# NEURAL CONTROL OF ARTIFICIAL LIMBS

by

Gurpreet Singh Dhillon

A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Bioengineering

The University of Utah

August 2011

The University of Utah Graduate School

## STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Gurpreet Singh Dhillon**

has been approved by the following supervisory committee members:

| | | |
|---|---|---|
| **Richard D. Rabbit** | , Chair | **11/28/2010** Date Approved |
| **Kenneth W. Horch** | , Member | **12/27/2010** Date Approved |
| **Sanford G. Meek** | , Member | **11/30/2010** Date Approved |
| **Douglas T. Hutchinson** | , Member | **12/14/2010** Date Approved |
| **William B. Rockwell** | , Member | **12/2/2010** Date Approved |

and by **Richard D. Rabbit** , Chair of

the Department of **Bioengineering**

and by Charles A. Wight, Dean of The Graduate School.

## ABSTRACT

Upper limb amputees desire an artificial arm that allows for multiple degrees of freedom of control over the movements of the prosthesis, coupled with direct sensory feedback. The goal of this work was to assess if it is feasible to interface artificial limbs to severed nerves of human upper limb amputees. Longitudinal intrafascicular electrodes were interfaced to severed nerve stumps of long-term human amputees. Initial studies conducted for two days following electrode implantation showed that it is possible to provide discrete, unitary, painless, graded sensations of touch, joint movement and position referred to the missing limb. Amputees were able to generate and control motor nerve activity uniquely associated with the missing limb movements. Longer term studies conducted for a period of up to 4 weeks showed recorded motor nerve activity and elicited sensations remained stable and there was no significant change in the stimulation parameters. Finally, amputees were able to control a modified Utah Artificial Arm. Results of our studies show that it is possible to interface an artificial limb to the severed nerves of upper limb amputees. Further work is required to refine the hardware which can be eventually incorporated into the artificial arm, allowing the amputees to wear the prosthesis and more precisely execute movements related to real life activities of daily living.

I dedicate this dissertation to my parents Gian and Gurbax Dhillon

and my grandfather Darshan S. Dhillon.

TABLE OF CONTENTS

## ACKNOWLEDGMENTS

I would like to thank my mentor Professor K. W. Horch without whom this project would not have been possible. My special thanks to Professor R.D. Rabbitt who gave me the opportunity to complete the written portion of this work, whilst I was in surgical residency. I am very grateful to my friend and colleague Dr. Stephen Lawrence who conducted this project with me. I thank all my committee members for their suggestions and guidance for successful completion of this project. Last but not least, thanks to my parents.

# CHAPTER 1

# INTRODUCTION

## Need for a More Naturally Controlled Artificial Limb

The aim of this dissertation research is to investigate if it is possible to develop a neurally controlled artificial arm for use by upper limb amputees. Actuators in the artificial arm will be controlled by motor nerve signals recorded via microelectrodes implanted in the nerve stumps. Sensory channels will be interfaced to the sensors in the artificial hand to provide tactile and proprioceptive feedback. Our aim is to provide smooth dexterous control of movements, such as graded pinch, elbow and wrist control. Success of this work will ultimately lead to the development of a more complex artificial arm, for use by upper limb amputees.

Between 1988-1996, 165,000 upper limb amputations were performed [1]. Upper limb amputations account for a majority (>68%) of the trauma related amputations. Approximately 23% and 69% of upper limb amputees are above and below the elbow, respectively [2]. A 1977 estimate cited approximately 358, 000 amputees of all types in the United States. Given the number of amputations performed annually, this figure has probably doubled over the last 30 years.

In both males and females, risk of traumatic amputations increases with age [1]. In addition to financial burden on the health care system and functional limitations, loss of limb results in serious psychological problems for amputees, which include diminished self-esteem, distortion of body image, depression and increased social isolation. Most of the amputees are of good health and have the potential to make positive contributions to society and their own welfare.

A majority of the upper limb amputees use either a body powered or battery operated prosthesis. The body powered prosthesis is controlled by gross body movements, usually related to the shoulder, chest or the residual arm stump. A system of cables operates the terminal device as either voluntary opening (the prehensor is normally closed) or voluntary closing modes. The body powered prosthesis is relatively cheap, rugged, and can be operated in harsh environment. Some amputees report indirect kinesthetic feedback which is probably provided through the system of cables used to control the terminal device [3, 4]. The externally powered or myoelectric arm is controlled by the EMG recorded by cutaneous electrodes placed on the amputees' residual stump muscles [5]. Neither the body powered nor the myoelectric systems allow the amputees to execute simultaneous, multiple-degree-of-freedom of control over the movements of the artificial arm (Childress, 1973 #458;Sears, 1991 #497;Jacobsen, 1982 #472) or provide sensory feedback.

LeBlanc states that only 50% of arm amputees wear a prosthesis of any type [2]. This may be due to the deficiency of the prosthetic control systems to provide the amputees with a more natural prosthesis that allows greater control over the terminal device, lack of prehension feedback and deficiency of simultaneous multidegree freedom of control [6]. Given the limitations of current upper limb prostheses, the type of artificial arm the amputees use is therefore guided by their work environment, social interactions, prosthesis reliability and ability to pay. For example, due to insufficient sensory feedback and the fragility of the artificial arm, the usefulness of the myoelectric prosthesis is limited in the industrial environment and the instead the amputees prefer to use the rugged body powered system [7]. Despite its shortcomings, more than 60% of amputees prefer the use of myoelectric prosthesis due to a combination of superior function and range of movements over the body powered system [8].

A survey by the Institute for Rehabilitation and Research revealed that both the upper and lower limb amputees desired a prosthesis that provided prehension feedback, greater control over the terminal device and allowed for execution of multiple, simultaneous movements [6]. Possible options include a more advance development of the myoelectric prosthesis, hand transplantation, limb regeneration or interfacing the arm to the amputee's nerve stumps.

## Peripheral Nerves, Motor Control, and Sensory Feedback

Mixed peripheral nerves are composed of motor and sensory neurons, which are organized into fascicles. Each fascicle is surrounded by a mechanically strong sheath, called the perineurium, comprised of flattened cells. This layer acts as a nerve-blood barrier and creates a local milieu of filtered plasma ions and proteins which bathe the delicate networks of neurons and supporting cells. A loose connective tissue called the epineurium binds together different fascicles into a nerve trunk. Fascicular pattern for a nerve trunk can be monofascicular (one large fascicle), oligofascicular (2-10 fascicles) and polyfascicular (>10).

Axons in the corticospinal tracts, which originate from the motor cortex, synapse with large diameter (~12 µm) myelinated peripheral nerve motor neurons ($A\alpha$) in the ventral horn of the spinal cord. Volitional commands from the motor cortex (which also receives inputs from the cerebellum, basal ganglia, higher centers and sensory cortex) can therefore be used to initiate or modify a limb movement. Sensory neurons in the peripheral nerve trunk enter the spinal cord by the way of the dorsal horn. In general, neurons that mediate proprioceptive feedback travel in the dorsal columns and those mediating temperature and painful sensations ascend in the spinothalamic tracts, to the thalamus and then to the sensory cortex. Nerve fibers that convey sensations from upper and lower extremities vary in sizes—large diameter myelinated fibers (Aβ, 6-12 μm) mediate sensations of touch and proprioception, whereas small diameter myelinated (Aδ, 1-6 μm) and unmyelinated (C fibers, <1 μm) neurons mediate temperature and painful sensations [9]. Furthermore, electrical stimulation preferentially activates larger diameter neurons, opening the possibility of selectively providing unimodal, painless sensations of touch and proprioception. In normal nerves, frequency of neural firing correlates with the intensity of a perceived sensation; therefore, tactile and position feedback from an artificial limb can be graded through modulation of frequency of nerve stimulation.

## Alternatives to Neurally Interfaced Artificial Arm

In principle, any system that provides graded sensory feedback referred to the missing limb and allows for simultaneous multidegree freedom of control can provide the amputee with a prosthesis which can be operated more naturally than what is available in current clinical practice.

## Multidegree Freedom of Control Using Electromyography

Myoelectric approaches include the Utah Artificial Arm, Ottobock Hand and Southampton Hand [5, 10-12]. Given that the Utah Artificial Arm has been cited as the most successful upper limb prosthesis, further research has been conducted to improve its performance to allow the amputee to execute simultaneous, multidegree freedom of control. Work by Drs. Sanford Meek and Steve Jacobson at the University of Utah involved placement of multiple electrodes over the chest and the stump muscles (up to 15 EMG sites). Five independent torques could be generated simultaneously [13]. Similar work has been conducted with other myoelectric protheses [14]. Although these systems worked well in the laboratory setting, they were considered too cumbersome for practical applications. Furthermore, the movements made by the amputee were not synonymous with intended movements of the prosthesis. Even if such a system could be implemented clinically, the problem of sensory feedback will remain.

### Tendon Movements to Control Limb Prosthesis

More recently, investigators have developed the Biomimetic Dextra Hand Prosthesis [15]. The system employs sensors to detect tendon movements in the limb stump, and through a microcontroller employing the use of residual kinetic imaging (RKI), translates this motion into individual digit movements of an artificial hand [15-17]. Unfortunately, the technology may be limited by the length of the forearm stump (muscle to tendon transition occurs in the distal half of the forearm) and extensive fibrosis resulting in unwanted movement of adjacent tendons. Furthermore, the system does not cater for sensory feedback. There are no long-term reports of the success of this prosthesis, although it has received positive attention in the lay press.

Providing Sensory Feedback

With a readily available myoelectric arm, researchers attempted to provide sensory feedback to allow amputees to execute closed loop control over the limb prosthesis. Of the methods investigated, some of the approaches included provide sensory feedback through cutaneous stimulation at the stump [18-24]. Both vibrotactile and electrocutaneous methods for providing sensory feedback have been extensively investigated in the laboratory setting [21-24]. These methods utilize frequency or amplitude modulation as methods for providing graded feedback. Since feedback is provided to the skin at the stump site, the amputee will have to learn to correlate sensation(s) at the stump with the perception(s) at the gripper. These systems have been incorporated into a functioning myoelectric prosthesis, but never materialized to a clinical application, as they were beset by a number of problems. These included limited channels of information transfer (at most 2), due to cross talk between stimulating channels, skin adaptation to the stimulus, variation in sensation due to movement between the device and the skin, relatively large power consumption mandating a bulky prosthesis or frequent battery changes, and difficulties with miniaturization of the mechanical feedback systems [21, 23, 25]. Many of these experiments were conducted in the 1970s and it can be argued that some of the impediments can be overcome with current technology, but due to advances in alternative, evolving technologies, researchers have seemed to have lost interest in mechanical sensory feedback systems.

Therefore, to date, it seems that multidegree freedom of control through EMG is not possible in clinical settings and neither is natural sensory feedback provided through stimulation of the skin at the stump site.

## Impediments to Interfacing Artificial Arm or Composite Tissue to Nerve Stumps

Evolution of neurally interfaced artificial limb technology has been hampered by a number of drawbacks which have included shortcomings in neural interface technology and problems associated with pathological changes in the nerve stump. Issues related with immunosupression and nerve regeneration have hindered progress of limb transplantation.

### Degeneration of the Proximal Nerve Stump

In normal intact nerves, using microneurography, stimulation of single sensory neurons has been shown to produce discrete, unimodal, tactile sensations referred to the nerve's innervation territory [26-28]. Similarly, stimulation of nerve fibers to muscles and joints can elicit sensations of joint position and movement [29-31].

For a functional neuroprosthesis, there are a number of impediments. Postaxotomy peripheral nerves undergo atrophy, degeneration, with loss of central connections. Sunderland estimates that anywhere between 6% and 85% fibers in the proximal stump survive axotomy [32]. Human cadaver studies of amputees have shown motor neuron loss of up to 50% or more [33]. Both electrophysiological [34, 35] and histological [32] studies demonstrate a decline in the diameter of myelinated sensory nerve fibers (A$\alpha$, A$\beta$), so that 12 months postaxotomy, cross sectional caliber of severed nerve fibers is less than 5 µm. With these changes, will it be possible to selectively activate nerve fibers that convey sensations of touch, movement and joint position without concomitant excitation of neurons that normally mediate painful sensations; or can any sensations be elicited at all? With atrophy and degeneration of motor neurons, will it be possible to record efferent activity associated with missing limb movements? With reduction in conduction velocity between 50% to 80% [36], will the amputee be able to control movements of the prosthesis with speed and precision necessary for intended real life movements? Using microneurography, investigators were able to elicit phantom limb sensations in human amputees [37, 38]. To what degree and accuracy CNS regions formally devoted to the missing limb are able to process sensory information and control motor outflow from the amputee nerve stump remains to be explored and will be evaluated in this study.

<u>Plasticity of the Central Nervous System</u>

Dynamic changes in the central nervous system lead to expansion of adjacent, intact limb regions into cortical areas formally occupied by representation of the missing regions of the amputated limb [39-42]. In animal models, somatic sensory and motor cortical representations can be modified by amputation and peripheral nerve lesions [43, 44]. Many of these studies have been conducted through microelectrode penetrations of the animal cortex and cannot be directly confirmed in humans. If such extensive, dynamic cortical changes occur in human subjects, will the amputees be able to generate and control motor nerve activity associated with the missing limb movements? Even if peripheral pathways are responsive to electrical stimulation, will the amputees be able to localize the sensations referred to the missing limb, and can these sensations be graded through systematic modulation of stimulation parameters?

Dynamic plasticity of the central nervous system may lead to reversal of many of the CNS reorganizational changes associated with limb amputation. For example, following functional recovery from nerve crush injury and repair of transected nerves, reorganizational changes take place in the region of the cortex formally devoted to the intact nerve [44, 45]. Sensory feedback and repetition of motor task may enhance functional recovery. For example, in normal individuals, repetitive performance of a simple, unskilled and skilled movement has been shown to induce cortical changes [46-48]. Indirect studies involving ‘normal’ human subjects, with normally functioning limbs, have shown that repetitive training enhances motor cortical representations and noticeable changes occur within a short period (30 min) of time [46]. It can be argued that once sensory feedback is restored and the amputee has been asked to practice phantom movements, reorganizational changes can be expected to take place very early on, and continue to evolve over time

Once an artificial arm is interfaced to the nerve stumps, can the amputee learn to refine motor control? Given the plasticity of the CNS, this may be possible. For example, the *motor cortex* receives sensory inputs from tactile and proprioceptive sensors [49-52] and alterations in sensory inputs from a region of a limb have been shown to modify the appropriate motor cortical areas. This may play a role in learning and skill acquisition [40, 53-55]. It is therefore possible that with afferent stimulation and repetitive practice of phantom movements, changes in cortical maps may be observed and this may be reflected in improved dexterity of motor control. Second, sustained electrical stimulation of the motor cortex has been shown to influence cortical plasticity [56]. Sensory reeducation following nerve repair has been shown to improve functional results, and this effect is probably centrally mediated [57]. Electrical stimulation of sensory fibers has been shown to alter receptive field sizes in the somatosensory cortex[58]. Further evidence that peripheral inputs can alter cortical representation is the incorporation of sensory input from skin islands into cortical representations of the recipient site [59, 60].

It is therefore evident that despite reduced representations of the missing limb, once sensory input has been restored and amputee practices phantom movements, it may be possible to improve motor control and sensory feedback through sensory feedback and motor control paradigms involving sensory reeducation and refinement of motor control.

Hand Transplantation

At the turn of the 21st century, hand transplant was making the national and international headlines. Whilst it is possible that in long-term composite tissue transplant may be the ideal option for amputees, with current medical strategies, there are a number of limitations and concerns [61]. In addition to ethical considerations and limited supply of donors, other impediments include surgical risks and complications related to immunosuppressive therapy-increase in the risk of cancer, life threatening infections and metabolic complications. By the year 2001, 14 hand transplants were performed, with 9 allotransplants surviving at least 1 year [62]. Unfortunately there has been no significant increase in long-term graft survival despite improved 1-year survival rates [61]. Results of solid organ transplant show that there is an 80% chance of the patient developing at least one infection and 40% of the deaths are due to infectious complications [63]. It is important to realize that these reports are for internal organs (kidney, heart and liver, for example), which are not subjected to the harsh external environment that the transplanted hand will be exposed to. Furthermore, unlike the kidney or the heart, the hand consists of multiple tissue components, such as skin, blood vessels, muscle, tendons and cartilage. Therefore, theoretically, there is increased likelihood of rejection related complications with hand as compared with transplant of other solid organs. Median age of survival for kidney transplants is between 7.5 to 9.5 years and success for hand transplant could theoretically be well below this [64].

Even if we made significant progress in tissue transplantation to the point that many of the disadvantages of immunosuppressive therapy were overcome, there is a problem of obtaining satisfactory nerve regeneration. According to Mackinnon, results of nerve repair have not changed significantly over the last 25 years [65, 66]. For example, less than 1% of adults who had repair of the median nerve at the wrist recovered normal function.  Regenerating neurons may make contact with the same receptor class but not necessarily the same receptive fields [67, 68]. This lack of topographic specificity coupled with growth of regenerating neurons through the wrong endoneurial tubes leads to cortical areas receiving aberrant sensory input, which may translate to poor functional results [68, 69].  Limb replantation has been practiced for over 40 years and unlike transplantation, rejection and associated problems with immunosupression are not a problem. Even though limb replantation provides better functional results than conventional prosthesis, many subjects achieve only limited return of sensory function and have poor motor function [70].  It seems for limb transplantation to provide a significant level of functional return, *both* problems with immunosuppression and nerve regeneration need to be addressed.

## Artificial Arm Interfaced to the Severed Nerve Stumps

To date, connecting artificial limb to severed neurons has received limited attention, perhaps because a near optimal neural interface was not available. To duplicate control of a normal limb, multiple, independent sensory feedback and motor control channels are required. Mass excitation and recording composite nerve activity from a nerve stump is not an option. Furthermore, neural interface should be biocompatible on a long-term basis and allow for multiple, independent sensory feedback and motor control channels. Coupled with a controller in the artificial arm, such a system should allow for simultaneous multidegree freedom-of-control of an artificial arm, with graded, localized sensory feedback provided through multiple independent sensory feedback channels.

### Extraneural Stimulation and Recording

Clippinger and colleagues made a first attempt to provide sensory feedback through stimulation of severed nerve stumps [71]. They used cuff electrodes, implanted around nerve stumps, to provide sensory feedback. Amputees reported sensations of vibration, digit movement and tactile perception. However, the number of sensory channels in associated with a given nerve trunk could not be defined because the topological selectivity of phantom sensations was poorly defined and referred sensations could not be graded through systematic modulation of stimulation parameters. Since the entire nerve trunk is stimulated through use of cuff electrodes, investigators attempted to use more novel techniques to elicit excitations of localized radial segments of the nerve trunk. Unfortunately, these techniques were limited in their effectiveness and could not be implemented clinically [72-76]. Despite these limitations, the work provided evidence that some sensory neurons remained functional and stimulated further research with cuff electrodes [77, 78]. As elicited sensations could not be modulated through variation in stimulation parameters, it was not known whether this was due to the stimulation technique or to reorganizational changes in the peripheral and central nervous system of neural pathways formally associated with the missing limb. Given that cuff electrodes elicit mass excitation of nerve tissue and record composite nerve activity, perhaps a more selective electrode is needed.

Intraneural Stimulation and Recordings: Animal Models

Longitudinal intrafascicular electrodes (LIFEs) have been developed and tested in animal models at the Neuroprosthetics Laboratory, University of Utah [79-81]. LIFEs are individually threaded into a fascicle and multiple implants can be done in one nerve. The rational is based on the knowledge that peripheral nerves are topographically and functionally organized both at the fascicular and the subfascicular levels [37, 38, 82-84]. When point sources are placed near nerve fibers and used for stimulation, due to the high curvature of the electric field near the point source, nerve fibers near the source are preferentially recruited before more distant fibers [85, 86]. LIFEs, with their 1mm recording/stimulating zone, act as point sources within a fascicle. Theoretically, with LIFEs, it will be possible to selectively excite a small cluster of sensory neurons near the stimulating zone.

LIFEs have been shown to record from a small number of individually separable units at subfascicular levels [79, 87, 88], on chronic basis, with signal-to-noise ratios which allow for real time identification of individual units [88, 89]. With activation restricted to a small cluster of neurons within a fascicle, LIFEs can provide controlled selective stimulation of a subset of nerve fibers using injected charges on the order of 1 to 5 nC [90, 91].

For control of an artificial limb, potential difference due to electro-chemical activity of motor neurons inside the fascicle can be differentially recorded between two LIFEs: one or more LIFEs implanted inside the fascicle and with an indifferent electrode tacked to the outer surface of the nerve trunk. The recording/stimulating zones of intrafascicular and indifferent electrode should be longitudinally aligned to optimize recordings with maximum signal-to-noise ratios. Signals produced by currents generated by motor or sensory axons are concentrated inside the nerve fascicle. Although amplitude of nerve signals is small, the voltage gradients between two LIFEs separated by a layer of perineurium, due to its insulating function, is relatively high. Theoretically, EMG signals, due to contractions of stump muscles, will be typically up to 3 orders of magnitude above motor nerve signals, and can therefore overcome the insulating function of the perineurium. As a result, they will appear as relatively large amplitude sources to *both* the intra- and extrafascicular LIFE electrodes, with a relatively small *voltage drop*. If a differential amplifier with a high common mode rejection ratio (≥100 dB) is employed, EMG signals are reduced to just above the background noise, whereas neural signals are amplified. LIFEs typically record from 10 separable units and allow for single unit activity above the noise envelope, with peak-to-peak amplitude of about 20 μV [87, 88]. Multiunit activity can be identified in chronic studies [79, 80].

Given that neurons mediating sensations from adjacent receptive fields tend to be topographically segregated, with LIFEs, it may be possible to provide sensation referred to discrete, localized regions of the skin. Even though there is evidence of considerable loss of sensory neurons in the proximal nerve stump, recent experiments have shown redundancy in proprioceptive feedback from the hand [92]. Furthermore, relatively more cutaneous nerve fibers are destined for the digits than for other regions of the upper limb. Therefore, even though there is degeneration of sensory neurons in the proximal nerve stump, given the higher density of innervation, some of the neurons mediating sensations from the finger tips are more likely to survive. To provide prehension feedback, only a very small number of the nerve fibers mediating tactile sensation are needed because we are interested in providing sensory feedback from only a *small* portion of a digit to provide *contact* feedback. Using microneurography, investigators have managed to elicit tactile sensations through stimulation of normal, intact nerves [82, 93, 94]. Therefore, if nerve fibers can be selectively stimulated to elicit discrete, unimodal, painless sensations, then it may be possible to provide sensations of touch and proprioception.

Postaxotomy, there is greater degeneration and loss of sensory than motor neurons [34, 35, 95, 96]. Given that we have evidence of viable sensory nerve fibers in axotomized nerves, some functional motor neurons must exist for recording and controlling actuators in an artificial limb. Again, it is not necessary to record from all the motor neurons formally innervating the amputated limb. This is because our aim is not to duplicate individual muscle movement but to provide information to the actuator about the direction and the magnitude of movement. To do this, all we need is to record from a subset of neurons formally controlling muscle groups to that joint. Theoretically, even recording from one neuron should be sufficient to control an actuator, although on a chronic basis, each LIFE can record from an average of 10 neurons with signal-to-noise ratios ≥ 1.4 [80].

## Research Design and Goals

This research is broadly divided into three phases. Phase I will involve implantation of LIFEs into severed nerves of long-term human amputees. The aim of this part of the study is to evaluate if amputees can generate and control volitional motor nerve commands associated with the missing limb movements and graded sensory feedback can be provided through stimulation sensory neurons.

During Phase II, we will track changes in the amputee's ability to modulate motor nerve activity recorded from severed neurons and changes in stimulation parameters used to provide sensory feedback.

Phase III will involve interfacing the artificial arm to human amputee nerve stumps. Sensory feedback will be provided through stimulation of sensors in the terminal device and recorded motor nerve signals will be channeled through a microprocessor to control actuators in the artificial arm.

## References

1. Dillingham, T.R., L.E. Pezzin, and E.J. MacKenzie, *Limb amputation and limb deficiency: epidemiology and recent trends in the United States.* South Med J, 2002. 95(8): p. 875-83.

2. LeBlanc, M.A., *Patient population and other estimates of prosthetics and orthotics in the U.S.A.* Orthotics & Prosthetics, 1973. 27(3): p. 38-44.

3. Gelberman, R.H., et al., *Sensibility testing in peripheral-nerve compression syndromes. An experimental study in humans.* J Bone Joint Surg Am, 1983. 65(5): p. 632-8.

4. Childress, D.S., *Powered limb prostheses: their clinical significance.* IEEE Transactions on Biomedical Engineering, 1973. 20(3): p. 293-303.

5. Jacobsen, S.C., et al., *Development of the Utah artificial arm.* IEEE Trans Biomed Eng, 1982. 29(4): p. 249-69.

6. Atkins, D., *Epidemiologic overview of individuals with upper-limb loss and their reported research priorities.* J. Prosthet. Orthot., 1996. 8(1): p. 2 - 11.

7. Northmore-Ball, M.D., H. Heger, and G.A. Hunter, *The below-elbow myoelectric prosthesis.* J. Bone Joint Surg., 1980. 62-B(3): p. 363-367.

8. Stein, R.B. and M. Walley, *Functional comparison of upper extremity amputees using myoelectric and conventional prostheses.* Arch Phys Med Rehabil, 1983. 64(6): p. 243-8.

