Published in final edited form as:

IEEE Trans Neural Syst Rehabil Eng. 2009 October ; 17(5): 469–477. doi:10.1109/TNSRE.2009.2034069.

Effect of Bipolar Cuff Electrode Design on Block Thresholds in High-Frequency Electrical Neural Conduction Block

D. Michael Ackermann Jr. [Graduate Student Member, IEEE],

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44109 USA and also with Cleveland FES Center, Cleveland, OH 44109 USA

Emily L. Foldes,

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44109 USA

Niloy Bhadra [Member, IEEE], and

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44109 USA

Kevin L. Kilgore

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44109 USA, and also with the Department of Orthopedics, MetroHealth Medical Center, Cleveland, OH 44109 USA, and also with Louis Stokes Veterans Affairs Medical Center, Cleveland, OH 44106 USA

D. Michael Ackermann: dma18@case.edu

Abstract

Many medical conditions are characterized by undesired or pathological peripheral neurological activity. The local delivery of high-frequency alternating currents (HFAC) has been shown to be a fast acting and quickly reversible method of blocking neural conduction and may provide a treatment alternative for eliminating pathological neural activity in these conditions. This work represents the first formal study of electrode design for high-frequency nerve block, and demonstrates that the interpolar separation distance for a bipolar electrode influences the current amplitudes required to achieve conduction block in both computer simulations and mammalian whole nerve experiments. The minimal current required to achieve block is also dependent on the diameter of the fibers being blocked and the electrode–fiber distance. Single fiber simulations suggest that minimizing the block threshold can be achieved by maximizing both the bipolar activating function (by adjusting the bipolar electrode contact separation distance) and a synergistic addition of membrane sodium currents generated by each of the two bipolar electrode contacts. For a rat sciatic nerve, 1.0–2.0 mm represented the optimal interpolar distance for minimizing current delivery.

Index Terms

Bipolar; depolarization; electrode; high frequency; nerve block; nerve cuff; peripheral nerve

I. Introduction

The delivery of high-frequency alternating currents (HFAC) has been shown to be a reversible and fast acting method of blocking peripheral nerves, and may provide a nondestructive treatment alternative for eliminating undesired and pathological neural activity for pain relief and spasticity control. Specifically, HFAC in the range of 5–40 kHz, delivered through small electrodes in direct contact with a peripheral nerve, cause the nerve

to stop conducting action potentials within ~100 ms [1]. This block is completely reversible by turning the HFAC off, and in most cases the nerve returns to full conduction within one second. Recent studies have thoroughly explored the effects of high-frequency alternating currents on whole nerves in frogs [1], rats [2], and cats [3], [4] and have demonstrated that HFAC is an effective means for blocking whole nerve conduction. A comprehensive review of HFAC neural conduction block work can be found in Kilgore and Bhadra [1].

An important feature of HFAC nerve block is that the characteristics of the block are very dependent on the frequency and amplitude of the high-frequency waveform. A true conduction block requires frequencies above 2–5 kHz [2]. Below 2 kHz, HFAC produces prolonged activity in the nerve and muscle. This may produce a reversible muscle fatigue, but nerve conduction is not blocked [1], [3]. The maximum frequency for HFAC block has not been evaluated experimentally, although frequencies as high as 40 kHz have been successfully utilized.

The effect of amplitude on block has been studied in detail, both experimentally and in mathematical simulation [2], [5], [6]. HFAC block requires sufficiently high amplitude in order to be effective. A “block threshold” has been identified, which is defined as the lowest amplitude at which an entire nerve is blocked. The block threshold increases with increasing frequency [2], [3], [5], [6]. If the amplitude of the HFAC is above block threshold, conduction block is maintained. It has been demonstrated that there is an amplitude region below block threshold where the HFAC produces a significant and prolonged nerve activity. This activity occurs when the amplitude of the HFAC is approximately 50%–70% of the block threshold [5], [7]. It is desirable to minimize the block threshold, because that enables HFAC block to be obtained with a minimal charge injection to the nerve and with minimal power requirements. In this manuscript, we examine whether electrode geometry can play a role in minimizing the HFAC block threshold.

As early as 1939, it has been known that electrode configurations could have an effect on the quality of HFAC block [8]. However, no formal study of the effects of electrode design on high-frequency block has been previously performed. As shown in Table I, a multipolar cuff electrode is the most commonly utilized method for producing HFAC block in previous animal studies [1]–[14]. About half of these studies have utilized electrodes with bipolar contacts. Because all of these studies utilized various waveform parameters and electrode materials, it is not possible to compare the published results to determine if specific electrode designs result in lower HFAC block thresholds. The present study focuses on a bipolar cuff electrode design and evaluates the effect of electrode contact separation distance on the block threshold. This is performed through computer simulations of mammalian axons and *in vivo* mammalian whole nerve experiments. A biophysical explanation for the observed phenomena is presented based on the simulations.

II. Methods

The effect of bipolar electrode spacing on HFAC nerve block was evaluated using both nerve membrane simulation and experimental *in vivo* testing. The nerve membrane simulations allowed rapid testing of a variety of parameters and can be utilized to predict the results of *in vivo* experimentation.

