A Transition Model for Finite Element Simulation of Kinematics of Central Nervous System White Matter

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Abstract-Mechanical damage to axons is a proximal cause of deficits following traumatic brain injury and spinal cord injury. Axons are injured predominantly by tensile strain, and identifying the strain experienced by axons is a critical step toward injury prevention. White matter demonstrates complex nonlinear mechanical behavior at the continuum level that evolves from even more complex, dynamic, and composite behavior between axons and the "glial matrix" at the microlevel. In situ, axons maintain an undulated state that depends on the location of the white matter and the stage of neurodevelopment. When exposed to tissue strain, axons do not demonstrate pure affine or non-affine behavior, but instead transition from non-affine-dominated kinematics at low stretch levels to affine kinematics at high stretch levels. This transitional and predominant kinematic behavior has been linked to the natural coupling of axons to each other via the glial matrix. In this paper, a transitional kinematic model is applied to a micromechanics finite element model to simulate the axonal behavior within a white matter tissue subjected to uniaxial tensile stretch. The effects of the transition parameters and the volume fraction of axons on axonal behavior is evaluated and compared to previous experimental data and numerical simulations.

Index Terms—Finite element methods, kinematics, transition kinematic model, white matter.

I. INTRODUCTION

XONAL injury is a primary cause for functional deficits following traumatic brain injury (TBI) and spinal cord injury (SCI), and therefore represents a critical target for injury prevention and treatment. Mechanical strain has been identified as the proximal cause of axonal injury, while secondary ischaemic and excitotoxic insults associated with the primary trauma potentially exacerbate the structural and functional

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damage [1], [2]. Many studies have attempted to identify the states of stress and strain in white matter using animal and finite element models and, sequentially, establish injury criteria through the use of actual accident data [3]–[11]. The material models employed in these finite element simulations of central nervous system (CNS) soft tissues heavily depend on phenomenological representations. The accuracy of these simulations depends not only on correct determination of the material properties, but also on precise depiction of the tissues' microstructure.

There have been several studies that have examined the kinematic response of axons in white matter axons to understand the micromechanical behavior and how the axons contribute to bulk, continuum level properties. Kinematic properties have been inferred from changes in axon morphology when the tissue is exposed to controlled stretch. The first studies by Bain *et al.* [12], using a guinea pig optic nerve model, demonstrated that: 1) axons maintain an initial undulated state; 2) axons straighten during stretch; and 3) axons do not demonstrate pure affine or non-affine behavior, but instead transition from non-affine-dominated kinematics at low stretch levels to affine kinematics at high stretch levels. Affine here (also in [12]) refers to the perfectly bonded of the interface of two different constituents within a composite.

This transition and the predominant kinematic behavior were then linked to the natural coupling of axons to each other via the glial matrix, especially oligodendrocytes that interconnect axons through myelination [13]. Axon kinematics was evaluated in the chick embryo spinal cord at different stages of myelination. Early in development, before significant myelination and, presumably, coupling via oligodendrocytes, non-affine kinematics dominated. As myelination increased, affine behavior became more prevalent [13] and tissue tensile stiffness also increased. When myelination was disrupted in the developing chick embryo by killing glia or by interfering with the connections of oligodendrocytes to axons, a significant decrease in the stiffness and strength of the tissue was observed [14].

These results support the notion that the degree of coupling within the tissue affects the continuum mechanical properties. Additionally, the degree of undulation and interaxonal coupling will also affect the strain experienced by an individual axon, and, therefore, when it becomes injured. Given this complex response of fibers within axon bundles in white matter, a microstructural finite element model (FEM) is necessary for an accurate representation of axon mechanics. A previous study implemented a representative volume element (RVE) approach to axon mechanics [10], but assumed fully coupled kinematics and produced results that did not match well with experimental observations. Herein we present an approach to generate and implement an RVE with adjustable kinematics. We adapted the transitional kinematic model (TKM) proposed in [12] to a micromechanical finite element analysis. In this TKM, when the undulation is greater than a critical value, the axon and matrix deform non-affinely. When the undulation is less than the critical value, the axon partially switches to deform affinely with the matrix.

