simulations of blast TBI high strain rate of 500 1/s loading condition has been applied on both ends of the MT structures, Fig. 9 (insert). The 'catastrophic' bundle failure was characterised by the initiation of rapidly increasing element failure and bundle length. Failure was evident at later times, as shown in Fig. 9. The simulation showed bundle failure occurring entirely by failure of the cross-links with the MT elements remaining intact. This mode of bundle failure, here referred to as MT pull-out, is characterised by failure of the Tau dimer cross-

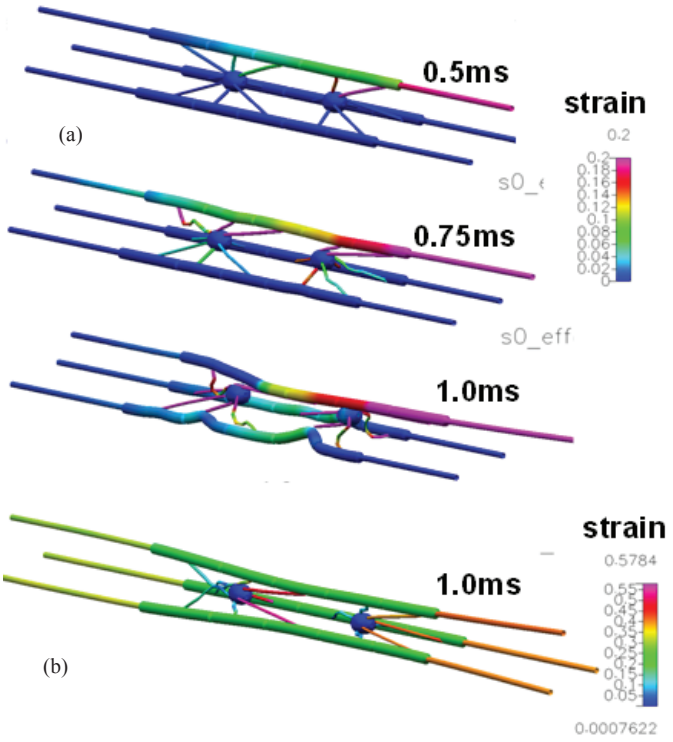

Figure 8. Predicted axon-oligodendrocyte displacement and axonal undulation (a) after dynamic stretch at top axon, and (b) to all three axons.

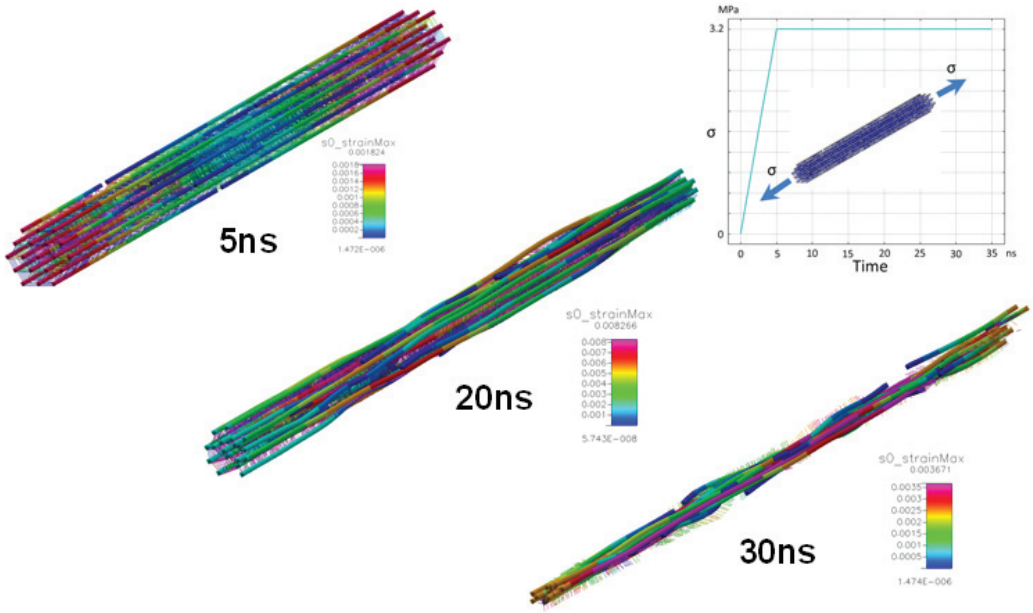

Figure 9. Predicted strain fields and deformations of a microtubule network cross-linked by Tau dimers (inset- loading conditions).

links leading to the MTs being pulled past one another and misaligned from the axial configuration. Pull-out of MTs may explain the significant elongation of axons following traumatic stretch seen in experiments. Axonal undulations observed following traumatic stretch injury are possibly a result of these combined effects of the failure of the cross-linked architecture and elongation and bending of the MT bundle.