A. Double-Cable Myelinated Nerve Fiber Model (MRG Model)

All simulations were performed in the Neuron simulation environment [15]. Single fiber axons were simulated using the MRG double-cable myelinated fiber model [16]. This model has previously been shown to be consistent with experimental observations of HFAC block [5]. As depicted in Fig. 1, the cable model is composed of single-segment nodal sections

composed of linear and nonlinear circuit elements, and multisegment double-layered internodal sections incorporating linear dynamics. The nonlinear nodal dynamics are of the Hodgkin–Huxley type [17], parameterized to match mammalian spike physiology [16]. The nonlinear components pertain to dynamics relevant for fast sodium, persistent sodium and slow potassium channels. Axon diameters of 5.7 μm , 7.3 μm , 10.0 μm , and 15.0 μm were evaluated. All axon-specific parameters are identical to those in [16], and are reproduced in Table II. The model was solved using backward Euler implicit integration using a time-step of 0.0045 ms.

B. Simulation Protocol for Bipolar Electrode Contact Separation

Both 51 node and 101 node axon models were evaluated for these simulations. Most simulations were performed in the 51 node model. The 101 node model was used for simulations of bipolar electrodes with intercontact separation distance greater than six node lengths, because block thresholds were influenced by edge effects for these simulations in a 51 node model. As shown in Fig. 1, two types of electrodes were simulated in the model as point sources: an extracellular bipolar electrode for delivery of the HFAC and an intracellular monopolar electrode to test for conduction block. The extracellular environment was assumed to be isotropic and homogenous with an extracellular resistivity of 500 Ωcm [18]. One of the extracellular bipolar electrode contacts was placed either directly above the center node, or above the center of the internode adjacent to the center node. The other contact was placed equidistant from the fiber and at various distances from the first contact. Electrode–fiber distances of 0.25 mm, 0.50 mm, 1.0 mm, and 1.50 mm were simulated. The bipolar separation distance ranged from 0.125–12 times the length of an internodal segment. Zero-mean 10 kHz sinusoidal currents were delivered through the bipolar electrode (current flowing from one electrode contact to the other). Preliminary simulations indicated that the waveform frequency did not significantly influence the effect of bipolar separation distance, so a frequency of 10 kHz was chosen to allow for a larger simulation time-step and therefore a reduced computational time. The intracellular electrode was used to test whether conduction block was achieved, using the protocol described previously [5]. The amplitude of the extracellular high-frequency current was varied using a binary search to find the block threshold (minimal current at which the axon achieved conduction block) with a resolution of 7 μA . For amplitudes at which block could be achieved, fiber activity stabilized within approximately 30 ms [5]. After 40 ms of the HFAC delivery a 0.1 ms, 10 nA current pulse was delivered at Node 0 (at one end of the fiber) using the intracellular electrode. The fiber was determined to be blocked if the action potential did not propagate through to the last node on the other side of the blocking electrode. The output measure of these simulations was the block threshold.

For a subset of the simulations (fiber diameter of 10.0 μm , electrode–fiber distance of 1.0 mm and bipolar separation of 0–8.0 mm), the second spatial difference of the extracellular voltage generated by the stimulating electrode was calculated along the fiber. This function has been termed the activating function [19] and has been shown to be a good predictor of membrane depolarization and excitation threshold for the stimulation of neurons [20]. The maximum of this function for a given bipolar contact separation distance was calculated by choosing the largest value of this discrete function as calculated for that separation distance.

C. Animal Experiments and Surgical Procedure

Acute experiments were performed in adult Sprague–Dawley rats. All protocols involving animal use were approved by our institutional animal care and use committee. The animals were anesthetized with intraperitoneal injections of Nembutal (Phenobarbital sodium). The left hind leg was shaved and an incision was made along the posterior aspect of the hind leg and thigh. The sciatic nerve was exposed from its most proximal aspect, just distal to the

sacral plexus, to the popliteal fossa. The common peroneal and sural nerves were severed. The gastrocnemius-soleus muscle complex was dissected, and the calcaneal (Achilles) tendon was severed from its distal attachment. The ipsilateral tibia was stabilized to the experimental rig via a clamp, and the calcaneal tendon was tethered to a force transducer with 1–2 N of passive tension. Fig. 2 shows the experimental setup.

Two nerve cuff electrodes were placed on the sciatic nerve as shown in Fig. 2. Both electrodes were silastic nerve cuff electrodes with a J-shaped cross-section and 3 mm × 1 mm rectangular platinum contacts for current delivery (the 1 mm dimension was along the longitudinal axis of the nerve) [2], [7]. The proximal electrode was used to generate gastrocnemius-soleus muscle twitches with the delivery of 1 Hz, 20 μ s supramaximal (typically 300–500 μ A) cathodic pulses. These pulses were delivered using a Grass S88 (Grass Technologies, West Warwick, RI) stimulator with a current-controlled output stage. This electrode was tripolar with 2.0 mm edge-to-edge contact spacing with the outer contacts electrically tied together. The proximal stimulating electrode was placed on the sciatic nerve within 1 cm of the sacral plexus. A distal electrode was used to deliver the HFAC blocking current. The distal electrode was bipolar with 1.0 mm of silastic between the edge of the two outer platinum contacts and each edge of the cuff. This electrode was placed such that the distal edge of the nerve cuff was at the common peroneal branch point as shown in Fig. 2. Current-controlled 40 kHz sinusoidal blocking waveforms were delivered through the bipolar electrode using a Keithley 6221 waveform generator.

