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Original Article

Asymmetric Rectangular Waveform in Stimulation with High Frequency Alternating Current Reduces the Threshold for Neural Conduction Block

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Abstract

Introduction
Abnormal neural impulses in the nervous system may lead to various diseases and disabilities. High frequency alternating currents (HFAC) has been used to block the propagation of such impulses and improve the symptoms or disabilities. The technique is safe, reversible, and relatively selective, and its reliability, the optimum stimulation parameters, and elimination of the onset response have been the focus of related studies in the last decade. In this work, a series of computational simulations were performed to evaluate the performance of asymmetric biphasic rectangular waveforms for HFAC.
Materials and Methods
Computer simulations were carried out in NEURON software based on the MRG model, a detailed model of mammalian peripheral nerve fibers. The current threshold for the block and the injected charge per phase were assessed for different forms of this waveform and compared with symmetric rectangular, sinusoidal, DC, and monophasic stimulations. The effect of fiber diameter and the stimulation frequency were also evaluated for this waveform.
Results
The threshold charge per phase to induce nerve conduction block was significantly lower for the proposed asymmetric biphasic stimulation. The minimum thresholds were achieved for the waveforms with short anodic long cathodic phases. The threshold was reduced with increasing the asymmetry of the waveform and reduction of the frequency.
Conclusion
Simulations performed in this study demonstrated that the proposed stimulation with asymmetric biphasic rectangular waveforms significantly reduces the current threshold and requires much less charge injection per phase to induce nerve conduction block. This is very important for clinical use due to less damage to the tissue.

Keywords: Asymmetric Biphasic Waveform, High Frequency Alternating Current, Nerve Conduction Block

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1. Introduction

Undesired neural activity in different parts of the nervous system may lead to various diseases and disabilities. Abnormal sensory activity after cancer treatment or ablation results in pain sensation. Abnormal motor activity results in Parkinson's disease and muscle spasm, as well as tremor in patients who have suffered a stroke [1]. On the other hand, abnormal activity in the autonomous nervous system may result in excessive sweating or secretion of saliva. If it is possible to block the propagation of action potentials along neural fibers, these disabling conditions may be reduced or eliminated [2].

Traditional approaches to block the propagation of neural activity (nerve conduction block) include surgical section or nerve crush, local use of analgesic or denaturing agents, and thermal ablation or cooling. However, these approaches have had problems including low success rate and/or irreversibility as well as side effects due to non-selective nature of the approach [2-3].

Nerve conduction block by high frequency electrical stimulation as an alternative approach has been introduced in 1939. Reboul and Rosenblueth reported experiments on the sciatic nerve of rats which demonstrated that high frequency stimulations up to 40 KHz, if strong enough, can induce nerve block [4]. In recent years, however, the use of high frequency alternating currents (HFAC) as a safe, rapidly reversible, and relatively selective approach for nerve block has been studied more seriously and the interest to use this technique to treat some diseases and disabilities has significantly increased [5-6]. Researchers have studied the effect of different stimulation parameters, the possibility of eliminating the onset response (transient neural activity generated before complete accomplishment of nerve block), and reducing the thresholds for nerve block experimentally as well as by conducting computer-based simulation studies.

Kilgore and Bhadra have conducted both simulation studies using McIntyre, Richardson and Grill (MRG) model, and experimental studies on bullfrog to demonstrate that sinusoidal and rectangular HFAC with frequencies from 2 to 20 kHz can effectively and completely block the nerve conduction. Based on these studies, they concluded that the most effective stimulation is 3 to 5 kHz sinusoidal stimulation [3].

Williamson and Andrews reported that sinusoidal stimulation could induce complete nerve block only for frequencies above 10 kHz. They stated that the reduced muscle force observed for frequencies below 5 kHz is due to reduction of available neurotransmitters in the neuromuscular junction [7].

