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Predicting myelinated axon activation using spatial characteristics of the extracellular field

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Abstract

Computation time required for modeling the nonlinear response of an axon to an applied electric field is a significant limitation to optimizing a large number of neural interface design parameters through use of advanced computer algorithms. This paper introduces two methods of predicting axon activation that incorporate a threshold that includes the magnitude of the extracellular potential to achieve increased accuracy over previous computationally efficient methods. Each method employs the use of a modified driving function that includes the second spatial difference of the applied extracellular voltage to predict the electrical excitation of a nerve. The first method uses the second spatial difference taken at a single node of Ranvier, while the second uses a weighted sum of the second spatial differences taken at all nodes of Ranvier. This study quantifies prediction accuracy for cases with single and multiple point source stimulating electrodes. While both new methods address the major criticism of linearized prediction models, the weighted sum method provides the most robust response across single and multiple point sources. These methods improve prediction of axon activation based on properties of the applied field in a computationally efficient manner.

1. Introduction

Animal models are common developmental tools for testing design factors in peripheral nerve interfaces, but anatomical differences between animal models and humans limit the direct translation to clinical application (Grinberg et al. 2008; Brill, K. Polasek, et al. 2009a). Computer models of neural interfaces are a vital tool to help fill the gap between preclinical and clinical testing when used to evaluate electrical interface designs.

Number and placement of electrodes, the stimulus amplitude, and the pulse duration at each electrode all influence the activation pattern within a nerve by affecting the resultant electric field. Calculation of the resultant field can be performed in several ways, and is outside the scope of this work. Determining axon activation within an electric field begins with sampling the electric potential in space along the length of an axon, creating a vector of voltages. This vector is applied to a model of the axon as a function of time, and the response of the nonlinear ion channels is solved numerically (McNeal 1976; Schiefer et al. 2008; Lu et al. 2008; McIntyre et al. 2002). This is a process that works well when predicting behavior of individual axons, but becomes a limitation when expanded to simulations of the whole nerve where hundreds to thousands of axons are solved numerically (Schiefer et al. 2008; Veltink et al. 1988). The work presented by Schiefer *et al.* involved simulating the activation patterns in a histology-based model of the human femoral nerve and required almost 24 million axon simulations taking approximately 90 days of computation time to complete (Schiefer et al. 2008). Schiefer *et al.* only investigated cases with one of 22 electrodes was active at a time. Expanding the investigation from a single

active contact to include two or three simultaneously active contacts would increase the number of electrode configurations to investigate from 22 to 231 or 1540, respectively. The increase in the number of combinations virtually eliminates the possibility of investigating field shaping with multiple active contacts or using evolutionary optimization methods for interface design.

The computational complexity of modeling axon response can be reduced by replacing the nonlinear ion channel dynamics with linearized approximations, but early attempts did not scale well to nerve-level modeling. McNeal's method of replacing nonlinear node dynamics with linearized versions required *a priori* knowledge of the electric field before the model could be simplified (McNeal 1976). Rattay's work focused on analyzing electric field shape to predict activation. Rattay's method could only provide relative axon recruitment order, though, requiring simulation using the nonlinear equations to determine activation (Rattay 1989). Warman *et al.* (Warman et al. 1992) developed an activation function dependent only on the second spatial difference of the voltage field ($\Delta^2 V_e$), an activation threshold, and the duration of the applied pulse. Determining the activation threshold required a one-time simulation of the nonlinear axon, but once completed, prediction of axon response was a purely algebraic function. This method has been used to enable evolutionary optimization algorithms for electrode design (Choi & Lee 2006). The accuracy of this method, however, has an undesirable dependence on electrode-to-axon separation (Moffitt et al. 2004). The dependency of the error in the Warman method as a function of separation is well behaved. Consequently, we hypothesize that a more accurate prediction is possible by accounting for the dependence of the activation threshold on magnitude of the extracellular voltage to predict activation.

2. Methods

This work presents two methods of predicting axon activation, one based on the second spatial difference of the extracellular potential at a single node. The second implements a weighted sum of the second spatial difference at all nodes. The performance of each was examined under conditions relevant to whole nerve simulation, and compared to results of nonlinear active axon simulations. Simulation results generated using the method presented by (Warman et al. 1992) were included for comparison. Performance was examined for cases of single and multiple point source stimulation. Single point source simulations were designed to explore sensitivity of a given method to the position, alignment, and fiber diameter variables that are often randomized in nerve-level simulation (Schiefer et al. 2008; Lertmanorat et al. 2006; Veltink et al. 1988). Multiple point sources aligned longitudinally with the axon are simulated to demonstrate the prediction accuracy for complex fields spanning multiple nodes of Ranvier. Performance was also examined under conditions similar to those used in previous literature to model neural response observed in live experiments (W. M. Grill & Mortimer 1996; Lertmanorat & Durand 2004).

