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A Nerve Cuff Electrode For Controlled Reshaping Of Nerve Geometry

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Abstract

The purpose of this study is the development of a nerve electrode that reorganizes nerve geometry slowly and controllably. The Flat Interface Nerve Electrode (FINE) can reshape the nerve into an elongated oval and provide selective stimulation. However, the rate of closure of this electrode is difficult to control. The Slowly Closing – FINE (SC-FINE) is designed with an opening height larger than the size of the nerve to accommodate initial swelling. The electrode closes slowly to reshape the nerve into the desired flat geometry. The SC-FINE is created by combining the reshaping properties of the FINE and the controllable degradation of Poly (DL lactic-co-glycolic acid (PLGA). Bonding 50/50 or 65/35 PLGA to a stretched FINE increased the opening heights (OH) on average from 0.1 mm to 1.66 ± 0.45 and 2.05 ± 0.55 mm respectively. The addition of the PLGA films controls the time course of closure over a period of 16 ± 1 days and 14 to 16 hours for the 50/50 and 65/35 SC-FINES respectively *in vitro*. An *in vivo* chronic experiment using 50/50 SC-FINES implanted in 28 rats with an average OH of 1.87 ± 0.34 mm show that the reshaping periods *in vivo* and *in vitro* are similar.

Keywords

FES; neural; prosthesis; compression; electrode; biodegradable; polymer

I. INTRODUCTION

Recent observations suggest that the cross-sectional geometries of nerve trunks are generally ellipsoid in shape and these geometries are created by the local anatomy of the surrounding tissue(1, 2). Experimental data also show that nerve cross-sectional geometries can also be reshaped by extraneural electrodes (3). Extraneural electrodes (4, 5), such as the spiral (6, 7) and the helix (8), have cylindrical cross-sections and have applications in Functional Electric Stimulation (FES) devices (5, 9). These electrodes are considered to be non-damaging to the nerve due to the self-sizing property they possess, which allows for short and long term nerve swelling. However, selectively activate central axon populations is problematic without specialized techniques (10–12). Conversely, intrafascicular electrodes (11, 13–18) are placed within fascicles in the immediate proximity of axons, and therefore achieve better selectivity. This increased selectivity is accomplished by penetrating the epineurium and perineurium, which may lead to nerve damage (19).

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To improve the selectivity of extraneural nerve electrodes, the Flat Interface Nerve Electrode (FINE) (20) was designed, built and tested. The FINE is designed to reorganize the transverse cross-section of the nerve and its fascicles into ovals by applying a small, non-circumferential force to the nerve. By realigning the fascicles within the electrode, the FINE provides both fascicular (20) and subfascicular (21) selectivity. The oval shape of the FINE improves the selectivity for stimulation and recording (20, 22), but the FINE's ability to quickly reshape nerve geometry may cause acute compression type injury (23). The duration of the reshaping period is unknown, but experimental observations suggest that within 12 hours the nerve is completely reshaped. In a study of chronic safety (24), three FINE designs were implanted in rats, each exerting a low, medium, or high force onto the nerve. Each FINE reshaped the nerve's geometry, but significant histological and physiological nerve damage only occurred in the electrode that exerted the highest force. The nerve damage is greatest seven days post-implant and recovers to normal 21 days post-implant, suggesting that once the nerve adjusts to the new geometry, it returns to normal function. This recovery corresponds to a neurapraxia (Sutherland Lesion 1) compression injury (23) and suggests that the reshaping period of the FINE may play a critical role in nerve damage, particularly during the first few days post-implantation when nerve swelling occurs.

In this study, the FINE is further developed to increase its initial opening height and to control the time course associated with reshaping. This further development is accomplished by attaching a biodegradable and biocompatible polymer called Poly (DL-lactic-co-glycolic) acid (PLGA) to the FINE. PLGA is currently the most widely used synthetic biodegradable co-polymer, and is used in technologies such as biodegradable suture and drug delivery systems (25, 26). PLGA can be easily molded into any configuration and its physical, chemical, mechanical, and degradation properties can be engineered to fit a specific need. Furthermore, the biocompatibility of PLGA is demonstrated in many biological facets (27).

This paper describes this modified FINE called the Slowly Closing Flat Interface Nerve Electrode or SC-FINE, and addresses the following three hypotheses: 1) the original opening height of the FINE can be increased by 1500% of the initial height to accommodate nerve swelling, 2) the time course of closure can be controlled over a longer time period to minimize trauma and 3) the *in vitro* time course of closure is similar to that obtained *in vivo*. Also described is a mechanical model to predict the opening height and facilitate the design of the electrode for various applications.

II. Methods

I. FINE Design

The Flat Interface Nerve Electrode (FINE), (figure 1) is designed to have a rectangular cross-sectional area and is fabricated using a common silicone injection mold process. This electrode was tested on the sciatic nerve of felines. The average diameter of the sciatic nerve is three millimeters and the nominal diameter of the largest fascicle is 1.2 mm (28). The height and width of the opening are chosen such that the area of the opening is sufficient to contain the entire nerve. The opening height is chosen equal to the smallest height fitted *in vivo*. This height allows for the alignment of fascicles within the electrode, as well as, reshaping of the largest fascicles. The width and thickness of the FINE are 8.38 mm and 1.27 mm respectively, and are chosen to minimize the force the electrode exerts.