Tai et al. have performed two simulation studies using the Hudgkin Huxley membrane model to demonstrate that sinusoidal stimulation is less effective in comparison with biphasic rectangular waveform [8] and suggested that if the pulse width is also changed with the frequency, the stimulation would be more effective [9].

Zhang et al. suggested that lower stimulation frequency is more appropriate for clinical use since the current thresholds for the block increases with the frequency [10].

Makouie et al. have used Schwarz-Reid-Bostock (SRB) model of myelinated fibers to demonstrate that a proposed waveform that is a combination of rectangular and sinusoidal waveforms can induce nerve block with lower charge injection in comparison with rectangular waveforms and the current threshold is also lower with this waveform for thicker neural fibers [11]. This is among a few papers which have studied the effect of the stimulation waveform on the performance of HFAC. More commonly, sinusoidal and/or symmetric rectangular waveforms have been used.

In the present article, the use of MRG model has been reported to study and compare the performance of asymmetric biphasic rectangular waveforms to induce nerve conduction block. Asymmetric biphasic rectangular waveform is a more general form of biphasic rectangular waveform in that the positive and negative phases of the waveform are not with the same amplitude, although the integral of one period of

the waveform is still zero. At the limit, the waveform is converged to very short but strong delta-like stimulations compensated with very weak but steady reverse charge injection.

2. Materials and Methods

In this study, the MRG model [12] of mammalian myelinated nerve fibers was used to simulate nerve conduction block by extracellular high frequency stimulation. MRG model is a topologically detailed realistic model of myelinated neural fibers based on the human, rabbit and rat experimental data, in which both of the nodes of Ranvier and the details of the myelinated parts of the axon are considered.

2.1. MRG Model

The MRG model is a double-cable model of axons, including the intracellular space and the space between the axon membrane and the myelin. As shown in Figure 1, a parallel conductance model is used for the nodes of Ranvier, including the fast sodium, persistent sodium, slow potassium, and leakage channels as well as the capacitive effect of the membrane. The internodes are also modeled as two layers of linear components. The model consists of 51 nodes of Ranvier and 50 internode parts. The internode regions of the axon are modeled as two myelin attachment paranode segments (MYSA), two main paranode segments (FLUT), and six internode segments (STIN). The dynamics of the node's membrane is determined by fast sodium (Naf), persistent sodium (Nap), slow potassium (Ks), linear leakage (Lk), and capacitance (Cm). The internodes are described as a double-cable structure with explicit linear models of the myelin sheet (Cm and Gm) and the axon membrane (Ci and Gi) [12].

The equations of the model have been described by McIntyre et al. [12]. The geometrical specifications of different parts of the model have been presented for fibers 5.7 to 16 μm in diameter, based on empirical data (Table 2 of [12]) and therefore the relationship between the axon diameter (d) and the intermodal distance (Δx) is described more realistically than a linear relationship (Δx=100d) used in conventional models.

The MRG model has been validated by comparing various parameters of neural firing from empirical data with simulation results including the action potential shape, the after potentials, the conduction velocity of the fiber and others [12].

Modifications were applied to the MRG model, including the use of extracellular mechanism, to obtain the MRG model response to extracellular stimulation.