9. Birder, L.A. and E.R. Perl, *Cutaneous sensory receptors.* Journal of Clinical Neurophysiology, 1994. 11: p. 534-552.

10. Jacobsen, S.C., et al. *Design of a multiple degree of freedom , force reflective hand master/slave with high mobility wrist*. in *3rd Topical Meeting on Robotics and Remote Systems*. 1989. Charleston, SC.

11. Sears, H.H., J.T. Andrews, and S.C. Jacobson, *Experience with Utah Arm. Hand and terminal device.*, in *Comprehensive management of upper limb amputees.*, D.J. Atkins and R.H.I. Meier, Editors. 1989, Springer-Verlag: New York. p. 194-210.

12. Kyberd, P.J. and P.H. Chappell, *The Southampton Hand: an intelligent myoelectric prosthesis.* J Rehabil Res Dev, 1994. 31(4): p. 326-34.

13. Meek, S.G., S.C. Jacobsen, and R.R. Fullmer. *Control inputs to a multi degree of freedom artificial arm*. in *1984 IEEE EMBS Conference*. 1984. Los Angeles.

14. Almstrom, C., P. Herberts, and L. Korner, *Experience with Swedish multifunctional prosthetic hands controlled by pattern recognition of multiple myoelectric signals.* Int Orthop, 1981. 5(1): p. 15-21.

15. Craelius, W., *The bionic man: restoring mobility.* Science, 2002. 295(5557): p. 1018-21.

16. Abboudi, R.L., et al., *A biomimetic controller for a multifinger prosthesis.* IEEE Trans Rehabil Eng, 1999. 7(2): p. 121-9.

17. Curcie, D.J., J.A. Flint, and W. Craelius, *Biomimetic finger control by filtering of distributed forelimb pressures.* IEEE Trans Neural Syst Rehabil Eng, 2001. 9(1): p. 69-75.

18. Carruthers, M.T.a.J.M.P., *Research into the possibility of a substitute for proprioception.* Proc. Inst. Mech. Engrs., 1969(183): p. 98-102.

19. Lovely, D.F., B.S. Hudgins, and R.N. Scott, *Implantable myoelectric control system with sensory feedback.* Med Biol Eng Comput, 1985. 23(1): p. 87-9.

20. Mann, R.W., *Efferent and Afferent control of an electromyographic, proportional-rate, force sensing artificial elbow with cutaneous display of joint angle.* Proc. Inst. Mech. Engrs., 1969(183): p. 86-92.

21. Phillips, C.A., *Sensory feedback control of upper- and lower-extremity motor prostheses.* CRC Critical Reviews in Biomedical Engineering, 1988. 16(2): p. 105-140.

22. Scott, R.N., *Feedback in myoelectric prostheses.* Clin Orthop Relat Res, 1990(256): p. 58-63.

23. Shannon, G.F., *A comparison of alternative means of providing sensory feedback on upper limb prostheses.* Med Biol Eng, 1976. 14(3): p. 289-94.

24. Shannon, G.F., *A myoelectrically-controlled prosthesis with sensory feedback.* Med Biol Eng Comput, 1979. 17(1): p. 73-80.

25. Mooney, V. and A.M. Roth, *Advances in percutaneous electrode systems.* Biomat., Med. Dev., Art. Org., 1976. 4(2): p. 171-180.

26. Horch, K.W. and G.S. Dhillon, *Neuroprosthetics : theory and practice*. Series on bioengineering and biomedical engineering. 2004, River Edge, NJ: World Scientific. xxv, 1261 p.

27. Marchettini, P., M. Cline, and J.L. Ochoa, *Innervation territories for touch and pain afferents of single fascicles of the human ulnar nerve. Mapping through intraneural microrecording and microstimulation.* Brain, 1990. 113(Pt 5): p. 1491-500.

28. Ochoa, J. and E. Torebjork, *Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand.* J Physiol, 1983. 342: p. 633-54.

29. Clark, F.J. and K.W. Horch, *Sensory processes and perception: Kinesthesia*, in *Handbook of perception and human performance*, K.R. Boff, L. Kaufman, and J.P. Thomas, Editors. 1986, John Wiley and Sons: New York.

30. Gandevia, S.C., *Illusory movements produced by electrical stimulation of low-threshold muscle afferents from the hand.* Brain, 1985. 108(Pt 4): p. 965-81.

31. Goodwin, G.M., D.I. McCloskey, and P.B. Matthews, *The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents.* Brain, 1972. 95(4): p. 705-48.

32. Sunderland, S., *Nerves and Nerve Injuries*. 2nd ed. 1978, New York: Chruchill Lingstone.

33. Kawamura, Y. and P.J. Dyck, *Permanent axotomy by amputation results in loss of motor neurons in man.* J Neuropathol Exp Neurol, 1981. 40(6): p. 658-66.

34. Gordon, T. and S.Y. Fu, *Long-term response to nerve injury.* Adv Neurol, 1997. 72: p. 185-99.

35. Gordon, T., et al., *Axotomy-induced changes in rabbit hindlimb nerves and the effects of chronic electrical stimulation.* J Neurosci, 1991. 11(7): p. 2157-69.

36. Cragg, B.G. and P.K. Thomas, *Changes in conduction velocity and fiber size proximal to peripheral nerve lesions.* Journal of physiology (London), 1961. 157: p. 315-327.

37. Schady, W., et al., *Responsiveness of the somatosensory system after nerve injury and amputation in the human hand.* Ann Neurol, 1994. 36(1): p. 68-75.

38. Schady, W., et al., *Peripheral projections of fascicles in the human median nerve.* Brain, 1983. 106: p. 745-60.

39. Cohen, L., et al., *Motor reorganization after upper limb amputation in man. A study with focal magnetic stimulation.* Brain, 1991. 114: p. 615-627.

40. Cohen, L.G., et al., *Plasticity of cortical motor output organization following deafferentation, cerebral lesions, and skill acquisition.* Adv Neurol., 1993. 63: p. 187-200.

41. Hall, E.J., et al., *Non-invasive brain stimulation reveals reorganized cortical outputs in amputees.* Neurosci Lett, 1990. 116(3): p. 379-86.

42. Sanes, J.N. and J.P. Donoghue, *Plasticity and primary motor cortex.* Annu Rev Neurosci, 2000. 23: p. 393-415.

43. Wall, J.T., D.J. Felleman, and J.H. Kaas, *Recovery of normal topography in the somatosensory cortex of monkeys after nerve crush and regeneration.* Science, 1983. 221(4612): p. 771-3.

44. Wall, J.T., et al., *Functional reorganization in somatosensory cortical areas 3b and 1 of adult monkeys after median nerve repair: possible relationships to sensory recovery in humans.* J. Neurosci., 1986. 6(1): p. 218-33.

45. Merzenich, M.M., et al., *Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys.* Neuroscience, 1983. 10(3): p. 639-65.

46. Classen, J., et al., *Rapid plasticity of human cortical movement representation induced by practice.* J Neurophysiol, 1998. 79(2): p. 1117-23.

47. Nudo, R.J., et al., *Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys.* J Neurosci, 1996. 16(2): p. 785-807.

48. Elbert, T., et al., *Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury.* 1994. 5(18): p. 2593-7.

49. Asanuma, H. and I. Rosen, *Functional role of afferent inputs to the monkey motor cortex.* Brain Res, 1972. 40(1): p. 3-5.

50. Rosen, I. and H. Asanuma, *Peripheral afferent inputs to the forelimb area of the monkey motor cortex: input-output relations.* Exp Brain Res, 1972. 14(3): p. 257-73.

51. Wise, S.P. and J. Tanji, *Supplementary and precentral motor cortex: Contrast in responsiveness to peripheral input in the hindlimb area of the unanesthetized monkey.* J Comp. Neurol., 1981. 195: p. 431-451.

52. Wong, Y.C., et al., *Spatial organization of precentral cortex in primates. I. Somatosensory inputs.* J. Neurophysiol., 1978. 41: p. 1107-1119.

53. Sanes, J.N., J. Wang, and J.P. Donoghue, *Immediate and delayed changes of rat motor cortical output representation with new forelimb configurations.* Cerebral Cortex, 1992. 2: p. 141-152.

54. Branner, A. and R.A. Normann, *A multielectrode array for intrafascicular recording and stimulation in sciatic nerve of cats.* Brain Res Bull, 2000. 51(4): p. 293-306.

55. Donoghue, J.P. and J.N. Sanes, *Plasticity of cortical representations and its implications for neurorehabilitation*, in *Principles and practice of rehabilitation medicine*, B.T. Shahani, Editor. 1994, Lippincott Williams & Wilkins Publishers.

56. Nudo, R.J., W.M. Jenkins, and M.M. Merzenich, *Repetitive microstimulation alters the cortical representation of movements in adult rats.* Somatosens. Mot. Res., 1990. 7(4): p. 463-83.

57. Dellon, A.L., *Evaluation of Sensibility and Reeducation of Sensation in the Hand.* 1981, Baltimore: Williams & Wilkins.

58. Recanzone, G.H., et al., *Receptive-field changes induced by peripheral nerve stimulation in SI of adult cats.* J Neurophysiol, 1990. 63(5): p. 1213-25.

59. Merzenich, M.M. and W.M. Jenkins, *Reorganization of cortical representations of the hand following alterations of skin inputs induced by nerve injury, skin island transfers, and experience.* J. Hand Ther., 1993. 6(2): p. 89-104.

60. Paneva-Holevich, E. and Y. Holevich, *Further experience with the bipedicled neurovascular island flap in thumb reconstruction.* J Hand Surg [Am], 1991. 16(4): p. 594-7.

61. Jones, N.F., *Concerns about human hand transplantation in the 21st century.* J Hand Surg [Am], 2002. 27(5): p. 771-87.

62. Lees, V.C. and S.J. McCabe, *The rationale for hand transplantation.* Transplantation, 2002. 74(6): p. 749-53.

63. Rubin, R.H. and L.S. Young, *Clinical approach to infection in the compromised host*. 4th ed. 2002, New York: Kluwer Academic/Plenum. xxv, 719 p.

64. Kouwenhoven, E.A., I.J. JN, and R.W. de Bruin, *Etiology and pathophysiology of chronic transplant dysfunction.* Transpl Int, 2000. 13(6): p. 385-401.

65. Mackinnnon, S.E. and A.L. Dellon, *Surgery of the peripheral nerve*. 1988: Thieme Medical Publisher.

66. Mackinnon, S.E. and A.L. Dellon, *Clinical nerve reconstruction with a bioabsorbable polyglycolic acid tube.* Plast Reconstr Surg, 1990. 85(3): p. 419-24.

67. Dykes, R.W., *Central consequences of peripheral nerve injuries.* Ann Plast Surg, 1984. 13(5): p. 412-22.

68. Horch, K., *Guidance of regrowing sensory axons after cutaneous nerve lesions in the cat.* J Neurophysiol, 1979. 42(5): p. 1437-49.

69. Rath, S. and C.J. Green, *Lack of topographical specificity in sensory nerve regeneration through muscle grafts in rats.* J Hand Surg Br, 1991. 16(5): p. 524-30.

70. Graham, B., et al., *Major replantation versus revision amputation and prosthetic fitting in the upper extremity: a late functional outcomes study.* J Hand Surg [Am], 1998. 23(5): p. 783-91.

71. Clippinger, F.W., R. Avery, and B.R. Titus, *A sensory feedback system for an upper-limb amputation prosthesis.* Bull Prosthet Res, 1974: p. 247-58.

72. Fang, Z.P. and J.T. Mortimer, *A method to effect physiological recruitment order in electrically activated muscle.* IEEE Trans Biomed Eng, 1991. 38(2): p. 175-9.

73. Fang, Z.P. and J.T. Mortimer, *Selective activation of small motor axons by quasi-trapezoidal current pulses.* IEEE Trans Biomed Eng, 1991. 38(2): p. 168-74.

74. Petrofsky, J.S., *Sequential motor unit stimulation through peripheral motor nerves in the cat.* Med Biol Eng Comput, 1979. 17(1): p. 87-93.

75. Sweeney, J.D., D.A. Ksienski, and J.T. Mortimer, *A nerve cuff technique for selective excitation of peripheral nerve trunk regions.* IEEE Trans Biomed Eng, 1990. 37(7): p. 706-15.

76. Veraart, C., W.M. Grill, and J.T. Mortimer, *Selective control of muscle activation with a multipolar nerve cuff electrode.* IEEE Trans Biomed Eng, 1993. 40(7): p. 640-53.

77. Anani, A.B., K. Ikeda, and L.M. Korner, *Human ability to discriminate various parameters in afferent electrical nerve stimulation with particular reference to prostheses sensory feedback.* Med. & Biol. & Eng. & Comput., 1977. 15: p. 363-373.

78. Clippinger, F.W., et al., *Afferent sensory feedback for lower extremity prosthesis.* Clinical Orthopaedics and Related Research, 1982. 169: p. 202-206.

79. Goodall, E.V., T.M. Lefurge, and K.W. Horch, *Information contained in sensory nerve recordings made with intrafascicular electrodes.* IEEE Trans Biomed Eng, 1991. 38(9): p. 846-50.

80. Lefurge, T., et al., *Chronically implanted intrafascicular recording electrodes.* Ann Biomed Eng, 1991. 19(2): p. 197-207.

81. Malagodi, M.S., K.W. Horch, and A.A. Schoenberg, *An intrafascicular electrode for recording of action potentials in peripheral nerves.* Ann Biomed Eng, 1989. 17(4): p. 397-410.

82. Hallin, R.G. and G. Wu, *Novel information on peripheral tactile mechanisms in man acquired with concentric needle electrode microneurography.* Behav Brain Res, 2002. 135(1-2): p. 11-8.

83. Hallin, R.G., *Microneurography in relation to intraneural topography: somatotopic organisation of median nerve fascicles in humans.* J Neurol Neurosurg Psychiatry, 1990. 53(9): p. 736-44.

84. Hallin, R.G., R. Ekedahl, and O. Frank, *Segregation by modality of myelinated and unmyelinated fibers in human sensory nerve fascicles.* Muscle Nerve, 1991. 14(2): p. 157-65.

85. Rattay, F., *Analysis of models for extracellular fiber stimulation.* IEEE Trans Biomed Eng, 1989. 36(7): p. 676-82.

86. Veltnik, P.H., et al., *A modeling study of nerve fascicle stimulation.* IEEE Trans Biomed Eng, 1989. 36(7): p. 683-692.

87. Goodall, E.V. and K.W. Horch, *Separation of action potentials in multiunit intrafascicular recordings.* IEEE Trans Biomed Eng, 1992. 39(3): p. 289-95.

88. Goodall, E.V., et al., *Analysis of single-unit firing patterns in multiunit intrafascicular recordings.* Med Biol Eng Comput, 1993. 31(3): p. 257-67.

89. McNaughton, T.G. and K.W. Horch, *Action potential classification with dual channel intrafascicular electrodes.* IEEE Trans Biomed Eng, 1994. 41(7): p. 609-16.

90. Nannini, N. and K. Horch, *Muscle recruitment with intrafascicular electrodes.* IEEE Trans Biomed Eng, 1991. 38(8): p. 769-76.

91. Yoshida, K. and K. Horch, *Selective stimulation of peripheral nerve fibers using dual intrafascicular electrodes.* IEEE Trans Biomed Eng, 1993. 40(5): p. 492-4.

92. Refshauge, K.M., S.L. Kilbreath, and S.C. Gandevia, *Movement detection at the distal joint of the human thumb and fingers.* Exp Brain Res, 1998. 122(1): p. 85-92.

93. Birznieks, I., et al., *Encoding of direction of fingertip forces by human tactile afferents.* J Neurosci, 2001. 21(20): p. 8222-37.

94. Torebjork, H.E., A.B. Vallbo, and J.L. Ochoa, *Intraneural microstimulation in man. Its relation to specificity of tactile sensations.* Brain, 1987. 110 ( Pt 6): p. 1509-29.

95. Gordon, T., et al., *Long-term effects of axotomy on neural activity during cat locomotion.* J Physiol, 1980. 303: p. 243-63.

96. Hoffer, J.A., R.B. Stein, and T. Gordon, *Differential atrophy of sensory and motor fibers following section of cat peripheral nerves.* Brain Res, 1979. 178(2-3): p. 347-61.

# CHAPTER 2

# RESIDUAL FUNCTION IN PERIPHERAL NERVE STUMPS OF AMPUTEES: IMPLICATIONS FOR NEURAL CONTROL OF ARTIFICIAL LIMBS

# Residual Function in Peripheral Nerve Stumps of Amputees: Implications for Neural Control of Artificial Limbs

**Gurpreet S. Dhillon, MD, Stephen M. Lawrence, PhD,**
**Douglas T. Hutchinson, MD,**
**Kenneth W. Horch, PhD,** ***Salt Lake City, UT***

**Purpose:** It is not known whether motor and sensory pathways associated with a missing or denervated limb remain functionally intact over periods of many months or years after amputation or chronic peripheral nerve transection injury. We examined the extent to which activity on chronically severed motor nerve fibers could be controlled by human amputees and whether distally referred tactile and proprioceptive sensations could be induced by stimulation of sensory axons in the nerve stumps.

**Methods:** Amputees undergoing elective stump procedures were invited to participate in this study. Longitudinal intrafascicular electrodes were threaded percutaneously and implanted in severed nerves of human amputees. The electrodes were interfaced to an amplifier and stimulator system controlled by a laptop computer. Electrophysiologic tests were conducted for 2 consecutive days after recovery from the surgery.

**Results:** It was possible to record volitional motor nerve activity uniquely associated with missing limb movements. Electrical stimulation through the implanted electrodes elicited discrete, unitary, graded sensations of touch, joint movement, and position, referring to the missing limb.

**Conclusions:** These findings indicate that both central and peripheral motor and somatosensory pathways retain significant residual connectivity and function for many years after limb amputation. This implies that peripheral nerve interfaces could be used to provide amputees with prosthetic limbs that have more natural feel and control than is possible with current myoelectric and body-powered control systems. (J Hand Surg 2004;29A:605–615. Copyright © 2004 by the American Society for Surgery of the Hand.)

**Key words:** Amputee, neuroprosthetics, peripheral nerve, motor control, somatosensory system.

---

From the Departments of Bioengineering and Orthopaedic Surgery, University of Utah, Salt Lake City, UT.
Received for publication August 20, 2003; accepted in revised form February 2, 2004.
Supported by a grant from the National Institute of Neurological and Communicative Disorders and Stroke of the National Institutes of Health.
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.
Reprint requests: Ken Horch, PhD, Department of Bioengineering, 50 S. Central Campus Dr, Room 2480, University of Utah, Salt Lake City, UT 84112.

0363-5023/04/29A04-0009$30.00/0
doi:10.1016/j.jhsa.2004.02.006

Body-powered and myoelectric control systems are the most widely used techniques for controlling upper-limb prostheses. There are a number of shortcomings with these systems, including a lack of prehension feedback and control limited to one movement at a time.[1] Short of limb regeneration, composite tissue transplantation has been offered as the next best option to providing the amputee with a functional limb.[2] Given the potential risks associated with hand transplantation,[3] an alternative is to interface an artificial limb to human amputee nerve stumps. With advancements in microfabrication techniques during the past 2 decades, there has been increased interest in the development of peripheral nerve interfaces for connecting an artificial limb to human amputee nerve stumps, thereby providing the recipient with closed loop control over the prosthesis.[4–7] It has been suggested that with such an interface efferent motor nerve signals could be used to control the actuators in the artificial limb, and stimulation sensory neurons in the nerve stumps would provide pseudonatural sensory feedback.

Even if a physical connection could be made between the artificial limb and the severed nerves it is not known whether it would be functional. There are a number of potential impediments to interfacing artificial limbs to severed nerves including changes in the proximal nerve stump, loss of central connections, and dynamic changes in cortical areas as a result of central nervous system (CNS) plasticity. These changes also may, in part, explain the poor results after peripheral nerve repair surgery. Because a multitude of peripheral factors play a role in recovery of function from nerve repair surgery it is difficult to gauge the degree to which the viability of the proximal nerve stump contributes to suboptimal results. By interfacing longitudinal intrafascicular electrodes (LIFEs) with microclusters of neurons within severed fascicles of proximal nerve stumps it is possible to investigate, in isolation, the viability of severed motor and sensory neurons and their related central neural connections.

Among the pathophysiologic changes in the proximal nerve stump there is a greater atrophy of myelinated sensory nerve fibers than of $\alpha$ motorneuron fibers.[8] Tactile and proprioceptive sensations are mediated by large-diameter myelinated fibers ($A\alpha\beta$) and painful sensations are conducted by small-diameter myelinated ($A\delta$) and unmyelinated C fibers.[9,10] Painless tactile sensations can be elicited through focal electrical stimulation of normal intact peripheral nerves because larger-diameter myelinated fibers are recruited before smaller nerve fibers.[11] This raises the question of whether it will be possible to selectively activate afferent nerve fibers in amputee nerve stumps that convey sensations of touch, movement, and joint position without concomitant excitation of neurons that normally mediate painful sensations. The amplitude of extracellularly recorded action potentials varies approximately with the square of conduction velocity, and the conduction velocity is proportional to the square root of the axon's radius,[12] so the amplitude of nerve recordings decreases with decreasing axonal size. This being the case, given the atrophy and degeneration of motor neurons after amputation, will it be possible to record efferent activity with sufficient signal-to-noise ratios to control an artificial limb?

After long-term limb amputation, neural pathways undergo degeneration or atrophy including loss of central connections.[8,13–22] Estimates of nerve fiber survivability have varied from 6% to 83%, with a loss of over 50% of $\alpha$ motor neuron cell bodies reported in human amputees.[23–25] Dynamic changes in the CNS lead to expansion of adjacent, intact, limb regions into cortical areas formerly representing the missing parts of the limb.[26–29] In animal models, somatic sensory and motor cortical representations can be modified by amputation and peripheral nerve lesion.[30–32] Most of these studies have involved microelectrode studies of animal cortex and have not been confirmed directly in human subjects. For nerve repair, although nerve atrophy is reversed after limb reinnervation,[33] results after reconstructive surgery are suboptimal[34] and the degree of regrowth of nerve fibers to skin receptors does not necessarily correlate with the level of functional recovery.[35] This suggests that central factors may play an important role in the process. Given that axotomy leads to cell death, loss of central neurons, and dynamic changes in the cortical areas formerly associated with the missing limb, will amputees be able to generate and control efferent activity related to missing limb movements? Even if peripheral pathways are responsive to electrical stimulation, will the stimulation produce sensations referred and localized to the missing limb, and will the sensations be graded through systematic modulation of stimulation parameters?

Peripheral nerves are organized somatotopically at both fascicular and subfascicular levels.[36,37] LIFEs were chosen to investigate the functionality of motor and sensory neurons in nerve stumps of human amputees because they can record from small clusters of neurons at a subfascicular level and can selectively activate subsets of nerve fibers within nerve fascicles by using injected charges on the order of 1 to 5 nC.[38–40] LIFEs have been shown to be biocompatible in chronic animal studies and can be removed without requiring further surgery.[41] CNS reorganization begins almost immediately after nerve section and reaches a peak within 3 to 4 weeks[31,42] and functional changes in the nerve stumps are most pronounced in the first 2 months after axotomy.[33,43] Only long-term amputees (0.25–15 yr; mean, 4 yr after amputation) were therefore invited to participate in this study.

## Methods

LIFEs were implanted in the severed nerves of 8 amputee subjects undergoing stump revision surgery. Details of LIFE fabrication and their electrochemical characteristics have been described elsewhere.[40,41,44] Institutional review board approval was obtained to implant the electrodes in the severed nerves of human volunteers and to conduct postoperative testing during a period of 2 days after full recovery from the anesthetic. All amputees were given adequate time to consent to the study and signed a written consent form that was approved by the institutional review board.

The distal ends of the LIFEs were attached to the pins of a miniature cable connector by using conductive silver epoxy that was cured thermally. A silicone rubber tube was used to provide strain relief for the fine LIFE wires. The connector assembly was embedded in glue and encased in a layer of silicone. A further layer of silicone was applied to the assembly to bond it to a circular silicone patch that was placed on the arm stump (Fig. 1).

LIFEs were implanted within the healthy portion of the nerve proximal to any terminal neuroma to maximize recording signal-to-noise ratios and to ensure that recording and stimulation were performed in a part of the nerve that still maintained some degree of somatotopic organization. At the site of implantation, 3 to 8 cm proximal to the end of the nerve stump, partial epineurial dissection was performed to allow visualization of the fascicle or fascicles. The proximal ends of the electrodes were threaded individually through the skin by using an 18-gauge needle as a trochar. Each electrode then was threaded into a 0.5- to 1.0-cm length of a fascicle with the aid of a 50-$\mu$m tungsten needle attached to its leading end. Once the 1-mm recording/stimulating zone was centered within the implantation zone, the tungsten needle was removed. A reference LIFE electrode was sutured to the epineurial surface of the nerve, adjacent and parallel to the intraneural electrodes. Median and/or ulnar nerves were implanted in upper-limb amputees and the common peroneal nerve was implanted in one lower-limb amputee.

