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High Frequency Mammalian Nerve Conduction Block: Simulations and Experiments

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Abstract—**High frequency alternating current (HFAC) sinusoidal waveforms can block conduction in mammalian peripheral nerves. A nerve simulation software package was used to simulate HFAC conduction block in a mammalian axon model. Eight axon diameters from 7.3 μm to 16 μm were tested using sinusoidal waveforms between 1 kHz to 40 kHz. Block was obtained between 3 kHz to 40 kHz and the current threshold for block increased linearly with frequency above 10 kHz. Conduction block was also obtained for all axon diameters, and the block threshold varied inversely with diameter. Upon initiation, the HFAC waveform produced one or more action potentials. These simulation results closely parallel previous experimental results of high frequency motor block of the rat sciatic nerve. During steady state HFAC block, the axons showed a depolarization of multiple nodes, suggesting a possible depolarization mechanism for HFAC conduction block.**

I. Introduction

Undesirable hyper-activity of neurons characterizes many diseases and results in pathological motor or sensory effects. Blocking these action potentials could help alleviate pain or stop unwanted motor effects such as muscle spasms and spasticity. High-frequency alternating currents (HFAC), applied directly to the nerve, have been shown to produce a quick-acting, quick reversing conduction block with a minimum of side effects [1]-[5]. Existing methods for treating these conditions, such as pharmacological, chemical treatments or surgical intervention all have significant disadvantages and are not consistently successful. Therefore, there remains a widespread clinical need for an effective, reliable and reversible nerve block that does not damage neural tissue.

The aim of this study was to understand the fundamental characteristics of the nerve response to HFAC waveforms at frequencies greater than 1 kHz. Investigators are just beginning to utilize mathematical models of the nerve membrane in order to develop an understanding of this phenomenon. Rattay showed an example of HFAC nerve conduction block at 2 kHz [6] in an unmyelinated Hodgkin-Huxley model. Tai et al. has presented sine wave block in an unmyelinated Hodgkin-Huxley model (at a temperature of 18.5 °C) [7]. Williamson and Andrews performed simulations in mammalian axon models [5] using sinusoidal waveforms and demonstrated conduction block between 5 to 20 kHz.

We previously identified several key features of high frequency motor block through randomized and repeated in-vivo experiments on the rat sciatic nerve using gastrocnemius muscle force as an output measure [4]. Voltage controlled HFAC sinusoidal waveforms at frequencies from 10 kHz to 30 kHz induced a complete and reversible motor block at all frequencies. There was a specific voltage, termed the block threshold, at each frequency, below which block was not obtained. These block thresholds showed a linear relationship with frequency where block threshold increased with increasing frequency. We identified three phases in the block phenomenon: an onset response consisting of a muscle twitch with a peak 2 to 8 times that of a normal twitch, a period of repetitive firing that varied in duration and a final steady state of complete or partial block. The onset activity (the first two phases) had a characteristic relationship in the amplitude-frequency space: repetitive firing was minimized at the highest frequencies and highest amplitudes.

The present simulation study was conducted to investigate the effects of HFAC frequency, axon diameter and electrode-to-nerve distance on the blocking response of an axon to sinusoidal HFAC in a mammalian axon model. Block threshold, defined as the minimum current needed to maintain block, was used as a standard measure across all variables under test. We also explored the onset response of the axon to HFAC, and the mechanism of block in the mammalian model. Finally, we analyzed the modeling results in the context of our previous experimental findings from mammalian peripheral nerve [4].

II. Methods

Computer simulations were carried out in Neuron (version 5.8), a nerve simulation software [8]. A mammalian axon model (the "MRG model") was developed by McIntyre et al. [9]. The nerve membrane model consisted of quantitatively defined equivalent electrical circuits for both the node and internode regions of the axon [9]. The nodes incorporated membrane dynamics for fast sodium, slow sodium, slow potassium and leakage channels. The simulation temperature was 37°C.

