SHORT COMMUNICATION: STAPP CAR CRASH CONFERENCE

Micromechanics of axonal injury in rapid tension and compression

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ABSTRACT – This study investigates the deformation and failure mechanisms of axonal components under rapid tension and compression using a recently developed microscale male axonal injury model. A white matter fiber strain profile from a real-world head impact simulation was scaled to apply tension and compression of up to 40% peak strain magnitude at a 5% increment as input. Axonal injury model simulations were successful without any numerical issue for all inputs with peak magnitude up to 35% for both tension and compression. Tension led to significant microtubule strain. In contrast, compression led to microtubule bending and buckling with minimal axial strain and no tau protein failure but higher neurofilament failure and axolemma strain due to microtubule undulation and contact. The distinct responses in tension and compression provide insights into the micromechanics of traumatic axonal injury and set the stage for further investigations using sex-specific axonal injury models in the future.

INTRODUCTION

A microscale axonal injury model estimates mechanical responses of various cytoskeletal components resulting from an impulsive load. The responses could inform the risk and level of sub-cellular damages such as microtubule (MT) breakage, failure of crosslinking tau proteins, neurofilaments (NF), and axolemma mechanoporation. Such a model is invaluable for the investigation of various triggering mechanisms of traumatic axonal injury (TAI).

A number of axonal injury models have been developed. However, most of them are limited to studying responses of a single MT or a bundle of MTs crosslinked by MT-associated protein (Peter and Mofrad 2012; Soheilypour et al. 2015). More recent axonal models include other mechanically relevant structures such as NF, axolemma, myelin, and Ranvier node, in addition to an isolated MT bundle (Zhu et al. 2016; Montanino and Kleiven 2018). Nevertheless, they remain limited to studying tension only with an assumed peak strain magnitude and strain rate, but without considering load recovery for the axon to return to an initial, (globally) undeformed state that is more realistic for real-world mild traumatic brain injury (mTBI), given that no apparent residual strain is anticipated in such an injury or sub-injury scenario.

Recently, our group has developed male and female axonal injury models to investigate the TAI triggering mechanisms (Zhang and Ji 2023). The models include all major axonal structures with the geometry of the axonal cross-section and the number of MTs reflecting the newfound sex differences in cultured human axons (Dollé et al. 2018). Using these sex-specific axonal injury models, a white matter fiber strain profile obtained from a real-world global head injury model simulation was used for microscale simulation. The profile was a complete cycle of tension that included a recovery phase to approximately return to a (global) zero-strain state. Both models successfully completed tension simulation at a peak strain magnitude of 18% at a strain rate of 9.5 s^{-1} and -19 s^{-1} for the loading and recovery phase, respectively. Further sensitivity study revealed that the models successfully completed simulation of peak strain at 30% and strain rate of 44 s^{-1}. The ability to complete simulation without numerical convergence issue is crucial, as it would avoid unrealistic constraint of the model to deform only along the axial direction due to the notorious "convergence issue" (Montanino and Kleiven 2018).

The challenge in axonal injury modeling is due to the use of a dynamic implicit non-linear solver and significant "contact" between various cytoskeletal components. In this study, we further stress-test the extent of input loading conditions for successful simulation of the male axonal injury model under rapid tension and compression, both of which can cause injury. Successful simulation with the male axonal injury model is more "challenging" than the female counterpart because of the greater number of MTs (13 for the male vs. 7 for the female (Zhang and Ji 2023)) that would exacerbate the nonlinear contact problem. This study provides insight into the range of admissible input for successful axonal injury modeling

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using the newly developed sex-specific axonal injury models.

METHODS

Baseline male and female axonal injury models were previously developed based on the morphology of cultured human axons in the corpus callosum (Zhang and Ji 2023). To reflect the average cross-sectional MTs—12 and 8 for the male and female, respectively (Dollé et al. 2018)—13 and 7 MTs were used for the male and female model, respectively. The MTs form a hexagonal pattern (thus, the number of MTs differed from experiment by 1). MT gaps were randomly generated by removing a ‘‘ring’’ of elements across the cross-section following an assumed normal distribution based on statistics from experiments.