Block thresholds were measured for the bipolar electrodes of various interpolar separation distances in five rats. Four bipolar separation distances were tested in each animal: 1.0 mm, 2.0 mm, 3.0 mm, and 4.0 mm were tested in two animals, and 0.5 mm, 1.0 mm, 2.0 mm, and 4.0 mm were tested in three animals. The order in which the electrodes were tested was block randomized for each animal, in three blocks. Each trial consisted of a period of approximately 5 s of 1 Hz proximal stimulation, followed by a period of proximal stimulation combined with a distal HFAC waveform. For each trial the HFAC amplitude was initially 9.0 mA_{peak}. After approximately 5 s (to allow for the onset activation to subside [2]), the amplitude of the high-frequency waveform was decremented by 0.1 mA per second until muscle twitches were detected. The lowest amplitude at which no muscle twitches were present was determined to be the block threshold. For trials in which 9.0 mA was not sufficient to block the nerve, the trial was repeated starting at 11.0 mA. For one trial 11.0 mA was not sufficient to block the nerve, and the block threshold was measured starting at 13.0 mA.

III. Results

A. Bipolar Block Simulations

The first plot in Fig. 3 shows the block thresholds found in bipolar block simulations for four fiber diameters with varying bipolar contact separations. The electrode contact closest to the intracellular electrode was fixed directly above the center node for these simulations, and the electrode to fiber distance was fixed at 1.0 mm. For all four fiber diameters, the block threshold was highest for the smallest separation distance. Block threshold decreased with increasing separation distance between 0 mm and 1.0 mm. Block thresholds reach a minimum at 2–3 node lengths for each of the fiber diameters simulated, as shown in Fig. 4. For separation distances larger than 3–4 node lengths the block threshold increases non-monotonically with increases in separation distance. Local minima tend to occur at separation distances that are integer multiples of the internodal length of the fiber, where both electrodes are directly over nodes. Local maxima occur when the second electrode is centered directly above an internode. This trend is particularly true for large diameter fibers.

The first plot in Fig. 3 shows that for large bipolar separation distances the block threshold asymptotically approaches the monopolar threshold for each fiber diameter simulated.

As is shown in Figs. 3 and 4, small diameter fibers have a higher threshold than large diameter fibers. The first plot in Fig. 3 shows that at very small separation distances, this difference becomes negligible, and at larger bipolar separation distances this difference in thresholds becomes more pronounced.

Fig. 5 shows the effect of the electrode–fiber distance on bipolar block thresholds with various interpolar separation distances for a $5.7\ \mu\text{m}$ fiber. There are two major trends with electrode–fiber distance. First, block thresholds increase nonlinearly with electrode–fiber distance for a given bipolar separation, as was previously shown for monopolar HFAC electrode simulations [5]. Second, the bipolar separation distance resulting in the minimum block threshold increases with electrode–fiber distance.

The second plot in Fig. 3 shows the maximum (peak value) of the activating function for a bipolar electrode [21] as a function of contact separation distance for an electrode–fiber distance of 1.0 mm. For a given bipolar separation distance, the peak of the activating function always occurs beneath the cathodic electrode at the peak of its sinusoidal blocking current. Since the blocking current is periodic in nature, the peak of the activating function occurs beneath one of the bipolar electrode contacts during one half-cycle and beneath the other electrode contact during the other half-cycle. As has been shown previously [22], this function exhibits a maximum at 1.25 times the electrode–fiber distance (1.25 mm in this simulation). The maximum of the bipolar activating function drops to zero when the distance between the bipolar electrodes is zero. The bipolar activating function asymptotically approaches the value of the monopolar electrode activating function for increases in the bipolar electrode separation greater than 1.25 mm. The bipolar activating function is within 5% of the maximum monopolar value at a separation distance of 3.0 mm.

It has previously been shown through simulation that when a fiber is blocked by HFAC, the nodal membrane potential near the electrode is maintained in a mean depolarized state due to a net inward sodium current [5]. The third plot in Fig. 3 shows the mean nodal membrane potential at each of the nodes along fibers of all four diameters at block threshold electrode current for a point source electrode at a distance of 1.0 mm from the fiber. As was shown previously [5], the mean nodal depolarization decays at a spatial rate that is dependent on the fiber diameter. For example, the mean depolarization decays to resting membrane potential by 5 mm from the electrode for $5.7\ \mu\text{m}$ fibers and decays to resting membrane potential by 7.5 mm for the $7.3\ \mu\text{m}$ fibers.

Fig. 6 shows the mean nodal membrane potential along a $7.3\ \mu\text{m}$ axon for an electrode–fiber distance of 1.0 mm at block threshold electrode current for both a monopolar and bipolar electrode. The bipolar electrode has a contact separation of 3.0 mm (four node lengths), and results in a double-peaked depolarization profile. The peaks of both depolarization profiles correspond to the nodes closest to the electrodes, and have equal values of $-53.9\ \text{mV}$. The monopolar electrode has a single-peak profile, with a peak potential of $-49\ \text{mV}$ corresponding to the node closest to the electrode. This dynamic steady-state depolarization is consistent with that previously published for monopolar simulations [5].