2.1 Axon models

All axon simulation waveforms were square, monophasic pulses. Applied pulse durations ranged from 20 μs to 10,000 μs . Active axon simulations incorporated the McIntyre, Richardson, and Grill (MRG) double-cable axon model. This model was chosen because the model of the internodal space and active ion channels was developed using numerous experimental data from mammalian myelinated axons (McIntyre et al. 2002). Subsequent studies using this model to simulate behavior have been experimentally confirmed, thereby showing the utility of the MRG model in predicting actual axon response (Wongsarnpigoon et al. 2010; Schiefer et al. 2010; Kuhn et al. 2008; Takahashi et al. 2007; Kilgore & Bhadra 2004). Passive axon models were created by replacing the non-linear ion channels of active axon models with a fixed conductance, $G_m = 0.007 \text{ [mS/cm}^2\text{]}$ (Warman et al. 1992; Moffitt

et al. 2004). All simulated axons were myelinated and consisted of 21 nodes of Ranvier and 20 internodal spaces. Axon dimensions and parameters were determined based on fiber diameter, as previously described (Schiefer et al. 2008; McIntyre et al. 2002). Fiber diameters used in this analysis ranged from 4 to 20 μm to span the physiologic range for myelinated, mammalian axons of the peripheral nervous system. The NEURON simulation environment (Version 7.0) (Hines & Carnevale 1997) was used to simulate the response of active and passive axon models to an applied extracellular potential field. In active axon simulations, activation was defined as an action potential that propagated along at least five nodes of Ranvier (Schiefer et al. 2008).

2.2 Activation prediction methods

Both new activation prediction methods incorporated a modified driving function (MDF) and an activation threshold in order to predict activation. Axons were predicted active if the output of the MDF, applied to the extracellular potential, exceeded the activation threshold. Activation thresholds varied with fiber diameter, pulse duration, and extracellular potential. In all verification tests the MDF was computed at each node of Ranvier and compared to the activation threshold to determine activation, because it was not known *a priori* where activation was likely to occur. Extracellular potentials and axon length were chosen to minimize potential edge effects of a finite length axon.

2.2.1 Modified Driving Functions (MDF)—The modified driving function for the first method, MDF_1 , used only the extracellular potential at a node of Ranvier, n , and the two adjacent nodes (eq. 1) (Izad 2009). MDF_1 is the second spatial difference, instead of the second spatial derivative, which includes the term Δx^2 , as used by Rattay (Rattay 1986). This method was termed the single node method.

$$\text{MDF}_1 = \Delta^2 V_{e_n} = V_{e_{n-1}} - 2V_{e_n} + V_{e_{n+1}} \quad (1)$$

Warman *et al.* showed that current induced in the membrane at a node of Ranvier was proportional to the second spatial difference of the extracellular potential (Warman et al. 1992). Warman *et al.* used a weighted sum of the currents at each node to account for redistribution of current when the extracellular potential induced current at more than one node. The second proposed method used similar concepts to account for extracellular potentials that influence more than single node of Ranvier, and was termed the weighted sum method. The modified driving function for this method, MDF_2 , was a weighted sum of second spatial differences along the axon.

$$\text{MDF}_2 = \sum_j W_{|n-j|}(PW, d) \cdot \Delta^2 V_{e_j} \quad (2)$$

Weights, $W_{|n-j|}$, were generated using the process outlined by (Warman et al. 1992). Briefly, using a passive axon model, the amount of depolarization caused by current injected at a node, j , was measured at the center node, n . A step function of current was applied to one node at a time, and the resulting depolarization was measured at the pulse durations of interest, making $W_{|n-j|}$ a function of pulse duration. The value for each $W_{|n-j|}$ was the ratio of depolarization caused by current injected at node j to the depolarization caused by current injected when $j=n$. This decoupled $W_{|n-j|}$ from the magnitude of current injected. Thus, the weight of the center node was 1.0 and decreased for each more distant node. Weight generation for the weighted sum method had two primary differences from the original Warman method: First, all weights were calculated using the MRG model, which was not yet developed at the time (Warman et al. 1992) was published, instead of the Sweeney axon

model. Second, weights were calculated separately for each fiber diameter. Weights generated for this work are included in supplementary table (Table S1). Simulation results obtained by replicating the full Warman method, as described in (Warman et al. 1992), were included separately for comparison and to highlight the improvement of each new method in addressing the limitations demonstrated by Moffitt *et al.* (Moffitt et al. 2004).

