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A Carbon Slurry Separated Interface Nerve Electrode (CSINE) for Electrical Block of Nerve Conduction

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Abstract

Direct current (DC) nerve block has been shown to provide a complete block of nerve conduction without unwanted neural firing. Previous work shows that high capacitance electrodes can be used to safely deliver DC block. Another way of delivering DC safely is through a separated interface nerve electrode (SINE) such that any reactive species that are generated by the passage of DC are contained in a vessel away from the nerve. This design has been enhanced by using a high capacitance carbon “slurry” as the electrode in the external vessel to extend the capacity of the electrode (CSINE). With this new design it was possible to provide 50 minutes of continuous nerve block without recharge while still maintaining complete recovery of neural signals. Up to 46 C of charge delivery was applied for a total of 4 hours of block with complete recovery. Because of the extended delivery time, it was possible to explore several properties of DC block that would not be revealed without the capability of a long duration continuous block. It was possible to

achieve complete block at lower values of DC if the block was applied for a longer period of time. Depending on the amount of charge applied during the block, the recovery was delayed for a period of time before complete force recovery was restored. These new properties provide novel techniques for device development to optimize charge delivery time and device powering concerns.

Keywords

Biomedical engineering; Biomedical electrodes; Carbon; Electrodes; Neural engineering; Neurology

I. Introduction

REVERSIBLE electrical nerve block is a potential alternative to conventional nerve block treatments. Electrical nerve block can establish complete conduction block in a peripheral nerve within a few seconds, and can be fully reversed within a few seconds as well, features that are unique compared to existing pharmacological or chemical nerve blocks. Electrical nerve block has no systemic effects other than the direct effect on the nerve that is blocked, allowing its use for highly localized solutions for the mitigation of pathological neural activity.

Direct current (DC) nerve block has been demonstrated as a viable modality of electrical nerve block that can be applied without causing any unwanted neural activity [1, 2]. Existing studies have examined nerve block in the peripheral nervous system including motor block in the sciatic [3-5], sensory nerves such as the saphenous [6] and the sural [7-11] and mixed motor/sensory such as the phrenic [12]. Applications for the autonomic system have also been explored on the vagus [13-16], and the paravertebral sympathetic nerve [17].

Direct current block has been shown to be rapidly effective (in less than a second) [1, 18]. The onset responses for DC motor block are small when compared to those from kiloHertz frequency nerve block, and can be completely eliminated with an amplitude ramp [3, 10, 18]. A novel implementation of direct current (DC) nerve block has been demonstrated that provides a complete block of motor fibers without onset activity [19].

One of the limitations of DC nerve block using conventional electrode materials is that if it is applied for a significant amount of time, reactive species generated at the electrode will build up in the tissue and cause nerve damage [20-22]. These reactive species are generated due to non-reversible Faradaic reactions. However, ongoing research has developed high capacity electrodes and charge balanced waveforms which allow DC to be delivered without relying on Faradaic reactions [18].

An additional way of preventing reactive species from reaching the nerve in DC nerve block is to separate the electrode in an isolated external vessel while still providing an ionic conduction path to the nerve [19]. This method was referred to as the Separated Interface Nerve Electrode (SINE). This electrode was compared in vivo to a bare platinum electrode. It was demonstrated that an irreversible nerve conduction occurs when applying DC through

the bare platinum electrode after 41 seconds. However, for the SINE electrode, DC could be applied for 270 seconds with complete reversibility [19].

For the SINE, both Faradaic and non-Faradaic charge transfer occurred at the electrode. However, the external vessel was filled with a quantity of saline such that the concentration of the Faradaic reaction products remained small and diffusion of those products out of the external vessel towards the nerve was slow. However, in order to maintain the concentration at a sufficiently low level for a sufficiently long time to provide clinically significant nerve block, the vessel would have to be prohibitively large.

In this study, the concept of high capacity electrodes was combined with the separated interface electrode to provide a solution that could deliver DC block for a prolonged period of time. A “slurry” comprised of a high surface area carbon (YP-50 Kuraray, Canoga Park, CA), combined with saline to form a stiff carbon slurry, was used to fill the external vessel (referred to as the Carbon SINE (CSINE)). All of the carbon in the slurry is electrochemically available for capacitive (doublelayer) charging. The slurry composition was selected so that it is both electrically conductive and ionically conductive. All of the carbon particles are in contact and therefore electrically connected together. This material increases the capacitance by a factor of 10^8 as compared to the smooth platinum electrode previously used [23] which should allow the device to deliver DC block for up to 48 hours at a time without relying on Faradaic reactions or requiring a recharge.

The use of high surface area carbons mixed with a liquid electrolyte to create electrochemical double layer capacitors with very high charge storage capabilities ($> 6 \text{ F/cm}^3$) is well known and commercial devices have been available since the 1970s following their development at the Standard Oil Co [24]. Here we employ the same concepts to deliver DC for an extended period of time without relying on Faradaic reactions. The objective of this study was to evaluate the properties of the CSINE over a wide range of parameters.