B. Experimental Results

Fig. 7 shows an example of complete conduction block using an electrode with a bipolar separation distance of 2.0 mm. The figure depicts a trial in which the block threshold was measured by decreasing the blocking current amplitude until partial nerve conduction block allows for small amplitude muscle twitches to be generated from the proximal stimulation.

The absence of muscle twitches during a proximal stimulation pulse indicates complete conduction block, and small amplitude muscle twitches indicate partial conduction block. The circle in Fig. 7 highlights the first muscle twitch which results from a partially conducted proximal stimulation pulse.

Fig. 8 shows the experimentally measured block thresholds with bipolar separation distance. The error bars represent the standard error of the mean. The largest block thresholds were measured for the electrodes with a 0.5 mm separation. The smallest block thresholds were measured for electrodes with bipolar separations of 1.0 and 2.0 mm. The mean block thresholds increased with bipolar electrode separation from 2.0–4.0 mm. A Tukey–Kramer multiple comparison test ($\alpha = 0.05$) showed the following statistically different groups: the block thresholds for the 1 mm and 2 mm cases were shown to be statistically different than the 0.5 mm and 4.0 mm cases, but were not statistically different from each other.

IV. Discussion

Our experimental and simulation results show that the bipolar electrode separation distance has an effect on the amplitude of extracellular electrode current required to achieve HFAC neural conduction block. The use of low blocking current amplitudes is potentially important for maintaining neural safety and the integrity of the electrode [23]. Therefore, using an electrode geometry which will minimize this current is an important issue.

Our simulations and experimental results are consistent with one another and show a similar trend for the relationship between bipolar contact separation and block threshold. Figs. 3 and 5 suggest that the smallest fibers furthest from the electrode will dictate the threshold current for a mixed whole nerve since they require the most current to achieve block for all values of separation distance. A rat sciatic nerve has myelinated efferent fibers with diameters ranging from 3–14 μm (mean of approximately 6 μm) and has a radius of approximately 0.5 mm [24]. As shown in Fig. 5, the model simulations show that block threshold is minimized for bipolar separation distances of 1.0–2.0 mm for 5.7 μm fibers (the smallest fibers we were able to simulate) at an electrode–fiber distance of 0.5 mm (block thresholds are within 10% of the minima for 0.9 mm separation distance 1.6 mm). Our experimental results showed that the block threshold was minimized for a narrow range of bipolar separations (1.0–2.0 mm), which is consistent with the model predictions for small fibers over this range of separation distance and electrode–fiber distance (the largest electrode–fiber distance occurring in our experimental prep with a rat sciatic nerve of 1 mm diameter is approximately 0.5 mm). This suggests that if given the diameter and fiber distribution of a particular nerve, the model could be used to predict the optimal bipolar contact separation for producing block with the lowest current injection.

A biophysical explanation for the trend seen in block threshold and bipolar separation is suggested by the simulations. There appear to be two phenomena which contribute to the shallow concavity of the curves shown in the first plot in Fig. 3 and in Fig. 4. The first is that smaller extracellular fields are generated by bipolar electrode contacts when they are close together for a given current. This shunting effect results in large block thresholds for small separation distances. The second phenomenon contributing to the shape of these curves relates to the intracellular sodium currents that depolarize the cell membrane to a blocked state. An extracellular electrode delivering HFAC will induce depolarizing sodium currents at the nodes closest to it [5]. For a bipolar electrode, these currents are induced at two sites along the neuron. These currents act synergistically to contribute to membrane depolarization over a wide range of bipolar separation distances. As a result, less electrode current is required for a bipolar blocking electrode than is required for a monopolar blocking electrode.

We will first consider the shunting effect in greater detail. It has been shown in previous studies that current shunts between the contacts of a bipolar electrode when they are close together and results in high activating stimulation thresholds for a small separation distance [21], [22]. The activating function is a measure of how much an extracellular field will induce a change in membrane potential of a neuron fiber subjected to that field [21]. Previously published high stimulation thresholds shown for small bipolar separation distance have been shown to be associated with a small activating function at these narrow separation distances [21], [22]. As a result, larger electrode currents are required to depolarize a neuron to the point of firing [21]. The second plot in Fig. 3 shows the trend of the activating function with bipolar separation in detail. Similarly, in this study we found that thresholds for nerve block (rather than stimulation) also trend inversely with the maximum of the activating function in this range. This is very similar to the trend previously shown with activation thresholds [22]. The explanation for this trend is likely very similar to that offered for the trend seen in activation thresholds: at small separation distances bipolar electrodes generate a small extracellular field and therefore an activating function with a small magnitude. This small activating function in turn results in small changes in membrane potential for a given electrode current [21], [22]. These changes in membrane potential (which are oscillatory for HFAC delivery) are integral to generating the high-frequency block. High-frequency nerve block depends on a membrane depolarization resulting from a sodium current generated at the node(s) closest to the electrode [5]. This sodium current is nonzero-mean and is the result of an oscillating membrane potential [5]. Hence, to achieve sufficient depolarization to achieve conduction block, a sufficient electrode activating function is required. When the bipolar separation equals 1.25 times the electrode–fiber distance, the activating function is maximized [22]. For stimulating currents this separation value represents the absolute minima of a relatively narrow range of optimal bipolar contact spacing for minimizing activation thresholds [22]. However, as shown in Fig. 3, in high-frequency neural conduction block, the range for which the block threshold is minimized is broad and shallow relative to the range predicted by the activating function for nerve stimulation.