II. Slowly Closing-FINE Manufacturing

The SC-FINE is built by bonding a co-polymer film onto a stretched FINE (figure 2). The FINE is stretched using a micromanipulator by 25% of its length (~ 2 mm). The PLGA co-

polymer is cut to dimension (0.5 cm by 1 cm) and is coated with a very thin layer of silicon primer (CF6-135, Nusil Silicone Technology, Carpinteria, CA). The primer is allowed to hydrolyze in room air for thirty minutes, while a very thin layer of silicone adhesive (MED1-4260, Nusil Silicone Technology, Carpinteria, CA) is applied to the top and bottom of the stretched FINE. The application of the silicon adhesive is done after the primer is hydrolyzed due to the quick curing time of the adhesives (5 minutes). The PLGA film is then placed onto the FINE while in the stretched position, and a heat gun is used to seal the polymer to the electrode. Each side is heated for approximately ten seconds, while the air is pushed out from in between the materials. The system is cured for 24 hours before releasing the stretch.

This process is done in a clean hood with all tools and materials first passing through a cleaning procedure. Once the film is made in the press, it is cut to the desired dimensions. The films are ultrasonicated for five minutes to remove any dust or particles.

Each SC-FINE (figure 3) is stored in a moisture free desiccator until ready for experimental use. The opening height is measured using a digital microscope camera (Olympus DP-10 Digital Camera, Melville, NY). Three digital images are taken of each electrode, and the new opening heights are determined using Scion Image (Scion Corporation, Frederick, Md), and the values averaged. A statistical power analysis is done to determine the amount of images needed to produce less than five percent error ($\alpha = 0.05$) in measurements of the opening heights. It was determined that three images are sufficient to reduce the measurement error to less than five percent.

III. Composite Beam Model

A composite beam model was developed to determine the relationship between the amount of stretch and the opening height of the composite electrode. The electrode model consists of two identical composite beams, each corresponding to a wall of the FINE and the co-polymer film (figure 4(a)).

The SC-FINE is modeled to determine the deflection at its center. Since the electrode, shown in figure 4(a), is symmetrical about the horizontal plane the opening height can be calculated by determining the deflection of one composite beam and doubling the amount to account for entire electrode. The beam is analyzed using standard composite beam theory (29) to determine the position of the neutral axis. The neutral axis is defined as the plane through the composite beam with zero stress or strain. The length of the neutral axis is equal to the original length of the electrode plus the applied stretch.

The deflection of the electrode is based upon the curvature of the composite beam. The curvature in the beam depends upon the end conditions of the beam. The end conditions are determined to be moment resisting because once each end of the FINE is cut the curvature increases. Given the end conditions, it is determined that the beam takes the shape that is shown in figure 4(c). The two identical fixed end beams have the same deflection with an inflexion point directly in the center of each beam. The deflection at the inflexion point is exactly half of the overall deflection in each beam. Thus, the overall deflection of the electrode can be determined by analyzing the center portion of the beam between each inflexion point (between points P and Q in figure 4(c)).

To determine the deflection in the center portion of the beam (figure 4(d)) a second known length is needed in addition to the known length of the neutral axis. It is assumed that the inner surface of the SC-FINE returns to the original length of the FINE since the Young's modulus of the silicone elastomer is much less than that of the co-polymer (see Appendix I).

Thus, the deflection (Y) can be found using simple geometric equations; the entire derivation is done in Appendix I.

$$Y = \left(R_i \left(1 - \cos \left(\frac{\theta}{2} \right) \right) \right)$$

Where R_i is the interior radius of the beam and θ is the angle between the inflection points. From Y the overall Opening Height (OH) is given by:

$$OH = 2 \times Y + 0.102 \text{ (mm)}$$

The deflection in the center portion, Y, is doubled once to account for the symmetry of the beam, and twice to account for the symmetry of the electrode. Finally, the original opening height of the FINE is added to determine the overall opening height of the SC-FINE.

IV. Biodegradable Film Fabrication

The PLGA (Birmingham Polymers, Birmingham, AL) co-polymer is polymerized into a very thin film using heat compression molding, by placing the polymer between two stainless steel plates (thickness .25 inches). Non-stick Mylar sheeting (Plastic Suppliers, Columbus, OH) lines each plate and is used to determine the thickness of the final film by placing spacers of known thickness around the perimeter of the Mylar sheeting. The sandwiched polymer is placed into a press (Carver Press, Wabash, IN), heated to 20°C higher than the melting temperature of the co-polymer ($T_m = 130^\circ\text{C}$), and held under a relatively light load (10,000 lbs) during initial heating of the co-polymer. After initial heating, the pressure is cycled between zero and a very high load (60,000 lbs) in order to push any air or excess polymer out through designed escape valves in the Mylar sheeting spacers. The pressure is cycled eight to ten times, after which the system is allowed an additional three minute heating period before cooling the new polymer film. The co-polymer film is cooled by submerging the system in ice water.

V. *In Vitro* Experiments

Two PLGA co-polymers are investigated to study the effect of film composition on the duration of the reshaping or closure period *in vitro*. The ratio of lactic to glycolic acid in the co-polymer determines the mechanical, chemical and degradation properties of the film. 50/50 and 65/35 lactic to glycolic PLGA co-polymers are used in the *in vitro* experiments.

Both types of SC-FINES are immersed in a Dulbecco's Phosphate Buffered Saline (DPBS) (Gilbo Inc., Cleveland, OH) bath maintained at 37°C for a period of no less than 20 days and no more than 30 days. The DPBS bath is changed every eight hours for the first two days, every day for the first week, and every week thereafter. Each day the electrodes are removed from the bath and three digital images are taken to study the rate of closure or the rate of reshaping over time. The experiments are terminated once the electrodes reach their final relaxed geometry, or when the hydrolyzed co-polymer starts to delaminate.