The results of the local axonal micro-damage simulations at various locations the brain can be used to develop 'local' cell/tissue- level injury criterial for various axonal structures[40]. Such a model could also provide initial conditions for modelling neurobiology of secondary injury/repair mechanisms such as dis/reassembly of MTs, kinetics of Tau phosphorylation, agglomeration, retrograde transport towards the soma and other effects involved in post-traumatic neurodegeneration.

4. DISCUSSION

Computational modelling of human head injury biomechanics has been investigated since the 1970s, first using approximate analytical and spring-mass-damper models[41] and in 1990s using FEM[42]. Currently FEM tools are routinely used to simulate impact biomechanics and primary brain injury problems, particularly in the automotive occupant safety applications. Advanced 3D FEM models of head/brain anatomy and biomechanics and injury have been pioneered at the Wayne State University resulted in the well-known WSUBIM (Wayne State University Brain Injury Model) FEM human head model[43]. Other teams have added various refinements including the improved resolution of the neck, subarachnoid CSF, bridging veins and other anatomical feature[9-10,44-46]. In the last few years, FEM head/brain biomechanics models have been adapted for modelling the blast TBI by incorporating head/face anatomical details and by coupling them to the blast physics CFD solvers[7,39,47-49]. In comparison to the blunt brain biomechanics model, the blast injury model has a loading force that is much faster and is spatially and temporally 'distributed' over the entire head during the shock wave propagation around the head. These models still need improvements in physics and numerics, e.g. high strain rate material properties, modelling the CSF flows and the presence of vasculature.

In the last few years a new trend of multiscale models has been recommended in which the macro-scale model of biomechanics and linked to micro-scale models of injury to various brain structures including axons, synapses and

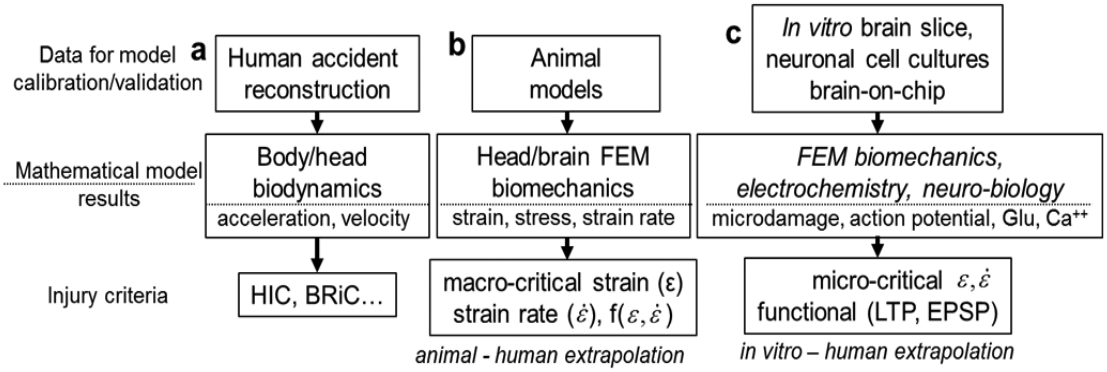

Figure 10. Comparison Injury criteria in a multiscale modelling framework.

microvasculature[6,50]. This paper demonstrates this concept on multisite modelling of blast TBI coupling macro- micro- and molecular-scale models of primary biomechanical injury. The main advantages of this approach are that it could be used to develop local neuro-tissue injury criteria and to link the primary biomechanical micro-injury results with the neuro-biochemical signalling pathways of secondary injury and repair.

In vehicle safety standards the injury criteria for TBI are predominantly based on macroscopic parameters such as head acceleration. Widely used injury criterion is the head injury criterion (HIC) is often criticised for not considering other factors that are important to brain injury such as impact direction and area of contact, stiffness of the impacting surface and the rotational accelerations[18]. Various alternative injury criteria have been proposed to alleviate HIC limitations including brain rotational injury criterion (BrlC)[21], the generalised acceleration model for brain injury threshold (GAMBIT)[51] and a criterion based on the total change of kinetic energy of the head during impact (HIP)[52]. These macro-scale injury criteria can be calibrated on the human accident reconstruction, Fig. 10(a), for which there is always a limited data. In reality the injury occurs in various tissues inside the brain and local tissue injury criteria may be more appropriate parameters. Experimental and computational analysis of brain biomechanics has shown that different regions of the brain respond differently to identical mechanical stimuli. Brain tissue specific injury parameters could be used to establish more definite injury criteraia that could be validated for example on animal models. Moreover, brain tissue level injury parameters such as strain, stress and strain rate are commonly determined using FEM based brain biomechanics simulations. These brain-level results could be used to calculate injury measures such as cumulative strain damage measure (CSDM) and maximum principal strain (MPS) which could be correlated with animal and human clinical data, Fig. 10(b).

