Sensitivity of temporal excitation properties to the neuronal element activated by extracellular stimulation

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Abstract

Measurements of the chronaxies and refractory periods with extracellular stimuli have been used to conclude that large diameter axons are responsible for the effects of deep brain stimulation (DBS). We hypothesized that because action potential initiation by extracellular stimulation occurs in the axons of central nervous system (CNS) neurons, the chronaxies and refractory periods determined using extracellular stimulation would be similar for cells and axons. Computer simulation was used to determine the sensitivity of chronaxie and refractory period to the neural element stimulated. The results demonstrate that chronaxies and refractory periods were dependent on the polarity of the extracellular stimulus and the electrode-to-neuron distance, and indicate that there is little systematic difference in either chronaxies or refractory periods between local cells or axons of passage with extracellular stimulation. This finding points out the difficulty in drawing conclusions regarding which neuronal elements are activated based on extracellular measurements of temporal excitation properties.

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1. Introduction

Deep brain stimulation (DBS) is used to treat a number of movement disorders, including essential tremor, multiple sclerosis, and Parkinson’s disease. However, the mechanisms by which high-frequency extracellular stimulation has its effects are unclear, and knowledge of the interactions between the applied currents and the neurons of the central nervous system (CNS) is lacking (Grill and McIntyre, 2001). This lack of knowledge prevents full understanding of the mechanisms of action of DBS and may hamper full development of this treatment.

A number of plausible hypotheses have been proposed for the mechanisms of DBS (Benabid et al., 2002; Dostrovsky and Lozano, 2002; Vitek, 2002). However, these hypotheses are difficult to support or refute because it is not known which neural elements are affected by stimulation. During extracellular stimulation in the CNS, local cells (neurons for which the cell bodies are close to the stimulating electrode) and axons of passage respond at similar stimulation thresh-
were modeled using the approach developed by McNeal (1975), and the conclusion from these studies was that the short chronaxies and refractory periods indicated that large diameter axons were the neuronal elements responsible for the observed effects of DBS. However, during extracellular stimulation in the CNS, action potential initiation in neurons for which the cell bodies were close to the electrode (local cells) occurs in the axon rather than in the cell body (McIntyre and Grill, 1999; Nowak and Bullier, 1998). Therefore, we hypothesized that chronaxies and refractory periods determined using extracellular stimuli would be similar for stimulation of axons of passage and local cells, thereby complicating interpretation of the neuronal elements responsible for a particular effect. The purpose of this study was to determine the sensitivity of extracellularly measured chronaxies and refractory periods to the neuronal element activated.

2. Methods

We used computer-based models of axons of passage and local cells to determine the sensitivity of chronaxie (Tch) and refractory period to the neuronal element being stimulated for a range of positions of an extracellular electrode (Fig. 1). The extracellular potentials, V, produced by passage of current, I, through the point source electrode positioned in an infinite homogeneous extracellular medium (resistivity, \( \rho = 500 \, \Omega \, \text{cm} \)) were calculated at each position, \( r_1 \), using \( V(p) = \frac{I(p)}{\pi \rho r_1} \). The details of the neural models are given in McIntyre and Grill (2000) and are summarized only briefly here. The 10 \( \mu \text{m} \) diameter axons of passage were modeled using the approach developed by McNeal (1976) with membrane properties that were appropriate for mammalian myelinated nerve fibers. The neuronal model of a local cell included a 15-node myelinated axon (identical to the axon of passage), connected to a three-dimensional six compartment soma, and a three-dimensional branching dendritic tree and had a geometry and membrane properties based on mammalian motoneurons. The model neurons were implemented in NEURON (Hines and Carnevale, 1997), and the transmembrane potential in response to the extracellular potentials was obtained by numerical solution to the non-linear differential (cable) equation using Crank–Nicholson implicit integration with a time step of 0.001 ms.

Chronaxies and refractory periods were determined for single axons of passage with the electrode positioned either directly over a node of Ranvier or over the middle of the internode of the axon, and for the local cell with the electrode positioned over the initial segment, over the cell body, and over the dendrites at six electrode-to-neuron distances: 0.1, 0.2, 0.5, 1, 2, and 5 mm (Fig. 1A), where the distance was defined between the location of the point source and the center of neural structure.

