Finite Element Modeling of Diffuse Axonal Injury Using Histologically Informed Microtubule Placements

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I. INTRODUCTION

Diffuse Axonal Injury (DAI), a subclass of Traumatic Brain Injury (TBI), is characterised by disruptions in white-matter axons. Although past studies have put great effort into understanding the pathogenesis of DAI, its exact mechanisms have yet to be fully revealed. Recent studies have proposed multi-scale in silico modeling frameworks down to the cellular and subcellular level for DAI investigation [1–3], of which the influence of a heterogeneous axonal cytoskeleton and the intracellular components on the mechanical response was considered. Despite the rich detail in such models, few studies have included the implementation of histological context with regards to microtubule (MT) terminations that occur in the axonal cytoskeleton. Zhang and Ji previously studied the significance of a random MT gap distribution using a bi-variate statistical model, where a normal distribution based on histological data was employed [4]. However, distributions of MT lengths have been found to be strongly right-skewed in histological data [5–6]. Moreover, there is a lack of data on MT lengths in mammalian axons and facets of MT distribution left to be explored within mechanical simulations. This study aims to advance the detail of our existing finite element (FE) axon model and investigate how using a histologically based MT length and termination distribution might affect injury thresholds.

II. METHODS

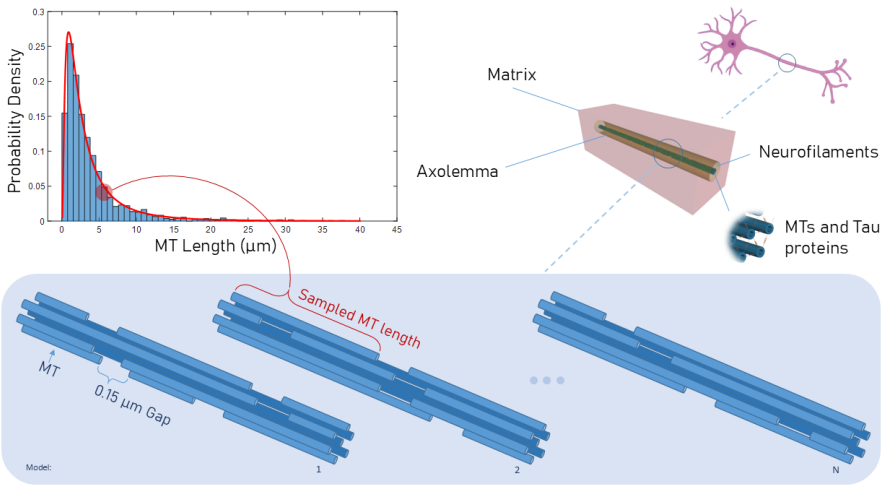

Fig. 1: Stochastic sampling of microtubule (MT) lengths for model creation.

Through the further advancement of a previously developed FE axon model [2–3], an automated modeling procedure was created that stochastically distributes MT terminations among 19 rows of MTs in a hexagonal array in an 8 µm distal segment of an axon (Fig. 1). Two separate studies were used to estimate two different stochastic distributions of MT lengths in hippocampal neurons, referred to as Distribution 1 [5] and Distribution 2 [6]. To determine the amount of models needed in order to get a proper representation of the stochastical variance of the mechanical response, Monte Carlo confidence-interval-based convergence was used, based on the 1st (maximum) principal Green-Lagrange axolemmal strain as an injury metric for mechanoporation [2]. After each additional model, the running mean and 95% confidence interval of the maximum strain were updated, and the number of models were considered sufficient when the relative half-width of the 95% confidence interval fell below a predefined tolerance (TBD). For comparison with the mechanical response of previous models, a reference model using a constant MT length of 4.02 µm [5] was created. A global uniaxal axonal strain of 25% was imposed using periodic boundary conditions, with a strain rate of 40 1/s, imposing rapid stretch for all models.

