Journal of Biomechanics 48 (2015) 1241–1247

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

A viscoelastic model for axonal microtubule rupture

Amir Shamloo [a,b,*,1], Farid Manuchehrfar [a,1], Hashem Rafii-Tabar [b]

[a] Center of Excellence in Energy Conversion (CEEC), School of Mechanical Engineering, Sharif University of Technology, P.O. Box 11155-9567, Tehran, Iran
[b] Institute for Research in Fundamental Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Accepted 10 March 2015

Keywords:
Axon
Microtubule
Rupture
Standard Linear Solid
Viscoelastic

ABSTRACT

Axon is an important part of the neuronal cells and axonal microtubules are bundles in axons. In axons, microtubules are coated with microtubule-associated protein tau, a natively unfolded filamentous protein in the central nervous system. These proteins are responsible for cross-linking axonal microtubule bundles. Through complimentary dimerization with other tau proteins, bridges are formed between nearby microtubules creating bundles. Formation of bundles of microtubules causes their transverse reinforcement and has been shown to enhance their ability to bear compressive loads. Though microtubules are conventionally regarded as bearing compressive loads, in certain circumstances during traumatic brain injuries, they are placed in tension. In our model, microtubule bundles were formed from a large number of discrete masses. We employed Standard Linear Solid model (SLS), a viscoelastic model, to computationally simulate microtubules. In this study, we investigated the dynamic responses of two dimensional axonal microtubules under suddenly applied end forces by implementing discrete masses connected to their neighboring masses with a Standard Linear Solid unit. We also investigated the effect of the applied force rate and magnitude on the deformation of bundles. Under tension, a microtubule fiber may rupture as a result of a sudden force. Using the developed model, we could predict the critical regions of the axonal microtubule bundles in the presence of varying end forces. We finally analyzed the nature of microtubular failure under varying mechanical stresses.

1. Introduction

The main goal of this study is to develop an appropriate model for studying the behavior of axonal microtubules in response to suddenly applied forces. Axons are one of the most important parts of the neuronal cells and axonal microtubules are fibers in axons. The main function of microtubules is to reinforce the neuronal axons. Microtubule bundles that are located in the inner part of the axons have polar orientation (Fadic et al., 1985). Microtubules have many cross links with their neighboring microtubules using tau proteins. These tau proteins are considered as one of the main elements for the axonal strength in response to the mechanical forces (Drechsel et al., 1992). Since microtubules can resist mechanical forces, these structures have been studied widely from biomechanical point of view. The size of microtubules and the spatial position of these bundles within axons have also been investigated widely (Fadic et al., 1985; Yu and Baas; 1994). There are other microstructural components within axons like microfilaments and different organelles. Microtubules can facilitate the transport of organelles within the axons since these organelles can move along microtubule bundles. Microfilaments are one of the other important parts of the neuronal cell cytoskeleton that in coordination with microtubules, keep the shape and integrity of axons.

Axonal injury is one of the most common central nervous system injuries (Smith et al., 2003; Sanjith, 2011). Most patients who are suffered from axonal injuries, after a period of time, experience deficits like eye problems, problems with executive functions, behavior changes, language deficits etc. (Adams et al., 1989; Sanjith, 2011; Blumbergs et al., 1989; Williams et al., 1990). The injuries of microtubules are shown to be one of the main consequences of the traumatic brain injuries happening during the damage to axons (Peter and Mofrad, 2012; Gennarelli et al., 1982). Some studies have revealed that the most axonal injuries that occur in specific areas of the brain are caused by the extensive strain in axonal microtubules (Margulies et al., 1990). Some experiments have also shown that the rupture of microtubules can cause the most severe damage in traumatic brain injuries (Tang-Schomer et al., 2010). Microtubules are shown to be ruptured under the axonal strain of about 50% (Janmey et al., 1991).

Some in-vitro models have studied the mechanical injuries of neurons (Kilinc et al., 2008, 2009; Meaney et al., 1994). The most

* Corresponding author at: Center of Excellence in Energy Conversion (CEEC), School of Mechanical Engineering, Sharif University of Technology, P.O. Box: 11155-9567, Tehran, Iran. Fax: +98 21 66165599.
E-mail address: shamloo@sharif.edu (A. Shamloo).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.jbiomech.2015.03.007
0021-9290/

common techniques to make brain injuries in experimental studies include cortical impact, weight drop and central or lateral fluid percussion (Meaney et al., 1994). Fluid percussion injuries have been found to bring about lesions in the lower brainstem (Dixon et al., 1988; Shima and Marmarou, 1991). Similar to the fluid percussion, cortical impact generates lesions and associated axonal injuries (Dixon et al., 1991). In contrast, it is shown that weight drop can create contusion around the impact region (Feeney et al., 1981).

To study the mechanism of damage to the neuronal axons, computer simulation can be very helpful in determining the effect of mechanical forces applied to the constitutive parts of the axons. There are several models developed by researchers for modeling microtubules, axons or neurons (Erickson and O'Brien, 1992; Flyvbjerg et al., 1994). In 2010, a mathematical model was used to study the dynamics of microtubules (Buxton et al., 2010). In this model, microtubule bundles were assumed to be composed of discrete masses. They posed linear springs between the masses, although in reality, this assumption may not be correct. On the other hand, microtubule bundles are shown to behave like viscoelastic materials. The viscoelastic behavior of axons has been verified in all experiments performed on axons.

