Stability of the Input–Output Properties of Chronically Implanted Multiple Contact Nerve Cuff Stimulating Electrodes

Warren M. Grill and J. Thomas Mortimer

***Abstract*—The objective of this investigation was to measure the input–output (I–O) properties of chronically implanted nerve cuff electrodes. Silicone rubber spiral nerve cuff electrodes, containing 12 individual platinum electrode contacts, were implanted on the sciatic nerve of seven adult cats for 28–34 weeks. Measurements of the torque generated at the ankle joint by electrical stimulation of the sciatic nerve were made every 1–2 weeks for the first 6 weeks post-implant and every 3–5 weeks between 6 weeks and 32 weeks post-implant. In three implants the percutaneous lead cable was irreparably damaged by the animal within 4 weeks after implant and further testing was not possible. One additional lead cable was irreparably damaged by the animal at 17 weeks post-implant. The three remaining implants functioned for 28, 31, and 32 weeks. Input–output curves of ankle joint torque as a function of stimulus current amplitude were repeatable within an experimental session, but there were changes in I–O curves between sessions. The degree of variability in I–O properties differed between implants and between different contacts within the same implant. After 8 weeks, the session to session changes in the stimulus amplitude required to generate 50% of the maximum torque (I50) were smaller (15 ±19%, mean ± s.d.) than the changes in I50 measured between 1 week and 8 weeks post-implant (34 ± 42%). Furthermore, the I–O properties were more stable across changes in limb position in the late post-implant period than in acutely implanted cuff electrodes. These results suggest that tissue encapsulation acted to stabilize chronically implanted cuff electrodes. Electrode movement relative to the nerve, de- and regeneration of nerve fibers, and the inability to precisely reproduce limb position in the measurement apparatus all may have contributed to the variability in I–O properties.**

***Index Terms*— Cat, electrical stimulation, electrode, neural prosthesis, neural stimulation, peripheral nerve, sciatic nerve.**

I. Introduction

ELECTRODES that enable selective stimulation of multiple independent populations of neurons offer promise for enhanced function of neural prosthetic devices [17]. For example, multichannel electrodes have been successful in providing independent information channels in cochlear prostheses [5], [28]. A large number of electrode designs are presently under development for selective activation of peripheral nerve trunks. These electrodes will provide the technology for future motor system neural prostheses allowing greater function and application to a larger patient population [24].

There have been a large number of theoretical and acute animal studies on the performance of various nerve electrodes designed for selective stimulation, but there is little information available on chronic studies of selective activation of peripheral nerve. Chronically implanted single channel intrafascicular electrodes exhibited variable shifts in threshold [3] and alterations in the population of recorded nerve fibers [16]. Single channel cuff electrodes have been used to chronically stimulate peripheral nerves [8], had stable impedances and stimulation thresholds over periods of years [21], and provided stable long-term recordings [7], [29]. The mean stimulation thresholds of bipolar pairs of epineural electrodes were stable, although the data presentation precluded determination of the threshold stability of individual electrode pairs [31].

Cuff electrodes are the most suitable nerve-based electrode for electrical activation of the human nervous system because they are the least invasive and easiest to install [26]. Previous clinical applications of cuff electrodes have used them only in an ON–OFF manner to activate entire nerve trunks. Initial work by McNeal and Bowman demonstrated the feasibility of selective stimulation of nerve trunks using a cuff electrode [22]. The conclusions from this work were that the electrode must fit snugly to the nerve trunk to achieve selectivity, and that selectivity was strongly dependent on electrode location. Sweeney *et al.* [30] also concluded that, with careful electrode positioning, selective stimulation with extraneural electrodes was possible. More recently, acute studies from our laboratory have demonstrated that multiple contact spiral nerve cuff electrodes can be used to effect selective activation of peripheral nerve trunk regions [13], [34]. The key developments in this technology were a cuff that can expand and contract to provide a snug yet noncompressing fit to the nerve [25], and a distributed array of contacts which made the performance of the electrode independent of the positioning of the cuff around the nerve. The results of these acute studies demonstrated that a multiple contact cuff could activate selectively and maximally individual fascicles of a nerve trunk. This led to the question of whether similar electrodes could be used to effect selective control of the nervous system on a chronic basis.

The aim of the chronic studies described in this paper was to measure the stability of the input–output (I–O) properties of chronically implanted multiple contact spiral nerve cuff electrodes. The current amplitude (input)-joint torque (output)

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properties were measured repeatedly within a measurement session and in different measurement sessions to determine the temporal stability of nerve cuff I–O characteristics. Input–output curves were also measured at different limb positions to determine the positional stability of nerve cuff I-O characteristics. Additionally, the effects of field steering currents were compared to the effects measured previously in acute experiments [13]. A detailed analysis of the neural and connective tissue response to the long-term presence of the electrodes will be presented in another manuscript. Preliminary results of these studies have been published in abstract form [10], [11].

II. Methods

Spiral nerve cuff electrodes, containing 12 individual platinum electrode contacts, each with its own lead, were chronically implanted on the right sciatic nerve of seven adult cats. Measurements of the torque generated at the ankle joint by electrical stimulation of the sciatic nerve were made every 1–2 weeks for the first 6 weeks post-implant and every 3–5 weeks between 6 and 32 weeks post-implant. Based on previous work on compression induced injury of peripheral nerve, six months was chosen as the minimum duration of the implants [19], [20]. All animal care and experimental procedures were according to NIH guidelines and were approved by the Institutional Animal Care and Use Committee of Case Western Reserve University.

A. The Electrodes

The fabrication of spiral nerve cuff electrode electrodes has been described in detail in previous publications [25], [34]. The 12 contact cuff electrodes used in this study contained four longitudinal tripoles of recessed platinum dot electrodes, each with a separate stainless steel wire lead, embedded within a bonded trilayer of silicone rubber sheeting. The design allowed implementation of a tripolar electrode configuration (cathode between two anodes) at four locations around the circumference of the nerve trunk.