II. Methods

A. CSINE Electrode

For the prototype CSINE electrode used in these experiments a 10 cc syringe was used as the external vessel. The carbon paste that was used to fill this syringe consisted of 3 g of carbon to 7 g of electrolyte (0.9 wt% saline). The maximum capacity of the electrode for this quantity of carbon can be estimated using the surface area of YP-50 carbon ($1500 \text{ m}^2/\text{g}$ of carbon) [25], an reversible potential change of 1 V and a specific capacitance of $20 \mu\text{F}/\text{cm}^2$

$$\begin{aligned}
 & 3g \times \left(\frac{1500m^2}{g} \right) \times \left(\frac{100cm}{m} \right)^2 \times \left(20 \frac{\mu F}{cm^2} \right) \times 1V \quad (1) \\
 & = 900 \text{ coulomb} = 250 \text{ mAh} \text{ or} \\
 & > 2.5 \text{ days continuous operation at } 4 \text{ mA} \\
 & \text{(current sufficient to block nerve conduction)}
 \end{aligned}$$

In this calculation, the 1V potential change is based on a slurry electrode that is pre-charged anodically to a potential of +0.5V vs Ag/AgCl (this upper potential limit is set to avoid carbon oxidation during the pre-charge), that is subsequently discharged to -0.5V vs Ag/AgCl, where the lower limit was chosen to be at least 100 mV positive of the thermodynamic potential required for hydrogen evolution.

A corrosion resistant graphite rod in contact with the slurry is used as a current collector and is connected to a current-controlled waveform generator (KI-6221 Keithley Instruments, Solon, Ohio) with a fixed compliance voltage of 100V. The containment interface is composed of a nylon 1.5 μm pore size syringe filter which prevents the carbon particles from leaching out into the tube containing the biocompatible medium down to the nerve.

The biocompatible medium consisted of physiological saline (0.9 wt %), contained in a 6 cm section of tubing with a 4 mm inner diameter. The nerve interface consists of a silicone tube nerve cuff that is placed around the nerve and allows the physiological saline to be ionically in contact with the nerve (inset, Fig. 1). The silicon nerve cuff has a hole in the center into which the tube containing the physiological saline is inserted. The tube containing the physiological saline has an additional cuff on the end which allows it to be secured to the nerve cuff using cyanoacrylate adhesive. A valve was placed in line on the silicone tube, so that an additional syringe filled with saline could be used to flush air bubbles out of the tubing when placed in vivo.

A one-hole rubber stopper was used to make a seal at the top of the syringe around the graphite rod. This prevented air from entering the syringe such that 1) the saline in the tubing leading to the nerve cuff would not leak out of the tubing, and 2) although oxygen reduction can occur at the surface of the slurry electrode, once the oxygen initially present in the slurry is consumed, no additional oxygen can enter. In this way the contribution of oxygen reduction to the charge transfer process is minimized.

For the in vivo experiments, a 19-gauge stainless steel hypodermic needle inserted subcutaneously, was attached to the return of the current generator. Since the needle does not have a high capacitance, we expect Faradaic reactions (specifically oxygen evolution) to occur at the return electrode. In the ultimate embodiment of this concept, high capacitance electrodes would be desirable for both the blocking and return electrodes.

The reactions at the return electrode also contribute to the total impedance of the system. The carbon slurry has negligible impedance due to its very high surface area. The impedance of the saline filled tubing (ca. 6,000 ohms) can be calculated from the conductivity of 0.9 wt % saline (ca. 20 mS/cm) and the length and inside diameter of the tubing (4" long, 1/8" ID). The impedance within the test animal from the nerve site to the return electrode comprises the other major contribution to the total impedance.

B. Electrode Testing

To better estimate the actual available charge storage capacity, the CSINE electrode was subjected to a constant 1 mA cathodic polarization while sitting in a beaker of saline. The counter electrode was a platinized Pt gauze contained in a separate well in the cell separated by a glass frit from the electrolyte where the working electrode sits. This arrangement was used to minimize pH changes near the working electrode during the test. The resulting linear change in the electrode's potential (measured with respect to a Ag/AgCl reference electrode) yields an estimate of the available capacitance ($C = I / (dV/dt)$).

C. In Vivo Experimental Setup

Acute experiments were conducted on six adult rats (Sprague-Dawley), weighing 400 grams to 450 grams under institutional approval. Animals were anaesthetized with inhaled Isoflurane to effect. Three short incisions were made on the lateral aspect of one thigh. The proximal incision was used to place a bipolar electrode around the sciatic nerve for proximal test stimulation. This electrode was attached to a Grass S88 stimulator (Grass Technologies, West Warwick, RI, USA) with a current controlled output to elicit maximally evoked muscle twitches. Proximal test stimulation was delivered at 1Hz, 20uS, and 0.40-1mA. The central incision exposed the sciatic nerve over a very short length, proximal to the branching of the common peroneal and tibial nerves, and was used to apply the CSINE tube electrode.