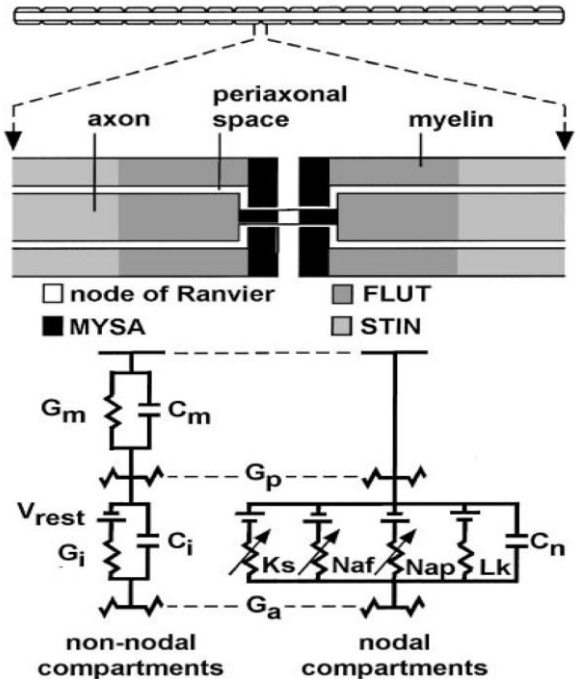

Figure 1. Multi-compartment double-cable model of mammalian axon that was used in this study for simulation of nerve conduction block. The figure is from [12].

2.2. Simulations

As demonstrated in Figure 2, the model consists of 51 nodes of Ranvier. A point source extracellular electrode was considered in front of the middle node (number 25) to apply the high frequency stimulation. It is assumed that the axon is placed in an infinite homogeneous volume conductor with resistivity of 500 Ωcm. The extracellular potential developed by the current injected from the electrode was obtained for each compartment of the model using the following equation:

$$V_e(j) = \frac{\rho_e I_{ext}}{4\pi\sqrt{(X_{elec}-X(j))^2+(Y_{elec}-Y(j))^2}} \qquad (1)$$

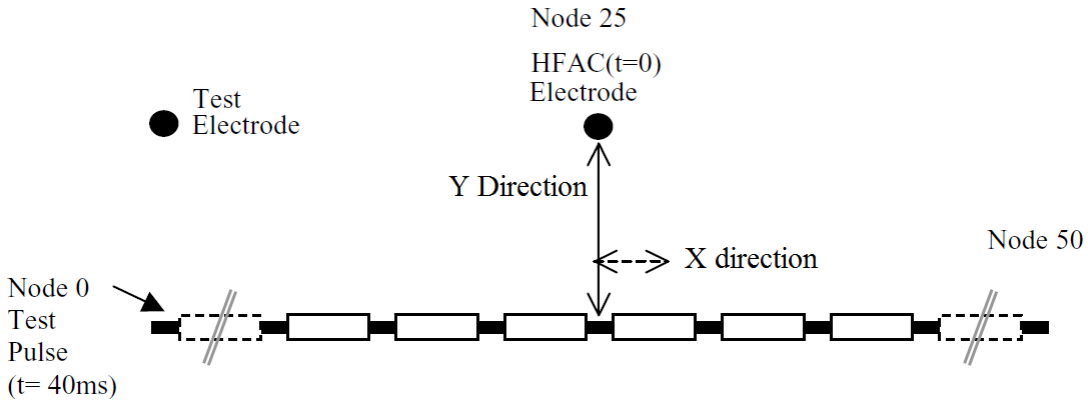

Figure 2. Positioning of the electrode for simulation of high frequency block. The electrode is placed in front of the middle node, 1 mm from the fiber to deliver high frequency blocking current. Another electrode is placed in front of the first node to generate a propagating action potential along the fiber.

where ρ_e is the extracellular resistivity, I_{ext} is the amplitude of the injected current, Y_{elec} is the distance of the electrode from the fiber (which is considered 1 mm), and X_{elec} is the longitudinal position of the electrode [13].

Computer simulations were performed using NEURON software (Version 7.1) [14]. The model was simulated with implicit Euler method with time steps of 0.001 ms. The total simulation time was considered 50 ms. In order to make the block phenomena distinguishable from the onset response, the test pulse for generating action potential was applied at time 40 ms, while the high frequency stimulation was applied from the beginning of the simulation. The membrane potentials of the nodes along the simulation time were saved in a file and were plotted and assessed in MATLAB version 7.1 (Mathworks). To validate the total implemented model, a sine wave of 10 kHz and 1334 μA in amplitude (block threshold) was applied to the electrode and the result (Figure 3a) was compared with those reported for the same stimulation at [15] (Figure 3b). In Figure 3, the membrane potentials are shown for the last node (right), middle node in front of the blocking electrode (middle), and the first electrode in front of the test electrode (left). The onset response can be observed as a few action potentials at the start of the simulation. The test action potential could not pass the blocked area and at the last node, only the onset response is seen.