The previous design of 12 contact spiral nerve cuff electrodes [34] was modified to improve selectivity and to make the electrode more suitable for chronic implantation. Simulation studies suggested that closer spacing between the anodes and cathode would improve spatial selectivity [4]. Therefore, the spacing between the electrodes in a row (i.e., the longitudinal distance between the anodes and the cathode in each tripole) was reduced from 5 to 3 mm. This also allowed a reduction in the overall width of the cuff from 2 to 1.2 cm. The length of the unrolled cuff was trimmed depending on the diameter of the nerve trunk to provide two full wraps of the cuff around the nerve trunk. The results of other modeling studies [14], [33] indicated that smaller electrode contacts would create a more spatially isolated excitatory field than the large contacts modeled by Chintalacharuvu *et al.* [4] and used in our previous work. Thus, the diameter of the exposed electrode contacts was reduced from 1.0 to 0.7 mm to improve further selectivity.

The 12 lead wires were routed out one end of the cuff and were gathered into a single lead cable, rather than six leads exiting from each end as in the acute design [34]. The wires were grouped together and passed through 3 mm sections of silicone rubber tubing (Dow Corning Silastic 602-205, 1.0 mm I.D., 2.2 mm O.D.) every 6 cm to form a cable. The sections of tubing were fixed to the lead wires using silicone rubber elastomer (Dow Corning MDX 4-4210).

The electrodes and attached lead cable were cleaned as previously described [9], packaged in sterilization tubes (Chex-All, Propper Manufacturing), sterilized with ethylene oxide gas, and allowed to de-gas for at least 7 days before implantation. The electrodes and leads were rinsed in a solution of 500 ml sterile saline and 1 gm sterile cefazolin sodium at the time of implant.

B. Implant Procedure

All chronic electrode implants were done using aseptic technique. Animals were initially sedated with xylazine (Rompun, 2.0 mg/kg, SQ), masked with 3.0% gaseous Halothane in O_2, intubated, and maintained at a surgical level of anesthesia with 1.5–2.0% gaseous Halothane in O_2. Body temperature Ringer's solution was administered (10 cc/kg/h, IV) during the implant procedure, body temperature was maintained with a heating pad, and heart rate and respiratory rate were continuously monitored. Immediately before and after the implant procedure, 100 mg of oxacillin sodium was administered IM.

The sciatic nerve of the right hindlimb was exposed in the thigh through a dorsal approach and mobilized for a length of 3–4 cm. The circumference of the nerve was measured using a piece of 6-0 Prolene suture (Ethicon Inc., Somerville, NJ), and an equivalent nerve diameter was calculated assuming a circular cross section [23]. An electrode chosen to provide a cuff diameter to nerve diameter ratio of 0.8 was implanted around the sciatic nerve proximal to the branching point into the tibial and common peroneal divisions. The choice of electrode size provided a snug fit between the cuff and the nerve, and ensured that the four tripoles were positioned at 90° intervals around the nerve trunk. The lead cable was tunneled subcutaneously to a percutaneous exit site between the shoulders, and all incisions were closed with Prolene suture.

Animal behavior was observed daily for the first week post-implant and then at least once per week thereafter. Observations included gait pattern, presence or absence of hock drop, presence or absence of knuckling of rear paws, and the animal's general attitude and activity level. A basic neurological examination was also conducted before each testing session including checking of paw withdrawal to light pinching, and toe-tapping during gait to observe limb corrections (placement reactions).

C. Measurement of Input–Output Properties

During testing sessions, animals were initially sedated with xylazine (Rompun, 2.0 mg/kg, SQ), masked with 3.0% gaseous Halothane in O_2, intubated, and maintained at a surgical level of anesthesia with 1.5–2.0% gaseous Halothane in O_2. Body temperature saline was administered (10 cc/kg/h, IV) during the testing procedure, body temperature was maintained with a heating pad, and heart rate and respiratory rate were continuously monitored. Typical test sessions were 4 h in duration.

Animals were mounted in an apparatus to measure the three-dimensional (3-D) isometric torque generated at the ankle joint by stimulation of the sciatic nerve [12]. Ankle torques about all three axes were measured (plantarflexion/dorsiflexion, internal rotation/external rotation, inversion/eversion). However, previous results demonstrated that inversion/eversion torques are insignificant at the cat ankle joint and the internal and external rotation torques are generally only 10–20% of the plantar- and dorsiflexion torques [12], [13], [15]. Therefore, the analysis was restricted to the latter torques. Twitch contractions in the ankle musculature were generated using controlled current, charge balanced biphasic rectangular pulses applied at 0.5 Hz. The amplitude of the primary phase of the stimulus (pulsewidth was 100 μs) was stepped between threshold and maximum to generate I–O curves of torque as a function of stimulus current amplitude using different active tripoles. The amplitude of the secondary recharge phase was controlled at 100 μA, and the duration of the secondary phase was imposed automatically by the stimulator to achieve charge balancing. Stimulus amplitude was set manually with calibrated potentiometers while stimulus pulsewidth was controlled by computer. The applied current was monitored on a storage oscilloscope by differentially measuring the voltage generated in a 100-Ω resistor in series with the electrodes.

A multiple function input–output board (NB-MIO-16H, National Instruments) in a Macintosh Quadra 950 running software written in LabView (National Instruments) was used to trigger the stimulus and record the torque responses. The torque signals were low pass filtered at 100 Hz and sampled at 200 Hz with a 12-bit analog-to-digital (A/D) converter. Five to ten twitch responses were collected at each stimulus amplitude and were averaged. The peak of the average torque twitch waveform was used as the measure of activation at each stimulus amplitude [12].

Input–output curves of ankle joint torque as a function of stimulus current amplitude were measured using each of the four tripolar electrode configurations within the cuff, and using each tripole in combination with field steering current from an anode 180° opposite the active cathode [13], [30], [34]. The amplitude of the transverse steering current was set equal to 90% of the transverse excitation threshold, and is referred to as "90% steering." Input–output curves were repeated within a measurement session to quantify short-term stability, and were measured at different ankle joint angles to determine the effect of limb position on I–O characteristics.

III. Results

The implant duration ranged from 28 to 34 weeks. In three implants the percutaneous lead cable was irreparably damaged by the animal within 4 weeks after implant and further testing was not possible. One additional lead cable was irreparably damaged by the animal at 17 weeks post-implant. In these four cases, the animals accessed and pulled on the lead wires. The three remaining implants functioned for 28, 31, and 32 weeks.