VI. *In Vivo* Experiments: Implant Procedure

All animal procedures were approved by the Institutional Animal Care and Use Committee of Case Western Reserve University. The experimental animals are male Zivic-Miller, Sprague-Dawley rats, weighing 350–410g at implant and fed commercial rat pellets and water *ad libitum* through the duration of the experiment. The experimental design required 14 rats with bilateral implants. Each electrode is randomly assigned to an animal.

Sterile surgical procedures are used. Intramuscular (IM) injection of a rat cocktail (Ketamine (1.5 ml), Xylazine (1.5 ml), Acepromazine (0.5 ml), 0.5–0.7 ml/kg) is used to induce anesthesia. The lower back of each animal is shaven and scrubbed with povidone-iodine swabsticks (Professional Disposables Inc., Mississauga, Ontario) in preparation for the surgical procedure. The depth of anesthesia is monitored by paw pinch and eye blink reflexes. A water heating pad maintained the animal's body temperature.

Each implant consisted of one 50/50 PLGA SC-FINE placed in a three centimeter stainless steel mesh cage (30) to prevent the effects of external forces on the electrode. Each electrode is processed as described previously in a clean environment and sterilized by dipping the electrode into a solution of Cefazolin (Apothecon, Princeton, NJ, one gram in 200 cc of sterile saline) before being placed within the steam sterilized stainless steel cage. Intraoperatively, the implant is rinsed in the same Cefazolin solution to further reduce the risk of infection and prevent particulate matter from adhering to the implant.

With the animal in the prone position the incision is made in the center of the lower back noting the position of the animal's hips and is extended three to four centimeters along the central line toward the tail region. Two subcutaneous pockets are made in the lateral aspects of the abdomen making sure that the implants do not rub against the hip of the animal. The implants are carefully inserted into each pocket and the site is irrigated with approximately one cc of Marcaine (Abbott Laboratories, North Chicago, IL). The skin incision is closed with wound clips (Fisher Scientific, Hanover Park, IL). The rat is returned to its bedding and monitored until fully recovered.

VII. Explant Procedure

The implants are removed in two explant periods, the first period is two days post implant and the second period is 12 days post implant. During each explant period, half (7) of the animals (14) are sacrificed. Intramuscular injection of a rat cocktail produced initial and surgical anesthesia. The wound clips are removed and the implants are freed by blunt dissection. The animals are then sacrificed with an intraperitoneal injection of sodium pentobarbital (1 cc/animal). The SC-FINEs are immediately removed from the cages and three digital images are taken.

VIII. Delamination Of Polymer Film

During each experiment the electrodes were monitored for signs of co-polymer film delamination. If film delamination is found, a value corresponding to the percentage of delamination is assigned for the entire electrode. For example, the electrode in figure 3(a) shows no delamination. Whereas, the electrode in figure 3(b) has 10% delamination of the co-polymer film (see arrows). Thus, if one of the two films delaminates fully, that corresponds to 50% delamination.

IX. Strain Analysis

A strain analysis is done to determine if the manufacturing process (stretching the FINE) of the SC-FINE changed the mechanical properties of the FINE. Comparison of the SC-FINE is done once the reshaping period is complete. Figure 5(a) shows a conceptual model of the measurement technique, which directly measures the force applied by the FINE. The change in the opening height of the FINE is defined as the displacement, Δd . As the micromanipulator is adjusted, the displacement of the FINE generates a force measured by the strain gauge.

III. Results

I. SC-FINE Opening Heights

The composite beam model provides one analytical relationship between the amount of stretch applied to the electrode and the new opening height. The model predicts an opening height of 1.63 mm when a stretch of two millimeters is applied to the FINE with a thickness of 1.27 mm. This opening height is not statistically different from experimental data (average OH = 1.66 ± 0.48 mm, $n = 28$) (two-sample t-test).

The validity of the model is further tested by predicting the value of the opening height with one millimeter of stretch applied to the FINE. The SC-FINES produced are made with 50/50 PLGA co-polymer with dimension of 0.5 cm by 0.9 cm by 0.2 mm. The average of 20 SC-FINES opening heights is 0.81 ± 0.23 mm. The model predicts a value of 0.87 mm, which is not significant from the mean value of the experimental work (two-sample t-test).

II. *In Vitro* Experiments

SC-FINES produced with either 50/50 or 65/35 PLGA films were built to investigate the effect of the biodegradable co-polymer layer on the electrode's new opening height and time course of closure. Forty-four 50/50 and ten 65/35 PLGA SC-FINES were measured to determine the opening height of the new oval geometry. Figure 6(a) and (b) show histograms of the opening heights of these electrodes. The mean new opening heights of the 50/50 and 65/35 SC-FINES increased from 0.102 mm to 1.66 ± 0.48 mm and 2.05 ± 0.55 mm respectively. There are statistical differences between these electrodes (Linear Anova, $p = 0.015$).

Following opening height measurements, the SC-FINE's are immersed in a bath of DPBS at 37°C to investigate their time course of closure. Figure 7 shows a typical example of a 50/50 PLGA electrode with an increased opening height and a controlled closure period over 28 days. Sixteen 50/50 PLGA SC-FINES were investigated until the closure period was complete. Figure 8(a) is a graph of opening height versus immersion time and shows the average time course of these electrodes over a period of twenty-eight days. These electrodes reached 90% closure in 16 ± 1 days post immersion with a final value of 173 ± 90 μ m.

Ten 65/35 SC-FINES were studied and the time course of closure, shown in figure 8(b), was much quicker than those of the 50/50 PLGA electrodes. These electrodes reached 90% closure in fourteen to sixteen hours post immersion and a final opening height of 150 ± 33 μ m. The magnified view of the first day of immersion shows the very fast reshaping period for these electrodes.

