INVITED REVIEW

A new computational approach for modeling diffusion tractography in the brain

Harsha T. Garimella, Reuben H. Kraft*
Department of Mechanical and Nuclear Engineering, Department of Biomedical Engineering, The Pennsylvania State University, University Park, PA, USA

How to cite this article: *Garimella HT, Kraft RH (2017) A new computational approach for modeling diffusion tractography in the brain. Neural Regen Res 12(1):23-26.*

Funding: *The authors gratefully acknowledge the support provided by Computational Fluid Dynamics Research Corporation (CFDRC) under a sub-contract funded by the Department of Defense, Department of Health Program through contract W81XWH-14-C-0045.*

Abstract
Computational models provide additional tools for studying the brain, however, many techniques are currently disconnected from each other. There is a need for new computational approaches that span the range of physics operating in the brain. In this review paper, we offer some new perspectives on how the embedded element method can fill this gap and has the potential to connect a myriad of modeling genre. The embedded element method is a mesh superposition technique used within finite element analysis. This method allows for the incorporation of axonal fiber tracts to be explicitly represented. Here, we explore the use of the approach beyond its original goal of predicting axonal strain in brain injury. We explore the potential application of the embedded element method in areas of electrophysiology, neurodegeneration, neuropharmacology and mechanobiology. We conclude that this method has the potential to provide us with an integrated computational framework that can assist in developing improved diagnostic tools and regeneration technologies.

Key Words: *embedded elements; finite element analysis; computational biomechanics; explicit axonal fiber tracts; neural regeneration; diffusion tractography*

Correspondence to:
Reuben H. Kraft, Ph.D., reuben.kraft@psu.edu.

orcid:
0000-0003-3084-1989 (Harsha T. Garimella)
0000-0001-8211-0681 (Reuben H. Kraft)

doi: *10.4103/1673-5374.198967*

Accepted: *2017-01-16*

Introduction
One aspect of designing, optimizing and applying neuro-regeneration technologies is having a sound understanding of the underlying injury or disease that requires regeneration. One possible way to achieve this level of understanding is through the study of damage or disease using "computational brain models." The types of computational brain models vary depending on the physics of interest. For example, biomechanical modeling solves Newton's second law using continuum mechanics with the primary objective to understand how external forces are translated through the tissue that may cross some injury thresholds, while models in computational neuroscience commonly solve the Hodgkin-Huxley system of equations to model electrical signal propagation in individual neurons connected into networks. Other fields where modeling is used include neuropharmacology, brain cancer modeling, mechanobiology, neuro-disease, behavioral modeling, and vasculature modeling. However, all of the modeling used in these fields suffer the problem of bridging length and time scales ranging from the whole brain organ to cellular or sub-cellular regimes. The method we describe in our recent paper (Garimella and Kraft, 2016) employs the embedded element method to computationally model axonal bundles in the brain, and we propose that the approach can help us bridge length scales, thus providing a possible linchpin for connecting all of these diverse modeling approaches. Here, we share some perspectives of the method.

As a start, we applied this method to quantify the biomechanical injury response of the brain. At present, there is no gold-standard, or widely accepted manner, to diagnose a mild traumatic brain injury or concussion in a quantitative fashion. In recent times, axonal strain (strain along axonal tracts) is gaining more prominence as a reliable injury threshold with more and more people from the biomechanics community using it to define injury. The damage predicted by this criterion might also be a more accurate damage measure as it is a more physiologically relevant injury criterion (Wright et al., 2013). While our recent paper focuses on the prediction of axonal injury, we would like to emphasize again that the application of this method should be considered as a first step towards the development of next generation computational brain modeling where multiple time and length scales, as well as physics, can be coupled together.

Essentially, the model includes a high-resolution finite element (FE) model of the human head with an explicit finite element mesh of the axonal fiber network superimposed through the embedded element technique. These finite element meshes were developed (independently) using the patient-specific magnetic resonance imaging and diffusion tensor imaging (DTI) data. Over the years, attempts have been made to leverage DTI to develop multi-scale finite element models to investigate axonal injury (a summary provided in our publication (Garimella and Kraft, 2016)). However, most of these studies used an averaging technique while transferring the axonal direction information from DTI to the FE models thus compromising the data transfer process. In our

Figure 1 Mechanical strains experienced by the axonal fiber tracts in the corpus callosum region of the brain for a concussive loading impact (Ji et al., 2015).
This image is taken from our recent work here (Garimella and Kraft, 2016) and more details about this image can be found in this publication.

approach, we used an explicit representation of the axonal fibers. The novelty of this work lies in the application of the embedded element approach to incorporate explicit axonal tractography into human head finite element models.