A 51 node model was used and the HFAC waveform was applied through an external point source electrode in a homogenous isotropic extracellular environment. The nodes at each end of the axon are sealed so that no current flows out of the axon. Block was analyzed by stimulating the axon

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at node 0 and testing conduction of action potentials through the axon by recording action potentials at node 50, as shown in Figure 1.

Block was evaluated for axon diameters from 7.3 µm to 16 µm using sinusoidal HFAC at frequencies between 1 kHz to 40 kHz.

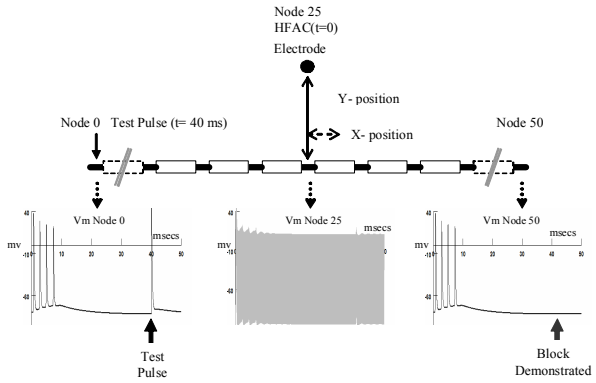

Figure 1. The myelinated axon model used to simulate sinusoidal high frequency block. A 51 node model is shown with an extracellular electrode placed opposite the central node (X position) at a distance of 1 mm from the axon (Y position). The bottom three panels show transmembrane voltages for nodes 0, 25, and 50 for a 50 ms simulation run. The simulation starts at t=0 with a 10 kHz HFAC sinusoid at 1.154 mA amplitude (2 µA above block threshold) in a 10 µm fiber. This HFAC initiates 4 APs at the onset before reaching a dynamic steady state (transmembrane voltage in node 25 fluctuates in phase with the HFAC sinusoid but maintains an average depolarized value). A test pulse is then injected at node 0 at t = 40 ms. This test pulse causes an action potential as seen in the panel for node 0 which is blocked as shown in the right panel for node 50.Block diagram of experimental setup.

III. Results

Conduction block was consistently obtained for all frequencies tested between 3 kHz and 40 kHz and for all axon diameters. An example of conduction block in the simulation is shown in Figure 1. Block could not be achieved below 2.2 kHz. With sufficient current, the only result was continuous firing of the axon. Inconsistent block was obtained between 2.2 to 3 kHz and was accompanied by numerous onset action potentials (APs). Previously, the only mammalian simulations done for HFAC conduction block were in topologically simpler axonal models and block was demonstrated between 5 to 20 kHz [5].

The thresholds increased monotonically, but in a non-linear manner, between 3 to 10 KHz, while between 10 to 40 kHz the block thresholds showed a linear relationship versus frequency (Figure 2). Previously, the concept of a block threshold has been hinted at [5] but not utilized as a measure of block across test variables. We believe that block threshold determinations are an important measure of HFAC block which allows comparisons across variables and across studies.

Figure 3 shows the relationship of block threshold to the diameter of the axon. Larger axons needed less current to be blocked. The difference in the thresholds for different diameters was also influenced by the frequency of the HFAC. Thus, smaller axons showed a larger threshold difference between different frequencies (higher frequencies

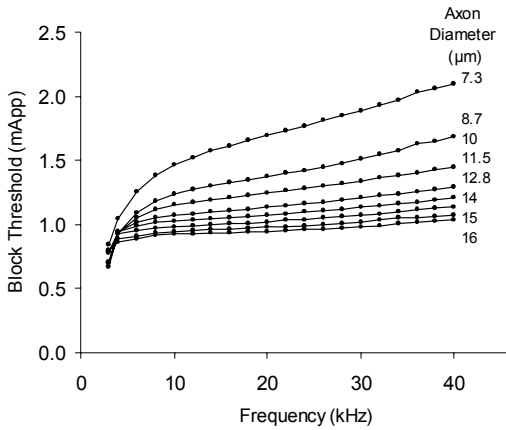

Figure 2. Block threshold as a function of HFAC sinusoid frequency showing block threshold in mA (peak to peak) over the frequency range of 3 to 40 kHz for all diameters modeled. No block was obtained below 2.2 kHz.

always needing larger currents). For the largest diameters, the threshold differences between different frequencies were much smaller. At the lowest frequencies, block was almost independent of diameter (Figure 3).