The return electrode for the CSINE was a 19-gauge stainless steel hypodermic needle inserted subcutaneously adjacent to the biceps femoris muscle. This location is sufficiently remote to have a negligible effect on the nerve. Also, there is considerable tissue between the needle and the nerve. This needle was attached to the return of the Keithley current generator. The distal incision exposed the Achilles tendon, which was cut and attached to a force transducer (Entran, Fairfield, NJ; resolution 0.005 N) which was used to measure twitches resulting from the proximal stimulation.

D. In Vivo Experimental Protocol

Each experiment involved generating supramaximal twitches in the gastrocnemius muscle via the proximal stimulating electrode. After five twitches, nerve block was initiated by delivering current through the CSINE. The current waveform consisted of a rectangular constant direct current delivered for 1-50 minutes. Proximal stimulation was maintained throughout the block period. At the completion of each block trial, the CSINE current was turned off and the reversibility of the block was confirmed by the return of gastrocnemius twitches. Proximal stimulation was turned off once complete recovery occurred, or the force was no longer increasing.

Maximum block was determined to be maximum force reduction for which increasing the applied blocking current produced no change in the force reduction. The residual force is the amount of force remaining after the maximum block is applied.

In preliminary experiments we determined that the CSINE could achieve block at a lower current if it was applied for a prolonged period, typically tens of seconds. In order to take advantage of this feature, yet still keep each trial length manageable so that we could test randomized repeated trials, we capped the block induction time at 30 seconds in this study. We therefore defined “**block threshold**” as the lowest value in which maximum block was achieved within 30 seconds. The block threshold amplitude was determined at the beginning of the experiment and was then used to calculate the values for the two types of experiments conducted with each animal (described below). Our results show that the block threshold likely decreased over the course of an experiment, but we did not recalculate the block threshold, thus keeping the tested amplitude levels consistent throughout the experiment.

In general, we determined the block threshold with a 1mA resolution. However, if the block threshold was less than 2mA, we increased the resolution to 0.1mA. This approach was taken as a trade-off between accurate estimation of block threshold and the search time required to obtain the estimate.

The force output with and without block was compared and the percentage of block was determined. The force generated from the proximal stimulus at pre-block was determined by averaging the last five force twitch recordings before the initiation of the block. The residual force was determined by averaging the last five force twitch recordings before the block was turned off. The percentage block was determined by dividing the residual force by the pre-block force and multiplying by 100. Complete block was defined as a block of 95% or greater.

To evaluate force recovery, two different metrics were evaluated. To determine the percent force recovery per trial, the force at the start of the trial was divided by the force at the end of the trial. The total reduction in force from the start of the experiment was evaluated by using the force at the start of the experiment and dividing by the force at the end of each trial.

Two types of experiments were performed, induction and recovery. In two animals, induction and recovery were performed on the same animal. In two animals, induction was only tested and in two animals only recovery was tested. This results in a total of six animals. For each of these experiments, the block threshold was determined at the beginning.

1) Block induction test: The DC values for 100%, 80%, 60%, and 40% of block threshold were determined and then randomized in sets of four. This randomization was repeated four times per animal for a total of 16 trials. For each test the designated level was applied until only the residual force was observed or a maximum time of 5 minutes was reached. The block induction time was determined by taking the standard deviation of the residual twitch forces and determining the point at which five twitches in a row were within

five standard deviations of the residual. The time for the first of these five twitches was recorded as the block induction time. A five-minute wait period occurred between trials.

2) Recovery Test: The amplitude for all recovery tests was set to the block threshold which was determined at the start of the experiment. Block times of 1T, 10T, and 50T were randomized in sets of three where T represents a time variable. In one animal, T was set to 40 seconds, and in the other three animals, T was set to 60 seconds. Randomizations were repeated three to four times per animal. The time for initial twitch recovery, and the additional time for 95% force recovery for the trial (if applicable) were recorded. The initial twitch recovery time was determined by taking the standard deviation of the residual and determining the point at which five twitches in a row were above five standard deviations of the residual. The time for the first of these five twitches was recorded as the initial twitch recovery time. A five-minute wait period occurred between trials.

E. Statistics

Normality of data was determined using the Shapiro-Wilk W Test in JMP Pro (14.0.0). A standard least squares model fit, fixed effects ANOVA was used to evaluate the effects of the selected independent variables. All independent variables were included in the model to determine the effect of each of the variables on the model. Variables with p value < 0.005 were further analyzed. Fit lines were evaluated for each data set.