As demonstrated in acute experiments [13], [34] different electrode configurations allowed selective and independent control of dorsiflexion and plantarflexion torques at every measurement session (Fig. 3). The long-term temporal stability of electrode input–output (I–O) relations were evaluated using I–O curves from 39 experiments across four implants. Twenty-six sets of I–O curves from eight experiments across 3 implants were used to evaluate position-dependent I–O properties.

All animals maintained normal activity patterns for the duration of the implant. All animals except one (#946) were walking normally within 24 h after implant, and thereafter maintained normal mobility and behavior. Cat 946 exhibited a "drop foot" in the implanted leg characterized by external rotation of the paw and dragging of the toes during walking. This condition appeared most severe 2 days after implant, and improved steadily thereafter. The toes no longer dragged 7 days post-implant, and gait was entirely normal by 12 days post-implant. In all other cases observation indicated normal gait patterns and the neurological tests revealed no abnormalities.

A. Positional Stability of Input–Output Properties

The effect of limb position on electrode I–O properties was determined by repeating measurements of I–O curves at different ankle joint angles. In contrast to the results obtained during acute experiments [10], [12], [13], chronically implanted cuff electrodes exhibited I–O properties that were not dependent on the limb position. I–O curves of plantarflexion torque as a function of stimulus current amplitude at three different positions of the ankle joint (70, 90, 110°) are shown in Fig. 1(a). The torque magnitudes changed as the joint angle changed as expected from the length-tension properties of skeletal muscle [27]. However, the shape of the curves was very similar at all positions. There was no change in either the threshold current or the current amplitude at which spillover occurred (second rise in the I–O curves, see [12], [13]). The similarity among the I–O curves was especially clear after each curve was normalized to the torque generated with a stimulus current amplitude of 550 μA, i.e., the maximum torque generated before spillover [Fig. 1(b)]. The invariance in the shape of the I–O curves measured at different ankle joint positions indicated that the same motor nerve fibers were being stimulated, and thus that there was no relative movement between the electrode and the nerve fibers at different limb positions.

Positional stability of I–O properties was assessed using methods previously described [6], [12], [13]. Analyses were conducted on I–O curves collected at least 8 weeks after implantation to ensure that tissue encapsulation had formed around the electrode. Each I–O curve in a set (i.e., at three different angles) was first normalized to its respective maximum torque. The normalized torques at the altered angles ($\pm$20°) were plotted as a function of the normalized torque at the initial angle with current as the independent variable [Fig. 1(c)]. The deviation of the actual torque from the torque predicted without position dependence (i.e., the unity slope line) was quantified as a percentage of the maximum torque.

The results from chronically implanted cuff electrodes indicated that the I–O properties of encapsulated nerve cuff electrodes were stable at different limb positions. Histograms of the deviations in I–O characteristics (expressed as a per-

