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Finite element modeling of traumatic brain injury: Areas of future interest

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Abstract

The use of the finite element (FE) method to simulate traumatic brain injury (TBI) has been an area under development and research for many years. The aim is to accurately reproduce and evaluate the resulting brain damage that would otherwise be inaccessible. Computational simulations can assist the diagnosis of injuries and early detection of long-term damage in order to advance preventative measures and implement early treatments. Here, we discuss a few new and emerging trends of FE models for TBI. We highlight advancements in two main areas: FE head models and brain tissue material models. We discuss how FE models can be improved to have greater anatomical and mechanical biofidelity, resulting in more accurate TBI simulations. Our aim is to stimulate future research activities in important areas that have so far been underexplored and can significantly accelerate the relevance of TBI FE models for clinical use in the future.

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Traumatic brain injury, Finite element method, Material modeling, Head models, Damage.

Introduction

A traumatic brain injury (TBI) results from a large, sudden force applied to the head and can entail a variety of clinical symptoms, both immediately and later in the future. Therefore, TBIs are a major public health issue with a continual rise in the incidence of TBI-related injuries and deaths. Finite element (FE) modeling presents an opportunity to better understand the effects and mechanisms of TBI and to develop efficient protective gear [1,2]. Furthermore, FE simulations can be used in clinical settings to provide information that is otherwise difficult to diagnose with traditional medical imaging technology.

TBIs are extremely complex and difficult to simulate. Therefore, to achieve the above mentioned goals, further research is needed. Many aspects of TBI modeling are currently researched, investigated and improved. Here, we highlight only a few aspects of interest, i.e., FE head model geometry and constitutive material models, as indicated in Figure 1. It is important that the FE simulations use head and material models that capture the geometric details and regional mechanical response accurately. As we continue to learn more about how the brain functions and responds to loading, advancements in both head and material models need to be implemented to capture this new information [3,4]. We strongly believe that the aspects discussed here present interesting opportunities to improve the biofidelity of simulations. We summarize the most recent and emerging trends regarding these two components with the hope of inspiring future research and advancements.