The percent force recovery per trial was evaluated using the charge delivered during the trial (charge per trial) and the cumulative charge delivered during the entire experiment as independent variables. The percent of force reduction over the entire experiment was also evaluated using the cumulative charge delivered and the elapsed time of the experiment.

For full block induction time, the independent variables included were: amplitude of DC (mA), and percentage of block threshold (10%, 80%, 60%, 40%), cycle of randomization (1-4), trial number and animal number. Trials in which full block (>95%) was achieved in less than 5 minutes were used for the analysis.

For the recovery trials, the twitch recovery, and the additional time until 95% force recovery for the trial were evaluated. Trials where the force recovery for the trial did not return to 95% were not included in the data for the 95% recovery time. The independent variables included were: Amplitude of DC (mA), and block time (sec).

In addition to the experimental independent variables, the charge per trial was also calculated for each trial by multiplying the amplitude of DC and the block time. The cumulative charge for the entire trial was also determined and included as an independent variable. In addition to evaluating the additional force recovery time with the independent variables, it was also evaluated with the twitch recovery time.

III. Results

A. Electrode Testing

An example of the polarization test results is shown in Fig 2 for a CSINE electrode containing 1 g of YP-50 carbon. For comparison, a low surface area glassy carbon electrode was subjected to a similar test, but at a much lower current of 10 μ A (Fig 2 bottom).

As seen in Fig 2, the potential of the low surface area electrode rapidly decays until a plateau is reached, indicative of the Faradaic reaction, the reduction of water, resulting in hydrogen evolution occurring. The final potential, ca. -1.15 V vs Ag/AgCl, is considerably more negative than the thermodynamic potential for hydrogen evolution due to the relatively slow kinetics for that reaction on glassy carbon. In contrast, the potential of the CSINE electrode decays non-linearly at first as the capacitance of such a highly porous and three dimensional electrode is smaller at shorter times or higher frequency and so is changing over time. However, after about 3000 s the potential decay becomes linear with time with a slope of $\sim 10 \mu$ V/s, equivalent to a capacitance of 100 F. The potential never reaches that of hydrogen evolution within the two hour time frame of the test. From Eq 1, we would estimate a capacitance of 300 F for this electrode with 1 g of carbon, indicating that about 30% of the carbon surface area in the slurry is accessible and participating in charge storage. More effective use of the available surface area can be obtained by adding a conductive additive to the slurry.

B. Blocking

Complete block was achieved in all six animals tested, with block thresholds ranging from -0.4 mA to -4.0 mA, with an average -1.55 mA. Twitch recovery after block was achieved in 100% of the trials. A force twitch recovery after block of 95% or greater was achieved in 87% of the trials. Fig 3 shows a complete instantaneous block with instant twitch recovery and complete force recovery.

The maximum cumulative charge that resulted in 95% recovery was 46 Coulombs of direct current nerve block (the maximum cumulative charge tested). Fig. 4 shows percent of force recovery per trial as the cumulated sum charge that was applied to the nerve for each animal. The percent of force recovery was calculated by using the average of five preblock force twitches as compared to the average of five postblock force twitches. In some instances, the force post-block exceeded the pre-block value resulting in a force recovery percentage larger than 100%.

The percent recovery data was determined to be normal based on the Shapiro-Wilk W Test ($p < 0.001$). A standard least squares model fit, Fixed Effects ANOVA using the cumulative charge, showed that the cumulative charge had a significant effect on the percent recovery ($p = 0.0036$). The charge per trial did not show any significant effect on percent recovery ($p = 0.8947$). A regression fit showed a very slow reduction (slope = 0.0003 %/mC) in the percent of force recovery per trial based on the cumulative charge with an R^2 value of 0.1209 (Fig. 4).

Fig. 5 shows the reduction in force from the beginning of the experiment due to rat preparation degradation. The force degradation is plotted vs the elapsed time of the experiment. The percentage of force reduction from the beginning of the experiment was determined to be normal based on the Shapiro-Wilk W Test ($p < 0.001$). A standard least squares model fit, Fixed Effects ANOVA using the Elapsed time, showed that the total elapsed time had a significant effect on the percent recovery from the start of the experiment ($p < 0.0001$). The cumulative charge indicated a less significant effect ($p = 0.0334$). A fit line for all animals (Fig 5) showed a significant reduction (slope = $-0.0626\%/min$) in the percentage of the force at the start of the experiment over time. The R^2 value of 0.3146 indicates a minimal correlation between the elapsed time and the percentage of force decline.

C. Block Induction Test

When an amplitude below the block threshold was applied, there was a delay before the force reduced to zero. This time period is the full block induction time. Fig. 6 shows an example of induction times for 100%, 80%, 60% and 40% of block threshold. As the block value is reduced, the induction time increases. At 40% of block threshold, complete block was not achieved within 5 minutes, at which point the test was terminated. For all the induction trials, a 95% block or greater was achieved within the five-minute window in 87.5% of the trials.