The reason for this broad and shallow range can be explained by the synergistic addition of sodium currents mentioned above. As shown previously by Bhadra, *et al.* [5], HFAC block depends on a net depolarization of the membrane caused by HFAC-induced inward sodium current. The spatially decaying membrane depolarization caused by this sodium current is shown in the third plot of Fig. 3 for four fiber diameters. Bipolar nerve block differs from bipolar nerve stimulation in an important way: bipolar HFAC block involves two contact sites where simultaneous sodium influx occurs since each contact acts as a cathode for one-half of a high-frequency cycle (in bipolar stimulation there is only one). Each of these two contacts acts to drive sodium into the neuron, with peak currents occurring during the cathodic cycle [5]. This inward nodal sodium current flows in both axial directions along the axon from the nodes closest to the electrode contacts, and this current leaks out of the membrane along the axon according to its axial and nodal membrane impedances just as classical cable theory predicts [21]. The spatial extent of the axial sodium current flow is sufficiently large (on the scale of millimeter) that the regions of current flow overlap for bipolar electrodes as demonstrated in the membrane depolarization plots shown in Fig. 6.

In short, the minima region shown in Figs. 3 and 4 occurs because the portions of the fiber activated by each of the bipolar electrode contacts contribute current to depolarize the membrane, and less current from a single node is required to achieve block than would be required when using a monopolar electrode. More specifically, the depolarized membrane potential generated at nodes beneath each of the electrode contacts results in an increased ohmic load (higher effective impedance) as seen by the sodium current generated by the other electrode contact. Because of this higher impedance, less inward sodium current (and

therefore less electrode current) is required at either electrode contact site to generate the same level of depolarization generated by a monopolar electrode. This augmentative effect is diminished for large bipolar separation distances due to the spatial decay of the membrane depolarization (as shown in the third plot of Fig. 3). For large bipolar separations, the effect is negligible and the bipolar block threshold asymptotically approaches the monopolar threshold.

As shown in Figs. 3 and 4, the block threshold shows a nonmonotonic increase with large bipolar separations. In these figures, local minima occur when both electrodes are centered over a node, and local maxima occur when one electrode is at the center of an internode. This phenomena is consistent with what has previously been shown for monopolar HFAC block [5], and simply occurs because the peaks of the activating function (which occur directly beneath the electrodes) are not well aligned with the nodes. This phenomenon is more pronounced for the large diameter fibers, because the internodal distances are larger than for the small diameter fibers.

This study focused on the effect of bipolar contact separation distance on block threshold. The bipolar electrode is the most simple multipolar electrode design and allowed for a straightforward investigation of multipolar electrode design in nerve block using HFAC. However, this work has implications for the effects of cuff electrode designs using more than two electrode contacts (e.g., tripolar, etc.). The findings of this study suggest that the intracellular depolarization profile resulting from a tripolar cuff, for example, would have three peaks, one induced by each electrode. The outer electrode contacts of a tripolar electrode each sink approximately half of the current generated by the inner electrode contact and would result in depolarization peaks of a lesser magnitude than the inner peak. These peaks would result in a lesser local depolarization than that generated by the center contact, potentially resulting in higher thresholds than bipolar electrodes for most contact separation distances. The lesser current at the outer peaks would very likely result in very high block thresholds for large tripolar separation distances since the total electrode current would need to be approximately twice the monopolar block threshold in the limit of large separation distances to prevent the generation of firing at the outer contacts (HFAC that is subthreshold for block results in continuous firing [2], [5], [7], [11]). Further work on the effects of electrode contacts with unequal currents on block thresholds is warranted.

The disparity in block thresholds between large and small diameter fibers, particularly for large bipolar separations, suggests that it may be possible to achieve fiber diameter selectivity in HFAC block. Selectively activating populations of small diameter fibers has been the goal of several studies attempting to mimic physiological recruitment of efferent neurons for motor neuroprosthetic systems [25]–[29]. For example, using a bipolar electrode with a wide electrode spacing (where the difference in block thresholds for the large and small fibers is the greatest) could potentially be used to block large fibers while leaving the small fibers in an activatable state.

V. Conclusion

We have shown through single fiber axon simulations and whole nerve animal experiments that block thresholds have a nonlinear relationship with bipolar electrode contact separation distance, and that there is a narrow range of bipolar separations for which the block threshold has a minima. The minimal current required to achieve block is also dependent on the diameter of the fibers being blocked and the electrode–fiber distance. For the rat sciatic nerve, this range was found to be 1.0–2.0 mm experimentally, which is consistent with our simulation results for small diameter fibers. As the bipolar contact separation approaches 4.0 mm, the block threshold is equivalent to monopolar electrodes and no advantage is gained

by utilizing a bipolar electrode with this distance of separation or larger. Single fiber simulations suggest minimizing the block threshold can be achieved by maximizing both the bipolar activating function and an augmentative interaction between inward sodium currents generated by each of the two bipolar electrode contacts. This study represents the first published formal study of electrode design for HFAC nerve block and suggests that multipolar electrode configurations can be manipulated to reduce charge injection at the electrode.