Chronaxies and refractory periods were also determined for populations of one hundred identical local cells or axons randomly positioned within an imaginary sphere of 3 mm radius with the electrode at the center (Fig. 1B). Each neuron within the populations was treated individually and there were no connections or interactions between the neurons. The center of the cell body of each local cell was positioned within the sphere, with respect to the position of the point source electrode at the center of the sphere, by generating random polar coordinates. As a result, the cell bodies of the local cells were uniformly distributed throughout the sphere and their axons exited the sphere. Similarly, the central node of each the 15-node long axons of passage was positioned within the sphere, with respect to the position of the point source electrode at the center of the sphere, by generating random polar coordinates. Thus, center nodes of the axons of passage were thus uniformly distributed throughout the sphere and the continuations of the axons exited the imaginary sphere. Three individually randomized populations of local cells and three individually randomized populations of axons of passage were generated and the results (Figs. 3–6) are expressed as the means across the populations.

2.1. Chronaxie

The minimum stimulus pulse amplitudes needed to generate propagating action potentials (thresholds) were determined to within ±0.1% via a binary search algorithm using monophasic rectangular cathodic or anodic stimuli with durations of 0.02–2 ms. Thresholds to generate propagating action potentials in 20, 50, and 80% of the local cells or the axons of passage in the population models were also determined using the same stimuli. The Weiss form of the strength-duration equation (Weiss, 1901), \( I_{th}(PW) = (1 + T_{ch}/PW)I_{th0} \), where \( I_{th} \) is the threshold current, \( I_{th0} \) the theebase current, \( T_{ch} \) the chronaxie, and PW is the pulsewidth, was used to fit the strength-duration data using least squares regression following logarithmic transformation of the pulsewidth and current threshold data to normalize the regression error across pulse durations (McIntyre and Grill, 1998). For the neuronal population models, chronaxies were determined using the threshold currents, at each pulsewidth, required to activate 20, 50 or 80% of the neurons in the populations, and will be referred to as the chronaxie of the population. Regression coefficients ranged from 0.95 to 0.99 for the single neuron data and 0.98 to 0.99 for the population data indicating that both sets of data were well fit by the equation.

2.2. Refractory period

Paired pulses were used to determine the refractory period by applying two rectangular cathodic or anodic pulses, each 0.2 ms long, and separated by an interpulse interval (IPI)
Fig. 1. Computer simulations were used to determine the strength–duration and refractory properties of extracellularly activated axons of passage and local cells, individually or in populations. (A) For measurements on single neurons the distance (r) between a point source electrode and the neuron was varied from 0.1 to 5 mm with the electrode positioned over the node or internode of the axon, or over the initial segment, soma, or dendrites of the local cell. Pulsewidth (PW) to determine strength–duration properties ranged from 0.02 to 2 ms, and interpulse interval (IPI) to determine refractory properties varied from 1 to 200 ms. (B) For population measurements, 100 individual local cells or passing axons were randomly distributed such that either the somas of the local cells or the central nodes of the passing axons were uniformly distributed within an imaginary 3 mm radius sphere with a point source stimulating electrode at the center. (C) Threshold currents as a function of pulsewidth or interpulse interval (symbols) were fit using least square regression (lines). Between 1 and 200 ms. The amplitude of the first pulse was equal to the threshold current for a single stimulus and the amplitude of the second pulse necessary to generate a second propagating action potential was determined as a function of the IPI. In the population models, local cells or axons that were counted as stimulated by the second pulse were only those that were also stimulated by the first pulse (i.e., other neurons that were excited by the second pulse, but not the first pulse were not included when determining the percent of the population that was activated by the second pulse).

A decaying exponential function, \( I_{th} = I_{sp}/(1 - e^{-(IPI - ARP)/\tau}) \), where \( I_{th} \) is the threshold current for the second pulse, \( I_{sp} \) the threshold current for a single pulse stimulus, \( ARP \) the absolute refractory period, and \( \tau \) is the recovery time constant (Miller et al., 2001), was fit to the data using least squares regression following logarithmic transformation. Regression coefficients ranged from 0.97 to 0.99 for the single neuron data and were \( \geq 0.99 \) for the population data indicating that both sets of data were well fit by the equation. In some instances, as the IPI was reduced the threshold for the second pulse increased and then decreased at short IPIs (generally less than 1.5 ms), and these data points were not included in the curve fits to determine the refractory period. This was due to temporal summation with residual charge on the membrane and the period of supernormal excitability that can follow an action potential (Deutsch, 1964; Szabo et al., 1974).
For comparison across conditions the refractory period was defined as the interpulse interval at which the second pulse threshold increased by 50% over the single pulse threshold, and was calculated from the parameters of the curve fit using \( RP = \ln(3) \cdot \tau + ARP \). For the neuronal population models, refractory periods were determined using second pulse amplitudes required to activate the same 20, 50 or 80% of the neurons in the populations, and will be referred to as the refractory period of the population.