2.2.2 Activation thresholds—The activation threshold for each method was generated using two steps. The first step involved performing active axon simulations using a set of extracellular voltage vectors and recording whether activation occurred. The second step was performed by plotting the activation results as a function of the spatial and temporal characteristics of the applied voltage vector. The activation threshold was defined as the boundary between the regions of activated and inactivated points.

The first step began with creating a set of extracellular voltage vectors to apply to the axon model. Each constructed vector had a unique combination of peak extracellular potential (V_e), and second nodal difference ($\Delta^2 V_e$) computed at the center node of Ranvier. The vector set was generated varying V_e from 0 to -500 mV, and $\Delta^2 V_e$ from 0 to 190 mV, each in 10mV steps, to yield 1020 unique vectors. With the three central nodal voltages set by the requirements to satisfy V_e and $\Delta^2 V_e$, the remaining nodal voltages were set to transition to a flat potential at the outermost nodes. This minimized edge effects that could influence the observed activation. The remaining internodal voltages were interpolated using a spline interpolation. Each vector was applied to fiber diameters ranging from 4 μm to 20 μm as a square, monophasic pulse for durations between 20 μs to 10,000 μs . At the end of each simulation, the axon was classified as active if an action potential propagated along at least five nodes of Ranvier. For the second step, results were plotted as a function of axon diameter, pulse duration, V_e , and the output of applying each method's respective MDF to the extracellular potential vector. The activation threshold was defined as the border between the regions of activation and inactivation. The activation threshold was implemented as a look up table in order to predict activation when analyzing extracellular potential in subsequent simulations. The resulting activation thresholds are offered for both methods in the supplemental materials (Tables S2 and S3).

2.3 Verification

2.3.1 Extracellular potential generation—Extracellular potential fields were generated for single and multiple point source electrodes. The conducting medium was assumed to be infinite, homogeneous, and anisotropic, with transverse conductivity $\sigma_t = 0.083 \text{ S/m}$ and longitudinal conductivity $\sigma_l = 0.33 \text{ S/m}$, as described by (Moffitt et al. 2004). The system is assumed radially symmetric. The extracellular voltage along the axon due to a single point source can be calculated from the distance between the axon and electrode, r , and the distance along the axon, z (eq.3).

$$V_e(z) = \frac{I_{ext}}{4\pi \sqrt{\sigma_l \sigma_t r^2 + \sigma_t^2 z^2}} \quad (3)$$

Multiple point sources were simulated by computing the contribution of each source individually and summing them to create the total voltage field. Therefore, the spatial model was assumed to be linear in nature and did not contain capacitive components. This is a reasonable and common assumption when modeling nerve cuff electrodes (Rattay 1989; Moffitt et al. 2004; Warman et al. 1992; Schiefer et al. 2008).

2.3.2 Verification cases—Verification for single point source stimulation involved varying either electrode-to-axon spacing (EAS) or alignment of the electrode to a node of Ranvier. In simulations where EAS was varied, the electrode was aligned with the center of a node of Ranvier (Figure 1.a). EAS was increased from 100 μm to 3000 μm with constant pulse width and fiber diameter, to determine performance under conditions similar to those outlined by (Moffitt et al. 2004). The sensitivity of alignment of the electrode to nodes of Ranvier was tested with an EAS of 200 μm while the electrode alignment was changed up to $\pm 50\%$ internodal lengths from a node (Figure 1.b). Relative recruitment threshold across diameters was tested with EAS set to 200 μm , with the electrode aligned with a node of Ranvier (Figure 1.a). To investigate pulse duration-dependent spatial selectivity, as observed by (W. M. Grill & Mortimer 1996), EAS was varied from 100 μm to 2000 μm for pulse durations 20, 50, 100, and 500 μs , with the electrode aligned to a node (Figure 1.a).

Multiple point source stimulation tested prediction accuracy in cases where stimulation pulses were not localized around a single node of Ranvier. The first case involved two point sources, each with 200 μm EAS (Figure 1.c). The first point source was aligned with a node of Ranvier, while the second point source was shifted in increments of 25% of the internodal length for up to eight nodes away from the first electrode. The amplitude of the second source was varied as a fraction of the first. Several fractions were tested, but the presented data is for the worst case where the amplitude of the second source is the same as the first. To extend the investigation to more complex electrode geometries, an alternating pattern of six anodic and five cathodic point sources was used to generate the extracellular potential (Figure 1.d). This design was based on a model and experimental study that showed that it was possible to change the recruitment order as a function of axon diameter through manipulation of the driving function (Lertmanorat & Durand 2004). The adjacent electrode spacing was increased from 400 μm to 1500 μm in 100 μm increments; while EAS was held at 200 μm . Anodic amplitudes were set to 70% of the cathodic amplitudes on all electrodes except the outermost, where amplitude was set to 40% of the cathodic amplitude. To investigate whether the presented prediction methods could capture the diameter recruitment reordering observed by (Lertmanorat & Durand 2004), adjacent electrode spacing was set to 650 μm , while EAS was changed from 50 μm to 300 μm .