Both models are 8 μm in length that incorporate MTs, tau, NFs, axolemma, myelin sheath, and extracellular matrix (ECM). MTs, axolemma, myelin sheath, and ECM were modeled as hexahedral solid elements (C3D8R). All other cytoskeletal connections were modeled using line connector elements (CONN3D2). The male model has a total of ~76.5 k solid elements and ~214.5 k connector elements, vs. ~71.7 k solid elements and ~204.4 k connector elements for the female model (excluding ECM). For MTs, axolemma, tau and NFs, a failure strain threshold of 50%, 34%, 100% and 100% was applied, respectively, based on literature. Once element strain reaches the threshold, it is (gradually) removed from simulation. Detailed model descriptions, various parameters, and extensive validations are reported earlier (Zhang and Ji 2023).

Using the same earlier fiber strain profile (Zhang and Ji 2023), we parametrically scaled the magnitude so that the peak strain ranged from -40% (compression) to 40% (tension) at a step size of 5% (excluding 0%). The same impulse duration was maintained. They were then each applied as input to the male axonal injury model for simulation, where appropriate axial displacements were prescribed to the two model ends. All other nodes were unconstrained to model a realistic axonal deformation in full six degrees of freedom (6 DOFs). Model simulation results were checked upon completion to identify the largest

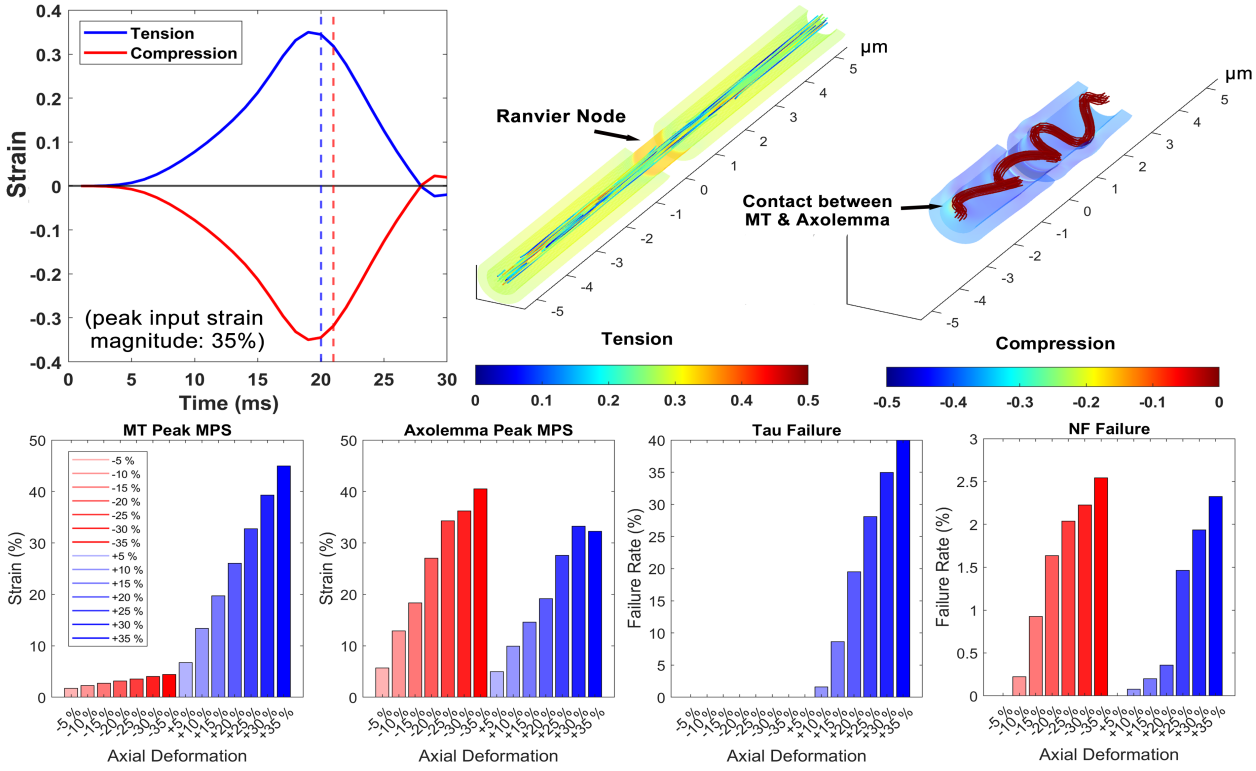

Figure 1. Normalized white matter fiber strain profile are used as input to the male axonal injury model. Under the largest compression and tension for successful simulation (at -35% and 35%, respectively; top left), the corresponding axonal deformation and axial strain, e33, are shown at the time of the largest MT maximum principal strain (MPS; upper right, as indicated in the strain profile in the upper left figure). The bottom row reports peak MPS of MT and axolemma as well as failure rates (in %) of tau and NF relative to input strain magnitude. Unlike in tension, MTs in compression mostly undergo bending and buckling, with little axial strain and no tau failure. However, compression led to higher NF failure rates and axolemma strains due to MT undulation and contact.

tension and compression peak strain magnitudes with successful model simulations, free of any numerical convergence issue to cause simulation failure. Results of peak strains in MTs, axolemma, as well as element length-weighted percentages of failure for tau and NFs were then compiled and compared.