3. Results

Computational models of local cells and axons of passage were used to determine the sensitivity of chronaxie \( (T_{ch}) \) and refractory periods to the neuronal element activated by extracellular stimulation.

3.1. Chronaxie

The chronaxies of single axons of passage and single local cells were dependent on the polarity of the extracellular stimulus and the electrode-to-neuron distance. Using monophasic anodic stimuli, chronaxies were similar whether the electrode was positioned over the axon (node, internode) or near the cell body (over the initial segment, soma, or dendrites) at all electrode-to-neuron distances (Fig. 2A). Using monophasic cathodic stimuli, chronaxies were longer when the electrode was positioned near the cell body (over soma or dendrites, \( T_{ch} \approx 0.3-0.7 \text{ ms} \)) and to a lesser degree over the initial segment \( T_{ch} \approx 0.2-0.3 \text{ ms} \) than when the electrode was positioned over the axon (node, internode, \( T_{ch} \approx 0.1-0.2 \text{ ms} \)), but only when the electrode was ≤0.5 mm from the neuron (Fig. 2B). For larger electrode-to-neuron distances, chronaxies measured with cathodic stimuli were comparable for all neural elements (\( T_{ch} \approx 0.1-0.2 \text{ ms} \)).

The chronaxies to activate different proportions (20, 50 or 80%) of populations of axons of passage or populations of local cells were dependent on the polarity of the stimulus and the proportion of the population that was stimulated (Fig. 3). With anodic stimuli chronaxies for populations of axons and populations of local cells were very similar (\( T_{ch} \approx 0.1-0.2 \text{ ms} \)) for all degrees of activation of the population. With cathodic stimuli, chronaxies of populations of axons were similar to those of populations of local cells when smaller proportions of the population were activated (20-50% activation). However, when 80% of the population was activated the \( T_{ch} \) of the local cell population (≈0.65 ms) was approximately five times longer than the \( T_{ch} \) of the population of axons.

3.2. Refractory period

Refractory periods were defined as the interpulse interval at which the threshold to generate an action potential with the second pulse increased by 50% over the single pulse
threshold. Refractory periods of single neurons were dependent on the polarity of the extracellular stimulus and the electrode-to-neuron distance. Using monophasic anodic stimuli, refractory periods were generally lower with the electrode positioned over the axon of passage (\(\sim \)1–2.2 ms; node and internode) than with the electrode positioned near the cell body (2.5–3.5 ms; initial segment, soma, dendrites), with the exception of initial segment at 0.1 and 1.0 mm (Fig. 4A). The difference in refractory periods between the neural elements became smaller as the electrode-to-neuron distance increased. Similarly, when using monophasic cathodic stimuli, refractory periods were shorter with the electrode positioned over the axon (node and internode) than with the electrode positioned near the cell body (initial segment, soma, dendrites) (Fig. 4B). However, the difference in refractory periods between the neural elements became much smaller as the electrode-to-neuron distance increased to \(\geq 1\) mm.

Refractory periods of populations of local cells and populations of axons of passage were dependent on the polarity of stimulus and the proportion of the population that was activated (Fig. 5). Using anodic stimuli, and with the requirement that the same cells or axons from the population were stimulated by both the first and second pulse (the conditioner and probe) of the two-pulse sequence, refractory periods of the populations of axons (\(\sim 2.2-2.5\) ms) were shorter than the refractory periods of the populations of local cells (\(\sim 2.9-3.0\) ms) when 20, 50 or 80% of the population was stimulated, but the differences were small. With cathodic stimulation the refractory periods for populations of axons (\(\sim 2.1-2.4\) ms) were lower than the refractory periods for populations of local cells (\(\sim 3.1-3.2\) ms) when 20 or 50% of the population was activated. However, when the proportion of the population activated was increased to 80%, the refractory period for the populations of local cells (\(\sim 17\) ms) was substantially longer that that of populations of axons (\(\sim 2.3\) ms).

