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Research Paper - Peripheral Nerve Interfaces for Neuroprostheses

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Silicone Molding and Lifetime Testing of Peripheral Nerve Interfaces for Neuroprostheses

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Abstract

Implantable peripheral nerve cuffs have a large application in neuroprostheses as they can be used to restore sensation to those with upper limb amputations. Modern day prosthetics, while lessening the pain associated with phantom limb syndrome, have limited fine motor control and do not provide sensory feedback to patients. Sensory feedback with prosthetics requires communication between the nervous system and limbs, and is still a challenge to accomplish with amputees. Establishing this communication between the peripheral nerves in the arm and artificial limbs is vital as prosthetics research aims to provide sensory feedback to amputees. Peripheral nerve cuffs restore sensation by electrically stimulating certain parts of the nerve in order to create feeling in the hand. Cuff electrodes have an advantage over standard electrodes as they have high selective stimulation by bringing the electrical interface close to the neural tissue in order to selectively activate targeted regions of a peripheral nerve. In order to further improve the selective stimulation of these nerve cuffs, there is need for finer spatial resolution among electrodes. One method to achieve a higher spatial resolution is to increase the electrode density on the cuff itself. Microfabrication techniques can be used to achieve this higher electrode density. Using L-Edit, a layout editor, microfabricated peripheral nerve cuffs were designed with a higher electrode density than the current model. This increase in electrode density translates to an increase in spatial resolution by at least one order of magnitude. Microfabricated devices also have two separate components that are necessary to understand before implantation: lifetime of the device and assembly to prevent nerve damage. Silicone molding procedures were optimized so that devices do not damage nerves *in vivo,* and lifetime testing was performed on test microfabricated devices to determine their lifetime *in vivo.* Future work of this project would include fabricating some of the designed devices and seeing how they compare to the current cuffs in terms of their electrical performance, lifetime, shape, and mechanical properties.

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Introduction

Every year, an estimated 185,000 people undergo upper or lower limb amputations [1]. Accounting for mortality and other factors, this is equivalent to around 2 million people living with amputations currently in the United States, of which almost 600,000 with hand and upper extremity limb loss [1]. Upper limb amputations can be extremely devastating to a patient; in addition to loss of sense and function, patients have trouble with both self-image and phantom limb pain [2, 3]. Artificial limbs have been able to solve most of these challenges, including increasing self-esteem and reducing pain associated with phantom limb syndrome. However, restoring sensory function of the hand and arms requires communication between the limbs and the nervous system, and has thus been and still is a challenge today. Recent advances in the research of peripheral nerve interfaces, specifically flat interface nerve cuff electrodes (CFINE), have demonstrated their potential in providing long term sensory feedback to upper limb amputees.

The peripheral nervous system consists of a network of nerves that connect the brain and spinal cord to the rest of the body, including the muscles and skin. The brachial plexus nerve network begins in the neck and branches out to smaller nerves that control movement and sensation in the upper arm [4]. The radial, median and ulnar nerves are the three major nerves that innervate the front and back of the hand and provide sensation and movement to those areas. Figure 1 shows the dermatome map of the human hand, describing which of the three nerves provides sensation and movement to different areas on the hand and palm. This figure shows that all three nerves innervate a different part of each hand, indicating that these nerves would all need to be stimulated in order to provide overall sensation in each hand.