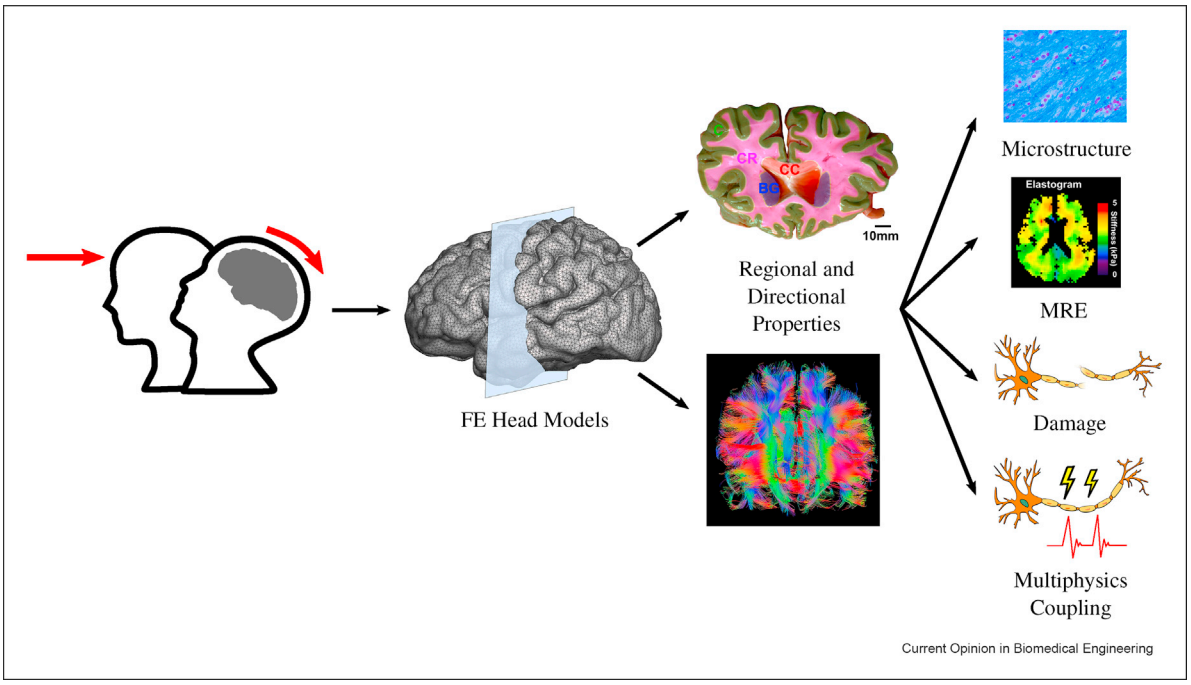
Head models

With an increase in computational power, FE head models have been able to increase in complexity and anatomical accuracy over the years. They have progressed from simple geometries like ellipsoids to complex anatomically accurate structures that include important sulci and gyri features and regional differentiation between white and grey matter within the brain and regional differentiation [3]. While there are many important aspects that can help improve the biofidelity of head models, such as model validation, skull–brain interface modeling, and injury prediction parameters, to just name a few, here we only focus on two specific topics, the inclusion of axonal fiber orientation and subject-specific head models. A full review on common head models and factors that affect TBI simulations can be found in the study by Madhukar et al. [2].

Explicit axonal fiber inclusion

White matter is a deep tissue of the brain that contains axons transmitting information throughout the brain. A TBI can cause damage to the axons resulting in a traumatic axonal injury (TAI) or diffuse axonal injury (DAI), which can cause functional impairment [7]. These injuries are difficult to detect non-invasively and, therefore, the prediction of TAI using FE simulations can be highly valuable for the clinical community.

Figure 1



A summary of recent and emerging trends to advance finite element (FE) simulations of traumatic brain injury (TBI). The brain subject to impact loading (left) is discretised using finite elements (center left). These FE head models ideally need to capture the regional mechanical properties of brain tissue (center right, top [5]) and information on the orientation of axonal fibers (center right, bottom). To account for regional properties *in vivo*, microstructure-based models and magnetic resonance elastography data integration are key future routes to explore (right, top: microstructure image shows white matter with Klüver-Barrera staining at 63× magnification [4]; MRE image is adapted from the study by Murphy et al. [6] licensed under CC BY-SA 3.0). In addition, FE models can account for damage mechanisms occurring during and after a TBI, e.g. through multiphysics coupling (right, bottom).

The orientations and locations of the axonal fibers can be acquired using diffusion tensor imaging (DTI) and the evaluation of fractional anisotropy (FA). To this end, the brain is discretised into small volume elements (voxels) within which the volume-averaged fiber orientations is given [8]. Furthermore, a complete realization of the axonal fiber network can be provided using whole brain tractography. This network can be included explicitly in the FE models or implicitly via the constitutive model. The latter approach is discussed in Section 3.1. In this section, we focus on the methods of explicit axon inclusion into FE models.

Explicit inclusion of axonal fibers makes it possible to capture an anisotropic mechanical response of white matter. This is often realized by using an embedded element technique [9], which involves explicitly mapping the axonal fiber network as either 1D truss [9] or cable [10] elements and adding them to a volumetrically meshed brain tissue model. This technique can cause a mass and stiffness redundancy in FE models, but various methods have been developed to mitigate this [11,12]. Zhou et al. [13] suggest that an extension is necessary whereby the real-time orientation of these fibers are used to capture the stresses and strains in this network during impact. Compared to models without explicit fiber inclusions, validated models showed differences in the location and thresholds of TAI [14,15,13]. The biofidelity and validity of this method, however, is still under debate.