4. Discussion

During extracellular stimulation of neurons, action potential initiation occurs in the axon, even with the stimulating electrode positioned over the cell body or dendrites (McIntyre and Grill, 1999; Nowak and Bullock, 1998). This observation led to the hypothesis that the temporal excitation characteristics, including chronaxie (\(T_{ch}\)) and refractory period, of local cells and axons of passage would be similar when determined using extracellular stimulation. In the present study computer simulations were used to determine the sensitivity of extracellularly measured \(T_{ch}\) and refractory period to the neuronal element stimulated.
The chronaxies and refractory periods measured with extracellular stimulation were dependent on a number of factors other than the neuronal elements that were stimulated. There were clear differences in both measures under certain conditions, but there was little systematic difference in either measure. This finding points out the difficulty in drawing conclusions regarding which neuronal elements are activated based on extracellular measurements of chronaxies and refractory periods.

The chronaxies measured with electrodes positioned near the cell body were, at most, a factor of \( \sim 7 \) greater than the chronaxies measured with electrodes positioned over the axon (Fig. 2), while the refractory periods measured with electrodes positioned near the cell body were, at most, a factor of \( \sim 10 \) greater than the refractory periods measured with electrodes positioned over the axon (Fig. 4). These differences were restricted to the cases when the electrode was delivering cathodic stimuli less than 1 mm from the neuron, and under the other conditions tested the chronaxies measured with electrodes positioned over the axon node and over the soma differed by a mean factor of only 1.1 (range 0.7–1.6) and the refractory periods differed by a mean factor of only 1.4 (range 1.0–2.1). Results from vitro experiments in a cortical slice preparation corroborate the finding that there is little difference between the chronaxies of axons and local cells activated by extracellular stimuli (Nowak and Bullier, 1998). Thus, the chronaxies and refractory periods measured with electrodes positioned close to the cell body (arrow in Fig. 6B) had lower thresholds for extracellular stimulation of cells (15 ms) was substantially longer than \( \tau_{\text{ch}} \) for extracellular stimulation of axons (0.27 ms), the mean \( \tau_{\text{ch}} \) for extracellular stimulation of local cells (0.38 ms) was comparable to that for extracellular stimulation of axons.

The difference in chronaxies and refractory periods of cells and axons with cathodic stimuli delivered close to the neurons, as well as the lack of difference in these measures under other conditions, reflect electrode-position- and polarity-dependent changes in the site and mode of action potential initiation by extracellular stimulation. Anodic stimuli, whether delivered near the cell body or over the axon, initiate action potentials at a virtual cathode that produces depolarization of the axon some distance from the electrode (McIntyre and Grill, 1999). Thus, the chronaxies and refractory periods measured with anodic stimuli were similar whether the electrode was positioned over the axon or near the cell body (Fig. 2A), and reflected the temporal properties of the axons. Catholic stimuli delivered over the axon initiate action potentials in the node closest to the electrode by direct depolarization (McIntyre and Grill, 1999; McNeal, 1976). Cathodic stimuli delivered near the cell body, however, initiate action potentials in the axon at regions that are hyperpolarized during the stimulus pulse and are depolarized following termination of the stimulus pulse by the flow of charge present on the soma and dendrites (McIntyre and Grill, 1999). Further, as the electrode-to-neuron distance is increased, the site of action potential initiation switches from axon nodes close to the cell body to nodes farther from the cell body (McIntyre and Grill, 1999). Thus, for electrodes positioned close to the cell body, chronaxies and refractory periods reflect the temporal properties of both the axon, where action potential initiation takes place, and the cell body/dendrites, the discharge of which drives depolarization of the axon. However, as the electrode-to-neuron distance is increased, the chronaxie and refractory period are dominated more by the temporal properties of the axon than the properties of the cell body, and the resulting measures are similar to those obtained with the electrode positioned over the axon. Thus, the observed temporal excitation properties of single neurons can be explained by reference to the site of action potential initiation with extracellular stimulation.

