Nerve conduction block utilising high-frequency alternating current

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Abstract—*High-frequency alternating current (AC) waveforms have been shown to produce a quickly reversible nerve block in animal models, but the parameters and mechanism of this block are not well understood. A frog sciatic nerve/gastrocnemius muscle preparation was used to examine the parameters for nerve conduction block in vivo, and a computer simulation of the nerve membrane was used to identify the mechanism for block. The results indicated that a 100% block of motor activity can be accomplished with a variety of waveform parameters, including sinusoidal and rectangular waveforms at frequencies from 2 kHz to 20 kHz. A complete and reversible block was achieved in 34 out of 34 nerve preparations tested. The most efficient waveform for conduction block was a 3–5 kHz constant-current biphasic sinusoid, where block could be achieved with stimulus levels as low as 0.01 μC phase^{-1}. It was demonstrated that the block was not produced indirectly through fatigue. Computer simulation of high-frequency AC demonstrated a steady-state depolarisation of the nerve membrane, and it is hypothesised that the conduction block was due to this tonic depolarisation. The precise relationship between the steady-state depolarisation and the conduction block requires further analysis. The results of this study demonstrated that high-frequency AC can be used to produce a fast-acting, and quickly reversible nerve conduction block that may have multiple applications in the treatment of unwanted neural activity.*

Keywords—*Conduction block, Alternating current, Depolarisation, High frequency*

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1 Introduction

MANY DISABLING medical conditions are characterised by undesirable nerve activity, resulting in unwanted sensation or muscle activity. If the action potentials travelling along these nerves could be arrested, the disabling condition could be reduced or eliminated. Therefore an effective and quickly reversible means of blocking nerve conduction would have many important clinical applications, such as blocking chronic peripheral pain and stopping unwanted motor activity, such as muscle spasms, spasticity, tics and choreas. Although there are many existing methods for surgically or pharmacologically blocking nerve impulses, all of these methods have significant disadvantages such as: non-specificity, serious side-effects, low success rates and nerve destruction. Therefore there is a widespread clinical need for a safe, reliable and reversible nerve block.

High-frequency alternating current (AC) waveforms have been shown to produce a quickly reversible nerve block under isolated conditions in frog, rat, cat and dog models (CATTELL and GERARD, 1935; REBOUL and ROSENBLUETH, 1939; TANNER, 1962; WOO and CAMPBELL, 1964; SOLOMONOW *et al.*, 1983; SOLOMONOW, 1984; BOWMAN and MCNEAL, 1986; ZHOU *et al.*, 1987; BARATTA *et al.*, 1989; RATTAY, 1990; HASSOUNA *et al.*, 1992; ISHIGOOKA *et al.*, 1994; LI *et al.*, 1995; SAWAN *et al.*, 1996; SHAKER *et al.*, 1998; WILLIAMSON, 1999; ABDEL-GAWAD *et al.*, 2001). However, the mechanism for this type of block is not known, and the reported results appear to be contradictory in many cases. In particular, it is not clear whether high-frequency nerve conduction block is due to a fatigue mechanism (HASSOUNA *et al.*, 1992) or to a true conduction block in the nerve membrane. The experimental methods of some studies have been questioned, with some claims that the nerves were not blocked at all, but rather the high-frequency produced a randomisation of activation (CAMPBELL and WOO, 1966; SWEENEY and MORTIMER, 1986), causing the nerve response recording to become indistinguishable from the background noise.

Investigators have rejected high-frequency block as not promising (PETRUSKA *et al.*, 1998) or undesirable (FANG and MORTIMER, 1991), or they have simply ignored it (ACCORNERO *et al.*, 1977). In this paper, we will demonstrate that high-frequency AC waveforms produce a nerve conduction block that is completely effective, repeatable and quickly reversible. The disparate reports in the literature are examined, and the

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waveforms utilised are compared for their effectiveness in producing conduction block. Finally, a mechanism for high-frequency conduction block is proposed, based on nerve membrane modelling and experimental evidence.

2 Literature concerning high-frequency block

The response of the nerve and muscle to trains of high-frequency AC waveforms was characterised by WEDENSKY (1903). The rapid failure of neuromuscular transmission following stimulation at frequencies in excess of 100 Hz has been referred to as 'Wedensky inhibition'. Bugnard and Hill studied the frequency response of the frog sciatic nerve up to 2500 Hz, demonstrating that the nerve response diminished at frequencies above 600 Hz. CATTEL and GERARD (1935) sought to determine if this diminished response was due to a fatigue mechanism in the neuromuscular junction or muscle, or whether the diminished response was due to a local alteration in the excitability of the nerve membrane under the high-frequency electrodes. They used a stimulation generated by capacitive discharges of alternating polarity at frequencies up to 2300 Hz. They concluded that there was a local decrease in excitability of the nerve membrane that could, in some cases, produce a block of nerve conduction through the affected region. A similar inhibitory effect of AC waveforms up to 40 kHz was demonstrated in the popliteal nerve of the cat (REBOUL and ROSENBLUETH, 1939).

The first demonstration of the use of a high-frequency sinusoidal waveform to produce a gradable block of nerve conduction was by TANNER (1962). He demonstrated that alternating current (probably sinusoidal) at 20 kHz could be used selectively to block nerve fibres of different sizes by varying the amplitude of the signal. These tests were performed on the sciatic nerves of frogs, utilising the recorded nerve compound action potential as the output measure. Blocking of large fibres was achieved at 4.9 V_{rms}, and a complete block of all activity was achieved at 10.2 V_{rms}.

WOO and CAMPBELL (1964) confirmed the findings of Tanner with a more detailed examination. They performed their experiments on the sciatic nerves of frogs and the tibial nerves of cats, using the nerve compound action potential or single-fibre recordings as the outcome measure. They used a 20 kHz AC (probably sinusoidal) waveform and substantiated the findings of Tanner. They performed single-fibre recordings and found that the response of the nerve varied as the stimulus amplitude was increased. At low amplitudes, axons rhythmically fired at a rate of approximately 100 Hz. The firing frequencies increased as the amplitude increased, up to a maximum firing frequency of 400–700 Hz. As the AC amplitude was increased above this, the axon firing became asynchronous. Finally, all firing activity ceased as the amplitude was further increased (typically 1–2 V).

At these levels, it was demonstrated that the AC stimulation produced a region of the nerve membrane that blocked conduction of action potentials. Despite the apparent success of this method, Woo and Campbell abandoned this method of nerve block in favour of a direct current (DC) block (CAMPBELL and WOO, 1966), which they found more reliable. However, direct current will damage both the electrode and nerve after a few minutes of continuous application (WHITMAN and KIDD, 1975; HURLBERT *et al.*, 1993) and is therefore not useful for chronic human applications.

The first practical application of high-frequency block was performed by Solomonow and his collegues (SOLOMONOW *et al.*, 1983; SOLOMONOW, 1984; ZHOU *et al.*, 1987; BARATTA *et al.*, 1989). High-frequency block was utilised to achieve normal recruitment order of nerve fibre diameter during electrical stimulation (smallest to largest fibres). Studies were performed using the sciatic nerve of the cat, with muscle force as the outcome measure. A broad frequency range was evaluated, and 600 Hz was identified as the optimum block frequency. It should be noted that these studies utilised a very different waveform from that used by the previous investigators. The waveform consisted of a monophasic current-controlled depolarising pulse lasting 50–100 μs, delivered at the specified frequency, as shown in Fig. 1. Monophasic stimulation is known to be damaging to both the tissue and the electrode (MORTIMER, 1981), and therefore it is unlikely that this waveform can be used in chronic clinical applications.

BOWMAN and MCNEAL (1986) evaluated the effect of capacitance-coupled, voltage-controlled rectangular pulses on nerve conduction over the range of 100–10,000 Hz. The waveform used in these studies consisted of a rectangular pulse of 50 μs duration immediately followed by an equal duration pulse of opposite polarity. At frequencies below 10 kHz therefore, there is an off-time between the delivery of each biphasic pair, as shown in Fig. 1. These experiments were performed on the sciatic nerves of cats, utilising the firing frequency of single fibres in the ventral roots as the outcome measure.

They found that a nerve conduction block could be achieved at 4 kHz with sufficient amplitude of stimulation (five times threshold voltage, apparently in the range of 7 V). The high-frequency stimulation produced an initial increase in firing that lasted 1–2 s, followed by a period of a few seconds where pulses could pass uninhibited through the high-frequency region, before a true conduction block was established. Once established, this block lasted at least 80 s, and conduction could be restored within 1 s after the cessation of block. They also found that a preconditioning high-frequency stimulus that was below the activation threshold could be used to allow the block to occur without the initial rise in firing frequency.

Recently, investigators in Montreal have focused on the 600 Hz conduction block produced by Solomonow, but using a biphasic waveform rather than a monophasic waveform (HASSOUNA *et al.*, 1992; LI *et al.*, 1995; SAWAN *et al.*, 1996; SHAKER *et al.*, 1998; ABDEL-GAWAD *et al.*, 2001). Unlike the Solomonow waveform, the Sawan waveform has a zero net charge, as shown in Fig. 1. SHAKER *et al.* (1998) reported the use of a 600 Hz block in the pudendal nerves of dogs to enable proper voiding by blocking unwanted sphincter activity. Sphincter pressure is utilised as the outcome measure. These investigators initially began their investigations utilising a 200–300 Hz waveform to produce a fast fatigue of the sphincter muscles to achieve a 'fatigue block' (HASSOUNA *et al.*, 1992; LI *et al.*, 1995; SAWAN *et al.*, 1996). They discovered, however, that if the frequency was increased to 600 Hz, they could achieve what appeared to be a true conduction block, rather that just a quickly fatiguing response.

Another attempt to utilise the methods of Solomonow to produce a block of sphincter activity was performed by ISHIGOOKA, *et al.* (1994). A monophasic waveform was used, with a constant amplitude of 10 V and a constant phase duration of 200 μs. The waveform was different from the Solomonow waveform because it was voltage-controlled rather than current controlled. This is likely to result in a biphasic current waveform being delivered to the nerve, as shown in Fig. 1. Although blocking was achieved in this study, it was not more than 60% effective; and the blocking effectiveness was essentially equivalent above 200 Hz. This is in direct contrast to the work of Solomonow, who showed a large increase in blocking effectiveness over the range of 200–600 Hz.