The full block induction time was compared to the percentage of block threshold. Induction times ranged from 0 seconds to 5 minutes at which time the test was terminated. The full block induction times were determined to be normal based on the Shapiro-Wilk W Test ($p < 0.001$). The percentage of block threshold (100%, 80%, 60%, 40%), was determined to be significant with $p = 0.0043$. The animal number was also significant with $p < 0.0001$. As shown in Fig. 7, a linear fit produces a downward trend (slope = $-1.238 \text{ sec}/\%$) in induction time as the percentage of block threshold increases but with an R^2 value of 0.156 indicating little correlation.

D. Recovery Test

At the termination of DC delivery there was a delay before the force twitches returned, referred to as the twitch recovery. Once the twitches return, there was an additional delay before a 95% force was restored (if applicable), referred to as the force recovery. Fig. 8 shows an example of 50 minutes of block at -3.2 mA . After the block was removed, twitches returned after 22.7 minutes. The 95% force recovery occurred after an additional 12.2 minutes.

The twitch recovery time, and the additional time until 95% recovery were determined to be normal based on the Shapiro-Wilk W Test ($p < 0.001$). For the twitch recovery, the charge per trial was determined to be significant ($p < 0.0001$), but the amplitude, duration, and cumulative charge were not ($p = 0.9837, 0.1686, 0.3846$ respectively). Fig. 9 shows the relationship between twitch recovery and charge per trial. The R^2 value of 0.8114 shows a strong correlation between the twitch recovery and the charge per trial.

For the 95% force additional recovery time, the model was determined to be significant ($p < 0.0001$), but none of the independent variables were significant (p values: Amplitude = 0.5531, duration = 0.1020, charge delivered = 0.7878), although cumulative charge had the lowest p value ($p = 0.02481$). However, when the cumulative charge was removed from the model, the model was determined to be not significant ($p = 0.6046$). The removal of any of the other independent variables resulted in the model being significant ($p < 0.0001$). This indicates that the cumulative charge has a strong effect on the significance of the model. Fig. 10 shows the relationship between the 95% force additional recovery time and cumulative charge. Although the R^2 value of 0.3949 indicates a weak correlation, this is largely due to the variance of the data.

To determine the relationship between the twitch recovery time and the 95% force additional recovery time, the 95% force additional recovery time was evaluated using the twitch recovery as an independent variable. For the 95% force additional recovery, the twitch recovery was determined to be significant ($p = 0.00003$). The relationship between the twitch recovery time and 95% force additional recovery time is shown in Fig. 11. The R^2 value of 0.5089 indicates a moderate relationship between the twitch recovery time and the 95% force additional recovery time.

IV. Discussion

In all six animals tested it was possible to achieve a 95% nerve block within 30 seconds of block application with block thresholds ranging from -0.4 mA to -4.0 mA. Variations in the surgical preparation resulted in residual twitches in some experiments due to differences in which non-blocked nerves were left intact. The differences in the block threshold are likely related to the placement of the cuff on the nerve as well as the surgical preparation.

These experiments demonstrated that the block threshold is not a single specific value, but depends on the duration of the application of the DC. As shown in Fig. 6, it was possible to apply a lower current for a longer period of time and still achieve complete block. As the current was increased, the induction time was reduced (Fig. 7). Block threshold was defined for this study as the lowest value at which complete block occurs in less than 30 seconds, but it was possible to achieve complete block at levels as low as 40% of the block threshold value. The induction time needed to achieve complete force block at by applying 40% of the block threshold, ranged from as low as 2 seconds up to 290 seconds, with some trials not blocking completely in that time period. Part of the variability in the data was due to the original definition of the block threshold. It can be seen in Fig. 7, showing the induction data, that instantaneous block ($t = 0$ seconds) is occurring in some trials for values well under the block threshold. This is probably due to an elevated initial estimate of the block threshold. If the initial estimate of the block threshold is high, percentage values well below the initial estimate also would also cause block in less than 30 seconds. It is also important to note that the individual animal was a highly significant factor in the induction time showing that the preparation and placement of the electrode likely effects how quickly block will occur. However, for any given application, using this information, it would be possible to tailor the block parameters to design the right compromise between responsiveness of block and the discharge time of the device.

We have previously demonstrated that the block generated by DC is localized to the region of the nerve inside or near the cuff electrode [1]. However, as shown in Figure 6, the activity induced by the initiation of DC block is confined to a few rapid twitches and these would not have a significant effect on the response of the neuromuscular junction or the muscle. Further, the muscle force can recover immediately upon the removal of the blocking current.