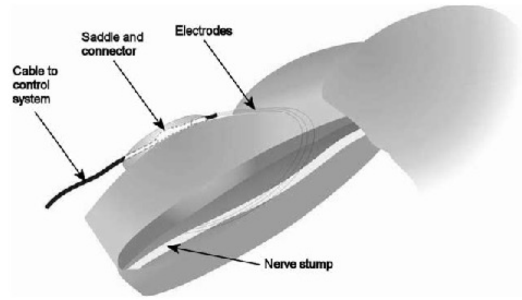


**Figure 1.** LIFEs were implanted in severed nerves 3 to 8 cm from the distal end of the nerve stump. The external ends of the electrodes were attached to a connector on a silicone rubber saddle attached to the subject's stump. A cable from the recording and stimulating equipment was plugged into the connector. Between experimental sessions the cable was disconnected and the saddle connector was covered with an elastic bandage to protect it from damage.

During a period of 2 days after implantation, electrophysiologic tests were performed to evaluate whether it is possible to record efferent activity associated with missing limb movements, and to elicit graded sensations referred to the missing limb through nerve stimulation.

### Motor Control

For recording, the subject was directed to make limb movements associated with the missing portion of the amputated limb. Motor signals were recorded in differential mode between a reference and an intraneural electrode, amplified (gain of ~20,000), bandpass filtered (0.3–4 kHz), sent to a loudspeaker with a noise clipper, and fed through a 16-bit analog-to-digital converter to a battery-powered laptop computer (Fig. 2). The subject was directed to select a movement that resulted in maximum audible activity. Once the subject had learned to generate motor activity associated with a motion of the missing limb, a simple computer game was used to evaluate the subject's control over the rate of action potential production and, therefore, the ability to modulate the missing limb motion.

Background noise was recorded and displayed on the laptop computer when the subject made no attempt to generate efferent activity related to missing limb movement. The investigator used these data to

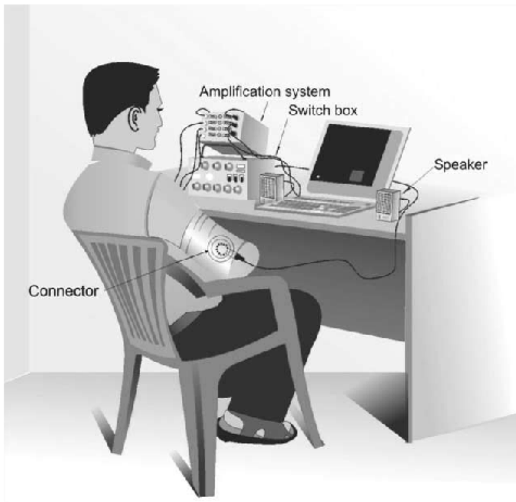


**Figure 2.** Experimental setup. The cable from the saddle connector lead to a stimulating and recording setup controlled by a laptop computer. During the motor control game the subject faced the computer screen.

set a minimum threshold level for detecting neural activity. The subject then was asked to make the missing limb movement and the recorded signals were used to set a threshold for detecting volitional motor nerve activity. This set the parameters for a Schmitt trigger to count action potentials within specified bin widths of time (eg, 200 ms). Minimum count corresponded to the subject making no attempt to create a missing limb movement. Maximum count was taken by having the subject make the selected missing limb movement at a level of effort that generated the most amount of neural activity.

Once these parameters were set, the subject was asked to control the position of a cursor on the computer monitor to strike a randomly appearing stationary target. The largest target size was 96 pixels in a 580-pixel–wide screen area. Cursor position was updated continuously and linearly related to the frequency of recorded motor signals. At the beginning of each trial the cursor appeared at the left edge of the screen. For the subject to score a hit he had to maintain the cursor in the target for at least 0.5 seconds. Simply striking the target, no matter how often within the duration of a trial, without maintaining position on the target was counted as a failure (Fig. 3A). The subject was allowed 5 to 10 seconds to score a hit and this was defined as one trial. The target appeared at a new random position for each trial. A set consisted of 10 trials.

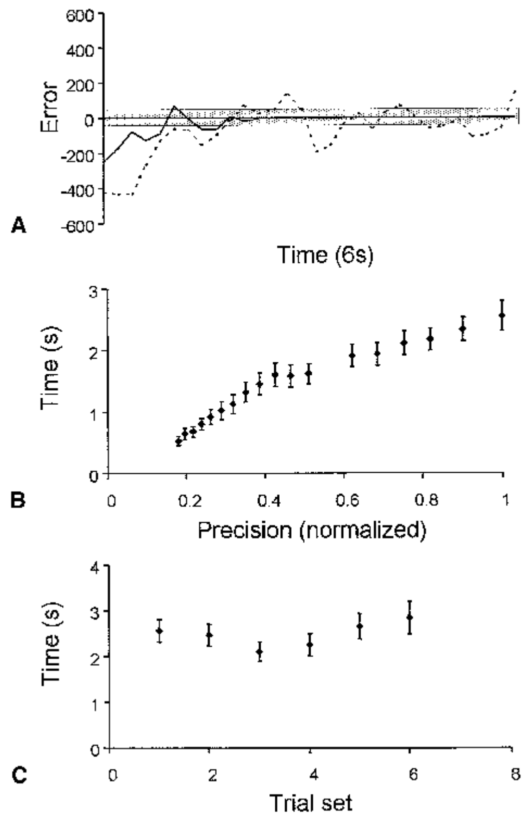


**Figure 3.** Volitional control of motor activity recorded with LIFEs. (A) Cursor position, controlled by the rate of production of action potentials recorded from a LIFE, is plotted relative to the target location as a function of time for a successful (solid line) and an unsuccessful (dotted line) trial. In the successful trial the subject hit the target (stippled zone on plot) and maintained the cursor within the target for over 0.5 seconds. In the unsuccessful trial the subject hit the target early on but was not able to keep the cursor within the target for the requisite 0.5-second period within the allocated time frame (6 s). Although the 2 trials started at different distances from the target, the subject was able to close in on the target within 2 seconds in both cases. This behavior was typical for all subjects. (B) The more precisely the cursor was positioned the longer it took to achieve that level of precision; that is, subjects could quickly approach the target but took more time to position the cursor reliably within the target. Precision here is defined relative to the target size. Placing the cursor within the target gave a precision of 1.0. Being within an area 10% larger than the target gave a precision of 0.9, and so forth (precision = size of the area centered on the target encompassing the cursor/area of the target). Each point represents the mean and SE for 6 sets of trials for 6 subjects. The $r^2$ values for the 6 individual sets of trials (pooled over all 6 subjects) varied between .87 and .98. (C) Time to successfully score hits did not change over different sets of trials, indicating that little learning was required to perform this task once subjects were able to control motor activity. Points show the mean and SE for each set of trials (first, second, and so forth) pooled for all 6 subjects.

### Sensory Feedback

To investigate whether it is possible to elicit sensations associated with the missing limb regions each electrode was stimulated separately either with monophasic, capacitively coupled, or biphasic, charge-balanced, rectangular current pulses of 250-$\mu$s duration and pulse amplitudes up to 200 $\mu$A. If the subject reported a discrete, distally referred sensation, a staircase method of limits was used to identify threshold and upper-limit pulse amplitudes for the sensation.[45] The threshold was defined as the lowest average pulse current at which the subject reliably could feel a sensation. The upper limit was defined as the current at which the nature or the location of the sensation changed or when the sensation became uncomfortable.

To evaluate whether it is possible to alter the perceived magnitude of these sensations a psychometric scaling task was used.[46] A stimulus amplitude midway between the threshold and upper limit was selected and pulse trains of 500-ms duration, with varying pulse frequency, were used to stimulate the nerve. The pulse train frequencies were distributed logarithmically, each presented a fixed number of times (typically 5) in pseudorandom order, with a time period of up to 5 seconds between successive trains. Subjects were asked to assign an open-ended number to the magnitude of the elicited sensation for each stimulus presentation.

The same paradigms for motor and sensory studies were used for the second day of testing. After completion of the study the electrodes were removed percutaneously by applying gentle longitudinal traction. This did not require application of an anesthetic.

## Results

### Motor Control

On the first day of testing all but 2 of the subjects were able to generate motor activity associated with missing limb movements. One of those who could not was able to do so on the second day after bringing back the phantom arm sensation that he had suppressed as part of his pain control procedure. Equipment problems precluded testing the other subject for motor activity on day 2.

The duration of recorded action potentials varied from 2 to 4 ms, which is longer than that recorded with LIFEs from normal nerves.[38] This may suggest that recorded signals were electromyographic (EMG) in nature, possibly owing to contraction of stump muscles. Electrodes were silent (ie, only background noise was recorded) for all the subjects in the absence of any attempted missing limb motion, and control of recorded motor activity was electrode specific. An attempted missing limb motion that produced activity on one electrode had little or no effect on activity recorded with other electrodes. Instead, the motor nerve activity associated with one motor channel would tend to appear as background noise on another motor electrode. This suggests that peripheral nerve motor neurons controlling different limb movements are organized into functionally distinct clusters and that different electrodes from which motor signals could be obtained were implanted in regions of the nerve that contained motor nerve fiber clusters controlling different muscle groups.

To detect EMG activity caused by possible contraction of the atrophied muscles in the stump region, an LIFE was sutured to the connective tissue at a distance of 1 cm from the implanted nerve, in line with the intraneural electrodes. Activity was recorded simultaneously from 2 intraneural electrodes and this external electrode (Fig. 4). Although there were places where signals were seen in common temporally (but not in fine structure) on all 3 electrodes, it was more common to see different signals on each of the electrodes. The duration of potentials on all 3 electrodes was similar to that seen in other subjects, even for signals recorded only on intraneural electrodes. Analysis of similar records has led us to believe that there are 3 possible sources of activity recorded on the intraneural electrodes: EMG artifact, neural signals controlling some residual stump muscles, and motor nerve signals conducted in transected neurons.

Once the subjects were able to generate repeated bursts of motor activity they were quickly able to modulate motor nerve discharges and move the cursor to different positions along the computer screen. Data were recorded after practice over several trials. Pooled data from all the subjects showed that there was a monotonic positive relationship between the precision of cursor control and the time taken to achieve this control (Fig. 3B). This was consistent among different trials, implying that, as with normal limbs, the more precise the movement, the greater the time taken to complete it.

The overall frequency of recorded motor potentials varied from 29 to 130 Hz, with a mean of 89 Hz. In general, subjects who could generate higher frequencies showed greater control over cursor position; the success rate for scoring a hit varied with the firing rate of recorded motor signals (linear correlation,

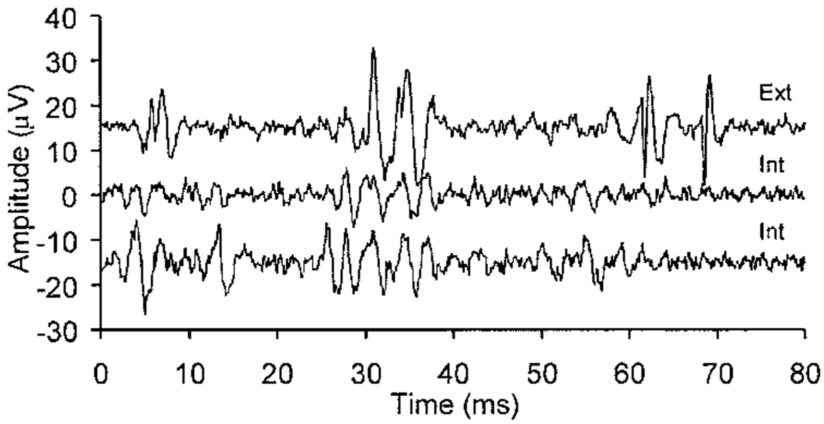


**Figure 4.** Motor (EMG) signals recorded simultaneously on 3 channels (offset for clarity). *Ext* was recorded from an extraneural electrode. The *Int* traces are from 2 different intrafascicular electrodes. The subject, with an amputation just below the elbow, was controlling missing thumb motion. Activity on *Ext* presumably reflected EMG activity recorded from neighboring muscles. Although there is activity on the 2 *Int* electrodes during the middle burst of *Ext* activity, in general the activity from the *Int* electrodes does not simply reflect the *Ext* activity, and activity on one *Int* electrode generally is not seen on the other *Int* electrode. This suggests that the *Int* recordings are not simply EMG artifacts.

$r^2 = .62$). Even when the subjects failed to score a hit they could still position the cursor near the target (Fig. 3A). This behavior was typical of all the subjects even when their success rate was limited. The time taken by the subjects to successfully strike the target did not show any systematic variation with the position of the target on the computer screen (linear and logarithmic correlations, $r^2 = .03$ and .05, respectively), and neither the time taken to score a hit (Fig. 4C) nor the success rate (not shown) over consecutive trials showed any statistically significant positive or negative trend.

## Sensory Feedback

Tactile sensations were the easiest to study because they were referred distally, mainly to digit tips, localized to small receptive fields, and generally consistent with findings from microneurographic activation of single sensory units in intact nerves.[11] In one patient the sensations tended to vary in terms of their nature and location during the first 2 stimulation runs but then settled during subsequent runs to either a tactile or proprioceptive nature. Otherwise, tactile sensations typically were reported as touch or pressure to a finger tip. Increasing the intensity of stimulation led to a spread of the sensation or caused it to take on a shock-like character. For example, one subject reported a sensation of touch between the thumb and the index finger (threshold, 17 $\mu$A) that persisted to a limit of 40 $\mu$A, and at 50 $\mu$A and 70 $\mu$A changed to mild and strong shock-like sensations, respectively.

Proprioceptive sensations initially tended to be more vague, but with practice we and the subjects soon learned how to bring them into focus. Proprioceptive sensations were felt either as movements of the whole digit or of individual joints, or as a change in joint position. The movements were perceived as either smooth or jerky flexions. For proprioceptive sensations the upper limit was defined at the point when further increment in the stimulation charge did not lead to any change in perceived joint flexion or when the digit became fully flexed. Individual finger joint sensations usually began with a sensation of distal interphalangeal joint movement and with increasing charge progressed to proximal interphalangeal and then metacarpophalangeal joint movements. Cessation of stimulation led to a perception that the joint had returned to its starting or rest position.

The operating range for stimulation (the ratio of the upper limit to the threshold) varied from approximately 2 to greater than 10, with a statistically significant tendency for higher ranges to be associated with lower thresholds. Thresholds lower than 10 nC always were accompanied by operating ranges that allowed one to safely choose a stimulus level that was detected readily but well below that required to elicit uncomfortable or painful sensations.

When tested on the second day the modality and the regional topography of elicited sensations did not

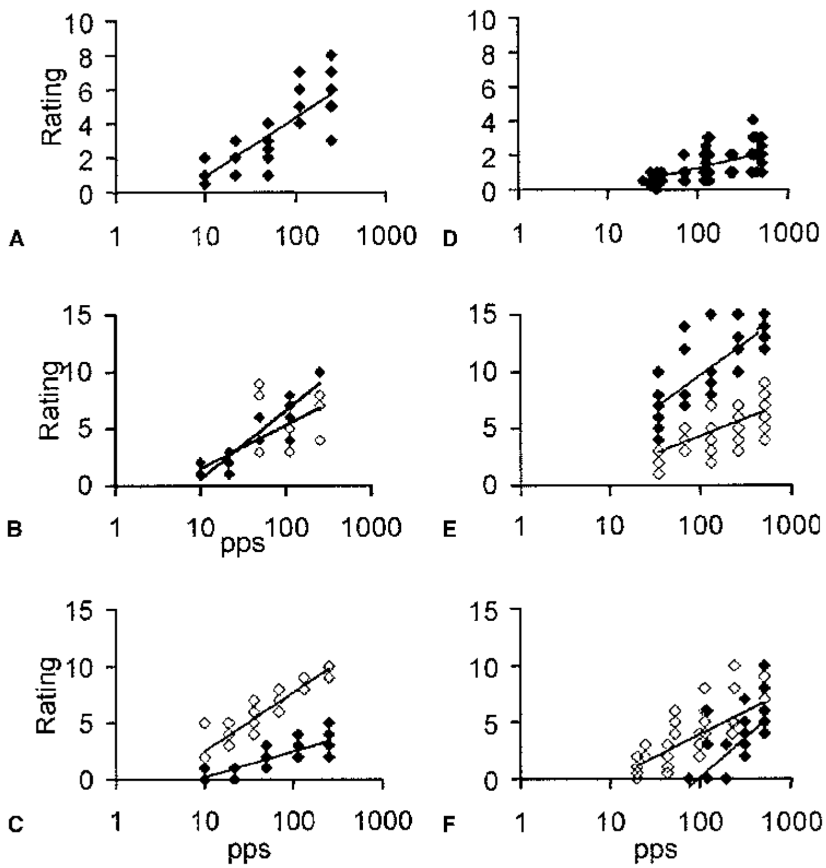


**Figure 5.** Estimations of sensation magnitude as a function of stimulus frequency (on a log scale). Subjects were asked to rate the apparent strength of the sensation on an open scale, after first having been presented with each of the stimuli in the set. At least 5 different frequencies were used in a set, each of which was presented to the subject 5 times in pseudorandom order. On many of the plots fewer total points appear owing to superposition of values. Lines show linear-log regressions, all of which have a slope significantly ($p < .05$) greater than 0. (A) In some cases there was no statistically significant difference in the data from one set of trials to the next for tactile sensations so the data were pooled before calculating the regression lines. In some cases there was a difference (B) between runs on a given day or (C) between days for tactile sensations. (D) In one case static position sense of the same finger was evoked from 2 different electrodes, with no statistically significant difference in the ratings of the magnitude of the sensations (ie, index finger position) between the electrodes, (E) but in another case 2 electrodes produced static position sensations (finger position) in different fingers (thumb and middle), with a statistically significant difference in the relation between perceived finger position and stimulus frequency for the 2 fingers. (F) In one case the sensation changed from a sense of rate of movement to a sense of position of the middle finger with stimulation through the same electrode from day 1 to day 2.

differ from that seen on the first day. The charge required to elicit a given sensation was consistent for the duration of the study. Stimulus strengths needed to elicit sensations (threshold mean ± standard error [SE] = 4.85 ± 0.72 nC, upper limit mean ± SE = 12.7 ± 1.4 nC) were similar to those that have been reported as being required to excite peripheral nerves through microneurography and intrafascicular stimulation.[11,40]

In none of the subjects was the sensation referred to the stump or region of the limb proximal to the nerve injury. Stimulation of different electrodes resulted in different sensations being referred to the missing limb; that is, the sensations were electrode specific. In only 2 subjects did 2 different electrodes elicit a similar sensation (Fig. 5D). Normally the perceived intensity of a stimulus is related to the firing rates of the sensory neurons responding to it. This relationship is preserved for both tactile and proprioceptive sensations in severed nerves of amputees (Fig. 5). Perceived magnitude of a tactile sensation or joint position for a static proprioceptive sensation increased with increasing stimulus frequency in all cases tested.

## Discussion

Potential impediments to interfacing artificial limbs to the peripheral nervous system of long-term (>3 mo) amputees include axotomy-induced loss of central connections, questionable viability of the proximal nerve stump, and reorganization of CNS areas related to the missing limb regions.

Although motor and sensory cortical representations of the truncated limb and nerves diminish significantly after amputation and taxotomy,[27,42,47,48] our study shows that in terms of controlling intended limb function, CNS reorganization seems to have limited functional consequences. For example, after peripheral nerve transection, that part of the somatosensory cortex serving the denervated area is taken over by inputs from adjacent regions.[28,31] In none of our subjects, however, was the sensation elicited by electrical stimulation of fibers in the nerve stump referred to the remaining part of the limb proximal to the injury, which implies that projections from peripheral sensory pathways maintain their appropriate central connections.[36] Once the amputees had learned to generate motor commands associated with motion of the missing limb, the level of control required by our experimental design did not require learning. Thus, in long-term amputees, either the neural pathways for control of missing limb motions remain intact or dynamic short-term cortical changes quickly come into play.[32,49]

CNS reorganization has been reported within minutes after manipulation of limb position.[32,49] Indeed, brief periods (30 min) of simple movement training can lead to cortical reorganization in human subjects.[50] This implies that reorganization of the cortical regions after limb amputation may be through unmasking of existing, functionally inactive pathways or modulation of synaptic strength rather than neuronal sprouting or retraction.[32,51–53] Therefore, reorganization after limb amputation might be reversed rapidly through a brief period of training, such as when the amputees attempted to bring back their missing or phantom limb body image in the present study.

Recent discoveries using functional magnetic resonance imaging to study cortical areas of the brain have shown that representations of different upper-limb regions are not demarcated strictly into discrete topographic areas of the classic homunculus. Instead, there are multiple foci representing a given limb movement, with extensive overlap of cortical representations of disparate limb regions, such as elbow and hand or fingers and the wrist regions.[54,55] Therefore, although discrete topographic regions of cortical areas devoted to the missing limb segment may diminish, this does not necessarily imply loss of functional central connections. In addition redundancy, with multiple parallel pathways controlling a limb movement, has been postulated to play a role in the recovery of stroke patients.[53] We believe this to be an unlikely mechanism in our subjects because unlike ischemia, which selectively can affect discrete anatomic regions, in amputees there is no reason to assume that CNS plasticity preferentially will affect some pathways more than others.

Regardless of the underlying mechanism or mechanisms, our results indicate that in long-term amputees residual functional connections remain or can be brought back rapidly with little practice. Although the effects of axotomy are more pronounced on sensory fibers than motor neurons, graded tactile and proprioceptive sensations could be elicited readily. Previous work has cited loss of central connections (both motor and sensory) after axotomy. Given the ability of the amputees to generate motor activity associated with attempts to control a missing limb movement within a short period of time, and given the easily identified, discrete, graded, and distally localized sensations elicited by electrical stimulation of the nerve stumps, without the need for any sensory reeducation, we infer that the central and peripheral pathways remain largely intact from the functional point of view.

One might assume that because the proximal nerve stumps remain viable for years after amputation that the duration of amputation should not affect the long-term sensory and motor recovery after composite tissue transplantation or prejudice the results of nerve repair surgery. Unfortunately, this appears not to be the case because long-term axotomy reduces successful regenerative capacity by up to 66%, as compared with results of immediate repair after nerve transaction injury.[56] This may be the consequence of the alteration in the biochemical modulators, signaling pathways, and other peripheral factors that play a role in nerve regeneration,[57] as opposed to a significant reduction in the numbers of functional proximal stump motor and sensory neurons.

The ability of the proximal nerve stump to conduct action potentials and the ability of the amputee to generate and control motor nerve commands and to localize sensations related to the missing limb may represent a major benefit for neuroprosthetics but they represent only a fraction of the difficulty for nerve repair surgery. The regenerating nerve fibers have to traverse atrophied endoneurial tubes embedded in the distal nerve stump and ideally need to exhibit both topographic and modality-specific selectivity in innervating atrophied end organs. It is tempting to conclude that if chemical mediators can be provided, then single-channel nerve conduits, containing a cocktail of growth factors, may enhance regeneration. The results of this approach may be suboptimal, however, because the growth factors must be provided in the correct spatiotemporal sequence and single-channel conduits may not be adequate to guide regenerating sprouts to the appropriate distal endoneurial tubes or allow correct fascicular alignment.[58–60] Previous work with animal models has provided conflicting evidence on the importance of the level of axotomy with respect to the viability of proximal stump neurons.[61] Our study included both above- and below-elbow amputees and we found no obvious differences in terms of electrical excitability and neuronal recordings.

Most upper-limb amputees strongly desire a prosthesis that requires less visual attention to operate, has prehension feedback, and can execute multiple movements simultaneously.[1] Current clinical upper-limb prostheses do not allow for simultaneous, multidegree freedom of control or provide natural sensations referred to the missing limb.[62,63] Our study provides a basis for developing a neurally controlled artificial arm through microneural interfacing with severed nerves. Because a given voluntary movement is executed by activation of one or more groups of motor units in one or more muscles, and because the motor nerve fibers associated with a muscle tend to run together in the peripheral nerve,[64–66] control of an actuator or joint movement in a prosthetic limb only requires that one record from one of these neuronal clusters. The evidence to date indicates that this is what intraneural electrodes do, and that motor neurons innervating different muscles are segregated topographically so that these electrodes only record signals associated with a single type of intended movement.

Once our subjects were able to generate motor activity they learned to control the neural signals rapidly (ie, within a few minutes) and there was no trend toward improved performance during the formal part of the testing. We cannot extrapolate from these results what would occur over longer periods of time when trying to control a neuroprosthetic arm. Studies specifically devoted to this issue are required and are well beyond the scope of the experiments reported here.

Our results also indicated that it may be possible to provide tactile and proprioceptive feedback from the joints and gripper of an artificial arm through intrafascicular stimulation. Because the sensations elicited tended to be discrete and of a defined modality (ie, touch, pressure, or position) for a given electrode, the location and modality of the referred sensation can be controlled by selecting an appropriate electrode and the magnitude of the sensation can be varied by modulating the frequency of stimulation.