Performance of these methods was compared against the Warman method (Warman et al. 1992) applied to the MRG model, as outlined in (Moffitt et al. 2004). The Warman method could be tuned to minimize error at a given EAS. In all results, the Warman method was tuned for EAS equal to either 200 μm or 1000 μm . In cases where only one set of data is presented from the Warman method, it is data optimized to the tested EAS of 200 μm . This, therefore, represents the best possible result of the method.

2.3.3 Performance measures—Three output measures were used in verification: stimulation threshold error, relative stimulation threshold, and computational run time. Stimulation threshold compares the current, I_{ext} , required for activation of the active MRG model to those obtained using the prediction methods. I_{ext} of (eq.3) was tuned using a binary search algorithm until the stimulation threshold was determined within 0.01% of the stimulation threshold magnitude. In cases of multiple point sources, all sources were scaled by the same factor. The recorded output for each simulation or prediction was the amplitude of I_{ext} required for activation. Stimulation threshold error was calculated in the same manner as (Moffitt et al. 2004) using (eq.4).

$$\text{Threshold Error}\% = \frac{I_{ext, \text{Prediction Method}} - I_{ext, \text{Active Axon}}}{I_{ext, \text{Active Axon}}} \cdot 100\% \quad (4)$$

This error is positive when a prediction method over-predicts the stimulation threshold of the MRG active axon model and is negative when the stimulation threshold is under-predicted. In the ideal case, threshold error would be zero or at least constant across all simulations, since constant error can be corrected for with a scale value applied to the prediction method results.

Relative stimulation thresholds were computed by normalizing the stimulation thresholds either across axon diameter or pulse duration. This was used to determine recruitment order across fiber diameter and was compared to the relative activation values for the active axon model in the same simulation conditions.

Computational run time was measured for the active axon simulation and both the single node and weighted sum prediction methods. Simulations were performed with an Intel® Core™ 2 Duo P8400 (Intel, Santa Clara, CA) processor and 4GB RAM. Computational load in addition to the simulation or prediction method run was controlled to be similar across all three cases. No thread optimization was used to run active axon simulations on more than one processing core at a time. Single node and weighted sum methods were performed using MATLAB (2009b, The MathWorks, Natick, MA) with no thread or multi-core optimization beyond the default settings. Four simulations of 4010 axons for pulse durations 20, 50, 100, and 200 μ s were performed, for a total of 16,040 simulations.

3. Results

3.1 Threshold value generation

The single node prediction method was chosen for its simplicity as well as the use of $\Delta^2 V_e$ in current literature as a computationally fast approximation (Wongsarnpigoon & W. M. Grill 2008; Moks, C R Butson, et al. 2009c). Plotting active axon results, where each point represents the result of a separate active axon simulation, against V_e and $\Delta^2 V_e$ of the applied extracellular field revealed two distinct regions of activation and inactivation with a smooth border between the two (Figure 2). This transition is highlighted with the dashed lines. The border between active and inactive regions was defined as the activation threshold for the single node prediction method. The threshold value was found to be a function of V_e , pulse duration, and fiber diameter (not shown). The dependence on fiber diameter is relatively small compared to the other factors, and for clarity the data is not presented.

The activation threshold for the weighted sum method was generated using the same input voltage vectors and active axon simulation results as the single node method. The difference from the single node method was that the ordinate value was the result of the MDF₂ applied to each voltage vector. The activation threshold for this method was found to be a function of V_e , pulse duration, and diameter (Figure 3). Diameter dependence was shown to have a greater influence at short pulse widths, and in general, threshold was lower for larger diameter axons.

3.2 Prediction performance with single point source

The two proposed prediction methods and the method from (Warman et al. 1992) were tested under single point source conditions and compared to active axon simulation results. Simulations similar to those performed by (Moffitt et al. 2004) demonstrate the improvement achieved by including V_e in the activation threshold (Figure 4.a). It was found that the Warman method could be optimized to minimize error at a certain EAS, but optimization did not change the fact that threshold error varied by almost 40% across all EAS. Both the single node and weighted sum methods showed error across all EAS that was more consistent and lower than the Warman method. The single node method varied by

7.1% across all EAS. The weighted sum method showed the least variation, with threshold error varying by 5.7%.

