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Are deformed neurons electrophysiologically altered? A simulation study

Tahereh Tekieh [a], Sohrab Shahzadi [b], Hashem Rafii-Tabar [c, **], Pezhman Sasanpour [c, a, *]

[a] Computational Nano-Bioelectromagnetics Research Group, School of Nano-Science, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran
[b] Functional Neurosurgery Research Center, Shohada Tajrish Neurosurgical Center of Excellences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Medical Physics & Biomedical Engineering, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

The electrophysiological outcome of neuron deformation is studied. This study is based on modeling the propagation of action potentials in a neuron with different deformed segments subject to an external mechanical compression. The proposed model is based on modified cable equation incorporating geometry variations. The study is performed for different degrees and number of deformations of the axon structure. The results of simulation show that the propagation speed, the refractory period, and the action potential broadening are all directly affected by variations in the geometry.

1. Introduction

Wide ranges of syndromes are associated with the compression of nerve fibers. A nerve can be compressed by means of an external force which may lead to ischemia where it is called entrapment neuropathy. Tumors, depending on where they grow, may cause problem relative to the tissue. Pituitary tumors can cause vision problems and headaches when they grow large and compress the surrounding nerves or the acoustic neuroma can press the cranial nerves, and as it grows larger it can protrude into the brain [1,2]. Carpal tunnel syndrome is another example of entrapment neuropathy which indicates the compression of median nerve and could affect the action potential of the nerve. In carpal tunnel syndrome the nerve action potential is small and the conduction velocity is decreased in 85% of the cases [3]. Other entrapment neuropathy syndromes exist such as restricted bed rest, pronator teres syndrome, Ulnar nerve lesion, meralgiaparaesthetica, sciatic nerve syndromes and common peroneal syndromes. Usually nerve conduction velocity test can determine the nerve damage and destruction [4–6].

The experimental studies in this domain involve the use of compressive forces on different nerves via methods developed by different research groups. The effect of compressive forces on peroneal nerves of rabbit was studied wherein it was found out that in larger nerve fibers the action potential conduction is more sensitive (decrease in conduction) to the compressive force, although all types of nerves conduction were blocked when the compressive force was sufficient. Briefly applied forces in this study decreased the conduction velocity which did not revert to the normal value within 2 h [7]. The studies on the nerve compression revealed that compressions could be both degenerative and regenerative. The studies also indicate that compression affects the velocity and the amplitude of neurons action potential. If the force were not severe enough, the action potential changes were temporary when the force was removed. Sometimes the force was large enough to block a nerve fiber [8]. The spinal cord compression has been carried out experimentally, where a group of rats were investigated by osmic acid staining and transmission electron microscopy (TEM) to show that demyelination occurs under spinal cord injury [9]. The spinal cord injury consequences, the extent and progression of tissue damage and the neuronal nuclei lost were investigated

* Corresponding author. Department of Medical Physics & Biomedical Engineering, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
** Corresponding author.
E-mail addresses: rafii-tabar@nano.ipm.ac.ir (H. Rafii-Tabar), pesasanpour@sbmu.ac.ir (P. Sasanpour).

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experimentally using post-traumatic residual spinal cord compression on rats [10,11], Three types of conduction block have been identified from guinea pig spinal cord compression. A decreased amplitude and increased latency of compound were observed [12]. The computational biomechanics studies have focused on multi-scale modeling in which the effect of traumatic stress on a membrane patch and its electrophysiological properties are coupled together. The model predicts the alteration of electrophysiological functions under damaging loads [13]. A more versatile program (Neurite) which simulates the propagation of electrical signals under mechanical loading has been presented which uses the same concept of multiscale coupling model [14]. In an injured Ranvier node the sodium channels became leaky, the ratio of the intact to the traumatized axolemma varied, and the excitability and ion homeostasis were simulated too [15]. There have been theoretical and computational mechanical studies which estimated the probability of diffuse axonal injury to study the axon integrity, degeneration and degrowth [16]. The physiological aspects of an axon under tension or compression are rarely reported. An electron micrograph of an optical nerve deformation is shown in Figs. 1-a and 1-b as an example. Conduction velocity, amplitude and duration of the action potential are the most essential parameters in an electrophysiological assessment and could be affected during the compression via a lumour, ac cyst or haematoma. A sensory action potential amplitude under 30 min pressure was reduced by 60% and the sensory conduction velocity was reduced by 25% [17]. Considering different structures of the axons, the compression and electrophysiological effects have been studied for unmyelinated axons. The governing equation of the pulse propagation in an unmyelinated axon under mechanical deformation has been modified accordingly. The gradual load has been applied to an unmyelinated axon and the effect of membrane deformation on the action potential behavior has been studied accordingly. To the best of our knowledge, there has been no theoretical modeling regarding the electrophysiological aspects of neuron deformation. Our model is applied to two-state neuron deformation geometries shown in Figs. 1-c and 1-d.