2.3. Asymmetric rectangular waveforms

Asymmetric biphasic rectangular waveforms as shown in Figure 4 are rectangular waveforms that although are not symmetric in positive and negative phases, but have a net charge injection of zero (the integral of the total waveform is zero). The waveform can be in four forms that are shown in the figure, for the special case of one phase twice the other in amplitude.

3. Results

Simulations were performed to evaluate and compare the performance of asymmetric biphasic rectangular waveforms to block the neural fibers. In comparison with high frequency sinusoidal stimulation (block threshold 1334 μA), application of symmetric biphasic rectangular waveform (as a special case of asymmetric waveform) resulted in reduced threshold of 1071 μA. This is in accordance with previous results reported by Tai et al. [8] that block threshold for sinusoidal stimulation was higher than with rectangular stimulation.

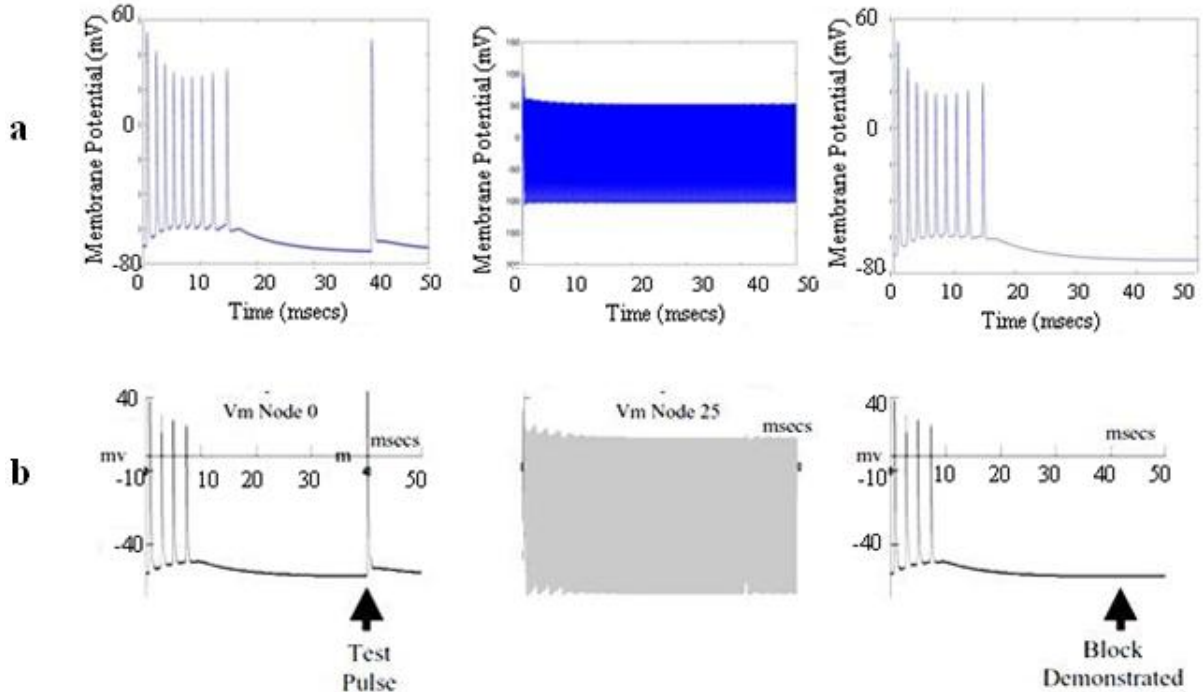

Figure 3. Comparison of the preliminary results of this article with those reported by Bhadra et al. [15]. a) The results of the implemented model. From left to right, the membrane potential on the node below the test electrode, below the blocking electrode and on the last node. b) The figure is borrowed from [15] to validate the implemented model. As seen, the responses are quite the same.