Embedded Element Technique in Structural Brain Mechanics

In this technique, the axonal fiber information, obtained from DTI, was converted into an explicit finite element mesh by discretizing the axonal fibers into smaller segments and converting these segments into “truss” type finite elements. Thus a single fiber consists of many truss elements. Then, the collection of connected truss elements making up the fiber network is embedded into the head model (developed using reported methods) using a global-to-local element constraint. This is a mesh superposition constraint where the embedded nodes follow the displacements of the host nodes (which make up the brain matrix), thereby projecting the strains from tissue onto the axonal pathways. At the same time, a reverse coupling phenomenon takes place where the stiffness of the host elements is increased by the stiffness of the fibers (in their respective directions) – thus imparting the much-needed anisotropic nature to the brain tissue.

To demonstrate the applicability of this method, in our publication (Garimella and Kraft, 2016), a finite element model of the human head with explicit axonal fiber tracts was developed and verified against published experimental scenarios (pressure and displacement). Once verified, this model was subjected to concussive loading conditions experienced by a real life football player. The damage predicted by the model matched well with other studies, thus strengthening our confidence in the model. One interesting observation from this study is the huge differences (location and extent) in injury predicted by different injury criterion for the same loading conditions. Secondly, we have found that the injury experienced by a patient depends on the direction of loading as well as the patient specific axonal architecture –thus emphasizing the importance of developing patient-specific finite element models in investigating injury. **Figure 1** shows the axonal strains obtained along the different axonal fiber tracts located in the corpus callosum region of the brain for a concussive loading scenario (Ji et al., 2015). This image is taken from our recent publication (Garimella and Kraft, 2016).

The advantages of the application of embedded element technique include avoiding fiber direction averaging methods (improving data transfer process from DTI to FE models), avoiding complex phenomenological models (Garimella et al., 2014) and incorporating explicit models of axonal fiber tracts. Apart from the above advantages, we believe that this embedded element method is important because it enables us to resolve the dynamics at the axonal fiber bundle length. The fiber length scale might be considered as the mesoscopic level of the brain (where the cellular level could be considered the microscale). Thus, by quantitatively modeling the transfer of loads from external loading down to the tract level the method may enable us to carry out the cellular level modelling efforts with more accurate loading and boundary conditions – thus bridging the gap between the macro and micro biomechanics of brain. From an injury perspective, these tracts can be used in studying the evolution of axonal injury, thus bridging a significant gap between engineering and medical imaging.

The approach described (and the model developed) enables us to track the mechanical response of the more anatomically significant axonal fiber tracts. For example, investigation of the injury response of uncinate fasciculus (a white matter tract connecting orbitofrontal cortex to the temporal pole and is responsible for attention, memory, and language related functions) might provide us with new insights into the memory and attention deficits observed in mild TBI subjects (Papagno, 2011). This fiber-based approach also enables us to incorporate damage functions at the tract level and thus permitting the study of the evolution of damage accumulated due to repeated sub-concussive impacts or blasts over time. With the advancement of imaging techniques like diffusion spectrum imaging (where fiber crossing is more frequent), this method is particularly useful as it offers no limitation of the number of fibers that can be incorporated into a particular finite element. The mathematical formulation of this approach also allows us to include slip behavior on to the axonal fibers – thus enabling us to develop models with a non-affine projection of strains in the axonal tract direction. In future, the head model developed here (once validated using medical imaging to establish confidence in prediction capability of the model) could be used in clinical environments as an injury prediction tool to locate injury (Garimella and Kraft, 2016).