For upper-limb amputees with multiple implants in disparate fascicles and different severed nerves (median, ulnar, radial, and musculocutaneous), recorded signals could be used to control different actuators in the prosthetic arm. Sensors in the joints and terminal device could be used to relay positional and tactile information to the nervous system. Closed-loop control of limb position, through implanted LIFEs, already has been shown in an experimental animal model with intact peripheral nerves.[67] Closed-loop control of a prosthesis will facilitate its incorporation into the subject's body image and improve the dexterity of control. The approach of interfacing artificial limbs to severed nerves can be accomplished either with LIFEs or other neural interfacing technologies that are in the process of development. Whatever the approach, it will not be possible to use percutaneous routing of electrodes to interface to the artificial arm because inevitably this will result in lead failure. Options for transmitting information between the implanted electrodes and the external circuitry include telemetry, percutaneous carbon connectors, or osseointegration.[68–70] Osseointegration has the additional advantage of allowing attachment of the prosthesis to the endoskeleton through a percutaneous titanium rod, which eliminates the need for socket and stump fit.[71]

The authors thank their anonymous subjects, without whose enthusiastic and dedicated participation this work would not be possible. The authors also give special thanks to the following individuals who graciously and freely provided their surgical services: John M. Bednar, MD, Philadelphia Hand Center, Philadelphia, PA; Edward Diao, MD, Department of Orthopaedic Surgery, University of California San Francisco Medical Center, San Francisco, CA; Neil F. Jones, MD, Department of Surgery, University of California Los Angeles Medical Center, Los Angeles, CA; Christian E. Sampson, MD, Department of Surgery, Brigham & Women's Hospital, Boston, MA; Jaspal S. Sandhu, MD, Guru Nanak Dev University, Amritsar, Punjab, India; Joseph Upton, MD, Department of Plastic Surgery, Harvard Medical School, Boston, MA.

## References


1. Atkins DJ, Heard DCY, Donovan WH. Epidemiologic overview of individuals with upper-limb loss and their reported research priorities. J Prosthet Orthot 1996;8:2–11.
2. Breidenbach WC III, Tobin GR II, Gorantla VS, Gonzalez RN, Granger DK. A position statement in support of hand transplantation. J Hand Surg 2002;27A:760–770.
3. Jones NF. Concerns about human hand transplantation in the 21st century. J Hand Surg 2002;27A:771–787.
4. Körner L. Afferent electrical nerve stimulation for sensory feedback in hand prostheses. Clinical and physiological aspects. Acta Orthop Scand 1979;178(suppl):1–52.
5. Kovacs GTA, Storment CW, Rosen JM. Regeneration microelectrode array for peripheral nerve recording and stimulation. IEEE Trans Biomed Eng 1992;39:893–902.
6. Kovacs GTA, Storment CW, Halks-Miller M, Belczynski CR Jr, Della Santina CC, Lewis ER, et al. Silicon-substrate microelectrode arrays for parallel recording of neural activity in peripheral and cranial nerves. IEEE Trans Biomed Eng 1994;41:567–577.
7. Dario P, Garzella P, Toro M, Micera S, Alavi M, Meyer U, et al. Neural interfaces for regenerated nerve stimulation and recording. IEEE Trans Rehab Eng 1998;6:353–363.
8. Hoffer JA, Stein RB, Gordon T. Differential atrophy of sensory and motor fibers following section of cat peripheral nerves. Brain Res 1979;178:347–361.
9. Horch KW, Tuckett RP, Burgess PR. A key to the classification of cutaneous mechanoreceptors. J Invest Dermatol 1977;69:75–82.
10. Birder LA, Perl ER. Cutaneous sensory receptors. J Clin Neurophysiol 1994;11:534–552.
11. Schady W, Ochoa JL, Torebjörk HE, Chen LS. Peripheral projections of fascicles in the human median nerve. Brain 1983;106:745–760.
12. Stein RB, Nichols TR, Jhamandas J, Davis L, Charles D. Stable long-term recordings from cat peripheral nerves. Brain Res 1977;128:21–38.
13. Carlson J, Lais AC, Dyck PJ. Axonal atrophy from permanent peripheral axotomy in adult cat. J Neuropathol Exp Neurol 1979;38:579–585.
14. Cragg BG, Thomas PK. Changes in conduction velocity and fibre size proximal to peripheral nerve lesions. J Physiol 1961;157:315–327.
15. Kiraly JK, Krnjević K. Some retrograde changes in function of nerves after peripheral section. Q J Exp Physiol Cogn Med Sci 1959;44:244–257.
16. Horch K. Central responses of cutaneous sensory neurons to peripheral nerve crush in the cat. Brain Res 1978;151:581–586.
17. Horch KW, Lisney SJW. On the number and nature of regenerating myelinated axons after lesions of cutaneous nerves in the cat. J Physiol 1981;313:275–286.
18. Horch KW, Lisney SJW. Changes in primary afferent depolarization of sensory neurones during peripheral nerve regeneration in the cat. J Physiol 1981;313:287–299.
19. Mendell LM, Munson JB, Scott JG. Connectivity changes of Ia afferents on axotomized motoneurons. Brain Res 1974; 73:338–342.
20. Milner TE, Stein RB. The effects of axotomy on the conduction of action potentials in peripheral sensory and motor nerve fibres. J Neurol Neurosurg Psychiatry 1981;44:485–496.
21. Risling M, Aldskogius H, Hildebrand C, Remahl S. Effects of sciatic nerve resection on L7 spinal roots and dorsal root ganglia in adult cats. Exp Neurol 1983;82:568–580.
22. Sumner BEH, Watson WERetraction and expansion of the dendritic tree of motor neurones of adult rats induced *in vivo*. Nature 1971;233:273–275.
23. Sunderland S. Nerves and Nerve Injuries. (2nd ed). New York: Churchill Livingstone, 1978:79–95.
24. Kawamura Y, Dyck PJ. Permanent axotomy by amputation results in loss of motor neurons in man. J Neuropathol Exp Neurol 1981;40:658–666.
25. Törnqvist E, Aldskogius H. Motoneuron survival is not affected by the proximo-distal level of axotomy but by the possibility of regenerating axons to gain access to the distal nerve stump. J Neurosci Res 1994;39:159–165.
26. Chen R, Cohen LG, Hallett M. Nervous system reorganization following injury. Neuroscience 2002;111:761–773.
27. Cohen LG, Bandinelli S, Findley TW, Hallet M. Motor reorganization after upper limb amputation in man. A study with focal magnetic stimulation. Brain 1991;114:615–627.
28. Elbert T, Flor H, Birbaumer N, Knecht S, Hampson S, Larbig W, et al. Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. Neuroreport 1994;5:2593–2597.
29. Hall EJ, Flament D, Fraser C, Lemon RN. Non-invasive brain stimulation reveals reorganised cortical outputs in amputees. Neurosci Lett 1990;116:379–386.
30. Sanes JN, Suner S, Donoghue JP. Dynamic organization of primary motor cortex output to target muscles in adult rats. I. Long-term patterns of reorganization following motor or mixed peripheral nerve lesions. Exp Brain Res 1990;79: 479–491.
31. Merzenich MM, Jenkins WM. Reorganization of cortical representations of the hand following alterations of skin inputs induced by nerve injury, skin island transfers, and experience. J Hand Ther 1993;6:89–104.
32. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. Annu Rev Neurosci 2000;23:393–415.
33. Davis LA, Gordon T, Hoffer JA, Jhamandas J, Stein RB. Compound action potentials recorded from mammalian peripheral nerves following ligation or resuturing. J Physiol 1978;285:543–559.
34. Mackinnon SE, Dellon AL. Surgery of the Peripheral Nerve. New York: Thieme Medical Publishers, 1988:89–130.
35. Jabaley ME, Burns JE, Orcutt BS, Bryant WM. Comparison of histologic and functional recovery after peripheral nerve repair. J Hand Surg 1976;1:119–130.
36. Hallin RG. Microneurography in relation to intraneural topography: somatotopic organisation of median nerve fascicles in humans. J Neurol Neurosurg Psychiatry 1990;53: 736–744.
37. Watchmaker GP, Gumucio CA, Crandall RE, Vannier MA, Weeks PM. Fascicular topography of the median nerve: a computer based study to identify branching patterns. J Hand Surg 1991;16A:53–59.
38. Goodall EV, Lefurge TM, Horch KW. Information contained in sensory nerve recordings made with intrafascicular electrodes. IEEE Trans Biomed Eng 1991;38:846–850.
39. Yoshida K, Horch K. Selective stimulation of peripheral

nerve fibers using dual intrafascicular electrodes. IEEE Trans Biomed Eng 1993;40:492–494.
40. Nannini N, Horch K. Muscle recruitment with intrafascicular electrodes. IEEE Trans Biomed Eng 1991;38:769–776.
41. Lefurge T, Goodall E, Horch K, Stensaas L, Schoenberg A. Chronically implanted intrafascicular recording electrodes. Ann Biomed Eng 1991;19:197–207.
42. Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. Neuroscience 1983;10:639–665.
43. Stein RB, Gordon T, Hoffer JA, Davis LA, Charles D. Long-term recordings from cat peripheral nerves during degeneration and regeneration: implications for human nerve repair and prosthetics. In: Jewett DL, McCarroll HR Jr, eds. Nerve Repair and Regeneration: Its Clinical and Experimental Basis. St. Louis: C.V. Mosby, 1980:166–177.
44. Malagodi MS, Horch KW, Schoenberg AA. An intrafascicular electrode for recording of action potentials in peripheral nerves. Ann Biomed Eng 1989;17:397–410.
45. Gelfand SA. Hearing: An Introduction to Psychological and Physiological Acoustics. 3rd ed. New York: Marcel Dekker, 1998: 470.
46. Stevens SS. Psychophysics. New Jersey: Transaction, 1986.
47. Cohen LG, Brasil-Neto JP, Pascual-Leone A, Hallett M. Plasticity of cortical motor output organization following deafferentation, cerebral lesions, and skill acquisition. In: Devinsky O, Berić A, Dogali M, eds. Electrical and Magnetic Stimulation of the Brain and Spinal Cord. New York: Raven Press, 1993:187–201.
48. Wall JT, Kaas JH, Sur M, Nelson RJ, Felleman DJ, Merzenich MM. Functional reorganization in somatosensory cortical areas 3b and 1 of adult monkeys after median nerve repair: possible relationships to sensory recovery in humans. J Neurosci 1986;6:218–233.
49. Sanes JN, Wang J, Donoghue JP. Immediate and delayed changes of rat motor cortical output representation with new forelimb configurations. Cereb Cortex 1992;2:141–152.
50. Classen J, Liepert J, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 1998;79:1117–1123.
51. Wall JT, Felleman DJ, Kaas JH. Recovery of normal topography in the somatosensory cortex of monkeys after nerve crush and regeneration. Science 1983;221:771–773.
52. Ramachandran VS, Rogers-Ramachandran D, Stewart M. Perceptual correlates of massive cortical reorganization. Science 1992;258:1159–1160.
53. Lee RG, van Donkelaar P. Mechanisms underlying functional recovery following stroke. Can J Neurol Sci 1995;22: 257–263.
54. Sanes JN, Donoghue JP, Thangaraj V, Edelman RR, Warach S. Shared neural substrates controlling hand movements in human motor cortex. Science 1995;268:1775–1777.
55. Rao SM, Binder JR, Hammeke TA, Bandettini PA, Bobholz JA, Frost JA, et al. Somatotopic mapping of the human primary motor cortex with functional magnetic resonance imaging. Neurology 1995;45:919–924.
56. Gordon T, Fu SY. Long-term response to nerve injury. In: Seil FJ, ed. Advances in Neurology. Vol. 72. Neuronal Regeneration, Reorganization, and Repair. Philadelphia: Lippincott-Raven, 1997:185–199.
57. Hudson TW, Evans GRD, Schmidt CE. Engineering strategies for peripheral nerve repair. Orthop Clin North Am 2000;31:485–498.
58. Rath S, Green CJ. Lack of topographical specificity in sensory nerve regeneration through muscle grafts in rats. J Hand Surg 1991;16B:524–530.
59. Horch K. Guidance of regrowing sensory axons after cutaneous nerve lesions in the cat. J Neurophysiol 1979;42: 1437–1449.
60. Horch KW, Burgess PR. Functional specificity and somatotopic organization during peripheral nerve regeneration. In: Jewett D, McCarrol HRJ, eds. Nerve Repair and Regeneration: Its Clinical and Experimental Basis. St. Louis: Mosby, 1980:105–109.
61. Ygge J. Neuronal loss in lumbar dorsal root ganglia after proximal compared to distal sciatic nerve resection: a quantitative study in the rat. Brain Res 1989;478:193–195.
62. Childress DS. Powered limb prostheses: their clinical significance. IEEE Trans Biomed Eng 1973;20:200–207.
63. Sears HH, Andrew JT, Jacobsen SC. Experience with the Utah arm, hand, and terminal device. In: Atkins DJ, Meier RH III, eds. Comprehensive Management of the Upper-Limb Amputee. New York: Springer-Verlag, 1989:194–210.
64. Sweeney JD, Ksienski DA, Mortimer JT. A nerve cuff technique for selective excitation of peripheral nerve trunk regions. IEEE Trans Biomed Eng 1990;37:706–715.
65. Veraart C, Grill WM, Mortimer JT. Selective control of muscle activation with a multipolar nerve cuff electrode. IEEE Trans Biomed Eng 1993;40:640–653.
66. Grill WM Jr, Mortimer JT. Quantification of recruitment properties of multiple contact cuff electrodes. IEEE Trans Rehab Eng 1996;4:49–62.
67. Yoshida K, Horch K. Closed-loop control of ankle position using muscle afferent feedback with functional neuromuscular stimulation. IEEE Trans Biomed Eng 1996;43:167–176.
68. Eriksson E, Bränemark P-I. Osseointegration from the perspective of the plastic surgeon. Plast Reconstr Surg 1994; 93:626–637.
69. Albrektsson T, Brånemark P-I, Jacobsson M, Tjellström A. Present clinical applications of osseointegrated percutaneous implants. Plast Reconstr Surg 1987;79:721–731.
70. Albrektsson T, Jacobsson M. Bone-metal interface in osseointegration. J Prosthet Dent 1987;57:597–607.
71. Albrektsson T, Bränemark P-I, Hansson H-A, Lindström J. Oseeointegrated titanium implants. Acta Orthop Scand 1981;52:155–170.

# CHAPTER 3

# EFFECTS OF SHORT-TERM TRAINING ON SENSORY AND MOTOR FUNCTION IN SEVERED NERVES OF LONG-TERM HUMAN AMPUTEES

Reprinted with permission from The American Physiological Society. Dhillon, G.S., Kruger, T.B., Sandhu, J.S., and Horch, K.W. Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. *J. Neurophysiology, 93*: 2625-2633; doi: 10.1152/jn/00937.2004.

# Effects of Short-Term Training on Sensory and Motor Function in Severed Nerves of Long-Term Human Amputees

**G. S. Dhillon,[1] T. B. Krüger,[1] J. S. Sandhu,[2] and K. W. Horch[1]**
[1]*Department of Bioengineering, University of Utah, Salt Lake City, Utah; and* [2]*Guru Nanak Dev University, Amritsar, Punjab, India*

Submitted 8 September 2004; accepted in final form 9 December 2004

**Dhillon, G. S., T. B. Krüger, J. S. Sandhu, and K. W. Horch.** Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. *J Neurophysiol* 93: 2625–2633, 2005; doi:10.1152/jn.00937.2004. Much has been studied and written about plastic changes in the CNS of humans triggered by events such as limb amputation. However, little is known about the extent to which the original pathways retain residual function after peripheral amputation. Our earlier, acute study on long-term amputees indicated that central pathways associated with amputated peripheral nerves retain at least some sensory and motor function. The purpose of the present study was to determine if these functional connections would be strengthened or improved with experience and training over several days time. To do this, electrodes were implanted within fascicles of severed nerves of long-term human amputees to evaluate the changes in electrically evoked sensations and volitional motor neuron activity associated with attempted phantom limb movements. Nerve stimulation consistently resulted in discrete, unitary, graded sensations of touch/pressure and joint-position sense. There was no significant change in the values of stimulation parameters required to produce these sensations over time. Similarly, while the amputees were able to improve volitional control of motor neuron activity, the rate and pattern of change was similar to that seen with practice in normal individuals on motor tasks. We conclude that the central plasticity seen after amputation is most likely primarily due to unmasking, rather than replacement, of existing synaptic connections. These results also have implications for neural control of prosthetic limbs.

## INTRODUCTION

Peripheral nerve amputation has been shown to produce changes in cortical sensory and motor representation in various mammalian species, including humans (Chen et al. 2002; Cohen et al. 1991; Elbert et al. 1994; Hall et al. 1990; Jones et al. 2002; Merzenich and Jenkins 1993; Merzenich et al. 1984; Sanes et al. 1990). This central plasticity is thought to involve both immediate mechanisms, such as synaptic unmasking, and long-term effects, such as central neuronal sprouting (Calford 2002; Théoret et al. 2004; Wall et al. 2002). Moreover, chronic peripheral nerve transaction also produces atrophic changes in both sensory and motor neurons, including reduction of motor neuron dendritic arborizations (Carlson et al. 1979; Cragg and Thomas 1961; Hoffer et al. 1979; Horch 1978; Horch and Lisney 1981a,b; Kawamura and Dyck 1981; Kiraly and Krnjevic 1959; Mendell et al. 1974; Milner and Stein 1981; Sumner and Watson 1971; Sunderland 1978; Törnqvist and Aldskogius 1994). Although there is some evidence in animals that chronically amputated nerves retain at least some function (DeLuca and Gilmore 1976; DeLuca et al. 1982; Edell 1986), little is known about the extent to which nerve stumps in human amputees retain useful sensory or motor capabilities (Clippinger et al. 1974).

Work by different groups have shown that it is possible to interface microelectrodes to small clusters of motor and sensory neurons at a subfascicular level (Branner and Normann 2000; Branner et al. 2001; González and Rodríguez 1997; Goodall et al. 1991; Kovacs et al. 1992; 1994; Yoshida and Horch 1993, 1996). A recent study with long-term human amputees, involving implantation of intraneural electrodes in severed nerve stumps, demonstrated that it is possible through discrete stimulation of small micro-clusters of sensory neurons to provide feedback related to touch/pressure and joint position sense and to use these same electrodes to record motor neuron activity related to volitional attempts to move joints in a phantom limb (Dhillon et al. 2004). This indicates that central plastic changes notwithstanding, chronic section of peripheral nerves in humans does not eliminate all of their central sensory and motor pathway connections. What was not determined, however, is if repeated use of these pathways would result in a rapid and significant improvement in their functionality.

The present study was an attempt to explore the question of the effects of experience on function in residual neural pathways associated with peripheral nerve stumps. In addition to its importance in providing information about the limits of CNS plasticity in adult humans, this work has implications about the feasibility of interfacing with amputee nerve stumps to provide natural, closed-loop control of artificial limbs (Dhillon et al. 2004).

## METHODS

Eight long-term (0.83–30 yr, average duration: ~7.3 yr) amputees voluntarily participated in the study. Institutional Review Board approval was obtained from both participating institutions, and the subjects were given adequate time to consider and provide informed consent. Although not selected on the basis of gender or handedness, all the subjects were right-hand dominant, adult males with an average age of 25.5 yr. All the amputations were of the right arm, above the elbow, and traumatic in nature. At the time of the study, the subjects were healthy and free from peripheral vascular disease or diabetes.

Fabrication procedures and performance characteristics of longitudinal intrafascicular electrodes (LIFEs) are described elsewhere (Lawrence et al. 2003, 2004; Lefurge et al. 1991; Malagodi et al. 1989; Malmstrom et al. 1998; McNaughton and Horch 1996; Nannini and Horch 1991). The distal ends of the LIFEs were attached to the pins

Address for reprint requests and other correspondence: K. Horch, Dept. of Bioengineering, 50 S. Central Campus Dr., Rm. 2480, University of Utah, Salt Lake City, UT 84112 (E-mail: k.horch@m.cc.utah.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

of a miniature cable connector using conductive silver epoxy, which was thermally cured. A silicon rubber tube was used to provide strain relief for the fine LIFE wires. The connector assembly was embedded in glue and encased in a layer of silicone. A further layer of silicone was applied to the assembly to bond it to a circular silicon patch that was placed on the residual arm.

LIFEs were implanted within the healthy portion of the nerve proximal to any terminal neuroma to maximize recording signal-to-noise ratios and to ensure that recording and stimulation were performed in a part of the nerve that still maintained some degree of somatotopic organization. Partial epineurial dissection was performed at the site of implantation to allow visualization of the fascicle(s). The proximal ends of the electrodes were individually threaded through the skin using an 18-gauge needle as a trochar. Each electrode was then threaded through a 0.5- to 1.0-cm length of a fascicle with the aid of a 50-$\mu$m-diam tungsten needle attached to its leading end. Once the 1-mm recording/stimulating zone of the electrode was centered within the fascicle, the tungsten needle was removed. A reference LIFE electrode was sutured to the epineurial surface of the nerve, level with the intraneural electrodes. More details on the implantation procedure are given in Dhillon et al. (2004).

After the amputees had fully recovered from the anesthetic, they underwent 2 wk of computer-aided motor and sensory studies to map the functionality of the implanted electrodes and the nerve fibers they interfaced with (Dhillon et al. 2004). The primary statistical analysis techniques used were regression analysis and ANOVA. After completion of the study, the electrodes were removed percutaneously by applying gentle longitudinal traction. This did not require application of an anesthetic.

### *Sensory input*

An initial mapping of the electrodes was made to determine which of them could be used to elicit tactile or proprioceptive sensations. To do so, each electrode was stimulated, through a current-controlled stimulus isolation unit driven by a D/A converter interface to a laptop computer, with charge balanced pulses of 300 $\mu$s duration, in a current range between 1 and 200 $\mu$A. Starting at a low current level, stimuli were increased until either the upper limit was reached or the subject reported a distinct sensation. If the subject reported a discrete, distally referred sensation, a staircase method of limits was used to identify threshold and upper limit pulse amplitudes for the sensation (Gelfand 1998). Threshold was defined as the lowest average stimulus pulse amplitude at which the subject could reliably feel a sensation. The upper limit was defined as the current at which the nature or the location of the sensation changed or when the sensation became uncomfortable.

A psychometric scaling task was employed to evaluate the relationship between stimulus amplitude and sensation magnitude (Stevens 1986). A stimulus amplitude midway between threshold and upper limit was selected and 500-ms-duration pulse trains, with various pulse frequencies, were used to stimulate the nerve. Initially, the subject was presented with sample trains at each of the pulse rates so he had a feel for the range of sensations that would be experienced. For testing, the pulse train frequencies were logarithmically distributed, presented a fixed number of times (typically five each) in pseudorandom order, with a time period of $\leq$5 s between successive trains. Subjects were asked to verbally assign an (open-ended) number to the magnitude of the elicited sensation for each stimulus presentation. Other than being instructed that a stronger sensation should result in a higher number, the subjects were not constrained in how they were to assign the numerical values. This procedure was used to avoid biasing them in the task (Stevens 1986). The subjects were not blindfolded or asked to close their eyes, but because the computer generated the stimuli automatically after a variable period following entry of the subject's report, they had no external cue as to when a stimulus was to be delivered.

In addition to sensory psychophysical magnitude estimation as a function of stimulus frequency, the effects of changes in stimulus amplitude on perceived sensation magnitude and on the referred distributions of touch/pressure sensations were studied in some of the subjects. These changes were mapped by having the subject verbally report where on their phantom hand the sensations were perceived as coming from and having them assign perceived sensory magnitude values for the different areas of sensation that developed as the stimulus strength was increased. For some of the instances in which proprioceptive (finger flexion) sensations were reported, the subject was asked to indicate the perceived finger position with the contralateral finger. The angle of the matching joint was then measured with a goniometer.

### *Motor control*

Candidate electrodes for evaluating motor control were identified by asking the amputee to attempt different movements in the amputated (phantom) part of the limb (e.g., the wrist or fingers) while recordings were made of neural activity from different implanted electrodes. Motor signals were recorded between the LIFE and the reference electrode with a differential amplifier (gain of ~20,000), band-pass filtered (0.3–4 kHz), sent to a loudspeaker with a noise clipper, and fed through a 16-bit A/D converter to a battery-powered laptop computer (Dhillon et al. 2004). The subject was directed to select a phantom movement that resulted in maximum audible activity. Once the subject had learned to generate motor neuron activity, a simple computer game was used to evaluate his control over the rate of motor neuron action potential production.

Basically, the subject was asked to modulate recorded neural activity to control a cursor on the computer screen so that it would overlap and stay within a displayed target (Dhillon et al. 2004). At the start of a trial, the target would appear randomly in a screen area 480 pixels wide, and the cursor would appear at the left end of the screen. The subject's task was to move the cursor and place it in the target for $\geq$500 ms (a "hit"). Simply placing the cursor in the target, no matter on how many occasions, counted as a failure unless the subject managed to hold the cursor in the target for the specified time.

As preparation for the task, background noise was recorded and displayed on the computer with the subject relaxed (in the absence of volitional motor output, recordings from the nerve stumps gave no indication of neural activity). This allowed the experimenter to set a minimum threshold level for detecting neural activity. The subject was then asked to generate neural activity, and the recorded signals were used to set an upper threshold for detecting action potentials. To simulate the properties of physiological motor control, the efferent activity (in the form of a pulse train from a Schmidt trigger based on these 2 threshold levels) was passed through a leaky integrator to provide the control signal. Time constants between 400 and 600 ms for the integrator were tested during the first day of training. With shorter time constants, amputees were able to control the cursor more precisely but found it difficult to hit targets on the far side of the practice screen area. With longer time constants amputees were able to freely move the cursor to all regions of the screen but precision was much reduced. As a compromise between these conditions, 500 ms was chosen as the standard time constant.

Given the settings for the spike detector and firing rate integrator, minimum output corresponded to the subject making no attempt at the phantom movement and maximum output was determined by having the subject make a maximal effort at the phantom movement. Minimum activity placed the cursor at the left edge of the screen, maximum activity placed it at the right edge.

Each testing set consisted of 20 10-s-long trials, and a subject was limited to completing two sets per day. All subjects started off with a target width of 96 pixels. After the subject managed to successfully perform this task with a success rate >75%, the task was made more difficult by reducing the size of the target to 68 and then 48 pixels. For one subject, who succeeded in hitting the smallest target >75% of the time, the dwell time requirement was increased to 750 ms for that target size.