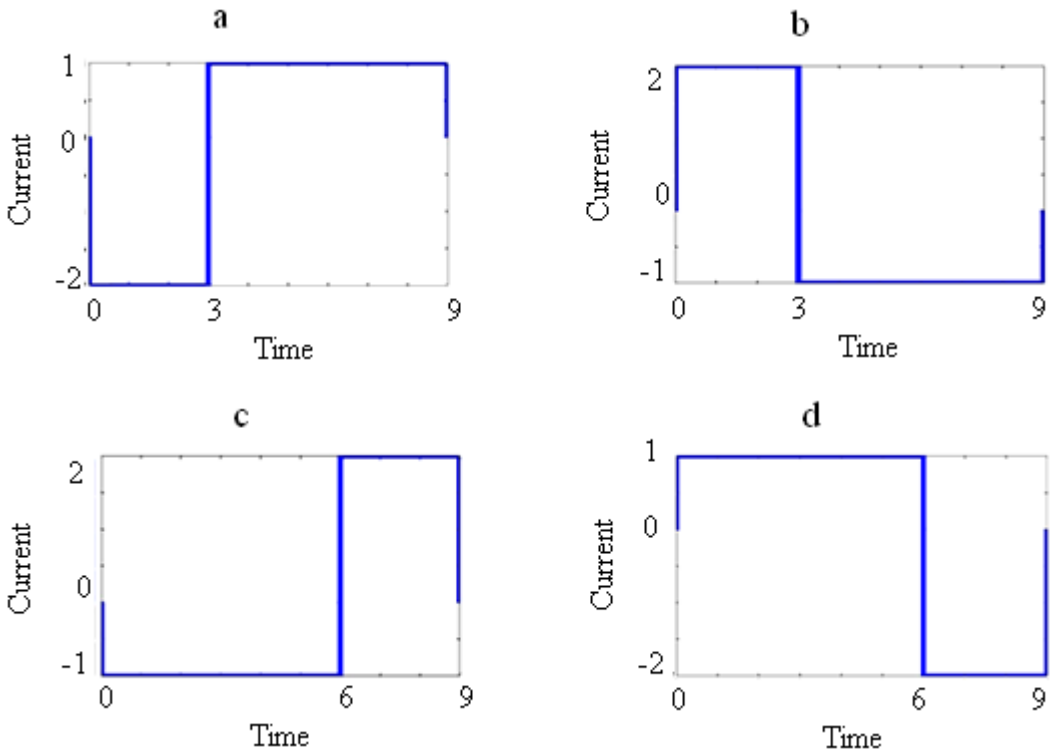

Figure 4. Four different forms of the asymmetric biphasic rectangular waveform as examples. The amplitude and the width of each phase are adjusted in a way that the integral of the waveform and therefore total injected current is equal to zero, make it appropriate for applying to the tissue with minimum tissue damage.

3.1. The charge/phase threshold for different phase width ratios

To evaluate the performance of asymmetric waveforms, the thresholds for the four forms of these waveforms (Figure 4) were obtained in a series of simulations. The ratio of the phase widths was equal to 2 for all of the four tested waveforms. For the waveform of 4a (i.e., negative short phase first) the current threshold (amplitude of the shorter phase) was obtained 891 μA which is well below the current threshold for sinusoidal and symmetric rectangular waveforms. However, to compare the performance of the four asymmetric waveforms, instead of the current threshold, the charge per phase threshold, i.e., the minimum charge per phase required for the block, was obtained. This can be calculated by multiplying the minimum amplitude to the width of a phase, and is similar for both phases of all the four waveforms. As an example, the charge/phase threshold for waveform of Figure 4a can be calculated as 59.4 nC, from the Equation (2), considering the stimulation frequency of 10 kHz.

