Fluid-structure interactions analysis of tension in an axon using finite elements modeling to investigate strain related neurological damages

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ABSTRACT

Study of axonal behavior under different environmental conditions can provide a better insight into the development of therapeutic approaches for healing after nerve damages. By modeling of sublayer in the form of a hyperelastic material and applying different pressures, the amount of strains tolerated by axon was calculated. Strains were applied at three different time intervals to examine the effects of different strain rates. For axon, a model containing microtubules with linear elastic properties, neurofilament and axolemma with linear viscoelastic properties was considered. Finite elements method and COMSOL software were used for discretization of the sublayer and the substructures of the axon. It was observed that the fluid regime in the channel did not affect the mechanical response of the axon. The strain was close to zero (at most 0.0001) and the stress was also negligible (at most, 70 N/m2). The results showed the major effect of microtubules on resisting against mechanical forces and on the overall integrity of the axons. Most of the strains were seen inside the axolemma, indicating the importance of its mechanical response to injury. Regarding the response to the strain rate, the most probable damage to the axon, comparable with the former corresponding reports will occur at the strain of 42% and strain rate of 19.1 s-1, respectively.

KEYWORDS

Traumatic Brain Injuries (TBI), Microfluidics, Finite Element, Fluid-Structure Interaction, Viscoelastic model.

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1. Introduction

Given the importance of the brain and nerve cells and the diseases and injuries associated with these cells, research in this area is very extensive. However, due to the specialized nature of the behavior of these cells, various studies have usually examined only one aspect of these cells. In this regard, extensive research on nerves has been done in each of the electrophysiological, chemical and mechanical behaviors alone [1, 2]. However, research that can show the effect of these factors together and comprehensively on the behavior of the nerve cell has not been done so far.

Microfluidic environments are very useful in cell engineering studies due to their ability to better simulate the internal environment of the body and the living space with which the cell is associated, and the fact that microfluidic devices provide the ability to stimulate and examine the cell in smaller dimensions. The microfluidic environment allows us to isolate and examine an axon in a specific way [3]. In this study, we try to investigate the behavior of axons under the influence of tension and strain, and as a result, observe the possibility of damage. In this regard, an attempt has been made to provide a general model of the axon and its components in a simple way. Cells are always under the influence of mechanical force. The knowledge of mechanobiology focuses on the effect of mechanical forces on the cell and molecular processes, and its main motivation is the discovery of how the cell senses mechanical stimulation, transmits it, and produces biological responses. The innovation of this research is considering axon components in the computational model and using fluid-structural interaction analysis. In other words, with a novel look at axon modeling and also using the fluid-structural interaction method, the purpose of this study is to investigate the mechanical responses of axons under mechanical loading conditions and to investigate the possibility of nerve damage by considering the components.

2. Methodology

To simulate a nerve cell axon, we need an understanding of the mechanical properties and structural geometry of the axon. Also, according to the microfluidic environment used in cell implantation, the properties and behavior of the substrate should be examined as needed. For this purpose, previous studies are used to extract the required data. Axon geometry is simplified and considered as a uniform cylinder. First, the properties and behavior of the substrate are investigated. Then, by examining the effect of the flow in the channel, an attempt is made to find the effect of the fluid on the solid inside the channel. Then, by examining the effect of strain rate and different strains, we will try to identify the effect of different loading regimes on the axon and the possibility of damage.

The axon structure is considered as a cylinder. Within this structure, microtubule fibers and neurofilaments are located [4]. The axon is considered as a uniform cylinder with a diameter of 1.5 mm and a length of 2400 mm. The reason for the long initial length considered is the microchannel geometry used, which covers the distance between the two compartments. Finally, to investigate the mechanical response, we suffice to a length of 40 mm from the axon so that the challenges regarding difference in dimensions and length-to-diameter ratio (1.5 to 2400), which leads to computational problems such as computational costs due to the needed meshing is prevented [5]. Also, in order to consider the internal structures of the axon, three parts of the internal parts of the axon were considered. We simulate the intra-axon microtubule filaments joined by TAU proteins as a cylinder with a diameter of 400 nm. The main and internal parts that make up the largest volume of axon structure are neurofilaments. This section was also simulated as a material with viscoelastic properties that covers the area between the membrane and the central structure of microtubules. Finally, the axon membrane is considered as a layer with a thickness of 200 nm and viscoelastic properties [5].

The system used consists of two layers of PolyDiMethylSiloxane (PDMS) [3]. The uniaxial strain is created by applying uniform pressure to a section of the substrate. The length of the part of the channel that is affected by the strain due to pressure is 2400 µm and has a length to width ratio of 1:16. The structure of the channels is designed on the second layer with a pattern of depth of 6 µm, width of 50 µm and a distance between the two channels of 50 µm. The total thickness of the first and the second layers are 75 µm and 70 µm, respectively [3].