In contrast to the macro-scale approaches of determining injury criteria for TBI, injury thresholds can also be defined based on the micro-scale (cellular, molecular) mechanisms of injury, Fig. 10(c). For example, *in vitro* and *in vivo* models of TBI offer a platform for quantifying mechanical thresholds for axonal injury directly. A formal multiscale procedure for coupling the cellular mechanisms of axonal injury to the deformation of brain tissue is developed. These models have been used to study the effects of cellular strain and strain rate on the injury response of neural cells. An axonal strain injury criterion was used as a measure of DAI. This injury criterion is based on the stretch injury response of neural axons. Strain thresholds were defined based on the onset of functional and structural damage observed in the experiments. A strain threshold of 18 per cent at strain rates of 30–60/sec for the optic nerve of a guinea pig in vivo was determined for the onset of electrophysiological impairment[53-54]. The micro-scale injury criteria could be used not only for the primary mechanical damage but also for evaluation of brain tissue secondary injury e.g. alternations of tissue morphology (e.g. axonal beading), electrophysiology (e.g. loss of action potentials) but also functional response such as synaptic and white matter plasticity, and long term potentiation and depression[28,55-56]. In vitro brain slice and the recently emerging organ-on-chip and human-on-chip technologies[57-59] provide foundation for the development of 'living', 'humanised' brain-on-chip devices that could be used to investigate various primary and secondary injury mechanisms but also responses to treatments such as hypothermia, electro/magnetic stimulation and pharmacological interventions. Fig. 10(c).

Computational models of neuro-biochemical signalling pathways of secondary injury and repair may provide invaluable assistance not only in better understanding of brain injury mechanisms but also in the development of novel diagnostic and therapeutic modalities. Experimental in vitro and animal models of TBI have shown that the primary micro-damage to various neuro-structures initiates a cascade of biophysical and neurochemical events, lasting from minutes to hours, resulting in either axonal, synaptic and vascular repair or permanent damage[59-60]. Development of secondary injury models involves construction of a conceptual mechanistic model of injury mechanisms, mathematical formulation of the underlying mechano-biology model and calibration/ validation of the model on available *in vitro* experimental data. In our recent publication we have developed a conceptual mechanistic model of synaptic injury mechanisms[28].

First ever mathematical model of primary biomechanical injury to axonal-oligodendrocyte structures and a damage to intra-axonal network of microtubules interconnected by Tau is presented. We envision two mechanistic mathematical models of post-acute response to both structures. A mathematical model of high strain-rate mechanical deformations of myelinated axons may be able to predict damage to axonal membrane (particlaty in the nodal areas), to myelin adhesion molecules and to oligodendrocyte processes. Inputs from this mechanical model could be used to simulate axonal depolarisation (water and electrolyte shifts), hyper-metabolism needed for repolarisation, disruption to propagation of action potentials and axonal local cytotoxic micro-edema leading to formation of retraction balls. These responses may provide partial explanation of recently reported 'white matter plasticity' in mTBI[61-63]. Mathematical models of the mechanical deformation and damage to intra-axonal MTs and associated protein Tau have been recently reported[24-25,30,38,64-65]. First even FEM based 3D micro-injury model of a large network of MTs (elastic beams) linked by Tau dimers (viscoelastic bar elements) is presented. The model has been used to simulate breakup of Tau dimers, Tau separation from MTs as well as breakup of individual MTs. The predicted concentration (number density) of Tau proteins separated from each other can be used as initial conditions for systems biology based models of Tau phosphorylation, conformational switch (folding) from the physiological *trans* to pathological *cis* isoforms, Tau aggregation and for modelling tau transport toward and accumulation in the somato-dendritic compartments, typically observed in CTE and in other neuropatholgies.

5. CONCLUSIONS

The paper presented a novel multiscale simulation

framework, CoBi, for modelling blast-induced TBI. The framework integrates several components including human body anthropometry and anatomy, computational mesh generation, both outside and inside the body for modelling the blast wave impact and body biodynamics/biomechanics. Our studies demonstrated that cumulative brain damage may result from multiple, time sequenced insults to the brain due to: primary blast and debris loads, body/head movement and head impacts on solid objects. The time/space resolved loading results from macro-scale simulations were used as inputs for modelling macro-scale head/brain biomechanics as well as micro/molecular scale mechanobiology of neuro-axonal structures most sensitive to injury. We presented a first ever mathematical model of primary injury to axon-oligodendrocyte structures and damage to intra-axonal network of microtubules. The results could be used to develop local neuro-tissue injury criteria and to link the primary biomechanical micro-injury results with the neuro-biochemical signalling pathways of secondary injury and repair.

6. DISCLAIMER

The views expressed in this paper are those of the authors and may not necessarily be endorsed by the U.S. Army or U.S. Department of Defense.

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