Twitch recovery occurred in 100% of the trials after up to 50 minutes of continuous block. Although it is possible to apply block with the SINE electrode for at least 50 minutes, instant recovery is impacted. After 50 minutes of block, the twitch recovery time ranged from a low of 11 minutes at -0.4 mA to a high of 32 minutes at -4.0 mA. The recovery time was not dependent on just the time of block but also on the charge, which is a combination of the time and the current delivered. Fig. 9 shows that the recovery time increases as the magnitude of the charge increases. Given that complete block can be achieved at lower values with a longer induction time, it should be possible to block at a lower value to achieve a shorter recovery time if desired.

Although twitch recovery reliably occurred in all trials, force recovery above 95% was impacted by cumulative charge application. As shown in Fig. 4, percent force recovery decreased slightly as the cumulative charge increased. Fig. 5 shows that the overall force decreases over the time of the experiment with the rate of decrease varying for each animal. This decrease in force is likely due to degradation of the preparation over time. In future experiments, a stimulating electrode can be placed on the sciatic distal to the block electrode to evaluate the force generated distal to the blocking site to determine if the decrease in force is due to the block alone, or is due to degradation of the experimental preparation [26].

In experiments in which the force recovered above 95%, the additional amount of time for 95% force recovery after twitch recovery was evaluated. Fig. 10 shows that as the cumulative charge increases, the amount of additional time needed for 95% force recovery increases. For the 95% force recovery, the cumulative charge was more significant than the charge delivered during a particular trial. This also points to a fatigue effect, since the cumulative charge is a function of the duration of the experiment. However, the effect is not due to time alone, since the charge for a given trial is also included in the cumulative charge calculation. This points to a dual factor effect in predicting the force recovery time.

Previous usage of the SINE electrode used a bare platinum electrode in a saline medium in the external vessel [19]. This electrode type was able to deliver up to 270 seconds of continuous DC with complete recovery. With the design enhancement of the carbon slurry electrode, the DC delivery was prolonged to 50 minutes with complete recovery. For the maximum duration of block delivery, 253 minutes (4 hours) of cumulative DC were applied at -0.4 mA over multiple trials, without a recharge while still retaining 95% recovery. In addition, the maximum cumulative charge delivered while retaining 95% recovery was 46 Coulombs, delivered at -4.0 mA. These numbers represent a substantial improvement of the capability of the SINE electrode. A larger or smaller capacity can be obtained by varying the size of the external vessel and the amount of slurry used. Also, if a recharge phase is added to restore the reversible potential difference to 1 V the total usage duration of the electrode

can easily be further extended. Given a maximum block threshold of -4.0 mA, we would expect two days of continuous operation before a recharge would be needed.

The blocking of axons is both dependent on the fiber size as well as the distance from the electrode. Smaller diameter fibers and fibers in the center of a nerve require a higher threshold to block [27]. For the blocking experiment, the proximal stimulation is chosen so that all of the motor fibers in the nerve are recruited to produce the maximum measured force. When a block is applied that produces instantaneous complete block, this means that the chosen level blocks all motor fibers essentially at the same time regardless of their diameter or distance from the electrode. However, due to the membrane capacitance and resistance, the time period depends on the RC time constant of the fiber. When a current is applied, the transmembrane voltage rises depending on the time constant of the system. For stimulation, it is well known that a longer pulse width reduces the required threshold for activation. This property is demonstrated in the strength duration curve for a system which depends on the fiber size as well as the electrode geometry. Similarly, for block, if the blocking current is applied for a longer period of time, a smaller current is needed to produce block. In a single axon, the block would occur once the sodium channel inactivation level has been reached. But in a nerve consisting of fibers of varying diameters and distances from the electrode, inactivation occurs over a spectrum of time constants producing a ramped blocking response as shown in Fig. 6. For the induction testing, the block threshold was chosen as the lowest value to cause block in 30 seconds, but the subthreshold values were still able to produce block if they were applied for a long enough period of time. As demonstrated in Fig. 7, the time period needed for block decreased as the percentage of block threshold was increased, which is a similar finding to the strength duration curve defined for electrical stimulation.

Although all conduction in the body is via ionic conduction, the SINE electrode also uses ionic conduction to isolate any reaction products formed in the external vessel from the nerve surface. Ions flow either through diffusion due to a concentration gradient, or migration due to an electric field. When a depolarizing current is applied to the electrode, ions flow between the terminals due to their mobility and charge builds up on the axon membrane increasing the transmembrane voltage causing block.

Assuming that the CSINE electrode is operating within the water window, the only Faradaic reaction of concern is the reduction of dissolved oxygen with concurrent generation of OH^- . The OH^- thus generated can be transported towards the nerve by either diffusion or migration. For the diffusion case, the transient solution to Fick's law yields a characteristic time on the order of $0.1 L^2/D$, when L is the length to be diffused and D is the diffusion coefficient. For L of 10 cm and D of $10^{-5} \text{ cm}^2/\text{s}$, this yields a characteristic time of 10^6 s , and therefore diffusion can be safely ignored on the time scale of these experiments.