III. *In Vivo* Experiments

Finally, twenty-eight 50/50 SC-FINES were built for an *in vivo* chronic implant designed to compare the rate of closure with the *in vitro* results. Figure 6(c) shows a histogram of the opening heights and a mean value of 1.87 ± 0.34 mm. Figure 8(c) shows the average opening heights from each chronic explant period and the average time course of closure for 28 50/50 SC-FINES *in vivo*. The average opening height of the first explant period, (two days post implant), is 0.490 ± 0.23 mm (490 μ m). The average opening heights at the final explant period (twelve days) is 0.200 ± 0.09 mm (200 μ m).

The relative time course of closure of the 50/50 SC-FINE *in vitro* and *in vivo* and the 65/35 SC-FINE *in vitro* are plotted in figure 9 for days zero, two, and 12. A comparison of the time courses of closure between the 50/50 and 65/35 SC-FINE experiments showed significant differences when using an ANOVA general linear model with a Tukey

comparison (50/50 *in vitro* / 65/35 *in vitro*, $p = 0.006$, 50/50 *in vivo* / 65/35 *in vitro*, $p = 0.036$). However, there was no statistical difference when comparing the time course of closure between the 50/50 *in vitro* and *in vivo* SC-FINEs ($p = 0.08$).

IV. Delamination Of Polymer Film

Delamination of the PLGA film was monitored throughout each experiment to determine if closure occurred from degradation or delamination of the co-polymer film. Figure 10(a), (b), and (c) show delamination results for 50/50 *in vitro*, 65/35 *in vitro* and 50/50 *in vivo* respectively at days 1 and 10 or days 2 and 12 (figure 10(c)). In figure 10(a), seven electrodes show a 10% delamination and two others at 20 and 30% delamination at day one. From the original seven electrodes with 10% delamination, six did not delaminate further for the duration of the experiment. The time course of closure of electrodes with 10% delamination throughout the closure period was compared to that of electrodes showing no sign of delamination. It was found that the closure periods are similar with no significant differences (data not shown). These results show that 10% delamination does not affect the time course of closure. One electrode delaminated further and eventually one side of the PLGA co-polymer film fully delaminated.

SC-FINEs built with 65/35 PLGA films show a greater frequency of delamination. Of the ten monitored electrodes, four showed 40% delamination or less at day one. Eight *in vivo* 50/50 PLGA SC-FINEs have delamination percentages of 50% or less at day two, and three others showed signs of delamination percentages of 50% or less at day twelve. Overall, 11 of the 28 electrodes showed signs of delamination, with only three over 30% at day one or two.

V. Strain Analysis

The measured force in the strain analysis is a linear function of the displacement. The slope of the measurements is defined as the spring constant. Figure 2–11B shows the force versus displacement results and the average spring constants of 26 SC-FINEs before the polymer is applied and after they have returned to their original geometry. The difference between the spring constants before and after are not significant (two-sample t-test, $p=0.577$). The mean values for before and after are 88.1 and 85.1 mN/mm.

IV. Discussion

One of the goals of peripheral electrode technology is to safely and selectively stimulate and/or record from each axon or very small populations of axons within a common nerve trunk. Reshaping nerve geometry into a flat configuration can achieve this goal (20–22). One initial response of neural tissue to the placement of extraneural electrodes is swelling due to surgical and mechanical trauma. Therefore, it is beneficial for an electrode to have self-sizing properties such as in the spiral and the helix electrodes (31). Also, electrodes must maintain the tight nerve-electrode interface required for selective stimulation and recording once the inflammation has recovered. Moreover, in most nerves, the cross-sectional geometry of the nerve is not cylindrical, but more an elongated oval (1, 2). Therefore, the Slowly Closing-FINE design, with its self sizing properties, can maintain a tight nerve-electrode interface and a final flat shape that is well suited for selective and safe nerve stimulation.

The electrode presented in this paper is modeled with a composite beam to study the relationship between the amount of stretch and the opening height of the electrode. During the development of the model, an assumption was made that stated the inner length of the final electrode returned to the length of the original electrode. This assumption was

necessary to simplify the analysis, and was validated using experimental techniques. Very small lines were drawn on the original FINE prior to producing the SC-FINE and the distances between them were measured. The same lines were re-measured after manufacturing the SC-FINE to determine the overall length. In ten electrodes it is found that, on average, the overall interior lengths returned to the original lengths with less than 10% error. This model may prove to be very useful in the future as a tool to aid in the design of an SC-FINE electrode. One may design the electrode to fit any specific nerve diameter and expected neural insult, as well as the final opening height needed to fit the engineering need of selectivity.

The *in vitro* experimental results show that the opening height of the FINE can be increased significantly using the new composite design that combines PLGA and silicone elastomer. The new design provides additional area for nerve swelling and allows the nerve to adjust slowly to the new geometry. The average opening heights of the 50/50 PLGA and 65/35 PLGA SC-FINES are increased by a minimum of 1600%, which is sufficient to contain the nerve and allow for nerve expansion during swelling.

The differences in average opening heights between the 50/50 and 65/35 SC-FINES could be attributed to differences in the co-polymer film. Poly (lactic acid) (PLA) is a semi crystalline amorphous polymer that is used where high mechanical strength and toughness are required. The addition of more hydrophobic PLA units to the co-polymer increases the mechanical stiffness of the corresponding film (32). This increase in mechanical stiffness is evident in the 65/35 PLGA films where small cracks were observed in a small population of the 65/35 SC-FINES.