Microtubule bundles have been recently studied widely (Shahinnejad et al., 2013; Teixeira et al., 2014). One of the recent studies used finite element method to model axons under tension and torsion (Shahinnejad et al., 2013). One of the other models for axon was suggested by Peter and Mofrad (2012). In their study, it was endeavored to model the axon under tension. In this model, microtubules were assumed to be positioned in a hexagonal form and each microtubule bundle was considered to have one discontinuity. Another model in 2014, studied the behavior of axonal microtubules and their connected tau proteins for different microtubule lengths when specific amounts of strain were applied to the network of microtubules (Ahmadzadeh et al., 2014). They showed that the applied strain rate to the axons plays an important role in microtubular break. They also showed that the stretch of tau proteins is related to their position relative to the ends of the microtubule bundles, the overall length of microtubules and the applied strain rate.

In our model, the dynamic response of microtubule bundles under the action of varying stresses was studied. It was intended to distinguish the critical areas of axons and microtubules that may be disconnected under tension. We also determined the steady state behavior of axons for different force rates and different force magnitudes. Microtubules were connected to their neighboring microtubules using tau proteins as one of the main features providing axonal stiffness. In Fig. 1, an axon within a neuronal cell is shown and axonal microtubules are positioned within the interior part of the axons. We employed a two dimensional (2D) computational model to investigate the dynamic response of axonal microtubules.

2. Geometry

As discussed earlier, the interior of an axon can be roughly thought as a network of relatively short microtubules cross-linked with tau proteins. The orientation of microtubules is in fact random but preferably lengthwise in the axon. The simplified microtubular geometry proposed by Peter and Mofrad (2012), consists of a hexagonal array of 19 rows. The cross-sectional view of the geometry reconstructed in our computational platform is presented in Fig. 2a. Since it is easier to work with non-dimensional equations, the characteristic length scale is assumed to be the distance between two neighboring points in the same bundle. According to Peter and Mofrad (2012), the microtubular spacing can be considered to be 4.5 (equivalent to 0.045 μm). Each row was assumed to be an ensemble of 800 point masses and the number of microtubules was considered to be nine. In our computational platform we randomly eliminated one of the SLS units between two point masses in a microtubule bundle to make a point of discontinuity. A bird's-eye view of the entire geometry is given in Fig. 2b. This figure also presents a close look at the points of discontinuities. The dashed lines represent cross-links attributed to tau proteins.

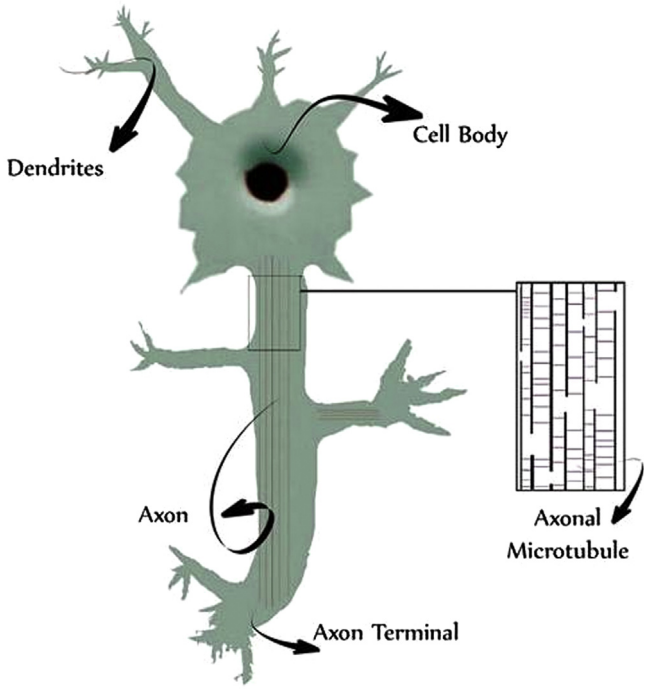

Fig. 1. Schematic of a neuron with an axon, dendrites, axonal terminals and microtubules.

3. Methods

3.1. Viscoelastic model

As shown in supplemental Fig. 1, SLS model that was used in this study consists of a spring that is in parallel with a series of dashpot-spring pair. The right arm consists of a spring, k_m and a damper, c. This arm is typically called Maxwell arm. The left arm is simply a linear spring, k.

As can be seen in Fig. 3, a discrete point mass, 'M', is linked to a stationary wall through a SLS unit. As the mass M is acted upon by a given force, '$F(t)$', the governing equations for its motion are written as Eqs. (1) and (2) where 'k' is the constant of the left arm spring, 'c' is the damping coefficient of the dashpot and 'k_m' is the spring constant of the Maxwell arm (right arm).

$$M\ddot{x} = F - kx - c(\dot{x} - \dot{x}_m) \tag{1}$$

$$c(\dot{x} - \dot{x}_m) - k_m x_m = 0 \tag{2}$$

As it is shown in Fig. 3, in these equations 'x' and 'x_m' are the positions of the point mass and the nodal point on the Maxwell arm.'$\dot{x}$' and '$\ddot{x}$' also define the first and second derivatives of 'x' with respect to time.

In order to simplify Eqs. (1) and (2), we divided these equations by 'M' and a step-like constant force was imposed on the stationary mass at the initial time. In this case the governing equations were simplified to the following equations:

$$\dot{x} = f_0 - \omega^2 x - 2\eta\omega(\dot{x} - \dot{x}_m) \tag{3}$$

$$\dot{x} - \dot{x}_m - \frac{\omega_m{}^2}{2\eta\omega} x_m = 0 \tag{4}$$

where $f_0 = F/M$, $\omega = \sqrt{k/M}$, $\omega_m = \sqrt{k_m/M}$, and $\eta = c/2\sqrt{Mk}$.

3.2. Forces

For the sake of generality, the initial spacing between the microtubules is considered to be χ times the initial spacing between two adjacent point masses in a