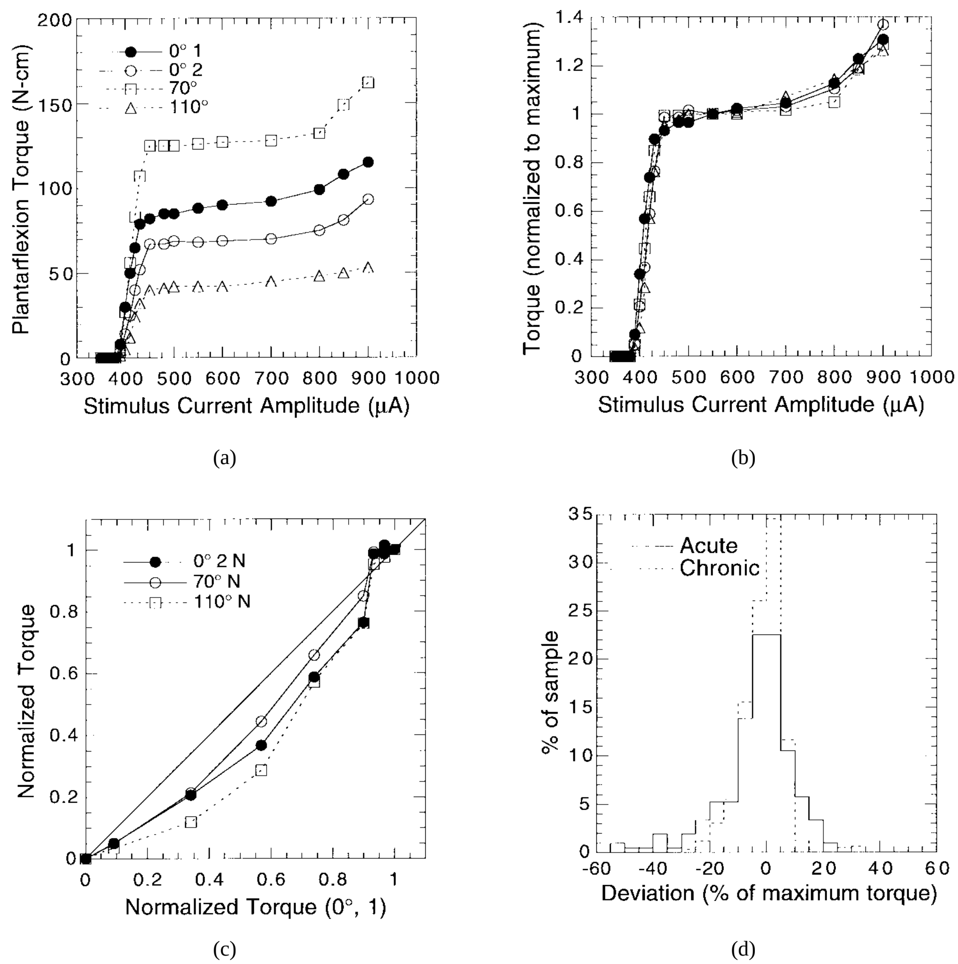


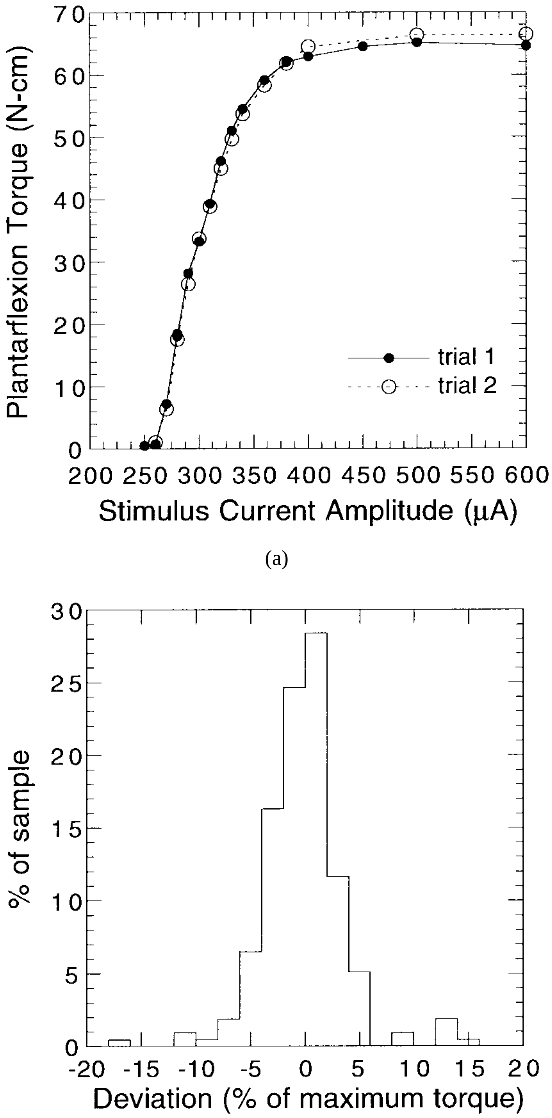
Fig. 1. Influence of ankle joint position on the input–output (I–O) properties of the nerve cuff stimulating electrodes. (a) Four trials of an I–O curve of plantarflexion torque as a function of stimulus current amplitude. The curves were generated by a tripole in a cuff that had been implanted for 25 weeks at three different positions of the ankle (75, 90, and 115°), as well as a curve repeated at 90° after measurements at the other two angles. (b) I–O curves from (a) normalized to the plateau torque generated with a stimulus current amplitude of 550 μA. (c) Normalized torque at the changed angles as a function of the normalized torque at the initial angle with current as the independent variable. The deviation of the actual torque from the torque predicted without position-dependence (i.e., unity slope line) was quantified as a percentage of the maximum torque. (d) Histograms of the deviations in I–O curves measured at different ankle joint angles in acute ($n = 209$ points from 28 sets of recruitment curves from five experiments) and chronic ($n = 327$ points from 26 pairs of I–O curves in eight measurement sessions in three animals) experiments.

centage of maximum torque) at different joint angles measured in the acute and chronic experiments are shown in Fig. 1(d). The absolute value of the deviation in the chronic implants ranged between 0 and 34% of the maximum torque ($|\text{percent deviation}| = 5.0 \pm 5.0\%$, mean $\pm$ s.d., $n = 327$ points from 26 pairs of I–O curves in eight experiments in three animals). The mean absolute deviation was significantly smaller in the chronic measurements than in the acute measurements (mean difference $= 3.8\%, p < 0.0001$, Mann Whitney U-test of the null hypothesis that the means were the same). Furthermore, the sample variance was significantly greater in the acute measurements than in the chronic measurements (variance of absolute deviation 95 versus 25, $p < 0.0001$, F-test of the null hypothesis that the ratio of the variances was equal to one).

Although 90% of the deviations in measurements with chronically implanted cuff electrodes were less than 10% of the maximum force, the mean deviation measured during changes in limb position was greater than the deviation measured between repeated curves at the same position (mean difference $= 2.4\%, p < 0.0001$, Mann Whitney U-test of the null hypothesis that the mean deviations were the same). Similarly, the sample variance was larger for the deviations between repeated measurements at different positions compared to repeated measurements at the same position (25 versus 9.6, $p < 0.0001$, F-test of the null hypothesis that the ratio of the variances was equal to one).

B. Short-Term Temporal Stability of Input–Output Characteristics

The short-term stability of the input–output characteristics was determined by repeated measurements of I–O curves two or more times during a testing session, separated by between 10 min and 3 h. Input–output curves were repeatable within a measurement session (Fig. 2). The short-term temporal stability of I–O properties was assessed using methods described above for analysis of position-dependent I–O properties. Each I–O curve in a set (i.e., at two different times) was normalized to its respective maximum torque. The normalized torque at



(a)

(b)

Fig. 2. Intrasession repeatability of the input–output (I–O) properties of the nerve cuff stimulating electrodes. (a) Two trials, conducted 15 min apart, of an I–O curve of plantarflexion torque as a function of stimulus current amplitude generated by 1 tripole in a cuff that had been implanted for 23 weeks. (b) Histogram of the deviations between I–O curves repeated within a measurement session ($n = 215$ points from 15 pairs of I–O curves from eight measurements sessions in four different animals). Over 95% of the differences were less than ±8% of the maximum torque.

the second time was plotted as a function of the normalized torque at the first time with current as the independent variable [see Fig. 1(c)]. The deviation of the actual torque from the torque predicted without time dependence was quantified as a percentage of the maximum torque. The deviation between two equi-current points on repeated I–O curves ranged from 0 to 20.6% of the maximum torque. The mean relative deviation between repeated points was not significantly different from 0 (deviation $= -0.061\% \pm 4.1\%$, mean ± s.d., $n = 215$ points from 15 pairs of I-O curves from 8 experiments across 4 implants, $p = 0.58$, sign test of the null hypothesis that the mean deviation was equal to zero). The twitch to twitch variability within a trial was less than the trial to