While axonal fibers show clear structural anisotropy within white matter, experimental data have not adequately confirmed that this translates into mechanical anisotropy [16,4]. Compared to the many other microstructural components found in brain tissue, axonal fibers only provide marginal mechanical strengthening and would, therefore, be unable to act as reinforcing fibers within white matter. As such, there is strong motivation to consider white matter to be mechanically isotropic. The necessity of using a computationally expensive method, such as the embedded element technique, should thus be carefully considered in TBI simulations.

While the necessity of modeling the anisotropy within white matter is a contentious issue, the link between local axonal strains and axonal damage is important to understand and model TAI [8,17]. By using the axonal fiber direction data from DTI and tractography, the stress and strain response of individual axons can be investigated in the post processing of TBI FE models

[18]. This assisted in making better predictions of the location of TAI, severity of axonal damage and damage of neural pathways in Refs. [19,20]. Various researchers also used this method to investigate the link between macroscopic effects of TBIs and the associated micro-axonal damage [21,22], [**23].

Fast, subject-specific head models

The ability to capture the unique features of an individual, both mechanically and geometrically, is key to provide accurate and useful FE models for TBI. Accounting for the subject-specific brain geometry is an important prerequisite for providing accurate injury predictions and fully understanding TBI mechanisms [20,24]. Another important aspect is capturing subject-specific mechanical properties, which is discussed in detail in Section 3.2.

The creation of subject-specific head models will need to be fast and accurate in order to be useful in a clinical setting. Several approaches have previously been explored and utilized to create head models of increasing accuracy. More information about these approaches is given in the study by Li et al. [20]. These current approaches, however, either use only tetrahedral elements or have difficulty in producing sufficiently smooth hexahedral meshes. Hexahedral elements are preferred over tetrahedral elements due to their mechanical stability in modeling incompressibility, but unfortunately, they create problems when meshing due to the jaggedness of the final mesh surface—despite attempts of smoothing. This causes stress concentrations and thus can lead to inaccuracies in the results.

Recently, an approach to create a completely smooth, hexahedral mesh that accurately depicts the anatomy of the brain by means of an image registration-based mesh morphing method was proposed [20,25], [**26], [*27]. Here, a displacement field is calculated that describes the transformations necessary to match a baseline model to the specimen model [*27]. These transformations are then applied to the mesh nodes assigning new coordinates while maintaining the interconnected nature of the mesh. This technique can model external and internal features such as grey and white matter regions as well as the ventricular system. The corresponding model creation reportedly takes approximately 2 h [25]. In the past, ensuring a suitable mesh quality has presented a limitation on the amount of distortion that can be applied. However, recently a suitable extension added the capability to also accurately create head models across the lifespan (newborn, 1Y, 2Y, adult, 92Y) and for pathological brains (hydrocephalus brain) [*27].

As the brain is structurally a highly complex organ, capturing anatomical complexities with a high quality FE mesh is one of the key prerequisites for the performance of accurate simulations. Creating complete, patient specific head models that capture complex geometric features could also provide interesting information on how anatomical differences affect the mechanical response during a TBI. This will be useful for the development of protective gear and is, thus, a worthwhile avenue of further exploration.

Material models

As experimental methods advance, new information on the material properties of the brain have become available. As such, material models of the brain need to advance to include these effects where necessary. Having more accurate and appropriate material models plays an important role in improving the biofidelity of FE simulations of TBIs. Here, we highlight four avenues of future research that have great potential for the further advancement of TBI models.

Regional and directional properties

Differences between the mechanical properties of white and grey matter are well understood and are often incorporated into FE head models. However, recently several studies have showed variations in both viscoelastic and hyperelastic material parameters even within these regions [28], [*29], [16,30–32]. The effects of this regional heterogeneity on the response of TBI simulations is certainly an area that should be investigated. The inclusion of regional material parameters can, however, be difficult to achieve due to limited experimental data. One avenue of incorporating regional material parameters is to consider the effects of the underlying microstructure and its composition on the macroscopic material response [33]. Micro-structurally motivated constitutive equations could be created and, using their unique histologies, the regional properties of the brain could be captured [34], [*35].