The application of HFAC produced a consistent pattern in the response of the axon as a function of increasing amplitude. At very low amplitudes there was a local change in transmembrane voltage, which followed the phases of the HFAC waveform, without producing any APs. As the amplitude was increased there was a threshold at which a single AP could be produced (Figure 4: line a). With minimal increase in amplitude, the axon responded with continuous firing, at approximately 300 to 450 Hz, that increased in frequency as amplitude increased. Further increase in amplitude caused a reduction in the firing rate.

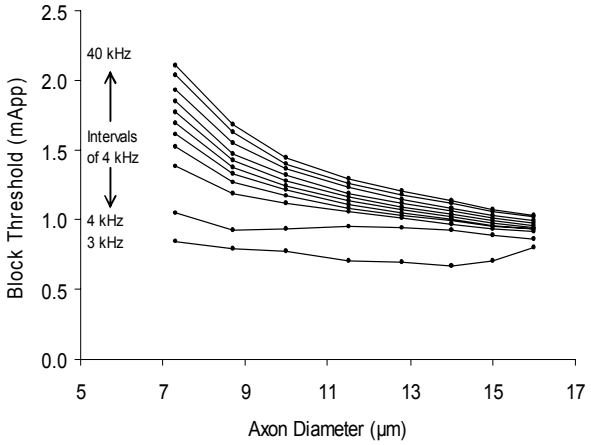

Figure 3. Block thresholds plotted as a function of axon diameter for frequencies between 3 and 40 kHz. Thresholds are lower for larger diameter axons. At 3 and 4 kHz, there is absence of axon size dependency.

However, the APs remained continuous. Finally, the number of APs again became finite at current levels that were approximately 0.6 to 0.7 times the block threshold. Further

decrease in the number of APs occurred before conduction block was attained at block threshold. Amplitudes higher than the block threshold maintained the conduction block and decreased the initial number of APs to between one and three. It was never possible to obtain a conduction block without firing at least one initial AP. Once block was obtained, all amplitudes above that threshold (amplitudes as high as four times block threshold were tested) also produced block with no increase in the initial firing.

Electrical currents produce activation or block of nerve conduction through their influence on the voltage-gated ion channels in the nerve membrane. This is accomplished either through a hyperpolarization block, in which the activation gates are caused to close; or a depolarization block, in which the inactivation gates are caused to close [10]. As shown in Figure 5, the nodes underneath the electrode experience an average depolarization during HFAC block, despite the fact that the current delivered by the electrode is charge-balanced. We found that the *average* steady-state depolarization for the node directly under the electrode was an excellent predictor of whether the axon would be blocked, regardless of other parameters such as frequency and axon diameter. Remote to the electrode, the axon has regions of slight hyperpolarization, but these are not sufficient to block conduction. Therefore, HFAC appears to block nerve conduction through the depolarization mechanism rather than a hyperpolarization mechanism.