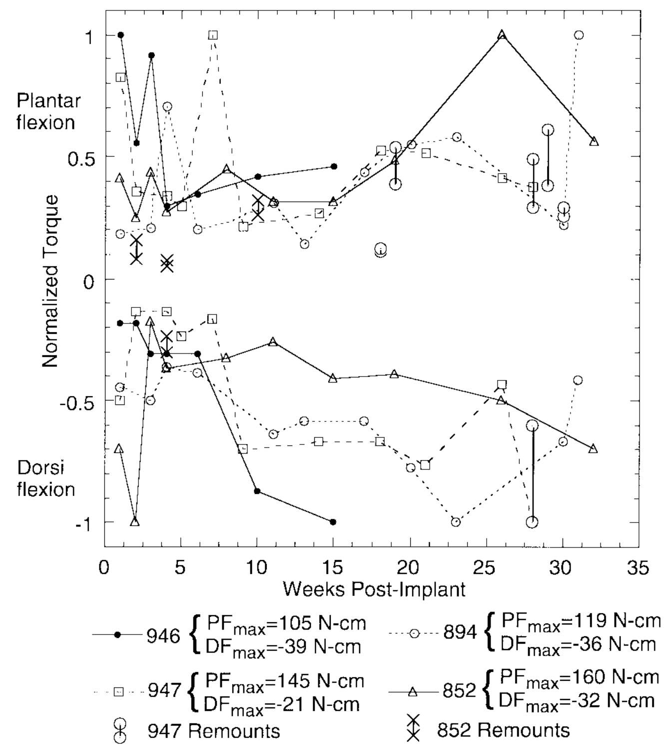
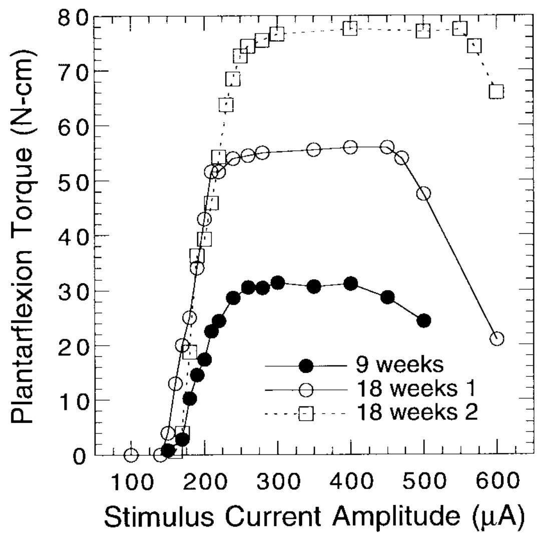


Fig. 3. Changes in maximum plantarflexion and dorsiflexion torque during the implant period. The maximum plantarflexion (PF) and dorsiflexion (DF) torque at each measurement session during the implant period have each been normalized by dividing by the maximum torque measured at any point during the post-implant period (values given in legend). The vertical lines connecting the symbols ("Remounts") indicate the change in maximum plantarflexion and dorsiflexion torque that occurred when the animal was dismounted and remounted in the measurement apparatus during the same measurement session.

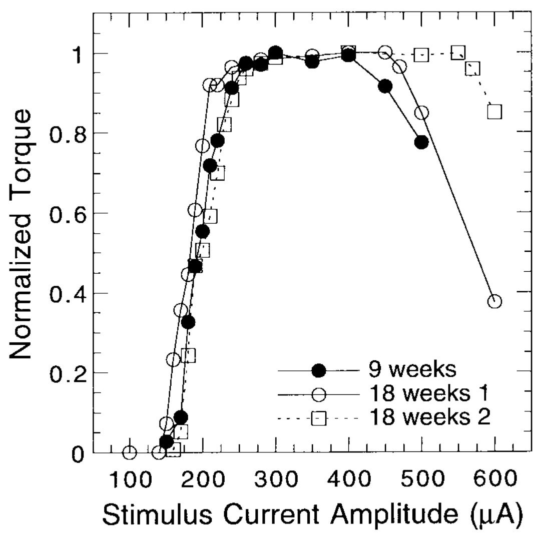
trial variability and is therefore not presented. A histogram of the deviations from all repeated measurements is shown in Fig. 1(b) (absolute deviation $= 2.6\% \pm 3.1\%$). Over 95% of the deviations were less than ±8% of the maximum torque indicating that I-O curves were extremely repeatable within an experimental session.

C. Long-Term Temporal Stability of Maximum Torque

The long-term stability of nerve cuff input–output properties was determined by repeated measurements of I–O curves at regular intervals during the post-implant period. There were changes in the maximum plantarflexion (PF) and dorsiflexion (DF) torques generated during different testing sessions. The joint torques generated by each implant were quantified by normalizing the torque in each measurement session to the maximum torque generated at any session during the duration of the implant. The normalized maximum torques as a function of time post-implant are plotted in Fig. 3 for the four functional implants. The slopes of linear regression lines ranged from -0.028 to 0.065 percent-of-maximum-torque/week, but there were only three cases where the slope of the regression line was significantly different from zero (947 DF, 852 PF, 946 DF). There was a low correlation between the maximum torque and the time post-implant ($r^2 = 0.33 \pm 0.30$, mean ± s.d., range $= 0.01 - 0.92, n = 8$), and in only 1 case was the



(a)



(b)

Fig. 4. An example of the stability of I–O properties within and between measurement sessions. (a) Three trials of an I–O curve of plantarflexion torque as a function of stimulus current amplitude generated by one tripole in a cuff that had been implanted for either 9 or 18 weeks. The animal was dismounted and remounted in the measurement apparatus between the two curves measured at 18 weeks. (b) The same I–O curves normalized to the maximum torque generated during each of the three trials.

change in torque strongly correlated with the time post-implant (946 DF, $r^2 = 0.92$). Note that this is the animal which exhibited a "drop foot" in the period immediately following the implant. There were also changes in the maximum torque that resulted from removing and remounting an animal in the apparatus between repeated measurements in the same session, and the magnitude of these changes are also shown in Fig. 3 ("Remounts").

There were session-to-session changes in the maximum torques generated by selective stimulation, however, these changes were not necessarily associated with changes in the nerve cuff I–O properties. An example is shown in Fig. 4(a) in which there was a large change in the maximum torque while the degree of activation (i.e., percentage of maximum torque) at equicurrent levels remained stable [Fig. 4(b)]. Similarly, although remounting at 18 weeks caused a large change in maximum torque, the degree of activation at equi-current levels remained stable. Overall, there was a weak correlation between the maximum torque and the current required to generate 50% of the maximum torque ($r^2 = 0.21 \pm 0.23$, mean ± s.d., range <0.01–0.712), and in only 5/32 cases was the correlation significant (Fisher's r to z). I–O curves were thus normalized to the maximum torques generated in each measurement session to isolate changes in electrode I–O properties from changes in maximum torque.