RESULTS

*Sensory input*

All of the subjects reported either tactile or proprioceptive sensations from one or more electrodes. In half of the subjects, both types of sensations could be elicited (through different electrodes). On the first day of testing or when electrical stimuli were first delivered on subsequent days, subjects sometimes reported sensations of spiders crawling on the region of the referred sensation. After stimuli were delivered for 30–60 s or when the stimulus amplitude was increased, this would stabilize to a sensation of pressure/touch, joint position or movement. Usually electrical stimulation resulted in unimodal (i.e., touch, movement, or static joint position) sensations that showed stable topography. In ~10% of the cases, the location of the referred sensation tended to wander during the first 2 days. For tactile sensations, this movement was between the tips of different digits (middle and the index finger or thumb and the index finger). Over the duration of the study, these sensations eventually stabilized to one or more finger tips. In all cases, the sensations were in the fascicular projection territories of the implanted nerve, suggesting a stable electrode position, stimulating a small cluster of neurons. In ~20% of the cases, sensations were confused as to being either movement or pressure, vibration in a digit, and a mixture of tugging and movement localized to the palm or the fingers. The majority (~70%) of the cases resulted in stable sensations of touch/pressure or joint position/movement sense that were localized to the digits. In general, sensations were discrete, unimodal, repeatable, and could be painlessly elicited over the duration of the study. With increasing stimulus current, sensations of touch/ pressure usually spread from distal (digit tip) to proximal locations (Fig. 1).

For proprioceptive sensations, amputees reported sensations related to finger flexion. If the sensation was that of a single joint movement, it was usually localized to the distal interphalangeal joint (DIP). With further increments in stimulus amplitude, the DIP flexion tended to increase and was followed by

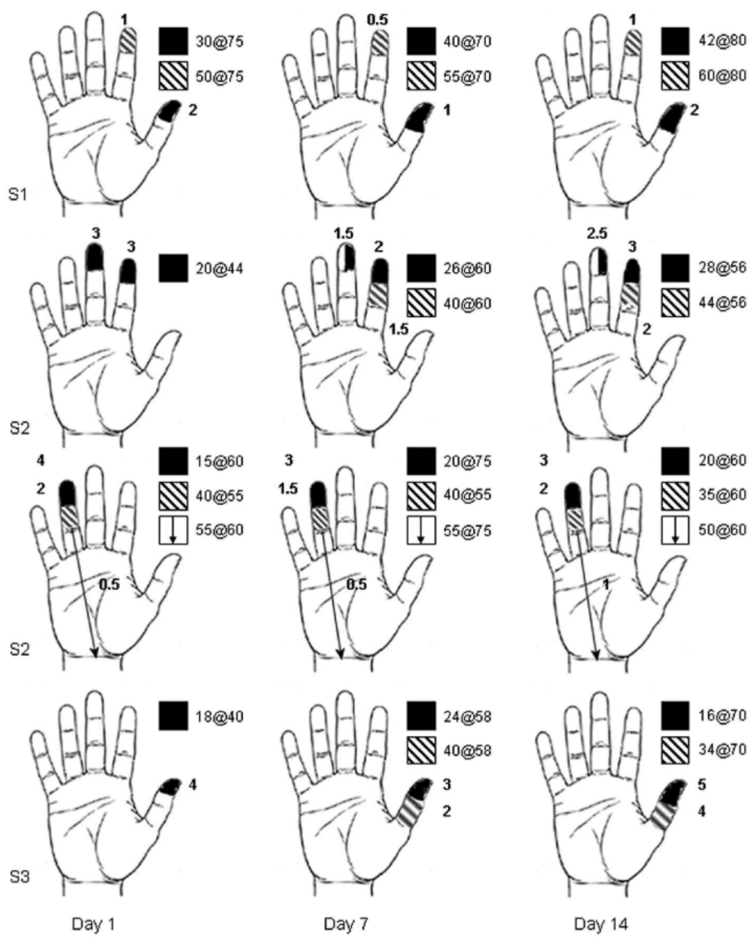


FIG. 1. Distributions and magnitudes of pressure/touch sensations with time and stimulus amplitude in 3 different amputees for whom this was systematically mapped over a 2-wk period. Tactile sensations were evoked with 300-$\mu$s duration stimulus pulse trains. The legends to the right of each drawing indicate the stimulus amplitude (in $\mu$A) and frequency (in pulses/s). The bold number near each shaded region is the psychometric magnitude scale number assigned by the subject to the intensity of the sensation from that part of the phantom hand with the strongest stimulus strength listed. The 1st drawing in a row is the result from day 1 of testing, the 2nd is from day 7, and the 3rd is from day 14. *Rows 2* and *3* are from 2 different electrodes in the same subject.

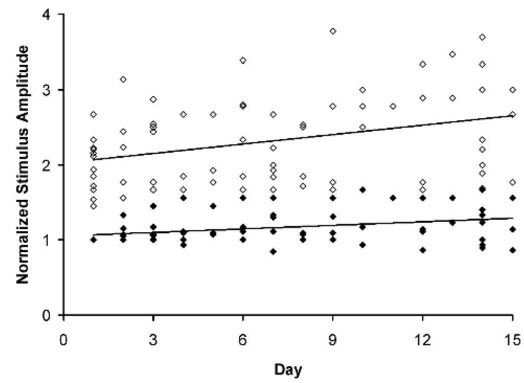


FIG. 2. Threshold (◆) and upper limit (◇) stimulus amplitudes as a function of time. For each of the 12 electrodes included in the figure, amplitudes are normalized to the threshold stimulus amplitude on the 1st day of testing for that particular electrode. Not all electrodes were tested for the full 15 days due to limitations in subject availability.

a sensation of PIP (proximal interphalangeal joint) flexion. Other amputees reported sensations of finger flexion involving the DIP, PIP, and MCP (metacarpal phalangeal) joints or just the flexion of the PIP.

During the course of the study, there was a small, but statistically significant (regression analysis, $P < 0.01$), increase in both the threshold and the upper limit for eliciting painless, unitary sensations of touch/pressure or joint movement, shown in Fig. 2 as values normalized to threshold for each subject on day 1. The mean value for threshold on day 1 was 7.0 ± 2.5 (SD) nC ($n = 12$).

By modulating stimulus frequency, the magnitude estimation, but not the modality or the topography, of referred sensations of touch/pressure or proprioception could be varied systematically: a logarithmic regression gave the best fit for the ratings of magnitude of sensation versus frequency of nerve stimulation (Fig. 3, *A* and *B*). However, indicating perceived finger position by matching it with the contralateral finger produced a more linear relationship between both stimulus amplitude and frequency and reported phantom finger position (Fig. 3, *C* and *D*). Visual inspection showed no systematic trend in the slopes of these regressions over the duration of the study, although they could change from one day to the next in some cases (Fig. 3*B*). This lack of a trend was confirmed by plotting slopes of the regression lines (normalized to the slope on day one) versus time. The data were best approximated by a linear regression with a slope not significantly different from 0 ($r = 0.04$, $P = 0.11$). Analysis of the variance of residuals around the regression lines for the magnitude scaling also showed no systematic trend over the course of the study, indicating no change in scatter of the data with time.

The resting position of a given phantom digit was consistently reported in full extension by the amputees. After stimulation with an impulse train of 500-ms duration, at different frequencies, subjects reported varying degrees of finger flexion (Fig. 3, *B* and *D*). At the end of the impulse train, the digit would be perceived as having returned back into its original position (full extension). At the upper limit of stimulus frequency, the terminal aspect of the finger would appear to dig into the palm, explained by the amputees as a clenched fist but involving only one digit. For all subjects reporting sensations of joint position, there was a general decline in the upper limit frequency (at which the joint was perceived as maximally flexed), averaging ~250 Hz at 2 wk. Frequency of stimulation was also correlated with the perceived rate of digit flexion, but the dominant effect was the change in the sense of static joint position. Amputees could judge the rate of movement as fast or slow but were unable to quantify it on a numerical scale. In one amputee, 5 days after initial testing, perceived finger flexion could no longer be systematically controlled through modulation of stimulation parameters. Instead the subject reported

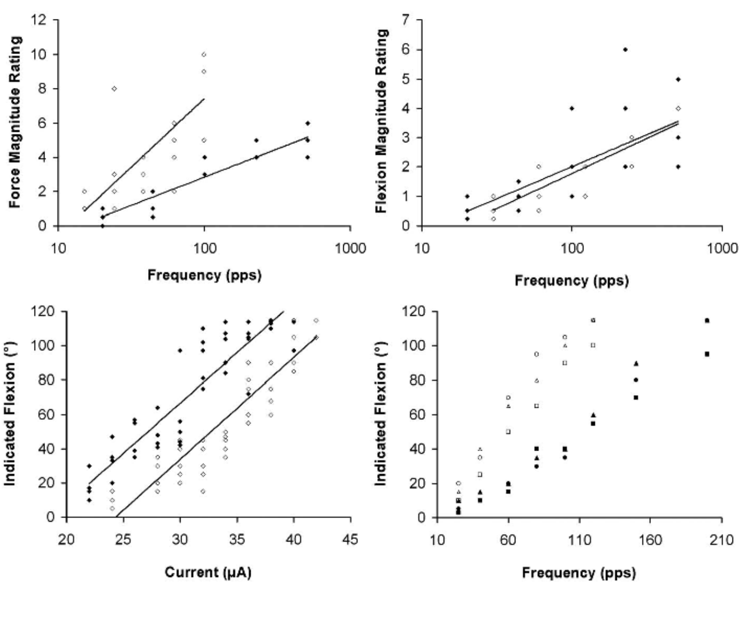


FIG. 3. Examples of psychometric sensory magnitude rating as a function of stimulation parameters. Each panel is based on data from a single subject, selected as a typical example of one or more specific points made in the text. *A*: magnitude estimates of pinch grip force as a function of stimulation frequency. ◆ results from testing on day 1; ◇ results from day 7 for *subject 3245*. The difference between slopes is not significant ($P = 0.62$). *B*: magnitude ratings of perceived finger flexion at the distal (DIP) and proximal (PIP) interphalangeal joints vs. stimulus frequency for *subject 4532*. The difference between slopes for day 1 (◆) and day 7 (◇) is significant ($P < 0.001$). *C*: reported phantom finger flexion as a function of stimulus amplitude for *subject 8726* on day 5 (◆) and day 6 (◇). The difference between slopes is not significant ($P = 0.89$). The stimulus pulse width was 300 $\mu$s, and the stimulus frequency was 100 Hz. *D*: the effect of stimulus current on perceived finger flexion as a function of stimulus frequency for 32 $\mu$A (●, ■, ▲) and 38 $\mu$A (○, □, △), 300-$\mu$s-duration pulses in *subject 4532*. In this case, the stimuli were presented in incremental, rather than pseudorandom, order.

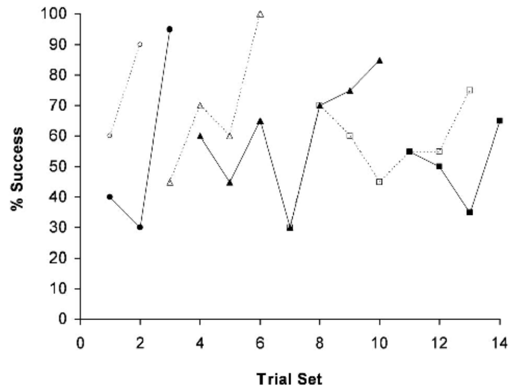


FIG. 4. Graded difficulty for motor control. Results are shown for two different, representative subjects (solid vs. dotted lines). Target dimensions were 96, 68, or 48 pixels wide, scores for which are represented with ○ and ●, △ and ▲, and □ and ■, respectively. The subject's task was to modulate neural activity associated with a phantom limb movement to control the trajectory of the cursor and place it in the target for ≥500 ms. A "trial set" consisted of 20 trials, and subjects were limited to participating in a maximum of 2 sets of trials per day. Thus the data shown took ~1 wk to collect for each subject. Once the subject managed to score with a success rate >75% in a given set of 20 trials, the target was reduced in size to the next level.

only two positions, full extension (no pulses applied) or full flexion (for any value of pulse amplitude or stimulation frequency between the threshold and upper limit). This behavior was not seen with any other electrode in this or other amputees. In all other cases, over the duration of the study perceptions of digit flexion became smoother and less jerky.

Two amputees also reported a sensation of closing and opening of a pincer grip between the thumb, index, and middle fingers. For a stimulation frequency <10 Hz, the grip was felt as open. At ~30 Hz, the index and the middle fingers were perceived as coming into contact with the thumb. With further increments in frequency, pinch force became stronger (Fig. 3*A*).

When defining threshold and upper limit stimulation parameters, subjects reported increasing flexion of fingers with increments in injected charge. This was formally investigated by keeping the frequency of nerve stimulation constant and varying the stimulus amplitude, which demonstrated that the perception of joint flexion/extension could be systematically modulated by varying the stimulus amplitude (Fig. 3*C*). In addition, the stimulus frequency required to provide a sense of full flexion depended on stimulus magnitude. In one subject, for example, with pulse amplitudes of 24, 28, and 32 $\mu$A (pulse width = 300 $\mu$s), the maximum frequency required for perception of full flexion of a digit was 510, 100, and 60 Hz, respectively. This dependence of joint-position sense on the interaction of frequency and charge was quantitatively investigated in one amputee by varying the amplitude and examining the frequency dependence of perceived joint excursion (Fig. 3*D*). In general, the higher the stimulus amplitude the lower the frequency required to produce the sensation of flexion to a given position. Similar observations were made in other subjects, although psychophysical evaluation was not conducted.

### *Motor output*

One or more electrodes recording controllable efferent activity were identified in six of the eight subjects. The success rates with which the subjects could strike and stay within ("hit") the target increased with experience (Fig. 4). Once an amputee managed to score hits in >75% of the trials for a given target size, the target size was reduced. After a reduction in the target size, success rate initially declined and then eventually increased in subsequent sets of trials. Over a period of <70 min experience with the task, subjects demonstrated improved cursor control, progressing from successfully positioning it within a 96 pixel wide target to hitting a 48 pixel wide target (Fig. 4). One subject (not shown) even succeeded in hitting the smallest target 70% of the time with a 750-ms dwell time requirement.

Within a given set of trials, time to score a hit declined for the largest target (linear regression, $r^2 = 0.43$, $n = 4$), but not for the middle or smallest target sizes. The was a small, but statistically significant, relationship between time to success and target size [96 pixel target = 4.8 ± 0.21 (SE) s, 68 pixel target = 4.3 ± 0.17 s, 48 pixel target = 5.0 ± 0.20 s; ANOVA, $P = 0.02$].

Some, but not all, subjects showed an increase with time in the maximal neural output (as defined in METHODS) they could generate to drive the cursor (Fig. 5).

## DISCUSSION

Distally referred sensations of touch and/or proprioception could be elicited in all of the subjects by electrical stimulation through one or more of the implanted LIFEs. This implies that sensory pathways retain at least some residual function even 30 yr after nerve amputation. Once established, the sensations evoked by such stimulation tended to remain stable in terms of modality (touch, joint movement, or joint position), referred location, and sensitivity (as measured by the slopes of the psychometric magnitude estimation curves). This implies that the extent of sensory experience provided by these experiments did not significantly alter the functionality of the residual sensory pathways. As discussed in the following text, it does

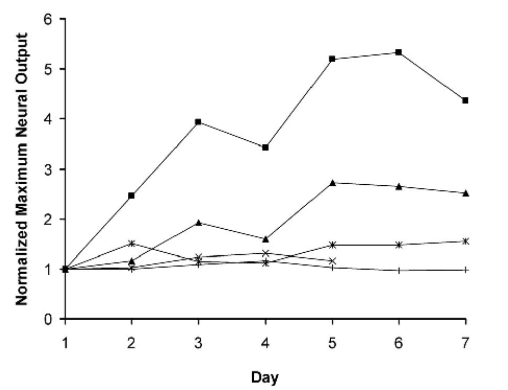


FIG. 5. Change in the maximum recorded neural output (as defined in METHODS) for cursor control for 5 different subjects. Data for each subject is normalized to the output recorded during a maximal effort by the subject on day 1.

not mean that continued or more extensive sensory practice would not do so.

We were unable to record volitionally induced neural activity in only two of the subjects. This does not mean that they did not have functional motor pathways, only that we were unable to identify them, perhaps due to the limited sampling provided by implanting only a few LIFEs in a given subject. Although motor performance did improve with time, given the generally limited increase in motor output seen with time, this improvement appears to be due more to practice with a novel task than to any significant change in central connectivity of the residual motor pathways. Given that the two longest (10 and 30 yr) amputees were among the subjects with good motor control, it appears that basic motor pathways are permanently established by early adulthood, even in the subsequent absence of effectors.

*Sensory input*

There was a small increase with time in the amount of charge per stimulus pulse needed to elicit a threshold sensation and somewhat larger increase in stimulus amplitude that could be delivered before the nature of the sensation changed. One might be tempted to interpret the former as being due to reactive changes around the active electrode stimulating sites, and the latter as being due to this plus, perhaps, a greater central tolerance for stimulation. However, note that all these measurements were made during the time when acute tissue responses to the surgery and implanted electrodes, such as edema, were active. One really needs to wait until these have resolved before making definitive statements about long-term effects and possible causes (Lefurge et al. 1991). One thing that did remain constant, though, was the relatively wide "safety zone" (the ratio of the upper limit to the threshold) for stimulation. Thus it was always easy to find a stimulus amplitude that reliably elicited a discrete, distally referred sensation without dropouts or spread, throughout the 2-wk period of the experiments.

In most cases, the elicited sensations could be systematically controlled through modulation of stimulus frequency and amplitude. Touch/pressure sensations were usually localized to the distal phalanx. With increasing stimulus amplitude, the sensation typically spread proximally. In the digits, the intensity gradient of referred phantom sensations was in the distal to proximal direction. This is consistent with the properties of the LIFEs as point stimulation electrodes, which stimulate progressively larger clusters of neurons with increasing charge injection (Meier et al. 1992; Nannini and Horch 1991), and the greater density of innervation as one moves distally along a digit (Vallbo and Johansson 1984).

Subjects showed a consistent ability to grade the intensity of elicited sensations over the duration of the study. However, there was no consistent pattern of improvement in this ability as evidenced by lack of definite trends in slopes of the regression lines or the variance of residuals around the regression lines. For the sensory studies, subjects were given random stimuli which elicited unitary, punctuate sensations for $<10$ min a day, and they graded the intensity of referred sensations without feedback as to what the stimulus level actually was. More experience, coupled with better feedback, may have improved their performance. Sensory reeducation has been shown to enhance sensory recovery after repair of nerve injuries (Dellon 1981; Mackin et al. 2002), but this recovery is not immediate: it occurs over many weeks. In the present study, sensory input was presented for only a short period of time ($<75$ min over the course of the study) and did not involve any formal training similar to that of sensory reeducation after nerve repair.

The location of elicited touch/pressure sensations either did not change or became better defined with time (e.g., *row 2* of Fig. 1), the latter presumably because amputees could distinguish between intensity gradients, suggesting some beneficial effects of sensory stimulation in activating "silent" regions of the somatosensory cortex. The sensations elicited by the LIFEs tended to cover a larger area than those reported with microneurographic stimulation of intact sensory nerves (Schady and Torebjork 1983; Schady et al. 1983). This may be related to the fact that our study was not designed to precisely map the sizes and the shapes of projected fields. Rather we were more interested in the stability of the elicited sensations and their spread with increasing charge injection. Therefore when the subjects indicated, for example, a sensation referred to the thumb tip, no extra time was spent on elucidating its precise topography, unless the subject volunteered the information. A more-detailed study needs to be undertaken to more precisely define the locations, sizes and shapes of evoked receptive fields. Still, with increasing stimulus strength there was a clear increase in the spread of tactile sensations.

For proprioceptive sensations, amputees reported either movement of a given finger joint or movement of the entire digit. Subjects could reliably distinguish different degrees of joint flexion, through either stimulus frequency or stimulus amplitude modulation. Two subjects consistently reported a referred sensation of phantom grip opening and closing. The perceived magnitude of this pincer grip between thumb, index, and the middle fingers could be reliably controlled through stimulus frequency or amplitude modulation. This finding suggests that the sensory fibers which mediate complex movement and touch sensations of pincer grip opening and closing are topographically grouped and segregated in peripheral nerves. The frequency at which the joint was perceived as maximally flexed (250 Hz on average at 2 wk) is comparable to the maximal frequency of firing of muscle spindle fibers (Clark and Horch 1986). In contrast, frequencies $\leq$510 Hz were correlated with stronger touch/pressure sensations (Fig. 3*A*). With time sensations related to finger flexion became smoother and less "jerky," suggesting positive benefits of providing input to sensory cortex.

Although further studies are needed to more carefully investigate the relationship of stimulus pulse charge and frequency of stimulation to joint position sense, we did find that, in general, the lower the stimulus amplitude, the higher the frequency range needed to provide a sense of full joint excursion (Fig. 3*D*). This is consistent with encoding of joint position and movement information by the total afferent inflow from the pertinent sensory receptors.

*Motor output*

For motor control, in contrast to the sensory studies, the amputees were actively concentrating on improving their performance and were not simply passive subjects. The subjects were able to generate motor neuron activity related to phantom limb movements and demonstrated improvement in cursor control with practice. For example, the subjects managed to increase the precision of cursor control and score hits in 96 pixel targets on day 1, and by the end of the study, the majority of the subjects could proficiently control the position of the cursor in a 48 pixel wide target. For some, but not all, of the subjects there was gradual increase in the neural activity recorded by LIFEs associated with increased precision of cursor control. That is, through learning and practice, the subjects were able to improve motor control outflow to nerve fibers that had not been connected to muscle for periods of months or years. This is evidence of dynamic plasticity of CNS areas concerned with motor control even in the absence of proprioceptive feedback.

*Implications for a neuroprosthetic arm*

Upper limb amputees strongly desire a prosthetic control system that provides prehension feedback from the terminal device (Atkins et al. 1996). Referred sensations of pressure/touch resulting from intraneural stimulation were projected within the distribution of digital nerves and not scattered randomly throughout the hand. This is consistent with animal studies that have demonstrated that such stimulation is sufficiently localized that it is possible to elicit independent stimulation of microclusters within and between fascicles (Branner and Normann 2000; Branner et al. 2001; Yoshida and Horch 1993). Because the spread and topography of a pressure/touch sensation could be controlled through modulation of stimulation parameters, a given electrode could be used as a sensory channel for providing sensory feedback from a portion of the opposing ends of the gripper. With implants in separate fascicles, it is possible to get sensations in different digits. With implants of two or more electrodes in a given fascicle, different sensations could be distinguished within a given digit. Technologies under development may allow for stimulation of individual sensory neurons, increasing the number of sensory channels and resolution of sensory feedback (Dario et al. 1998; Donoghue 2002; González and Rodríguez 1997; Kovacs et al. 1992, 1994; Wallman et al. 2001).

For prehension feedback, sensors in the tip of the artificial hand/gripper would be adequate. Indeed, from a practical point of view the precise topography of elicited sensation does not need to be mapped for providing touch/pressure feedback from the gripper of the artificial arm. Rather it is only necessary that the modality of the elicited sensation be appropriate and that its referred location corresponds to the gripper. Because the intensity of the referred sensations can be reliably modulated, amputees would have appropriate information about contact and grip force.

Normal proprioception may not reflect a sense of joint angle (Scott and Loeb 1994; Soechting 1982), and recent work has demonstrated that extrinsic muscles of the hand signal fingertip position sense more precisely than individual joint angles (Biggs et al. 1999). Even though our subjects could distinguish flexion of different IP joints, information about the location of the terminal aspect of the artificial hand/gripper may be all that is required for prosthetic control. Furthermore, joint position sense from the digits is relatively poor as compared with that from more proximal joints (Clark et al. 1995). When appropriate nerves are implanted for control of artificial limbs, we would expect better results for more proximal joint position sense.

In short, our study implies that if a neuroprosthetic arm were to be interfaced to the residual nerve stumps, amputees might be able to improve control over its movements and incorporate it into their body image through the effects of training, learning and central plasticity.

*Limitations of this study*

The subjects received <10 min of sensory experience on a daily basis. Because they were not informed of what the actual stimulus amplitude or frequency was, they received essentially no graded feedback to use in "improving" their performance. This was necessary to guard against them picking up on some cue other than the strength of a sensation for the tactile ratings or perceived finger position for the proprioception ratings to use in producing their responses. Subjects were provided with a similarly limited amount of motor experience, although in this case feedback was provided on their performance. Clearly amputees receiving a wealth of sensory re-education and motor control training may show greater improvements in sensory perception and motor control than reported here. On the other hand, the fact that even a short period of training can lead to measurable improvement in phantom limb motor control implies that human amputees show dynamic plasticity that may be comparable to that demonstrated in normal subjects after practice of simple movements.

The second limitation to the study is that we really can't say much about how the residual functions in the nerve stump central pathways compare with those in normal subjects. Ethical and regulatory constraints on human subject experimentation preclude implanting LIFEs in intact peripheral nerves, and similar data cannot be obtained via microneurographic studies that are not suitable for recording from and stimulating the same set of nerve fibers over periods of weeks.

ACKNOWLEDGMENTS

We thank the anonymous subjects who gave of time and effort to participate in this study, and Dr. Steve Lawrence who helped design the electrode system.