Section 2.1 considered the explicit inclusion of axonal fibers within the white matter of the brain tissue. Here, we consider the implicit inclusion of the axonal fiber network via constitutive equations. In the literature, the anisotropy of white matter is captured by two common material models: the Puso and Weiss model and the Holzapfel–Gasser–Ogden (HGO) model [36]. FE head models have incorporated the HGO [37,38] and the Puso and Weiss material model [39] using DTI data and whole brain tractography [40]. Findings from rat [41] and human [37,42] models that use these anisotropic material laws suggest that TAI thresholds should be based on the axonal strains and not the macroscopic strains in TBI simulations. These models, however, only considered the tensile contribution of the axonal fibers. A recent extension to the HGO model proposed by Madouh and Ramesh [43] accounted for shear anisotropy as well. Using a 2D model, comparisons to the

HGO model showed significant differences. A validated 3D head model also used this extended material model to enhance the shear response of the brain under dynamic loading [44]. However, the authors suggest that further experimental research is needed to explore the full contribution of the axonal fibers under various loading modes. Since the significance of anisotropy in white matter is still under debate, one must consider if its addition is worthwhile given the added complexities of these material models [16]. While these models may provide useful insights into the damage mechanisms and thresholds of TAI from axonal strain data, isotropic models, such as the Ogden model, have suitably captured the macroscopic mechanical response of white matter under various loading modes [5] [*35].

Subject-specific material properties

Brain tissue may exhibit different mechanical properties *in vivo* compared to *ex vivo* [4,45]. This should be considered when modeling TBI. Magnetic resonance elastography (MRE) is an emerging technology that provides the ability to acquire *in vivo* experimental data non-invasively. MRE probes the tissue stiffness and linear viscoelasticity of the brain at high frequencies and small strains. It is able to distinguish between individual locations of the brain and thus provide regional mechanical properties [*46]. In addition, it can determine different material properties resulting from differences in gender and age [*46]—thus allowing for subject-specific material properties to be included in brain models.

Traditionally, MRE data analysis assumed an isotropic material behavior. However, more recently researchers proposed various methods that account for the anisotropy of white matter: Using MRE, Schmidt et al. and Smith et al. determined parameters for an incompressible transversely isotropic material for *ex vivo* porcine brain [47] and *in vivo* human brain white matter [48], respectively. Babaei et al. and McGarry et al. used transversely isotropic material models that account for near incompressibility to model homogeneous human muscle [49] and heterogeneous brain matter [50] respectively, by incorporating DTI data.

Also a few TBI studies have been conducted using FE head models informed by MRE data. Madhukar and Ostoja−Starzewski incorporated the heterogeneities of white matter into an Ogden hyperelastic material with a viscoelastic contribution from a Prony series [51]. Giudice et al. used a quasi-linear viscoelastic model on a subject-specific brain model [**26] and Alshareef et al. used a linear viscoelastic model and heterogeneous MRE data to conduct simulations on five mechanically and anatomically informed subject-specific models [52]. While these studies present an important step forward in achieving clinically relevant TBI models, they all agree that there are still limitations concerning the use of MRE data. Firstly, there are possible inaccuracies in the material models as properties determined through MRE measurements are based on the assumption of a linear viscoelastic material, whereas brain tissue is known to exhibit a nonlinear viscoelastic behavior [4,53]. To accommodate for this, Madhukar and Ostoja−Starzewski scaled the linear MRE parameters to create relative stiffness values to be used in their nonlinear viscoelastic model [51], while Giudice et al. directly calibrated the nonlinear material parameters from the MRE data using an inverse FE approach [**26]. Secondly, MRE is unable to test brain tissue at strain rates or magnitudes that would be injurious owing to the obvious ethical issues. This is not ideal for TBI simulations, which occur at high rates and large strains. Alshareef et al. attempted to accommodate for this by using *ex vivo* dynamic shear testing to calibrate their data [52].