Acknowledgments

This work was supported by the National Institute of Biomedical Imaging and Bioengineering under Grant R01-EB-002091.

References

1. Kilgore K, Bhadra N. Nerve conduction block utilizing high-frequency alternating current. *Med Biol Eng Comput.* 2004; 42:394–406. [PubMed: 15191086]
2. Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. *Muscle Nerve.* 2005; 32:782. [PubMed: 16124008]
3. Bhadra N, Bhadra N, Kilgore K, Gustafson KJ. High frequency electrical conduction block of the pudendal nerve. *J Neural Eng.* 2006; 3:180. [PubMed: 16705274]
4. Tai C, Roppolo JR, de Groat WC. Block of external urethral sphincter contraction by high frequency electrical stimulation of pudendal nerve. *J Urol.* 2004; 172:2069. [PubMed: 15540791]
5. Bhadra N, Lahowetz E, Foldes S, Kilgore K. Simulation of high-frequency sinusoidal electrical block of mammalian myelinated axons. *J Comput Neurosci.* 2007; 22:313–326. [PubMed: 17200886]
6. Williamson RP, Andrews BJ. Localized electrical nerve blocking. *IEEE Trans Biomed Eng.* Mar. 2005 52(3):362. [PubMed: 15759566]
7. Miles JD, Kilgore K, Bhadra N, Lahowetz E. Effects of ramped amplitude waveforms on the onset response of high-frequency mammalian nerve block. *J Neural Eng.* 2007; 4:390. [PubMed: 18057506]
8. Rosenbluth A, Reboul J. The blocking and deblocking effects of alternating currents on nerve. *Am J Physiol.* 1939; 125:251–264.
9. Reboul J, Rosenbluth A. The action of alternating currents upon the electrical excitability of nerve. *Am J Physiol.* 1939; 125:205–215.
10. Baratta R, Ichie M, Hwang SK, Solomonow M. Orderly stimulation of skeletal muscle motor units with tripolar nerve cuff electrode. *IEEE Trans Biomed Eng.* Aug; 1989 36(8):836–843. [PubMed: 2759642]
11. Bowman B, McNeal D. Response of single alpha motoneurons to high-frequency pulse trains. *Appl Neurophysiol.* 1986; 49:121–138. [PubMed: 3827239]
12. Tanner JA. Reversible blocking of nerve conduction by alternating-current excitation. *Nature (London).* 1962; 195:712. [PubMed: 13919574]
13. Woo MY, Campbell B. Asynchronous firing and block of peripheral nerve conduction by 20 kC alternating current. *Bull Los Angel Neuro Soc.* 1964; 29:87. [PubMed: 14169956]
14. Boger A, Bhadra N, Gustafson KJ. Bladder voiding by combined high frequency electrical pudendal nerve block and sacral root stimulation. *Neurourol Urodynamics.* 2008; 27:435.
15. Hines ML, Carnevale NT. The NEURON simulation environment. *Neural Computat.* 1997; 9:1179.
16. McIntyre C, Richardson A, Grill W. Modeling the excitability of mammalian nerve fibers: Influence of afterpotentials on the recovery cycle. *J Neurophysiol.* 2002; 87:995–1006. [PubMed: 11826063]
17. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol.* 1952; 117:500. [PubMed: 12991237]

18. Richardson AG, McIntyre CC, Grill WM. Modelling the effects of electric fields on nerve fibres: Influence of the myelin sheath. *Med Biol Eng Comput.* 2000; 38:438. [PubMed: 10984943]
19. Rattay F. Analysis of models for external stimulation of axons. *IEEE Trans Biomed Eng.* 1986; 33:974. [PubMed: 3770787]
20. Warman EN, Grill WM, Durand D. Modeling the effects of electric fields on nerve fibers: Determination of excitation thresholds. *IEEE Trans Biomed Eng.* Dec; 1992 39(12):1244–1254. [PubMed: 1487287]
21. Rattay F. Analysis of models for extracellular fiber stimulation. *Biomed Eng.* 1989; 36:676–682.
22. Holsheimer J, Wesselink WA. Optimum electrode geometry for spinal cord stimulation: The narrow bipole and tripole. *Med Biol Eng Comput.* 1997; 35:493. [PubMed: 9374053]
23. Merrill D. Electrical stimulation of excitable tissue: Design of efficacious and safe protocols. *J Neurosci Methods.* 2005; 141:171. [PubMed: 15661300]
24. Prodanov D, Feirabend HKP. Morphometric analysis of the fiber populations of the rat sciatic nerve, its spinal roots, and its major branches. *J Comparative Neurol.* 2007; 503:85.
25. Van Bolhuis AI. A nerve stimulation method to selectively recruit smaller motor-units in rat skeletal muscle. *J Neurosci Methods.* 2001; 107:87. [PubMed: 11389945]
26. Grill WM, Mortimer JT. Stimulus waveforms for selective neural stimulation. *IEEE Eng Med Biol Mag.* Jul-Aug;1995 14(4):375–385.
27. Fang ZP, Mortimer JT. Selective activation of small motor axons by quasitrapezoidal current pulses. *IEEE Trans Biomed Eng.* Feb; 1991 38(2):168–174. [PubMed: 2066126]
28. Koldewijn EL. Selective sacral root stimulation for bladder control: Acute experiments in an animal model. *J Urol.* 1994; 151:1674. [PubMed: 8189596]
29. Lertmanorat Z, Durand D. Extracellular voltage profile for reversing the recruitment order of peripheral nerve stimulation: A simulation study. *J Neural Eng.* 2004; 1:202–211. [PubMed: 15876640]
30. Cattel M, Gerard R. The inhibitory effect of high-frequency stimulation and the excitation state of the nerve. *J Physiol.* 1935; 83:407–415. [PubMed: 16994640]
31. Joseph, L.; Haeffele, BD.; Butera, RJ. Conduction block induced by high frequency AC stimulation in unmyelinated nerves. *Conference Proceedings: ...IEEE EMBS Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. Conf.; 2007. p. 1719*
32. Gaunt R, Prochazka A. Transcutaneously coupled, high-frequency electrical stimulation of the pudendal nerve blocks external urethral sphincter contractions. *Neurorehabil Neural Repair.* 2009; 23:615. [PubMed: 19109445]
33. Ackermann D, Foldes E, Bhadra N, Kilgore K. Conduction block of peripheral nerve using high frequency alternating currents delivered through an intrafascicular electrode. *Muscle Nerve.* 2009