The disparate results in the literature make it difficult to ascertain either the mechanism of high-frequency block or its potential usefulness for clinical applications. The optimum frequency for block is reported as being anywhere from 200 Hz to 20 kHz. Both sinusoidal and rectangular waves have

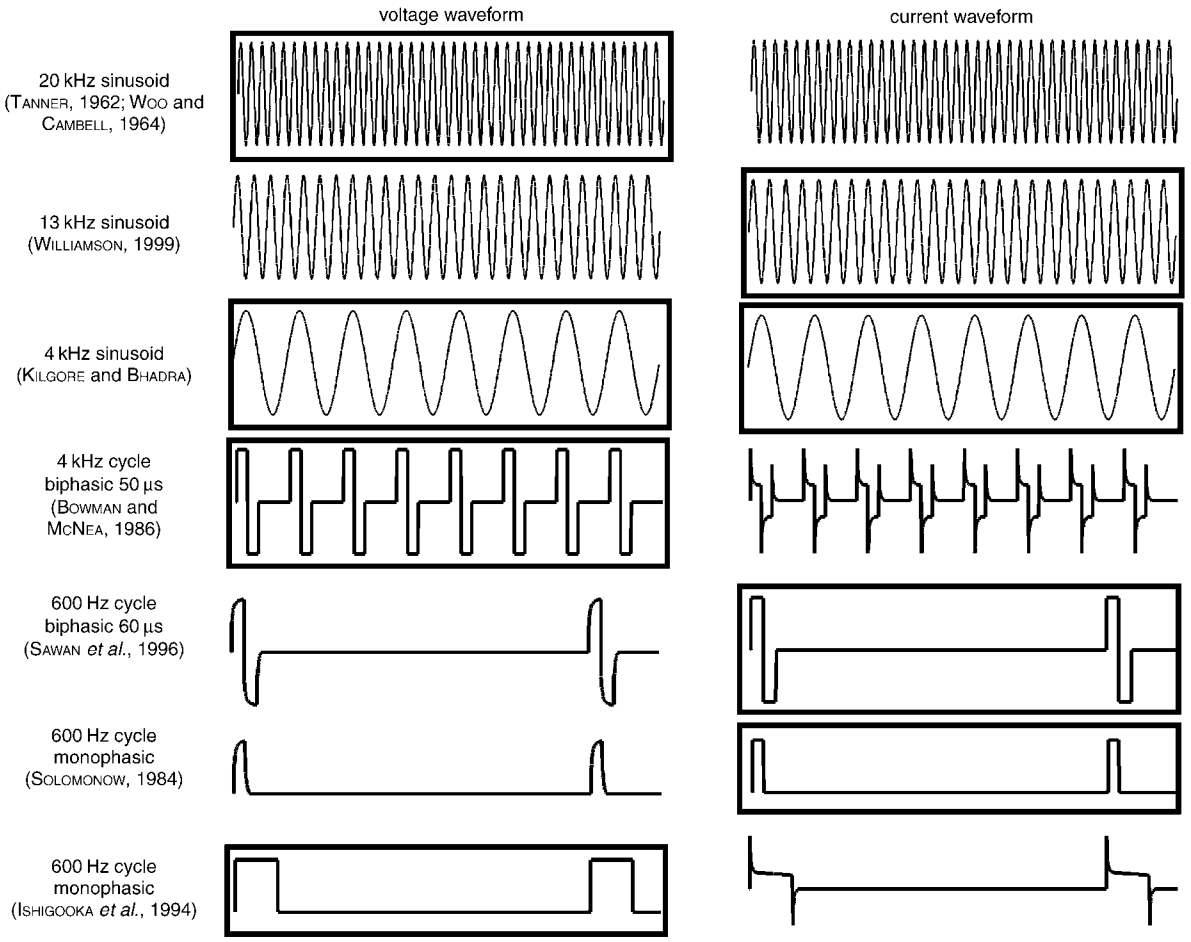

Fig. 1 *AC waveforms used for blocking, as reported in literature and as evaluated in this study. Box surrounding a waveform indicates whether investigation utilised voltage-controlled or current-controlled waveform. Un-controlled parameter (either voltage or current) delivered to nerve is estimated based on our experimental measurements using our electrode. Actual waveforms may have been slightly different owing to differing electrode–tissue impedances. Note that no two investigations have utilised same waveform, and so no true comparisons can be made among previously published results*

been used, with differing effects. Both monophasic and biphasic stimulation have been used, without any direct comparison of these two waveforms. Stimulus was delivered using voltage-controlled or current-controlled output stages, through a variety of electrode types and configurations. The nerve compound action potential was used as the output criteria in some studies, whereas muscle force was the output criteria in others. In addition to these variations between studies, there have been no data presented regarding the actual stimulation pattern experienced by the nerve; i.e. the current delivered to the tissue was not directly measured.

As it has been demonstrated that the important property of electrical stimulation is charge delivery, not the voltage (Mortimer, 1981), we estimated the probable current waveform of the different blocking waveforms from the literature, based on *in vivo* impedance testing with frogs. The results are summarised in Fig. 1 and demonstrate the distinctions between the waveforms used. In fact, no two groups of investigators have used identical waveforms, with the possible exception of Tanner (1962) and Woo and Campbell (1964), who used 20 kHz sinusoids (presumably, although the waveform shape is not explicitly stated in either paper).

To ascertain the true effect of high-frequency stimulation on nerve conduction, we sought to perform a series of experiments that would clarify these results, with the goal of determining the true potential of high-frequency waveforms to be used as a method for blocking nerve conduction *in vivo*. Based on the work of Bowman and McNeal (1986), we hypothesised that a high-frequency (5–20 kHz), biphasic, current-controlled waveform would produce the most effective block while maintaining a zero net charge, thus providing the potential for safe, chronic use in humans.

3 Methods

3.1 *Animals and surgical procedure*

Acute studies were performed in adult bullfrogs. The sciatic nerve was exposed along its entire length through a dorsal incision and cut at the level of the spinal cord. The gastrocnemius muscle was exposed, and the Achilles tendon was cut as distally as possible. The origin of the gastrocnemius was exposed, and the femur and tibia were cut, leaving a portion of the bone still attached to the muscle. All branches of the sciatic nerve, except the tibial nerve, were cut. The sciatic–tibial nerve was removed along with the entire grastrocnemius muscle. The muscle–nerve preparation was kept moist with mineral oil. All experiments were conducted at room temperature. This preparation typically allowed 1–2 h of experimentation time. The experiment was repeated with the second leg in each frog. This preparation allowed the use of electrodes that completely encircled the nerve, because they could be slipped over the cut end of the nerve.

The origin of the gastrocnemius muscle was clamped in a special fixture, using the bone to help hold the muscle in place. A strong suture was tied to the distal tendon and connected to

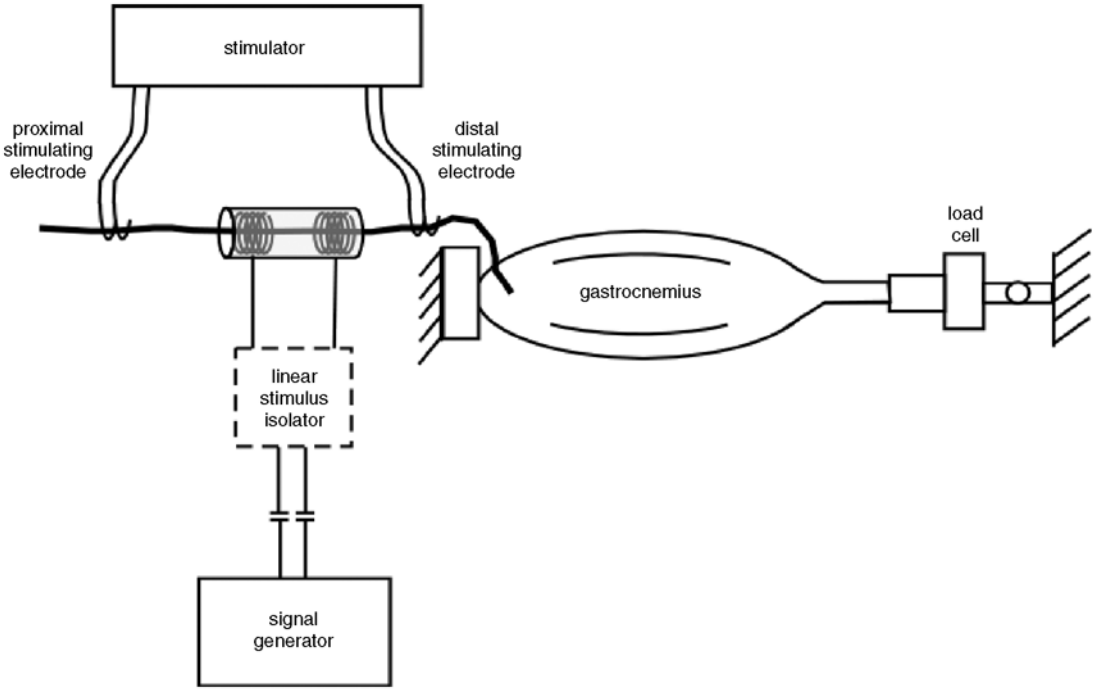

Fig. 2 *Block diagram of experimental set-up. All experiments included proximal stimulating electrode and blocking electrode. Distal stimulating electrode was used in some experiments to verify continued function of neuromuscular junction. For voltage-controlled waveforms, direct capacitively coupled output of signal generator was used. For current-controlled waveforms, linear stimulus isolator was used to generate blocking waveform*

an in-line force transducer* to measure tendon tension. The muscle was pre-tensioned with approximately 1–2 N of passive tension.