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III. INITIAL FINDINGS

For each of the two distributions, 30 models were generated and subjected to uniaxial stretching, characterised by the global axonal strain. The results revealed cross-model variations in axolemmal strain, with the magnitude of variation increasing with the level of global axonal strain in both distributions (Fig. 2). With this amount of model realisations, the relative half-width of the 95% confidence interval was 0.04 for Distribution 1, and 0.03 for Distribution 2, corresponding to a relative precision of 4% and 3%, respectively, in the estimated mean of the 1st principal axolemmal strain. The response of the reference model with a constant MT length is included as a baseline comparison. Upon visual inspection, strain localisations in the axolemma are largely coincident with areas that have high MT termination density. An example of this can be seen in Fig. 3, where the strain fringes of the axolemma and MTs are isolated from the rest of the cytoskeletal components.

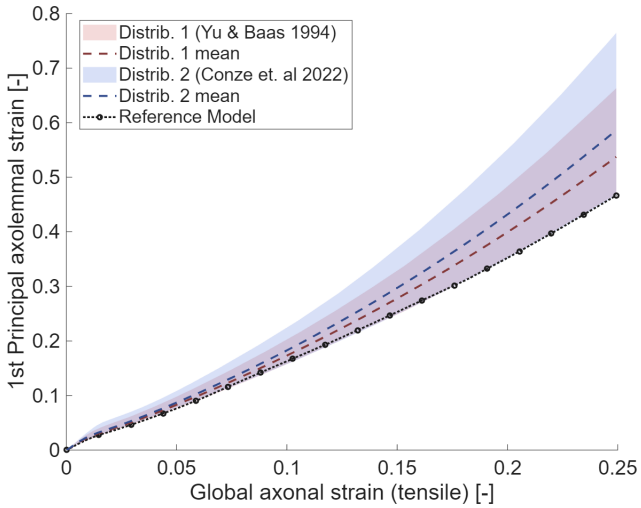

Fig. 2: 1st Principal Green-Lagrange strain in the axolemma during the injury process, using two distributions to represent stochastic MT termination placements.

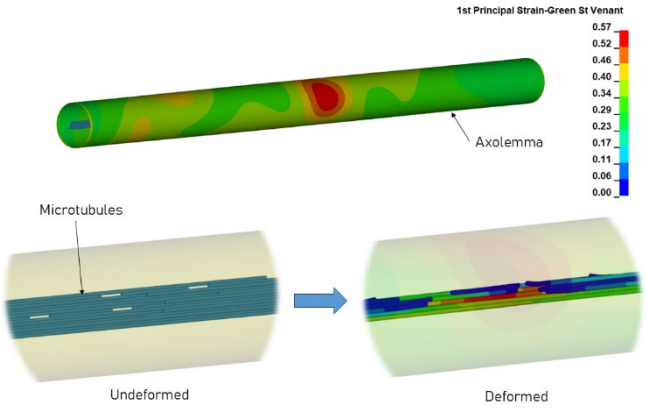

Fig. 3: Example of strain localisation in the axolemma (upper row), coincident with areas that have a high termination density (lower row, with transparent axolemma).

IV. DISCUSSION

The variation in the mechanical response seen in Fig. 2, suggests a strong influence of the frequency and location of MT terminations. Using the 1st principal axolemmal strain as an injury metric for mechanoporation, a simplified assumption of a constant MT length may greatly underestimate the strain. This is due to the stochastic appearance of the localisation of MT termination gaps, that have the chance to appear in varying degrees when using a histology-based distribution. With larger gap clustering, the axolemma becomes more load bearing, resulting in strain localisation in these areas. This can be confirmed when comparing the location of clustered gaps and the largest strains present in the axolemma. Our finding highlights the importance of the MT length and termination position when investigating axonal injury in uniaxial tension, which is relevant for further simulation of DAI and the investigations of the injury mechanisms involved.

Since the MT length distributions stem from embryonic rat and mouse hippocampal neurons in culture embryonic hippocampal neuron cultures [5–6], they likely underrepresent the structural heterogeneity of mature human white-matter axons. Because cultured embryonic axons exhibit distinct differences such as developmental dynamics and potentially shorter MT polymers than adult long-tract axons, the resulting estimates of MT overlap and termination density should be interpreted as approximate rather than definitive. Despite this, the results highlight the significance of the occurrence of these termination gap clusters when determining injury thresholds, regardless of the distribution that is used.

V. REFERENCES

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