Stimulation threshold error was influenced by electrode alignment to the node. (Figure 4.b) The Warman method results varied between 3.1% and -8.1% and oscillated between over-estimation and under-estimation. The other two methods were much flatter across most of the range, but both showed an increase in over-prediction of the stimulation threshold when the electrode was directly between two nodes of Ranvier. The single node method exhibited the largest swing in error, peaking at 20.8%. The weighted sum method was flattest across the widest range and threshold error peaks at 7.6%. These values shifted as axon diameter and pulse duration were changed. When axon diameter was increased to 20 μm , the single node method error peaked at 20.4% and the weighted sum method error peaked at 6.1%; both retained the same general shape as Figure 4.b. The Warman method error oscillated between -69.4% and -82.2% with diameter set to 20 μm . With diameter set at 4 μm , the single node error peak was 15.0% and the weighted sum peak was 4.4%, while the Warman error shifted to oscillate between 146.5% and 165.7%.

Relative recruitment order as a function of axon diameter with a single point source electrode showed that the two proposed methods match the predictions of the active axon simulations better than did the Warman method (Figure 4.c). Stimulation thresholds were largest for the smallest fiber diameter across all prediction methods and the active axon simulations, as expected. The single node and weighted sum methods both matched the relative recruitment order and magnitude of the active axon model, where the Warman method showed a much greater variation in threshold change from the smallest to the largest fibers.

The final single point source electrode investigation focused on stimulation thresholds as a function of pulse duration and EAS. Pulse durations used were 20, 50, 100, and 500 μs and EAS ranged from 100 to 2000 μm . This was similar to the work presented by Grill and Mortimer (W. M. Grill & Mortimer 1996) where they used the active model developed by (Sweeney et al. 1987). All thresholds were normalized to the peak threshold value found across all pulse durations and EAS values for a given method. All three methods demonstrate the increased spatial selectivity for short pulse durations observed by Grill and Mortimer (W. M. Grill & Mortimer 1996) (Figure 5).

3.2 Prediction performance with multiple point sources

Multiple point sources were arranged along the axon axis to investigate performance under more complex fields. Threshold error for two point sources arranged along the axon axis demonstrated performance differences between the single node and weighted sum methods (Figure 6). Threshold error from the Warman method varied by as much as 32.2% across EAS. The single node method displayed a larger absolute swing of 42%, with the largest error occurring when the two electrodes are aligned with adjacent nodes of Ranvier. The behavior of the weighted sum method is the smoothest of the three methods, with a maximum threshold error of 14.1%.

The investigation using multiple point sources was extended to the pattern of alternating anodic and cathodic point sources outlined in the methods. All three methods exhibited large variation in predicting the activation threshold (Figure 7.a). The single node method changed the most, with error between 42.4% over-prediction to 24.9% under-prediction of the threshold. The weighted sum method changed less with a peak over-prediction of 45.8% and under-prediction of 0.7%. The Warman method changed with a peak 35.3% over-prediction to 11.4% under-prediction when the EAS optimization and actual EAS match at 200 μm , a slightly larger range than the weighted sum method. The results with the Warman

method tuned to EAS of 1000 μm are not shown for clarity, but showed an over-prediction between 13% and 71.6%. The other two methods do not require optimization for different EAS values.

The eleven-electrode pattern was used to investigate whether these methods could demonstrate the same relationship between threshold and axon diameter observed by (Lertmanorat & Durand 2004). The relative thresholds across all diameters tested were plotted for the three approximations and the active axon simulation, with adjacent electrode spacing set to 650 μm and EAS set to 50 μm and 300 μm (Figure 8). With EAS equal to 50 μm , the single node and weighted sum methods tracked the active axon simulation results well, with an increase in the activation threshold peaking around 14-16 μm diameter fibers (Figure 8.a). The Warman method, however, did not track the active axon results. When EAS was 300 μm , the weighted sum method tracked the active axon simulations best (Figure 8.b). The single node method did not track the active simulation results well, with peaks at 12 μm and 18 μm and relatively low thresholds for small diameter fibers. The Warman method did not track the behavior of the active axon.

3.3 Computational run time

Computational run times were measured to quantify the computational efficiency provided by the single node and weighted sum methods. Simulation run time results showed a marked increase in computational speed over the active axon simulations for both the single node and weighted sum methods (Table 1).

4. Discussion

4.1 Activation thresholds are a function of extracellular potential

Results from the active axon simulations revealed an important dependence on V_e for the activation threshold. The single node method exhibited increasing threshold with decreasing V_e values, whereas the weighted sum method showed a decreasing threshold with decreasing V_e values (Figure 2 versus 3). The single node method only accounts for $\Delta^2 V_e$ at a single node of Ranvier. For cathodic stimulation, $\Delta^2 V_e$ will be positive and large at the node most likely to activate. $\Delta^2 V_e$ at the two nodes adjacent to this node, however, will also be large but negative. Because the weighted sum method includes these nodes with negative $\Delta^2 V_e$, the result of the MDF₂ will be lower. This effect is increased in cases of low V_e and high $\Delta^2 V_e$, leading to a general shift of the ordinate values down for the weighted sum as $\Delta^2 V_e$ increases.