Ion transport by migration is governed by the product of an ion's concentration and its electric mobility. Given the differences in concentration (0.001 M for OH^- , 0.155M for Na^+ and Cl^- in 0.9 wt% saline), the transference number for OH^- is 1% at best, and is much lower away from the CSINE electrode where the OH^- concentration is low.

With regards to the twitch recovery, after the current is removed, ions will diffuse away from the membrane and the transmembrane voltage will return to a resting value. A longer time period of block and a larger applied current results in a larger charge build up on the membrane. In order to restore the resting potential, a larger amount of time needs to pass before the ions can diffuse away from the membrane. This is demonstrated in Fig. 9. As the applied charge is increased, the amount of time required for twitch recovery is increased.

For this system there are two compartments that need to be addressed for the purposes of diffusion (fig 12). There is the space around the nerve that is composed of the pocket of tissue that contains the electrode to nerve interface. Then there is the nerve itself consisting of the fascicles surrounded by perineurium and epineurium. These two compartments have different diffusion properties based on the composition of the tissue [28-31] and electrode geometry. It is possible that the biphasic nature of the recovery consisting of a twitch recovery followed by a force recovery as shown in Fig. 8, can be explained by these two compartments. One possible theory is that diffusion away from the nerve in the electrode compartment occurs first, but this doesn't result in any measureable conduction restoration. The diffusion from the fascicles occurs more slowly and is demonstrated by a gradual increase in the muscle force as shown in Fig. 8. The gradation in the restoration is a reversal of the induction phenomenon in that smaller and deeper fibers will be restored first. It is important to note that the nerve compartment is nested inside the electrode compartment. It is possible that because of this interrelated conformation, the time period for twitch recovery and force recovery are dependent on each other as shown in Fig. 11.

As a check of diffusion as a potential mechanism, we consider the cylindrical diffusion of ions away from the nerve. Assuming a characteristic radial dimension on the order of 0.5 mm, and a diffusion coefficient of $10^{-6} \text{ cm}^2/\text{s}$, consistent with the somewhat restricted diffusion due to the viscous nature of the fluid [30, 31], a relaxation time on the order of 1000 seconds is estimated, consistent with the twitch and force recovery times shown in Fig. 11.

Three design issues which should be considered with the CSINE electrode approach are: 1) the compliance voltage needed to conduct current down the length of tubing between the SINE electrode and the nerve 2) the heating of the electrolyte within that tubing as a result of current flow and 3) the pH change at the interface of the nerve. The impedance of the system was measured to be in the range 30-60 Kohms. The maximum applied voltage based on the current source compliance limit was 103 V. While an external current source would be capable of driving a 103 compliance voltage, for an implantable solution, this may not be a possibility. However, the tubing length and diameter determine the impedance properties of the system and therefore an implantable solution may be able to accommodate a shorter and wider tube to decrease the impedance. Also, a narrow tube results in the possibility of a heating effect since the temperature rise is proportional to the impedance of the tubing. Further benchtop testing is being pursued to determine the amount of heating at the nerve interface. In addition to testing the temperature change, the change in pH is being evaluated in benchtop testing. Calculations of the capacity of the electrode indicate that it can be run for 2.5 days without a recharge. Once the capacity of the electrode has been depleted, it is expected that hydrogen evolution will occur, causing the pH in the external vessel to

increase. A benchtop test is being developed to verify the theoretical calculations and demonstrate that no reactive species are being generated at, or transported to, the nerve interface thereby preventing nerve damage.

The CSINE study has expanded the length of time that DC can be applied without a recharge. Previous studies have used high capacitance cuff electrodes to apply DC for short periods followed by a recharge phase [18]. However, during the recharge phase, block is interrupted, making it difficult to provide a continuous block. In addition, a DC delivery device using microfluidic valves and a separated nerve interface has been developed that also extends DC delivery [32, 33]. It is possible that the CSINE can be combined with this device to either reduce its size or increase its capacity. A combined device would provide a recharge phase for the CSINE which would increase its capacity. The use of the high capacitance materials would decrease the need to switch the microfluidic valves thereby reducing wear on the valves and extending the life of the device.

Although this study has focused on motor nerve block, there are opportunities for nerve block in the motor, sensory and autonomic systems. Recent studies have indicated that variations in the types of voltage-gated sodium channels present in small-diameter nociceptive fibers make them susceptible to DC nerve block at lower thresholds than motor fibers [34]. This finding allows for lower block thresholds which could further increase the capacity of the CSINE, reduce the voltage compliance needed, and lower the temperature changes taking place in the tubing of the CSINE. It is possible that there are other subsets of fibers in the autonomic system that are preferentially affected by DC block that would be good targets for DC block.