The time course of closure results show that the time for nerve reshaping can be controlled and prolonged beyond the 12 hour reshaping period of the FINE by a minimum of 16 days using the 50/50 SC-FINE. However, the opening height of both types of SC-FINES did not return to their initial value (0.102 mm). The differences in initial and final opening heights could be attributed to many different factors. One possibility is that a small residual amount of PLGA film left on the electrode could increase the opening height. However, this layer does not have the mechanical properties to maintain the curvature. Another possibility is that the increase in opening is caused by stretching the silicone elastomer beyond its elastic region. However, the results from the strain analysis study, in which the spring constants are very similar, do not support this theory. Another possibility is that the thin layer of silicon adhesive applied to the stretched FINE to seals the PLGA film to the FINE could affect the final opening height. This hypothesis was tested separately (data not shown), and the thin layer did not cause the increase in the original opening height. However, the combination of the PLGA film and thin layer of adhesive together may explain the increase in final resting opening height.

The average opening heights of the 50/50 SC-FINE *in vivo* at day 12 are 20% higher than the final opening height of the 50/50 SC-FINE *in vitro* study. The twelve day chronic period was chosen due to reports in the literature that *in vivo* degradation of PLGA films occurs faster than *in vitro* degradation (33–35). The statistical analysis between these experiments shows no differences between day 12 for the *in vitro* and *in vivo*, thus the electrodes are not fully closed by day 12 *in vivo*.

Although the 50/50 SC-FINES average opening height decreased rapidly from the initial value of 1.66 mm, it is still at least 400% larger than the original value of 0.102 mm two days after implant allowing swelling to occur. Moreover, the closure of the electrode is nearly complete by 16 days post-immersion or implant as indicated by the lack of significant differences between the opening heights at day 16 and all subsequent points. This period of

closure is similar to the duration of fibrous tissue encapsulation. Tissue encapsulation of implants depends on many factors such as the shape and size of the implant, the materials from which it is fabricated and interactions between the implant and the surrounding tissue (36). The time period for complete fibrous encapsulation is unclear but reports suggest that the acute phase of fibrin formation is complete within two weeks (36, 37), thus allowing enough time for reshaping using the 50/50 SC-FINE.

The rapid initial closure of the opening heights in both SC-FINEs could be explained by the degradation properties of the co-polymer film or by the applied stress on the degradation rate. Thin PLGA films are characterized by bulk degradation and by an autocatalytic effect. This effect has been studied in thin PLGA film of different thicknesses (10 and 100 μm) *in vitro*, and it was found that thicker films degrade faster than corresponding thin films (38). This is due to the accumulation of intermediate degradation products, such as carboxylic groups, over time in the center of the film that leads to faster central degradation (38, 39). If the autocatalytic effect occurs at the same rate in both types of films, the 65/35 PLGA film should degrade slower and have better mechanical properties compared to the 50/50 PLGA film. The autocatalytic effect plays a role in the rapid decrease in opening heights seen in both SC-FINE experiments due to the co-polymer's thickness (200 μm), but fails to explain the differences in closure periods between the 50/50 and 65/35 PLGA SC-FINEs.

By adding more hydrophobic lactic units to the PLGA ratio, slower co-polymer degradation should occur due to poly (lactic acids) limited water uptake in thin films (32). However, the results presented above do not support this mechanism since SC-FINEs made with 65/35 PLGA co-polymer reach full closure within one day compared to 16 days for the 50/50 SC-FINEs. The degradation properties could also be enhanced by the stress applied to the film by the FINE, helping to explain the rapid decrease in both SC-FINEs. Moreover, stress induced degradation could be further enhanced if the co-polymer film is weakened by the formation of a crack, thereby, explaining the fast decrease in opening heights observed in the 65/35 SC-FINEs.

The stress on the film could also generate delamination, decreasing further the closure period of the SC-FINE. The initial stages (first day or two) are the most important because most of the reshaping is accomplished in this period. However, the results suggest that the manufacturing procedure is adequate to bond the PLGA to the FINE, with only three electrodes delaminating further than 30% over all experiments on day one or two. These results suggest that the closure of the electrodes is due to the degradation and not delamination of the films.

V. Conclusions

A new composite nerve cuff electrode has been designed and tested to increase the opening height and slowly reshape peripheral nerve geometry. The original opening height of the electrode is increased by a minimum of 1600% compared to the final resting opening height by the addition of PLGA co-polymer film to the FINE. The time course of closure is determined by the properties of the biodegradable co-polymer and can be prolonged from 12 hours to a minimum of 16 days using 50/50 SC-FINEs. The degradation rates are similar *in vitro* and *in vivo*.

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APPENDIX I

COMPOSITE BEAM DERIVATION

A composite beam model was developed to determine the relationship between the amount of stretch and the opening height of the composite electrode. The electrode model consists of two identical composite beams, each corresponding to a wall of the FINE and the co-polymer film (figure 4(a)). The model is compared to preliminary data collected by stretching electrodes two millimeters using a micromanipulator.

The purpose of the model is to determine the deflection at the center of the electrode. Each beam is analyzed using standard composite beam theory (29) to determine the position of its neutral axis. The neutral axis is defined as the plane through the composite beam that has zero stress or strain. The neutral axis ($\bar{y}$) is found by scaling the width of the silicone elastomer such that the Young's modulus ratio (1) of the silicone elastomer and the PLGA co-polymer create a new homogeneous beam. Figure 4(b) shows the cross-sectional view of the original and scaled homogeneous beam. The Young's modulus for typical Silastic is 2.5 N/mm² and the modulus of the PLGA co-polymer film of thickness 0.2 mm ranges from 1400–2800 N/mm² (average 2100 ± 700 N/mm²) (Birmingham Polymers, Inc.). The average Young's modulus of the co-polymer is used in all calculations.

$$\frac{E_{\text{silicone}}}{E_{\text{co-polymer}}} = 0.00119 \quad (1)$$

The neutral axis ($\bar{y}$) is given by (29):

$$\frac{\left[(T_p \times W_p) \left(\frac{T_p}{2} \right) + (T_s + W_s) \left(\frac{T_p + T_s}{2} \right) \right]}{\left[(W_p + T_p) + (W_s + T_s) \right]} = \bar{y} \quad (\text{from the top of the beam}) \quad (2)$$

$T_{p,s}$ and $W_{p,s}$ are the Thickness and Width of the polymer and the silicone elastomer in the scaled cross-section of the composite beam as seen in figure 4(b). W_s is scaled by the ratio of the Young's modulus (1) to create the homogenous beam. The length of the neutral axis is equal to the original length of the electrode plus the applied stretch.