3.2 *Electrical stimulation and block*

In all experiments, two electrodes were placed on the sciatic–tibial nerve, as shown in Fig. 2. One electrode was placed near the cut (proximal) end of the nerve and was used to generate an electrically stimulated muscle response. The second electrode was placed between the stimulating electrode and the muscle and was used to generate the high-frequency conduction block. In some experiments, a third electrode was placed between the blocking electrode and the muscle and used to stimulate the muscle to verify that the neuromuscular junction was not fatigued. The stimulating electrodes consisted of two platinum wires hooked around the nerve. The blocking electrode consisted of two platinum wires, 0.3 mm in diameter, wrapped in a spiral. Each wire made five complete spirals around the nerve. The total length of each contact was 5 mm, with 5 mm between the two contacts. Both electrodes were placed inside a silastic tube, with a total length of 15 mm and an inner diameter of 2 mm. The approximate geometrical surface area of this electrode was 22 mm^2. The electrode impedance varied as a function of frequency and individual preparation, but was typically between 5 kΩ and 10 kΩ for frequencies in the range of 2–10 kHz. In some experiments, a monopolar nerve cuff electrode was used, in which the electrode encircling the nerve was identical to a single spiral electrode in the bipolar cuff. The remote electrode was a needle placed into the tissue surrounding the remaining portion of the femur.

A two-channel stimulator was used to deliver the stimulating pulses[†]. A constant current stage was used[‡]. Constant current stimuli were delivered at approximately twice the stimulus that produced the maximum muscle twitch response. Typical parameters were 10–100 μA amplitude for a 200 μs duration pulse. Stimulus frequency for the proximal electrode was either 0.2 Hz, for evaluating twitch responses, or 10 Hz, for evaluating tetanic responses. When a distal electrode was used, a stimulus rate of 0.25 Hz was utilised. The two stimulus channels were asynchronous with respect to each other, and the pulse trains were manually initiated at the beginning of each trial.

The high-frequency blocking stimulus was the controlled variable in these experiments. A waveform generator** was used to generate the high-frequency waveform. A 3 μF capacitor was placed in series in each output line of the waveform generator to reduce DC leakage. To produce a constant current waveform, the waveform generator was connected to a linear stimulus isolator[††] that converted the voltage-controlled waveform generator output to a current-controlled waveform. The linear stimulus isolator attenuated the output at input frequencies above approximately 1 kHz. The attenuation was recorded for the frequency range from 100 Hz to 20 kHz across a 10 kΩ load, and the recorded current amplitude was adjusted based on this calibration. The attenuation was −1 dB at 2 kHz, −2.6 dB at 5 kHz, −4.6 dB at 10 kHz, and −6.1 dB at 20 kHz.

Both the current and voltage delivered to the tissue were recorded in four of the preparations. A 100 Ω resistor was placed in series with one electrode lead, and the voltage across this resistor was input into a differential amplifier[‡‡] with a gain of 1 and an input impedance greater than 10 MΩ. The amplifier output and the direct voltage output of the waveform generator were recorded by computer using an analogue-to-digital (AD) input with an input impedance of 1 MΩ*. The nerve response was periodically recorded, both with and without any AD input

*Entran, Fairfield, NJ, USA

[†]Grass S88, Grass Telefactor, West Warwick, RI

[‡]Grass stimulus optical isolator

**Wavetek Model 395, Fluke, Everett, WA, USA

[††]LSI395, World Precision Instruments, Sarasota, FL, USA

[‡‡]Frederick Haer and Co.

*National Instruments

connected, to verify that the leakage currents did not affect the threshold amplitude for conduction block.

3.3 *Experimental procedures*

The response of the nerve before, during and after high-frequency block was recorded in individual trials. In each trial, the stimulation by the proximal electrode was initiated and continued throughout the duration of the trial. After 10–20 s, the conduction block was initiated and typically maintained for 30–60 s. The block was then stopped, and the recovery response of the nerve to the continuing proximal stimulation pulses was recorded for at least 10 s after the cessation of block. In those experiments where a distal electrode was used, the stimulation to the distal electrode was delivered midway through the block. Three distal pulses were applied while the block was maintained. Both twitch and tetanic responses were evaluated.

Multiple experiments were performed to evaluate the effect of high-frequency AC stimulation on the nerve. The frequency range studied was 600 Hz–20 kHz, but the majority of experiments were concentrated on the 2 kHz–5 kHz range, where block was most effective. The following stimulation parameters were compared in separate experiments: constant current against constant voltage; sinusoid against rectangular wave; and bipolar against monopolar electrodes. In addition, the waveforms described in the literature (see Fig. 1) were also tested for the effectiveness of the block, and they were compared with the sinusoidal and rectangular waveforms.

3.4 *Computer simulation of high-frequency AC nerve conduction block*

To determine the mechanism for high-frequency AC nerve conduction block, a computer simulation of the nerve membrane and electrode was developed, based on the NEURON software package (HINES and CARNEVALE, 1997), utilising the membrane parameters determined by MCINTYRE *et al.* (2002). This simulation provides a means for visualising the electrophysiological behaviour of the nerve membrane and has been utilised elsewhere (MCINTYRE and GRILL, 1998; RICHARDSON *et al.*, 2000; KRAUTHAMER and CROSHEK, 2002).

The nerve membrane model consisted of quantitatively defined equivalent electrical circuits for both the node and internode regions of the axon (RICHARDSON *et al.*, 2000; MCINTYRE *et al.*, 2002), based on the nerve membrane model developed by MCNEAL (1976). The node model circuit consisted of a parallel combination of a non-linear sodium conductance a linear leakage conductance and a membrane capacitance. The values of the parameters describing the activation and inactivation kinetics of the sodium channel were those determined by MCINTYRE and GRILL (1998). The internode region was modelled as a circuit composed of two layers of linear components. This model was selected because it more accurately simulates the response of neurons *in vivo* (MCINTYRE *et al.*, 2002) and because it includes representations of the paranode regions. These features were expected to be important in identifying the mechanisms of high-frequency block. The modelled axon consisted of a 21 node section, with a total length of 28 mm and a fibre diameter of 10–14 μm.

The specific parameters used were based on MCINTYRE *et al.* (2002): node length = 1 μm; myelin attachment paranode length = 3 μm; main paranode length = 56 μm; internodal section length (six per internode) = 213.5 μm; nodal capacitance = 2 μF cm^{-2}; internodal capacitance = 2 μF cm^{-2}; myelin capacitance = 0.1 μF cm^{-2}; axoplasmic resistivity = 70 Ω-cm; peri-axonal resistivity = 70 Ω-cm; myelin conductance = 0.001 S cm^{-2}; myelin attachment paranode conductance = 0.001 S cm^{-2}; main segment paranode conductance = 0.0001 S cm^{-2}; internode segment conductance = 0.0001 S cm^{-2}; maximum slow K^+ conductance = 0.08 S cm^{-2}; maximum persistent Na^+ conductance = 0.01 S cm^{-2}; nodal leakage conductance = 0.007 S cm^{-2}; Na^+ Nernst potential = 50 mV; K^+ Nernst potential = −90 mV; leakage reversal potential = −90 mV; rest potential = −80 mV; and temperature = 37°C.

Our experimental results (described below) indicated that the motor nerve does not fire repetitively with high-frequency stimulation, and therefore the maximum fast Na^+ conductance was reduced from 3.0 S cm^{-2} to 2.8 S cm^{-2} in some simulations to reduce repetitive firing in the modelled neuron. This reduction did not change the shape of the propagated action potential and resulted in a decrease in action potential peak of only 6% with a slowed conduction velocity. The specific parameters of this model were developed to simulate the observed responses of mammalian neurons, and no attempt was made directly to correlate simulated and experimental high-frequency block parameters.

An external electrode was modelled as a single point source located 1000 μm away from the axon and centred over the middle node. The extracellular potentials experienced in each compartment of the model were calculated, assuming an infinite homogenous anisotropic medium (longitudinal resistivity = 300 Ω-cm; transverse resistivity = 1200 Ω-cm) (RANCK and BEMENT, 1965). The equivalent intracellular current at each compartment was calculated from each extracellular potential (WARMAN *et al.*, 1992; RICHARDSON *et al.*, 2000), based on a membrane model consisting of two layers of a linear leakage conductance in parallel with the membrane capacitance (MCINTYRE *et al.*, 2002).

The simulation was conducted by generating a current-controlled sinusoidal waveform at the blocking electrode at frequencies from 3 kHz to 10 kHz. The amplitude of the blocking waveform was varied over the range of 50–1000 $\mu A_{p\text{-}p}$ at each frequency. After the transmembrane potential reached a steady state across all segments, an action potential was generated at one end of the axon, so that it had to propagate through the region of applied block. A successful block was defined as the condition where no action potential was propagated to the node at the opposite end of the axon.

4 Results

4.1 *High-frequency block experimental results*

A complete and reversible conduction block was achieved in all 34 sciatic nerve preparations tested (18 frogs). Typically, block was achieved using a 3–5 kHz sinusoidal waveform with an amplitude of 3–4 V peak to peak ($V_{p\text{-}p}$) or 0.3–1.6 $mA_{p\text{-}p}$. In some preparations, a complete block was achieved with amplitudes as low as 2.4 $V_{p\text{-}p}$. Fig. 3 shows the range of blocking amplitudes for 12 sciatic nerves that were tested using a 5 kHz voltage-controlled sinusoid. The median amplitude for a 100% block was 4.4 $V_{p\text{-}p}$. Partial block was achieved with a median of 2.5 $V_{p\text{-}p}$. At lower amplitude levels (median 2.0 $V_{p\text{-}p}$), the 5 kHz sinusoid either produced a strong tetanic response (described below), or did not produce any obvious change in the twitch response. A complete block was achieved in individual preparations at frequencies as low as 1000 Hz and as high as 20 kHz. In all cases where a 100% block was achieved, the block was maintained at higher amplitudes, up to the highest amplitude tested (10 $V_{p\text{-}p}$ or 5.5 $mA_{p\text{-}p}$). The threshold for block tended to decrease slightly over the course of a single experimental session.

