SB³C2023
Summer Biomechanics, Bioengineering and Biotransport Conference
June 4-8, Vail, CO, USA

SEX DIFFERENCES IN AXON DYNAMIC BEHAVIOR UNDER AXIAL LOADING AND UNLOADING

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INTRODUCTION

Biological sex is a significant risk factor for traumatic brain injury (TBI). However, there has been little attention to sex differences in concussion until recently. Diffuse axonal injury (DAI) is one of most prominent pathologies found in all severities of TBI. At the axonal level, there are significant sex morphological differences as observed in ultrastructure studies (e.g., smaller in microtubule (MT) density and axon cross-sectional area and with fewer MTs than male axons [5]).

To-date, studies on axonal injury are focused on injury triggering mechanisms, such as microtubules (MTs) tear [1], strain concentration around the Ranvier node, [2] and interaction among various axonal substructures [3]. These axonal injury models offer valuable insight into the potential causes of heterogenous DAI pathologies. However, no study exists to investigate sex differences in axonal substructural responses.

To facilitate a systematic investigation into sex differences in DAI at the microscale, we have developed a parameterized modeling approach for automatic and efficient generation of sex-specific axon models according to specified geometrical parameters. In this study, baseline female and male axon models in the corpus callosum with random MT gap locations are generated for model calibration and validation. We then report results of sex differences of MT and Ranvier node peak strain amplification and tau protein and neurofilament (NF) failures under a realistic dynamic input generated from a real-world impact simulation that contains both a loading and an unloading phase.

METHODS

Baseline unit female and male FE models of 8 um in length were developed. The main cytoskeleton components of both axon models include MTs, axolemma, myelin sheath, Ranvier node, MT-associated protein (MAP), tau and NF network. Both models explicitly meshed all major axonal substructures and adopted their respective averaged geometrical parameters according to the literature, as reported in (Table 1). To maximize geometrical radial symmetry and to facilitate meshing, 7 MTs were retained for a typical female model (1 MT in the center with 6 additional ones to form a one-layered hexagonal pattern), and 13 MTs were retained for a typical male axon (with 6 additional MTs in the second layer), respectively. They reflect the average of 8 and 12 MTs. To avoid ambiguity, they are also referred to as MT7 and MT13 models.

Table 1 | Geometrical features of axonal substructures [2–4]

Axolemma radius	# of MTs	MT. spacing	MT inner radius	MT outer radius	g-ratio*
200/300 nm	7/13	30 ± 2.5 nm	7.0 ± 0.75 nm	12.5 ± 1.5 nm	0.65 ± 0.075
MT length	NF		Axolemma thickness	Ranvier node	MT gap length
4.02 ± 5.28 um	Fill remaining space.		8 ± 0.75 nm	1 um	0.12 um

*g-ratio, the ratio of the inner axonal diameter to the total outer (myelin sheath) diameter

Most axonal substructures were assigned with linear viscoelastic material properties based on the literature. Material properties for the NF were calibrated for both MT7 and MT13 models with a hertz contact experiment to ensure their responses fall within the experimental measurement corridor. With the calibrated NF stiffness, the baseline models were then validated against in-vivo experimental tension dataset [7] by simulating a quasi-static uniaxial tension experiment (30% peak strain at a rate of 0.17 s^{-1}). MT breakage and Axolemma rupture behaviors were simulated using a strain failure threshold of 50% and 34%, respectively. For tau and NF, a 100% failure threshold was adopted based on relevant literature, above which the corresponding elements would produce a zero-reaction force. Elements after failure

were deleted for subsequent simulation. Baseline models were then used to simulate axonal stretch from a real-world impact. Specifically, a strain history curve (Figure 1a) in the corpus callosum obtained from a previous simulation of a reconstructed real-world head impact using the anisotropic Worcester Head Injury Model V1.0.

Axon dynamic behaviors depend on MT gap configurations. They are quantified by using a bivariate probability strategy. The unit axon model length (L) was used to define a series of discrete "sampling lengths". Starting from the shortest sampling length (Ls) chosen to be 5% of L, the entire axon model was scanned axially to identify the maximum number of MT gaps (N) falling within the specified length. The pair of parameters, (Ls, N), were then used to characterize the MT gap configuration. For each sex, ten thousand (N=10,000) models with baseline geometrical parameters (Table 1) were created, from which the bivariate distribution probability, (Ls, N), was calculated.

For each simulation, 5 axon models were generated for each MT gap configuration with a nonzero probability for each sex. Peak strain amplifications in MT relative to peak input strain were obtained, along with the associated tau and NF failure rates. They were then organized according to the bivariate MT gap configurations to obtain corresponding averaged responses, from which sex differences in responses were compared. All simulations were conducted in SIMULIA Abaqus with the implicit non-linear FEA solver (32 CPUs, 64GB).