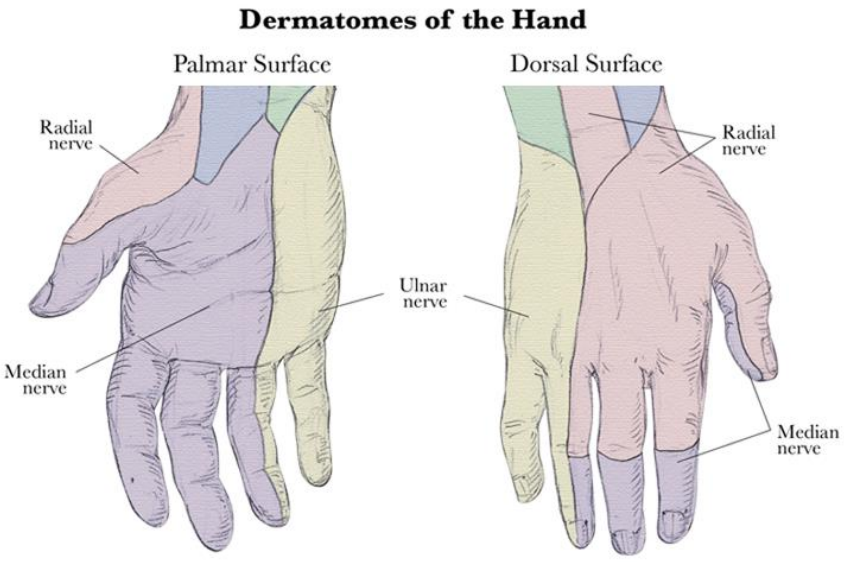

Figure 1: Dermatomes of the Hand, showing innervation of radial, ulnar and median nerves to various parts of the hand. *Source: Busti, Anthony J., MD. Dermatomes of the Hand. Digital image. EBM Consult. N.p., June 2015. Web.*

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The ability to electrically stimulate parts of peripheral nerves is possible in large part due to the geometry and shape of peripheral nerves. The basic building block of the nervous system is the nerve cell, or neuron. Neurons have three main parts to them: the cell body, dendrites and the axon. The cell body and dendrites are at the terminal ends of the neuron and are essential as they contain cellular organelles and receive inputs to the cell, respectively. The axon lies in between these two parts of the neuron and are capable of transmitting an impulse from the cell body to other neuronal cells. Building up from the bottom, axons wrapped in neural tissue are bundled together into what are called fascicles, which are then wrapped in neural tissue. Multiple fascicles constitute a whole nerve. Peripheral nerves are flat or elongated rather than cylindrical in their cross-section [5]. The organization of the nerves is such that having an elongated cross-section would allow fascicles to be lined up side by side more so than in a cylindrical cross-section.

The CFINE is used as the peripheral nerve interface for this application both due to the geometry of the peripheral nerves and the properties of the CFINE itself. These flat interface nerve cuff electrodes are designed from two independent electrodes: the flat interface nerve electrode (FINE) and the cuff electrode. Cuff electrodes come in a variety of shapes and sizes, but their basic principle is to wrap around the trunk of a nerve [6]. By having close contact between the electrodes and the neural tissue, lower stimulation is necessary to send current down a nerve fiber [6]. Flat interface nerve electrodes (FINE) are rectangular in shape and have electrodes laid across their cross-section. Two FINE pieces that are connected either through molding or fabrication create a cuff, or the CFINE. While one side of the cuff is connected during buildup of the device, the other side is sutured together once the cuff has been placed on a nerve. When placed on a peripheral nerve, the CFINE applies small forces that further flatten and elongate the nerve without causing damage or changing its natural shape [5]. By only applying forces on the two sides of the nerve, these nerve cuffs increase the surface area for contact and allow better access to the fascicles [7]. When the cuff in properly in place, current can be passed through the electrodes to stimulate the fascicles in the region where each electrical contact nears the nerve. The flattening of the nerve prevents applied current from travelling aimlessly in physiological fluid.

With better access to the fascicles in the nerve, CFINEs can provide more selective stimulation. Contacts on the CFINE are selective to, and align with innervation areas from different parts of the median, ulnar and radial nerves [7]. With a larger surface area on the nerve, the fascicles are realigned within the electrode, so that there is fascicular selectivity [8]. With this increase in selectivity, there is more certainty that the contacts on the cuff can access the desired region of the nerve to stimulate different regions in the hand. Figure 2 shows two different images of the CFINE: the top image shows a dimensional view of the cuff and the bottom image shows how the CFINE is placed on a nerve.

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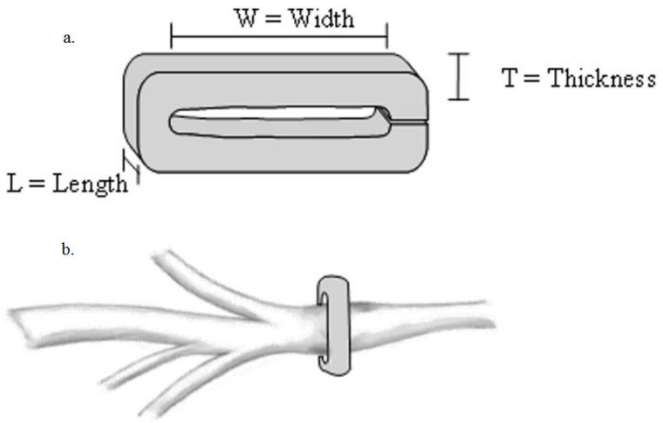