Fig. 4 shows an example of a typical 100% block of frog sciatic conduction using a 3 kHz sinusoidal voltage-controlled

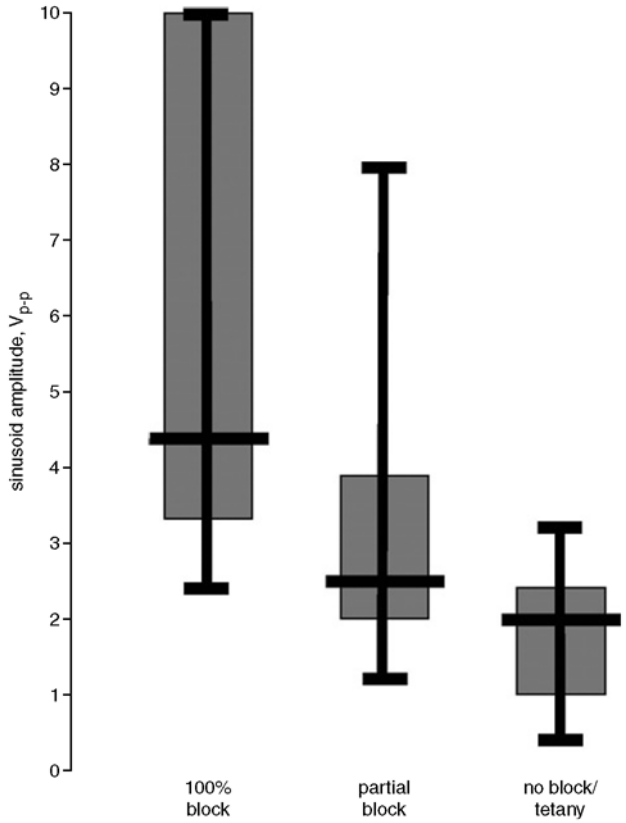

Fig. 3 *Block parameters for 5 kHz voltage-controlled sinusoidal waveform. Graph shows median, minimum, maximum, first and third interquartile ranges for voltage necessary to produce: 100% block; partial block; either no block or strong tetanic response. Values were obtained from 12 legs in 7 frogs using bipolar electrodes. In all cases, block was maintained at amplitudes above minimum necessary to produce 100% block. Differences between each group are statistically significant ($p < 0.01$)*

waveform. This trial shows that the block produced an onset muscle twitch that is identical to the twitch response obtained from the proximal stimulation. The block was immediate, completely eliminating the conduction of the first proximal pulse that occured 2 s after block initiation. Three pulses were produced by the distal stimulating electrode, demonstrating that the block does not affect the muscle or the neuromuscular junction. The block was maintained for 40 s. Typically, the cessation of block also produced a twitch response in the muscle, although this twitch was often of lower amplitude than the onset response.

Finally, the block was shown to be completely and instantly reversible. Fig. 4 shows that the recovery occured within 500 ms, with no decrease in the twitch amplitude. A similar response can be obtained using tetanic proximal and distal stimulation, as shown in Fig. 5. The tetanic block more clearly demonstrates the immediate initiation and cessation of the block. The distal electrode is able to generate a tetanic response from the muscle, confirming that the block is occurring in the nerve, under or near the blocking electrode.

The waveform shape or controlled parameter (voltage or current) did not appear to be major factors in the effectiveness of the block. For current-controlled sinusoidal waveforms, the complete block thresholds were within the same range as for voltage-controlled sinusoidal waveforms, based on our electrode impedance of 5–10 kΩ. The electrode–tissue impedance appears to act like a pure resistance at the frequencies tested, and therefore the waveform delivered to the tissue is very similar in either current-controlled or voltage-controlled waveforms. In addition, there was no appreciable difference in the characteristics of the responses for rectangular waves compared with sinusoidal waves. On a charge per phase basis, each produced blocks at the same amplitudes and frequencies in the preparations where they were directly compared.

Complete block was achieved at a threshold amplitude and at all amplitudes greater than the threshold (up to the maximum amplitude of 10 V_{p-p}). There was no obvious difference in the character of the block when the amplitude was at threshold as against when the amplitude was two or three times greater.

A partial block, defined as a muscle twitch force during block that was between zero and maximum force, could be achieved by reducing the amplitude of the blocking waveform below the threshold for 100% block. Fig. 6 shows an example of a series of blocks at different amplitudes, producing a range of blocking effectiveness from 100% down to 0% over a range of 500 μA. It was difficult to achieve a repeatable partial block, particularly in the range of 20–80% block. Often, the amplitude necessary to

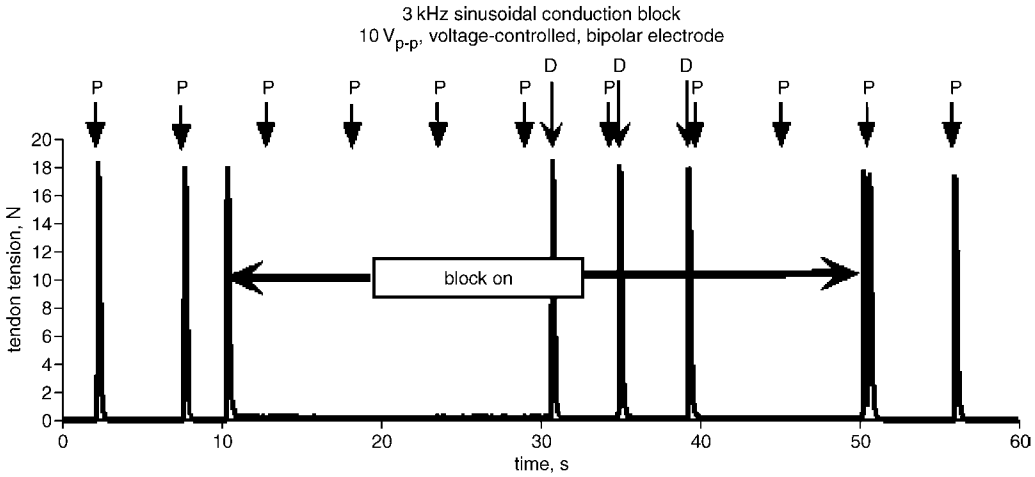

Fig. 4 *Nerve conduction block using 3 kHz sinusoidal voltage-controlled waveform with amplitude of 10 V_{p-p}. Proximal electrode P delivered supramaximum stimulus at 0.2 Hz throughout course of trial, as indicated by arrows. Blocking waveform was initiated at 10 s and turned off at 50 s. Initiation and cessation of conduction block produces single muscle twitch response. 100% block is achieved throughout period of block, as demonstrated by flat baseline starting at 10 s. After block had been active for 20 s, distal electrode D delivered supramaximum stimulus at 0.25 Hz for three pulses. Trial demonstrates quick initiation and cessation of block. Note that nerve is able to conduct action potential from proximal electrode approximately 500 ms after cessation of block (50.5 s)*

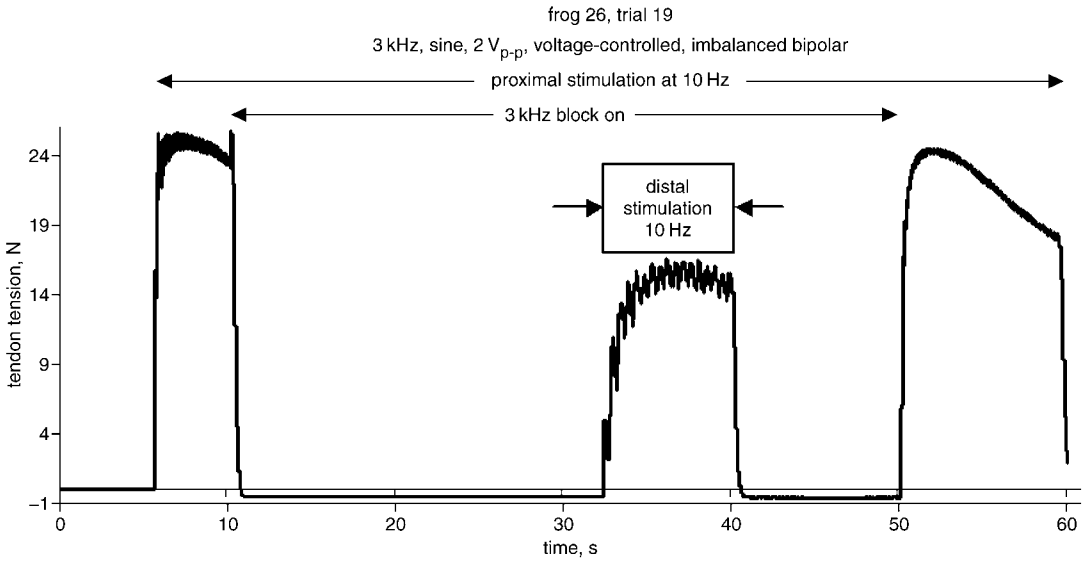

Fig. 5 *Nerve conduction block of tetanic stimulus. 10 Hz supramaximum stimulus was delivered to proximal electrode beginning 6 s into trial, producing tetanic contraction of grastrocnemius. Proximal stimulus remained on for 53 s. 10 s into trial, 3 kHz sinusoidal waveform, voltage-controlled, 2 V_{p-p} was delivered through bipolar electrode. 100% block was achieved within 1 s and maintained for 40 s, when blocking waveform was turned off. Tetanic force response immediately recovered to pre-block level before falling off owing to muscle fatigue. During period of block, 10 Hz stimulus was delivered to distal electrode, demonstrating continued viability of neuromuscular junction and muscle*

produce these partial blocks decreased over time, possibly owing to changes in the electrode–nerve impedance.

A quickly decaying tetanic response was obtained in many of the preparations at amplitudes slightly below that necessary for complete or partial block, as shown in Fig. 7. This type of response was characterised by an initial twitch response of the muscle, which decayed to less than 50% of peak force within 1 s. A tonic level of muscle force, typically 20–50% of peak, was then maintained for many tens of seconds. This response has been described elsewhere (FORBES and RICE, 1929; BOWMAN and MCNEAL, 1986; JAVEL *et al.*, 1987; WILLIAMSON, 1999) and is referred to as neural conduction fatigue. Neural conduction fatigue produced a depressed response to the proximal stimulation that often lasted beyond the cessation of the stimulus for tens of seconds. For example, in Fig. 7, the muscle force recovers back to the original level after approximately 2 min. In some cases, this neural fatigue was associated with a complete block of proximal stimulation conduction, but, in other cases, the proximal stimulation could be partially conducted through the entire nerve.