RESULTS

For each simulated axon model, we consistently observed MT undulation, regardless of the sex or specific MT gap configurations. They all started near the end of the unloading phase and sustained even after the completion of unloading. The undulation behavior agreed well with TEM findings observed immediately after dynamic stretch injury. Case illustrations are shown in Figure 1.

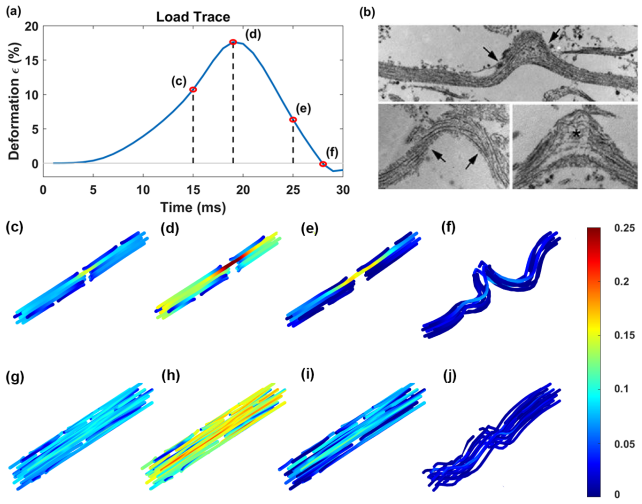

Figure 1: (a) Corpus callosum fiber strain time history as input applied to the axon models. (b) MT undulation in dynamic stretch injury test [6]; From (c) to (j): MT strain distributions in deformed states at selected time points (as indicated in (a)) for a typical female and male axon model.

With the applied input (peak strain of 18%), none of the MTs or Ranvier nodes in any model exceeded their failure strain thresholds. In general, higher MT strain amplifications occurred when there were more MT gaps within a shorter sampling length for both female and male models. However, peak strain amplifications in the Ranvier node were mostly uniform for both models and were insensitive to the gap configuration. Figure 2a-b report tau and NF failure rate (element length-weighted percentage of failed elements) progressions over time for a female and a male axon model with their most common MT gap configurations. The male model had a higher tau failure, but the female axon model had a much higher rate for NF failure.

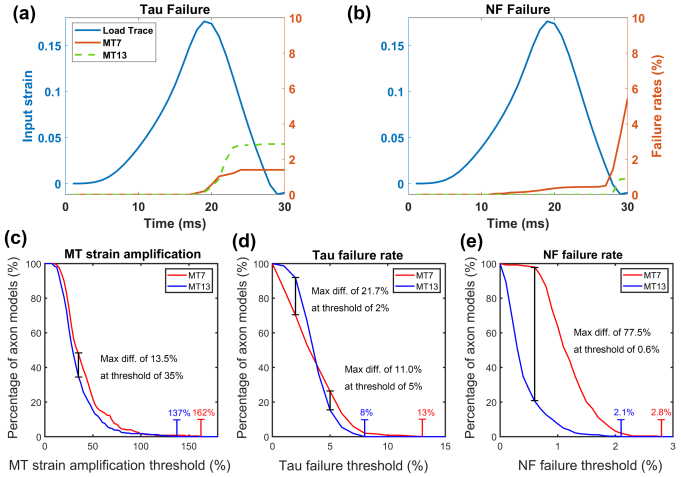

Figure 2: Tau (a) and NF (b) failure rates over time for a female and a male axon (MT7 and MT13, respectively); Percentages of female and male axon models with MT peak strain amplification (c), tau (d) and NF (e) failure rates exceeding a range of thresholds for each sex.

Using a large sample of axon models with random MT gaps for each sex, the percentages of axon models with MT peak strain amplifications exceeding a range of thresholds were compared, as well as those with tau and NF failure rates above a given threshold across their respective value ranges (Figure 2c-e). For MT strain amplification and NF failure, female axon models always had a higher percentage of above-threshold responses across the value ranges. For tau failure, however, the sex difference depended on the threshold value, itself.

DISCUSSION

We find axonal substructural responses in terms of peak strain amplifications in MTs and the Ranvier node as well as NF failure rates in female axons are considerably higher than those in male axons in dynamic tensile loading and unloading. The underlying reason are largely due to the sex-related difference in the cross-sectional number of MTs and the random nature of MT gaps. Both random MT gaps in model and the unloading phase in dynamic tension are critical to reproducing MT undulation as observed experimentally. The study may lead to an improved understanding of sex differences in injury vulnerability at the microscale as well as the biomechanical mechanism of DAI in general.

ACKNOWLEDGEMENTS

Funding is provided by NSF CMMI 2114697. Simulations were conducted using a high-performance computing system acquired through the NSF MRI grant DMS-1337943 to WPI.

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