II. TRANSITIONAL KINEMATIC MODEL

A kinematic switching model was implemented based on previous kinematic interpretations of experimental results of the mechanical behavior of CNS white matter. The ABAQUS finite element package [15] and python scripting language are used for the analyses. The model assumes that the fraction of the axonal and glial populations experiencing affine deformation increases with applied elongation [12]. The microstructural behavior of tissue component was successfully represented by a transitional model that assumes a gradual coupling of the glial matrix to the undulated axons, where each axon displays a unique tortuosity at which it transitions from non–affine to affine behavior.

The pure affine model, the non-affine model, and the microstructural transitional model are briefly described herein. For an undulated axon, the tortuosity (T) is defined as the ratio of the true length and end-to-end length of an undulated axon. Following Bain *et al.*'s work, the geometry of an undulated axon can be modeled as a periodic wave [12]:

$$y(z) = A_0 \cos\left(\frac{2\pi z}{P_0}\right) \tag{1}$$

where A_0 and P_0 are the amplitude and period of the wave and z is the axis along the length of the axon. For the pure affine model, the tortuosity of the deformed axon can be approximated based on the applied stretch level (λ) and its initial tortuosity (T_0)

$$T_t = T_0 \left[\frac{1}{\lambda^3} + \frac{1}{T_0^2} \left(1 - \frac{1}{\lambda^3} \right) \right]^{1/2}.$$
 (2)

For the non-affine model,

$$T_t = \frac{1}{\lambda} T_0, \text{ for } \lambda < T_0 \text{ and } T_t = 1.0, \text{ for } \lambda \ge T_0$$
 (3)

In the case of the TKM, the critical transitional tortuosities of all axons within the tissue constitute a transitional interval, $[T_1, T_2]$, defined by a lower bound T_1 and an upper bound T_2 . For $T < T_1$, axons are coupled to the surrounding cells, while for $T > T_2$, axons are not affected by the glial cell matrix and are uncoupled to them. For the guinea pig optic nerve white matter, the lower and upper bounds are 0.98 and 1.08, respectively.

To implement the transitional model in a finite element framework, each axon was assigned a tortuosity value drawn randomly from a uniform distribution in the interval, [0.98, 1.08], at which it switches from non-affine to affine. Since tortuosity can never be lower than 1.0, which corresponds to a perfectly straight axon, the percentage of axons that will never switch to affine is

TABLE I PERCENTAGE OF TIE CONSTRAINT OF THE AXON/EXTRACELLULAR MATRIX INTERFACE AT DIFFERENT STRETCH LEVELS

Stretch Levels	Percentage of Tie Constraint
1.0	8%
1.06	20%
1.12	44%

20%, no matter how much stretch is applied. The histogram of axon tortuosity in [12] is used to approximate the percentage of axons that may switch from non-affine to affine at a given stretch level. First, a uniform distribution is mapped onto the distribution of axons with a tortuosity between 1.0 and 1.08, at which an axon possibly switches. Second, to approximate the number, the histograms are binned into 0.02 bins, i.e., [1.0, 1.02], [1.02, 1.04], [1.04, 1.06], [1.06, 1.08], with corresponding possibility of switching of 100%, 75%, 50%, and 25%. Using data from the histograms of different stretching ratio, the percentages of axons that have been coupled to the cellular matrix at stretching ratio of 1.0, 1.06, and 1.12 are 8%, 20%, and 44%, respectively, as on Table I. In a FEM application, when the axons and matrix are partially coupled, "tie" constraints are applied to the nodes of a certain percentage of the axon/matrix interface according to the axon's current tortuosity. The rest of the axon/matrix interface is left uncoupled for the frictionless contact.