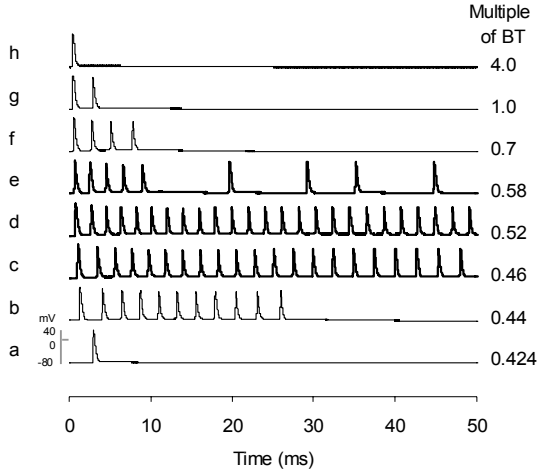

Figure 4. Onset firing in a 16 µm axon using a 20 kHz HFAC sinusoid at a 1 mm electrode-to-axon distance using current amplitudes which were multiples of the block threshold (0.964 mA). Thick black lines (c, d, and e) indicate continuous and infinite firing. At 0.424 x block threshold (a) there is a single action potential fired. As amplitude is raised, the number and frequency of the firing increases (b, c, and d) and then this trend reverses above 0.52 x block threshold (e and f) until only 2 action potentials are fired at block threshold (g). At 4 x block threshold only one action potential is fired (h).

IV. Discussion

We have demonstrated conduction block in the MRG mammalian model over a wide range of frequencies, between
3 kHz to 40 kHz (Figure 2). Block was inconsistent between 2.2 to 3 kHz. Continuous repetitive APs were fired below 2.2 kHz and block was unattainable. Frequencies above 40 kHz also produced block. However, for this study, we used 40 kHz as our upper frequency cutoff. Previously, the only mammalian simulations done for HFAC conduction block were in topologically simpler axonal models and block was demonstrated between 5 to 20 kHz [5].

Experimentally, we obtained consistent and repeatable motor block over the range of 10 to 30 kHz in in-vivo experiments on the rat sciatic nerve [4] with voltage-controlled sinusoids and using gastrocnemius muscle force as an output measure. HFAC higher than 30 kHz also produced block but we did not explore that range in depth since we constrained the maximum blocking voltage to 10 Vpp. At frequencies lower than 10 kHz, continuous tetanic or intermittent contractions of the gastrocnemius muscle were observed. The continuous firing below 2.2 kHz, seen in our modeling, relates to this experimental continuous AP production resulting in either muscle or neuromuscular junction fatigue.

The block thresholds from the model showed a non-linear relationship to the HFAC frequency between 3 kHz to 10 kHz and a linear relationship between 10 kHz to 40 kHz (Figure 2). In our experiments we measured block thresholds by stepping the amplitude in 1 Vpp decrements from 10 Vpp and noting the minimum voltage at which complete block persisted. Our experimental results showed a robust linear relationship of voltage controlled block thresholds to the sinusoidal frequency between 10 kHz to 30 kHz [4]. The voltage threshold at 30 kHz was approximately 9 Vpp compared to 3 Vpp at 10 kHz. Due to the variability in the electrode impedance between animals this corresponded to blocking currents of 1 mA to 11.8 mA. In the model, the range of current across all axon diameters and HFAC frequencies for a representative 1 mm electrode-to-axon distance was 0.8 mA to 2.1 mA (0.93 mA to 1.89 mA between 10 kHz to 30 kHz for all diameters). We believe that experimental block threshold determinations are an important measure of HFAC block which allows comparisons across variables and across studies. The results of this study demonstrate that high frequency sinusoidal waveforms can produce a block of nerve conduction in whole mammalian motor nerves. The block is demonstrated to be 100% effective in blocking motor activity and is completely reversible in less than 1 second.

The block onset is often marked by a large "on" response. Experimentally, we found two phases in the onset activity of HFAC motor block. The first phase was the onset response which manifested as a large summated twitch in the muscle. Karu et al [11] have shown in human experiments that N-let stimulation (where N was a number of rapid stimulation pulses of two or more) resulted in summation of

twitch force which could be as large as six times a normal single muscle twitch (when N = 6). The N-let response is a summated muscle twitch and includes muscle physiology that is not a part of the axon model. However, the N-let phenomenon is produced by repeated stimulation of the nerve at a high frequency, so it is reasonable to expect that repetitive firing in the nerve will produce a similar N-let twitch response. We hypothesized that this onset response is a result of the HFAC initially stimulating the nerve at the maximal rate that the refractory period of the nerve allows, leading to an N-let response from the muscle. Our model results show this type of activity at onset with the number of onset APs being between two and five at block threshold.