Results

While we applied this embedded element method to study the injury biomechanics of brain tissue in our published paper (Garimella and Kraft, 2016), our new perspective is gained by imagining where else this method could be applied. With the exception of axonal injury and structural mechanics, none of the other proposed modeling areas were discussed in the previous publication. For example, in some studies involving chronic traumatic encephalopathy (CTE), electro-magnetics/electro-mechanics, physics-informed structural connectome modeling (Kraft et al., 2012), and mechano-biological applications, this method could be readily used. Whereas, in other areas such as disease modeling, vasculature, neuro-pharmacology, and cancer modeling, we speculate the application of this method based on our perspective of the underlying numerical algorithms. This new perspective is also aided by the fact that the axonal fiber network is explicitly meshed – enabling us to solve any partial differential equation on these discretized fibers. Some of the different ideas and examples that can benefit from this approach are proposed below:

• **Chronic traumatic encephalopathy**: A major prospect of this approach is its capability in acting as a bridge for load transfer from the macro to micro length scales in human brain. The mechanical response, experienced by the individual axonal fiber tracts can be used as input conditions in cellular level models – that can be used in improving our understanding of brain injury. For example, the mechanical response of the axonal fiber tracts can be used as input to high-resolution single axon models. These models can then be used in studying the dynamic response of microtubule bundles and the behaviour of tau proteins – thus enabling us to understand the origin of neuropathological events and the resulting neurodegenerative disorders such as chronic traumatic encephalopathy (CTE) (Gavett et al., 2011; Ghajeri et al., 2017).

• **Electro encephalogram (EEG) applications**: Modeling the axonal tracts could provide high-resolution sources of electrophysiological activity in the brain and can be used in developing advaced electrophysiological models -- thus allowing us to develop structure-function models (Bojak et al., 2010; Finger et al., 2016). These models could be very useful in developing more accurate description of electric field inside the skull – thus producing a more accurate calculation of forward EEG solution (Bangera et al., 2010). Similar to mechanical behaviour, electromagnetic behaviour is shown to be anisotropic (Wolter et al., 2006), and this embedded element approach resolves this anisotropy. Apart from this, the introduction of mechanics into these electrophysiological models might also enable us in developing electromechanical models of axonal pathways and thus full head electromechanical models. These models might be useful in understanding the global electrophysiological deficits caused due to localized structural deformations.

• **Connectome modeling/computational neuroscience**: Some of the recent studies (Jirsa et al., 2010) used connectomics to model brain networks and used ad-hoc deletion of edges and nodes (Alstott et al., 2009) to account for the brain disruption under injurious conditions. However, the model produced here can be used in developing the capabilities of these neuro-computational models by introducing a physics-based approach for injury prediction (Kraft et al., 2012) – and thus structural connectome analysis.

• **Mechanobiological applications**: The white matter informed anisotropic fiber reinforced brain models, when combined with diffusion based growth, might enable us to develop more accurate brain growth models – thus predicting the evolution of axonal strain under these situations. One particular application of these growth models is the prediction of axonal damage during complex surgical operations such as decompressive craniectomy (Weickenmeier et al., 2016).

• **Neuro-disease modelling applications**: Some of the recent studies (Muñoz, 2013), have shown that the progression of some neuro-diseases might be understood more clearly by investigating the spread and buildup of certain proteins along axonal pathways present in the brain. The explicit fiber models, used here, could be used in developing dynamic disease spreading models using finite element and diffusion based techniques. These models might help us understand the propagation of neurodegenerative diseases - whose clinical understanding is currently limited by the inadequate knowledge of evolution and progression of these brain diseases.

• **Vasculature modeling**: As pointed out before, the embedded element technique is a mesh-superposition technique – thus enabling us to incorporate FE meshes of highly complex structures into the brain mesh. Thus, this enables us to include the complex cerebral vasculature structure into the brain model – which were shown to significantly affect the brain response in computational models (Hua et al., 2015). These models might also help us study the origin and evolution of vascular injury under extreme loading scenarios. These models might also be useful in studying the behavior of blood flow during injurious conditions – thus enabling us to model the pathophysiology of drug therapies (Neuropharmacology).