III. MICROMECHANICS-BASED FINITE ELEMENT METHOD

By taking the advantage of the known kinematics of axons and surrounding cellular matrix, one may implement the model into a FEM to investigate the stress and strain fields of the tissue that have been found to be responsible for mechanical damage to the axons [1]. The stress and the strain fields of a given domain can be simulated with direct 3D finite element analysis [10], [11], [16], if the constituents' mechanical properties and proper boundary conditions (BCs) are known. If the domain is suitably selected so that it reflects the microstructure of the soft tissue, i.e., the geometry and distribution of the axons and the matrix, the macroscopic material properties can thus be derived from the response of the selected domain, which is called a representative volume element (RVE) of the heterogeneous material, see more discussion on RVE size and its representation in [17].

In this simulation, an RVE that consists of six serial segments of undulated axons and matrix for the white matter microstructure is generated (see Fig. 1). From simulations in [10], we set our initial volume fraction (v_f) of axons at 53%. Each segment can be prescribed a different degree of tortuosity by defining the undulation of the segment with a cosine wave. Segments one through six having representing tortuosities 1.17, 1.05, 1.26, 1.13, 1.09, 1.21, respectively. The resulting average tortuosity of the whole RVE is 1.13, which was chosen to match the data described in [12]. Three different RVEs (A, B, and C) are statistically generated each having unique tie locales (see Fig. 1). Axons and glia matrix are each represented by the Ogden isotropic, large deformation, hyperelastic material model



Fig. 1. Illustration of tie locations along the axonal direction for three RVEs (A, B, and C) at different applied stretch levels (λ equals 1.0, 1.06, and 1.12) of the TKM. The locations where the extracellular matrix is tied to the axon are marked in red color. The initial tortuosities of axon segments 1 through 6 are also labeled. The cross-section of the RVE is illustrated in the inset.

in the strain energy form [10], [18]:

$$W = \frac{2\mu}{\alpha^2} (\lambda_1^{\alpha} + \lambda_2^{\alpha} + \lambda_3^{\alpha} - 3)$$
(4)

where μ and α are material parameters, and λ_i are principal stretches. The Ogden model has been applied to describe soft tissues at the continuum level. Meaney [18] developed a microstructure model, which differentiates the behaviors of the axon and the surrounding matrix, to explain the behavior of guinea pig's optic nerve. The material parameters were given by comparing the structural model with an equivalent Ogden's model. Based on works in [3], [18], Karami *et al.* has justified $\mu = 290.8$ Pa for axon and $\mu = 96.9$ Pa for matrix, and $\alpha = 6.19$ for both [10], which are also used here.

The degree of interaction between the axon and glia is controlled by altering the percentage of tied nodes at the axon/matrix interface. General frictionless surface contact is applied to the interface, but "tie" constraints are partially applied to introduce glial coupling. Only nodes in segments with tortuosity smaller than 1.08 are eligible to be tied. When using the TKM, we assume that the model derived from the experimental data on the real tissue consisting of a large number of axons is also applicable to a single axon consisting of several segments with different tortuosities. The RVE is stretched to stretch ratios of 1.06, 1.12, and 1.25, which represent the stretch levels at which undulation was characterized, as in [12], in sequential steps. The percentage of tied area in those segments is updated as described in Table I. In steps from 1.06 to 1.12 and from 1.12 to 1.25, import analyses are performed using the updated tied conditions and the results stored in the immediate previous step. Three models are run for each volume fraction, which differ by randomly assigning the tied locations along the length of the axon. The tied locations are illustrated stepwise in Fig. 1 along with the deformed profiles along the axon direction. Periodic boundary conditions are applied to the RVE to mimic the constraint exerting on the RVE by its neighboring RVEs. The periodic bound conditions are given as





Fig. 2. Tortuosity of individual axon segments decreases due to stretching. Large initial tortoucities are presented with faster axon undulation as the applied strain increases.

where u_i is the displacement component on the surface of the RVE, L_j is a periodic vector of periodicity, and $\bar{\varepsilon}_{ij}^0$ is a averaged strain being applied. The periodic vector is a vector from a point in one RVE to a corresponding point in another unit cell. In this paper, all components of $\bar{\varepsilon}_{ij}^0$ vanish except $\bar{\varepsilon}_{33}^0$, where subscript 3 is along the global axon direction. The performance of the model is evaluated by comparing the predicted average tortuosity at each stretch level to the experimental results in Bain *et al.* [12].