There are many clinical applications for DC nerve block. For motor systems, many diseases result in spasticity which obstructs function and recovery. In the sensory system, chronic neuropathic pain due to trauma or illness can permeate all activities of daily living. In the autonomic system, many chronic diseases such as cardiac arrhythmias are a result of pathological neural activity. Conventional medical treatment can alleviate some of the symptoms, but usually have significant side effects and short lasting results. Electrical nerve block produces a rapid response, rapid reversal, and highly localized solution to the mitigation of pathological neural activity. The CSINE in its current embodiment would be well suited for acute conditions such as post-operative pain, where a percutaneous short term solution would be acceptable. However, using the high capacitance carbon material prolongs the delivery time making it possible to evolve a smaller device that could be implanted and recharged on a long duty cycle. The properties of induction and recovery time could also be leveraged to optimize the device design to reduce size and power consumption. Further study of the CSINE is underway to fully characterize the device and develop novel solutions which can be deployed to a wide variety of conditions

V. Conclusion

The CSINE has been shown to be an effective method to deliver DC nerve block without producing a prolonged reduction in nerve conduction. A greater than 95% block within 30 seconds could be achieved with the CSINE at -0.4 mA to -4.0 mA. It could be achieved in

0-290 seconds at amplitudes down to 40% of block threshold. It was reversible to a 95% force recovery level in 87% of the trials, and even after 50 minutes of block, force recovery occurred within 20 minutes. Up to 46 C of charge delivery could be delivered with only a 5% decrease in twitch force over four hours of DC block.

Several properties of this method have been identified that can be used to design application appropriate devices. The use of a carbon slurry filled buffer vessel can increase the length of application time. If instantaneous block is not required, a lower current could be used for block which would extend the run time of the device both electrochemically and from a power consumption point of view. If the block is applied for a long period of time, recovery will be delayed, but it may be possible to mitigate this effect, by using a lower current. There are many improvements to the design that could be implemented to create a more robust device. The extended run time of this device and the configurability of the waveform would enable the device to be deployed as a take home solution to replace pharmacological forms of pain control.

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Fig. 1.

In vivo Experimental Setup. The CSINE electrode consists of a buffer vessel containing a high capacitance solution to contain reactants outside the body. A tube containing a biocompatible conducting medium is placed near the nerve to produce block. Block is produced by a current generator (Keithley 6221). Muscle twitches are elicited by stimulation at a proximal bipolar electrode. Force output is measured by a force transducer attached to the gastrocnemius tendon.

Fig. 2.

Potential transient for CSINE vs low surface area carbon. A CSINE electrode containing 1 g of carbon was subjected to a 1 mA cathodic current (orange dashes). Hydrogen evolution is not reached within the 2 hour time period. The slope of the fitted line 10×10^{-6} V/s. A low surface area carbon electrode (blue, dash-dot line) was subjected to a much lower cathodic current of $10 \mu\text{A}$ and reached hydrogen evolution in 20 seconds.

Fig. 3.

Example of complete instantaneous block with immediate twitch recovery. A burst of onset activity can be seen at 10 s when the DC is turned on due to the lack of a ramping phase. This trial was performed after 37 C of cumulative charge over previous trials.

Fig. 4.

Percent of Force Recovery versus the Cumulative Charge of Applied Block. The cumulative charge of applied block for sequential trials was calculated over the duration of each experiment. This cumulative charge is compared to the percent recovery for a given trial. The R^2 value of 0.1209 indicates that there is minimal direct correlation between the cumulative charge and the force recovery. The data shown is combined for all six animals.

Fig. 5.

Reduction of Force Over the Duration of Experiment. The percent reductions of force from the initial force recording was determined for each rat. Overall there is a significant reduction of the force over time, although with variations of slope for each animal.

Fig. 6.

Block Induction Times for Varying Levels of Block. As the level of block is lowered, the time it takes for block to occur increases (induction time). For 40% of the block threshold, block is not achieved within the five-minute test window.

Fig. 7.

Full Block Induction Time as Related to the Percentage of Block Threshold. As the percentage of block threshold increased, the induction time is reduced. Five trials at 40% and one trial at 60% did not result in full block within five minutes and are not included in this figure. The fit line and confidence interval for the “Time to Induction Plateau” are shown.

Fig. 8.

Example of twitch and force recovery timing. After the block is turned off, there is a period during which complete block is maintained before force twitches are observed (see inset). Once the twitches reappear, there is an additional time period before the full force is recovered.

Fig. 9. Effect of Charge per trial on Twitch Recovery. As more charge per trial is delivered, the amount of time needed for twitches to return increases.

Fig. 10.

Effect of Cumulative Charge on 95% force additional recovery. As the amount of charge accumulates over time, the additional time needed for 95% force recovery increases.

Fig. 11.

Relationship between twitch recovery and 95% force additional recovery. As the twitch recovery increases, the 95% force additional recovery increases proportionally.

Fig. 12.

Diagram of compartments adjacent to the CSINE. The implantation of the CSINE includes a compartment around the outside of the nerve as well as the components of the nerve itself.