2. Materials and methods

The propagation of action potential in the neuron structures has been studied employing the cable theory by considering the effect of ionic currents within the Hodgkin-Huxley model [19]. The standard cable theory considers the neuron as a simple fiber with a constant diameter. Considering the deformation of the uniform structure of neuron to any specified shape, the modified cable equation was proposed in Ref. [20]. In order to incorporate the effect of different ionic compartments, we have inserted these effects within the Hodgkin-Huxley model, i.e.

$$\left(C_m\frac{\partial V_m(z,t)}{\partial t}+I_{ion}\right)\frac{ds}{dz}=\frac{r}{2(R_e+R_i)}\frac{\partial^2 V_m(z,t)}{\partial z^2}+\frac{1}{(R_e+R_i)}\frac{dr}{dz}\frac{\partial V_m(z,t)}{\partial z} \quad (1)$$

where C_m denotes the membrane's capacitance per unit area. R_e and R_i denote the extracellular and intracellular axial resistances. V_m stands for transmembrane potential, r,z and s are the coordinate variables depicted in Fig. 1-e. I_{ion} represents the sum of different ionic current components (Na, K and other components). The details of the derivation of the above equation can be found in Ref. [20]. Due to the fact that the applied load is smooth and gradual enough not to affect the distribution and density of the membrane components or even destroying them, the typical Hodgkin-Huxley parameters were taken into account. The Hodgkin-Huxley membrane current (i_{ion}) is written as:

$$i_{ion}=g_L(V-E_L)+g_{Na}m^3h(V-E_{Na})+g_Kn^4(V-E_K) \quad (2)$$

Where g_L is the leak conductance, E_L is the reversal potential for the leak conductance. g_{Na} denotes the sodium conductance and E_{Na} is the reversal potential for the sodium channel. g_K is the potassium conductance and E_K is the reversal potential for the potassium channel. m,h,n, are the gating functions which take on the values between 0 and 1, and represent the probability for key steps in opening or closing of a channel. Each of the gating variables m, h, and n also obey a differential equation of the form

$$\frac{dy}{dt}=\alpha_y(V)(1-y)-\beta_y(V)y=\frac{y_\infty(V)-y}{\tau_y(V)} \quad (3)$$

$$y_\infty(V)=\frac{\alpha_y(V)}{\alpha_y(V)+\beta_y(V)} \quad (4)$$

$$\tau_y(V)=\frac{1}{\alpha_y(V)+\beta_y(V)} \quad (5)$$

where y = m, h, n, $\beta_y(V)$ is the rate that the gate switches from the open state to the closed state, $\alpha_y(V(t))$ is the rate that the gate switches from the closed state to the open state, $y_\infty(V)$ is the steady-state fraction of open gates, and $\tau_y(V)$ is the time constant associated with the change in the fraction of open gates. The functional forms of $y_\infty(V)$ and $\tau_y(V)$ were actually found experimentally by Hodgkin and Huxley by fitting voltage clamp data [19]. The parameters used in the model are shown in Table 1.

Thus, the complete set of equations (Equations (1) and (2), gating variables (3)) consist of the coupled nonlinear differential equations which describe the generation and propagation of action potentials for any configuration of axons. The set of equations are solved numerically within the finite difference method using the central difference and the forward difference schemes for spatial and temporal derivatives, via our own MATLAB-based code. The values of the time-step and the grid size (spatial discretization) were selected to provide stability and convergence [21].

3. Results and discussion

In order to compare the effect of neuron deformation with the standard shape of neuron, we have analyzed the propagation of the action potential for five cylindrical unmyelinated nerves gradually being compressed. The study has been performed for two types of pulse and direct current excitations and each parameter has been calculated before and after compression. In this regards, Fig. 2 depicts the time behavior of the action potential propagation for three structures, considering the pulse and continuous excitations. Figs. 2-a–2-c show the time behavior of the action potential propagation along the considered geometries. Fig. 2-a shows the results for a bent axon with its radius gradually changing from 0.5 μm to 0.2 μm. As can be seen, the propagation is in the natural form. In Fig. 2-b the axon is bent to 0.1 μm so a slight change in the membrane voltage is recognizable, leading to a decrease in amplitude. When the bending is extended, a blockage of the action potential is visible in that specific point, as depicted in Fig. 2-c. From the specific point the rest of the fiber experiences a delay. The same structures have been considered with direct current injection to measure the membrane voltage difference. The results (Figs. 2-d–2-f with the same structure of a,b,c) show that the action potential decreases before the deepest point in the fiber and increases