In our in-vivo experiments we obtained onset response amplitudes in the range of one to eight times that of single twitch amplitudes [4]. Bowman and McNeal identified an initial firing in the nerve (at a rate of 500 Hz) at the onset of the block that lasted one to two seconds [2]. Woo and Campbell, investigated HFAC block in cats using single fiber recordings and found that the axons went through a period of rapid firing before a true conduction block occurred [1]. Similar responses from a mammalian axon model have been previously described [5].

The second phase in the onset phenomenon in our experiments was a period of tetany or repetitive fasciculations of parts of the muscle [4]. This activity showed a typical relationship in the HFAC frequency-amplitude space, being decreased with combined higher frequencies and higher amplitudes. The model results show similar trends with the frequency and total time of repetitive firing being affected by both the HFAC frequency and the current amplitude. Our model does not incorporate the frequency-dependent impedance of the electrode-to-nerve interface and thus cannot fully depict the onset phenomenon. In the future, finite element models of electrodes that have realistic representations of the electrode surface and current distributions, combined with frequency dependant modeling of the extracellular impedance, could help explain the phenomenon of repetitive firing.

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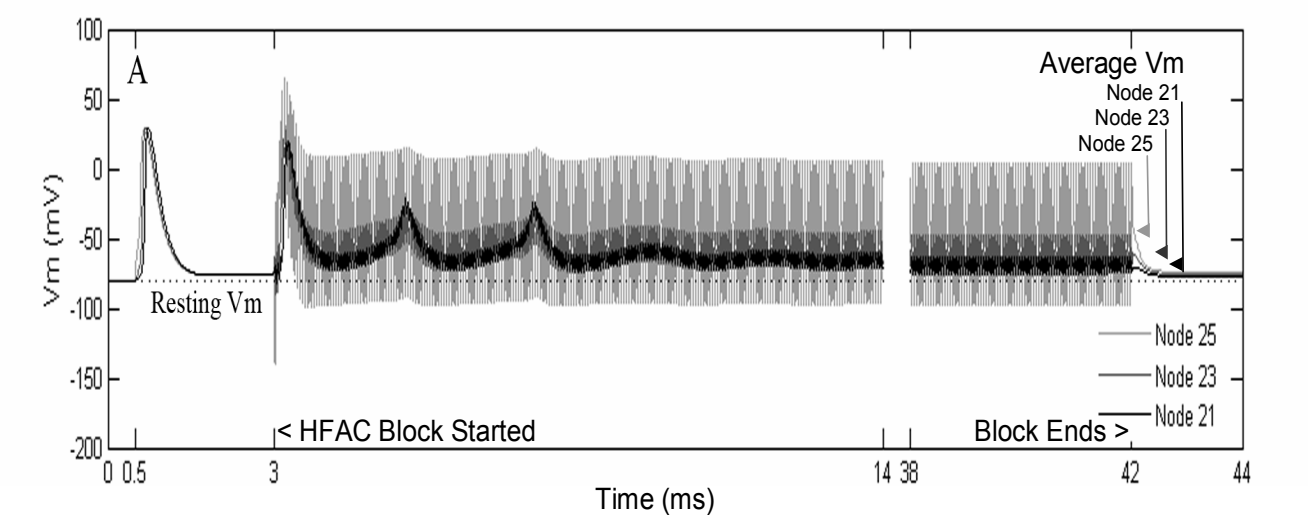

Figure 5. Transmembrane voltage over time during HFAC block for the node directly under the electrode (Node 21) or lateral to the electrode (Nodes 23 and 25). The transmembrane voltage at the lateral nodes oscillates but is always depolarized, despite the fact that the HFAC is charge balanced. The central node maintains an average depolarization of approximately -50mV. When the HFAC is turned off (at 42ms), the transmembrane voltage jumps to the average level before decaying down to the resting voltage.