Charge/Phase = The width of a phase × The current threshold for that phase (2)

In comparison, the charge/phase threshold was reduced to 46.4 nC for the waveform of Figure 4b and was obtained 49.4 nC and 57 nC for the waveforms of Figures 4c and 4d, respectively. Therefore, it was concluded that the charge/phase threshold is reduced significantly when the cathodic phase is wider with lower amplitude. Based on the results of this preliminary study, the waveform of Figure 4b was used for the rest of the simulations. The order of cathodic and anodic phases of the waveform should not have any effect on the threshold, since the waveform is repetitive. The small difference between thresholds for waveforms of 4b and 4c, or 4a and 4d may be due to the computational errors and were neglected since they were small.

To evaluate the effect of phase width ratio on the block threshold, the simulations were repeated for the waveform of Figure 4b, but with different phase width ratios. The results are demonstrated in Figure 5. Interestingly, increasing the asymmetry of the waveform (higher phase width ratios) results in lower charge/phase thresholds.

Although monophasic stimulus pulses are not appropriate for clinical use due to the resulted tissue damage, the thresholds for DC and high frequency monophasic stimulation were also obtained in a series of simulations. The current threshold for DC stimulation was 435 μA and for monophasic stimulation, it was 848 μA. To make the results comparable, the amount of charge was calculated for 50 μs, half of the period of high frequency stimulations. For DC stimulation, the value was obtained as 21.75 nC. Although relatively small, it is still higher than the required charge with asymmetric waveforms with phase width ratios of higher than 10. The charge threshold for monophasic stimulation was calculated as 42.4 nC which is higher than the threshold for pulse width ratios of higher than 4. These results suggest that the asymmetric biphasic stimulation has higher performance in blocking the neural fibers even in comparison with DC and monophasic stimulations.

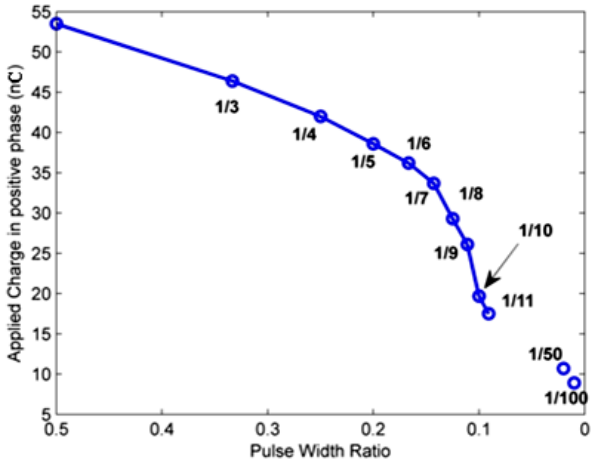

Figure 5. The charge/phase threshold required for neural block for a fiber 1 mm from the electrode, for different phase width ratios of asymmetric biphasic waveforms. The threshold reduces significantly with increasing the asymmetry of the waveform (higher phase width ratios). The last two points are obtained for ratios of 50 and 100, for which simulations were performed with the time steps of 0.0001 μs to reduce the probable computational errors.

3.2. The effect of fiber diameter on the block threshold

The block thresholds for asymmetric biphasic stimulation were also obtained for different fiber diameters. As shown in Figure 6, the threshold is reduced for fibers thicker in diameter.

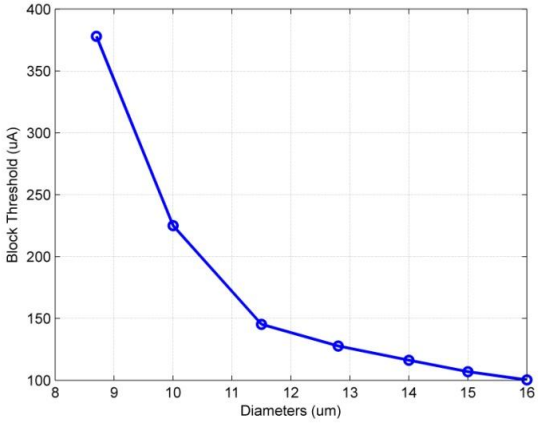

Figure 6. The effect of fiber diameter on the block threshold (amplitude of larger phase) for 10 KHz asymmetric rectangular waveforms with 0.1 phase width ratio.