D. Long-Term Temporal Stability of Input–Output Properties

There were session to session changes in the current required to generate a particular level of muscle activation (i.e., percentage of maximum torque). An example of I-O curves collected with the same tripole at four different measurement sessions between 17 weeks and 32 weeks post-implant is shown in Fig. 5(a). There were differences in the maximum torque evoked in each of the four sessions, and the torque magnitude of each curve was normalized to the maximum torque generated before spillover in each measurement session as shown in Fig. 5(b). This example illustrates a case where there were shifts in the threshold current between measurement sessions, but where the shape of the I–O curves remained stable.

To quantify the stability of nerve cuff I-O properties, the currents required to generate 20% (I_{20}), 50% (I_{50}), and 80% (I_{80}) of the maximum torque before spillover were calculated and compared between measurement sessions. The time progression of the current parameters (I_{20}, I_{50}, I_{80}) are shown for each of the tripoles in each of the 4 long-term implants in Fig. 6. The largest changes in the current parameters were observed during the period immediately following implantation. After 8 weeks the I–O properties were more stable, although there were instances of changes even after long periods of implantation. Similarly, the changes in the difference between I_{80} and I_{20} (indicative of the shape of the I–O curve) were largest in the early post-implant period and stabilized thereafter.

There was a great deal of variability between the stability of the I–O properties of electrodes in different animals and different tripoles within the same animal (Fig. 6). The variability between tripoles and animals is illustrated by the fact that the slopes of the regression lines fit to the I_{50} as a function of time post-implant data for each tripole in each animal ranged from -32 μA/week to 4 μA/week (-13 ± 12 μA/week, mean ± s.d., $n = 16$). The variations in I_{50} were poorly accounted for by changes in the time post-implant with regression coefficients ranging from 0.004 to 0.561 (0.32 ± 0.18, $n = 16$), and in only 5/16 cases was the slope of the regression line significantly different from zero.

Since linear regression described the changes in the current parameters poorly, histograms of the changes in I50 were constructed to quantify the early and late temporal stability of I–O characteristics. The session to session changes in I_{50} were calculated and expressed as a percentage of the I_{50} of the previous measurement session. Histograms of the percentage changes in I_{50} between 1 and 8 weeks post-implant ($n = 59$

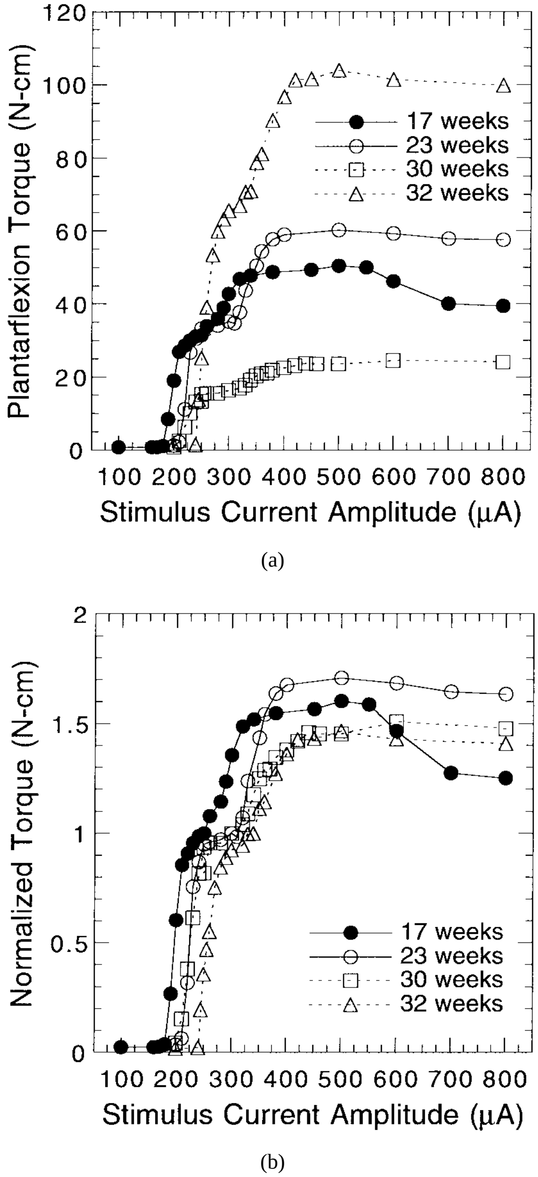


Fig. 5. An example of the stability of I–O properties between measurement sessions. (a) Four trials of an I–O curve of plantarflexion torque as a function of stimulus current amplitude generated by 1 tripole in a cuff that had been implanted for 17, 23, 30, or 32 weeks. (b) The same I–O curves normalized to the maximum torque generated during each of the four measurement sessions.