Figure 2: a. CFINE design drawing with dimensions b. Positioning of CFINE on sciatic nerve of a cat. *Source: [8]*

In addition to designing the CFINE with the right specifications, there are other factors that need to be addressed before the electrodes can be implanted in the body. Since these electrodes function to restore sensation in upper limb amputees, they need to survive for the lifetime of the patient. Lifetime testing of the electrodes needs to be performed in order to ensure that they can survive *in vivo* for a long period of time. To test this, electrodes undergo lifetime pulsing in a saline solution to see how they function under conditions close to their intended application. When implanted, not only should these cuffs function for the lifetime of the patient, but they should also not damage the nerves. Encapsulating the device in silicone will need to occur so that when implanted, the sharp edges of the device do not damage the nerves. The silicone molding process needs to be refined so that the device is properly covered in silicone to ensure no damage will come to the nerve.

Methods

Microfabricated Cuff Electrodes

In order to microfabricate peripheral nerve cuff devices with a higher electrode density than current models, these devices must first be designed and imported onto mask files. To design these devices, a program called L-Edit is used. L-Edit is a layout editor used to draw two dimension versions of masks for integrated circuit fabrication. Since microfabricated devices follow the same microfabrication process as integrated circuit and semiconductor devices, L-Edit can be used to draw out the individual layers and design of the device before it is turned into a mask. Once the masks are designed, they are used as guidelines for etching the devices onto silicon wafers. Biocompatible metals are used for the electrode and trace regions of the devices, whereas biocompatible polymers are used to fill the edges of the device and the spaces between both traces and electrodes. The polymer also functions to insulate and protect the metal traces and electrodes.

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Silicone Molding

After the devices are released from wafers, they are encapsulated in silicone so that they will not damage the nerves when implanted in the arm. The molding process is a manual, single-device procedure, so each device must be individually molded in the silicone. For this process, the type of silicone chosen is extremely important. As this implant is designed to be in use long term, the silicon needs to be medical grade, biocompatible, and reliable for long term implantation. It is also important to note the stiffness of the cured silicone; if the silicone is too stiff, it could break and expose the electrodes, whereas if it was too flexible, if would be extremely difficult for the surgeon to place on the nerve.

Proper mixing of the silicone is fundamental to the molding process. The silicone is first measured out in a defined ratio that will allow the silicone to not be too flexible or too stiff when cured. While there is a suggested ratio for each type of silicone, the best ratio will be determined through trial and error. Once the silicone has been measured out, it is placed in a silicone mixer where it is spun at high speeds under vacuum to remove air bubbles and thoroughly mix the two components. The device is placed in a block mold designed specifically for each segment of the device and silicone is injected. Once the device is covered in silicone, the mold is placed in an oven so that the silicone can completely cure. Afterwards, the device is ready for testing or implantation.

Lifetime Testing

One of the biggest challenges that these neural interfaces have to overcome is longevity. Since restoration of sense and function of the upper limbs is necessary for the patient's lifespan, the electrodes need to be reliable for the entire time that they are in use. Standard reliability test would be too time-consuming as there is no realistic way to test the lifetime of the interfaces. In this case, accelerated lifetime testing can be performed.

There are two methods of failure in implantable microfabricated devices: failure of the polymer or failure of the electrodes. Since these devices will be implanted in the arm, they will be in constant contact with physiological saline. Since polymers adsorb moisture and ions over time, using these accelerated soak tests to determine how long the device can survive before the polymer insulation fails due to moisture uptake is important.

Devices are tested by having the insulated regions of the device submerged in PBS, a buffer solution that mimics physiological fluid. The device is placed under higher temperature conditions in order to accelerate the soak test. Over time, impedance analysis is used to determine whether moisture has been adsorbed by the polymer, causing device failure.

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Results and Discussion

Silicone Molding

Developing the recipe for mixing and the ratio for the silicone took many trials and tests. While the exact values for the ratio and mixer recipes are proprietary to the lab, the methods used to obtain these results speak to the success of this process.

To determine the proper ratio for mixing silicone so that it would have the correct stiffness for its application took multiple trials. Previous trials for this process had found that the suggested ratio created silicone that was too stiff for encapsulating the devices. Silicone that is too stiff could pose issues during implantation, if the surgeon has trouble maneuvering the device to where it needs to be, or it could crack and expose the device when implanted. With this information, the ratio was cut in half and the silicone was measured, mixed and injected into the mold to encapsulate the device. The cured silicone was too flexible for the device, which would make guiding the device during implantation difficult. The original ratio was tested again, and was found to possess the proper level of stiffness for device application.