• **Brain cancer modeling**: Previous research (Swanson et al., 2000) produced observations showing that glioma cells migrate quickly (faster growth) in white matter compared to grey matter (Jbabdi et al., 2005). The migration of these cells tend to prefer the direction of fiber tracts (Belien et al., 1999; Swanson et al., 2000; Yoshida et al., 2002; Giese et al., 2003; Jbabdi et al., 2005). Thus, growth models of these cells (modeled using diffusion principles) along the explicit axonal fiber tracts could prove to be a useful tool in analyzing the resulting mechanical deformations induced in the surrounding tissue. This could be particularly promising in surgical applications (Mori et al., 2002).

We should also note the possible connection between physical models of axonal injury and the modeling of functional deficiencies in brain dynamics. Previous efforts focused on modeling brain function, where some explored the role of structure (as given by diffusion tensor imaging) (Greicius et al, 2009; Honey et al., 2009) in the functional activity. In this way the embedded element method for structural connectomes could be combined with existing functional connectome models to elucidate possible brain structure-function relationships, which would be especially interesting for brain damage, *i.e*., the study of damaged connectomes. This would only be enabled by the explicit representation of axonal tracts (that form the brain networks), as is done in the embedded element approach.

Limitations

While this method has several advantages, and could be used in different modeling approaches as discussed above, we should also be careful about its limitations including volume redundancy and interpenetration (inbiomechanical applications). An in-depth discussion on the limitations associated with this technique (and the ways in which these limitations can be addressed) was included in our publication (Garimella and Kraft, 2016).

Conclusion

Computational modeling has been used to study a wide range of physics in the brain. However, as we gain more knowledge about how the brain works, we will need new methods that enable interconnected models. In this manuscript, we have provided some perspectives about how the embedded element method has the potential to connect these currently disjointed areas. This is made possible because of the explicit representation of axonal fiber tracts the embedded element enables. A model integrating these different approaches could enhance our understanding of the pathophysiology underlying the different brain injury or disease mechanisms – resulting in the development of improved diagnostic tools and regeneration technologies.

Acknowledgments: *The authors thank Dr. Sam Slobounov and Dr. Brian D. Johnson for the data provided. All the DTI/DSI data used here is being provided by The Pennsylvania State University Center for Sports Concussion Research and Service, University Park, USA. This work was supported in part through an instrumentation grant funded by the National Science Foundation through grant OCI-0821527. We would also like to acknowledge The Pennsylvania State University Social, Life, and Engineering Sciences Imaging Center (SLEIC), High Field MRI Facility for providing access to the imaging equipment. The authors thank The Pennsylvania State University Institute for Cyberscience for providing the computational resources required for this work.*

Author contributions: *HTG and RHK designed the study, developed the method, interpreted its potential applications, drafted the paper and revised the paper.*

Conflicts of interest: *None declared.*

References

Alstott J, Breakspear M, Hagmann P, Cammoun L, Sporns O (2009) Modeling the impact of lesions in the human brain. PLoS Comput Biol 5:e1000408.

Bangera NB, Schomer DL, Dehghani N, Ulbert I, Cash S, Papavasiliou S, Eisenberg SR, Dale AM, Halgren E (2010) Experimental validation of the influence of white matter anisotropy on the intracranial EEG forward solution. J Comput Neurosci 29:371-387.

Belien AT, Paganetti PA, Schwab ME (1999) Membrane-type 1 matrix metalloprotease (MT1-MMP) enables invasive migration of glioma cells in central nervous system white matter. J Cell Biol 144:373-384.

Bojak I, Oostendorp TF, Reid AT, Kotter R (2010) Connecting mean field models of neural activity to EEG and fMRI data. Brain Topogr 23:139-149.

Finger H, Bönstrup M, Cheng B, Messé A, Hilgetag C, Thomalla G, Gerloff C, König P (2016) Modeling of large-scale functional brain networks based on structural connectivity from DTI: comparison with EEG derived phase coupling networks and evaluation of alternative methods along the modeling path. PLoS Comput Biol 12:e1005025.

Garimella HT, Kraft RH (2016) Modeling the mechanics of axonal fiber tracts using the embedded finite element method. Int J Numer Method Biomed Eng doi:10.1002/cnm.2823.

Garimella HT, Kraft RH (2016) Validation of embedded element method in the prediction of white matter disruptions in concussions. Proceedings of the International Mechanical Engineering Congress and Explosion ASME IMECE 2016, November 11-17, 2016, Phoenix, Arizona, USA.