3.3. The effect of stimulation frequency on block threshold

The simulations were repeated for different stimulation frequencies to obtain the effect of frequency on the block threshold of asymmetric biphasic waveform. As shown in Figure 7, the block threshold is absolutely increasing with the frequency between 5 to 30 kHz.

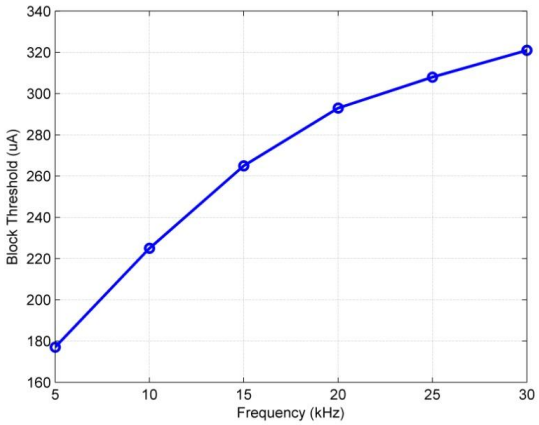

Figure 7. The effect of stimulation frequency on the block threshold (amplitude of larger phase) for asymmetric biphasic waveform with phase width ratio of 0.1 and fiber diameter of 10 μm.

4. Discussion

The results suggested that the proposed asymmetric rectangular waveform is superior to rectangular and sinusoidal waveforms previously have been used for nerve conduction block, in the sense that the block can be induced with much less charge injection per phase, and therefore lower current threshold. This is very important for practical use of high frequency alternating current stimulation and to reduce the tissue and electrode damage in long term.

The charge injections for monophasic stimulation and DC stimulation (for the same time of a phase of stimulation) were obtained higher than biphasic stimulations with large enough asymmetry.

The current threshold to induce block was decreasing with the fiber diameter. This is in accordance with the results reported in [16] for rectangular waveform based on CRRSS fiber model and in [15] for sinusoidal waveform based on MRG model.

The block threshold was absolutely increasing with the frequency in the tested range of 5-30 KHz. This is in accordance with the results reported in [9] for rectangular waveform based on Hodgkin and Huxley model of the membrane and in [17] based on Frankenhauser-Huxley model, and also in accordance with the results reported in [15] for sinusoidal waveform based on MRG model of the fiber.

Previous studies have suggested that a rapid block with minimum onset response can be achieved using high frequency and amplitude stimulation [18]. It is suggested that starting the stimulation with high frequency and amplitude and then reducing the frequency and amplitude of stimulation to the minimum can minimize the onset while keeping the current injection and tissue damage small in long term [19].

5. Conclusion

In this study, a detailed model of mammalian peripheral myelinated fibers was implemented to suggest that high frequency asymmetric

biphasic rectangular stimulation is more efficient in blocking the neural fibers, in comparison with the previously used sinusoidal and symmetric rectangular stimulations.

The inconvenience of the onset response and the tissue damage of long term stimulation are two problems that prevent the clinical acceptance of HFAC. The proposed waveform can reduce the tissue damage significantly due to much smaller charge injection required. Therefore, the authors believe that this study is a significant step towards the clinical use of HFAC stimulation, though the onset response still exists and should be eliminated by some other methods.

A relationship between the current threshold with the stimulation frequency and fiber diameter was shown which was qualitatively similar to the previous reports for other waveforms and models.

In the future studies, the results presented here based on simulation of electrical stimulation should be validated experimentally, and the above described method can also be tested to evaluate the resulted onset response, so that a safe and reversible protocol of stimulation is developed for clinical trials.

Acknowledgements

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