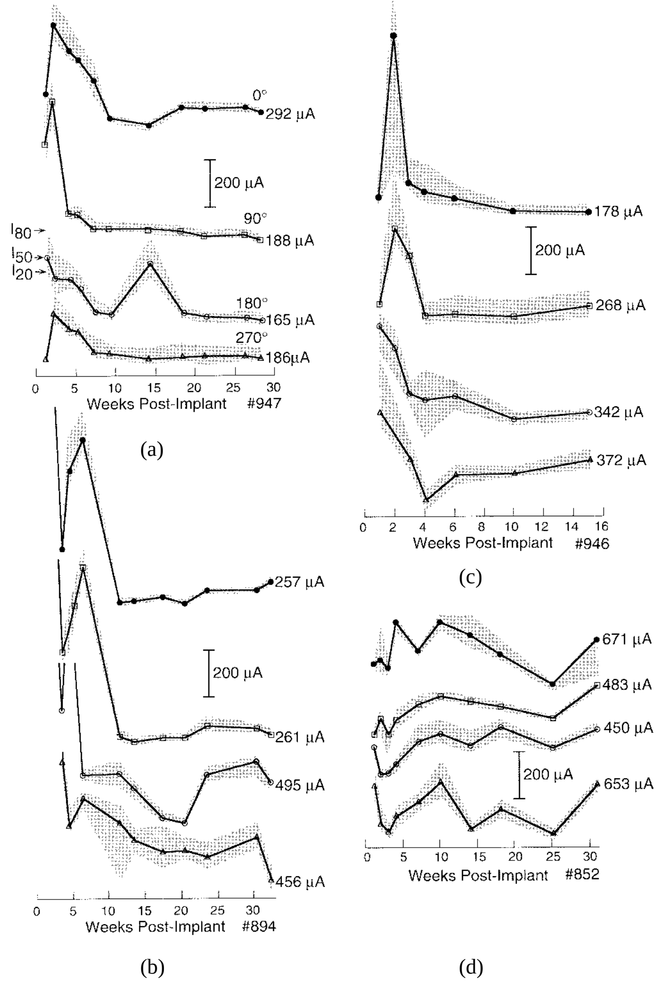


Fig. 6. Temporal progression of the I–O properties of the nerve cuff stimulating electrodes. Each panel (a)–(d) shows the results from each of the four long-term functioning implants, and each trace within a panel shows data from each of the four tripoles. The solid lines indicate the stimulus current amplitudes required to generate 50% of the maximum torque (I_{50}) and the limits of the gray band indicate the currents required to generate 20% (I_{20}) and 80% (I_{80}) of the maximum torque, as a function of time post-implant. The value of I_{50} at the last measurement session is shown at the right of each curve.

points from 19 measurement sessions across four implants) and between 8 and 32 weeks post-implant ($n = 60$ points from 20 measurement sessions across four implants) are shown in Fig. 7. During the period between 1 and 8 weeks post-implant there was a great deal of variability in the I–O properties, and only 57% of the changes were between ±15%. In contrast to the results in the early post-implant period, 70% of the changes in the period after 8 weeks post-implant were between ±15%. The mean absolute change in I_{50} was significantly smaller in the period after 8 weeks than in the period between 1 and 8 weeks post-implant (34.2 ± 42.0% between 1–8 weeks versus 15.4 ± 19.1% after 8 weeks, $p < 0.0001$, Mann Whitney U-test of the hypothesis that the two populations had the same mean). Furthermore, the variance was significantly greater during the early post-implant period than in the later period (2945 between 1–8 weeks versus 607 after 8 weeks, $p < 0.0001$, F-test of the null hypothesis that the ratio of the variances was equal to 1). Thus, the I-O properties were more temporally stable in the period after 8 weeks post-implant than between 1 and 8 weeks post-implant.

E. Effects of Steering Current on Input–Output Characteristics

Previous analysis of I–O curves from acute experiments indicated that subthreshold transverse field steering current improved spatial selectivity of activation of different fascicles in a nerve trunk [13]. The improvement in selectivity was indicated by significant increases in the maximum torque generated before spillover and significant increases in the dynamic range of current between threshold and spillover. Input–output data from encapsulated cuff electrodes indicated that 90% steering current generated similar increases in the spatial selectivity of activation by chronically implanted nerve cuff electrodes.

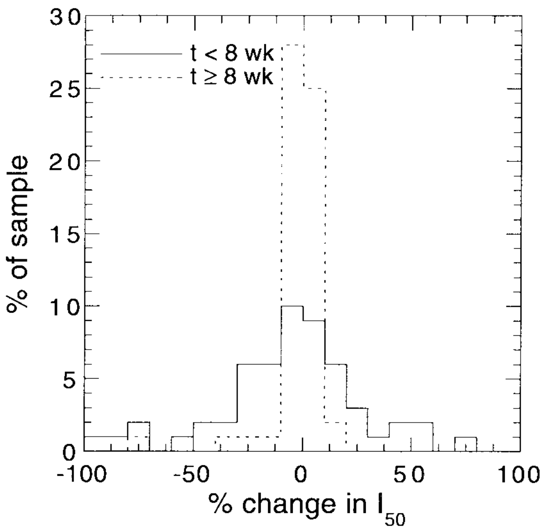


Fig. 7. Histograms of the session to session changes in the current required to generate 50% of maximum torque (I_{50}) during the period between 1 and 8 weeks post-implant ($n = 59$ points from 19 measurement sessions across four implants) and during the period between 8 and 32 weeks post-implant ($n = 60$ points from 20 measurement session across four implants).

All analyses were done on I–O curves collected at least 8 weeks post-implant to ensure that tissue encapsulation had formed around the electrode. Transverse 90% steering current generated a significant increase in the dynamic range between threshold and spillover for I–O curves from chronically implanted cuffs (range of increase $= -1100\ \mu\text{A}{-}4250\ \mu\text{A}$, mean increase $= 166\ \mu\text{A}, p = 0.034$, one-tailed paired t-test of the null hypothesis that the mean dynamic ranges were the same, $n = 51$ pairs of I–O curves from 15 experiments in 4 animals). Transverse field steering current also increased the maximum torque generated before spillover (range of increase $= -10$ N-cm to $+20$ N-cm, mean increase =1.4 N-cm, $p = 0.022$, one-tailed paired t-test of the null hypothesis that the mean maximum torques were the same, $n = 51$ pairs of I–O curves from 15 experiments in four animals).

IV. Discussion

Twelve contact spiral nerve cuff electrodes were chronically implanted on cat sciatic nerve to measure the temporal and positional stability of electrode input–output (I–O) characteristics. Although I–O properties were very stable within an experimental session, there was variability in the I–O characteristics between measurement sessions. The degree of session to session variability was different for each tripole within an implant and across implants. Results from previous studies indicate that the thresholds of cuff electrodes containing circumneural band electrodes were stable over periods of years [21], but these results do not necessarily mean that the same nerve fibers were activated in each test session. The stability of thresholds of tripolar spiral nerve cuffs implanted on sacral nerve roots of dogs was variable between implants, and the current required to arrest action potential propagation varied during the implant period [2]. Similarly, the ability to generate unidirectionally propagating action potentials, and the currents required to do so, were variable for bipolar cuff electrodes implanted on dog pudendal nerves [18].