Biographies

D. Michael Ackermann, Jr. (GS'09) received the B.S. degree in biomedical engineering from Vanderbilt University, Nashville, TN, in 2004, and the M.S. degree in biomedical engineering, in 2007, from Case Western Reserve University, Cleveland, OH, where he is currently working toward the Ph.D. degree in biomedical engineering.

His research interests include neurostimulation, nerve conduction block, implantable device design, computational neuroscience and neuroprosthetics for the restoration of motor control and other applications.

Emily L. Foldes received the B.S. degree in electrical engineering and biomedical engineering from Washington University, St. Louis, MO, in 2004, and the M.S. degree in biomedical engineering from Case Western Reserve University, Cleveland, OH, in 2007.

She is currently working as a Biomedical Engineer in the Department of Biomedical Engineering at Case Western Reserve University, Cleveland, OH and is part of the Cleveland Functional Electrical Stimulation Center. Her research interests include using electrical stimulation and implantable medical devices for clinical applications.

Niloy Bhadra (M'05) received the M.B.B.S degree and the M.S. degree in orthopaedic surgery from Calcutta University, India, in 1982 and 1985, respectively, and the M.S. and Ph.D. degrees in biomedical engineering from Case Western Reserve University, Cleveland, OH, in 2000 and 2005, respectively.

He became a Fellow of the Royal College of Surgeons, Edinburgh, U.K., in 1989. He is currently Research Assistant Professor in the Department of Biomedical Engineering, Case Western Reserve University. His research interests include rehabilitation engineering, functional electrical stimulation, neural prostheses, and nerve conduction block.

Kevin L. Kilgore received the B.S. degree in biomedical engineering from the University of Iowa, Iowa City, in 1983, and the M.S. and Ph.D. degrees in biomedical engineering from Case Western Reserve University, Cleveland, OH, in 1987 and 1991, respectively.

He is currently FES Program Manager in the Department of Orthopaedics at MetroHealth Medical Center, Biomedical Engineer in the Research Service of the Louis Stokes Cleveland Veterans Affairs Medical Center, and Adjunct Assistant Professor in the Department of Biomedical Engineering, Case Western Reserve University. He is an Associate Director in the Cleveland FES Center. His research interests are in the clinical applications of functional electrical stimulation to provide hand and arm function for individuals with paralysis, and in the application of electrical currents to control unwanted neural activity.

Fig. 1.

The double cable myelinated axon model used to simulate high-frequency conduction block. The model included dynamics accounting the following ionic currents: slow potassium, K_s , fast sodium, Naf , persistent sodium, Nap , and linear leakage, Lk . The passive network representing the fiber geometry accounted for capacitance contributions from the nodal membrane, C_n , internodal axolema, C_i , and myelin sheath, C_m , and for bulk ionic conductance of axoplasm, G_a , periaxonal space, G_p , internodal axolema, G_i , and myelin sheath, G_m . A simulated extracellular bipolar point source electrode was placed opposite the central node, and an intracellular point source electrode was placed in the first node. Inset used with permission (McIntyre, Richardson and Grill 2004 [16]).

Fig. 2. Photograph of experimental prep. A: Toothed tendon clamp. B: Gastrocnemius-soleus muscle complex. C: Sciatic nerve. D: Bipolar block electrode. E: Tripolar proximal stimulation electrode.

Fig. 3.

Block thresholds with bipolar separation distance, maximum value of the activating function with bipolar separation distance and mean nodal membrane potential along axon during block. The abscissa is consistent between plots to allow comparison of the trend seen with block thresholds and the two phenomena that contribute it. The first plot shows simulation results showing block threshold as a function of the bipolar separation distance for fibers with diameters of 5.7 μm , 7.3 μm , 10.0 μm , and 15.0 μm . Monopolar thresholds for each fiber size are overlaid. Electrode–fiber distance was 1.0 mm for all simulations. The second plot shows the maximum value of the continuous activating function with bipolar separation distance; Electrode–fiber distance was 1.0 mm. The third plot shows the mean nodal membrane potential at quasi-steady-state, QSS, for each of the nodes along fibers of diameters 5.7 μm , 7.3 μm , 10.0 μm , and 15.0 μm at block threshold electrode current for a point source electrode. Electrode–fiber distance was 1.0 mm.