Due to the general structure of the microtubule and the behavior that shows itself in different loading conditions, a linear elastic model is used to describe its properties [6]. The axon or axolemma membrane is a bilayer lipid structure that separates the intracellular part from the extracellular part. The ion channels that affect the electrical activity of neurons are located on this section. The axon membrane is located on an actin-spectrin skeleton that plays the largest role in membrane stiffness[7]. In this model, an integrated structure with linear viscoelastic properties was used to show the membrane behavior [5]. The third and final part in the axon structure are neurofilaments which are intermediate filaments that are parallel to the microtubule filaments and up to 10 times greater in number [8]. These filaments determine the axon diameter and maintain the overall integrity of the neurofilament network and attach it to the plasma membrane and microtubules [9]. Finally, using a linear viscoelastic model and considering the spring-damper model, properties were considered with accuracy close to the actual behavior [5]. In order to create a mesh in this research, COMSOL Multyphysics was used. Tetrahedral elements were used to discretize the solid part and Prism elements were used for the fluid part. The uniform pressure applied to the substrate at 11%, 25% and 42% strains is 3.5 psi, 8.5 psi and 14.5 psi, respectively.

3. Results and Discussion

The overall response of axons to loads and displacement values in the total axon volume is investigated as shown in Figure 1. Due to the geometry of the problem and its constraints, the axon is expected to act like a double beam into which a uniaxial strain has been applied. As it can be seen in the figure, the maximum values of deformation are in the central parts of the axon. To study the axon behavior more accurately, the stress and strain values at different points and different axon components must be examined. The effects of strain damage on the microtubule appear to be dependent on strain values. However, in the central region of the load where the highest strain is observed, B-tubulin marking indicates significant degradation of the microtubule compared to areas with less strain. Fluorescent markers also confirm this [3]. Results showed that most of the stress on the axon is borne by internal microtubules which is in line with previous findings that the main factor regarding integrity of the axon structure is the strength of microtubule filaments [5].

4. Conclusions

This study largely attempted to include the structural components of axons such as microtubules, neurofilaments, and Axolemma. With acceptable approximations, a computational model was obtained that simulated the actual behavior of the axon. A noteworthy point in this simulation was the study of axon internal microtubules as a uniform cylinder with properties commensurate with real microtubules. The results of this research could open a new window in the engineering design of cell experiments based on the principles of mechanobiology. Also, using the results of this study, an important step can be taken to determine the extent of axon injury in concussions.

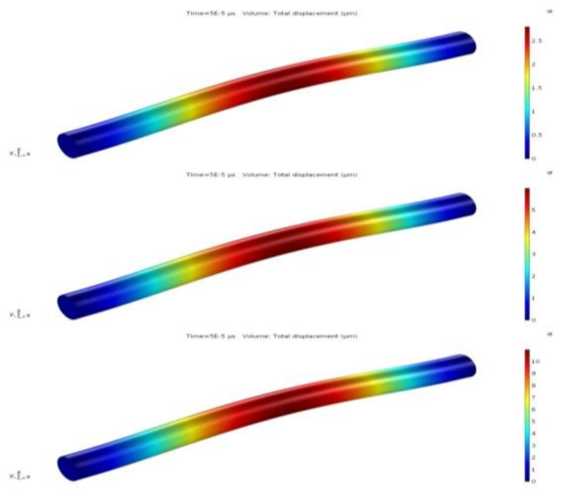

Figure 1. Axon displacement for 11%, 24% and 42% strains.

5. References

[1] M.A. Hemphill, S. Dauth, C.J. Yu, B.E. Dabiri, K.K. Parker, Traumatic brain injury and the neuronal microenvironment: a potential role for neuropathological mechanotransduction, Neuron, 85(6) (2015) 1177-1192.

[2] A. Goriely, S. Budday, E. Kuhl, Neuromechanics: from neurons to brain, Advances in Applied Mechanics, 48 (2015) 79-139.

[3] J.-P. Dollé, B. Morrison III, R.S. Schloss, M.L. Yarmush, An organotypic uniaxial strain model using microfluidics, Lab on a Chip, 13(3) (2013) 432-442.

[4] N. Abolfathi, A. Naik, M. Sotudeh, G. Karami, M. Ziejewski, Diffuse axonal injury and degradation in mechanical characteristics of brain white matter, in: Summer Bioengineering Conference, American Society of Mechanical Engineers, 2008, pp. 229-230.

[5] A. Montanino, S. Kleiven, Utilizing a structural mechanics approach to assess the primary effects of injury loads onto the axon and its components, Frontiers in neurology, 9 (2018) 643.

[6] D. Bray, M.B. Bunge, Serial analysis of microtubules in cultured rat sensory axons, Journal of neurocytology, 10(4) (1981) 589-605.

[7] T.D. Pollard, J.A. Cooper, Actin, a central player in cell shape and movement, science, 326(5957) (2009) 1208-1212.

[8] P.C. Wong, J. Marszalek, T.O. Crawford, Z. Xu, S.-T. Hsieh, J.W. Griffin, D.W. Cleveland, Increasing neurofilament subunit NF-M expression reduces axonal NF-H, inhibits radial growth, and results in neurofilamentous accumulation in motor neurons, The Journal of cell biology, 130(6) (1995) 1413-1422.

[9] C. Leterrier, P. Dubey, S. Roy, The nano-architecture of the axonal cytoskeleton, Nature Reviews Neuroscience, 18(12) (2017) 713-726.