The deflection in the center of the each beam is symmetrical between each half of the beam because the deflection at the inflexion point is exactly half of the overall deflection in each beam (figure 4(c)). Since the deflection is symmetrical in each half of the beam, the overall deflection of the electrode can be determined by analyzing the center portion of the beam between each inflection point (between points P and Q in figure 4(c)). In order to analyze the deflection a second known length is needed in addition to the known length of the neutral axis. Assuming the inner surface of the SC-FINE returns to the original length of the FINE, because the modulus of the silicone elastomer is much less than that of the co-polymer, then a second length is known. By doing this, the deflection can be found using simple geometric equations. Start with the equation of an arch:

$$R_i = \frac{L_i}{\theta} \quad (3)$$

R_i is the interior radius of the beam and θ is the angle between the inflection points, both values are unknown, but L_i , the interior length, is a known value based on the assumption discussed above. θ is also equal to:

$$\theta = \frac{L_{NA}}{R_{NA}} \quad (4)$$

where L_{NA} and R_{NA} are the length and radius of the neutral axis, in which only the length is known. Substituting equation 4 into 3:

$$R_i = \left(\frac{L_i}{L_{NA}} \right) \times R_{NA} \quad (5)$$

R_{NA} can be defined as:

$$R_{NA} = (t + R_i) \quad (6)$$

where t is the distance between the neutral axis and the inner surface, the two known lengths. Substituting equation 6 into 5 gives an expression for the R_i :

$$R_i = \frac{t}{\left[\left(\frac{L_{NA}}{L_i} \right) - 1 \right]} \quad (7)$$

Once the inner radius is found, θ (figure 2–4D) is determined from equation 1 and halved to determine Y , the deflection of the center portion of the beam (figure 2–4D), from which the opening height can be determined using:

$$Y = \left(R_i \left(1 - \cos \left(\frac{\theta}{2} \right) \right) \right) \quad (8)$$

The overall Opening Height (OH) is given by:

$$OH = 2 \times 2Y + 0.102 \text{ (mm)} \quad (9)$$

The above equation describes the opening height of the electrode given the amount of stretch. The deflection in the center portion, Y , is doubled once to account for the symmetry of the beam, and twice to account for the symmetry of the electrode. Finally, the original opening height of the FINE is added to determine the overall opening height of the SC-FINE.

BIBLIOGRAPHY

1. Gustafsan, KJ.; Grill, WM. A Novel Neural Prosthesis for Bladder Control. Third National VA Rehabilitation Research and Development Conference; Cleveland, Ohio. 2002. 2002
2. Gustafsan, KJ.; Neville, J.; Syed, I.; Davis, JA.; Triolo, RJ. Fascicular Anatomy of the Human Femoral Nerve: Implication for Standing Neural Prostheses Utilizing Nerve Cuff Electrodes. 34th Annual NIH Neural Prosthesis Workshop; Bethesda, Maryland. 2003. 2003
3. Larsen JO, Thomsen M, Haugland M, Sinkjaer T. Degeneration and regeneration in rabbit peripheral nerve with long-term nerve cuff electrode implant: a stereological study of myelinated and unmyelinated axons. *Acta Neuropathol (Berl)*. 1998; 96(4):365–378. [PubMed: 9797001]
4. Goodall EV, de Breij JF, Holsheimer J. Position-selective activation of peripheral nerve fibers with a cuff electrode. *IEEE Trans Biomed Eng*. 1996; 43(8):851–856. [PubMed: 9216158]
5. Veraart C, Grill WM, Mortimer JT. Selective control of muscle activation with a multipolar nerve cuff electrode. *IEEE Trans Biomed Eng*. 1993; 40(7):640–653. [PubMed: 8244425]
6. Naples GG, Mortimer JT, Scheiner A, Sweeney JD. A spiral nerve cuff electrode for peripheral nerve stimulation. *IEEE Trans Biomed Eng*. 1988; 35(11):905–916. [PubMed: 3198136]