The differences in chronaxies and refractory periods of populations of local cells and axons of passage were dependent on the proportion of the population that was activated, and the differences were only substantial when 80% of the neurons were activated. This effect occurred as a result of the recruitment order of differently positioned neurons within the imaginary sphere (Fig. 6). Local cells with their cell bodies positioned to the right of the point source electrode (arrow in Fig. 6B) had lower thresholds for excitation than cells with their cell bodies positioned to the left of the point source electrode (arrowhead in Fig. 6B). Thus, when 20 or 50% of the population of cells was activated with a cathodic stimulus, a disproportionate number of the activated neurons (20/20 and 43/50, respectively) were those with their cell bodies to the right of the electrode and their axons in close proximity to the electrode. Under these conditions, the resulting chronaxies and refractory periods were dominated by the temporal properties of the axon, and there was little systematic difference between the either chronaxies or refractory periods of populations of axons and populations of local cells. When the activated proportion of the population was increased to 80%, it included a larger number of neurons positioned to the left of the electrode (arrowhead in Fig. 6B): 36/80 of the activated local cells had their cell bodies to the left of the electrode and 44/80 of the activated local cells had their cell bodies to the right of the electrode. Under these conditions, the temporal properties of the cell body/dendrites contributed to the resulting chronaxies and refractory periods, and there was a large difference in both the chronaxies and the refractory periods of populations of axons and populations of local cells.

In contrast to the case of local cells activated by cathodic stimuli, with anodic stimuli approximately equal proportions of the local cells had their cell bodies positioned to the right of the electrode and to the left of the electrode across the three levels (20, 50, and 80%) of activation (Fig. 6A). The chronaxies and refractory periods measured with anodic stimuli were thus similar for populations of axons and populations of local cells, and reflected the temporal properties of the axon.
the effects of DBS may need to be reconsidered.

the conclusions that large diameter axons are responsible for neural elements (passing axons or axons of local cells), and will be dominated by the chronaxies of the most excitable population stimulated). Therefore, these measurements conducted with threshold level stimuli (i.e., a low proportion of responsible for the effects of DBS (see Section 1) were con-

Fig. 6. Recruitment order of neurons within the population models. (A) Number of the excited neurons that had their cell body (local cells) or central node (axons) positioned to the right of the electrode when 20, 50 or 80% of the population was activated. The solid line shows the number of the excited neurons positioned to the right of the electrode when 20, 50 or 80% of the population was activated, if equal proportions were stimulated from the left and from the right. The points are the mean number of neurons determined from three independently randomized populations, and the error bars, which in some cases are smaller than the symbols, show 1 standard deviation of the mean. (B) Population model of one hundred individual local cells randomly distributed such that the somas were uniformly distributed within an imaginary 3 mm radius sphere with a point source stimulating electrode at the center showing examples of neurons with their cell bodies to the left of the electrode (arrow) and examples of neurons with their cell bodies to the left of the electrode (arrowhead).

4.1. Experimental measurements of temporal excitation properties

During extracellular stimulation the chronaxies of different neuronal elements overlap and do not enable unique determination of the neuronal element stimulated. Although with intracellular activation the chronaxies of many cell bodies exceed 1 ms, with extracellular activation they are below 1 ms (Asanuma et al., 1976; Nowak and Bullier, 1998; Ranck, 1975; Stoney et al., 1968; Swadlow, 1992) and lie within the ranges determined for extracellular activation of axons (Li and Bak, 1976; Nowak and Bullier, 1998; Ranck, 1975; West and Wolsentcroft, 1983). Further, in some regions of the brain the $T_{ch}$ for extracellular stimulation of local cells may actually be less than the $T_{ch}$ for activation of the axons of the same neurons. For example, in the rostro-