IV. RESULTS

A typical change of segmental tortuosity along with the applied strain levels is illustrated in Fig. 2. The tortuosity of highly undulated segments, which demonstrate non-affine kinematics, decreases drastically with increasing stretch. As the applied strain level increases and axon segments become less undulated, coupling is gradually engaged to the axons and matrix and the tortuosity decreases slowly.

The overall tortuosity of RVEs decreases as the applied stretch level increases as plotted in Fig. 3. Although the tied locations along the axon segment are randomly assigned (as illustrated in Fig. 1), the overall curves are very consistent for both models with axon v_f of 53% and 80%. When there is no extracellular matrix and axons behavior is purely non-affine, tortuosity continues to decrease until all axons are perfectly straight. This should occur when the stretch level reaches the maximum tortuosity of the unstretched axons. The tortuosity of an RVE with higher axon volume fraction decreases more rapidly than that with lower axon volume fraction, likely because less extracellular matrix introduces a smaller coupling effect on the behavior of axons. Therefore, as the axon volume fraction increases, the tortuosity change curve resides closer to the non-affine regime. Predictions from the analytical non-affine and affine models in [12] are also shown in Fig. 3.

The tortuosity changes measured in experiments and predicted by other numerical models, such as a pure affine micromechanics model in [10] and partially tied model in [11] are also plotted. Karami *et al.*'s micromechanics FE model



Fig. 3. Comparison of model predictions on overall tortuosity change with applied strains. Experimental data are from [12]. The randomly tied axons with v_f of 53% and 80% present close correlation to the experimental data.



Fig. 4. Comparison of predicted stress–strain behavior of the TKM and the models in [10] and [11]. The tie levels at different stretch intervals for the TKM RVEs are: 8% for [1, 1.06], 20% for [1.06, 1.12], and 44% for [1.12, 1.25]. As seen, increased coupling between axons and matrix (namely, tie recruitment) results in stiffening of the white matter.

assumes that axons and extracellular matrix are perfectly bonded together [10]. Hence, tortuosity evolution of their model is very close to that from the analytical affine model given in (2). Both of these models predict a very slow drop of tortuosity when an RVE subjects to uniaxial loading as compared to the experimental data. We improved the micromechanics FE model by applying partial coupling to the axon and matrix [11]. By prescribing only 5% of the axon/matrix interface as tied, the evolution of tortuosity began to approach the experimental averages reported by Bain *et al.* [12], but did not decrease as quickly at small strains.

The RVE stress–strain curves of the current TKM, the partially tied model in [11], and the perfectly bonded model in [10] are plotted in Fig. 4 (axon v_f of 53%). As demonstrated, the stiffness of the transitional kinematic model at stretch level up to 1.12 (5–20% tie) is smaller than that in the other two models, whereas it becomes larger at higher stretch levels (44% tie) as the extracellular matrix coupling with the axon is increased resulting in stiffened material behavior [14]. The perfectly bonded model yields the largest stiffness among the models at small stretch ($\lambda < 1.12$).

V. CONCLUSION

In this transition model, both RVEs with axon volume fraction of 53% and 80% yield satisfactory curves very close to the experimental results. The current transitional model yields much better prediction on the tortuosity changes resulting from uniaxial stretching than the pure affine kinematics model through perfect bonding of axon and matrix and the partially tied model. Currently, the RVEs only consist of limited segments having representative tortuosities ranging from 1.05 to 1.26. A more desirable 3-D micro-structural tissue model that consists of a large amount of axons having the statistical signature of a real tissue is being explored. The correct kinematics of axon and matrix is also critical for future stress and strain field analysis using the finite element method.

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