The most important aspect of these new methods is recognizing the impact that the magnitude of the extracellular potential has on the activation threshold. This relationship has not been reported previously. Including the activation threshold dependence on V_e improved the prediction accuracy over the Warman method (Figure 4.a), addressing errors in the linearized models and activation prediction presented by Moffitt (Moffitt et al. 2004). Axon diameter dependence was the other unique factor included in the activation threshold of the single node and weighted sum methods, which contributed to the improved accuracy in relative activation across fiber diameter, but otherwise the observed impact to accuracy was small in comparison. These findings are applicable in modeling studies that rely on $\Delta^2 V_e$ to predict activation volumes (Choi & Lee 2006; C B Maks, C R Butson, et al. 2009c; C.R. Butson & McIntyre 2008). The implication of increased threshold at low extracellular potential is that actual activation will be less than that predicted using a constant threshold value. This could significantly affect interpretation of modeling studies working to predict the mechanisms and active brain regions resulting from treatments and therapies, such as deep brain stimulation for movement disorders.

4.2 Single point source performance

The analysis of the presented prediction methods was designed to investigate aspects important to nerve-level modeling. Placement within a nerve, alignment of the nodes of Ranvier, and axon diameter are the important randomized variables included in a nerve-level simulation (Schiefer et al. 2008; Veltink et al. 1988; Grinberg et al. 2008). Both the weighted sum and single node methods were robust to changes in EAS. Accuracy of these methods should not be affected by randomized placement within the simulated nerve, whereas the Warman method would require tuning for each EAS to minimize error (Figure 4.a). To verify that the MRG model was appropriate for investigating electrode-node alignment, MRG axon simulation results were compared to experimental data presented by (Roberts & Smith 1973). The MRG axon simulations reflected this data well as alignment was changed (Results not shown). Changing electrode-node alignment showed the weighted sum method most closely matched the behavior of the MRG axon model (Figure 4.b). The flat response observed for most electrode-node alignments using these methods is important because nodal alignment is usually randomized with a uniform probability distribution. The weighted sum method stimulation threshold error was below 2% across 90% of the uniform distribution range and below 5% across 95.8% of the uniform distribution range. The single node method was much more sensitive to misalignment than the weighted sum method, with stimulation error maintained below 2% over only about 60% of the distribution and below 5% for less than 80% of the uniform distribution. Predictions based on both new methods should be robust as axon diameter is randomized; as both new methods also showed relative activation thresholds that closely matched the active MRG axon results (Figure 4.c). Recruitment order is important, but so is the relative magnitude between diameters. The Warman method results illustrate how poor relative magnitude tracking may hide other effects. The Warman method results showed the correct recruitment order, but the relative change from diameter to diameter was too great. It appears that there may have been an increase in threshold for fiber diameters 14-16 μ m in Figure 8.a, but the change is dwarfed by the change in threshold as a function of diameter.

4.3 Performance differences between methods

With the exception of the electrode alignment to the node of Ranvier, the two proposed methods are effectively equivalent for single point source stimulation. When the pulse was localized to the space around a single node of Ranvier, as was generally the case with the single point source, both the single node and weighted sum methods could account for the important aspects of the stimulation waveform. The weighted sum method starts to outperform the single node method when the spatial extent of the non-zero field extends beyond the area around a single node and significant current redistributes to the investigated node. Single and multiple point source data supports this as accuracy decreased compared to the weighted sum method (Figures 4.a, b; 6; 8.b).

4.4 Replicating key findings from literature

Two of the simulations performed were chosen specifically to test activation prediction performance under conditions used in literature presenting key findings. This is not to suggest that these methods can or should be used in future studies about specific axon activation behavior, but is offered instead to show that these methods do capture important behavior useful to nerve electrode design and gaining insight into behavior in electrically stimulated systems. The first set of simulations regarding replicating key findings looked at the relationship between pulse duration and spatial selectivity observed and experimentally confirmed by Grill and Mortimer (W. M. Grill & Mortimer 1996). The results of all three prediction methods demonstrated behavior similar to the active axon simulations and reflected the results published by Grill and Mortimer.