Present addresses: G. S. Dhillon, Michael E. DeBakey Dept. of Surgery, Baylor College of Medicine, Houston, TX 77030; T. B. Krüger, Fraunhofer—Institute for Biomedical Engineering, Ensheimer Strasse 48, 66386 Sankt Ingbert, Germany; and J. S. Sandhu, Guru Nanak Dev University, Amritsar, Punjab, India

GRANTS

This work was supported by a grant from the National Institute of Neurological Disorders and Stroke.

REFERENCES

**Atkins DJ, Heard DCY, and Donovan WH.** Epidemiologic overview of individuals with upper-limb loss and their reported research priorities. *J Prosthet Orthotics* 8: 2–11, 1996.

**Biggs J, Horch K, and Clark FJ.** Extrinsic muscles of the hand signal finger tip location more precisely than they signal the angles of individual finger joints. *Exp Brain Res* 125: 221–230, 1999.

**Branner A and Normann RA.** A multielectrode array for intrafascicular recording and stimulation in sciatic nerve of cats. *Brain Res Bull* 51: 293–306, 2000.

**Branner A, Stein RB, and Normann RA.** Selective stimulation of cat sciatic nerve using an array of varying-length microelectrodes. *J Neurophysiol* 85: 1585–1594, 2001.

**Calford MB.** Dynamic representational plasticity in sensory cortex. *Neuroscience* 111: 709–738, 2002.

**Carlson J, Lais AC, and Dyck PJ.** Axonal atrophy from permanent peripheral axotomy in adult cat. *J Neuropathol Exp Neurol* 38: 579–585, 1979.

**Chen R, Cohen LG, and Hallett M.** Nervous system reorganization following injury. *Neuroscience* 111: 761–773, 2002.

**Clark FJ and Horch KW.** Kinesthesia. In: *Handbook of Perception and Human Performance*, edited by Boff KR, Kaufman L, and Thomas JP. New York: Wiley, 1986, p. 13-1–13-62.

**Clark FJ, Larwood KJ, Davis ME, and Deffenbacher KA.** A metric for assessing acuity in positioning joints and limbs. *Exp Brain Res* 107: 73–79, 1995.

**Clippinger FW, Avery R, and Titus BR.** A sensory feedback system for an upper-limb amputation prosthesis. *Bull Prosthet Res* 10- 22: 247–258, 1974.

**Cohen LG, Bandinelli S, Findley TW, and Hallet M.** Motor reorganization after upper limb amputation in man. A study with focal magnetic stimulation. *Brain* 114: 615–627, 1991.

**Cragg B and Thomas PK.** Changes in conduction velocity and fibre size proximal to peripheral nerve lesions. *J Physiol* 157: 315–327, 1961.

**Dario P, Garzella P, Toro M, Micera S, Alavi M, Meyer U, Valderrama E, Sebastiani L, Ghelarducci B, Mazzoni C, and Pastacaldi P.** Neural interfaces for regenerated nerve stimulation and recording. *IEEE Trans Rehab Eng* 6: 353–363, 1998.

**Dellon AL.** *Evaluation of Sensibility and Reeducation of Sensation in the Hand.* Baltimore, MD: Williams and Wilkins, 1981.

**DeLuca C and Gilmore LD.** Voluntary nerve signals from severed mammalian nerves: long-term recordings. *Sci* 191: 193–195, 1976.

**DeLuca CJ, Gilmore LD, Bloom LJ, Thomson SJ, Cudworth AL, and Glimcher ML.** Long-term neuroelectric signal recording from severed nerves. *IEEE Trans Biomed Eng* 29: 393–402, 1982.

**Dhillon GS, Lawrence SM, Hutchinson DT, and Horch KW.** Residual function in peripheral nerve stumps of amputees: implications for neural control of artificial limbs. *J Hand Surg* 29A: 605–615, 2004.

**Donoghue JP.** Connecting cortex to machines: recent advances in brain interfaces. *Nat Neurosci* 5, *Supplement*: 1085–1088, 2002.

**Edell DJ.** A peripheral nerve information transducer for amputees: Long-term multichannel recordings from rabbit peripheral nerves. *IEEE Trans Biomed Eng* 33: 203–214, 1986.

**Elbert T, Flor H, Birbaumer N, Knecht S, Hampson S, Larbig W, and Taub E.** Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. *Neuroreport* 5: 2593–2597, 1994.

**Gelfand SA.** *Hearing: An Introduction to Psychological and Physiological Acoustics.* New York: Dekker, 1998.

**González C and Rodríguez M.** A flexible perforated microelectrode array probe for action potential recording in nerve and muscle tissues. *J Neurosci Methods* 72: 189–195, 1997.

**Goodall EV, Lefurge TM, and Horch KW.** Information contained in sensory nerve recordings made with intrafascicular electrodes. *IEEE Trans Biomed Eng* 38: 846–850, 1991.

**Hall EJ, Flament D, Fraser C, and Lemon RN.** Non-invasive brain stimulation reveals reorganised cortical outputs in amputees. *Neurosci Lett* 116: 379–386, 1990.

**Hoffer JA, Stein RB, and Gordon T.** Differential atrophy of sensory and motor fibers following section of cat peripheral nerves. *Brain Res* 178: 347–361, 1979.

**Horch K.** Central responses of cutaneous sensory neurons to peripheral nerve crush in the cat. *Brain Res* 151: 581–586, 1978.

**Horch KW and Lisney SJW.** Changes in primary afferent depolarization of sensory neurons during peripheral nerve regeneration in the cat. *J Physiol* 313: 287–299, 1981a.

**Horch KW and Lisney SJW.** On the number and nature of regenerating myelinated axons after lesions of cutaneous nerves in the cat. *J Physiol* 313: 275–286, 1981b.

**Jones EG, Woods TM, and Manger PR.** Adaptive responses of monkey somatosensory cortex to peripheral and central deafferentation. *Neuroscience* 111: 775–797, 2002.

**Kawamura Y and Dyck PJ.** Permanent axotomy by amputation results in loss of motor neurons in man. *J Neuropathol Exp Neurol* 40: 658–666, 1981.

**Kiraly JK and Krnjevic K.** Some retrograde changes in function of nerves after peripheral section. *Q J Exp Physiol Cogn Med Sci* 44: 244–257, 1959.

**Kovacs GT, Storment CW, Halks-Miller M, Belczynski CR, Jr, Della Santina CC, Lewis ER, and Maluf NI.** Silicon-substrate microelectrode arrays for parallel recording of neural activity in peripheral and cranial nerves. *IEEE Trans Biomed Eng* 41: 567–577, 1994.

**Kovacs GTA, Storment CW, and Rosen JM.** Regeneration microelectrode array for peripheral nerve recording and stimulation. *IEEE Trans Biomed Eng* 39: 893–902, 1992.

**Lawrence SM, Dhillon GS, and Horch KW.** Fabrication and characteristics of an implantable, polymer-based, intrafascicular electrode. *J Neurosci Methods* 131: 9–26, 2003.

**Lawrence SM, Dhillon GS, Jensen W, Yoshida K, and Horch KW.** Acute peripheral nerve recording characteristics of polymer-based longitudinal intrafascicular electrodes. *IEEE Trans Neur Sys Rehab Eng* 12: 345–348, 2004.

**Lefurge T, Goodall E, Horch K, Stensaas L, and Schoenberg A.** Chronically implanted intrafascicular recording electrodes. *Ann Biomed Eng* 19: 197–207, 1991.

**Mackin EJ, Callahan AD, Osterman AL, Skirven TM, Schneider LH, and Hunter JM.** *Hunter, Mackin and Callahan's Rehabilitation of the Hand and Upper Extremity.* St. Louis: Mosby, 2002.

**Malagodi M, Horch KW, and Schoenberg AA.** An intrafascicular electrode for recording of action potentials in peripheral nerves. *Ann Biomed Eng* 17: 397–410, 1989.

**Malmstrom JA, McNaughton TG, and Horch KW.** Recording properties and biocompatibility of chronically implanted polymer-based intrafascicular electrodes. *Ann Biomed Eng* 26: 1055–1064, 1998.

**McNaughton TG and Horch KW.** Metallized polymer fibers as leadwires and intrafascicular microelectrodes. *J Neurosci Methods* 70: 103–110, 1996.

**Meier JH, Rutten WLC, Zoutman AE, Boom HBK, and Bergveld P.** Simulation of multipolar fiber selective neural stimulation using intrafascicular electrodes. *IEEE Trans Biomed Eng* 39: 122–134, 1992.

**Mendell LM, Munson JB, and Scott JG.** Connectivity changes of Ia afferents on axotomized motoneurons. *Brain Res* 73: 338–342, 1974.

**Merzenich MM and Jenkins WM.** Reorganization of cortical representations of the hand following alterations of skin inputs induced by nerve injury, skin island transfers, and experience. *J Hand Ther* 6: 89–104, 1993.

**Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, and Zook JM.** Somatosensory cortical map changes following digit amputation in adult monkeys. *J Comp Neurol* 224: 591–605, 1984.

**Milner TE and Stein RB.** The effects of axotomy on the conduction of action potentials in peripheral sensory and motor nerve fibres. *J Neurol Neurosurg Psychiat* 44: 485–496, 1981.

**Nannini N and Horch K.** Muscle recruitment with intrafascicular electrodes. *IEEE Trans Biomed Eng* 38: 769–776, 1991.

**Sanes JN, Suner S, and Donoghue JP.** Dynamic organization of primary motor cortex output to target muscles in adult rats. I. Long-term patterns of reorganization following motor or mixed peripheral nerve lesions. *Exp Brain Res* 79: 479–491, 1990.

**Schady WJL and Torebjork HE.** Projected and receptive fields: a comparison of projected areas of sensations evoked by intraneural stimulation of mechanoreceptive units, and their innervation territories. *Acta Physiol Scand* 119: 267–275, 1983.

**Schady WJL, Torebjork HE, and Ochoa JL.** Cerebral localisation function from the input of single mechanoreceptive units in man. *Acta Physiol Scand* 119: 277–285, 1983.

**Scott SH and Loeb GE.** The computation of position sense from spindles in mono- and multiarticular muscles. *J Neurosci* 14: 7529–7540, 1994.

**Soechting JF.** Does position sense at the elbow reflect a sense of elbow joint angle or one of limb orientation? *Brain Res* 248: 392–395, 1982.

**Stevens SS.** *Psychophysics.* New York: Wiley, 1986.

**Sumner BEH and Watson WE.** Retraction and expansion of the dendritic tree of motor neurones of adult rats induced in vivo. *Nature* 233: 273–275, 1971.

**Sunderland S.** *Nerves and Nerve Injuries.* New York: Churchill Livingstone, 1978.

**Théoret H, Merabet L, and Pascual-Leone A.** Behavioral and neuroplastic changes in the blind: evidence for functionally relevant cross-modal interactions. *J Physiol* 98: 221–233, 2004.

**Törnqvist E and Aldskogius H.** Motoneuron survival is not affected by the proximo-distal level of axotomy but by the possibility of regenerating axons to gain access to the distal nerve stump. *J Neurosci Res* 39: 159–165, 1994.

**Vallbo AB and Johansson RS.** Properties of cutaneous mechanoreceptors in the human hand related to touch sensation. *Hum Neurobiol* 3: 3–14, 1984.

**Wall JT, Xu J, and Wang X.** Human brain plasticity: an emerging view of the multiple substrates and mechanisms that cause cortical changes and related sensory dysfunctions after injuries of sensory inputs from the body. *Brain Research Reviews* 39: 181–215, 2002.

**Wallman L, Zhang Y, Laurell T, and Danielsen N.** The geometric design of micromachined silicon sieve electrodes influences functional nerve regeneration. *Biomat* 22: 1187–1193, 2001.

**Yoshida K and Horch K.** Closed-loop control of ankle position using muscle afferent feedback with functional neuromuscular stimulation. *IEEE Trans Biomed Eng* 43: 167–176, 1996.

**Yoshida K and Horch K.** Selective stimulation of peripheral nerve fibers using dual intrafascicular electrodes. *IEEE Trans Biomed Eng* 40: 492–494, 1993.

# CHAPTER 4

# DIRECT NEURAL SENSORY FEEDBACK AND CONTROL OF A PROSTHETIC ARM

# Direct Neural Sensory Feedback and Control of a Prosthetic Arm

Gurpreet Singh Dhillon and Kenneth W. Horch, *Member, IEEE*

***Abstract*—Evidence indicates that user acceptance of modern artificial limbs by amputees would be significantly enhanced by a system that provides appropriate, graded, distally referred sensations of touch and joint movement, and that the functionality of limb prostheses would be improved by a more natural control mechanism. We have recently demonstrated that it is possible to implant electrodes within individual fascicles of peripheral nerve stumps in amputees, that stimulation through these electrodes can produce graded, discrete sensations of touch or movement referred to the amputee's phantom hand, and that recordings of motor neuron activity associated with attempted movements of the phantom limb through these electrodes can be used as graded control signals. We report here that this approach allows amputees to both judge and set grip force and joint position in an artificial arm, in the absence of visual input, thus providing a substrate for better integration of the artificial limb into the amputee's body image. We believe this to be the first demonstration of direct neural feedback from and direct neural control of an artificial arm in amputees.**

***Index Terms*—Peripheral nerve implant, prosthetic limb control, sensory feedback.**

## I. Introduction

IT IS generally agreed that user acceptance of modern artificial limbs by amputees would be significantly enhanced by a system that provides appropriate, graded, distally referred sensations of touch and joint movement, and that the functionality of limb prostheses would be improved by a more natural control mechanism [1]–[8]. In addition, it has been reported that phantom limb pain, which can affect up to 80% of amputees, can be ameliorated in some cases by sensory training that limits the extent of somatosensory cortical reorganization [9]–[12]. Although different sensory feedback systems have been tried, including whole nerve stimulation, none of them have been widely adopted clinically, presumably because they have not provided discrete, natural, distally referred sensations [13]–[19]. Similarly, control strategies for artificial arms generally require that the user translate some unrelated motion into the intended motion of the arm (but see [20] for a recent exception). We believe that these problems can be solved by a direct neural interface with nerve fibers in the peripheral nerve stumps that allows feedback information to be provided through sensory pathways originally associated with the missing parts of the arm, and that allows control signals to be derived from neural activity generated by the amputee in attempting to move the missing elbow, wrist, or fingers.

The intent of the present study was to demonstrate that appropriate, distally referred sensory feedback about joint position and grip force from an artificial arm could be provided to an amputee through stimulation of the severed peripheral nerves, and that motor command signals appropriate for controlling joint position and grip force could be obtained by recording motor neuron activity from these nerves. As a feasibility study, issues of optimizing sensory discrimination through nerve stimulation or motor control ability through nerve recording were not addressed, but have been left for future work.

## II. Methods

Longitudinal intrafascicular electrodes (LIFEs) [21]–[23] were implanted within fascicles of severed nerves in six male, long term (range 10–360 months, average 96 months post-amputation), upper limb (amputation level at or below elbow) human amputees. The electrodes were exteriorized percutaneously, and connected to external circuitry interfaced with a laptop computer. Following completion of the study, the electrodes were removed percutaneously by applying gentle longitudinal traction. Institutional Review Board approval was obtained for the study, all amputees were given adequate time to consent to the study, and all signed an approved, written consent form.

### A. Electrodes

Details of electrode design, fabrication, recording and stimulation properties have been extensively presented previously [21]–[29]. LIFEs were fabricated from commercially available 25-$\mu$m-diameter, Teflon insulated platinum-iridium wire (A-M Systems #7750). Each electrode consisted of a 20–30-cm-long wire from which insulation was removed over a 1 mm length, approximately 5 cm from the leading end of the electrode. Platinum black was electrodeposited on this recording/stimulating zone to produce a low impedance interface (1–3 k$\Omega$ at 1000 Hz). To insert the flexible LIFE into the nerve fascicle, a 50-$\mu$m-diameter tungsten needle was chemically bonded to the leading end of the electrode using cyanoacrylate adhesive. The other end of the LIFE was connected to saddle connector, which was adhered to the skin surrounding the point where the percutaneous electrodes exited the arm. This connector was used to interface outside circuitry (recording and stimulation hardware) to the electrodes.

Manuscript received January 25, 2005; revised June 5, 2005; accepted June 27, 2005. This work was supported by a grant from the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health.

G. S. Dhillon is with the Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX 77030 USA.

K. W. Horch is with the Department of Bioengineering, University of Utah, Salt Lake City, UT 84112 USA (e-mail: k.horch@m.cc.utah.edu).

Digital Object Identifier 10.1109/TNSRE.2005.856072

### B. Electrode Implantation, Evaluation of Electrode Function, and Subject Training

Surgical procedures, mapping of motor and sensory electrode functions, evaluation of stimulation and motor control parameters, and subject training with computer controlled stimuli and simulated tasks have also been described in detail elsewhere [30], [31], so only a brief description will be provided here.

To insure that recordings could be made from motor neurons innervating the extrinsic muscles of the hand, the electrodes were implanted in the median nerve above the point where motor fibers start branching to those muscles [32]–[34] in four of the subjects. Electrodes were implanted in the median nerve in the forearm for the other two subjects, who were not used for evaluation of motor control. Following limited external neurolysis to visualize the Bands of Fontana, the tungsten needle was used to thread the LIFE into a given fascicle, centering the 1-mm recording/stimulating zone in the fascicle. The needle was then cut off and the distal end of the electrode was tacked in place using a 8-0 nonabsorbable suture. A reference electrode having the same physical dimensions and electrical properties as the LIFEs was placed at the level of implantation but outside the nerve fascicles. Four to eight electrodes were implanted in each subject.

Sensory feedback channels were identified by applying short duration (500 ms) pulse trains with varying current-controlled pulse amplitudes at a fixed pulsewidth (300 $\mu$s) to individual electrodes. This identified which electrodes could be used to elicit distally referred sensations of touch/pressure or proprioception, and defined the threshold and upper current limit for the sensation. Once these parameters were identified, psychophysical testing was done to map the relationship between stimulus frequency and sensation intensity (or perceived position of a joint). Stimulation frequencies of 250 and 500 Hz were found to be upper limits for position and pressure sensations, respectively. The minimum stimulus frequency was 10 Hz. In all subjects, one or more electrodes were capable of providing sensory input.

Motor control channels were identified by connecting individual electrodes and the reference electrode to a differential amplifier (gain of ~20 000, bandpass filter 0.3–4 kHz), the output of which was fed to a loudspeaker (Fig. 1). The subject was instructed to attempt a missing limb movement (such as finger flexion) while listening to the nerve activity over the loudspeaker. In each of the subjects implanted in the upper arm, one or more electrodes provided motor signals. For an electrode from which motor nerve activity could be recorded in response to such attempts, recorded signals were fed via a 16 bit digital-to-analog converter to a laptop computer and the amount of neural activity associated with a given limb movement was quantified. The subject was asked to control the position of a cursor on the computer screen by modulating this motor activity. The position of the cursor was linearly related to the level of motor activity: minimal output placing it at the left end of the screen, maximal output placing it at the right edge of the screen. The goal was to place the cursor and make in stay within a randomly appearing stationary target for a specified period of time (e.g., 0.5 s). Subjects were scored on the percentage of time they succeeded in this task in a given block of trials. As performance improved above a set level, the task was made more difficult by changing target size or changing the time constraints.

Fig. 1. Experimental setup. Shown is a photograph taken during a typical motor control training session. Percutaneous intrafascicular electrodes implanted in the median nerve of the subject's amputated arm were connected by a cable to a multichannel, differential amplifier. Switches allowed any given electrode to be connected to any one of the amplifiers. Outputs from two of the amplifiers were supplied to loudspeakers so the subject and the experimenter could monitor recorded neural activity by ear. The outputs from the amplifiers were fed into a laptop computer via 16 bit analog-to-digital converters. In the present experiments, only one amplifier channel was used at a time. Initial phase of training consisted of using the loudspeaker monitor to identify electrodes on which neural activity could be recorded while the subject attempted to move individual fingers or the wrist of the amputated hand. Once a suitable electrode was identified, the subject's task was use this activity to control the position of a cursor on the computer screen as described in the text. Next, the subject was instructed to modulate the motor activity to control the position of the elbow of the artificial arm or the force exerted by the hand. During testing, once training was over, the subject was turned facing away from the equipment and was blindfolded to eliminate any visual cues as to the task or his performance. Loudspeakers were disconnected so there were no auditory cues. For sensory feedback, stimulus waveforms generated by the computer were fed via a digital-to-analog converter to a current controlled stimulus isolation unit which was connected to the desired intrafascicular electrode.

### C. Nerve–Arm Interface

Computer-aided training studies were conducted for up to 7 days [31]. Experiments with a modified Utah Artificial Arm (Motion Control Inc.) were conducted over a one week period immediately following the training period (Fig. 1). A force (strain gauge) sensor in the thumb of the hand and a position (angle) sensor in the elbow of the prosthesis were used to provide sensory feedback. Input from one or the other of these sensors was logarithmically mapped to the stimulus frequency delivered to the selected stimulating electrode (tactile sensation for force, proprioception for position), within the frequency limits determined in the psychophysical evaluations described above [30], [31].

Actuators in the elbow and hand were controlled in torque and force mode, respectively. Neuronal firing rate recorded from a motor control electrode was used to control these actuators. The control signal was generated by a process equivalent to leaky integration of the neural firing rate with a linear decay rate.

Specifically, recordings of activity during rest and maximal voluntary effort at making the intended movement were used to set a threshold level for detecting neural events (spikes). Each spike added a fixed increment to the output control signal, which decayed linearly over a selected time period (typically 0.5 s). The net control signal was thus the linear sum of the contributions from each spike detected within this decay period. The gain of the control signal was set so that a slightly submaximal effort produced full elbow flexion or full grip force.

### *D. Sensory Input*

Due to constraints on the time available to work with individual subjects, three of the subjects were used for tactile and proprioceptive sensory feedback evaluation. In each of these subjects, one tactile and one proprioceptive electrode were selected for testing. Prior to the testing, training paradigms involved three and then five different force or position matches with visual feedback. Varying levels of indentation or force were applied to the strain gauge sensor on the thumb and the subject was asked to rate them, without the visual feedback, by using an open numerical scale for indentation [31], [35] or by squeezing a pinch force meter for force. For joint position sense, the elbow of the artificial arm was moved to different positions and the subject was asked to match the perceived angle of elbow flexion/extension, again without the visual feedback, through movements of the contralateral, intact arm.

### *E. Motor Output*

Motor control was assessed in the other three subjects, using only one of the available motor channel electrodes in each. This was done by asking the subjects to control grip force (two subjects) or elbow position (one subject), without visual feedback. Prior to testing, each subject was given adequate time to acquaint and train himself for a given movement, usually for a period of up to 30 min, on a daily basis. For grip force control, the subjects were asked to match three levels of force (typically 22, 44, and 67 N) and then, after successfully matching more than 70% of the target values, five force levels (typically ranging from 13 to 67 N). Subjects had to match the target value within 5 s and the steady state read out was taken as the value for applied force. The matched position was assigned to the nearest target. Following proficiency at five levels, the subjects were asked to control force applied by the hand for any value set randomly in the range 22–67 N. For elbow position control, a similar training paradigm was used following which the subject was directed to match various randomly set angles of his intact arm with the artificial arm.

## III. Results

### *A. Sensory Input*

All three subjects could judge changes in indentation or force applied to the thumb sensor [Fig. 2(a)]. The slopes of linear regression lines fit to the data were significantly different from zero ($p < 0.001$, $r^2$ values ranged from 0.80 to 0.87 at the end of the experimental period). The regression slopes showed a significant increase with time in one subject ($p < 0.05$) but not in the other two ($p > 0.1$). There was a significant decline in the

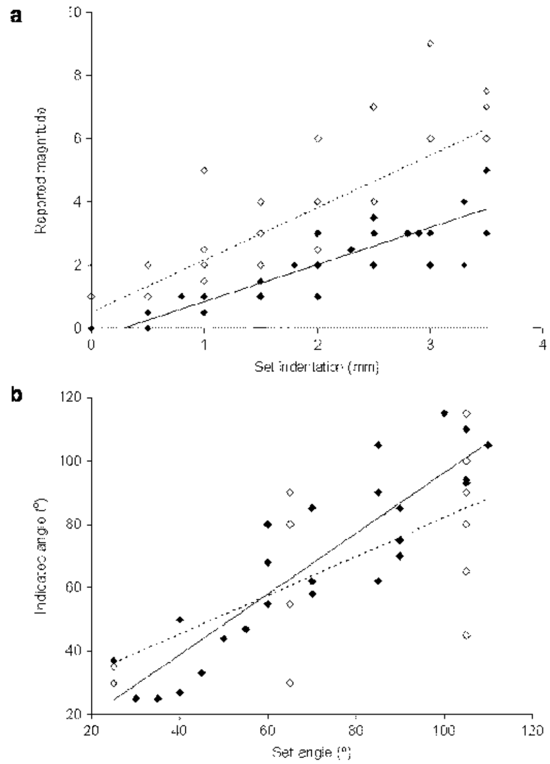


Fig. 2. Sensory input. (a) Psychometric sensation magnitude reported by subject 4532 (on an open scale) versus indentation applied to the thumb sensor by the experimenter on day 1 (open symbols, dotted line) and day 7 (filled symbols, solid line). (b) Matching position of the contralateral, intact elbow set by subject 8726 versus position of the artificial arm elbow set by the experimenter on day 1 (open symbols, dotted line) and day 4 (filled symbols, solid line). Data were collected in repeated up and down sequences on the first day and in random order on the last day.

variance of residuals around the regression lines in two of the amputees ($p < 0.01$), but not in the third ($p = 0.1$).