7. Sweeney JD, Ksienski DA, Mortimer JT. A nerve cuff technique for selective excitation of peripheral nerve trunk regions. *IEEE Trans Biomed Eng.* 1990; 37(7):706–715. [PubMed: 2394459]
8. Agnew WF, McCreery DB, Yuen TG, Bullara LA. Histologic and physiologic evaluation of electrically stimulated peripheral nerve: considerations for the selection of parameters. *Ann Biomed Eng.* 1989; 17(1):39–60. [PubMed: 2537589]
9. Grill WM, Kirsch RF. Neuroprosthetic applications of electrical stimulation. *Assist Technol.* 2000; 12(1):6–20. [PubMed: 11067578]
10. Altman KW, Plonsey R. Point source nerve bundle stimulation: effects of fiber diameter and depth on simulated excitation. *IEEE Trans Biomed Eng.* 1990; 37(7):688–698. [PubMed: 2394457]
11. Veltink PH, van Alste JA, Boom HB. Multielectrode intrafascicular and extraneural stimulation. *Med Biol Eng Comput.* 1989; 27(1):19–24. [PubMed: 2779293]
12. Veltink PH, van Veen BK, Struijk JJ, Holsheimer J, Boom HB. A modeling study of nerve fascicle stimulation. *IEEE Trans Biomed Eng.* 1989; 36(7):683–692. [PubMed: 2744792]
13. Bowman BR, Erickson RC 2nd. Acute and chronic implantation of coiled wire intraneural electrodes during cyclical electrical stimulation. *Ann Biomed Eng.* 1985; 13(1):75–93. [PubMed: 3873885]
14. Branner A, Stein RB, Normann RA. Selective stimulation of cat sciatic nerve using an array of varying-length microelectrodes. *J Neurophysiol.* 2001; 85(4):1585–1594. [PubMed: 11287482]
15. Meier JH, Rutten WL, Boom HB. Force recruitment during electrical nerve stimulation with multipolar intrafascicular electrodes. *Med Biol Eng Comput.* 1995; 33(3 Spec No):409–417. [PubMed: 7666688]
16. Nannini N, Horch K. Muscle recruitment with intrafascicular electrodes. *IEEE Trans Biomed Eng.* 1991; 38(8):769–776. [PubMed: 1937510]
17. Rutten WL, Meier JH. Selectivity of intraneural prosthetic interfaces for muscular control. *Med Biol Eng Comput.* 1991; 29(6):NS3–NS7. [PubMed: 1813744]
18. Yoshida K, Horch K. Selective stimulation of peripheral nerve fibers using dual intrafascicular electrodes. *IEEE Trans Biomed Eng.* 1993; 40(5):492–494. [PubMed: 8225338]
19. Peters, A.; Palay, S. *The Fine Structure of the Nervous System: Neurons and their Supporting Cells.* New York, New York: Oxford University Press; 1991. *Connective Tissue Sheaths of Peripheral Nerves*; p. 384–394.
20. Tyler DJ, Durand DM. Functionally selective peripheral nerve stimulation with a flat interface nerve electrode. *IEEE Trans Neural Syst Rehabil Eng.* 2002; 10(4):294–303. [PubMed: 12611367]
21. Leventhal, DK.; Durand, DM. Subfascicle Stimulation Selectivity Using a FINE. *Engineering in Medicine and Biology Society; Proceedings of the 22nd Annual International Conference of the IEEE*; 2000. 2000.
22. Perez-Orive J, Durand DM. Modeling study of peripheral nerve recording selectivity. *IEEE Trans Rehabil Eng.* 2000; 8(3):320–329. [PubMed: 11001512]
23. Lundborg G, Dahlin LB. Anatomy, function, and pathophysiology of peripheral nerves and nerve compression. *Hand Clin.* 1996; 12(2):185–193. [PubMed: 8724572]
24. Tyler DJ, Durand DM. Chronic Response of Rat Sciatic Nerve to the Flat Interface Nerve Electrode. *Ann Biomed Eng.* 2003
25. Lamprecht A, Rodero Torres H, Schafer U, Lehr CM. Biodegradable microparticles as a two-drug controlled release formulation: a potential treatment of inflammatory bowel disease. *J Control Release.* 2000; 69(3):445–454. [PubMed: 11102684]
26. Kim HK, Park TG. Microencapsulation of dissociable human growth hormone aggregates within poly(D,L-lactic-co-glycolic acid) microparticles for sustained release. *Int J Pharm.* 2001; 229(1–2):107–116. [PubMed: 11604263]
27. Lu L, Mikos AG. The importance of new processing techniques in tissue engineering. *MRS Bull.* 1996; 21(11):28–32. [PubMed: 11541498]
28. Tyler, DJ.; Durand, DM. Functionally selective stimulation of peripheral nerves: electrodes that alter nerve geometry [PhD]. Cleveland, OH: Case Western Reserve University; 1999.
29. Popov, E. *Engineering Mechanics of Solids.* 2 ed.. Upper Saddle River, New Jersey 07458: Prentice-Hall, Inc.; 1999.

30. Voskerician G, Shive MS, Shawgo RS, Recum H, Anderson JM, Cima MJ, et al. Biocompatibility and biofouling of MEMS drug delivery devices. *Biomaterials*. 2003; 24(11):1959–1967. [PubMed: 12615486]
31. McNeal DR, Waters R, Reswick J. Experience with implanted electrodes. *Neurosurgery*. 1977; 1(2):228–229. [PubMed: 308202]
32. Kohn, J.; Langer, R. Bioresorbable and Bioerodible Materials. In: Ratner, B.; Hoffman, A.; Schoen, F.; Lemons, J., editors. *Biomaterials Science*. San Diego, California: Academic Press; 1996. p. 64-72.
33. Cam D, Hyon SH, Ikada Y. Degradation of high molecular weight poly(L-lactide) in alkaline medium. *Biomaterials*. 1995; 16(11):833–843. [PubMed: 8527598]
34. Tracy MA, Ward KL, Firouzabadian L, Wang Y, Dong N, Qian R, et al. Factors affecting the degradation rate of poly(lactide-co-glycolide) microspheres in vivo and in vitro. *Biomaterials*. 1999; 20(11):1057–1062. [PubMed: 10378806]
35. Lu L, Peter SJ, Lyman MD, Lai HL, Leite SM, Tamada JA, et al. In vitro and in vivo degradation of porous poly(DL-lactic-co-glycolic acid) foams. *Biomaterials*. 2000; 21(18):1837–1845. [PubMed: 10919687]
36. Grill WM, Mortimer JT. Electrical properties of implant encapsulation tissue. *Ann Biomed Eng*. 1994; 22(1):23–33. [PubMed: 8060024]
37. Anderson JM. Inflammatory response to implants. *ASAIO Trans*. 1988; 34(2):101–107. [PubMed: 3285869]
38. Lu L, Garcia CA, Mikos AG. In vitro degradation of thin poly(DL-lactic-co-glycolic acid) films. *J Biomed Mater Res*. 1999; 46(2):236–244. [PubMed: 10380002]
39. Kranz H, Ubrich N, Maincent P, Bodmeier R. Physicomechanical properties of biodegradable poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) films in the dry and wet states. *J Pharm Sci*. 2000; 89(12):1558–1566. [PubMed: 11042603]

Figure 1. FINE Design

A three dimensional drawing of the Flat Interface Nerve Electrode, showing the opening for the nerve and its dimensions, Width, Length, Thickness, Opening Height and position on the sciatic nerve.