The second case was chosen to explore stimulation designed to influence recruitment order. Lertmanorat et al. found that recruitment order could be influenced by manipulating $\Delta^2 V_e$ sampled at the nodes to increase stimulation threshold for larger axons above that for smaller axons (Lertmanorat & Durand 2004), and later confirmed this experimentally (Lertmanorat et al. 2006). The two key findings by Lertmanorat et al. were that first, that recruitment order can be influenced by the electrode arrangement, and second, that this effect is reduced as EAS increased. We found that both the single node and weighted sum methods could be used to draw the first conclusion, with both showing increased stimulation threshold for axons 14-16 μm in diameter (Figure 8.a). Only the weighted sum method illustrated that with increased EAS, the re-ordered recruitment order effects were largely lost, as was the case with the active axon simulations (Figure 8.b). The Warman method results failed to support either of the two conclusions.

4.5 Computational run time comparison

The results of the measured computational run times show that both the single node and weighted sum methods provided several orders of magnitude of increased computational efficiency, as expected. For this simulation set, the single node method was 8% faster than the weighted sum method. This helps to quantify the relative computation cost of the more complex weighted sum method over the single node method. The additional cost of 8% of computational speed is small when considering the benefit of increased prediction accuracy for the weighted sum method over the single node method. With either of the new methods, one million axons can be simulated in less than 10 seconds with minimal error or loss of insight, compared to nearly 2 days for the active model.

4.6 Applicability to other models

In this paper, we have shown that this method can predict activation of the double-cable MRG axon model. The method is also extensible to other non-linear neural models. This method has been applied to single-cable models with infinite myelin resistance using channel dynamics described by (Frankenhaeuser & Huxley 1964) or by Sweeney *et al.* (Sweeney et al. 1987). In both cases, a distinct boundary between inactivation and activation was observed that had a similar dependence on V_e as that seen with the MRG model (results not shown). This indicates that the behavior observed here is not merely an artifact of the double-cable formulation nor the MRG model channel dynamics. Threshold boundaries observed with these additional models were different from the MRG-based threshold. Consequently, activation thresholds and weights need to be generated for the nonlinear axon model used. Fiber diameter also affected the threshold level, so threshold and weight values should be generated for the range of fiber diameters of interest.

The approximation does not require that the axon path be constrained to a straight line. Activation prediction has been performed accurately for axons following non-straight paths through an external electric field (results not shown). Because the proposed methods are based only on the extracellular potential at nodes of Ranvier, and do not depend on how the extracellular potential was generated, a tortuous axon path would only result in different potential values at the nodes. This assumes that bends in the axon are not such that they cause model variations of intracellular conductivity or channel dynamics. The final caveat is that these methods have only been applied to axons that are long enough to avoid termination effects from cell bodies or synapses. Therefore, this method is not appropriate for prediction in cases of termination, dendrites, cell bodies, split axons, or other configurations where intracellular conductivities or models that differ between adjacent compartments.

Recent work has included a more detailed accounting of the effects of the axon on the resulting electric field (C R Butson et al. 2011). In many cases the influence of axons on the stimulating electric field is neglected in nerve level simulations (Lertmanorat et al. 2006; Schiefer et al. 2008; Choi & Lee 2006). The presented methods only consider the extracellular potential at the nodes of Ranvier and are not dependent on how the field is generated. If more detail to the extracellular potential field generation is to be considered, *e.g.* the influence of surrounding active axons, the present methods of analysis should still predict activation within this more complicated field.

5. Conclusion

We have presented two activation prediction methods that perform better than previous prediction methods and are computationally efficient. Performance of both new methods shows a decreased dependence on electrode-axon geometry over previous methods, bringing activation prediction closer to an analysis of the spatial and temporal properties of the applied electric field. The weighted sum method exhibits the best prediction accuracy among the three investigated methods, and should be selected for applications when electric field extends beyond the area around a single node of Ranvier. This method is computationally faster than numerically solving the nonlinear axon dynamics by orders of magnitude, but maintains important behavior of the axon. This allows nearly instantaneous determination of activation patterns in whole nerve simulations, and opens the door to applications of stimulation design using evolutionary optimization methods or quickly evaluating and understanding design tradeoffs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A

Threshold Generation and Activation Prediction

Generating the activation threshold data is the most computationally intensive part of the proposed methods. It requires active axon simulations for a set of extracellular voltage vectors repeated across the range of fiber diameters and pulse durations of interest. Once the activation threshold is generated, it can be used repeatedly in analyzing extracellular potentials to predict activation without simulating active axon models. The purpose of this section is to provide additional details on how to generate activation thresholds and perform activation prediction. Activation thresholds are generated as follows:

1. Create array of test vectors, each satisfying a pair of unique parameters V_e and A^2V_e at the center node. Set the remaining nodal voltages to transition to flat potential at the ends of the axon, and interpolate the internodal voltages.
2. Simulate each voltage vector, fiber diameter, and pulse duration combination with the following characteristics:
 - a. Allow a short time for the model to stabilize before stimulus is applied
 - b. Apply the extracellular voltage vector to the active axon model in time as a square pulse of cathodic excitation for the given pulse duration
 - c. Allow time after the end of the pulse for action potentials to propagate
3. Determine which nodes fully depolarized in order to detect whether action potentials were triggered and propagated

4. For each simulation result, plot whether the fiber was activated or not. These results are plotted as a function of fiber diameter, pulse duration, V_e at the center node, and the result of applying the MDF to the extracellular potential vector used for that particular simulation.
5. Record the threshold as the boundary between regions of activation and inactivation.