Garimella HT, Yuan H, Johnson BD, Sloubounov SL, Kraft RH (2014) A two fiber anisotropic constitutive model of Human Brain with intravoxel heterogenity of fiber orientation using Diffusion Spectrum Imaging. ASME IMECE2014-39107:V003T03A011.

Gavett BE, Stern RA, McKee AC (2011) Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. Clin Sports Med 30:179-188, xi.

Ghajari M, Hellyer PJ, Sharp DJ (2017) Computational modelling of traumatic brain injury predicts the location of chronic traumatic encephalopathy pathology. Brain doi:10.1093/brain/aww317.

Giese A, Bjerkvig R, Berens ME, Westphal M (2003) Cost of migration: invasion of malignant gliomas and implications for treatment. J Clin Oncol 21:1624-1636.

Greicius MD, Supekar K, Menon V, Dougherty RF (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 19:72-78.

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P (2009) Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A 106:2035-2040.

Hua Y, Lin S, Gu L (2015) Relevance of blood vessel networks in blast-induced traumatic brain injury. Comput Math Methods Med 2015:928236.

Jbabdi S, Mandonnet E, Duffau H, Capelle L, Swanson KR, Pelegrini-Issac M, Guillevin R, Benali H (2005) Simulation of anisotropic growth of low-grade gliomas using diffusion tensor imaging. Magn Reson Med 54:616-624.

Ji S, Zhao W, Ford JC, Beckwith JG, Bolander RP, Greenwald RM, Flashman LA, Paulsen KD, McAllister TW (2015) Group-wise evaluation and comparison of white matter fiber strain and maximum principal strain in sports-related concussion. J Neurotrauma 32:441-454.

Jirsa VK, Sporns O, Breakspear M, Deco G, McIntosh AR (2010) Towards the virtual brain: network modeling of the intact and the damaged brain. Arch Ital Biol 148:189-205.

Kraft RH, McKee PJ, Dagro AM, Grafton ST (2012) Combining the finite element method with structural connectome-based analysis for modeling neurotrauma: connectome neurotrauma mechanics. PLoS Comput Biol 8:e1002619.

Mori S, Frederiksen K, van Zijl PC, Stieltjes B, Kraut MA, Solaiyappan M, Pomper MG (2002) Brain white matter anatomy of tumor patients evaluated with diffusion tensor imaging. Ann Neurol 51:377-380.

Muñoz S (2013) Time-varying network models of neurodegenerative disease spread in biological neural networks. SUNFEST:64.

Papagno C (2011) Naming and the role of the uncinate fasciculus in language function. Curr Neurol Neurosci Rep 11:553-559.

Pedersen PH, Edvardsen K, Garcia-Cabrera I, Mahesparan R, Thorsen J, Mathisen B, Rosenblum ML, Bjerkvig R (1995) Migratory patterns of lac-z transfected human glioma cells in the rat brain. Int J Cancer 62:767-771.

Swanson KR, Alvord EC, Jr., Murray JD (2000) A quantitative model for differential motility of gliomas in grey and white matter. Cell Prolif 33:317-329.

Weickenmeier J, Butler CAM, oung PG, Goriely A, Kuhl E (2016) The mechanics of decompressive craniectomy : Personalized simulations. Comput Methods Appl Mech Eng doi:10.1016/j.cma.2016.08.011.

Wolters CH, Anwander A, Tricoche X, Weinstein D, Koch MA, MacLeod RS (2006) Influence of tissue conductivity anisotropy on EEG/MEG field and return current computation in a realistic head model: a simulation and visualization study using high-resolution finite element modeling. Neuroimage 30:813-826.

Wright RM, Post A, Hoshizaki B, Ramesh KT (2013) A multiscale computational approach to estimating axonal damage under inertial loading of the head. J Neurotrauma 30:102-118.

Yoshida D, Watanabe K, Noha M, Takahashi H, Teramoto A, Sugisaki Y (2002) Tracking cell invasion of human glioma cells and suppression by anti-matrix metalloproteinase agent in rodent brain-slice model. Brain Tumor Pathol 19:69-76.