Fig. 4.

Simulation results showing block threshold with bipolar separation distance for fibers with diameters of 5.7 μm , 7.3 μm , 10.0 μm , and 15.0 μm . Monopolar thresholds for each fiber size are overlaid. Abscissa has been normalized to the internodal length of the fiber for each diameter. Electrodefiber distance was 1.0 mm for all simulations.

Fig. 5.

Simulation results showing block threshold with bipolar separation distance for a $5.7 \mu\text{m}$ fiber for various electrode-fiber distances (Yelec) with one electrode contact centered over a node. Overlaid is block threshold with bipolar separation distance for a $5.7 \mu\text{m}$ fiber with an electrode-fiber distance of 1.0 mm, and one electrode contact centered over an internode.

Fig. 6. Mean nodal membrane potential along a $7.3 \mu\text{m}$ axon at block threshold electrode current for both a monopolar and bipolar electrode with separation distance of 3.0 mm (four node lengths). Electrode–fiber distance was 1.0 mm.

Fig. 7.

Example of complete conduction block using an electrode with bipolar separation distance of 2.0 mm. The trial demonstrates measurement of the block threshold by decreasing the blocking current amplitude until partial nerve conduction block allows for small amplitude muscle twitches to be generated from the proximal stimulation. Arrows represent the timing of the proximal stimulation pulses. Grey bar shows the relative amplitude of the high-frequency sinusoidal current. The circle shows the first small amplitude muscle twitch resulting from partial conduction block as the blocking current amplitude is decreased.

Fig. 8.
Experimentally measured block threshold (mA) with bipolar separation distance. Points represent the mean block threshold for all experiments, error bars represent standard error of the mean.

TABLE I
Summary of Electrodes Shown in Published Studies to Produce Successful HFAC Conduction Block

First Author & Year	Electrode Type	Number of Contacts: (*=Mono, **=Bi, ***=Tri)	Electrode Conductor Material	Electrode Contact Separation Distance	Species
Cattell 1935 [30]	Not Described	Not Described	Silver & Calomel	Not Described	Frog (likely)
Rosenbluth 1939 [8]	Wires	**	Ag/AgCl	0.5 mm – 3.5 mm	Cat
Reboul 1939 [9]	Wires	**	Ag/AgCl	~ 1.0 mm (likely)	Cat
Tanner 1962 [12]	Not described	**	Platinum	Not Described	Frog
Woo 1964 [13]	Not described	**	Not Specified	Not Described	Frog / Cat
Baratta 1989 [10]	Cuff	***	Stainless Steel	3.0 mm	Cat
Bowman 1986 [11]	Cuff	**	Braided Platinum	Not Described	Cat
Kilgore 2004 [1]	Cuff	**	Platinum Wire Coils	5.0 mm	Frog
Tai 2004 [4]	Cuff	***	Stainless Steel	~ 2.0 mm (likely)	Cat
Williamson 2005 [6]	Cuff	***	Stainless Steel	4.0 mm	Rat
Ni, Bhadra 2005 [2]	Cuff	***	Platinum	2.0 mm	Rat
Na, Bhadra 2006 [3]	Cuff	***	Platinum	Not Described	Cat
Miles 2007 [7]	Cuff	***	Platinum	2.0 mm	Rat
Joseph 2007 [31]	Suction	**	Glass with electrolyte (likely)	Not Described	Sea Slug
Boger 2008 [14]	Cuff	***	Platinum	Not Described	Cat
Gaunt 2009 [32]	Cuff	**	Stainless Steel	2.0 mm	Cat
Ackermann 2009 [33]	Intrafascicular μ Wires	**	Stainless Steel / Tungsten	1.5 mm–3.0 mm	Rat

TABLE II

Model Parameters

Parameter	Value
Axoplasmic Resistivity	70 Ω -cm
Internodal Capacitance	2 μ F/cm ²
Internodal Section Length (x6)	Diameter Dependent
Internode Segment Conductance	0.0001 S/cm ²
K ⁺ Nernst Potential	-90 mV
Leakage Reversal Potential	-90 mV
Main Paranode Length	Diameter Dependent
Main Segment Paranode Conductance	0.0001 S/cm ²
Maximum fast Na ⁺ Conductance	3 S/cm ²
Maximum persistent Na ⁺ Conductance	0.01 S/cm ²
Maximum slow K ⁺ Conductance	0.08 S/cm ²
Myelin Attachment Paranode Conductance	0.001 S/cm ²
Myelin Attachment Paranode Length	Diameter Dependent
Myelin Capacitance	0.1 μ F/cm ²
Myelin Conductance	0.001 S/cm ²
Na ⁺ Nernst Potential	50 mV
Nodal Capacitance	2 μ F/cm ²
Nodal Leakage Conductance	0.007 S/cm ²
Node Length	1 μ m
Periaxonal Resistivity	70 Ω -cm
Resting Membrane Potential	-80 mV
Temperature	37° C