The subjects could also consistently judge the static position of the elbow joint in the artificial arm [Fig. 2(b)]. Linear regression ($p < 0.05$ for the first run, $p < 0.001$ subsequently) best described the relationship between actual and sensed joint positions of the artificial arm. There was a general increase in the slopes of the regression lines with time, which was statistically significant ($p < 0.05$) in two of the three subjects. A statistically significant ($p < 0.05$) decline in the variance around the regression lines with time was seen in only one subject.

### *B. Motor Output*

For grip force control, linear regression ($p \gg 0.05$ for non linearity), with a significant nonzero slope ($p < 0.001$), provided the best fit for the correlation between the target and the applied force ($r^2$ values of 0.86–0.90, at the end of the testing period). Sample data from one of the two subjects is shown in Fig. 3(a): the other subject gave similar results. Analysis of variance around the regression lines indicated a significant

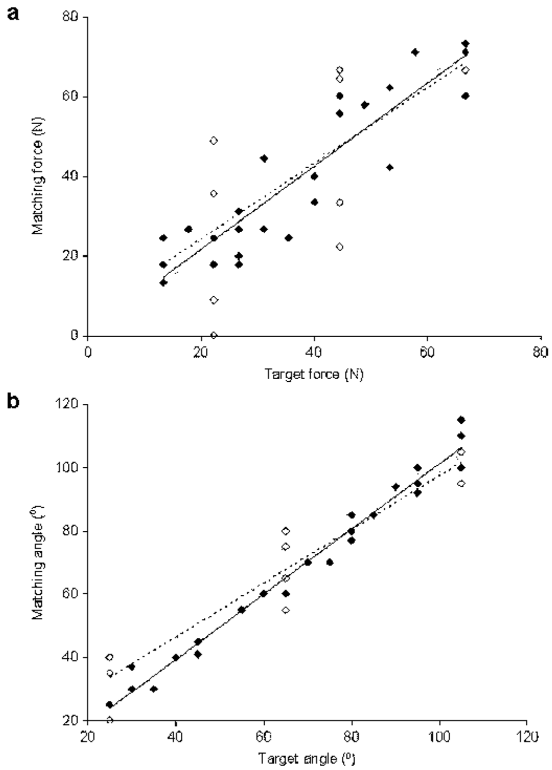


Fig. 3. Motor output. (a) Hand force applied by subject 9018 versus target force set by the experimenter on day 1 (open symbols, dotted line) and day 6 (filled symbols, solid line). (b) Position of the artificial arm elbow set by subject 8276 versus target position of the contralateral, intact elbow set by the experimenter on day 1 (open symbols, dotted line) and day 5 (filled symbols, solid line). Data were collected in repeated up and down sequences on the first day and in random order on the last day.

$(p < 0.01)$ reduction with time in both subjects, with no significant change in the slopes of the regression lines.

For elbow control, linear regression ($p \gg 0.5$ for non linearity), with a significant nonzero slope ($p < 0.04$ for day one, otherwise $p < 0.001, r^2$ up to 0.98), described the relationship between target and matched elbow flexion/extension angles [Fig. 3(b)]. There was a significant increase in the slopes $(p < 0.01)$ and decline in the variance of residuals around the regression line $(p < 0.01)$ with time for this subject.

## IV. Discussion and Conclusion

These results indicate that appropriate, graded, distally referred sensations can be provided through stimulation of amputee nerve stumps with intrafascicular electrodes and that these sensations can be used to provide feedback information about grip strength and limb position. In addition, control of grip strength and limb position can be effected by recording volitional motor activity from the peripheral nerve stumps with these electrodes. Indications of improved performance (reduced variance and increased regression line slopes), in at least some of the subjects over the short period tested, suggest that further training would provide even better feedback and control. The extent to which this can reverse the cortical plastic changes seen after amputation is still to be determined, but evidence from studies of the effects of experience on cortical representation of sensory and motor information [36]–[38] suggest that it will have a significant impact, and may help provide a pain-free integration of the artificial arm into the amputee's body image.

As a feasibility study with a limited number of subjects and relatively short duration, this work did not address issues of optimization of sensory stimulation paradigms, optimal processing of motor control signals, different training regimes, or improving the operational characteristics of the artificial arm. Nor did we explore closed-loop, nonvisual control of the artificial arm. However, the data presented here do provide an adequate rationale and basis for pursuing these issues.

On the hardware side, things to be considered include provision of either an implanted, bidirectional telemetry system or a viable, permanent percutaneous connector system as an interface to the intraneural electrodes. An artificial arm and hand needs to be designed with continuous, simultaneous, neural control of multiple degrees of freedom and continuous sensory feedback of limb position and tactile events. A method of accommodating or eliminating stimulus artifacts while simultaneously stimulating and recording from peripheral nerve stumps needs to be implemented. All of these are within the grasp of current technology, although design constraints on weight and power supply requirements make designing a new generation of artificial arm that meets these criteria an interesting challenge.

Once an adequate hardware platform is in place, the stage will be set to explore closed-loop control of an artificial arm based solely on neural control and feedback. This would include optimizing stimulation parameters and motor control strategies to minimize the number of channels (electrodes) needed, and exploring different training approaches to maximize the functional utility of the neuroprosthetic arm. In particular, one would like to develop a system that allows the amputee to practice movements and acquaint him/herself with pseudonatural sensory feedback from the prosthesis in the home and work environment. The end result of which, ideally, would be to get the amputee to the point of feeling that the arm is part of his/her body and using it without conscious effort or thought.

## Acknowledgment

The authors thank T. Krueger, S. Lawrence, and S. Meek for technical assistance, and G. S. Ghuman, C. Singh, and J. S. Sandhu for clinical assistance.

## References

[1] D. J. Atkins, D. C. Y. Heard, and W. H. Donovan, "Epidemiologic overview of individuals with upper-limb loss and their reported research priorities," *J. Prosthetics Orthotics*, vol. 8, pp. 2–11, 1996.

[2] S. C. Jacobsen, D. F. Knutti, R. T. Johnson, and H. T. Sears, "Development of the Utah artificial arm," *IEEE Trans. Biom. Eng.*, vol. BME-29, pp. 249–269, 1982.

[3] M. D. Northmore-Ball, H. Heger, and G. A. Hunter, "The below-elbow myoelectric prosthesis," *J. Bone Joint Surgery*, vol. 62-B, pp. 363–367, 1980.

[4] T. A. Rohland, "Sensory feedback for powered limb prostheses," *Med. Bio. Eng.*, vol. 12, pp. 300–301, 1975.

[5] M. Lotze, W. Grodd, N. Birbaumer, M. Erb, E. Huse, and H. Flor, "Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain?," *Nature Neurosci.*, vol. 2, pp. 501–502, 1999.

[6] H. H. Sears and J. Shaperman, "Proportional myoelectric hand control: An evaluation," *Amer. J. Phys. Med. Rehabil.*, vol. 70, pp. 20–28, 1991.

[7] R. B. Stein and M. Walley, "Functional comparison of upper extremity amputees using myoelectic and conventional prostheses," *Arch. Phys. Med. Rehabil.*, vol. 64, pp. 243–248, 1983.

[8] G. S. Dhillon and S. Meek, "Challenges to developing a neurally controlled upper limb prosthesis," in *Neuroprosthetics: Theory and Practice*, K. W. Horch and G. S. Dhillon, Eds. Hackensack, NJ, 2004, pp. 1005–1034.

[9] H. Flor, T. Elbert, S. Knecht, C. Wienbruch, C. Pantev, N. Birbaumer, W. Larbig, and E. Taub, "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, vol. 375, pp. 482–484, 1995.

[10] N. Birbaumer, W. Lutzenberger, P. Montoya, W. Larbig, K. Unertl, S. Töpfner, W. Grodd, E. Taub, and H. Flor, "Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization," *J. Neurosci.*, vol. 17, pp. 5503–5508, 1997.

[11] H. Flor, T. Elbert, W. Mühlnickel, C. Pantev, C. Wienbruch, and E. Taub, "Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees," *Experimental Brain Res.*, vol. 119, pp. 205–212, 1998.

[12] H. Flor, C. Denke, M. Schaefer, and S. Grüsser, "Effect of sensory discrimination training on cortical reorganization and phantom limb pain," *Lancet*, vol. 357, pp. 1763–1764, 2001.

[13] F. W. Clippinger, R. Avery, and B. R. Titus, "A sensory feedback system for an upper-limb amputation prosthesis," *Bull. Prosthetics Res.*, vol. 10–22, pp. 247–258, 1974.

[14] R. W. Mann, "Prostheses control and feedback via noninvasive skin and invasive peripheral nerve techniques," in *Neural Organization and Its Relevance to Prosthetics*, W. S. Fields, Ed. New York: Intercontinental Medical, 1973, pp. 177–195.

[15] C. A. Phillips, "Sensory feedback control of upper- and lower-extremity motor prostheses," *CRC Critical Rev. Biomed. Eng.*, vol. 16, pp. 105–140, 1988.

[16] G. F. Shannon, "A comparison of alternative means of providing sensory feedback on upper limb prostheses," *Med. Biol. Eng.*, vol. 14, pp. 289–293, 1976.

[17] ——, "A myoelectrically-controlled prosthesis with sensory feedback," *Med. Biol. Eng. Comput.*, vol. 17, pp. 73–80, 1979.

[18] O. Sueda, "Evaluation of sensation apparatus for hand prosthesis and controllability of hand proshtesis," *Biomechanisms*, pp. 171–184, 1972.

[19] C. F. Walker, G. R. Lockhead, D. R. Markle, and J. H. McElhaney, "Parameters of stimulation and perception in an artificial sensory feedback system," *Journal of Bioengineering*, vol. 1, pp. 251–260, 1977.

[20] T. A. Kuiken, G. A. Dumanian, R. D. Lipschutz, L. A. Miller, and K. A. Stubblefield, "The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee," *Prosthetics Orthotics Int.*, vol. 28, pp. 245–253, 2004.

[21] S. M. Lawrence, G. S. Dhillon, and K. W. Horch, "Fabrication and characteristics of an implantable, polymer-based, intrafascicular electrode," *J. Neurosci. Methods*, vol. 131, pp. 9–26, 2003.

[22] M. Malagodi, K. W. Horch, and A. A. Schoenberg, "An intrafascicular electrode for recording of action potentials in peripheral nerves," *Ann. Biomed. Eng.*, vol. 17, pp. 397–410, 1989.

[23] T. G. McNaughton and K. W. Horch, "Metallized polymer fibers as leadwires and intrafascicular microelectrodes," *J. Neurosci. Methods*, vol. 70, pp. 103–110, 1996.

[24] T. Lefurge, E. Goodall, K. Horch, L. Stensaas, and A. Schoenberg, "Chronically implanted intrafascicular recording electrodes," *Ann. Biomed. Eng.*, vol. 19, pp. 197–207, 1991.

[25] E. V. Goodall, T. M. Lefurge, and K. W. Horch, "Information contained in sensory nerve recordings made with intrafascicular electrodes," *IEEE Trans. Biomed. Eng.*, vol. 38, no. 9, pp. 846–850, Sep. 1991.

[26] K. Yoshida and K. Horch, "Selective stimulation of peripheral nerve fibers using dual intrafascicular electrodes," *IEEE Trans. Biomed. Eng.*, vol. 40, no. 5, pp. 492–494, May 1993.

[27] ——, "Closed-loop control of ankle position using muscle afferent feedback with functional neuromuscular stimulation," *IEEE Trans. Biomed. Eng.*, vol. 43, no. 2, pp. 167–176, Feb. 1996.

[28] J. A. Malmstrom, T. G. McNaughton, and K. W. Horch, "Recording properties and biocompatibility of chronically implanted polymer-based intrafascicular electrodes," *Ann. Biomed. Eng.*, vol. 26, pp. 1055–1064, 1998.

[29] S. M. Lawrence, J. O. Larsen, K. W. Horch, R. Riso, and T. Sinkjær, "Long-term biocompatibility of implanted polymer-based intrafascicular electrodes," *J. Biomed. Materials Res.*, vol. 63, pp. 501–506, 2002.

[30] G. S. Dhillon, S. M. Lawrence, D. T. Hutchinson, and K. W. Horch, "Residual function in peripheral nerve stumps of amputees: Implications for neural control of artificial limbs," *J. Hand Surgery*, vol. 29A, pp. 605–615, 2004.

[31] G. S. Dhillon, T. B. Krüger, J. S. Sandhu, and K. W. Horch, "Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees," *J. Neurophysiol.*, vol. 93, pp. 2625–2633, 2005.

[32] S. Sunderland, *Nerves and Nerve Injuries*, 2nd ed. New York: Churchill Livingstone, 1978.

[33] F. H. Netter, *Atlas of Human Anatomy*, 2nd ed. East Hanover, NJ: Novartis, 1997.

[34] F. H. Martini, M. J. Timmons, and M. P. McKinley, *Human Anatomy*. Englewood Cliffs, NJ: Prentice-Hall, 2000.

[35] S. S. Stevens, *Psychophys.*. New York: Wiley, 1986.

[36] J. Classen, J. Liepert, S. P. Wise, M. Hallett, and L. G. Cohen, "Rapid plasticity of human cortical movement representation induced by practice," *J. Neurophys.*, vol. 79, pp. 1117–1123, 1998.

[37] A. Karni, G. Meyer, P. Jezzard, M. M. Adams, R. Turner, and L. G. Ungerleider, "Functional MRI evidence for adult motor cortex plasticity during motor skill learning," *Nature*, vol. 377, pp. 155–158, 1995.

[38] A. Pascual-Leone, D. Nguyet, L. G. Cohen, J. P. Brasil-Neto, A. Cammarota, and M. Hallett, "Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills," *J. Neurophys.*, vol. 74, pp. 1037–1045, 1995.

**Gurpreet Singh Dhillon** photograph and biography not available at the time of publication.

**Kenneth W. Horch** (M'88) received the B.S. degree from Lehigh University, Bethlehem, PA, and the Ph.D. degree from Yale University, New Haven, CT.

He is currently Professor of Bioengineering and Professor of Physiology at the University of Utah, Salt Lake City.

Dr. Horch is a Fellow of the American Institute for Medical and Biological Engineering (AIMBE).

CHAPTER 5

# FUNCTIONAL INTEGRITY OF KEVLAR® FIBER AND PLATINUM-IRIDIUM INTRAFASCICULAR ELECTRODES IMPLANTED IN HUMAN AMPUTEE NERVE STUMPS

Longitudinal intrafascicular electrodes (LIFEs) have been shown to record separable multiunit activity on a long-term basis, and could potentially serve as a stable interface for long-term control of neuroprosthetic devices. Previous studies involving implantation of Pt-Ir LIFEs in feline peripheral nerves demonstrated gradual shift in the recorded population of neurons and attenuation of signal-to-noise ratios of recorded action potentials [1]. This was attributed to relatively high stiffness of Pt-Ir leadwires compared to the endoneurial tissue.

A fine tubular network of exceedingly delicate peripheral nerve axons and endoneurial extracellular matrix behaves more like a highly viscous gel rather than a structural tissue. This viscoelastic property allows it to easily conform to different body positions/posture without any noticeable change in electrochemical activity. For a long-term implantation, it is important to have intraneural electrodes that demonstrate good mechanical biocompatibility so that there is minimal disruption of neural tissue. With negligible intraneural drift of intrafascicular electrodes, there will be insignificant change in the population of cells being recorded, and this will allow for reliable control of neuroprosthetic device(s). PolyLIFEs, which are up to 50 times more flexible than Pt-Ir wire, were developed at the Neuroprosthetics Laboratory, University of Utah, to address some of the shortcomings of Pt-Ir-based LIFES, namely mismatch in the bending moments of endoneurial tissue and intrafascicular electrodes, resulting in micromotion at the electrode-neural interface [2].

In the course of longer term human studies (lasting 2 to 4 weeks), both polyLIFEs and Pt-Ir electrodes were implanted in severed nerve stumps of long-term human amputees. Sensory stimulation and recording studies were conducted to explore changes in elicited sensations and the ability of subjects to control volitional motor nerve activity due to effects of training and CNS plasticity. Electrode resistance was measured periodically during the study.

## Methods

Methods to fabricate Pt-Ir and polyLIFEs have been described in detail elsewhere [2, 3], and will not be discussed here. Human subject selection, silicone connector design, the implantation procedure and experimental set up for recording nerve signals has been detailed in Chapters 2 and 3. Impedance was measured at the beginning of nerve function studies by passing sinusoidal current ~ 0.6 μA, at a frequency of 1 KHz across the electrode of interest. An EKG electrode, applied to the skin surface of the stump, with a thin layer of conductive jelly, served as a return electrode. The voltage drop across the recording/stimulating zone was amplified, sent via analog-to-digital converter and displayed on a laptop computer screen. Digital read out was proportional to the measured voltage and therefore the interfacial impedance at the recording/stimulating zone. Digital output, which was proportional to impedance of the electrode, was used for data analysis. All the values are normalized to initial digital output to look for trend(s) in impedance.

## Results

A total of 33 polyLIFEs and 20 Pt-Ir LIFEs were studied for up to a period of 4 weeks. Impedance of the LIFEs used in this study was in the range of 2 to 4 KΩ. A total of ~51% (17/33) polyLIFEs permanently failed by the end of the study period. Complete failure was defined when the recording system showed an open circuit, with impedance above the range for the impedance meter. For the duration of the study, all of the 20 Pt-Ir electrodes remained functional.

Electrodes were fabricated with initial impedance values in the range of 2 to 4 KΩ. Figures 5.1 and 5.2 show relative change in the impedance of polyLIFEs and Pt-Ir LIFEs, respectively. Relative impedance was defined as the ratio of measured impedance during the course of the study to the initial impedance measured following electrode implantation. Figure 5.2 shows a small increase in impedance of Pt-Ir LIFEs but analysis of the slope of the regression line showed this to be statistically insignificant ($p < 0.05$). Results of this study are consistent with previous experiments conducted with polyLIFEs implanted in feline dorsal roots. Researchers found no significant change in impedance over a period of 6 months [4].

We did find *inconsistent* behavior of 52 % (9/17) of polyLIFEs that eventually failed (Table 5.1). These electrodes showed complete loss of conductivity, return towards normal conduction and impedance during the same or subsequent testing session(s), and then eventually permanent failure over the course of the study. Regression analysis of the change in impedance of leads that failed showed no general trend. During each testing

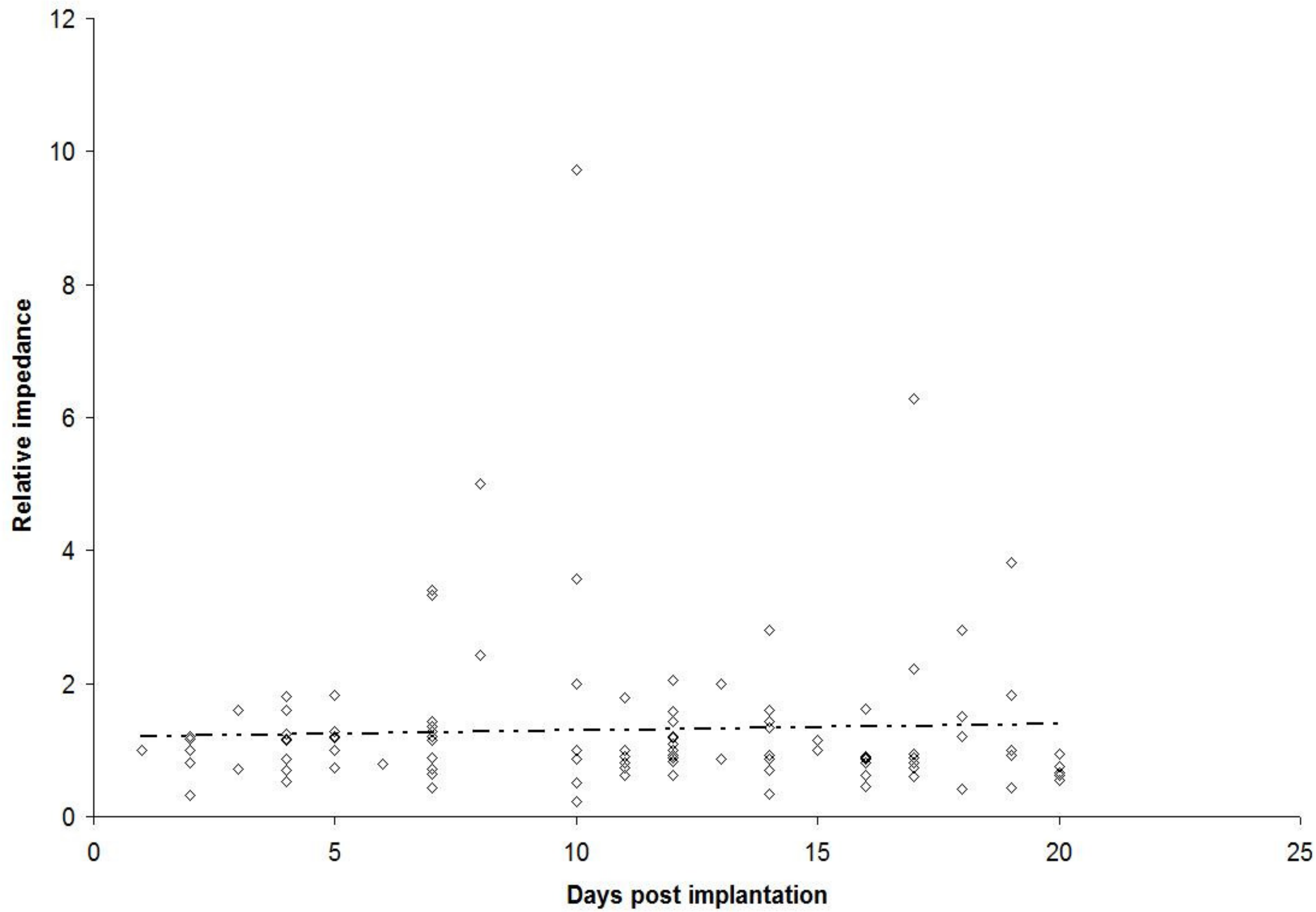


*Figure 5.1*. Variations in impedance values of polyLIFES over the duration of the implant.

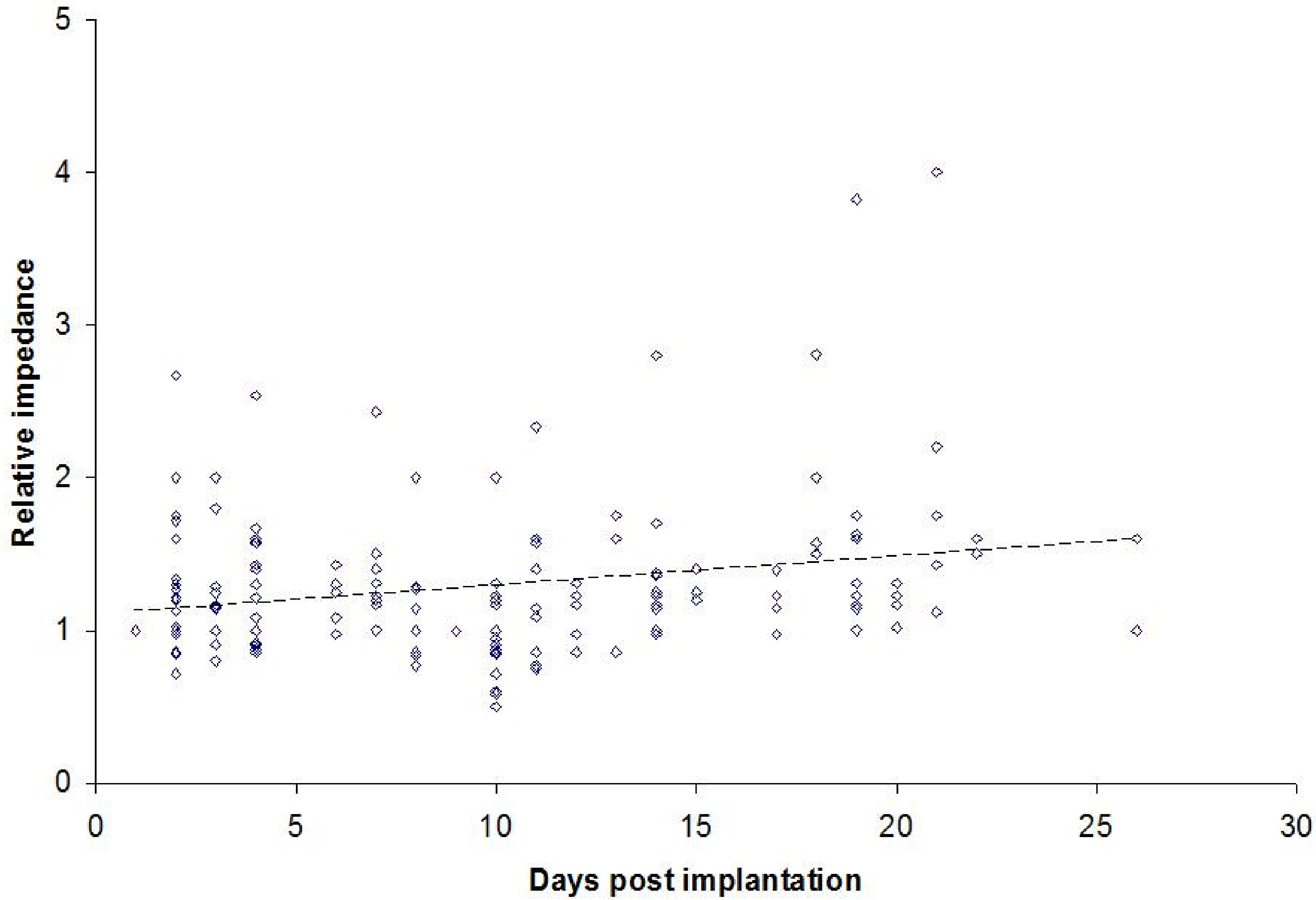


*Figure 5.2*. Variations in impedance values of Pt-Ir LIFEs over the duration of the implant.