A complete block could be achieved with all the biphasic waveforms published in the literature, but we could not achieve a complete block with the monophasic waveforms. The comparison of the response of the nerve to the different, previously published waveforms is shown in Fig. 8. None of the previously published waveforms was as efficient (in terms of charge per phase) at blocking as a continuous sinusoid or rectangular wave. The biphasic waveform of BOWMAN and MCNEAL (1986), which consisted of a rectangular wave followed by a brief off period, was only slightly less effective than continuous rectangular waveforms with similar phase durations. The biphasic Sawan waveform, at 600 Hz, required amplitudes in excess of 4 mA_{p-p} to achieve a complete block, and this block demonstrated a neural fatigue mechanism of block. The Sawan waveform produced a post-block depression in twitch response of at least 70%, and the nerve did not fully recover from this depression after 2 min.

Both monophasic waveforms produced only a partial block at the levels tested. The Solomonow waveform produced a

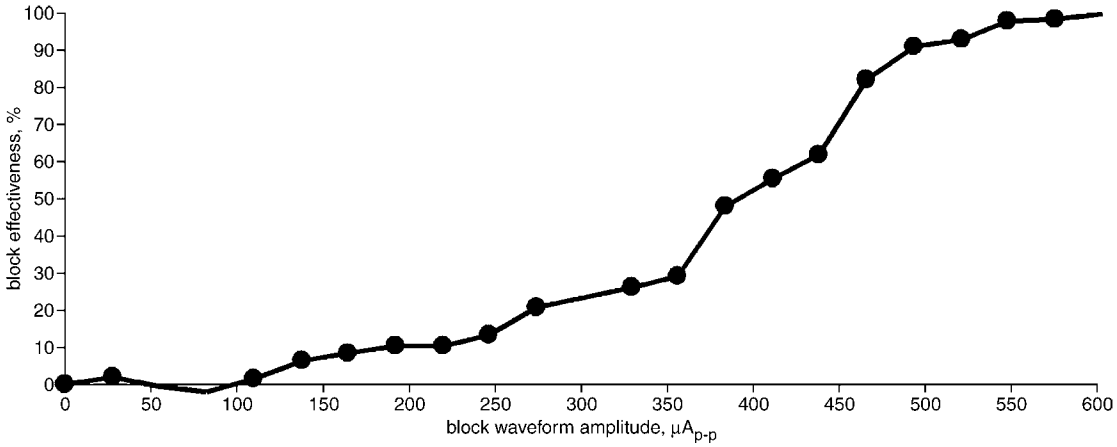

Fig. 6 *Graded block of muscle force using high-frequency AC blocking waveform. Block was achieved using 5 kHz sinusoidal waveform delivered through monopolar cuff electrode. Current amplitude of sinusoid was controlled and varied from 0 to 604 μA in steps of 27 μA. Peak twitch force at each level of block was recorded and normalised to peak twitch force just prior to initiation of block. 0.2 Hz supramaximum stimulus was delivered through proximal electrode to generate muscle twitches*

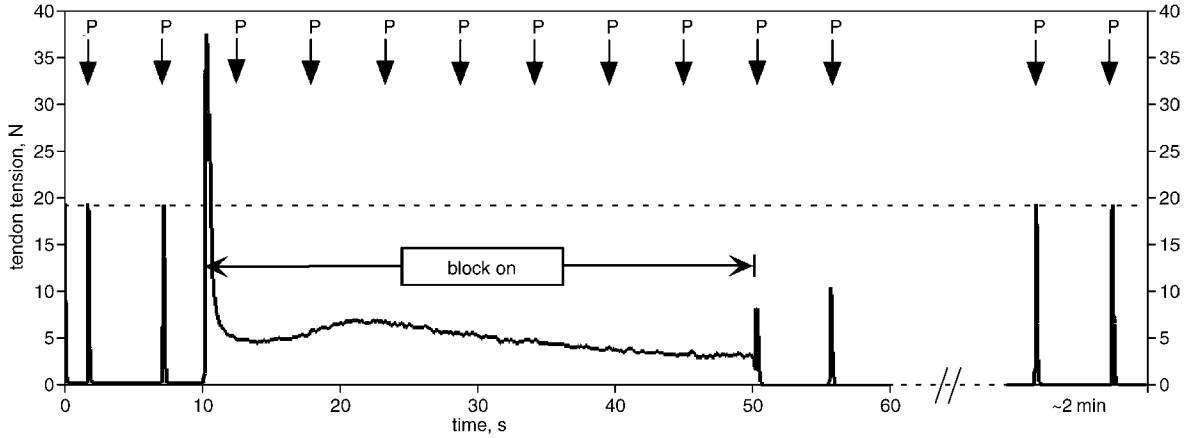

Fig. 7 *Example of 'neural conduction fatigue' response to high-frequency AC waveform. Proximal stimulation is delivered throughout trial at 0.2 Hz. When AC waveform is initiated at 10 s, there is very large twitch response from muscle, followed by quick decrease to tetanic level that is 20–30% of twitch response. After cessation of block at 50 s, twitch response from proximal electrode is diminished to approximately 60% of initial value. However, after 2 min of rest, nerve and muscle recover completely from neural fatigue*

strong tetanic response of the muscle that resulted in quick neural conduction fatigue. A 10% block was produced at an amplitude of 1.25 mA. The maximum amplitude tested was 16.9 mA, and it is possible that a further increase in the stimulus amplitude would have produced a complete block. The Ishigooka waveform produced a tetanic response at all amplitudes tested.

4.2 *High-frequency block nerve membrane modelling results*

High-frequency sinusoidal stimulation produced a conduction block in the nerve membrane simulations at amplitudes of 100–800 $\mu A_{p\text{-}p}$. A typical example of the nerve membrane modelling results is shown in Fig. 9. During the first cycle of the high-frequency waveform, the membrane is depolarised under the electrode, and an action potential is generated that propagates in both directions. This is followed by the generation of successive action potentials that are approximately 2–3 ms apart. In the example shown in Fig. 9, a total of four action potentials are generated by the 5 kHz sinusoid. The paranode regions under the electrode experience a progressively increasing bias towards depolarisation, as shown in Fig. 9*b*. With continued delivery of the sinusoid, the paranode regions become sufficiently depolarised that action potentials can no longer propagate through them. This is shown in Fig. 9, where a test action potential generated 95 ms after the initiation of the sinusoid is blocked.

The depolarisation in the paranode regions extends to all 21 nodes in the model in the steady state, as shown in Fig. 10. During the initial cycles of the sinusoidal waveform, the nodes on either side of the electrode show regions of hyperpolarisation. These regions are referred to as 'virtual anodes' (RANCK, 1975; WARMAN *et al.*, 1992) and have been experimentally demonstrated (SWEENEY and MORTIMER, 1986). However, as additional cycles of the sinusoidal waveform are delivered, all paranode regions experience a constant bias towards depolarisation. With successive cycles of the waveform, the number of nodes experiencing this depolarisation bias spread out in both directions. After a sufficient number of cycles, the entire axon experiences depolarisation, even during the anodic phase of the sinusoid. When the depolarisation at the central nodes is sufficiently high, action potentials will no longer travel through the central region of the membrane, and a conduction block is established. The block is established within 100 ms, although the exact timing of the block was not examined in detail. Block timing was primarily dependent on waveform

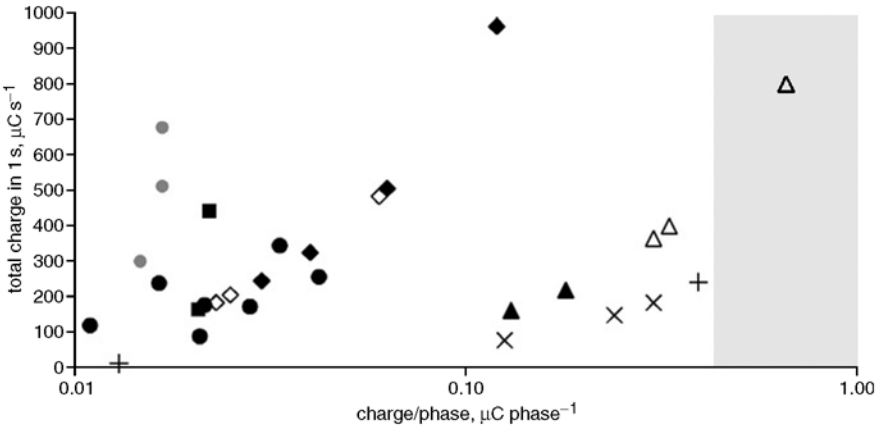

Fig. 8 *Comparison of block success and charge delivery for various AC blocking waveforms. Closed symbols indicate that 100% block was achieved at levels indicated. Open symbols indicate that partial or no block was achieved. Complete block could not be achieved with (×) Solomonow or (+) Ishigooka waveforms. Total charge delivered in 1 s is sum of both cathodic and anodic phases of stimulus as delivered over period of 1 s. Note that net charge is zero for all waveforms except for monophasic Solomonow and Ishigooka waveforms. Continuous sinusoidal or rectangular waveforms of 2–20 kHz produced 100% effective blocks at lowest charge per phase values. In all cases, charge per phase is well below previously established safe levels for low-frequency stimuli, which is indicated by shaded region (0.4 μC phase^{-1}). (●) 2–7 kHz sinusoid; (●) 10–20 kHz sinusoid; (■) square wave; (◆) Bowman and McNeal waveform; (▲) Sawan waveform*