Once the threshold is recorded, activation predictions can be made with simple computations and the use of a look up table. To predict whether activation would occur given an extracellular potential, apply the MDF to the extracellular potential vector. Using the look up table, and interpolation if necessary, determine the threshold for activation, taking into account fiber diameter, pulse duration, and V_e . If the result of the MDF is greater than the activation threshold, then the axon is predicted active. Activation thresholds and weight values should be recalculated for any major changes in the underlying axon model, as we have observed that threshold values change as different channel dynamics are implemented.

Because of the overhead required for generating the activation thresholds, these methods are most applicable for determining the response of many axons under many different applied electric fields. It does not make sense as a replacement for running tens of thousands of axons if the threshold and weighted sum values have not been generated, since the threshold generation would require active axon simulations on that order. While in this work the set of extracellular voltage vectors were created using a regular spacing of V_e and $\Delta^2 V_e$, a binary search algorithm could instead be employed to find the threshold transition and reduce the number of simulations required for generating the activation threshold. To reduce overhead when using the MRG axon model, the authors have included the weights and threshold values generated for this work in the supplemental materials.

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Figure 1. Electrode-axon geometries used for investigating prediction method performance. a) Electrode is aligned with a node of Ranvier, while electrode-to-axon spacing (EAS) is changed. b) EAS is held constant while alignment of the electrode is changed. c) Two-electrode configuration where one is always aligned with a node of Ranvier, while inter-electrode spacing is increased. EAS of each electrode is held constant. d) Eleven-electrode pattern of alternating anodic and cathodic stimulation, where either adjacent electrode spacing or EAS is changed.

Figure 2.

Activation results plotted as a function of the extracellular voltage (V_e) and the second nodal difference ($\Delta^2 V_e$) of the applied waveform taken at the center node of Ranvier. Each point represents the result of a simulation. Clear activation and inactivation regions are present. The activation threshold is the transition between these regions. The activation threshold decreased as extracellular voltage and pulse duration increased.

Figure 3.

Activation thresholds generated by applying the weighted sum equation (eq.2) to the extracellular voltage vectors used in Figure 2 and plotting the transition between activation and inactivation regions for diameters of 6, 10, 16, and 20 μm at pulse durations a) 20 μs and b) 200 μs .

Figure 4.

Results from the activation prediction methods tested with a single point source electrode and 100 μ s pulse duration. a) Electrode is aligned with a node of Ranvier, but electrode-to-axon spacing (EAS) is increased. b) EAS is 200 μ m, but alignment of the electrode to the center node of Ranvier is varied. c) Relative recruitment order across axon diameter with the electrode aligned to a node of Ranvier and EAS set to 200 μ m. Thresholds are normalized to the maximum threshold value found across diameters within a given prediction method.

Figure 5. Relative stimulation thresholds plotted across pulse duration values and EAS values for a) active axon simulations, b) the Warman method, c) the single node method, and d) the weighted sum method. All methods demonstrate the increased spatial selectivity for short pulse durations originally presented by (W. M. Grill & Mortimer 1996) Results presented are for a 10 μm diameter axon.

Figure 6. Stimulation threshold error when the spacing between two electrodes arranged longitudinally to the axon is increased. Pulse duration is 100 μs , fiber diameter is 10 μm , and EAS is 200 μm .

Figure 7. Threshold error for an arrangement of six anodic and five cathodic electrodes arranged in an alternating pattern longitudinally to a 10 μm diameter axon. a) Threshold error as a function of space between two adjacent electrodes. Example extracellular waveforms from this analysis are shown for adjacent electrode spacing of b) 500 μm and c) 1000 μm .

Figure 8.

Normalized stimulation threshold as a function of axon diameter for an alternating six-anode, five-cathode electrode pattern aligned longitudinally to the simulated axon. Adjacent electrode spacing was set to 650 μm with pulse duration equal to 20 μs . Results are plotted for active axon simulations and the three activation prediction methods. Results are shown for electrode-to-axon spacing values of a) 50 μm and b) 300 μm .

Table 1

Computation Runtime - 16,040 Axons

Method	Time (s)
Active Axon	2701.96
Single Node Method	0.126
Weighted Sum Method	0.137