The mixing recipe was the other aspect of the silicone molding process that needed adjusting. The recipe was altered to include a variety of different speeds and pressures, and the silicone was mixed to determine the quality of the silicone given each change in recipe. It was determined that mixing the silicone at faster speeds under vacuum for a couple minutes was the best way to ensure that no bubbles are present in the silicone. The working recipe that is currently being tested mixes the silicone at a speed that increases at constants interval until it reaches the fastest rate under vacuum.

Lifetime Testing

The two devices that were tested under the setups described in the methods section are currently still running. Until there is electrode failure or leakage in the electrode array, there is uncertainty in the lifetime of the electrode. However, for the length of time that the electrodes have undergone clinical lifetime pulsing, these devices can survive in vivo. The device that was tested under this setup survived 70 days in accelerated conditions, which is equivalent to more than 6 years of pulsing at body temperature.

Conclusion/Future Work

In order to design neural electrodes that can be implanted in the arm to restore sensation, developing the silicone molding process and performing electrode lifetime testing is extremely important. The improvement in silicone molding ensures that the device, when implanted, functions properly without damaging nerves. In addition, testing the lifetime of the electrodes makes certain that the devices can survive for long periods of time in vivo. Understanding these

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two aspects of neural interfaces will help further this project as it moves towards fabrication and testing of demo devices.

With the development of the silicone mixing process, this project can continue and focus on designing a proper mold for the CFINE devices. Using the layout and design of the devices, a plastic mold will be created that will assemble the cuff together. The mold should be designed such that the electrodes will not be covered in silicone and the region that connects the two sides of the cuff is flexible enough that it can be bent and sutured together without interfering with the nerve or the electrodes on the device.

Once the design of the device is finalized, the next step will be to fabricate demo devices. Lifetime testing and silicone molding procedures can be performed on these devices in order determine their lifetime and ensure that the devices will not cause any nerve damage. Once the testing and molding procedures are done on these devices, they can also be compared to the current cuffs in order to see how their electrical and mechanical performances compare.

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References

1. Ziegler-Graham, Kathryn, Ellen J. Mackenzie, Patti L. Ephraim, Thomas G. Travison, and Ron Brookmeyer. "Estimating the Prevalence of Limb Loss in the United States: 2005 to 2050." Archives of Physical Medicine and Rehabilitation 89.3 (2008): 422-29. Alegin Faith Foundation. Web.
2. Candido, K. D., GC Chang Chien, and Z. McCormick. "Phantom Limb Pain." *Encyclopedia of the Neurological Sciences (2nd Edition)* (2014): 878-83. *Science Direct*. Web.
3. Marasco, P. D., K. Kim, J. E. Colgate, M. A. Peshkin, and T. A. Kuiken. "Robotic Touch Shifts Perception of Embodiment to a Prosthesis in Targeted Reinnervation Amputees." *Brain* 134.3 (2011): 747-58. *Oxford University Press*. Web.
4. Mayo Clinic Staff. "Brachial Plexus Injury." Mayo Clinic. Mayo Foundation for Medical Education and Research, 17 Mar. 2015. Web. 02 May 2016.
5. Tyler, D.J., and D.M. Durand. "Functionally Selective Peripheral Nerve Stimulation with a Flat Interface Nerve Electrode." IEEE Trans. Neural Syst. Rehabil. Eng. IEEE Transactions on Neural Systems and Rehabilitation Engineering 10.4 (2002): 294-303. Web.
6. Loeb, G.E, and R.A. Peck. "Cuff Electrodes for Chronic Stimulation and Recording of Peripheral Nerve Activity." Journal of Neuroscience Methods 64.2 (1996):95-103. Web.
7. Choi, A.Q., J.K. Cavanaugh, and D.M. Durand. "Selectivity of Multiple-contact Nerve Cuff Electrodes: A Simulation Analysis." IEEE Transactions on Biomedical Engineering IEEE Trans. Biomed. Eng. 48.2 (2001): 165-72. Web.
8. Caparso, A. V., D. M. Durand, and J. M. Mansour. "A Nerve Cuff Electrode for Controlled Reshaping of Nerve Geometry." Journal of Biomaterials Applications 24.3 (2008): 247-73. Web.

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