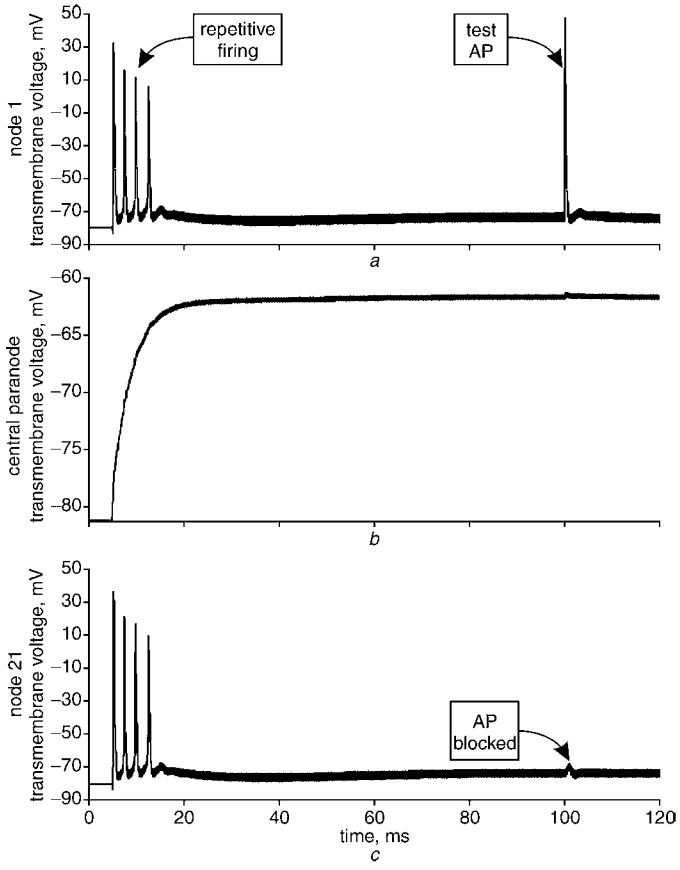

Fig. 9 *Computer simulation showing transmembrane voltage developed over time in 21-node axon model. External point source electrode is positioned directly above central node (node 11), 1 mm away from axon. Waveform delivered by electrode is a 5 kHz sinusoid with amplitude of 100 $\mu A_{p\text{-}p}$. (a) and (c) Transmembrane voltage for nodes on each end of model; (b) paranode voltage for central node. Note different vertical scale for (b). Four action potentials (APs) are spontaneously generated during first 15 ms of sinusoidal waveform. Central paranode region experiences steadily rising depolarisation owing to sinusoid, as shown in (b). This depolarisation spreads to adjacent paranodes and continues to increase slowly for at least 100 ms. In this simulation, test AP was generated in node 1 at 100 ms. This AP cannot propagate through region of depolarised paranodes and is blocked before it reaches other end of axon (node 21), as shown in (c)*

amplitude, with higher amplitude waveforms producing a static depolarisation more quickly.

5 Discussion

The results of this study demonstrate that high-frequency stimulation, when properly delivered, can produce a block of nerve conduction in whole motor nerves. The block is demonstrated to be 100% effective in blocking motor activity and is completely reversible in less than 500 ms. Muscle twitches and tetanic responses can be blocked. Within the parameter range tested, a continuous sinusoidal or rectangular waveform at 3–5 kHz appears to provide the most consistent block at the lowest charge per phase. Typical amplitudes that produced block were 3–5 $V_{p\text{-}p}$ or 0.5–2 $mA_{p\text{-}p}$, although this amplitude is probably dependent on the electrode surface area, nerve diameter and electrode–nerve interface. The promising results of this study justify further study to explore the possibility of the clinical application of this form of nerve conduction block.

It was possible to use the amplitude of the high-frequency waveform to produce a graded block of the muscle response. A graded block may be extremely useful as a method for controlling muscle spasticity, where a complete block would result in temporary paralysis. If the spastic muscle force can be reduced rather than eliminated, it may enable the individual to regain enough natural control to accomplish functional activities. Within a single acute trial, the percentage of block could be controlled to within $\pm 10\%$. However, repeated trials demonstrated some variability in the amplitudes producing graded block. This may be owing to changes in the electrode–tissue interface over time. It will be necessary to examine graded block in a fully encapsulated and stable electrode–tissue preparation to determine whether this feature is stable enough to be utilised in clinical applications.

The conduction block was determined to occur in the region of the nerve under or near the blocking electrode. Following the example of BOWMAN and MCNEAL (1986), we used a stimulating electrode positioned between the blocking electrode and the muscle to demonstrate that the muscle could still be activated distal to the blocked region to produce an equivalent maximum twitch response. This provides conclusive evidence that this mechanism of conduction block is not due to a distal effect at the neuromuscular junction or muscle, such as neurotransmitter depletion or muscle fatigue, as has been previously assumed (SWEENEY and MORTIMER, 1986).

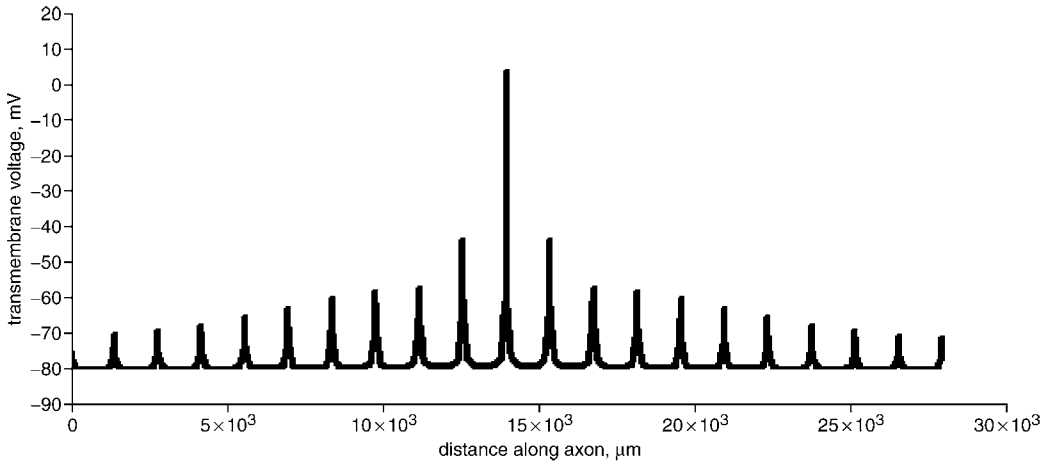

Fig. 10 *Computer simulation showing transmembrane potential developed at all 21 nodes in nerve membrane model. External point source electrode is positioned directly above central node, 1 mm away from axon. Waveform delivered by electrode is 5 kHz sinusoid with amplitude of 100 $\mu A_{p\text{-}p}$. Figure shows steady-state depolarisation that occurs after sinusoid has been delivered for 95 ms. Note that there are no regions of hyperpolarisation. Large depolarised region produces very effective nerve conduction block, as shown in Fig. 9*

Using a simulation of the nerve membrane response to high-frequency AC waveforms, we identified a probable mechanism for block. High-frequency stimulation produces a depolarisation of the nerve membrane over a broad region extending beyond the electrode itself. This depolarisation is maintained at a steady state across multiple nodes, with no regions of hyperpolarisation. This pattern is in contrast to the application of DC or low-frequency stimulus pulses, which produce a region of depolarisation directly under the electrode, flanked by hyperpolarised regions on either side, known as 'virtual electrodes' (RANCK, 1975; WARMAN *et al.*, 1992).

Depolarisation of the nerve membrane is known to increase the threshold for activation and produce conduction block (ZIMMERMAN, 1968; SASSEN and ZIMMERMAN, 1973; GRILL and MORTIMER, 1997). When depolarisation of the nerve membrane is maintained at a sufficiently high level, voltage-gated Na+ channels remain closed after the transmission of a single action potential. Therefore it appears probable that high-frequency AC waveforms produce a block of nerve conduction by establishing a region of constantly depolarised nerve membrane, despite the fact that there is a zero net charge delivered to the tissue. To our knowledge, this mechanism has not been previously described. This effect remains to be demonstrated experimentally, and it must be acknowledged that the nerve membrane model utilised has not been validated for the frequencies we evaluated. However, the simulation results are consistent with our experimental observations regarding high-frequency conduction block.

One hypothesis regarding the effect of high-frequency block is that it produces a fast-acting and fast-recovering 'neural conduction fatigue', first discussed by FORBES and RICE (1929) and described by many others (BOWMAN and MCNEAL, 1986; JAVEL *et al.*, 1987; WILLIAMSON, 1999). The mechanism for this type of fatigue is not clearly understood, but is probably the result of the depletion of a necessary agent for action potential generation, such as ATP (YAROWSKY and INGVAR, 1981) or cyclic AMP (KNEDLITSCHEK *et al.*, 1994); or it could be due to the loss or build-up of ions near the nerve membrane (as suggested by CATTELL and GERARD (1935)). The results of Bowman and McNeal, indicating an increased nerve response followed by conduction block after many seconds, confirm the existence of this mechanism, which is distinct from synaptic fatigue due to neurotransmitter depletion.

In our experiments, a neural fatigue response could often be obtained at amplitudes below that necessary for conduction block. An example of this type of response is shown in Fig. 7. As the stimulation amplitude was increased, the neural fatigue occurred more quickly. This follows the pattern described by BOWMAN and MCNEAL (1986) and WILLIAMSON (1999). Our experiments demonstrate, however, that a true nerve conduction block occurs at higher amplitudes and is not due to a neural fatigue mechanism, because the nerve conduction block we obtained does not depend on the firing of multiple action potentials. A complete block was achieved following a twitch response of the muscle that was of the same duration and magnitude as the response from a single stimulating pulse. In this situation, each neuron must be firing a single action potential prior to complete block, and therefore the block achieved by higher-amplitude, high-frequency AC waveforms is not due to neural fatigue.

An alternative hypothesis regarding the effect of the high-frequency AC waveform is that it prevents the nerve membrane from repolarising in time to conduct the next action potential (JAVEL *et al.*, 1987; KRAUTHAMER and CROSHEK, 2002). However, the concept that high-frequency stimulation maintains the nerve in a constant refractory period does not match the experimental evidence. It has been shown that nerves can fire action potentials as high as 700 Hz for brief periods (WOO and CAMPBELL, 1964). When higher-stimulation frequencies are applied, the nerve responds at a rate that is a submultiple of the applied frequency (BOWMAN and MCNEAL, 1986). This demonstrates that the nerve is able to recover from an absolute refractory period while the suprathreshold stimulation is still being applied. KRAUTHAMER and CROSHECK (2002) have reported a slight increase in the refractory period during such high-frequency stimulation, but this increase is relatively small. There is no evidence to suggest that higher-amplitude pulses would extend the refractory period to infinity. Our simulations show that it is the depolarisation generated by the alternating current, not the inability of the nerve to recover from the refractory period, that results in a conduction block.