Analyses of the stability of I–O properties were conducted based on percentages of maximal torque because there was session to session variability in the maximum torque values. There was no systematic trend in maximum torques as a function of time post-implant (Fig. 3), and in all cases different electrode configurations allowed selective and independent control of dorsiflexion and plantarflexion torques at every measurement session. There were changes in the maximum torques that resulted from remounting of the instrumented leg within a measurement session (Figs. 3 and 4). The magnitude of these changes was in some cases comparable to the session to session changes in maximum torque, and thus variations in animal mounting could have contributed to variability in the maximum torque. Similarly, mounting variations could account for some of the variability in the input–output properties. The changes in the current amplitude required to generate 50% of maximum torque (I_{50}) that occurred as a result of remounting varied from 8 to 37% of the value of I_{50} measured before remounting ($|\text{percent change in } I_{50}| = 16 \pm 11\%$, mean $\pm$ s.d.). Previous measurements have documented the repeatability of the measurement instrumentation [12], and thus the changes in maximum torque and I_{50} which resulted from remounting were likely the result of variations in animal positioning, joint angles, muscle lengths, and electrode-nerve positioning. These results indicate that variations in animal mounting could have contributed to the variability in I–O properties measured in these studies, and this is a confounding factor when considering the long-term stability of the I–O properties of the electrodes.

Input–output properties were most variable in the period between 1 and 8 weeks post-implant, and less variable between 8 and 25 weeks post-implant. The temporal variations of I–O properties could arise from several sources: changes in the induced fields resulting from formation of tissue encapsulation, changes in the position of the motor fibers relative to the electrodes due to alterations in the nerve trunk geometry, changes in electrode position relative to the motor nerve fibers resulting from electrode movement, and variability in the physiological properties of the neuromuscular system including degeneration and regeneration of the stimulated nerve fibers. Each of these potential sources of variability in the I–O properties is considered in the following paragraphs.

Changes in the composition of the tissue around the electrodes most likely contributed to the variability in the I–O properties in the early post-implant period. Microscopic examination of transverse sections through the cuff showed that the implanted electrodes were surrounded, inside and outside, by fibrous tissue encapsulation from 50 μm to 1 mm thick. Previous measurements with chronically implanted electrode arrays fabricated from the same materials as the cuff electrode indicated that the resistivity of the tissue around implanted electrodes changes most in the period between 1 and 6 weeks post-implant, and remains relatively constant after 6 weeks post-implant [9]. These results are also consistent with the time course of the tissue response to biocompatible implants, which is most active in the first several weeks post-implant and relatively inactive thereafter [1]. Thus, some of the measured changes in the early period were likely the result of the formation of the encapsulation tissue between the electrodes and the nerve trunk.

Previous studies with nerve cuff electrodes indicated that the geometry of the sciatic nerve was altered by the presence of the cuff. Although the cat sciatic nerve does not necessarily have a circular cross section *in vivo*, all nerves were observed to have assumed a circular cross section after acute implants lasting less than 24 h [34]. Sciatic nerves implanted with spiral nerve cuffs for six months were also found to have a circular cross section [23]. Additionally, experiments with penetrating electrodes indicated that the components of the nerve are capable of moving within 16 hours to accommodate external forces [32]. Thus, repositioning of the components of the nerve could contribute to instability of I–O properties in the period immediately after implantation, but would not be expected to cause changes over the time scale of the present study.

Movement of the electrode relative to the nerve trunk could contribute to the observed variations in I–O properties. Results from acute studies on the effects of joint angle changes on I–O curves indicated that electrode movement did cause alterations in I–O properties [10], [13]. Within a measurement session, the I–O properties of encapsulated multiple contact cuff electrodes were stable at different limb positions, and histological examination indicated that the cuffs were bound to the nerve by fibrous tissue encapsulation. These results suggest that the tissue encapsulation acted to stabilize the cuff electrode and prevent relative movement between the cuff and the nerve trunk during changes in the ankle joint angle. However, there may have been relative movement between the cuff and nerve between measurement sessions. The encapsulation tissue did contain regions of active fibroblasts, mononuclear leukocytes, and polymorphonuclear leukocytes, indicating the presence of an acute inflammatory reaction, which could have be due to movement of the electrode relative to the nerve. Thus, movement of the nerve cuff relative to the underlying tissue, and subsequent changes in the position of the individual contacts relative to the individual fascicles, could have contributed to changes in the I–O properties between measurement sessions. Relative movement between the cuff and the nerve may also have contributed to the changes in I–O properties that occurred due to remounting within a measurement session.

Variability in the properties of the neuromuscular system, including degeneration and regeneration of the stimulated nerve fibers, could also have contributed to variability in the I-O properties. No neurological deficits were observed other than the "drop foot" in cat 946 immediately after implantation (see Results). Similarly, no systematic changes in the current parameters (I_{20}, I_{50}, I_{80}) or the maximum torque were observed that would indicate a persistent degradation of the underlying nerve fibers [2]. Histological examination revealed focal areas of abnormal morphology in five of seven implanted nerves, including perineural thickening, proliferation of endoneural connective tissue, and thinned myelin. These morphological changes could have resulted in variations in excitability and contributed to the observed changes in I–O properties. Finally, normal variability in the physiological system (e.g., daily variations in excitability or force production) could have contributed to the observed changes in I–O properties.

The results of these studies demonstrate that multiple contact spiral nerve cuff electrodes can be used to effect selective activation of the nervous system on a long-term basis. In the absence of animal intervention the electrodes functioned well. However, there were appreciable session to session changes in the output torques evoked by a particular input current. The changes in input–output properties were variable within tripoles (i.e., properties might vary between two concurrent measurement sessions, but not between the next), within implants, and across implants (Fig. 6). No clear source was identified for the variability, but electrode movement, degeneration and regeneration of the stimulated nerve fibers, and variability in animal mounting in the measurement apparatus all likely played a role. It is not clear whether this level of variability in the I–O properties is acceptable for a functional motor prostheses, as there are no comparable measurements in the literature. Furthermore, this will likely be strongly dependent on the algorithms used to command and control the device.

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