Figure 2. Annotated Manufacturing Steps of the SC-FINE

(a) The FINE. (b). The FINE is stretched and a thin 200 μm PLGA film is attached. (c). The stretch is released and the FINE springs into a new geometry created by the addition of the PLGA film, with a new opening height. (d). Over time in an aqueous medium the PLGA film is weakened and the FINE relaxes back to its original geometry and hence reshaping the nerve that is passing through the electrode.

Figure 3. Example SC-FINE and the Measurement of Delamination of PLGA Film

(a). Picture of a 50/50 PLGA SC-FINE at day zero, from the digital image the opening height of the center portion of the electrode is determined. Also, the PLGA film is shown with no delamination. (b). Picture of same electrode from (a) but the film on top of the electrode is curling on one end and has delaminated from the electrode; this amount of delamination is assigned a percentage of 10%. On the bottom portion the film is curled in one area and no delamination has occurred, therefore no percentage is assigned.

Figure 4. Composite Beam Model

(a). Three dimensional drawing of the Slowly Closing Flat Interface Nerve Electrode (SC-FINE) and half of the SC-FINE to show the electrode's symmetry. (b). Cross-section of the one side of the electrode showing the dimensions of the original composite beam and the scaled composite beam to determine the neutral axis. (c). Drawing of the beam with two fixed ends, also shown is the curvature of the SC-FINE. The symmetry of the electrode reduces the model so that the area between points P and Q can be analyzed to determine the deflection. (d). Magnified view of the box in C, showing the parameters of the model, Y is the deflection that determines the overall deflection of the SC-FINE.

Figure 5. Mechanical Characterization of the Experimental FINEs

The apparatus to measure the FINE force as a function of displacement. The electrode is attached to a cantilever strain gauge that measures the force to displace the electrode.

Figure 6. Histograms of Opening Heights for Each of the Experiments

(a). New opening heights for forty-four in-vitro 50/50 PLGA SC-FINES. (b). New opening heights for ten in-vitro 65/35 PLGA SC-FINES. (c). New opening heights for 28 PLGA SC-FINES for an in-vivo experiment. All three sets of electrodes were processed using the same method.

Figure 7. Time Course of Closure for an 50/50 PLGA SC-FINE

A typical example of one SC-FINE's time course of closure over a twenty-eight day period using 50/50 PLGA co-polymer.

Figure 8. Average Time Course of Closure of the SC-FINEs

(a). Chart shows the average and standard deviation for each day of the closure period for 16 50/50 PLGA SC-FINEs, with 90% closure occurring 16 ± 1 days post immersion in DPBS maintained at 37°C . (b). Average closure period for ten 65/35 PLGA SC-FINEs, with 90% closure of the electrode occurring between 14 and 16 hours post immersion. The expanded view is the closure period over the first day of immersion. (c). Average reshaping period of 28 50/50 PLGA SC-FINEs explanted on days two and twelve from a chronic subcutaneous implant in rats.

Comparison Plot of Opening Heights

Figure 9. Comparison of Opening Heights

Chart shows opening heights for day zero, two and twelve for all three experiments, 50/50 *in-vitro*, *in-vivo* and 65/35 *in-vitro*. The 50/50 PLGA SC-FINEs *in-vitro* and *in-vivo* show no statistical differences from one another on each day compared. An Anova general linear statistical model was used with a Tukey comparison ($p = 0.08$). The 65/35 PLGA SC-FINEs showed a statistical difference from both the 50/50 electrode experiments (50/50 *in-vitro* $p = 0.006$, 50/50 *in-vivo* $p = 0.036$).

Figure 10. Delamination Percentages for Each Experiment

(a). Sixteen 50/50 PLGA SC-FINEs were monitored for delamination throughout the reshaping period. A total of eight electrodes showed delamination of less than 30% on day one and maintained that percentage of delamination through day 10. Two other electrodes showed a 50% delamination after a 10 day period of immersion. (b). Ten 65/35 PLGA SC-FINEs were monitored and total of four electrodes showed delamination percentage on day one of 40% or less. All of these percentages increased by day 10. (c). Twenty-eight 50/50 PLGA SC-FINEs were monitored at day two and twelve after explant. Eight of the 14 electrodes explanted on day two showed delamination percentages of 50% or less, and 3 of the 14 electrodes explanted on day twelve showed delamination percentages of 50% or less.

Figure 11. Stiffness Measurement

The stiffness analysis is done with the FINE (before immersion) and with the SC-FINE (after immersion) completely reshaped. The results show no statistical difference between the slopes of the two sets of electrodes. The average slopes are 88.10 mN/mm ($n = 30$) and 85.34 mN/mm ($n = 30$) for the before and after FINEs and SC-FINEs respectively.

Table 1

Comparison of opening heights between the model predictions and the experimental data

Opening Height	Amount of Stretch	
	1 mm	2 mm
Predicted	0.87	1.63
Measured	0.81 ± 0.23	1.66 ± 0.48