Nerve conduction block can be produced by the application of very low levels of direct current to the nerve (PETRUSKA *et al.*, 1998). Therefore it is important to eliminate the possibility that the block observed at high frequencies is not simply due to leakage currents from the devices used to generate the high-frequency waveforms (HUANG *et al.*, 1998). To minimise this effect, we placed large capacitors in series with the output of our waveform generator, but it is not possible completely to eliminate leakage currents. We examined whether the DC offset played a role in the blocking effectiveness by adding an intentional DC offset to the sinusoidal waveform delivered to the nerve. Offsets of both polarity were tested up to ± 200 mV. The blocking effect occurred at the same AC amplitude, regardless of the applied offset. Given these results, it is unlikely that DC leakage currents are responsible for the observed blocking effect.

An examination of the literature pertaining to AC block has revealed many misunderstandings regarding the application of this type of block. As we have shown, the difference in the waveforms used is sufficient to explain the disparate results. For example, SOLOMONOW (1984) found that the optimum blocking frequency was 600 Hz, whereas BOWMAN and MCNEAL (1986) reported an optimum at 8 kHz or higher. This can be explained by the difference in waveforms. The Solomonow waveform was current-controlled and monophasic. Monophasic stimulation at high frequencies would maintain a net charge on the nerve membrane and therefore probably produces a block through the same mechanism as direct current block (FIELDS *et al.*, 1979). Once the frequency reaches a point where the net charge is maintained at a constant level sufficient to produce block, no further improvement in block effectiveness would be gained by increasing the frequency. This is demonstrated in the results shown by SOLOMONOW *et al.* (1983), where block effectiveness is constant over the range of 600 Hz–14 kHz.

BOWMAN and MCNEAL (1986) and SAWAN *et al.* (1996) used biphasic waveforms with a zero net charge. Rectangular waveforms were used, but the output was voltage-controlled in the case of Bowman and McNeal, and current-controlled in the case of Sawan *et al.* Bowman and McNeal tested a wide range of frequencies and found that block could be achieved very quickly at the highest frequencies tested (4–10 kHz). Sawan *et al.*, on the other hand, only tested frequencies below 1 kHz, utilising 600 Hz, based on the work of Solomonow.

In our experience, both of these waveforms are capable of producing a 100% block of nerve conduction. However, the off time between cycles appears to reduce the efficiency of these waveforms, and they tend to block through the mechanism of neural conduction fatigue. To minimise charge injection while maintaining a 100% block, we found that it was more effective to use a continuous sinusoid or rectangular wave. It should be noted that the linear stimulus isolator used in our experiments attenuated frequencies above 2 kHz, and therefore the current-controlled Sawan waveform had a slower rising edge than that used by SAWAN *et al.* (1996). Therefore our results may slightly overestimate the currents required by this waveform for block.

However, we have found similar current requirements between rectangular and sinusoidal waveforms, and so the effect of this difference is probably minimal.

The use of a 20 kHz sinusoid to produce block, as reported by TANNER (1962) and WOO and CAMPBELL (1964), has apparently not been evaluated by any of the more recent investigations. It is not clear why this is the case. WILLIAMSON (1999) tested current-controlled sinusoidal waveforms in a single rat and found that the optimum frequency for block was 13 kHz. Our results show that block can be obtained using a wide range of frequencies, including 20 kHz and 13 kHz, but that 3–5 kHz produced complete blocks at the lowest peak-to-peak signal amplitude and lowest charge per phase. These differences may be due to the different species used (frog, rat, cat) and the nerve temperature. Our experiments were performed at room temperature, which slows conduction and could alter the optimum block frequency.

A key remaining question regarding the use of high-frequency block in clinical applications is to determine if the blocking waveform has any damaging effect on the neuronal tissue. The important parameters regarding the safe delivery of electrical currents to neuronal tissue have been identified as the charge per phase the charge density per phase and the frequency (PUDENZ *et al.*, 1975; MORTIMER, 1981; YUEN *et al.*, 1984; MCCREERY *et al.*, 1990; 1992; 1995; AGNEW *et al.*, 1990; TYKOCINSKI *et al.*, 1995; HUANG and SHEPHERD, 1999).

The charge per phase of 0.01–0.04 $\mu C\,phase^{-1}$ and approximate charge density of 0.05–0.2 $\mu C\,cm^{-2}\,phase^{-1}$ used to produce block in our experiments are a factor of ten or more below the published, reported safe level of stimulation of 0.4–2.0 $\mu C\,phase^{-1}$ and 3.0–40 $\mu C\,cm^{-2}\,phase^{-1}$ (PUDENZ *et al.*, 1975; MORTIMER, 1981; YUEN *et al.*, 1984; MCCREERY *et al.*, 1992). The dependence of neural damage on frequency is likely to be a more important issue for the nerve conduction block waveform. For stimulus frequencies of 1–3 kHz, non-damaging parameters have been reported at 0.009–0.03 $\mu C\,phase^{-1}$ and 4.9–7.0 $\mu C\,cm^{-2}\,phase^{-1}$ (MITCHELL *et al.*, 1997; HUANG and SHEPHERD, 1999), which are within the range used in this study for motor block. However, the dependence of neural damage on stimulus frequency appears to be due to the increased activity of the nerve in response to the high-frequency stimulation, an effect termed the 'mass action' effect (MCCREERY *et al.*, 1992). If mass action is the only factor, the blocking waveform may not show the same dependence of neural damage on frequency, because it does not cause any activity in the nerve. It will be necessary to determine if this hypothesis is true by conducting a chronic *in vivo* study of electrical block, with subsequent histological examination of the nerves.

Our study focused on the block of motor activity and did not study the potential of high-frequency AC waveforms to produce a block of sensory activity. It is likely that a complete sensory block will require higher amplitudes of blocking current. TANNER (1962) demonstrated that a 20 kHz sinusoidal waveform could block gamma fibres at approximately twice the amplitude required for a block of alpha-fibre activity. A complete block of sensory activity has yet to be demonstrated clinically and is an important area of future investigation.

The clinical potential of a nerve conduction block that can be quickly initiated and quickly reversed is enormous. Unwanted or unco-ordinated generation of nerve impulses is a major factor in many disabling conditions, such as peripheral pain, spinal cord injury, stroke, cerebral palsy and multiple sclerosis. For example, unregulated nerve impulses produce spasticity in stroke, cause spasms in spinal cord injury, and generate neuroma pain in amputation. If these impulses can be intercepted along the peripheral nerves through which they travel, then the disabling condition can be reduced or eliminated. Although there are a few existing methods for surgically or pharmacologically blocking nerve impulses, none of these methods is broadly applicable or successful, and they are non-specific, with sometimes serious side-effects, or are permanently destructive to the nerve. High-frequency block, if demonstrated to be safe for chronic use, has the potential to be applied in all of these cases.

6 Conclusions

The capacity of high-frequency AC waveforms (2 kHz and higher) to block nerve conduction has been demonstrated. The most effective and desirable waveform for block was determined to be a 3–5 kHz biphasic sinusoid. A complete block of motor activity was achieved with amplitudes of 3–5 $V_{p\text{-}p}$ or 0.5–2 $mA_{p\text{-}p}$. Conduction block can be achieved with both bipolar and monopolar electrodes. The degree of block can be graded to within +/−10% of the total force output. It was demonstrated that high-frequency AC produces a true block of action potential conduction in the nerve membrane in the region near the blocking electrode. The block mechanism is distinct from synaptic and neural conduction fatigue.

Computer simulation of high-frequency AC demonstrated a steady-state depolarisation of the nerve membrane, and we hypothesise that the conduction block is due to this tonic depolarisation. The precise relationship between the steady-state depolarisation and the conduction block will require further analysis. Our results explain some of the apparent discrepancies in the literature and demonstrate the clinical potential of high-frequency block. Future work needs to be done to demonstrate that this waveform is not damaging to neural tissue.

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References

ABDEL-GAWAD, M., BOYER, S., SAWAN, M., and ELHILALI, M. M. (2001): 'Reduction of bladder outlet resistance by selective stimulation of the ventral sacral root using high frequency blockade: a chronic study in spinal cord transected dogs', *J. Urol.*, **166**, pp. 728–733

ACCORNERO, N., GIORGIO, B., LENZI, G. L., and MANFREDI, M. (1977): 'Selective activation of peripheral nerve fibre groups of different diameter by triangular shaped stimulus pulses', *J. Physiol.*, **273**, pp. 539–560

AGNEW, W. F., MCCREERY, D. B., YUEN, T. G., and BULLARA, L. A. (1990): 'Local anaesthetic block prevents against electrically-induced damage in peripheral nerve', *J. Biomed. Eng.*, **12**, pp. 301–308

BARATTA, R., ICHIE, M., HWANG, S. K., and SOLOMONOW, M. (1989): 'Orderly stimulation of skeletal muscle motor units with tripolar nerve cuff electrodes', *IEEE Trans. Biomed. Eng.*, **36**, pp. 836–843

BOWMAN, B. R., and MCNEAL, D. R. (1986): 'Response of single alpha motoneurons to high-frequency pulse trains', *Appl. Neurophysiol.*, **49**, pp. 121–138

CAMPBELL, B., and WOO, M. Y. (1966): 'Further studies on asynchronous firing and block of peripheral nerve conduction', *Bull. Los Ang. Neurol. Soc.*, **31**, pp. 63–71

CATTEL, M., and GERARD, R. W. (1935): 'The 'inhibitory' effect of high-frequency stimulation and the excitation state of nerve', *J. Physiol.*, **83**, pp. 407–415

FANG, Z. P., and MORTIMER, J. T. (1991): 'Selective activation of small motor axons by quasi-trapezoidal current pulses', *IEEE Trans. Biomed. Eng.*, **38**, pp. 168–174

FIELDS, R. W., O'DONNELL, R. P., and TACKE, R. B. (1979): 'Effects of variations in rectangular pulse duty cycle and intensity on pulsating direct current electro-analgesia of cat tooth pulp', *Arch. Oral Biol.*, **24**, pp. 509–514