Table 5.1

Conductive Behavior of PolyLIFEs.

| PolyLIFE behavior | Electrode # |
|---|---|
| Total electrodes | 33 |
| Normally conducting and then permanent loss | 8 |
| Intermittently conducting (IC) prior to permanent failure | 9 |
| Total permanent failure | 17 |
| Electrodes IC but functional by the end of study | 5 |
| Total functional by the end of study | 11 |

session when electrodes showed periods of loss of conduction, the equipment, including the connections, were thoroughly inspected to ensure that this unexpected change in impedance was related to conductivity of the leadwires and was not a consequence of faulty experimental set up. No recordings could be made with electrode leads that temporarily failed in a given testing session. Towards the end of the study, 35% of the 14 intermittently conductive electrodes (5/14) remained functional. The majority of polyLIFE failures occurred in the first 14 days (Fig. 5.3).

Regression analysis indicated that there was no overall change in the impedance values of Pt-Ir LIFEs during the course of the study. Unlike polyLIFEs, there was no temporary break in conductivity. Furthermore, all of the Pt-Ir LIFEs remained functional for the duration of the implant. These results are in agreement with studies conducted with Pt-Ir LIFEs implanted in feline peripheral nerves which showed no evidence of

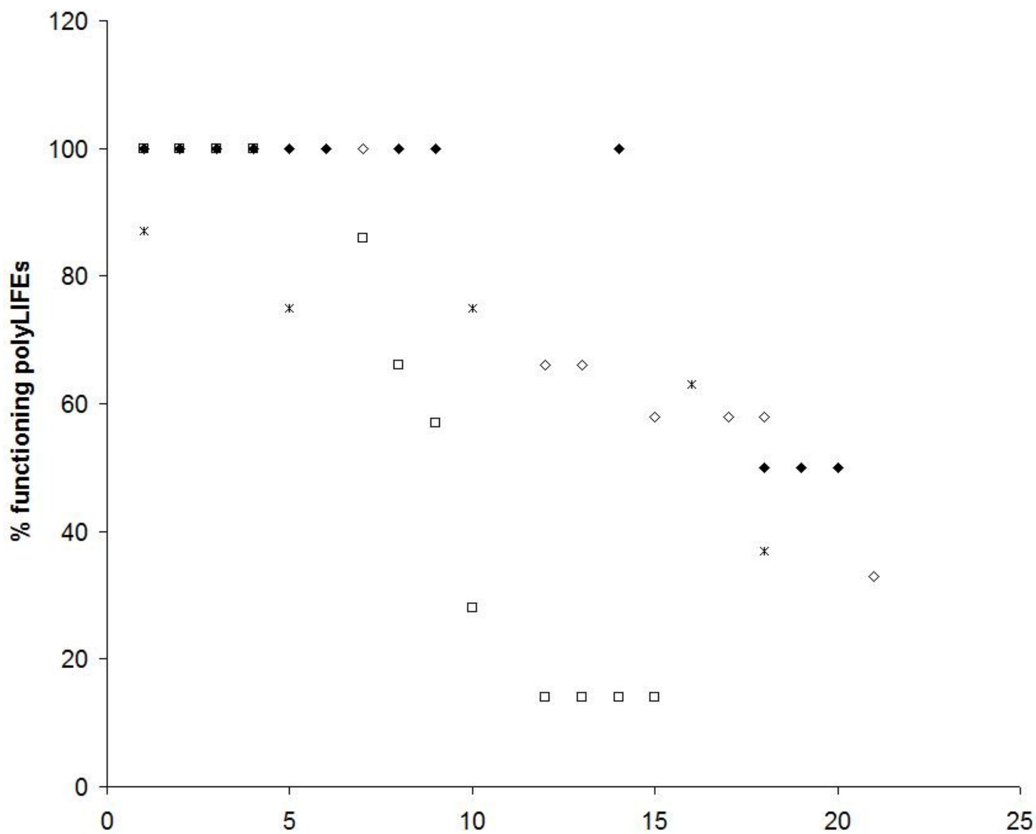


*Figure 5.3.* Percentage of functional polyLIFEs in different patients.

electrode failure or significant change in interfacial impedance during the first month of the study.

## Discussion

PolyLIFEs and Pt-Ir intrafascicular electrodes, with similar recording stimulation characteristics, were used to test the functional integrity of motor and sensory axons over a period of up to 4 weeks. Chapters 3 and 4 report results of neural stimulation and recording of volitional motor nerve activity. These electrodes displayed a distinct behavior in terms of interfacial impedance and robustness.

Microscopic and failure mode analysis of explanted electrodes was not conducted and we can only postulate the most likely reason(s) for failure of electrical conductivity of polymer-based intrafascicular electrodes. Our results are consistent with earlier studies conducted with PolyLIFEs implanted in dorsal roots for a period of 2 to 6 months. Possible causes for loss of conductivity include i) delamination of sputtered metal in the recording/stimulating zone and ii) leadwire failure.

Delamination of platinum black coating in the recording/stimulating zone is unlikely to be the cause for complete loss in electrical conductivity. This is because there is normally a 10-fold reduction in interfacial impedance when effective surface area and roughness of the recording/stimulating zone is increased through electroplating with platinum black [5, 6]. Therefore, even if there was complete loss of the electroplated platinum, impedance in the range 20 to 40 KΩ would have been recorded due to conduction by sputtered metallic layer at the recording/stimulating zone. With their high tensile stiffness and yield strain, relative to the metals used, Kevlar®-based polyLIFEs are designed to withstand cyclical strain, but mismatch in mechanical properties between Kevlar® fibers and metallic coatings could result in the development of cracks in the conductive layer. The fact that polyLIFEs showed no overall change in interfacial impedance shows that metallization was robust enough to withstand any stresses imparted on the intraneural portion of the electrode.

The most likely cause for complete loss of electrical conductivity is consistent with failure of the insulated, conductive segment of the leadwire which was exteriorized percutaneously and connected to a saddle connector. Failure points, due to kinking and stress risers, include where the electrode exited from the nerve stump, skin and at the electrode-connector interface. Cracks in the conductive layer of electrode leadwires could explain the observed phenomenon of transient loss of conductivity of many of the polyLIFEs that eventually failed.

In terms of leadwire failure, minor damage due to crack formation is unlikely to result in a significant increase in impedance, as contribution of lead wire to total resistance is relatively small (30Ω/cm) [2]. There was no consistent change in the impedance of electrodes prior to and immediately following a temporary break in electrical conductivity (Fig. 5.4). In fact, some polyLIFEs showed a dramatic drop in impedance following temporary break in electrical conductivity, and no significant change thereafter. Some electrodes showed complete loss and then restoration in electrical conductivity, when tested multiple times during a single session, even though there was no observable trend in their impedance over the course of the study. Eventually, there was permanent loss of conduction. It seems that broken/cracked segment(s) of the electrode are maintained in apposition through silicone coating, and as a result, change in electrode conductivity is difficult to predict until further stresses lead to complete disruption of cracked segment(s) of the electrode, resulting in permanent failure.

Maximum increase in impedance of 85% of Pt-Ir electrodes was approximately 2-fold during the course of the study. With a baseline range of 2 to 4 KΩ, this corresponds to peak impedance around 8 KΩ, which is well within the capabilities of LIFEs to record separable multiunit action potential activity. Previous studies conducted with implants in feline peripheral nerves showed stabilization of impedance after a small increase during the first month, and 100% of Pt-Ir LIFEs remained functional for a period

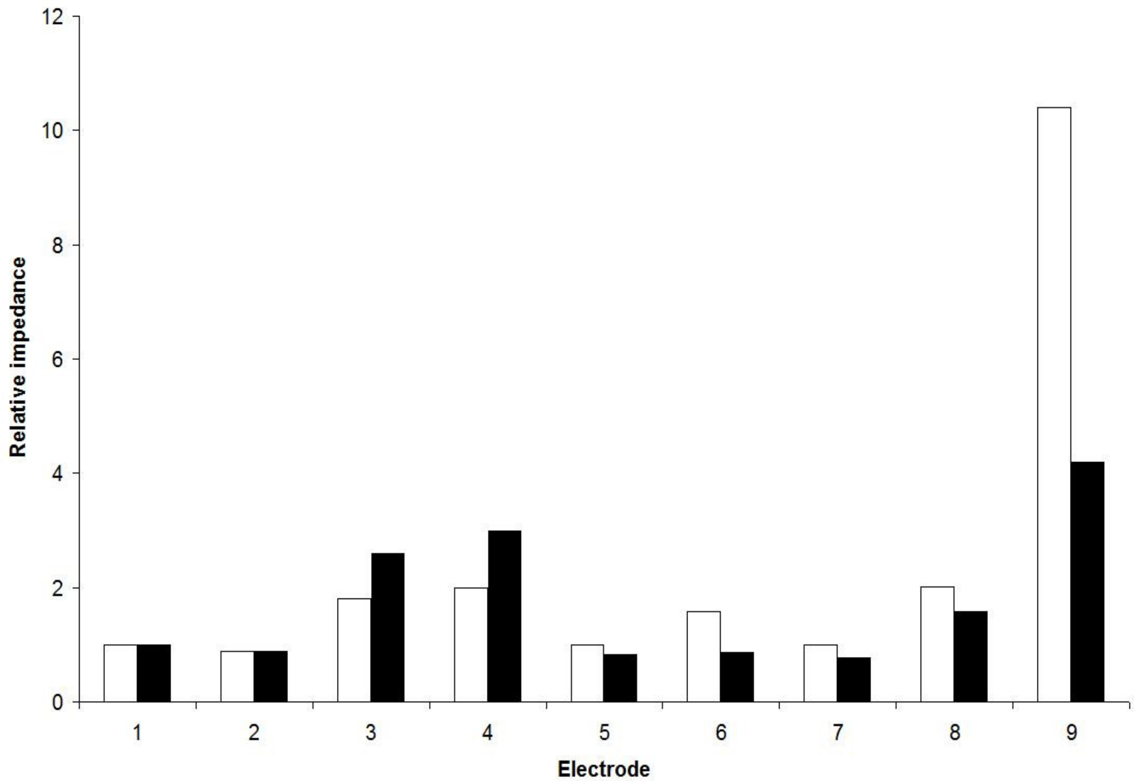


*Figure 5.4*. Values for different polyLIFEs that failed intermittently, immediately before (white bars) and after (shaded bars) first episode of failure.

of up to 3 months. Although our results are consistent with studies conducted in animal models, it is not possible to extrapolate the survivability of Pt-Ir electrodes to amputees controlling a neuroprosthetic arm for daily activities. This is because in real life, amputees will be actively contracting muscles at the stump site and this will impart significant cyclical stresses on the implanted Pt-Ir LIFEs, resulting in potential electrode drift and eventually lead failure, due to work hardening. This study does show that if ‘stress free’ implantation and connector system can be developed, then it may be possible to implant Pt-Ir LIFEs which may be able to function for many months/years, with no significant change in impedance or lead failure. Even though laboratory tests show that polyLIFEs can outlive Pt-Ir LIFEs when stressed through continuous cyclical motion, other factors such as kinking may be responsible for failure of metalized Kevlar® fiber leadwires [3].

## Conclusion

This was a short-term study, so it is not possible to make detailed conclusion about electrode behavior in terms of long-term human implants. Despite their shortcomings, impedance of functional polyLIFEs remained stable over the duration of the implant. A significant number of these electrodes failed over the course of the study, probably due to the development of cracks in the metal layer. Our experimental procedure may have favored Pt-Ir electrodes as a relatively immobile segment of the limb was used and these electrodes were relatively free from cyclical stresses that will be present in real life situation, with implants made in the vicinity of actively contracting stump muscles.

## References


1. Lefurge, T., et al., *Chronically implanted intrafascicular recording electrodes.* Ann Biomed Eng, 1991. 19(2): p. 197-207.

2. McNaughton, T.G. and K.W. Horch, *Metallized polymer fibers as leadwires and intrafascicular microelectrodes.* J Neurosci Methods, 1996. 70(1): p. 103-10.

3. Lawrence, S.M., G.S. Dhillon, and K.W. Horch, *Fabrication and characteristics of an implantable, polymer-based, intrafascicular electrode.* J Neurosci Methods, 2003. 131(1-2): p. 9-26.

4. Malmstrom, J.A., T.G. McNaughton, and K.W. Horch, *Recording properties and biocompatibility of chronically implanted polymer-based intrafascicular electrodes.* Ann Biomed Eng, 1998. 26(6): p. 1055-64.

5. Agnew, W.F. and D.B. McCreery, *Neural prostheses : fundamental studies.* Prentice Hall biophysics and bioengineering series. 1990, Englewood Cliffs, N.J.: Prentice Hall. xiv, 322 p.

6. Malagodi, M.S., K.W. Horch, and A.A. Schoenberg, *An intrafascicular electrode for recording of action potentials in peripheral nerves.* Ann Biomed Eng, 1989. 17(4): p. 397-410.

# CHAPTER 6

# CONCLUSION

## Neurally Controlled Artificial Arm

An ideal artificial arm is one that provides force and joint position feedback and allows the amputee to perform simultaneous, multidegree freedom-of-control, smooth, dexterous, movements in a closed loop fashion. Sensors in the terminal device need to provide real time sensory feedback related to discriminative touch and slip detection. Pseudo-natural sensory feedback and direct volitional control should allow the amputee to integrate the prosthesis into his/her body image. Neural interface should be stable with minimal electrode drift. Tissue encapsulation should not raise stimulation range anywhere close to what is perceived as damaging to the delicate network of peripheral nerve axons.

## Summary of Research

The purpose of this research project was to address the fundamental question of whether it is possible to interface the artificial limb to the severed nerve of upper limb amputees, record volitional motor nerve signals for control of actuators and provide graded sensory feedback from sensors in the joints and the gripper. For the purposes of this research, we used LIFEs, which are intraneural electrodes, and can record from a microcluster of motorneurons and stimulate sensory nerve fibers at a subfascicular level.

These properties notwithstanding, LIFEs can be easily explanted percutaneously, by applying gentle longitudinal traction.

In Chapter 2 we demonstrated presence of viable motor and sensory neurons in severed nerves of long-term (>> 2 months) human amputees. Through intrafascicular recordings, we managed to detect sustained, volitional motor nerve activity associated with movements of the missing limb. The amputees quickly (within a few minutes) learned to modulate recorded motor nerve activity, and use it successfully to control the trajectory of a cursor on a computer screen. Through stimulation of sensory channels, it was possible to provide graded position and tactile feedback.

In Chapter 3 we explored changes in stimulation parameters and volitional control over a period of up to 4 weeks. There was a small increase in the charge per stimulus needed to elicit a threshold sensation and in the stimulus amplitude needed before the nature of the sensation changed (upper limit for a given sensation). Even though the amputees could consistently grade the intensity of a sensation, our data showed that there was no consistent pattern to suggest learning was taking place over the period of the implant. For motor control, subjects were able to generate and modulate motor nerve activity associated with a given phantom movement. Through learning and training, they were able to improve the motor outflow and demonstrate greater precision of volitional control associated with neural activity recorded from severed motor neurons. This was possibly due to unmasking of pre-existing pathways due to dynamic, short-term CNS plasticity.

In Chapter 4 through interfacing of recording/stimulation circuitry directly to the artificial arm, we demonstrated that it is possible for amputees to judge and set grip force and joint position in absence of visual feedback.

In Chapter 5 we addressed the issue of electrode impedance. There was no significant change in the measured interfacial impedance of polyLIFEs and Pt-Ir LIFEs over the duration of the study. However, we did find that a significant number of polyLIFEs showed failure of electrical conductivity.

## Limitations of Our Research

For the acute phase of the study, our very strict criteria (injury >2 months duration) excluded many potential volunteers. Although we may surmise that any individual, regardless of the duration of injury, should have been enrolled into the study, this may have introduced greater subject variability and the need to enroll more volunteers.

In longer term studies, we noted no significant change in the subject's ability to grade and discriminate elicited sensations over the duration of the study. At first, this is a surprising result, given the dynamic, short- and long-term plasticity of the sensory cortex. Either restoration of sensory input leads to almost immediate unmasking of pre-injury pathways, or we did not provide sufficient sensory reeducation. In clinical practice, in order to enhance recovery following nerve repair surgery, sensory reeducation is provided over a period of weeks to months [1]. Furthermore, almost continual sensory input during performance of daily tasks provides the sensory cortex with a wealth of information which can result in central reorganization and neuro-plastic changes related to learning and training. With our experiments, we simply disconnected the stimulation circuitry following sensory nerve testing and reconnected it on the next session, which was usually the following day. A more realistic approach would have been to incorporate a self-contained sensory stimulation unit interfaced to sensory channels, so that our study participants had the benefit of almost continuous sensory feedback and therefore pseudo-natural sensory reeducation. For our study, it may have been premature to invest time and money in this kind of set up, since we did not know if long-term recording or stimulation would have been successful. Due to these limitations in our experimental design, there is no evidence to indicate improvement in the subject’s ability to more precisely discriminate and grade elicited sensations over the duration of the study. Our findings are consistent with basic science studies which have shown that short-term alterations in sensory feedback can result in central reorganization, but such changes are temporary and do not result in more permanent central representations associated with restored transmission of neural activity through ‘silent’ sensory pathways [2-4].

Sensation was tested in each electrode separately. We did not explore changes in perceived sensation(s) and sensory overlap (if any) when two or more sensory channels are activated simultaneously. This information can be used to define the dimensions and sensitivities of tactile sensors in the artificial hand. For control of the artificial arm, we did not explore optimum processing of motor nerve signals, define different sensory stimulation paradigms and training regimens. As this was a feasibility study with limited number of subjects, we did not explore nonvisual, closed loop control of the artificial arm.

## Future Directions

As we were investigating the role of intraneural interfacing for control of prosthetic limbs, Dr. Kuikan and colleagues demonstrated 'targeted reinnervation' could be used to execute simultaneous, multidegree freedom-of-control of a myoelectric prosthesis, with a potential to provide sensory feedback [5-8]. This is a giant leap over traditional methods of myoelectric control. Unlike neural interfacing, this approach does not require development of additional technology for transcutaneous transfer of signals to and from actuators and sensors in a prosthetic arm. However, there is a potential drawback of dennervating normally functioning muscles and the efficacy with which multichannel sensory feedback can be provided remains to be established.

LIFEs were exteriorized percutaneously and the leads were connected to a silicon based saddle connector. For much longer term studies, this is not a viable option. Alternative approaches include a percutaneous connector [9, 10], telemetry [11-14] or osseointegrated artificial arm. Each has its advantages and disadvantages. I favor osseointegrated neuroprosthetic arm because this will eliminate some of the problems associated with the socket fit and will allow more natural integration of an artificial arm into the amputee's body image. No such prosthesis exists, although in recent years there have been significant advances in the field of osseointegration [15-20], paving the way for development of skeletal integration of an artificial arm.

Further work with polyLIFEs needs to address the problems associated with loss of electrical conductivity. Appropriate changes in manufacturing techniques need to be implemented to prolong their longevity to cater extended period (many years) of implantation. More detailed sensory stimulation paradigms need to be developed and optimized to explore long-term benefits of providing sensory feedback. Sensory and motor control algorithms need to be developed to enable design of sensors and actuators integrated into an artificial arm. Issues related to optimal processing of motor control signals and improved operational characteristics of the artificial arm need to be addressed. Closed loop control and detailed experimental paradigms need to be developed to evaluate if movements of the artificial arm can be made rapidly enough with a degree of precision and dexterity in a context that will reflect the intended real life use of the prosthesis.

For longer term studies, amputees need to be provided with the artificial arm. Individuals lack interest in a study of this nature which does not provide them with any direct benefits. Many of our amputees asked if they will be recipients of the artificial arm, and some of them declined participation when told otherwise. Through careful selection, which should also involve psychological assessment, the number of patients can be limited to less than half a dozen but all individuals should directly benefit from studies proposed for the next phase of the project. The design of the artificial arm should be such that the amputee can use the prosthesis in his/her home environment and come to the laboratory for periodic testing. In the interim, information from the prosthesis should be transmitted remotely to the laboratory so that the researchers can contact the subject if they note change in the performance of the artificial arm, motor control or sensory feedback.

Recently groups in China and Italy have demonstrated, through human studies, the feasibility of using intraneural electrodes (specifically LIFEs) to control artificial limbs [21, 22]. These studies should add to the momentum of interfacing artificial limbs directly to the human nervous system. In the next decade, we should see exciting developments in this field of neuroprosthetic technology and its clinical implementation.

## References


1. Dellon, A.L., *Evaluation of Sensibility and Reeducation of Sensation in the Hand.* 1981, Baltimore: Williams & Wilkins.

2. Brasil-Neto, J.P., et al., *Rapid reversible modulation of human motor outputs after transient deafferentiation of the forearm: a study with transcranial magnetic stimulation.* Neurology, 1992. 42: p. 1302-1306.

3. Brasil-Neto, J.P., et al., *Rapid modulation of human cortical outputs following ischemic nerve block.* Brain, 1993. 116(511-525).

4. Sanes, J.N., J. Wang, and J.P. Donoghue, *Immediate and delayed changes of rat motor cortical output representation with new forelimb configurations.* Cerebral Cortex, 1992. 2: p. 141-152.

5. Dumanian, G.A., et al., *Targeted reinnervation for transhumeral amputees: current surgical technique and update on results.* Plast Reconstr Surg, 2009. 124(3): p. 863-9.

6. Kuiken, T., *Targeted reinnervation for improved prosthetic function.* Phys Med Rehabil Clin N Am, 2006. 17(1): p. 1-13.

7. Kuiken, T.A., et al., *Targeted muscle reinnervation for real-time myoelectric control of multifunction artificial arms.* JAMA, 2009. 301(6): p. 619-28.

8. Miller, L.A., et al., *Improved myoelectric prosthesis control using targeted reinnervation surgery: a case series.* IEEE Trans Neural Syst Rehabil Eng, 2008. 16(1): p. 46-50.

9. Campbell, P.K., et al., *A chronic intracortical electrode array: preliminary results.* J Biomed Mater Res, 1989. 23(A2 Suppl): p. 245-59.

10. Clippinger, F.W., R. Avery, and B.R. Titus, *A sensory feedback system for an upper-limb amputation prosthesis.* Bull Prosthet Res, 1974: p. 247-58.

11. Bhadra, N., et al., *Implementation of an implantable joint-angle transducer.* J Rehabil Res Dev, 2002. 39(3): p. 411-22.

12. Kilgore, K.L., et al., *An implanted myoelectrically-controlled neuroprosthesis for upper extremity function in spinal cord injury.* Conf Proc IEEE Eng Med Biol Soc, 2006. 1: p. 1630-3.

13. Mojarradi, M., et al., *A miniaturized neuroprosthesis suitable for implantation into the brain.* IEEE Trans Neural Syst Rehabil Eng, 2003. 11(1): p. 38-42.

14. Tsuchida, Y., N. Hama, and M. Takahata, *An optical telemetry system for underwater recording of electromyogram and neuronal activity from nontethered crayfish.* J Neurosci Methods, 2004. 137(1): p. 103-9.

15. Xu, W., D.H. Xu, and A.D. Crocombe, *Three-dimensional finite element stress and strain analysis of a transfemoral osseointegration implant.* Proc Inst Mech Eng [H], 2006. 220(6): p. 661-70.

16. Manurangsee, P., et al., *Osseointegrated finger prosthesis: An alternative method for finger reconstruction.* J Hand Surg [Am], 2000. 25(1): p. 86-92.

17. Hagberg, K., et al., *Osseointegrated trans-femoral amputation prostheses: prospective results of general and condition-specific quality of life in 18 patients at 2-year follow-up.* Prosthet Orthot Int, 2008. 32(1): p. 29-41.

18. Lundborg, G., J. Besjakov, and P.I. Branemark, *Osseointegrated wrist-joint prostheses: a 15-year follow-up with focus on bony fixation.* Scand J Plast Reconstr Surg Hand Surg, 2007. 41(3): p. 130-7.

19. Lundborg, G., P.I. Branemark, and B. Rosen, *Osseointegrated thumb prostheses: a concept for fixation of digit prosthetic devices.* J Hand Surg [Am], 1996. 21(2): p. 216-21.

20. Albrektsson, T., et al., *Present clinical applications of osseointegrated percutaneous implants.* Plast Reconstr Surg, 1987. 79(5): p. 721-31.

21. Jia, X., et al., *Residual motor signal in long-term human severed peripheral nerves and feasibility of neural signal-controlled artificial limb.* J Hand Surg Am, 2007. 32(5): p. 657-66.

22. Micera, S., et al., *On the control of a robot hand by extracting neural signals from the PNS: preliminary results from a human implantation.* Conf Proc IEEE Eng Med Biol Soc, 2009. 2009: p. 4586-9.