RESULTS

The largest tension and compression peak magnitudes with successful model simulation were both 35%, at an average strain rate magnitude of 25 s^{-1} over the impulse duration (instantaneous peak strain rate of 51.5 s^{-1}). Axonal deformation at the largest MT maximum principal strain (MPS) is shown in **Figure 1** for the two loading conditions. Simulations failed at 40% strain for both tension and compression. The bottom row in the figure shows peak MPS of MT and axolemma as well as failure rates of tau and NF. Compression caused significant MT buckling but with minimal MT strain and no tau failure compared to tension. However, it also led to a higher axolemma strain and NF failure rate due to significant MT undulation and the resulting contact with axolemma. In tension, axolemma peak MPS showed a sudden increase during the unloading phase as a result of MT-axolemma contact (not shown). In large compression, significant MT-axolemma contact also caused axolemma to fail. No MT breakage occurred in any of the simulations in this study. **Figure 2** compares axonal deformation at the end of the load recovery phase, which was maintained even after load removal.

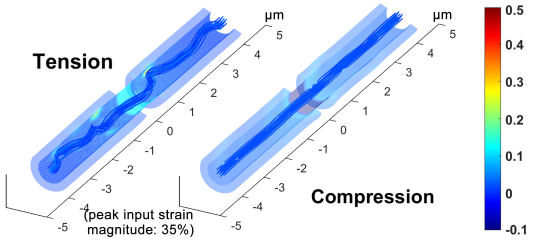

Figure 2. Deformation at the end of the load recovery phase for tension (left) and compression (right).

DISCUSSION

The extremely small physical dimension of the axonal model (e.g., 8 μm in length along the axial direction and 0.6 μm in diameter of the axolemma for the male axon model, compared to centimeters for the global brain model) makes it infeasible to use an explicit scheme for axonal injury simulation. Therefore, implicit dynamic scheme is typically used. However, this approach is susceptible to modeling convergence issues due to significant "contact" between various structural components. As a result, some axonal injury models constrain nodal motion to only occur in the axial direction (Montanino and Kleiven 2018). This is not realistic as it precludes reproducing MT undulation known to occur in experiments.

Here, we stress-tested the newly developed male axonal injury model to identify the maximum tension and compression strain magnitudes for successful simulation in full 6 DOFs, without any unrealistic nodal constraints. We found that the largest peak input strains with successful simulations without any convergence issue were 35% for both tension and compression. Compression led to MT bending and buckling, resulting in minimal axial strain and no tau protein failure but higher axolemma strain and NF failure compared to tension.

For the female axonal injury model, we expect larger admissible input strain magnitudes for successful tension and compression simulation. This is because the female model includes fewer MTs across the axonal cross-section. Thus, less severe contact is anticipated between axonal components, which would alleviate numerical challenges in model simulation.

These results are important to understand the admissible loading conditions for the newly developed sex-specific axonal injury models. They are important for designing a training dataset to develop a deep learning axonal injury model for much more efficient simulation (e.g., <1 sec vs. hours otherwise). The deep learning surrogate would be critical for enabling large-scale biomechanical modeling of TAI in the future.

Obviously, model responses depend on a range of assumptions (Zhang and Ji 2023). Our axonal injury models do not include slower molecular processes such as protein recruitment or reformation. They are outside the dynamic time frame of consideration here. Nevertheless, our axonal models succeeded in axon-level validations using data from both quasi-static contact and dynamic stretch injury. On the other hand, no quantitative component-level validations are possible at this stage, as no such dynamic experimental data are available to the best of our knowledge.

CONCLUSION

This study successfully stress-tested the male axonal injury model to investigate the deformation and failure mechanisms of various axonal components in tension and compression. These findings provide insights into the micromechanics of TAI and set the stage for further investigations using sex-specific axonal injury models in the future.

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