FORBES, A., and RICE, L. H. (1929): 'Quantitative studies of the nerve impulse IV. Fatigue of the peripheral nerve', *Am. J. Physiol.*, **90**, pp. 119–145
GRILL, W. M., and MORTIMER, J. T. (1997): 'Inversion of the current-distance relationship by transient depolarization', *IEEE Trans. Biomed. Eng.*, **44**, pp. 1–9
HASSOUNA, M., DUVAL, F., LI, J. S., LATT, R., SAWAN, M., and ELHILALI, M. M. (1992): 'Effect of early bladder stimulation on spinal shock: experimental approach', *Urology*, **40**, pp. 563–573
HINES, M. L., and CARNEVALE, N. T. (1997): 'The NEURON simulation environment', *Neur. Comput.*, **9**, pp. 1179–1209
HUANG, C. Q., SHEPHERD, R. K., SELIGMAN, P. M., and CLARK, G. M. (1998): 'Reduction in excitability of the auditory nerve following acute electrical stimulation at high stimulus rates: III. Capacitive versus non-capacitive coupling of the stimulating electrodes', *Hear. Res.*, **116**, pp. 55–64
HUANG, C. Q., and SHEPHERD, R. K. (1999): 'Reduction in excitability of the auditory nerve following electrical stimulation at high stimulus rates. IV. Effects of stimulus intensity', *Hear. Res.*, **132**, pp. 60–68
HURLBERT, R. J., TATOR, C. H., and THERIAULT, E. (1993): 'Dose-response study of the pathological effects of chronically applied direct current stimulation on the normal rat spinal cord', *J. Neurosurg.*, **79**, pp. 905–916
ISHIGOOKA, M., HASHIMOTO, T., SASAGAWA, I., IZUMIYA, K., and NAKADA, T. (1994): 'Modulation of the urethral pressure by high-frequency block stimulus in dogs', *Eur. Urol.*, **25**, pp. 334–337
JAVEL, E., TONG, Y. C., SHEPHERD, R. K., CLARK, G. M. (1987): 'Responses of cat auditory nerve fibers to biphasic electrical current pulses', *Ann. Otol. Rhinol. Laryngol. Suppl.*, **128**, pp. 26–30
KNEDLITSCHEK, G., NOSZVAI-NAGY, M., MEYER-WAARDEN, H., SCHIMMELPFENG, J., WEIBEZAHN, K. F., and DERTINGER, H. (1994): 'Cyclic AMP response in cells exposed to electric fields of different frequencies and intensities', *Radiat. Environ. Biophys.*, **33**, pp. 141–147
KRAUTHAMER, V., and CROSHECK, T (2002): 'Effects of high-rate electrical stimulation upon firing in modelled and real neurons', *Med. Biol. Eng. Comput.*, **40**, pp. 360–366
LI, J. S., HASSOUNA, M., SAWAN, M., DUVAL, F., and ELHILALI, M. M. (1995): 'Long-term effect of sphincteric fatigue during bladder neurostimulation', *J. Urology*, **153**, pp. 238–242
MCCREERY, D. B., AGNEW, W. F., YUEN, T. G., and BULLARA, L. (1990): 'Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation', *IEEE Trans. Biomed. Eng.*, **37**, pp. 996–1001
MCCREERY, D. B., AGNEW, W. F., YUEN, T. G., and BULLARA, L. (1992): 'Damage in peripheral nerve from continuous electrical stimulation: comparison of two stimulus waveforms', *Med. Biol. Eng. Comput.*, **30**, pp. 109–114
MCCREERY, D. B., AGNEW, W. F., YUEN, T. G. H., BULLARA, L. A. (1995): 'Relationship between stimulus amplitude, stimulus frequency and neural damage during electrical stimulation of sciatic nerve of cat', *Med. Biol. Eng. Comput.*, **33**, pp. 426–429
MCINTYRE, C. C., and GRILL, W. M. (1998): 'Sensitivity analysis of a model of mammalian neural membrane', *Biol. Cybern.*, **79**, pp. 29–37
MCINTYRE, C. C., RICHARDSON, A. G., and GRILL, W. M. (2002): 'Modeling the excitability of mammalian nerve fibers: influence of afterpotentials on the recovery cycle', *J. Neurophysiol.*, **87**, pp. 995–1006
MCNEAL, D. R. (1976): 'Analysis of a model for excitation of myelinated nerve', *IEEE Trans. Biomed. Eng.*, **23**, pp. 329–337
MITCHELL, A., MILLER, J. J., FINGER, P. A., HELLER, J. W., RAPHAEL, Y., and ALTSCHULER, R. A. (1997): 'Effects of chronic high-rate electrical stimulation on the cochlea and eighth nerve in the deafened guinea pig', *Hear. Res.*, **105**, pp. 30–43
MORTIMER, J. T. (1981): 'Motor prostheses', in BROOKHART, J. M., MOUNTCASTLE, V. B., BROOKS, V. B., and GEIGER, S. R. (Eds): 'Handbook of physiology, section 1: the nervous system – vol. II motor control, Part 1' (Amer. Physiol. Soc., Bethesda, USA, 1981), Chap. 5, pp. 155–187
PETRUSKA, J. C., HUBSCHER, C. H., and JOHNSON, R. D. (1998): 'Anodally focused polarization of peripheral nerve allows discrimination of myelinated and unmyelinated fiber input to brainstem nuclei', *Exp. Brain Res.*, **121**, pp. 379–390
PUDENZ, R. H., BULLARA, L. A., JACQUES, S., and HAMBRECHT, F. T. (1975): 'Electrical stimulation of the brain. III. The neural damage model', *Surg. Neurol.*, **4**, pp. 389–400
RANCK, J. B., and BEMENT, S. (1965): 'The specific impedance of the dorsal columns of the cat: an anisotropic medium', *Exp. Neurol.*, **11**, pp. 451–463
RANCK, J. B. (1975): 'Which elements are excited in electrical stimulation of mammalian central nervous system: a review', *Brain Res.*, **98**, pp. 417–440
RATTAY, F. (1990): 'Electrical nerve stimulation: theory, experiments and applications' (Springer-Verlag, Wien, New York, 1990), pp. 183–185
REBOUL, J., and ROSENBLUETH, A (1939): 'The action of alternating currents upon the electrical excitability of nerve', *Am. J. Physiol.*, **125**, pp. 205–215
RICHARDSON, A. G., MCINTYRE, C. C., and GRILL, W. M. (2000): 'Modelling the effects of electric fields on nerve fibres: influence of the myelin sheath', *Med. Biol. Eng. Comput.*, **38**, pp. 438–446
SASSEN, M., and ZIMMERMANN, M. (1973): 'Differential blocking of myelinated nerve fibers by transient depolarization', *Pflugers Arch.*, **341**, pp. 179–195
SAWAN, M., HASSOUNA, M. M., LI, J. S., DUVAL, F., and ELHILALI, M. M. (1996): 'Stimulator design and subsequent stimulation parameter optimization for controlling micturition and reducing urethral resistance', *IEEE Trans. Rehabil. Eng.*, **4**, pp. 39–46
SHAKER, H. S., TU, L. M., ROBIN, S., ARABI, K., HASSOUNA, M., SAWAN, M., and ELHILALI, M. M. (1998): 'Reduction of bladder outlet resistance by selective sacral root stimulation using high-frequency blockade in dogs: an acute study', *J. Urol.*, **160**, pp. 901–907
SOLOMONOW, M., ELDRED, E., LYMAN, J., and FOSTER, J. (1983): 'Control of muscle contractile force through indirect high-frequency stimulation', *Am. J. Phys. Med.*, **62**, pp. 71–82
SOLOMONOW, M. (1984): 'External control of the neuromuscular system', *IEEE Trans. Biomed Eng.*, **31**, pp. 752–763
SWEENEY, J. D., and MORTIMER, J. T. (1986): 'An asymmetric two electrode cuff for generation of unidirectionally propagated action potentials', *IEEE Trans. Biomed Eng.*, **33**, pp. 541–549
TANNER, J. A. (1962): 'Reversible blocking of nerve conduction by alternating current excitation', *Nature*, **195**, pp. 712–713
TYKOCINSKI, M., SHEPHERD, R. K., and CLARK, G. M. (1995): 'Reduction in excitability of the auditory nerve following electrical stimulation at high stimulus rates', *Hear. Res.*, **88**, pp. 124–142
WARMAN, E. N., GRILL, W. G., and DURAND, D. (1992): 'Modeling the effects of electric fields on nerve fibers: determination of excitation thresholds', *IEEE Trans. Biomed. Eng.*, **39**, pp. 1244–1254
WEDENSKY, N. E. (1903): 'Die Erregung, Hemmung und Narkose', *Pfluger's Arch.*, **100**, p. 1
WHITMAN, J. G., and KIDD, C. (1975): 'The use of direct current to cause selective block of large fibres in peripheral nerves', *Br. J. Anaesth*, **47**, pp. 1123–1132
WILLIAMSON, R. (1999): 'A new generation neural prosthesis', PhD dissertation, University of Alberta, Edmonton, Alberta, Canada
WOO, M. Y., and Campbell, B. (1964): 'Asynchronous firing and block of peripheral nerve conduction by 20 Kc alternating current', *Bull. Los Angeles Neurol. Soc.*, **29**, pp. 87–94
YAROWSKY, P. J., and INGVAR, D. H. (1981): 'Neuronal activity and energy metabolism', *Fed. Proc.*, **40**, pp. 2353–2362
YUEN, T. G., AGNEW, W. F., and BULLARA, L. A. (1984): 'Histopathological evaluation of dog sacral nerve after chronic electrical stimulation for micturition', *Neurosurg.*, **14**, pp. 449–455
ZHOU, B., BARATTA, R., and SOLOMONOW, M. (1987): 'Manipulation of muscle force with various firing rates and recruitment control strategies', *IEEE Trans. Biomed. Eng.*, **34**, pp. 128–139
ZIMMERMANN, M. (1968): 'Selective activation of C-fibers', *Pflugers Archiv.*, **301**, pp. 329–333

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