Taken together, MRE is still an emerging technology and, with further development and advancements, could provide valuable *in vivo* data to improve the biofidelity of FE head models and, as such, enhance their ability to predict the short and long-term effects of a TBI.

Long-term damage modeling

The damage and long-term effects of repetitive or mild TBIs is an area that is gaining interest within the TBI community. Continuum damage models that account for history-dependent and cumulative damage mechanisms observed in the brain after TBIs have begun to emerge. These models attempt to capture the temporary and permanent response of brain tissue under large loadings. For example, the softening behavior of the brain under large repetitive strains, as described by the Mullins effect, was captured by using the pseudo-elasticity theory [54]. Using fractional calculus, Voyiadjis and Sumelka were able to model the evolution of a scalar damage parameter which was able to replicate the experimentally observed degradation of brain tissue in tension [55]. Additionally, models using constitutive equations combined with continuum damage models attempted to capture the damage and rupture of axonal fibers in FE head models [54], [**56] [*57]. Begonia et al. suggested a physiologically motivated material model that links damage parameters through axon stretch limits and presents an interesting avenue of research to be explored [*57].

Most of the previous studies used models that are either 2D or represent small 3D regions of brain tissue. These models have yet to be used in full FE head models. Additionally, these models only account for axonal fiber damage, while the possibility of matrix softening independent of the axonal fiber network or the death of cells remain as open problems. Other progressive brain conditions, such as atrophy [58] and chronic traumatic encephalopathy [59], have also only been investigated using simplified models.

One of the biggest hindrances to the advances in this field is the lack of experimental data. Many assumptions were made based on either the observed responses of other biological tissues or non-biological materials. Understanding how the macroscopic load is transferred to the microstructure of brain tissue could greatly assist in capturing the real damage effects of mild and repetitive traumatic brain injuries [*35]. In addition, the use of microstructurally motivated material models could assist in closing this knowledge gap. Importantly, the response of microstructural components of brain tissue could serve as biological indicators of long-term damage [60]. The clinical relevance of understanding the repercussion of repetitive and mild head traumas using FE models is clear, as such advances in this field are highly worthwhile.

Multi-physics coupling

Along with the immediate and long-term mechanical damage associated with TBI, researchers have recently explored the functional impairment and secondary injury processes. Experimental studies have showed that changes to the mechanosensation and -transduction [61,62], mechanoporation [63], [**23] [64] and electromechanics [65] of brain tissue due to a TBI can provide useful insights into how brain disorders develop. For example, a recently developed electromechanical model aimed to capture the effects of mechanical axonal damage on the electrophysiological function of the brain [**56]. Understanding these relationships through multi-physics modeling and FE simulations could assist in understanding the functional impairment that can result from TBIs.

Conclusion

FE modeling has the potential to play an important role in the prediction and prevention of TBIs and associated neurodegenerative diseases in the future. By continually advancing both geometric features and material models, FE head models have become more accurate and can allow for subject-specific predictions relevant to address important clinical questions. Here, we have summarized some of the recent and emerging trends within TBI research that we believe present interesting research directions to explore in the future. In the following, we list the steps we consider important to push the frontiers in FE TBI modeling:

- To date, there is no comprehensive experimental data set that quantifies the regional material properties within the brain under impact loading and the associated damage behavior. In this respect, the investigation of how the local microstructure of brain tissue influences the material properties and, in turn, how macroscopic loading is transferred to the microscopic (cell) scale will be key to develop microstructurally motivated constitutive equations for more accurate heterogeneous brain models.
- Advancements in MRE technology and the appropriate incorporation of the corresponding data into FE head models accounting for large strains and nonlinear viscoelastic material behavior will be an important step towards reliable subject-specific models that capture the *in vivo* properties of human brain tissue.
- While FE models of TBI have mostly accounted for axonal fiber damage, other effects such as matrix softening independent of the axonal fiber network or the death of cells should additionally be considered and explored in the future.
- Advancements in the area of multi-physics coupling can significantly assist in understanding the functional impairment caused by TBIs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data were used for the research described in the article.

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