The chronaxies and refractory periods of populations of neurons were strongly influenced by the relative position of the neuronal elements with respect to the electrode and thus their thresholds for activation. Experimental measurements of $T_{ch}$ and refractory period of the neuronal elements responsible for the effects of DBS (see Section 1) were conducted with threshold level stimuli (i.e., a low proportion of the population stimulated). Therefore, these measurements will be dominated by the chronaxies of the most excitable neuronal elements (passing axons or axons of local cells), and the conclusions that large diameter axons are responsible for the effects of DBS may need to be reconsidered.
Tentials in single neurons. Modeling results suggest that the properties have been based on the generation of action potential (masking). Previous measurements of strength–duration neuronal activity, or alterations in ongoing neuronal activity, or effects on populations of axons and local cells. We extended the simulation of effects on single neurons to populations of neurons as the effects of deep brain stimulation or other applications of CNS stimulation are likely mediated by effects on populations of neurons, rather than effects on single cells. However, while the position of the cell bodies and axon nodes within the populations were randomized their orientations were not. The parallel organization of the axons and local cells in the present population model may limit the applicability of these results to situations having neurons with different orientations. The membrane properties of the model neurons were based on those of mammalian motoneurons. The model was able to reproduce fundamental excitation properties of mammalian motoneurons, and sensitivity analyses showed the excitation properties to be quite robust (McIntyre and Grill, 2000).

The finding that action potential initiation occurs in the axon appears to be robust to model geometry and membrane parameters. It was also observed in a model employing Hodgkin–Huxley membrane dynamics with increased maximum sodium conductance (McIntyre and Grill, 1999), in a very accurate model of a mammalian spinal motor neuron (McIntyre and Grill, 2002), and in a model of a thalamocortical relay cell (Grill and McIntyre, 2001). Therefore we expect that the findings with this model are robust and this is supported by similar findings in a model employing scaled Hodgkin–Huxley dynamics (Grill and McIntyre, 2001).

Experimental measurements and the model-based analyses both assume that the effects of CNS stimulation are mediated by excitation, whereas effects may be mediated by transynaptic inhibition, electrical blockade of ongoing neuronal activity, or alterations in ongoing neuronal activity (masking). Previous measurements of strength–duration properties have been based on the generation of action potentials in single neurons. Modeling results suggest that the $T_a$ for generation of electrical block of local neurons by anodal surround hyperpolarization (14.5 ms) is substantially longer than the $T_a$ to generate electrical excitation of the same neuron (0.32 ms) (McIntyre and Grill, unpublished observations). Further, the $T_a$ of different neuronal elements may be dependent on the stimulation frequency and the effect may be different for different neural elements. Most experimental measurements have been made using single pulse stimuli, and single stimuli were used in this modeling study, as well. However, measurements of the $T_a$ and refractory periods for the effects of deep brain stimulation were made using high-frequency trains of stimuli and the pattern of stimulation may influence the estimated temporal excitation parameters of the neurons. Further, the threshold to alter or disrupt already active neurons may be different than the threshold to excite quiescent neurons and this may also impact the temporal excitation properties.

4.2. Limitations of approach

Computer-based cable models of extracellular stimulation of CNS neurons and axons of passage were used to compare the chronaxies and refractory periods of axons and local cells. We extended the simulation of effects on single neurons to populations of neurons as the effects of deep brain stimulation or other applications of CNS stimulation are likely mediated by effects on populations of neurons, rather than effects on single cells. However, while the position of the cell bodies and axon nodes within the populations were randomized their orientations were not. The parallel organization of the axons and local cells in the present population model may limit the applicability of these results to situations having neurons with different orientations. The membrane properties of the model neurons were based on those of mammalian motor neurons. The model was able to reproduce fundamental excitation properties of mammalian motoneurons, and sensitivity analyses showed the excitation properties to be quite robust (McIntyre and Grill, 2000).

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4.3. Conclusion

Computer-based models of axons of passage and local cells were used to test the hypothesis that the temporal excitation characteristics (chronaxie, refractory period) of local cells and axons of passage would be similar when determined using extracellular stimulation. In general, the differences between the chronaxies of cells and axons measured with extracellular stimulation were not large and did not differ in a systematic manner. This lack of sensitivity of the $T_a$ to the neuronal element stimulated arises because action potential initiation occurs in the axon, even with the electrode positioned over the cell body (McIntyre and Grill, 1999). The results support the hypothesis that there is little systematic difference in either chronaxies or refractory periods between local cells or axons of passage with extracellular stimulation.

An alternative means to determine whether the observed effects of stimulation are mediated by local cells or axons of passage is manipulation of the stimulation waveform. Using asymmetrical stimulation waveforms that excite preferentially either axons or local cells (McIntyre and Grill, 2000), one could either measure the threshold to effect or the magnitude of the effect evoked with equal current amplitudes. This provides a potential alternative that may be more sensitive to the neuronal element stimulated than the measurement of chronaxies or refractory periods.

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